Changes in haemoglobin levels during hospital course and long-term outcome after acute myocardial infarction

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Aims To study the prevalence and long-term prognostic significance of changes in haemoglobin levels during hospital course in survivors of acute myocardial infarction (AMI).

Methods and results A prospective study involving 1390 patients who were admitted with AMI. Median follow-up was 24 months. Multivariable Cox models were used to evaluate the relationship between nadir and discharge haemoglobin and mortality after hospital discharge. Anaemia was present in 248 patients on admission (17.8%) and in 502 patients at discharge (36.1%). Nadir haemoglobin during hospital course was 1.3 g/dL lower (IQR 0.6–2.2) when compared with baseline haemoglobin (P, 0.0001).

Low nadir haemoglobin and discharge haemoglobin were strongly associated with increased mortality. After adjusting for clinical variables and ejection fraction, the hazard ratios for a 1 g/dL decrease in nadir haemoglobin and discharge haemoglobin were 1.36 (95% CI 1.19–1.55; P, 0.0001) and 1.27 (95% CI 1.16–1.40; P, 0.0001), respectively.

Conclusion The development of anaemia during hospitalization for AMI is frequent and is associated with an increased long-term mortality.

KEYWORDS Anaemia; Heart failure; Myocardial infarction; Prognosis

Introduction

Recent studies have shown that anaemia on admission is an independent indicator of in-hospital or short-term mortality in patients with acute coronary syndromes.1,2 Anaemia is usually viewed as an acute risk factor because of the risks associated with bleeding complications3,4 and its potential to decrease oxygen supply to the ischaemic myocardium.5

Very little information exists regarding the long-term prognostic impact of anaemia after hospital discharge.2,6

Pharmacological interventions such as anti-thrombotic and thrombolytic therapy, as well as invasive procedures are potential sources for blood loss in patients admitted with acute myocardial infarction (AMI).1–4 Bleeding is currently the most common non-cardiac complication of therapy in patients with acute coronary syndromes. However, anaemia can develop or worsen during hospitalization even in the absence of overt bleeding.7,8 Therefore, many patients who survive the acute event are discharged with haemoglobin levels that are lower than admission values. The prognostic consequences of the changes in haemoglobin concentrations in patients with acute infarction have not been studied.

In patients with chronic heart failure (HF), the adverse cardiovascular effects of anaemia are well established.9,10 In addition to its effect on oxygen delivery, anaemia is associated with adaptive haemodynamic changes that may have deleterious effects on myocardial remodelling.11–13 In this context, the presence or the development of anaemia during AMI may impose haemodynamic load during a period of active left ventricular (LV) remodelling and contribute to the development of HF.

The aim of the present study was to prospectively determine the effect of changes in haemoglobin levels during hospital stay on long-term outcome among survivors of AMI. To this end, we evaluated the relationship between the presence and severity of anaemia at baseline, or anaemia occurring during hospital stay, and long-term mortality and HF after hospital discharge.

Methods

Patients

The study cohort consisted of patients enrolled in a prospective observational trial designed to study predictors of post-infarction HF. Patients presenting to the intensive coronary care unit were eligible for the study if they had a diagnosis of MI14 and were alive at the time of discharge. LV ejection fraction (LVEF) was determined in all patients prior to hospital discharge. To avoid possible...
confounding effects, patients were excluded if they had known malignancy, inflammatory disease, surgery, or trauma within the previous month. The study was conducted in accordance with the principles of the Declaration of Helsinki and approved by the institutional review committee on human research.

Assessment of renal function
Estimated glomerular filtration rate (eGFR) was calculated using the abbreviated MDRD (Modification of Diet in Renal Disease) study equation.15

Haemoglobin measurements
Haemoglobin concentration was determined on admission and at 24-, 48-, and 72-h thereafter. After the first 72-h from admission, haemoglobin concentrations were obtained at various time points according to the discretion of the treating physician. For the present analysis, the following haemoglobin values were used: (i) admission haemoglobin, (ii) nadir haemoglobin (the lowest haemoglobin value during hospital stay), and (iii) discharge haemoglobin (the last haemoglobin levels obtained during hospital stay). Bleeding complications were defined according to the Thrombolysis in Myocardial Infarction (TIMI) criteria16 and data on blood transfusions was collected.

