Article Type: Original Article

ORIGINAL ARTICLE

Postoperative outcomes following cardiac surgery in non-anaemic iron replete and iron deficient patients - an exploratory study

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Keywords: anemia: iron-deficiency; cardiac surgical procedures; iron; outcome assessment (health care)

Short title: Influence of non-anaemic iron deficiency on outcome after cardiac surgery

Accepted: 1 October 2017

Summary

Iron-deficiency anaemia is strongly associated with poor outcomes after cardiac surgery. However, pre-operative non-anaemic iron deficiency (a probable anaemia precursor) has not been comprehensively examined in patients undergoing cardiac surgery, despite biological plausibility and evidence from other patient populations of negative effect on outcome. This exploratory, retrospective cohort study aimed to compare an iron deficient group of patients undergoing cardiac surgery with an iron replete group. Consecutive, non-anaemic patients undergoing elective coronary artery bypass grafting or single valve replacement in our institution between January 2013 and December 2015 were considered for inclusion. Data from a total of 277 patients were analysed, and were categorised by iron status and blood haemoglobin concentration into iron deficient (n = 109) and iron replete (n = 168) groups. Compared with the iron replete group, patients in the iron deficient group were more likely to be female (43% vs. 12%, iron deficient vs iron replete, respectively), older, with a mean (SD) of 64.4 (9.7) vs. 63.2 (10.3) years, and have a higher pre-operative EuroSCORE (median IQR[range]) of 3 (2 – 5[0-10]) vs. 3 (2 – 4[0-9]), with lower pre-operative haemoglobin of 141.6 (11.6) vs. 148.3 (11.7) $g.l^{-1}$). Univariate analysis suggested that iron deficient patients had a longer hospital length of stay (7 (6 – 9 [2 – 40]) vs. 7 (5 – 8 [4 – 23]) days; p = 0.013) and fewer days alive and out of hospital at post-operative day 90 (83 [80 – 84]{0 – 87} vs. 83 [81 – 85]{34 – 86}, p = 0.009). There was no evidence of an association between iron deficiency and either lower nadir haemoglobin, or higher requirements for blood products during inpatient stay. After adjusting the model for pre-operative age, sex, renal function, EuroSCORE and haemoglobin, the mean increase in hospital length of stay in the iron deficient relative to the iron replete group was 0.86 days (bootstrapped 95% confidence interval -0.37 – 2.22, p = 0.098). This exploratory study suggests there is weak evidence of an association between non-anaemic iron deficiency and outcome after cardiac surgery after controlling for potentially confounding variables.

Introduction

It has long been recognised that iron-deficiency anaemia is associated with poor outcomes after cardiac surgery. Patients proceeding to surgery with this condition have a higher requirement for allogeneic red blood cell transfusion, a longer hospital stay, incidence of acute kidney injury and 30-day mortality [1]. Patients with non-anaemic iron deficiency who are in the early stages of iron depletion have not been as comprehensively studied.

While clinicians most commonly associate iron with haemoglobin (and oxygen carrying capacity), iron plays important roles in the metabolism of many cell types [2]. In other patient populations, non-anaemic iron deficiency has been linked to a variety of negative health outcomes, including poorer metrics of physical and mental wellbeing [3], and exercise capacity [4]. Consensus statements [5] and evidence-based guidelines [6] have extrapolated from other patient groups (notably pre-menopausal women, endurance athletes and heart failure) and recommend correction of non-anaemic iron deficiency prior to major surgery. One of few studies of iron deficiency, rather than anaemia alone in cardiac patients, found that in a sample of 100 patients, 37 had iron deficiency, with 25 being iron deficient but not anaemic [7]. These authors acknowledged the limitation of a small sample in looking for associations, with the only significant finding being increased transfusion in the iron deficient group.

To further determine if non-anaemic iron deficiency may have a measurable effect on postoperative outcome in cardiac surgery, we undertook a retrospective exploratory analysis of all non-anaemic elective patients who underwent isolated coronary artery bypass grafting or single valve replacement between January 2013 and December 2015 who had an accurate iron status recorded pre-operatively. We proposed that patients who were iron deficient would have a longer length of hospital stay, a lower number of days alive and out of hospital (the total number of days the patient spent at home and alive in the first 90 days after the initial surgical procedure), and a higher rate of allogeneic blood transfusion and lower nadir haemoglobin relative to those patients who were iron replete.

