Prognostic impact of hemoglobin concentration at one to three months after coronary surgery

Fausto Biancari[1,2,3], Tuomas Tauriainen[2], Qiyao Zhang[4], Giuseppe Gatti[5], Francesco Santini[6], Marisa De Feo[7], Marco Zanobini[8], Timo Mäkikallio[3], Francesco Onorati[9], Stefano Rosato[10], Paola D'Errigo[10], Giovanni Mariscalco[11], Magnus Dalén[4]

[1]*Heart and Lung Center, Helsinki University Hospital, University of Helsinki, Helsinki, Finland;*
[2]*Department of Surgery, Oulu University Hospital and University of Oulu, Oulu, Finland;*
[3]*Department of Medicine, South-Karelia Central Hospital, University of Helsinki, Lappeenranta, Finland;*
[4]*Department of Molecular Medicine and Surgery, Department of Cardiac Surgery, Karolinska Institutet, Karolinska University Hospital, Stockholm, Sweden;*
[5]*Division of Cardiac Surgery, Cardio-thoracic and Vascular Department, Azienda Sanitaria Universitaria Giuliano Isontina, Trieste, Italy;*
[6]*Division of Cardiac Surgery, Ospedale Policlinico San Martino, University of Genoa, Genoa, Italy;*
[7]*Department of Cardiothoracic Sciences, Monaldi Hospital, University of Campania "Luigi Vanvitelli", Naples, Italy;*
[8]*Cardiovascular Department, IRCCS Centro Cardiologico Monzino, Milan, Italy;*
[9]*Division of Cardiac Surgery, University of Verona Medical School, Verona, Italy;*
[10]*Global Health Department, Italian Health Institute, Rome, Italy;*
[11]*Department of Cardiovascular Sciences, Clinical Sciences Wing, University of Leicester, Glenfield Hospital, Leicester, United Kingdom*

Arrived: 13 September 2022
Revision accepted: 14 November 2022
Correspondence: Fausto Biancari
e-mail: faustobiancari@yahoo.it

INTRODUCTION

There is a consensus of agreement among several studies on the negative prognostic impact of anemia on the early outcome of cardiovascular surgery[1,2]. A growing body of evidence suggests that pre-operative treatment of anemia and iron deficiency with intravenous iron, particularly when administered with erythropoietin, may increase the concentration of hemoglobin (Hb) with a reduced risk of allogeneic blood transfusion[3-6]. However, current knowledge of the benefits of, and possible harm from, iron administration before cardiac surgery is rather limited[4,6] and patient blood management strategies[7] are not widely implemented. Importantly, no data on the prevalence and prognostic impact of anemia several weeks after cardiac surgery are available. In the present study, we aimed to investigate the effect of post-operative anemia 1-3 months after surgery on the late survival of patients who had undergone isolated coronary artery bypass grafting (CABG).

MATERIALS AND METHODS

Patient population and data collection

The European Multicenter Study on Coronary Arterial Bypass Grafting (E-CABG) registry includes consecutive patients who underwent isolated CABG at 16 European cardiac surgery centers from January 2015 to May 2017. The project is registered at clinicaltrials.gov (NCT02319083). The study was approved by the Institutional Review Board or ethical committee of each participating center. The Ethical Committee of the sponsor institution granted permission to perform this study (Ethic Committee Name: Pohjois-Pohjanmaan Siraanhoitopiiri; approval Code: 195/2014; approval date: 20/10/2014). Data on pre-operative, operative, and early post-operative variables and outcomes were prospectively collected. Eight of the participating centers agreed to a retrospective collection of data. This included data on late events and this subset of patients forms the basis of this analysis. Data on the date of death was collected retrospectively from institutional and national electronic registries and by contacting regional hospitals, general practitioners, patients and their relatives. Anemia was defined as baseline Hb concentration <12.0 g/dL in women and <13.0 g/dL in men. The primary outcome of this study was 5-year all-cause mortality. Participating hospitals shared a policy of administration of blood transfusion when post-operative Hb concentration was <90 g/dL on the day of surgery and during post-operative day 1, and <80 g/dL after that.