Study endpoints
The primary endpoints of the study were: (i) all-cause mortality; (ii) development of HF, defined as readmission to hospital for the management of HF (defined by the presence of new symptoms of dyspnoea with pulmonary venous congestion on X-ray with interstitial or alveolar oedema and one or more concurrent signs, including ventricular gallop rhythm, bilateral post-tussive rales in at least the lower third of the lung fields, and elevated venous pressure). The diagnosis of HF was confirmed using hospital records and discharge summaries. Following hospital discharge, clinical endpoint information was acquired by reviewing the national death registry and by contacting each patient individually and independently reviewing the hospital course for major clinical events if the patient had been re-hospitalized. In addition, data was collected on recurrent infarction events.

Statistical analysis
The baseline characteristics of the groups were compared using analysis of variance for continuous variables with post-test for linear trend and using the linear-by-linear χ² test for categorical variables. Changes in haemoglobin at different time points were carried out with the Friedman test, followed by pair-wise comparisons using the Wilcoxon signed-rank test with Bonferroni correction.

Multivariable logistic regression model was used to determine independent predictors of haemoglobin drop during hospitalization. Variables known to be potential contributors to anaemia in patients with acute coronary syndromes4,4,7 were considered in the multivariable process (age, gender, eGFR, diabetes, smoking habit, Killip class at admission, use of antiplatelet agents, heparin, GP IIb/IIIa receptor blockers and thrombolytic therapy, percutaneous coronary revascularization). The linearity of the logit among the continuous variables used in the multivariable analysis was confirmed with the Box–Tidwell test.

Survival curves for various groups were constructed using the Kaplan–Meier method, and comparisons were made using the log-rank test. Cox proportional hazard modelling was performed to test the association between haemoglobin levels at various time points and mortality. Admission haemoglobin, nadir haemoglobin, haemoglobin drop during hospital course, and discharge haemoglobin were entered into the model as either continuous variables or categorical variables (quartiles of the distribution).

Variables thought to have clinical importance, and those with \(P < 0.1\) in the univariable analysis, were included in a Cox multivariable model. The following baseline clinical characteristics were considered in the model: age, gender, prior infarction, prior HF, history of diabetes, history of hypertension, smoking status, Killip class on admission, anterior location of infarction, ST-elevation infarction, thrombolytic therapy, primary angioplasty, coronary revascularization during index hospitalization, and LVEF stratified as above or below 45%. In addition, because changes in haemoglobin values during hospitalization may be related to the length of hospital stay we also adjusted for this variable.

The proportional hazards assumption was confirmed by testing whether the hazard ratio changed with time. This was done by testing the interaction of the variable with time using this multiplicative term as a time-dependent covariate. There was no evidence to suggest that the assumption was invalid. When continuous variables were tested for linearity, nadir haemoglobin had to be transformed to its natural logarithm before inclusion in the Cox regression analysis.

Because anaemia is related to HF and reduced kidney function, which are frequent in patients with AMI, additional analyses were performed after stratifying the study population based on the presence of preserved (LVEF \(\geq 45\%\)) or reduced systolic function and presence of normal or mildly impaired eGFR (\(\geq 60\) mL/min), or moderately/severely impaired eGFR (\(\leq 59\) mL/min).

Cox proportional hazards modelling was also used to determine the relationship between quartiles of haemoglobin at various time points and admission for the treatment of HF. Known predictors of the development of HF in patients following MI17 (age, LVEF, baseline heart rate, Killip class at admission, history of hypertension and diabetes, previous infarction) and other potential predictors were considered (gender, previous HF, anterior infarction, ST-elevation infarction, and use of reperfusion therapy) if they demonstrated association with HF on univariable analysis (\(P < 0.1\)). Statistical analyses were performed using the SPSS statistical software version 12.0 (Chicago, IL, USA).

Results
Between July 2001 and June 2005, 1606 patients who were willing to participate were identified. We excluded 216 patients due to malignancy (n = 40), inflammatory disease (n = 10), surgery or trauma within the previous month (n = 29), missing repeated haemoglobin measurements (n = 22), and in-hospital death (n = 115). The study population consisted of the 1390 remaining patients.