Methods

We conducted a retrospective analysis of all consecutive patients who underwent elective, primary, on-pump coronary artery bypass grafting (CABG) or single valve replacement between January 2013 and December 2015. Data that we extracted included a combination of prospectively collected data for statewide audit and outcome reporting (Australian and New Zealand Society of Cardiac Surgery National Audit Database), and retrospective extraction from electronic medical records (Cerner Corporation, North Kansas City, MO). We excluded patients from the analysis sample if they were anaemic at the time of pre-anaesthetic assessment, received parenteral iron administration in the four weeks prior to surgery, were taking oral iron supplementation at the time of surgery, and if iron status could not be determined. Anaemia was defined as a haemoglobin (Hb) of less than 120 $g.l^{-1}$ for females and less than 130 $g.l^{-1}$ for men (WHO criteria) [8]. This study was formally registered with, and approved by the Austin Health human research ethics committee with a waiver of individual participant informed consent.

For the purpose of the analyses, we stratified patients into two groups based on iron status; iron deplete (ID) and iron replete (IR). Iron deficiency was defined as a serum ferritin of less than 100 $\mu g.l^{-1}$, or 100 to 300 $\mu g.l^{-1}$ with transferrin saturation (TSAT) less than 20% and/or C-reactive protein (CRP) > 5$mg.ml^{-1}$ [6,9].

We collected data describing pre-operative characteristics, including specifically: age (years); sex; height (cm); weight (kg); pre-operative EuroSCORE; previous percutaneous coronary intervention; hypercholesterolaemia; end-stage renal failure requiring dialysis; hypercholesterolaemia; peripheral vascular disease; and left ventricular ejection fraction. These variables were taken from the previously referenced National Audit Database, and are, in part, used for pre-operative risk stratification. We derived body mass index (BMI [$kg.m^{-2}$]) and body surface area (BSA [m^2]) from these data. Pre-operative laboratory assessments included baseline Hb ($g.l^{-1}$), serum ferritin ($\mu g.l^{-1}$), TSAT (%), CRP ($mg.l^{-1}$), serum creatinine ($\mu mol.l^{-1}$) and estimated glomerular filtration rate (eGFR) ($ml.min^{-1}$). Intra-operative data included the operating surgeon, whether or not the patient received an intra-operative anti-fibrinolytic agent (tranexamic acid or aminocaproic acid), time spent on cardiopulmonary bypass, and procedure. Postoperative data included: total length of acute and subacute hospital stay (days); length of intensive care stay (days); requirement for and details of return to theatre and the reason; requirement for and details of readmission to acute care within the first 90 postoperative days; nadir Hb during hospital stay; Hb on hospital discharge; requirement for allogeneic red blood cell transfusion and/or blood products during inpatient stay; inpatient mortality; inpatient complications; and days alive and out of hospital at post-operative day 90 (DAOH-90). Unlike more days of hospital stay, which is a negative outcome, more DAOH-90 is a positive outcome. With respect to inpatient complications, stroke was defined as an embolic cerebrovascular accident with permanent neurological deficit, and gastrointestinal complication was defined as acute bowel ischaemia or upper or lower gastrointestinal haemorrhage.

The primary outcome measure was length of inpatient stay, including acute inpatient care and subsequent, continuous sub-acute care or rehabilitation. Secondary outcomes were DAOH-90, nadir Hb, and requirement for blood products during inpatient stay.

We did not undertake a formal sample size calculation. Every patient who underwent surgery in our institution between January 2013 (when iron studies were included as part of routine pre-operative testing regardless of haemoglobin) and December 2015 was considered for inclusion. The analysis sample of 277 patients represents a cohort 3.5-fold the size of the nearest comparable study [7]. This sample size allows the detection of a standardised mean difference of 0.4 standard deviation (SD) with 90% power, and a two-sided 5% level of significance using a two-sample t-test and a ratio of 40:60 of ID to IR.

Continuous data are presented as mean with SD or median (IQR[range]), if data were considered skewed. Categorical data are presented as frequency and percentages. Missing data was removed variable by variable, except where missing data precluded the accurate assessment of iron status, in which case the entire patient was removed from the analysis. There were 13 missing data points in the final analysis cohort, all of which were CRP.