Statistical analysis

The Mann-Whitney test, the χ^2test, Fisher's exact test, and repeat measure analysis with

Blood Transfus 2023; 21: 296-300 doi: 10.2450/2022.0206-22

the between-subjects effects test were used for univariate analysis. Univariable and multivariable analysis of late mortality was performed using the Cox proportional hazards model with the Harrell's C and Somers' D as measures of predictive power of the regression model. The ability of Hb concentrations to predict late mortality was estimated also with the receiver operative characteristic (ROC) curve for time-dependent outcome (Stroccurve for Stata). All tests were two-sided. p<0.05 was considered statistically significant. Statistical analyses were performed using SPSS v.25 (IBM Corporation, Armonk, NY, USA) and Stata v.15.1 (StataCorp LLC, TX, USA) statistical softwares.

Table I – *Patients' baseline characteristics, operative data, and main early outcomes*

Co-variates	N. (%) / mean (SD)
Baseline risk factors	
Age (years)	66.7±9.0
Female	98 (16.8)
eGFR (mL/min/1.73 m²)	77±20
Diabetes	194 (33.3)
Prior stroke/TIA	52 (8.9)
Atrial fibrillation	59 (10.1)
Pulmonary disease	52 (8.9)
Extracardiac arteriopathy	70 (12.0)
LVEF ≤50%	196 (33.7)
Critical pre-operative state	37 (6.4)
Recent STEMI	30 (5.2)
Emergency procedure	27 (4.6)
N. of diseased vessels	2.8±0.5
EuroSCORE II (%)	2.9±4.5
Operative data	
N. of distal anastomoses	3.2±0.9
Off-pump surgery	93 (16.0)
BIMA grafting	171 (29.4)
Early post-operative outcomes	
Stroke	8 (1.4)
Resternotomy for bleeding	21 (3.6)
Deep sternal wound infection	23 (4.0)
N. of transfused RBC units	1.3±2.7
AKI	149 (25.6)
Hemoglobin concentrations (g/dL)	
Before surgery	13.6±1.6
Nadir concentration after surgery during index hospitalization	9.8±1.6
1-3 months after surgery	12.2±1.8
Anemia	
Before surgery	153 (26.3)
After surgery during index hospitalization	571 (98.1)
1-3 months after surgery	334 (57.4)

Continuous variables are reported as the mean ± standard deviation (SD). Categorical variables are reported as counts and percentages. Anemia is defined as baseline hemoglobin concentration <12.0 g/dL in women and <13.0 g/dL in men. AKI: acute kidney injury according to the KDIGO citeria; BIMA: bilateral internal mammary artery; eGFR: estimated glomerular filtration rate according to the CKD-EPI equation; EuroSCORE: European System for Cardiac Operative Risk Evaluation; LVEF: left ventricular ejection fraction; RBC: red blood cells; TIA: transient ischemic attack. Clinical variables are defined according to EuroSCORE II criteria.

RESULTS

A total of 2,948 patients underwent surgery at the participating centers from January 2015 to May 2017. Of these, 2,342 patients were excluded from the analysis because of lack of data on Hb concentration at a check-up at 1-3 months, 24 patients because of lack of data on pre-operative or perioperative Hb concentration. Overall, 582 (19.8%) patients were included in the present analysis. Patients' characteristics are summarized in **Table I**. Of the 582 patients analyzed, 528 (90.7%) had undergone surgery at the Oulu University Hospital, Finland, and the Karolinska Institute, Sweden, because these centers are responsible for routine post-operative control of patients for their catchment area. Data on late outcome of these two centers are from National registries and are, therefore, expected to be complete. Mean follow-up of this series was 4.9±1.0 years. Five-year mortality of this series was 8.8%.

Post-operative measurement of Hb concentration was taken after a mean 1.8±5.5 months (median 1.7 months) after surgery. There was a significant difference in Hb concentration before surgery (during the index hospitalization) and 1-3 months after surgery between patients who died after that timeframe and survivors (between-subject effects: p=0.002; when adjusted for gender: p=0.001; **Figure 1**). However, this was mainly due to differences in Hb concentration at 1-3 months post-surgery. In univariate Cox proportional hazards analysis, Hb concentration at 1-3 months post-surgery had a significant impact on 5-year all-cause mortality (HR: 0.691; 95% CI: 0.606-0.788; Harrell's C: 0.676; Somers' D: 0.351). The survival area under the ROC curve at 5 years was 0.321. Pre-operative concentrations of Hb tended to be associated with an increased risk of 5-year all-cause

