Prognostic Impact of Hemoglobin Drop During Hospital stay in Patients with Acute Coronary Syndromes [35]

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ABSTRACT

Introduction: Bleeding is currently the most common non-cardiac complication of therapy in patients with acute coronary syndromes (ACS), and may itself be associated with adverse outcomes. The aim of this study was to determine the effect of hemoglobin drop during hospital stay on outcome among patients with ACS.

Methods: Using Cox proportional-hazards modeling, we examined the association between hemoglobin drop and death or myocardial infarction (MI) at 6 months in 1172 patients admitted with ACS to an intensive cardiac care unit. Patients were stratified according to quartiles of hemoglobin drop: Q1, ≤0.8 g/dL; Q2, 0.9-1.5 g/dL; Q3, 1.6-2.3 g/dL; Q4, ≥2.4 g/dL. We also identified independent predictors of increased hemoglobin drop (≥2.4 g/dL) using multivariate logistic regression analysis.

Results: Median nadir hemoglobin concentration was 1.5 g/dL lower (IQR 0.8-2.3) compared with baseline hemoglobin (p<0.0001). Independent predictors of increased hemoglobin drop included older age, renal dysfunction, lower weight, and use of thrombolytic therapy, glycoprotein IIb/IIIa inhibitors, nitrates, and percutaneous coronary intervention. Higher levels of hemoglobin drop were associated with increased rates of 6-month mortality (8.0% vs. 9.4% vs. 9.6% vs. 15.7%; p for trend=0.014) and 6-month death/MI (12.4% vs. 17.0% vs. 17.2% vs. 22.1%; p for trend=0.021). Using Q1 as reference group, the adjusted hazard ratio (HR) for 6-month

RESUMO

Impacto prognóstico da redução intra-hospitalar da concentração de hemoglobina em doentes com síndrome coronária aguda

Introdução: As hemorragias são actualmente a complicação terapêutica não-cardíaca mais comum em doentes com síndrome coronária aguda (SCA) e podem estar associadas a eventos adversos. O objectivo deste estudo foi determinar o efeito da queda da concentração de hemoglobina durante o internamento hospitalar no prognóstico de doentes com SCA.

Métodos: Foi utilizado o modelo de riscos proporcionais de Cox para estudar a associação entre a queda de hemoglobina e a ocorrência de morte ou enfarte do miocárdio aos 6 meses em 1172 doentes admitidos na nossa Unidade de Cuidados Intensivos Cardíacos com SCA. Os doentes foram estratificados de acordo com o quartil de queda de hemoglobina (quartil 1: ≤0,8 g/dL; quartil 2: 0,9-1,5 g/dL; quartil 3: 1,6-2,3 g/dL; quartil 4: ≥2,4 g/dL). Foram ainda identificados os preditores de uma queda elevada da concentração de hemoglobina (≥2,4 g/dL) utilizando um modelo de regressão logística multivariada.

Resultados: A hemoglobina mínima mediana foi 1,5 g/dL inferior (IQR 0,8-2,3 g/dL) relativamente à hemoglobina da admissão (p<0.0001). Os preditores independentes de uma queda elevada da concentração de hemoglobina incluíram idade avançada, disfunção renal, baixo peso, administração

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mortality and 6-month death/MI among patients in the highest quartile of hemoglobin drop was 1.83 (95% confidence interval [CI] 1.08-3.11; p=0.026) and 1.60 (95% CI 1.04-2.44; p=0.031) respectively. Considered as a continuous variable, the adjusted HR for 6-month mortality was 1.16 (95% CI 1.01-1.32; p=0.030) per 1 g/dL increase in hemoglobin drop.

Conclusions: A decrease in hemoglobin frequently occurs during hospitalization for ACS and is independently associated with adverse outcomes.

Key words

Acute coronary syndrome; Myocardial infarction; Bleeding; Hemoglobin; Anemia; Prognosis; Blood transfusion.

de terapêutica fibrinolítica, inibidores da glicoproteína IIb/IIIa, nitratos, e a realização de intervenção coronária percutânea.

Os doentes com níveis mais elevados de queda de hemoglobina apresentaram maior mortalidade aos 6 meses (8,0% *versus* 9,4% *versus* 9,6% *versus* 15,7%; *p*=0,014) e maior incidência de morte ou enfarte do miocárdio aos 6 meses (12,4% *versus* 17,0% *versus* 17,2% *versus* 22,1%; *p*=0,021). Utilizando o quartil 1 como referência, o *hazard ratio* (HR) ajustado para mortalidade aos 6 meses e ocorrência de morte/enfarte do miocárdio aos 6 meses para os doentes no quartil mais elevado de queda de hemoglobina foi 1,83 (intervalo de confiança [IC] 95% 1,08-3,11; *p*=0,026) e 1,60 (IC 95% 1,04-2,44; *p*=0,031), respectivamente. Introduzida no modelo como variável contínua, o HR ajustado de morte aos 6 meses para cada aumento de 1 g/dL na queda de hemoglobina foi 1,16 (IC 95% 1,01-1,32; *p*=0,030).

Conclusões: Durante o internamento por SCA é frequente uma queda na concentração de hemoglobina, a qual está associada de forma independente a um risco mais elevado de eventos adversos aos 6 meses.

Palavras-Chave

Síndrome coronária aguda; Enfarte do miocárdio; Hemorragia; Hemoglobina; Anemia; Prognóstico; Transfusão

INTRODUCTION

Contemporary treatment of acute coronary syndromes (ACS) includes the combined use of anticoagulants and antiplatelet agents, coupled with early use of cardiac catheterization and revascularization in high-risk patients[1,2]. Although this approach has improved the rate of recurrent ischemic coronary events, it has also increased the potential for bleeding complications. Bleeding has itself been associated with a higher risk of ischemic events and death in observational analyses[3-5], although it has been suggested that bleeding may often be merely a marker for patients at higher risk for adverse outcomes[6]. There are also data suggesting that blood transfusion may contribute to the increased cardiovascular risk associated with bleeding[7-9]. The Fifth Organization to Assess Strategies in Ischemic Syndromes (OASIS-5) trial showed that the reduction in bleeding at 9 days with fondaparinux was associated with lower long-term mortality and morbidity in patients with non-ST-segment elevation ACS[10].