We undertook univariate analysis to examine the differences in baseline demographic characteristics, clinical parameters, and post-operative outcomes between the ID and IR groups. For binary and categorical variables we used the chi-square test or Fisher's exact test (expected count less than five). For continuous variables, we tested for normality using the Shapiro-Wilk test, and analysed normally distributed data using a two-sample t-test, and we used the Wilcoxon rank sum test in other situations. In addition, we analysed cumulative incidence curves using the Kaplan-Meier method for length of stay and DAOH-90, and compared these between the ID and IR groups using a log rank test.

We undertook multivariate analysis on the primary outcome, length of inpatient stay after surgery. A causal diagram was used to select confounders to include in the model: we included pre-operative age; sex; eGFR; EuroSCORE and Hb in the multivariate model. A 95% confidence interval of the mean difference between ID and IR was calculated using a bootstrap percentile interval approach with 500 resampled datasets. We performed statistical analyses using the 'R' software (The R Foundation for Statistical Computing, Vienna, Austria) and SAS, version 9.4 (SAS Institute, Cary, NC). We have reported this study using the STROBE guidelines [10].

Results

We screened a cohort of 448 consecutive patients who had undergone elective CABG or single valve surgery during the study period (Figure 1). With respect to subjects excluded from data analysis, we excluded twenty-seven patients (6%) from the dataset as they had received a parenteral iron infusion to correct iron deficiency prior to surgery; 10 (2%) due to oral iron therapy; 76 (16%) due to insufficient information in the medical record to determine iron status; and finally 58 (13%) due to anaemia. Of the final analysis cohort (n = 277), 109 (39%) were classified as ID, and 168 (61%) classified IR. There were two deaths in the study cohort.

Pre-operative characteristics and laboratory parameters for each group are outlined in Tables 1 and 2, respectively. Patients in the ID group were more likely to be female ($p < 0.001$), older ($p = 0.007$), shorter in height ($p < 0.001$), and by extension, have a higher BMI ($p = 0.02$). ID patients also demonstrated a higher EuroSCORE ($p = 0.007$). Height, BMI and EuroSCORE are partly dependent on sex and age, and may be accounted for by the higher proportion of female patients in the ID group. No other significant differences with respect to pre-operative morbidity were noted between the groups (specifically prior percutaneous coronary intervention, peripheral vascular disease, hypercholesterolaemia and left ventricular ejection fraction < 50%). Relative to the IR group, the ID patients had a lower pre-operative Hb (p < 0.001), a lower serum ferritin (p < 0.001), lower TSAT (p < 0.001) and a lower creatinine (p = 0.002), although this did not translate to a higher eGFR (p = 0.59).

Surgical variables are listed in Table 3. A reduction in chest drain output at four hours (median 210ml in ID vs 283ml in IR, p = 0.005) was noted. Despite this difference, it is unlikely that this metric was clinically significant with respect to the primary outcome measure. No other differences between the two groups were apparent.

We undertook both univariate and multivariate analyses. The hospital length of stay in the ID group was longer compared to IR group; 7 (6 – 9 [2 – 40]) vs. 7 (5 – 8 [4 – 23]) days; p = 0.013). Similarly, iron deficiency was associated with fewer days alive and out of hospital at day 90; 83 (80 – 84 [0 – 87]) vs. 83 (81 – 85 [34 – 86]) days, p = 0.009). The cumulative probability of hospital length of stay (Figure 2) and days alive and out of hospital at day 90 (Figure 3) illustrate differences over time between the two groups. There was no evidence of a difference in the following: return to theatre for any reason (p = 0.12); return to theatre for bleeding (p > 0.99); length of intensive care stay (p = 0.22); readmission to hospital (p = 0.42); or mortality (p = 0.15). Whilst the nadir Hb was lower in the ID group (p = 0.013) (Table 4), there was no evidence of significant differences in allogeneic red cell transfusion; 62 (37%) vs. 48 (44%), a difference of +7%, (95% CI -5 – 19%,) p = 0.26; or requirement for blood products (p = 0.89).

We undertook multivariate analysis of the hospital length of stay, adjusting for the following confounding demographic factors: pre-operative age; sex; estimated glomerular filtration rate; EuroSCORE; and haemoglobin. Following multivariate analysis, the difference in length of stay was no longer apparent, mean 0.86 days with bootstrapped 95% CI (-0.37 - 2.22 days), p = 0.098.