The clinical characteristics of patients according to quartiles of baseline haemoglobin are shown in Table 1. Patients with lower haemoglobin values were older, more likely to be females, and had higher baseline creatinine levels. They were more likely to have a history of diabetes and hypertension and less likely to have a history of smoking and present with ST-elevation infarction; they presented with higher heart rates and higher Killip class and had lower LVEF. They were more likely to undergo revascularization during the index hospitalization and to receive thrombolytic therapy and glycoprotein IIb/IIIa receptor blockers.

Using the World Health Organization definitions (haemoglobin <13 g/dL in men and <12 g/dL in women), anaemia was present in 248 patients on admission (17.8%). During hospital course, major and minor bleeding occurred in 3.7% and 9.7% of patients, respectively. Changes in haemoglobin levels during hospital stay are depicted in Figure 1. Median nadir haemoglobin concentration was 1.3 g/dL lower (IQR 0.6–2.2) when compared with baseline haemoglobin (\(P < 0.0001\)), and the number of patients
with anaemia increased to 667 (48.0%). At discharge, haemoglobin values were significantly higher when compared with nadir values (median 0.5 g/dL; IQR 0.0–1.1, \( P < 0.0001 \)), and the number of patients with anaemia decreased to 502 (36.1%).

Multivariable logistic regression model identified several predictors of a reduction in haemoglobin concentration above median (1.3 g/dL), including moderately or severely reduced (<60 mL/min) eGFR (OR 1.4; 95% CI 1.1–2.0; \( P = 0.02 \)), thrombolytic therapy (OR 1.6; 95% CI 1.2–2.1; \( P = 0.001 \)), percutaneous coronary revascularization (OR 1.9; 95% CI 1.5–2.5; \( P < 0.0001 \)), diabetes (OR 1.3; 95% CI 1.1–1.7; \( P = 0.03 \)), and Killip class above I on admission (OR 1.9; 95% CI 1.4–2.5; \( P < 0.0001 \)).

Anaemia and mortality

The median duration of follow-up after hospital discharge was 24 months (range 6–48 months). During the follow-up period, 157 patients died. Table 2 shows the results of unadjusted and adjusted Cox regression models for mortality according to baseline haemoglobin, haemoglobin drop during hospital stay, nadir haemoglobin, and discharge haemoglobin. There was a graded inverse unadjusted relationship between baseline haemoglobin and post-discharge mortality. However, the effect of baseline haemoglobin on mortality observed in crude analyses was markedly attenuated by adjustments for other clinical variables and LV EF.

In contrast, in a multivariable Cox proportional hazards model adjusting for other potential clinical predictors of mortality and for LV EF, there was a significant independent direct association between haemoglobin drop during hospital stay and post-discharge mortality (Table 2). In addition, there was a strong inverse association between nadir haemoglobin and post-discharge mortality (Table 2, Figure 2). Using pre-discharge haemoglobin in the same model gave similar results (Table 2).
Additional analyses were performed after dividing the study population into eight groups based on nadir haemoglobin quartile and presence of preserved (LVEF ≥45%) or reduced systolic function. Figure 3A shows that the graded increase in risk associated with decreasing quartiles of nadir haemoglobin was present in both patients with reduced and preserved LVEF. Similar results were observed in patients with normal or mildly impaired eGFR as a continuous variable, the HR for HF was 1.17 (95% CI 1.04–1.31; P = 0.008). The incidence of recurrent infarction was not significantly different across quartiles of nadir haemoglobin (11.1%, 6.4%, 9.6%, and 9.1%, respectively; P for trend = 0.67).

Anaemia and heart failure

During median follow-up of 2 years, 150 patients were admitted for the treatment of HF. At 2 years, Kaplan-Meier survival free of HF was 79.3% (95% CI 74.3–84.3), 87.8% (95% CI 84.1–91.4), 92.6% (95% CI 89.9–95.4), and 94.3% (95% CI 91.7–97.0) in the first, second, third and fourth haemoglobin quartile, respectively (Figure 4). After adjustments clinical variables and LVEF, compared with patients in the upper nadir haemoglobin quartile, the adjusted HRs for HF progressively increased with lower quartiles of nadir haemoglobin [third quartile 0.9 (95% CI 0.5–1.7); second quartile 1.6 (95% CI 0.9–2.8); first quartile 1.8 (95% CI 1.1–3.1); P for trend = 0.004]. Using nadir haemoglobin as a continuous variable, the HR for HF was 1.17 per 1 g/dL decrease in nadir haemoglobin (95% CI 1.04–1.31; P = 0.008). The incidence of recurrent infarction was not significantly different across quartiles of nadir haemoglobin (11.1%, 6.4%, 9.6%, and 9.1%, respectively; P for trend = 0.67).