Several definitions of bleeding have been used in clinical trials and registries, leading to disparities in the reported incidence of bleeding events within the same population[11]. Bleeding assessed with clinical criteria (such as the Global Use of Strategies to Open Occluded Coronary Arteries [GUSTO] bleeding scale)[12] appears to be more important than that assessed by laboratory criteria (such as the Thrombolysis In Myocardial Infarction [TIMI] classification)[13]

in terms of predicting clinical outcomes in patients with ACS[14]. Nevertheless, limited data exist regarding the effect of hemoglobin concentration changes on outcome among patients with ACS[15]. The aim of the present study was to determine the predictors and prognostic impact of hemoglobin drop during hospitalization among patients with ACS in a real-world setting.

METHODS

Patients

For this analysis, we included 1172 patients admitted to our six-bed intensive cardiac care unit (ICCU) with ACS between January 2004 and March 2007. Patients considered in the present study had a history of chest pain at rest or other symptoms suggestive of an ACS, with the most recent episode occurring within 24 hours of admission. This could be associated with either transient or persistent ST-segment elevation, ST-segment depression, or T-wave inversion on the electrocardiogram, or elevated levels of biomarkers of myocardial damage. The biomarkers used were cardiac troponin I (cTnI) and creatine kinase MB mass assay (CK-MB), with a threshold for positivity of 0.06 and 3.5 ng/mL respectively. Patients included had at least two determinations of hemoglobin concentration (the first on admission) separated by 24 hours. Patients with unstable angina and a normal ECG on admission (n=17) were also included. Left ventricular ejection fraction (LVEF) was assessed by echocardiography within 2 to 6 days of admission. Glomerular filtration rate (GFR) was estimated using the four-component Modification of Diet in Renal Disease (MDRD) equation[16]: Estimated GFR (ml per minute per 1.73 m^2 of body surface area) = 186 x (serum creatinine [mg/dL])$^{-1.154}$ x (age [in years])$^{-0.203}$. For women, the value was multiplied by 0.742. Although this was a retrospective study, clinical data regarding demographic and presentation characteristics, medical history, and in-hospital medication and procedures were collected prospectively and recorded on a computer database of ACS patients admitted to our institution's ICCU.

Hemoglobin measurements

Hemoglobin concentration was determined on admission and every 24 h thereafter while the patient remained in the ICCU. Hemoglobin concentration was also determined before and 8 h after percutaneous coronary intervention as routine procedure in our center. After discharge from the ICCU, hemoglobin concentrations were obtained according to the discretion of the treating physician. In the present study, we analyzed admission hemoglobin and nadir hemoglobin (the lowest hemoglobin value during hospital stay). Discharge hemoglobin (the last hemoglobin level obtained during hospital stay) was also analyzed among survivors of hospitalization. Hemoglobin drop during hospital course was defined as the difference between admission hemoglobin and nadir hemoglobin (g/dL). Patients in whom the initial value was the lowest were assigned a "drop" of 0 (n=110). Data on blood transfusions were collected. Bleeding complications were defined according to TIMI criteria[13]. Major bleeding was defined as intracranial hemorrhage or a ≥5 g/dL decrease in hemoglobin concentration; minor bleeding was defined as a ≥3 g/dL decrease in hemoglobin concentration if blood loss was observed, and as a ≥4 g/dL decrease in hemoglobin concentration if not. Data on bleeding and hemoglobin decline occurring after coronary artery bypass graft (CABG) surgery were not included in our analyses (this intervention was performed in referral centers).

Follow-up and outcomes

The primary end point was six-month all-cause mortality. Secondary end points were occurrence of the composite of death or myocardial infarction (MI). Patients were monitored for at least six months or until the primary endpoint was reached. Follow-up was by telephone, and by review of the databases and medical records of the hospital. Mortality follow-up was complete for 1145 patients (98% of the study sample) at six months.

Statistical analysis

Patients were grouped according to quartiles of hemoglobin drop during hospital stay. The baseline characteristics of the groups were compared using chi-square tests for categorical variables and analysis of variance for continuous variables. A test for trend across ordered groups was performed for the four groups of hemoglobin drop.

Multivariate logistic regression analysis was performed to determine independent predictors of increased hemoglobin drop during hospital course. Variables included in the analysis were age, gender and weight; history of diabetes mellitus, MI, hypertension, or coronary artery revascularization; smoking status, GFR, baseline hemoglobin, and Killip class at admission; use of heparin, glycoprotein IIb/IIIa inhibitors, thrombolytic therapy, intravenous inotropic agents, nitrates, coronary angiography, percutaneous coronary revascularization, and intra-aortic balloon pump insertion.

Cox proportional-hazards modeling was performed to test the association between hemoglobin drop and adverse events at six-months. Multivariable-adjusted Cox models were constructed by forcing hemoglobin drop or nadir hemoglobin as either continuous or categorical variables (quartiles of the distribution) into the models and including all other covariates associated with six-month adverse events. The threshold for retaining a variable in the final multivariable model was set at $p<0.1$. The covariates considered in the model were age, gender, history of diabetes, history of hypertension, history of dyslipidemia, smoking status, prior MI, treatment with cardiac medications (aspirin, beta-blockers, angiotensin-converting enzyme [ACE] inhibitors, statins) before hospitalization, history of coronary artery revascularization, baseline GFR (per 10 ml/min/1.73 m^2 decrement), Killip class on admission, admission heart rate, systolic and diastolic blood pressure at presentation, ST-elevation infarction, baseline hemoglobin concentration, thrombolytic therapy, percutaneous or surgical coronary artery revascularization during hospitalization, LVEF stratified as above or below 50%, length of hospital stay, and blood transfusion. Additional models were developed excluding patients who underwent CABG surgery (n=141), and excluding patients who died during the index hospitalization (n=47). For each model, the proportional hazards assumption was tested and found to be appropriate.

Kaplan-Meier analysis was used to illustrate 6-month event-free survival for patients who had different degrees of hemoglobin drop. The log-rank test was used to test the equality of the survivor function across groups, and the test for trend of the survivor function was performed across the ordered groups. All p values were two-sided, and a p value of less than 0.05 was considered to indicate statistical significance. Statistical analyses were performed using SPSS version 13.0 (SPSS Inc., Chicago, Illinois, USA).