Discussion

We conducted a single centre retrospective study of non-anaemic patients undergoing cardiac surgery, and found that those who were iron deficient were likely to have a longer postoperative in-hospital stay than patients who were iron replete, and to have a shorter 'days alive and out of hospital at post-operative day 90'. However, a number of factors are potential confounders: female sex; age; co-morbidities (as measured by predictive risk scoring such as EuroSCORE); and lower pre-operative Hb. Nevertheless, even after adjusting for these factors, the trend for patients with iron deficiency being in hospital up to two days longer than those who are iron replete persisted, despite a loss of statistical significance. The other endpoints were not explored in a multivariate analysis.

There is substantial biological plausibility as to why non-anaemic iron deficiency may independently influence postoperative outcome, including length of stay. Iron has an integral role in homeostasis; 65% of total body iron is in erythropoiesis, 10% is stored in myoglobin and about 25% is involved in mitochondrial function through the respiratory chain [11]. Whilst evidence that non-anaemic iron deficiency has a negative impact on day to day function is limited to smaller studies [4,12], there are data suggesting that correction of non-anaemic iron deficiency in fit, healthy women leads to substantial improvements in mental wellbeing and exercise capacity, separate to the anticipated benefits for erythropoesis [3,13–16]. Evidence of the impact of non-anaemic iron deficiency has extended beyond exercise physiology, particularly to patients with heart failure. Multiple large, well conducted RCTs have shown benefits of the treatment of iron deficiency in the presence and absence of anaemia, with reductions in all-cause mortality and hospitalisation due to heart failure, as well as marked improvements in exercise tolerance and quality of life [17–19]. These studies were subsequently confirmed by meta-analysis [20,21].

The association between non-anaemic iron deficiency and postoperative outcomes has several possible explanations. First, non-anaemic iron deficiency may lead to lower starting and nadir haemoglobin, with subsequent detriment to oxygen carrying capacity. Second, patients with non-anaemic iron deficiency are generally more unwell with more comorbidities (as suggested by the increased EuroSCORE), with non-anaemic iron deficiency as a non-modifiable marker of illness that, whilst signaling the potential for a worse outcome, cannot necessarily be corrected. Third, non-anaemic iron deficiency acts by an as yet undefined mechanism, possibly related to mitochondrial or respiratory chain function. This mechanism has been implicated in the role of iron deficiency in heart failure [2].

Despite the presence of good quality evidence of benefit for the correction of non-anaemic iron deficiency in other populations, there are limited peri-operative data. Piednoir and colleagues found that a non-anaemic iron deficiency sub-group had greater transfusion rates ($p < 0.05$) after a broad range of cardiac surgical procedures [7]. Our results showed a point estimate increase of 7% for allogeneic transfusion in the ID group relative to the IR group, with a confidence interval ranging from a small, clinically unimportant decrease to a large clinically important increase. This may be explained by our patient population, which focused on surgical procedures that carried a lower rate of blood loss (CABG and single valve surgery). Our study supports a key finding of Piednoir et al, that even older women are far more likely to be iron deficient than men [7]. The link between menstrual blood loss and iron deficiency in pre-menopausal women is well known [22,23]. Our findings suggest that this finding remains true into the post-menopausal years, which has been noted in previous population surveys [24]. The higher proportion of women in the ID group also explains the differences in body habitus between the groups and to some extent the EuroSCORE.

Creating a definitive link between non-anaemic iron deficiency and poor peri-operative outcomes is important, as opinion leaders are increasingly advocating for correction of non-anaemic iron deficiency in patients undergoing major surgery. For the most part, this advice has a strong basis in biological plausibility, but evidence remains limited. In a recent international consensus statement, the authors advocate iron supplementation in any patient with a TSAT of less than 20%, regardless of iron status [5], and the National Blood Authority Guidelines from Australia suggest the same for patients with a serum ferritin less than 100 $\mu g.l^{-1}$ [6]. However the benefits and risks (particularly infection) of iron therapy, including intravenous iron in peri-operative patients with non-anaemic iron deficiency, are unclear [25].