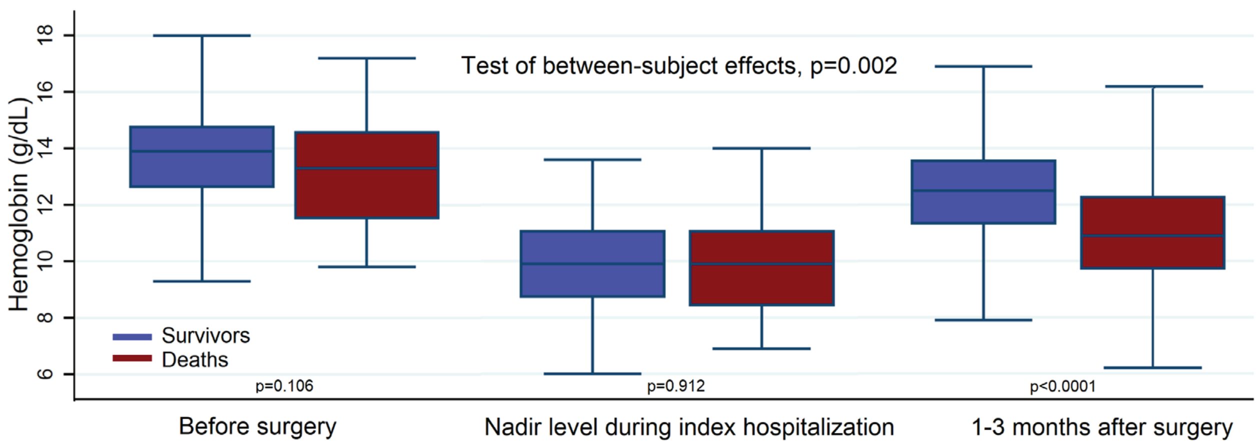

Figure 1 - Hemoglobin concentrations before isolated coronary surgery, its nadir concentration during the index hospitalization and 1-3 months after surgery. Test of between-subjects effects is for repeated measures evaluation.
p-values below the boxplots are according to the Mann-Whitney test at each study interval.

mortality (HR: 0.870; 95% CI: 0.749-1.011; Harrell's C: 0.550; Somers' D: 0.100). Nadir concentration of Hb during the index hospitalization was not associated with increased risk of late death (HR: 1.029; 95% CI: 0.872-1.215; Harrell's C: 0.515; Somers' D: 0.030).

Multivariable analysis showed that age (HR: 1.071; 95% CI: 1.032-1.112), extracardiac arteriopathy (HR: 2.048; 95% CI: 1.133-3.701), left ventricular ejection fraction ≤50% (HR: 2.742; 95% CI: 1.618-4.645), and estimated glomerular filtration rate according to the CKD-EPI equation (HR: 0.980; 95% CI: 0.968-0.993) were all independent predictors of 5-year all-cause mortality. When adjusted for these co-variates along with gender, Hb concentration 1-3 months after surgery was associated with an increased risk of 5-year all-cause mortality (HR: 0.750; 95% CI: 0.649-0.866) with a rather high predictive ability (Harrell's C: 0.785; Somers' D: 0.571). Pre-operative and perioperative concentrations of Hb were not predictive of late mortality. At 1-3 months of follow-up, 334 (57.4%) patients had anemia and their risk of 5-year mortality was significantly increased compared to those without anemia at this study interval (12.3 *vs* 4.0%; adjusted HR: 2.518; 95% CI: 1.260-5.030; Harrell's C: 0.779; Somers' D: 0.558) (**Figure 2**).

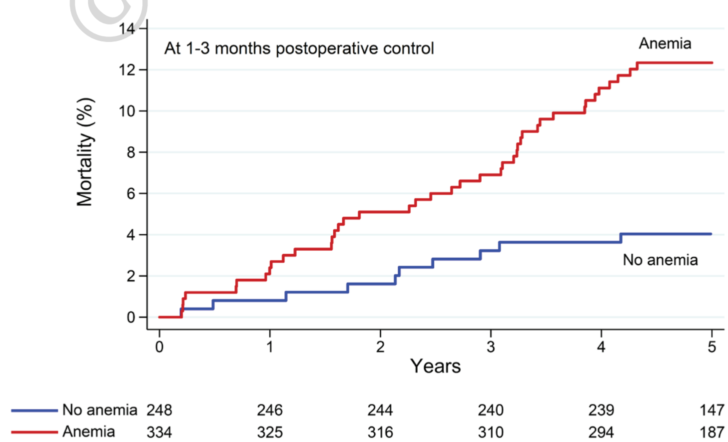

Figure 2 - Kaplan-Meier's estimates of 5-year all-cause mortality in patients with and without anemia 1-3 months after coronary surgery