Effect of blood transfusion

Eighty-five patients (6.1%) received blood transfusions during hospital course. All patients receiving transfusions were in the lower nadir haemoglobin quartile, and 67 patients (79%) remained in the lower discharge haemoglobin quartile after receiving blood transfusions. Therefore, patients in the lower nadir haemoglobin quartile were reclassified into two groups according to transfusion status. Compared with patients in the upper nadir

Table 2 Unadjusted and adjusted Cox's proportional hazards model for mortality according to baseline, nadir and discharge haemoglobin analysed as categorical and continuous variable

<table>
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<th>Events (%)</th>
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<th>P trend</th>
<th>Adjusted HR (95% CI)</th>
<th>P-value</th>
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<td>First (≤13.1)</td>
<td>361</td>
<td>76 (21.1)</td>
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<td>26 (7.3)</td>
<td>1.0 (0.6–1.7)</td>
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<td>24 (7.3)</td>
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<td>1.3 (0.8–2.2)</td>
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<td>58 (17.0)</td>
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<td>1.7 (1.1–2.8)</td>
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<td>1.76 (1.57–1.97)</td>
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<td>1.36 (1.19–1.55)</td>
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<td>8.5 (4.7–15.6)</td>
<td>&lt;0.0001</td>
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<td>3.3 (1.7–6.3)</td>
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<td>Continuous (per 1 g/dL decrease)</td>
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<td>1.48 (1.37–1.60)</td>
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<td>1.27 (1.16–1.40)</td>
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<td>First (≤11.9)</td>
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<td>&lt;0.0001</td>
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<td>15 (4.4)</td>
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*All models were adjusted for age, gender, eGFR, previous infarction, hypertension, diabetes, smoking, ST-elevation infarction, Killip class, heart rate, and blood pressure on admission, coronary revascularization, LVEF, and length of hospital stay.

*The distribution of nadir haemoglobin was skewed. Therefore, a natural log transformation was applied to normalize distribution of the data. HR represents a 1-SD increment in ln haemoglobin drop.
haemoglobin quartile, the adjusted HR for death was 3.0 (95% CI 1.7–5.5, \( P = 0.0003 \)) for patients in the lower nadir haemoglobin quartile who were transfused and 2.2 (95% CI 1.3–3.7, \( P = 0.002 \)) for patients in the lower nadir haemoglobin quartile who were not transfused.

Discussion

In a prospective study of patients who survived an episode of AMI we found a graded inverse independent association between anaemia during hospital course and at discharge and adverse long-term outcome. The lowest haemoglobin concentrations during hospital stay were most strongly associated with poor outcome, and remained independent predictor of long-term mortality after adjustment for multiple clinical variables and for LVEF.

There was a striking increase in the prevalence of anaemia during hospital course. In addition to blood loss, several other mechanisms may contribute to the development of anaemia or impair the ability to recover from an acute blood loss in patients with AMI. Patients who developed anaemia had more evidence of congestion (Killip class II–IV), suggesting that haemodilution might contribute to anaemia. A robust inflammatory response is an integral component of the response to tissue injury in patients with AMI, and persists for several weeks.\(^\text{18}\) The infarction-related inflammatory state with excess cytokine production may suppress erythropoiesis\(^\text{19,20}\) and impair intestinal iron absorption.\(^\text{21}\) Use of angiotensin converting-enzyme inhibitors may contribute to anaemia by inhibiting erythropoiesis.\(^\text{22}\) Finally, low baseline haemoglobin was associated with reduced eGFR, and baseline eGFR corresponding to stage III to IV chronic kidney disease was a strong predictor of a reduction in haemoglobin level.

![Figure 2](https://academic.oup.com/eurheartj/article-abstract/28/11/1289/2887388)

**Figure 2** Kaplan–Meier plot showing the crude cumulative incidence of death according to quartiles of nadir haemoglobin.