RESULTS

Baseline characteristics

Between January 2004 and March 2007, 1228 patients were admitted to the ICCU of our institution with the diagnosis of ACS. We excluded 56 patients due to missing repeated hemoglobin measurements (21 of these patients died within 24 hours after admission, 8 patients were transferred in the first 24 hours to referral centers for emergency cardiac surgery for mechanical complications [n=4] or rescue percutaneous coronary intervention [n=4], and 27 patients had a single hemoglobin determination on admission). The final study population consisted of the remaining 1172 patients (592 had ST-segment elevation MI, 542 had non-ST-segment elevation MI, and 38 had unstable angina).

Forty-seven patients died during hospitalization, and 74 patients died in the follow-up after hospital discharge and before 6 months. According to the World Health Organization criteria (hemoglobin <13 g/dL in men and <12 g/dL in women), anemia was present in 244 patients on admission (20.8%) and in 458 survivors at discharge (40.7%). During hospitalization, major and minor bleeding (TIMI criteria) occurred in 25 (2.1%) and 87 (7.4%) patients respectively.

Median nadir hemoglobin concentration was 1.5 g/dL lower (IQR 0.8-2.3) than baseline hemoglobin ($p<0.0001$). Hemoglobin drop during hospital course ranged from 0 to 8.3 g/dL. The clinical characteristics of patients according to quartiles of hemoglobin drop are shown in *Table I*. Patients with higher decline of hemoglobin concentration were less likely to be females, presented more frequently with ST-segment elevation, more often had renal dysfunction (GFR <60 ml/min/1.73 m^2), and had higher blood pressure and heart rate on admission. Although patients with higher hemoglobin drop during hospital course had

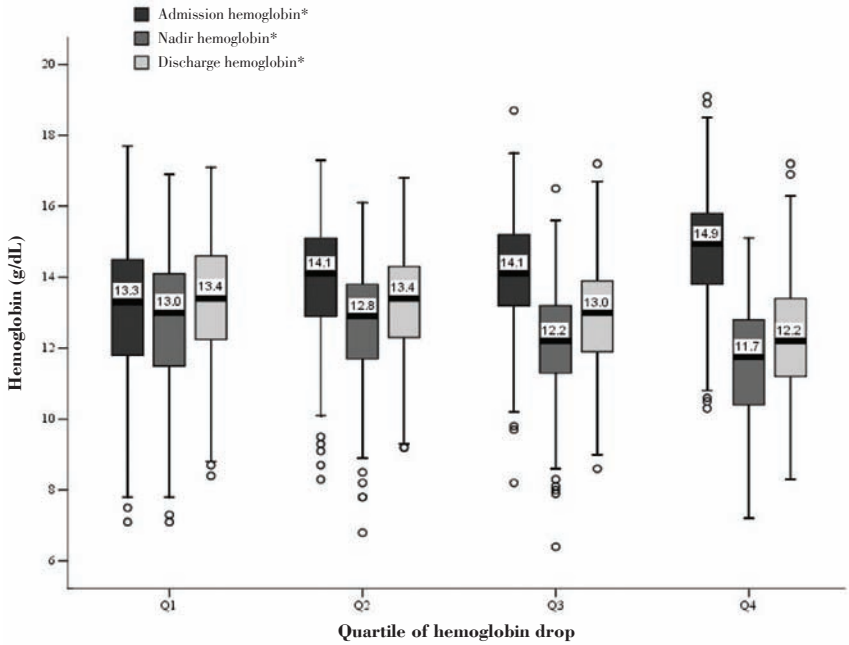

Figure 1. **Box-and-whisker plots of changes in hemoglobin concentration during hospital course according to quartile of hemoglobin drop. Data labels in each box refer to median values of hemoglobin concentration (g/dL).**
*p<0.0001 for trend across ordered groups.

Table I. **Baseline clinical characteristics according to quartiles of hemoglobin drop**

Characteristic	Quartile of hemoglobin drop during hospital course (range, g/dL)				
	First (n=318) (≤0.8)	Second (n=289) (0.9-1.5)	Third (n=276) (1.6-2.3)	Fourth (n=289) (≥2.4)	p for trend
Demographic					
Age (years)	64±13	64±13	66±14	65±13	0.43
Female gender	109 (34.3)	78 (27.0)	79 (28.6)	63 (21.8)	0.008
Weight (kg)	75.0±13.0	74.2±13.3	74.8±11.6	73.9±12.3	0.72
Medical history					
Diabetes mellitus	85 (26.7)	81 (28.0)	80 (29.0)	80 (27.7)	0.94
Hypertension	195 (61.3)	182 (63.0)	191 (69.2)	176 (60.9)	0.15
Dyslipidemia	145 (45.6)	142 (49.1)	132 (47.8)	133 (46.0)	0.81
Current smoking	69 (21.7)	73 (25.3)	61 (22.1)	80 (27.7)	0.28
Prior MI	56 (17.6)	56 (19.4)	52 (18.8)	41 (14.2)	0.36
Prior PCI	10 (3.1)	15 (5.2)	12 (4.3)	13 (4.5)	0.65
Prior CABG	14 (4.4)	13 (4.5)	7 (2.5)	6 (2.1)	0.24
Medications at presentation					
Aspirin	74 (23.3)	83 (28.7)	67 (24.3)	59 (20.4)	0.13
Beta-blocker	61 (19.2)	69 (23.9)	55 (19.9)	45 (15.6)	0.10
ACE inhibitor	69 (21.7)	80 (27.7)	79 (28.6)	65 (22.5)	0.12
Statin	83 (26.1)	91 (31.5)	76 (27.5)	62 (21.5)	0.06
Presentation characteristics					
ST elevation	127 (39.9)	138 (47.8)	143 (51.8)	184 (63.7)	<0.0001
Killip class >I	60 (18.9)	63 (21.8)	69 (25.0)	74 (25.6)	0.17
SBP (mmHg)	134±25	136±26	141±27	143±29	<0.0001
DBP (mmHg)	75±15	76±15	79±16	82±18	<0.0001
Heart rate (bpm)	74±17	75±19	78±19	80±21	0.002
Renal dysfunction*	64 (20.1)	46 (16.0)	61 (22.1)	76 (26.3)	0.022
Hemoglobin (g/dL)	13.1±1.8	13.8±1.6	14.0±1.6	14.7±1.7	<0.0001
WBC count (10^3/ul)	9.7±3.0	10.7±3.6	11.1±3.8	12.2±4.5	<0.0001
Platelet count (10^3/ul)	209±61	216±66	229±71	229±79	<0.0001
Blood glucose (mg/dL)	143±76	155±72	165±76	178±94	<0.0001