When only data from two Scandinavian centers were analyzed (528 patients), at 1-3 months of follow-up, 290 (54.9%) patients had anemia and their risk of 5-year mortality was significantly increased compared to those without anemia at this study interval (12.1 *vs* 4.2%; adjusted HR: 2.516; 95% CI: 1.248-5.070; Harrell's C: 0.785; Somers' D: 0.571).

When cut-off of post-operative anemia was set at 13.0 g/dL, independently of gender, its incidence was 60.8% and it was associated with increased risk of 5-year mortality (adjusted HR: 2.049; 95% CI: 1.020-4.117; Harrell's C: 0.776; Somers' D: 0.553). Pre-operative anemia with a cut-off of 13.0 g/dL, independently of gender, was not associated with increased risk of late mortality (adjusted HR: 0.769; 95% CI: 0.435-1.358).

Linear regression identified risk factors associated with low Hb concentration at a 1-3 months check-up. These were: age ($p<0.0001$), female gender ($p=0.006$), pre-operative Hb concentration ($p<0.0001$), diabetes ($p<0.0001$), number of transfused red blood cells (RBC) during index hospitalization ($p<0.0001$), post-operative acute kidney injury ($p<0.0001$), and creatinine concentration at 1-3 months post surgery ($p<0.0001$). Antithrombotic drugs at discharge were not associated with low Hb concentration later at check-up.

DISCUSSION

The main results of the present multicenter study showed: 1) over half the patients had anemia 1-3 months after CABG; 2) post-operative low Hb concentration was predicted by pre-operative anemia, perioperative blood transfusion, acute kidney injury, and concurrent creatinine concentration, among other variables; 3) anemia detected several weeks after CABG was associated with a marked increase in risk of 5-year mortality.

The present findings suggest that the negative prognostic impact of anemia seems to be more evident a few weeks after cardiac surgery compared to the pre-operative period. Importantly, over half the patients had anemia at 1-3 months due to significant blood loss and its likely associated iron deficiency. However, in the post-operative setting, hemodilution secondary to heart failure, or even acute kidney injury, cannot be ruled out. Results of our analysis were also adjusted for pre-operative left ventricular ejection fraction, which was itself an independent predictor of 5-year mortality, but not of low post-operative Hb concentrations. On the contrary, both post-operative acute kidney injury and increased creatinine concentrations at 1-3 months after surgery were associated with low Hb concentrations. Indeed, acute kidney injury may lead to edema, and, in turn, anemia might be related to dilution in a larger distribution volume. Furthermore, renal failure may contribute to refractory anemia in the elderly[8]. However, since the nadir concentration of Hb during the index hospitalization was as low as 99.8 g/dL, Hb concentration at 1-3 months could, for the most part, reflect the perioperative loss of erythrocyte mass and failure to replace it during this timeframe.

The present findings suggest that pre-operative strategies to improve Hb concentration before cardiac surgery in anemic patients may be a valid measure to reduce the risk of post-operative anemia and the need for blood transfusion[9]. Indeed, analysis showed that both pre-operative Hb concentration and the number of transfused RBC were predictive of low Hb concentration at 1-3 months after surgery. Similar measures to increase Hb concentration later after surgery may potentially contribute to reducing the risk of mortality.

This study has some limitations which might have affected the validity of the present findings. 1) Data on baseline, operative, and early post-operative variables were collected prospectively, while data on late events were collected retrospectively, mostly from national electronic registries. 2) No data on the administration of iron and/or erythropoietin after surgery were available (these therapies were not part of the routine treatment of post-operative anemia in our hospitals). 3) There are no data on the cardiac causes of death of these patients.