Apart from the overall impact of non-anaemic iron deficiency on outcomes, the incidence of anaemia and iron deficiency in this cohort, and the marked differences relative to other previously published studies are worthy of further comment. In a large, UK-wide audit of over 19,000 patients across 12 cardiac surgical centres in 2016, Klein et al demonstrated an overall incidence of anaemia of 31%, with the range across individual centres being 23 – 45% [26]. In 2017, Muñoz et al described an incidence of anaemia of 40% in a sub-group of 691 cardiac surgical patients [27]. For those having isolated CABG the incidence was 33%, and for isolated valve repair/replacement the incidence was 41%. In those patients who were not anaemic (Hb > 130 $g.l^{-1}$), 45% were described as having an abnormal iron status, defined as absolute iron deficiency (serum ferritin < 30 $\mu g.l^{-1}$), inadequate iron stores (serum ferritin < 100 $\mu g.l^{-1}$ with TSAT > 20%), or iron sequestration (serum ferritin > 100 $\mu g.L^{-1}$ and TSAT < 20%). In contrast, after exclusion of patients who had received iron supplementation or whose iron status could not be determined, the incidence of anaemia in our subjects was 18%, and the incidence of non-anaemic iron deficiency was 33%. Whilst disparities in the definitions used for iron deficiency and anaemia may partially explain the marked difference between our results and those of Klein et al and Muñoz et al, it is also likely that geographic and population differences (perhaps with respect to genetic makeup, diet and other demographic features) have a key role to play.

This study has limitations, largely as a consequence of its retrospective and exploratory nature. Firstly, whilst the sample size was defined by the available data set during the collection period, a power calculation was not performed, and Type 2 error cannot be excluded. Nonetheless, this study was three-fold the size of the nearest comparable study [7]. Secondly, while data were able to be collected for all readmission episodes at our institution, we cannot exclude the possibility that some patients were readmitted to other hospitals without our knowledge, with implications for any associated results (including days alive and out of hospital). Thirdly, retrospective data collection from clinical records increases the number of patients with incomplete data sets. In this study, 13 individual data points were missing, all of which were pre-operative CRP (representing 3.8% of data points for this variable). However, none of these missing data prevented iron status from being determined.

In summary, we have undertaken a retrospective, single-centre, cohort study of non-anaemic patients, comparing the postoperative outcomes of an iron deficient group following elective CABG or single valve cardiac surgery, with an iron replete group. While univariate analysis suggested that patients with iron deficiency had a longer hospital length of stay, subsequent multivariate correction for a variety of interacting factors showed that this association was weak. These findings support future, prospective observational studies to further determine the impact of non-anaemic iron deficiency on important, patient-centred, postoperative outcomes, and to appropriately design randomised trials of interventions such as iron therapy for this condition.

Acknowledgements

The authors would like to extend their gratitude to Associate Professor George Matalanis and the other surgeons of the Austin Health Department of Cardiac Surgery for allowing access to their patient demographic and outcome data, and to Ms. Margaret Shaw (cardiac surgery database manager) for her assistance in extracting relevant data. No external funding or competing interests declared.

Table 1 Pre-operative characteristics of iron deplete (ID) and iron replete (IR) subjects. Value are number (proportion), mean (SD) and median (IQR [range]).

Characteristics	**ID** **n = 109**	**IR** **n = 168**
Female	47 (43%)	20 (11%)
Age (years)	66 (9.6)	63 (10.3)
Height (cm)	165.9 (9.2)	170.8 (10.1)
Weight (kg)	82.7 (17.8)	84.3 (17.6)
BMI ($kg.m^{-2}$)	30.0 (5.8)	29.5 (14.4)
BSA (m^2)	1.94 (0.23)	1.99 (0.21)
EuroSCORE	3 (2 – 5 [0 – 10])	3 (2 – 4 [0 – 9])
Prior PCI	18 (17%)	22 (13%)
Hypercholesterolaemia	89 (82%)	134 (80%)
Peripheral vascular disease	11 (10%)	18 (11%)
Haemodialysis	0 (0%)	1 (0.6%)
LVEF > 50%	86 (79%)	122 (72%)
LVEF 40 – 50%	14 (13%)	31 (18%)
LVEF 30 – 40%	7 (6%)	10 (6%)
LVEF < 30%	2 (2%)	6 (5%)

BMI, body mass index; BSA, body surface area; PCI, percutaneous coronary intervention; LVEF, left ventricular ejection fraction.

Table 2 Pre-operative laboratory parameters of iron deplete (ID) and iron replete (IR) subjects. Value are mean (SD) and median (IQR [range]).