ACE: angiotensin-converting enzyme; CABG: coronary artery bypass grafting; DBP: diastolic blood pressure; MI: myocardial infarction; PCI: percutaneous coronary intervention; SBP: systolic blood pressure; WBC: white blood cell.
*Glomerular filtration rate <60 ml/min/1.73 m^2.
Data are presented as number (%) of patients (categorical variables) or mean value ±SD (continuous variables). Glomerular filtration rate, hemoglobin, WBC and platelet counts, and blood glucose were determined on admission.

higher hemoglobin concentrations on admission, their levels of nadir and discharge hemoglobin were lower than in patients in the lowest quartile of hemoglobin drop (p<0.0001) (*Figure 1*). In addition, patients with higher hemoglobin drop had higher white blood cell and platelet counts, and higher blood glucose levels on admission (all p<0.0001) (*Table I*).

The use of thrombolytic agents, unfractionated heparin, and percutaneous coronary revascularization procedures was more frequent among patients with higher levels of hemoglobin drop during hospital stay, with a trend towards increased use of glycoprotein IIb/IIIa receptor blockers in these patients. Moreover, patients with higher hemoglobin decline were also more frequently treated with ACE inhibitors, nitrates and intravenous vasopressor therapy, and more often received blood transfusions. Patients with increased hemoglobin drop more often had left ventricular systolic dysfunction (LVEF <50%) on echocardiography, and were more likely to develop heart failure during hospital stay (*Table II*). Mean duration of hospital stay was significantly longer for patients in the highest quartiles of hemoglobin reduction (6.7 vs. 7.3 vs. 8.5 vs. 9.6 days, p<0.0001 for trend).

Independent predictors of a ≥2.4 g/dL reduction in hemoglobin (75th percentile) in a multivariate logistic regression model included older age, lower GFR, higher admission hemoglobin, lower weight, and use of intravenous inotropic agents, thrombolytic therapy, glycoprotein IIb/IIIa inhibitors, nitrates, and percutaneous coronary intervention (*Table III*).

Table II. **Management, angiographic and echocardiographic features, and outcomes of patients according to quartiles of hemoglobin drop**

Characteristic	Quartile of hemoglobin drop during hospital course (range, g/dL)				
	First (n=318) (≤0.8)	Second (n=289) (0.9-1.5)	Third (n=276) (1.6-2.3)	Fourth (n=289) (≥2.4)	p for trend
In-hospital medication					
Aspirin	317 (99.7)	288 (99.7)	275 (99.6)	289 (100)	0.80
Beta-blocker	278 (87.4)	252 (87.2)	239 (86.6)	255 (88.2)	0.95
Statin	311 (97.8)	282 (97.6)	273 (98.9)	285 (98.6)	0.57
ACE inhibitor	277 (87.1)	265 (91.7)	258 (93.5)	269 (93.1)	0.020
Nitrates	172 (54.1)	192 (66.4)	191 (69.2)	211 (73.0)	<0.0001
Thienopyridine	223 (70.1)	187 (64.7)	180 (65.2)	175 (60.6)	0.10
UFH	39 (12.3)	59 (20.4)	73 (26.5)	81 (28.2)	<0.0001
LMWH	303 (95.3)	274 (94.8)	256 (93.4)	269 (93.4)	0.68
GP IIb/IIIa receptor blockers	8 (2.5)	13 (4.5)	13 (4.7)	21 (7.3)	0.053
Thrombolytic therapy	61 (19.2)	73 (25.3)	83 (30.1)	112 (38.8)	<0.0001
IV inotropic agents	9 (2.8)	16 (5.5)	11 (4.0)	31 (10.7)	<0.0001
Blood transfusion	7 (2.2)	5 (1.7)	7 (2.5)	19 (6.6)	0.003
Procedures					
Cardiac catheterization	218 (68.6)	202 (69.9)	195 (70.7)	199 (68.9)	0.94
PCI	77 (24.2)	83 (28.7)	92 (33.3)	111 (38.4)	0.001
CABG	34 (10.7)	43 (14.9)	33 (12.0)	31 (10.7)	0.36
Intra-aortic balloon pump	1 (0.3)	1 (0.3)	1 (0.4)	3 (1.0)	0.55
LVSD	169 (54.0)	168 (59.8)	179 (66.1)	210 (73.2)	<0.0001
Outcomes					
Killip class II-IV	94 (29.6)	95 (32.9)	97 (35.1)	129 (44.6)	0.001
In-hospital mortality	6 (1.9)	12 (4.2)	10 (3.6)	19 (6.6)	0.032
6-month mortality	25 (8.0)	26 (9.4)	26 (9.6)	44 (15.7)	0.014
6-month death/MI	39 (12.4)	47 (17.0)	47 (17.2)	62 (22.1)	0.021

Data are presented as number (%) of patients (categorical variables) or mean value ±SD (continuous variables).
ACE: angiotensin-converting enzyme; CABG: coronary artery bypass grafting; GP: glycoprotein; LMWH: low molecular weight heparin; LVSD: left ventricular systolic dysfunction; MI: myocardial infarction; PCI: percutaneous coronary intervention; UFH: unfractionated heparin.

