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Is hemoglobin variation a linear predictor of mortality in acute coronary syndrome?

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ABSTRACT

Background and objectives: Coronary artery disease is a common health problem. The aim of this study was to evaluate the prognosis impact on mortality of the variation of hemoglobin (Hb) levels during hospitalization time.

Methods: The retrospective observational study included 2640 patients admitted for acute coronary syndrome in a single coronary care unit from May 2004 until June 2013.

The primary endpoint was all cause of death at 1 year of follow up time, and secondary endpoint was all cause of death at 2 years of the follow up time.

Results: Four groups were created according to the quartiles of Hb variation (admission Hb minus lowest Hb value) during the hospitalization time: group 1: ≥2.1 g/dL with 627 patients; group 2: >1.1 and <2.1 g/dL with 666 patients; group 3: >0.3 and ≤1.1 g/dL with 686 patients and group 4: ≤0.3 g/dL with 661 patients.

A total of 84 patients (3.2%) died during the first year of the follow up. More patients died in group 1 and 4 (6.4% vs 3.7% vs 3.7% vs 6.8%, Log-Rank = 0.023). At 2 years of follow-up, the results were similar, with higher mortality in group 4 (7.3% vs 4.3% vs 4.6% vs 9.2%, Log-Rank = 0.003).

Multivariate analysis showed that Hb variation > 1.1 was an independent predictor of mortality (hazard ration = 0309 95% confidence interval, 0.136–0.702; $P = 0.005$).

Conclusion: The patients with the lower baseline hemoglobin and the variability of Hb highest than 1.1 mg/dL had the worse prognosis with high mortality rate during the follow up time.

1. Introduction

Coronary artery disease (CAD) is a common health problem worldwide, and in 2013 was the most common cause of death globally, resulting in 8.14 million deaths (16.8%) up from 5.74 million deaths (12%) in 1990 [1].

Secondary prevention following an acute coronary syndrome (ACS) event is a key as further ischemic events are common following the index event. Risk prediction tools have identified a number of factors which impact on risk of death and myocardial infarction following an ACS event [2,3,4]. However, patient prognosis at hospital discharge continues to vary markedly, some studies have pointed out the relationship between CAD and anemia.

Anemia at admission is a frequent finding in patients with acute coronary syndrome, and has been observed in up to 15% of patients with myocardial infarction, reaching 43% in elderly patients [5]. Anemia can adversely influence prognosis in the patients by various mechanisms, such as decreasing the oxygen content of the blood supplied to jeopardized myocardium and by increasing myocardial oxygen demand through necessitating a higher cardiac output to maintain adequate systemic oxygen delivery [6].

In many studies, anemia has been shown to be an independent risk factor for adverse cardiovascular (CV) outcomes in patients with heart failure and in patients undergoing percutaneous coronary intervention, and several others showed that anemia associated with bleeding complications had a poor prognosis, prolong hospitalization time and raise costs of treatment [7].

Thus, the aim of this study was to evaluate the prognosis impact on long term mortality of the variation of hemoglobin (Hb) levels during hospitalization time for ACS.

2. Methods

2.1. Patient population and protocol

The retrospective observational study included 2640 patients admitted for ACS (38.6% with ST elevation acute myocardial infarction (AMI), 58.2% non-ST elevation AMI and 3.2% new or presumed new Left bundle branch block (LBBB)), in a single coronary care unit from May 2004 until June 2013. Patients > 18 years with ACS, diagnosed by the presence of at

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Table 1
Baseline characteristics.

	Group 1	Group 2	Group 3	Group 4	*P*-value
Men	72.1	65.9	67.1	60.8	<0.001
Age, mean (SD), y	68 (12)	69 (13)	68 (13)	68 (13)	NS
Score Grace, mean (SD), y	145 (36)	141 (36)	137 (36)	141 (39)	<0.001
Score TIMI, mean (SD), y	2.7 (1.4)	2.7 (1.5)	2.7 (1.6)	2.1 (1.6)	NS
KK class I at admission	82.5	84.7	87.3	83.8	NS
KK class II at admission	12.4	12.3	10.1	10.6	NS
KK class III at admission	3.0	1.5	1.5	2.9	NS
KK class IV at admission	2.1	1.5	1.2	2.7	NS
Hb admission, mean (SD), y	14.4 (1.7)	13.6 (1.6)	13.0 (1.9)	12.3 (2.1)	<0.001
Hb minimum, mean (SD), y	10.8 (2.0)	11.8 (1.7)	12.0 (2.0)	11.9 (2.2)	<0.001
LVEF, mean (SD) %	48 (12)	50 (11)	52 (11)	51 (12)	<0.001

Hb, hemoglobin; KK, Killip class; LVEF, left ventricular ejection fraction; SD, standard deviation.
Data are expressed as percentages or mean (standard deviation).

least two of the following criteria: thoracic pain, new changes on ST-T segment on electrocardiogram or increase in myocardial markers (such troponin), were included. Patients with myocarditis, or type 2, 4 or 5 myocardial infarction were excluded. Readmissions to the same coronary care unit were not considered for statistical analysis.

The population was divided in four groups according to the quartiles of Hb variation during the hospitalization time (admission Hb minus lowest Hb value): group 1: ≥2.1 g/L, n = 626 patients; group 2: >1.1 and <2.1 g/L, n = 666 patients; group 3: >0.3 and ≤1.1 g/L, n = 686 patients; group 4: ≤0.3 g/L, n = 661 patients.