Laboratory parameters	**ID** **n = 109**	**IR** **n = 168**
Haemoglobin (g.l-^{1})	141.6 (11.5)	148.3 (11.7)
Ferritin (μ g.l^{-1})	75 (50 – 98 [13 - 294])	242 (169 – 340) [100 - 1262]
TSAT (%)	19 (16 – 25 [4 – 42])	27 (23 – 33 [2 - 66])
CRP (mg.l^{-1})	1.9 (0.9 – 3.6 [0.1 – 10.0])	1.8 (0.9 – 3.3 [0.3 – 26.1])
Creatinine (μ mol.l^{-1})	80 (68 – 94) [47 – 159]	86 (77 – 97 [45 – 704])
eGFR (ml.min^{-1})	86 (66 – 112 [26 - 295])	87 (70 – 110 [11 - 356])

TSAT, transferrin saturation; CRP, C-Reactive Protein; eGFR, estimated Glomerular Filtration Rate.

Table 3 Conduct of surgery variables in iron deplete (ID) and iron replete (IR) subjects. Value are number (proportion) and median (IQR [range]).

Conduct of surgery	**ID** **n = 109**	**IR** **n = 168**
CABG	72 (66%)	124 (74%)
AV surgery	26 (24%)	33 (20%)
MV Surgery	11 (10%)	11 (6%)
CPB time (min)	102 (85 – 122 [36 – 331])	109 (85 – 129 [41 – 237])
Anti-fibrinolytic	85 (77%)	125 (72%)
Chest drain output at 4 hours (ml)	210 (150 – 340 [70 – 1350])	283 (200 – 385 [60 – 3150])

CABG, Coronary Artery Bypass Grafting; AV, aortic valve; MV, mitral valve; TV, tricuspid valve; PV, pulmonary valve; CPB, cardiopulmonary bypass. Significant p-values are reported in the results section.

Table 4 Univariate outcome analysis in iron deplete (ID) and iron replete (IR) subjects. Values are number (proportion) and median (IQR [range]).

Outcomes	**ID n = 109**	**IR n = 168**	**p-value**
Hospital LoS (days)	7 (6 – 9 [2 – 40])	7 (5 – 8 [4 – 23])	0.013**
DAOH-90 (days)	83 (80 – 84 [0 – 87])	83 (81 – 84 [34 – 86])	0.009**
Nadir Hb ($g.l^{-1}$)	75 (68 – 89 [54 – 115])	80 (70 – 94 [50 – 124])	0.03**
Allogeneic PRBC	48 (44%)	62 (37%)	0.24*
Coagulation factors or platelets	28 (26%)	41 (24%)	0.81*
Discharge Hb ($g.l^{-1}$)	96 (88 – 105 [67 – 145])	95 (87 – 104 [71 – 133])	0.66**
Return to OT (any)	7 (6.4%)	4 (2.3%)	0.12*
Return to OT (bleeding)	2 (1.8%)	4 (2.4%)	> 0.99*
ICU LoS (days)	3 (2 – 3 [0 – 9])	3 (2 – 3 [1 – 11])	0.22**
Post-operative MI	0 (0%)	1 (0.6%)	> 0.99*
Pneumonia	1 (0.9%)	5 (3.0%)	0.41*
Tracheostomy	0 (0%)	0 (0%)	> 0.99*
Stroke	1 (0.9%)	1 (0.6%)	> 0.99*
CVVHF	0 (0%)	2 (1.2%)	0.52*
Deep sternal wound infection	0 (0%)	0 (0%)	> 0.99*
GI complication	1 (0.9%)	2 (1.2%)	> 0.99*
Readmission	13 (11.9%)	15 (8.9%)	0.42*
Mortality	2 (1.8%)	0 (0%)	0.15*

Hb, haemoglobin; PRBC, packed red blood cells; OT, operating theatre; LoS, length of stay; DAOH-90, days alive and out of hospital on post-operative day 90; MI, myocardial infarction; CVVHF, continuous venovenous haemofiltration; GI, gastrointestinal. * Fisher’s exact test, ** Wilcoxon test.

Figure legends

Figure 1 STROBE-style study flowchart outlining recruitment to and exclusion from the analysis sample.

Figure 2 Cumulative incidence curves for ID (-----) and IR (——) groups for the primary outcome measure, length of hospital stay (days); p-value = 0.012.