Clinical outcomes

Figure 2 shows the Kaplan-Meier curves for 6-month survival by quartiles of hemoglobin drop. Survival decreased significantly as hemoglobin drop severity increased. Higher levels of hemoglobin drop were associated with increased rates of 6-month mortality (8.0% vs. 9.4% vs. 9.6% vs. 15.7%; p for trend=0.014) and 6-month death/MI (12.4% vs. 17.0% vs. 17.2% vs. 22.1%; p for trend=0.021). *Table IV*

Table III. **Independent predictors of increased hemoglobin drop***

Variable	ß-coefficient	OR (95% CI)	p
Age (per 1-year increase)	0.02	1.02 (1.01-1.04)	0.012
GFR (per 10-ml/min/1.73 m^2 decrement)	0.08	1.08 (1.02-1.15)	0.008
Weight (per 10-kg increment)	-0.16	0.85 (0.75-0.98)	0.021
IV inotropic agents	1.17	3.21 (1.69-6.09)	<0.0001
Thrombolytic therapy	0.57	1.77 (1.12-2.81)	0.014
Glycoprotein IIb/IIIa inhibitors	0.85	2.34 (1.18-4.63)	0.015
Nitrates	0.50	1.65 (1.17-2.33)	0.004
PCI	0.59	1.80 (1.23-2.64)	0.002
Admission hemoglobin (per 1-g/dL increment)	0.55	1.74 (1.54-1.96)	<0.0001

*Hemoglobin drop ≥2.4 g/dL (75th percentile)
GFR: glomerular filtration rate; PCI: percutaneous coronary intervention

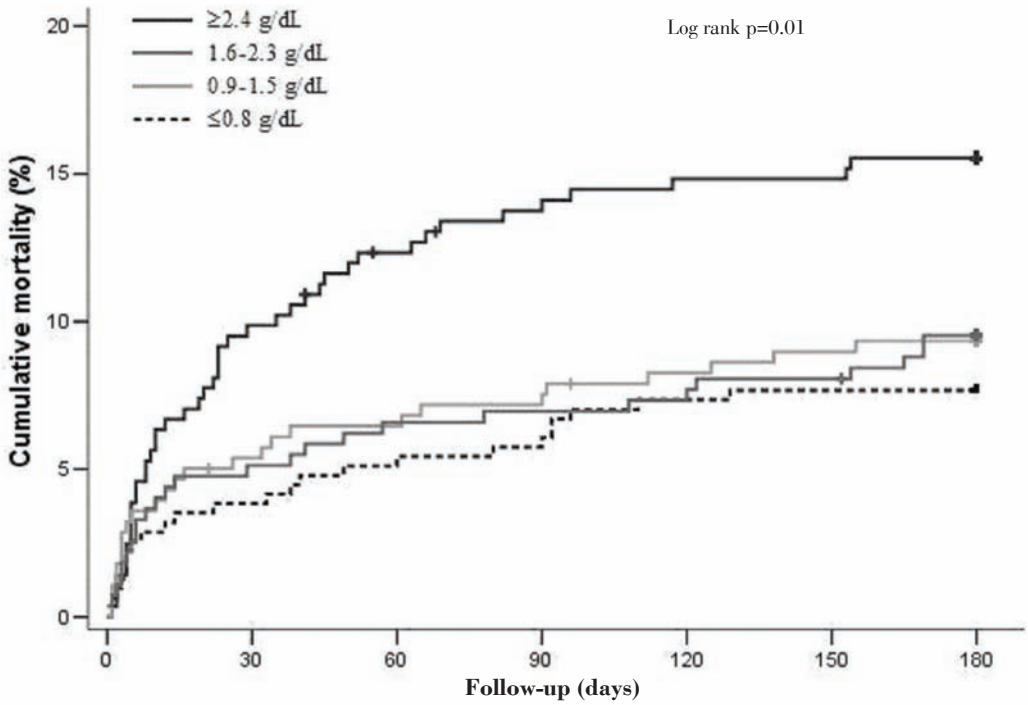

Figure 2. **Kaplan-Meier curve for overall mortality according to quartile of hemoglobin drop (range, g/dL) during hospital course.**

Table IV. **Hazard ratios for death according to quartiles of hemoglobin drop and nadir hemoglobin during hospital course.**

	6-month mortality (%)	Unadjusted HR (95% CI)	Adjusted HR (95% CI)
Quartiles of hemoglobin drop (range, g/dL)			
First (≤0.8)	8.0	1.0‡	
Second (0.9-1.5)	9.4	1.23 (0.71-2.15)	1.33 (0.74-2.39)
Third (1.6-2.3)	9.6	1.25 (0.72-2.18)	1.25 (0.71-2.23)
Fourth (≥2.4)	15.7*	2.12 (1.29-3.48)	1.83 (1.08-3.11)
Quartiles of nadir hemoglobin (range, g/dL)			
First (≤11.0)	24.4	6.38 (3.45-11.81)	2.33 (1.12-4.84)
Second (11.1-12.3)	11.5	2.94 (1.52-5.69)	1.77 (0.85-3.71)
Third (12.4-13.4)	3.1	0.75 (0.32-1.79)	0.62 (0.24-1.57)
Fourth (≥13.5)	4.1†	1.0‡	

*p=0.014 for trend; †p<0.0001 for trend; ‡This group served as the reference group

presents the results of unadjusted and adjusted Cox regression models for 6-month mortality by quartiles of hemoglobin drop and nadir hemoglobin. After adjustment for potential confounders, patients in the highest quartile of hemoglobin decline had worse outcomes than patients in the first quartile (reference group). The adjusted hazard ratios (HR) for 6-month mortality and 6-month death/MI among patients in the highest quartile of hemoglobin drop were 1.83 (95% confidence interval [CI] 1.08 to 3.11; p=0.026) and 1.60 (95% CI 1.04 to 2.44; p=0.031) respectively, compared with patients in the lowest quartile of hemoglobin drop.

increased 6-month mortality rates (*Figure 4*).

Further analyses were performed excluding patients who underwent CABG surgery (n=141) from the study population. In the selected population of patients not undergoing CABG surgery, results were similar to those reported for the initial patient population. Increased hemoglobin drop was associated with higher 6-month mortality. Compared with patients in the lowest quartile of hemoglobin drop, the adjusted HR for 6-month mortality among patients in the highest quartile of hemoglobin drop was 2.44 (95% CI 1.37-4.35; p=0.002). For each 1-g/dL increase in hemoglobin drop the adjusted HR