2.2. Data collection and endpoint

Clinical, analytical, and demographic data were retrospectively extracted using dedicated software used in coronary care unit. Since data is systematically registered for every patient, there were no missing data for the analyzed parameters. Levels of serum hemoglobin, lipids, glucose, creatinine, sodium, potassium, troponin I were measured by routine laboratory methods.

All patients underwent standard echocardiographic evaluation and were submitted to a coronary angiography and percutaneous coronary intervention if indicated according to available guidelines.

The follow up was conducted by personal interview in the outpatient ward, reviewing hospital registries, telephone contact and reviewing official mortality records, and was obtained for every patient included.

During patient data collection confidentiality was always respected. This was approved by the ethics committee of the hospital.

The primary endpoint was all cause of death (cardiovascular or non-cardiovascular) at 1 year of follow up time, and secondary endpoint was all cause of death at 2 years of the follow up time.

2.2.1. Statistical analysis

Continuous data were normally distributed as evaluated with Shapiro-Wilk test, and therefore is presented as mean ± standard errors of the mean, and those with a skewed distribution were expressed as medians (semiquartile range).

Dichotomous variables are presented as frequencies (percentage). Patients were divided into four groups according to Hb variation. Comparison of data between groups was made using one way analysis of variance for continuous data, and chi-square (or Fisher exact test, as appropriate) for dichotomous data.

All variables with a significant *P*-value ≤ 0.10 for all cause mortality were tested using a multivariate Cox-regression test, with all variables in the final model reaching a *P*-value < 0.05.

Relevant variables with significant between groups differences in univariate analysis (age, type of ACS, heart rate, admission Killip class, left ventricular function, maximum troponin, minimum hemoglobin, and prior use of acetylsalicylic acid, beta-blockers and statins) were also included in the model to adjust the final analysis for all possible confounders. Survival curves were constructed by Kaplan-Meier method and were compared using the log rank test.

All analysis was performed with SPSS for windows, version 16.0 (SPSS Inc.; Chicago, Illinois, United States). A 2-side *P*-value ≤ 0.05 was considered statistically significant.

Table 2
Cardiovascular risk factors.

	Group 1	Group 2	Group 3	Group 4	*P*-value
Arterial hypertension	75.3	76.8	73.5	74.8	NS
Dyslipidemia	73.6	75.7	72.7	73.1	NS
Smoking	18.2	16.1	16.2	14.7	NS
Diabetes mellitus type I	4.2	3.5	3.8	3.2	NS
Diabetes mellitus type II	26.6	25.9	25.9	30.1	NS
Previous know coronary disease	18.2	18.9	23.8	26.2	<0.001
Previous PTCA	9.6	10.8	13.8	14.3	<0.001
Previous CABG	2.9	3.7	5.3	6.4	<0.001

CABG, coronary artery bypass graft; PTCA, percutaneous transluminal coronary angioplasty.
Data are expressed as percentages or mean (standard deviation).

Table 3
Chronic medication.

	Group 1	Group 2	Group 3	Group 4	*P*-value
ASA	35.5	41.7	43.8	44.4	NS
Another antiplatelet	17.6	19.4	17.5	19.8	NS
Beta-blockers	22.0	27.7	34.8	33.8	<0.001
ACE inhibitors/ARB	41.9	45.7	46.3	42.8	NS
Statins	39.9	40.3	48.6	46.0	NS
Loop diuretics	28.9	25.8	27.4	32.6	NS
Insulin	11.6	10.0	14.1	10.3	NS
Oral antidiabetic agents	15.4	16.1	22.1	19.5	NS

ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blockers; ASA, acetylsalicylic acid.
Data are expressed as percentages or mean (standard deviation).

3. Results

During the follow up time were hospitalized 2640 patients with ACS. The baseline characteristics of the patients are presented in Table 1. The mean age of the population was 68 ± years, and 66.4% were male.

At admission hemoglobin levels was higher in group 1 (14.4 ± 1.7 g/dL; vs 13.6 ± 1.6 g/dL; vs 13.0 ± 1.9 g/dL; vs 12.3 ± 2.1 g/dL, *P* < 0.001).

There were significant differences between groups regarding baseline characteristics. Patients in group 1 had a higher Grace score (145 ± 36; vs 141 ± 36; vs 137 ± 36; vs 141 ± 39, *P* = 0.002), most often present ST elevation acute myocardial infarction (38.7% vs 26.4% vs 21.9% vs 18%, *P* < 0.001), had more anterior descendent artery disease (74.7% vs 63.1% vs 60.4% vs 58.8%, *P* < 0.001) and were more revascularized by percutaneous coronary intervention (PCI) or by coronary artery bypass grafting (CABG). Also, the patients in group 1 had the higher peak of troponin I level during the hospitalization time (72.2 ± 96.2; vs 40.1 ± 57.6; vs 23.3 ± 39.4; vs 22.4 ± 43.1, *P* < 0.001), and had the lower left ventricular ejection fraction (48% vs 50% vs 52% vs 51%, *P* < 0.001).

Table 4
After discharge medication.

	HR 95% CI	*P*-value
Age, years	2.287 (1.313–3.981)	0.003
LVEF, %	3.295 (1.896–5.727)	<0.001
Troponin I, ng/mL	4.148 (2.178–7.900)	<0.001
Killip class III/IV	3.692 (2.444–5.578)	<0.001
Hemoglobin variation > 1.1 g/dL	2.149 (1.500–3.078)	0.005

ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blockers; ASA, acetylsalicylic acid.
Data are expressed as percentages or mean (standard deviation).