Figure 3 Cumulative incidence curves for ID (-----) and IR (——) groups for the secondary outcome measure, days alive and out of hospital at post-operative day 90; p-value = 0.009.

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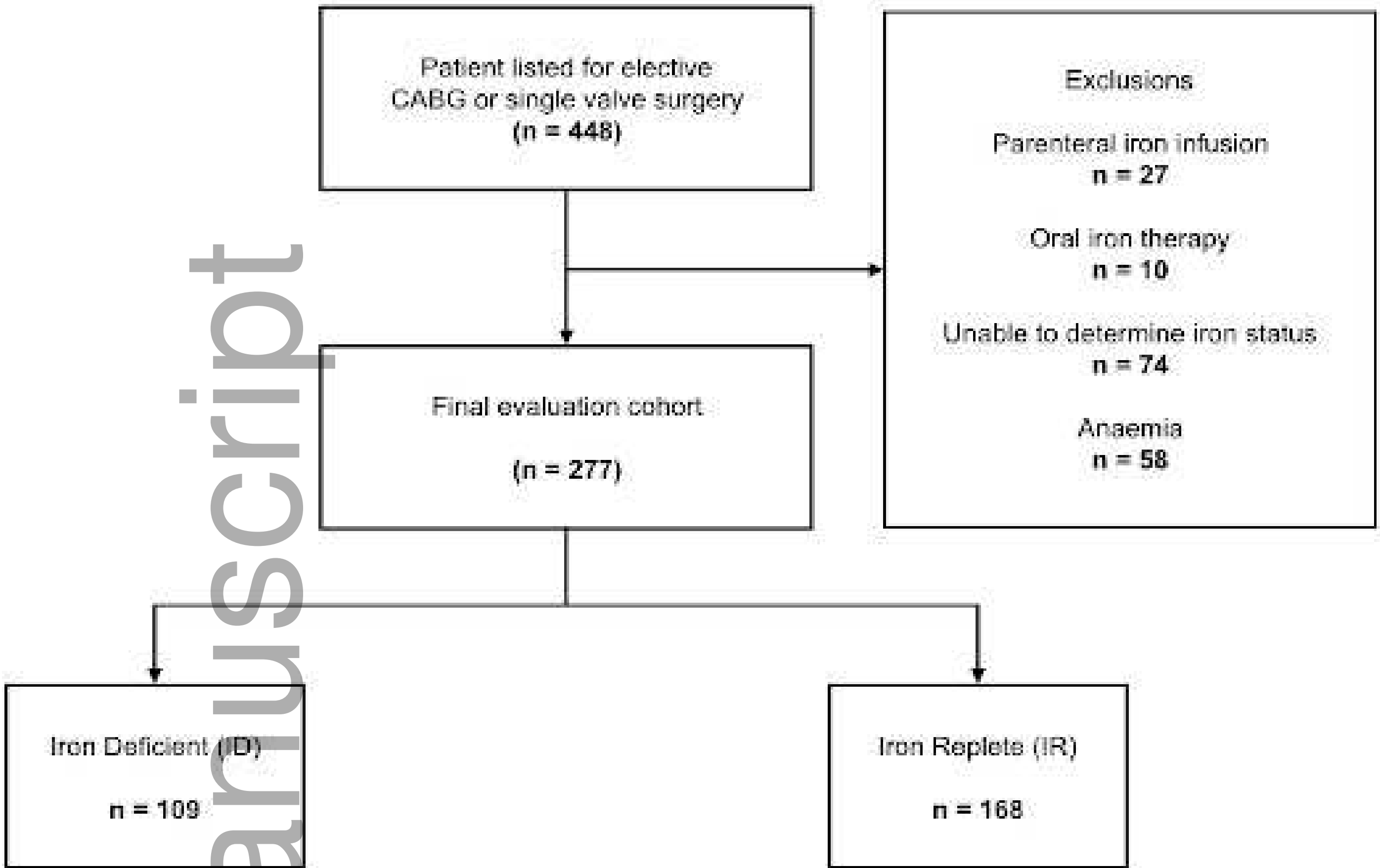

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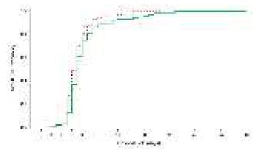

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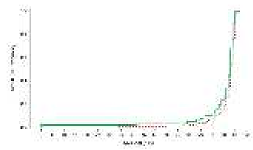

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