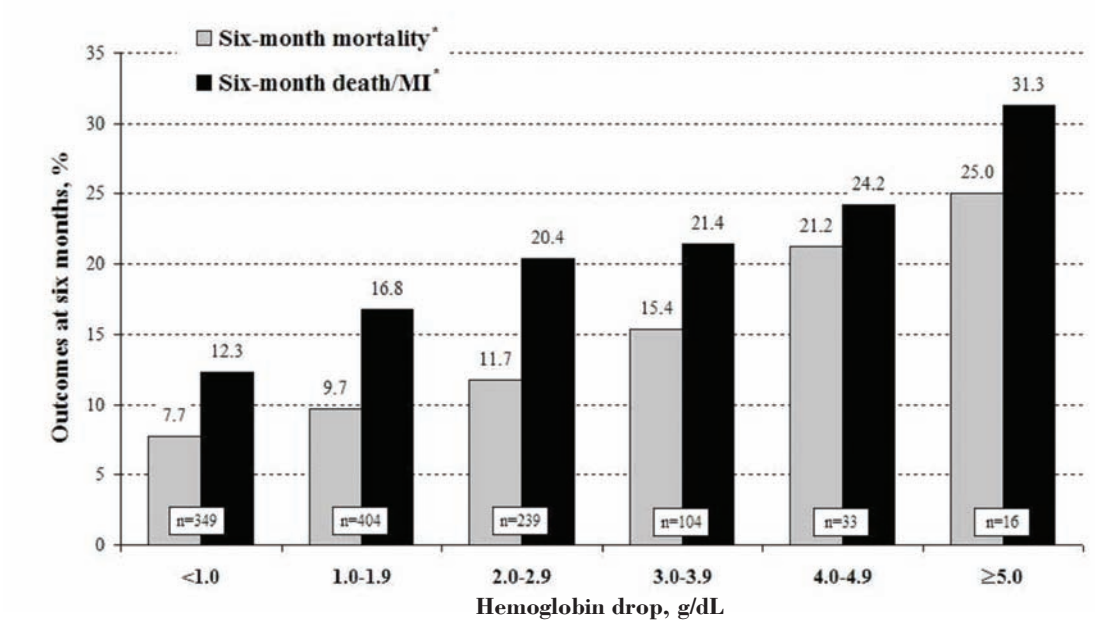

Figure 3. **Crude six-month mortality and six-month death/myocardial infarction (MI) according to hemoglobin drop (g/dL). At the top of each column, the rates of six-month mortality and death/MI (% of patients) are noted. Data labels at the bottom of the columns refer to the number of patients in each group of hemoglobin drop.**
*p<0.001 for trend.

When considered as a continuous variable in 1-g/dL increments, a graded relationship was seen between hemoglobin drop and 6-month death and death/MI (*Figure 3*). The adjusted HR for each 1-g/dL increase in hemoglobin drop was 1.16 (95% CI 1.01 to 1.32; p=0.030) and 1.12 (95% CI 1.01-1.25; p=0.041) for 6-month mortality and 6-month death/MI respectively (*Table V*). Since thrombolytic therapy and intravenous inotropes were strong predictors of an increased hemoglobin drop, we also analyzed our data stratified by initial diagnosis. In both ST-elevation MI and non-ST-elevation ACS, higher levels of hemoglobin drop were associated with

for 6-month mortality was 1.31 (95% CI 1.12-1.53; p=0.001).

Moreover, results were similar after excluding patients who died during the index hospitalization (n=47) from the analyses. Higher levels of hemoglobin drop during hospital stay were still associated with increased mortality at six months in patients who survived the hospitalization. For each 1-g/dL increase in hemoglobin drop the adjusted HR for 6-month mortality was 1.19 (95% CI 1.00-1.41; p=0.045).

Nadir hemoglobin was strongly associated with mortality at six months. A tendency for a J-shaped rather than monotonic relationship

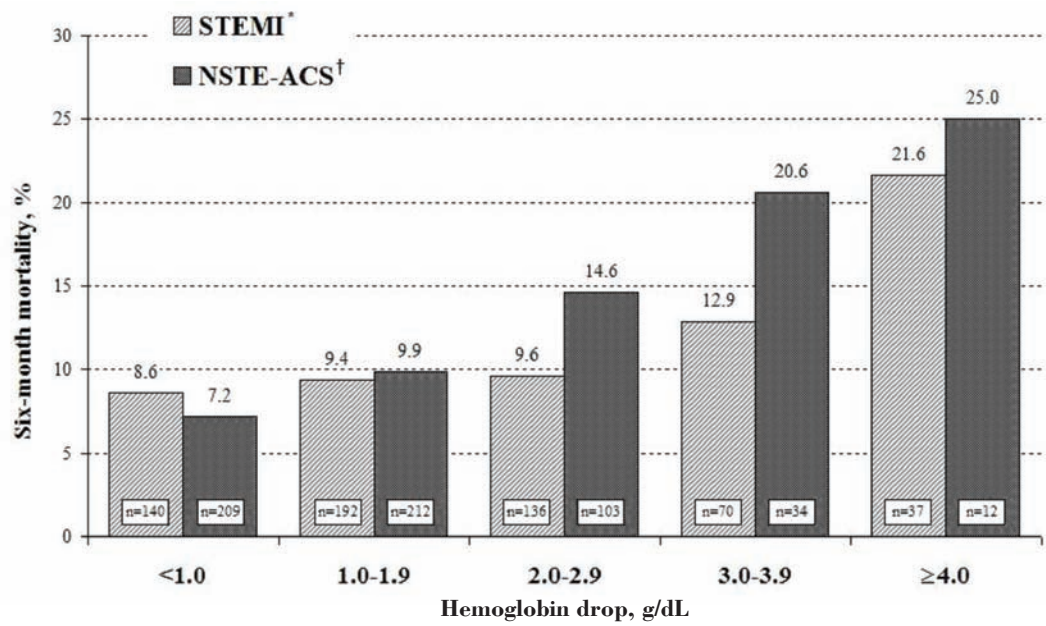

Figure 4. **Crude six-month mortality according to hemoglobin drop (g/dL), stratified by type of acute coronary syndrome: ST-segment elevation myocardial infarction (STEMI) and non-ST-segment elevation acute coronary syndromes (NSTE-ACS). At the top of each column, the rates of six-month mortality (% of patients) are noted. Data labels at the bottom of the columns refer to the number of patients in each group of hemoglobin drop.**
*p=0.04 for trend; †p=0.001 for trend.

Table V. **Independent predictors of six-month mortality**

Variable	HR (95% CI)	p
Age (per 1-year increase)	1.03 (1.01-1.06)	0.002
Killip class >I	2.12 (1.41-3.19)	<0.0001
Left ventricular systolic dysfunction*	2.30 (1.34-3.97)	0.003
GFR (per 10-ml/min/1.73 m^2 decrement)	1.11 (1.03-1.19)	0.007
Hemoglobin drop (per 1-g/dL increase)	1.16 (1.01-1.32)	0.030
Coronary revascularization	0.48 (0.29-0.78)	0.003
Blood transfusion	1.94 (1.06-3.55)	0.032

*Left ventricular ejection fraction <50% as estimated by echocardiography. GFR: glomerular filtration rate.

was observed between nadir hemoglobin and adjusted mortality. The adjusted HR for 6-month mortality for patients in the lowest quartile of nadir hemoglobin was 2.33 (95% CI 1.12-4.84; p=0.024), compared with patients in the highest quartile (*Table IV*).