![Figure 3](https://academic.oup.com/eurheartj/article-abstract/28/11/1289/2887388)

**Figure 3** Adjusted hazard ratios (and 95% confidence intervals) for mortality after hospital discharge according to quartiles on nadir haemoglobin and (A) LVEF; (B) eGFR. The percentage of events in each group is given on each bar.
It is widely recognized that blood loss in patients admitted for acute coronary syndromes can be substantial. However, reduction in haemoglobin is generally viewed in the context of the acute risk associated with bleeding. The results of the present analysis demonstrate that the prognostic implications of worsening anaemia and low haemoglobin levels that frequently occur during the course of hospital stay extend beyond the early phase of infarction and are important in predicting two major outcomes in patients who survive the acute event. The graded association between nadir and pre-discharge haemoglobin and mortality and HF suggests that low haemoglobin concentrations may be causally related to adverse outcome.

Several mechanisms may explain the association between anaemia and post-discharge mortality and HF. The adaptive responses to anaemia may lead to LV dilatation and eccentric remodelling, which may have deleterious effects on the myocardium, including higher oxygen consumption, increased diastolic wall stress, interstitial fibrosis, and accelerated myocyte loss. The ability of anaemia to promote LV dilatation may be particularly deleterious in the post-infarction period.

In addition, patients who develop anaemia during the acute phase of infarction are expected to exhibit greater neurohormonal activation, which may persist if anaemia is not corrected. One of the most important mechanisms that lead to late development of HF and death in survivors of MI is progressive LV remodelling, which is closely linked to the degree of neurohormonal activation. Importantly, patients with preserved LVEF also incurred a graded increased risk of death with decreasing quartiles of nadir haemoglobin. This finding is consistent with recent findings in patients with HF.

Previous studies have shown that anaemia at baseline is associated with adverse in-hospital or 30-day outcomes. However, the relationship between baseline haemoglobin and long-term outcome is controversial. Nikolsky et al. reported that anaemia at baseline was an independent predictor of 1-year mortality in patients with AMI who underwent primary angioplasty. Cavusoglu et al. have shown that anaemia at baseline was an independent predictor of the composite endpoint of death or AMI at 24 months. In contrast, in 30,341 patients hospitalized for AMI, the presence of anaemia at baseline failed to be an independent predictor of 1-year mortality. The lack of an association between baseline anaemia and long-term outcome in the later study and in the present study probably reflects the striking changes that occur in haemoglobin levels during hospital course. Indeed, the number of patients with anaemia increased from 17.8% on admission to 36.1% at discharge, and nearly half of the patients had anaemia at some point during their hospital stay.

Anaemia has been traditionally investigated in the context of HF. Anaemia is a known comorbid condition in HF and is associated with poor clinical outcomes, including lower maximal exercise tolerance, recurrent hospitalizations, and increased mortality. The association between anaemia in the acute phase of infarction and future admissions for the treatment of HF suggests that anaemia can promote the development of HF after acute cardiac injury.

Previous studies provided conflicting results with regard to the effect of blood transfusion on 30-day mortality in patients with acute coronary syndromes. In the absence of randomized controlled clinical trials, the risks and benefits of blood transfusion in patients with acute coronary syndromes remain uncertain.
coronary syndromes are not known. In the present study, anaemia during hospital course and at discharge was associated with a striking increase in mortality after hospital discharge. In addition, 79% of the patients receiving transfusions remained in the bottom discharge haemoglobin quartile, and therefore at risk for long-term mortality. These results emphasize the need to examine the effect of blood transfusion in the context of long-term outcomes and the haemoglobin levels achieved after transfusion.

Study limitations
Several study limitations should be considered in the interpretation of the results. In contrast to previous studies, baseline haemoglobin was not associated with mortality in our study. The focus of our study was to examine the relationship between changes in haemoglobin concentration after hospital discharge. Thus, the prognostic implications of transient vs. persistent anaemia could not be fully analyzed.

Conclusion
Our data suggest that anaemia during the course of hospital stay and at discharge is a predictor of long-term mortality and HF in survivors of AMI and provides prognostic information beyond that provided by risk factors and the degree of LV systolic dysfunction. Nadir haemoglobin concentrations appear to be the best predictor of long-term outcome.

Conflict of interest: none declared.

References