The strength of this study lies in the availability of reliable late survival data from these two Scandinavian centers and the sample size. In fact, a post-hoc analysis (alpha 0.05; power 0.80) based on Hazard Ratio (3.667) of 5-year mortality for post-operative anemia showed that only 13 patients in each study group would have been sufficient to reject the null hypothesis.

CONCLUSIONS

The results of this study demonstrate that over half the patients undergoing isolated CABG are anemic 1-3 months post surgery. Persistence of anemia a few weeks after surgery is associated with a marked increase in the risk of late mortality. Further studies are needed to confirm this finding, to evaluate the causes underlying post-operative anemia, and to assess whether treatment of post-operative anemia may improve the late outcome of these patients.

AUTHORSHIP CONTRIBUTIONS

BF had full access to all the study data, and is responsible for its integrity and the accuracy of the data analysis. BF, TT, ZQ, GG, SF, DFM, ZM, MT, OF, MG, DM: concept and design; BF, TT, ZQ, GG, SF, DFM, ZM, MT, OF, MG, DM: acquisition, analysis, or interpretation of data; BF and RS: drafting of the manuscript and statistical analysis; BF, GG, SF, DFM, ZM, MT, OF, MG, DM, RS: study supervision. All Authors critically reviewed the manuscript for important intellectual content.

Keywords: *cardiac surgery, coronary artery bypass grafting, cardiac surgery, blood transfusion, anemia.*

The Authors declare no conflicts of interest.

REFERENCES

1. Padmanabhan H, Siau K, Curtis J, Ng A, Menon S, Luckraz H, et al. Preoperative anemia and outcomes in cardiovascular surgery: systematic review and meta-analysis. Ann Thorac Surg 2019; 108: 1840-1848. doi: 10.1016/j.athoracsur.2019.04.108.
2. D'Errigo P, Biancari F, Rosato S, Tamburino C, Ranucci M, Santoro G, et al. Transcatheter aortic valve implantation compared with surgical aortic valve replacement in patients with anaemia. Acta Cardiol 2018; 73: 50-59. doi: 10.1080/00015385.2017.1327627.
3. Elhenawy AM, Meyer SR, Bagshaw SM, MacArthur RG, Carroll LJ. Role of preoperative intravenous iron therapy to correct anemia before major surgery: a systematic review and meta-analysis. Syst Rev 2021; 10: 36. doi: 10.1186/s13643-021-01579-8.
4. Gupta S, Panchal P, Gilotra K, Wilfred AM, Hou W, Siegal D, et al. Intravenous iron therapy for patients with preoperative iron deficiency or anaemia undergoing cardiac surgery reduces blood transfusions: a systematic review and meta-analysis. Interact Cardiovasc Thorac Surg 2020; 31: 141-151. doi: 10.1093/icvts/ivaa094.
5. Kaufner L, von Heymann C, Henkelmann A, Pace NL, Weibel S, Kranke P, et al. Erythropoietin plus iron versus control treatment including placebo or iron for preoperative anaemic adults undergoing non-cardiac surgery. Cochrane Database Syst Rev 2020; 8: CD012451. doi: 10.1002/14651858.CD012451.pub2.
6. Spahn DR, Schoenrath F, Spahn GH, Seifert B, Stein P, Theusinger OM, et al. Effect of ultra-short-term treatment of patients with iron deficiency or anaemia undergoing cardiac surgery: a prospective randomised trial. Lancet 2019; 393: 2201-2212. doi: 10.1016/S0140-6736(18)32555-8.
7. Tibi P, McClure RS, Huang J, Baker RA, Fitzgerald D, Mazer CD, et al. STS/SCA/AmSECT/SABM Update to the clinical practice guidelines on patient blood management. J Cardiothorac Vasc Anesth 2021; 35: 2569-2591. doi: 10.1053/j.jvca.2021.03.011.
8. Lippi G, Franchini M, Salvagno GL, Montagnana M, Targher G, Guidi GC. Determinants of anaemia in the very elderly: a major contribution from impaired renal function? Blood Transfus 2010; 8: 44-8. doi: 10.2450/2009.0082-09.
9. Totonchi Z, Noohi F, Futuhi F, Azarfarin R, Radbin P. Effects of recombinant erythropoietin on hemoglobin levels and blood transfusion needs in patients with preoperative anemia undergoing cardiac surgery. Ann Card Anaesth 2022; 25: 466-471. doi: 10.4103/aca.aca_42_21.