Blood transfusion

Thirty-eight patients (3.2%) underwent at least one blood transfusion. Mean (±SD) nadir hemoglobin value among transfused patients was 8.0±0.7 g/dL (range, 6.4 to 9.4) compared with 12.4±1.6 g/dL (range, 7.5 to 16.9) among nontransfused patients (p<0.0001). Transfused patients had a higher absolute rate of death (40.5% vs. 9.6%; p<0.0001) and death/MI (48.6% vs. 16.0%; p<0.0001) at 6 months compared with nontransfused patients. After adjustment for comorbidities, clinical presentation, hospital treatment, and hemoglobin drop, blood transfusion was independently associated with an increased risk of 6-month mortality (adjusted HR 1.94, 95% CI 1.06 to 3.55; p=0.032) and 6-month death/MI (adjusted HR 1.77, 95% CI 1.03 to 3.04; p=0.039) (*Table V*).

DISCUSSION

In this single-center observational study, we found a graded independent association between higher levels of hemoglobin drop during hospitalization and increased mortality in patients admitted with ACS. Our findings provide additional evidence to previous reports regarding the impact of bleeding and anemia

on prognosis among patients who have had an ACS[3-5,17,18].

Current management of ACS patients with anticoagulants, antiplatelet agents, thrombolytic treatment (in the case of ST-elevation MI), and percutaneous or surgical revascularization has improved the rate of ischemic events at the cost of a higher risk of bleeding complications[19]. Predictors of an increased decline in hemoglobin concentration in our study included older age, reduced GFR, lower weight, higher admission hemoglobin, and the use of intravenous inotropic agents, thrombolytic therapy, glycoprotein IIb/IIIa inhibitors, nitrates, and percutaneous coronary revascularization procedures. These risk factors were similar to previously identified determinants of major bleeding in a large registry of ACS[5]. Previous data are heterogeneous regarding female gender as a risk factor for bleeding[3,5,7,18]. In the present study, female gender was not associated with increased hemoglobin drop. In our patient population, women were more often admitted with non-ST-elevation ACS (55.0% in women vs. 47.3% in men; p=0.019), had lower baseline hemoglobin concentration (12.6±1.5 g/dL vs. 14.4±1.6 g/dL; p<0.001), and less frequently underwent thrombolytic treatment (17.9% vs. 32.0%; p<0.001), percutaneous coronary intervention (18.5% vs. 35.8%; p<0.001), and glycoprotein IIb/IIIa inhibitors (2.7% vs. 5.5%; p=0.047), thus partly explaining the lower hemoglobin drop among women.

Hemoglobin drop and development of anemia among patients hospitalized with ACS may result from different mechanisms in addition to blood loss. In our study, patients with increased levels of hemoglobin decline more often developed signs of heart failure and congestion, and were more frequently treated with nitrates and ACE inhibitors. Furthermore, although these patients had higher hemoglobin concentrations on admission, they developed lower nadir hemoglobin levels. These findings suggest that hemodilution might be involved in hemoglobin drop during hospital course. Previsdomini et al.[20] described a mean hemoglobin decrease of 1.29±0.79 g/dL during the first 12 to 24 hours (remaining constant during the rest of hospital stay) in 103 nonbleeding patients with ACS in an intensive care unit. The authors hypothesized that this decrease is due to "internal hemodilution" by nitroglycerin and normalization of the previous stress-induced hemoconcentration. Providing further evidence for the latter hypothesis, we also found that patients with higher hemoglobin drop had increased levels on admission of common markers of stress such as white blood cell count, platelet count, and blood glucose. We observed that patients who eventually had greater hemoglobin drop during hospitalization had higher blood pressure on admission, which may be due to increased neurohumoral activation on presentation and later normalization of stress-induced hemoconcentration. Chronic use of ACE inhibitors may contribute to anemia by inhibiting erythropoiesis, although their role in the acute setting is not clear[21]. Diagnostic phlebotomy may also contribute to blood loss and cause anemia in hospitalized patients[22]. However, the use of small volume blood containers and reduction of the frequency of sampling after discharge from the ICCU suggests that phlebotomy has a minor role in hemoglobin decline in our patient population[20,23].

Major contributors to hemoglobin drop in our study included the use of therapeutic agents such as thrombolytic therapy and glycoprotein IIb/IIIa inhibitors. We also observed that older age, lower body weight, and reduced GFR were associated with increased hemoglobin decline. These three factors, among others, have previously been associated with excess dosing of unfractionated heparin, low molecular weight heparin, and glycoprotein IIb/IIIa inhibitors in an analysis from the CRUSADE registry[24]. In that report, dosing errors predicted an increased risk of major bleeding and were associated with increased mortality[24]. Although we do not have data regarding the dose of antithrombotic agents and glycoprotein IIb/IIIa inhibitors used in our population, these findings may suggest that dosing errors might have contributed to bleeding and hemoglobin drop in our patients.

Although 25% of patients had a decline in hemoglobin of at least 2.4 g/dL during hospital course, major and minor bleeding (TIMI criteria) occurred in only 2.1% and 7.4% of our population respectively. Furthermore, among 106 patients in our study who had a hemoglobin drop of 3 to 4 g/dL, only 43 (40.6%) had an observed blood loss. This implies that clinically occult bleeding, such as unrecognized gastrointestinal

oozing, might have contributed to a significant hemoglobin drop[19,25].

Our study suggests that hemoglobin decline is common during hospitalization for ACS and is associated with worse prognosis, in terms of death and MI, after adjustment for baseline characteristics and interventions, including blood transfusion. This is consistent with recent observational data suggesting that bleeding is associated with a higher risk of ischemic events and death[3-5,17,18]. Aronson and colleagues[15] have previously shown that nadir and discharge hemoglobin levels have a strong impact on death and occurrence of heart failure in the short and long term among survivors of MI. Our data on consecutive patients with ACS are in agreement with the findings by Aronson et al., and shed further light on the prognostic impact of hemoglobin drop during hospitalization. The 16% adjusted increase in the risk of death for each 1-g/dL increment in hemoglobin drop in our study compares to the 21% adjusted increase in the risk of post-discharge death for each 1-g/dL increment in hemoglobin drop in the aforementioned report[15].

Several possible mechanisms may underlie the association of hemoglobin decline and bleeding with adverse outcomes. The development of anemia with inherent risk of inadequate tissue oxygen delivery is probably one of the mechanisms involved in the association of hemoglobin drop with increased mortality and re-infarction[19]. Patients with increased levels of hemoglobin drop had lower levels of nadir hemoglobin concentration, and nadir hemoglobin was strongly associated with increased mortality in our study and previous reports[15]. We found a non-significant tendency for a J-shaped relationship between nadir hemoglobin and adjusted mortality. This finding was not reported in previous studies and is most likely due to chance.

Bleeding often leads to the discontinuation of antithrombotic therapy, which might result in ischemia, MI, stent thrombosis, hemodynamic decompensation, and arrhythmias[17]. It may also result in hemodynamic compromise, greater neurohormonal activation, exaggeration of inflammatory response, and platelet activation, which portends an increased risk of recurrent ischemic events[3,15,19]. Furthermore, transfusion may also add to the risk. In our study, blood transfusion was independently associated with a 1.9-fold higher risk of 6-month mortality, after adjustment for baseline characteristics, hemoglobin drop, and interventions. This finding is consistent with previous reports on adverse effects of transfusion in patients with ACS[7-9]. However, transfusion may reflect a more critical condition and many factors involved in the clinical decision to transfuse cannot be adjusted for in a statistical model[26]. Although the mechanisms linking adverse outcomes with red-cell transfusion remain unclear, several factors may contribute. It was shown recently that transfusion of older units of red cells (more than 14 days of storage) is associated with worse outcomes after cardiac surgery[27]. This finding provides more evidence in support of the concept that progressive functional and structural changes undergone by red cells during storage may underlie the increased risk associated with blood transfusion in some patients. Stored red cells are depleted in intracellular 2,3-diphosphoglycerate, which shifts the oxyhemoglobin dissociation curve to the left and reduces oxygen delivery to the tissues[28]. Stored red cells are also depleted in nitric oxide and adenosine triphosphate, and may act as a nitric oxide sink, resulting in vasoconstriction and reduced oxygen carriage by the blood[3,29]. Storage of red cells also results in decreased deformability, increased adhesiveness and aggregability, and accumulation of proinflammatory bioactive substances, thereby triggering or worsening ischemic events[27,30]. Potentially deleterious consequences of a transfusion on cardiac performance may also include increased blood viscosity, fluid overload, and immune suppression[26].

Wu and colleagues[31] reported that in elderly patients with MI, blood transfusion was associated with lower short-term mortality if baseline hematocrit was ≤30.0%. However, in a randomized trial of critically ill patients, there was a nonsignificant difference in mortality between patients administered transfusion at hemoglobin of 7 g/dL versus those administered transfusion at a hemoglobin of 10 g/dL[32]. Recently, Alexander et al.[33] analyzed the association between transfusion and in-hospital mortality as a function of nadir hematocrit in non-ST-segment elevation ACS patients in the CRUSADE registry. No significant adverse

effects with transfusion were found in those with nadir hematocrit of <30%, and there was a strong trend to benefit when nadir hematocrit was ≤24%. The small sample size did not allow us to perform a similar analysis in our population. A randomized trial of transfusion strategies is required to clarify the indications for its use in this setting.

Our study provides further support for the potential importance of reducing bleeding risk in the treatment of ACS patients. This should involve the careful use of pharmacological therapy and reperfusion/revascularization strategies. Particular attention should be paid in elderly patients and in renal dysfunction. Possible options include correct dosing of unfractionated heparin, low molecular weight heparin, and glycoprotein IIb/IIIa inhibitors according to weight and renal function, consideration of fondaparinux as well as bivalirudin, use of gastroprotective agents, and careful use of dual antiplatelet therapy. The choice of a radial vascular approach over the femoral route (which was used in >90% of patients in our study) may also help to reduce bleeding risk[1,2].

LIMITATIONS

There are several limitations to be considered when our study is interpreted. First, this was a retrospective observational and non-randomized study conducted at a single hospital, and as such, both identified and unidentified confounders may have influenced the outcomes and causality could not be determined. Second, patients (n=8) transferred in the first 24 hours to other centers for urgent cardiac surgery or coronary revascularization were excluded from analysis. Third, hemoglobin determinations after discharge from the ICCU were obtained according to the discretion of the attending cardiologist, except after percutaneous coronary intervention; transfusions were not accounted for in the calculation of nadir hemoglobin; and data on bleeding events and hemoglobin decline occurring after CABG surgery were not evaluated. Therefore, some patients may have been misclassified regarding hemoglobin decline during hospital course. Fourth, the small sample size did not allow us to analyze the association between transfusion and outcome as a function of nadir hemoglobin. Fifth, we were unable to explore possible relationships between antithrombotic and antiplatelet therapy (dosing, timing, and cessation), hemoglobin drop, and observed outcomes. In addition, no prospective data were collected regarding the use of gastrointestinal protective agents (histamine-2 antagonists, proton pump inhibitors), which should have been considered in the Cox model. Finally, data regarding minimal bleeding without significant hemoglobin drop (<3 g/dL) were not collected for the entire patient population. Therefore, we were unable to perform a stratified analysis of patients who presented clinical bleeding events versus those who did not bleed, and to correlate hemoglobin drop with clinical bleeding events. Future observational studies designed to address these issues are required to better explore the mechanisms that underlie the relationship between hemoglobin drop and adverse outcomes.

CONCLUSIONS

Our data show that a decrease in hemoglobin is frequent during hospitalization for ACS and is independently associated with adverse events in follow-up. Predictors of increased hemoglobin decline were identified and include older age, renal dysfunction, lower weight, higher baseline hemoglobin, and use of thrombolytic therapy, glycoprotein IIb/IIIa inhibitors, nitrates, intravenous inotropic agents, and percutaneous coronary intervention. The development of anemia and blood transfusion may partly contribute to the worse outcomes observed with higher levels of hemoglobin drop.

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