European Journal of Therapeutics

DOI: 10.5152/EurJTher.2019.19050

Original Research

Baseline Hemoglobin Levels Predict All-Cause Mortality After Saphenous Vein Graft Interventions

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ABSTRACT

Objective: Reduction in the baseline hemoglobin level is associated with poor outcomes in many cardiovascular conditions including percutaneous interventions of the native coronary arteries. However, this association has not been studied in patients with saphenous vein graft disease undergoing elective percutaneous intervention.

Methods: In this study, we evaluated the baseline hemoglobin levels of 105 patients undergoing saphenous vein graft intervention. The mean follow-up period was 42.4±18.4 months, and the outcome of our study was all-cause mortality.

Results: Twelve patients suffered all-cause mortality; the mean baseline hemoglobin levels of these patients were 2 g/dL lower (11.7±1.0 vs. 13.7±1.5, p=0.005) and their ejection fractions were 22% lower (49.3±10.8 vs. 38.3±12.4, p=0.014) than those of the patients without all-cause mortality. A hemoglobin cut-off value of 12.55 g/dL discriminated all-cause mortality with an accuracy of 85% (sensitivity: 83.3%, specificity: 76.4%, p≤0.001). Survival curve showed a survival benefit of 21 months for patients with hemoglobin levels higher than 12.55 g/dL (cumulative survival 95.3% vs. 70%, log rank p-value=0.001).

Conclusion: The baseline hemoglobin levels may be associated with all-cause mortality in patients undergoing elective saphenous vein graft interventions.

Keywords: All-Cause mortality, baseline hemoglobin, saphenous vein graft interventions

INTRODUCTION

It is known that the outcomes of saphenous vein graft (SVG) percutaneous coronary interventions (PCIs) are worse than those of native coronary artery PCIs (1). Moreover, some comorbid factors may contribute to these poor outcomes. Anemia is a well-known factor that increases the risk of cardiovascular events (2-3). There is an association between reduced baseline hemoglobin levels and the poor outcomes of PCI (4-6). Some studies have shown that this association included PCI of patients with previous coronary artery bypass graft (CABG); however, in those studies, the majority of lesions were observed in the native vessels, which included both arterial and venous conduits. Therefore, evidence-based data in the literature regarding SVG PCI are lacking. This study aimed to analyze the impact of the baseline hemoglobin levels on all-cause mortality in patients undergoing SVG PCI.

METHODS

We evaluated the baseline hemoglobin levels of 105 patients undergoing SVG PCI at our hospital from January 2013 to December 2018. Indications for revascularization included stable angina and all types of acute coronary syndrome (ACS). Patients who were treated using a stent and had angiographic success were included the study. Patients with missing data for hemoglobin levels were excluded. In this study, patients were evaluated according to an institutionally approved protocol (TOBB ETÜ Hospital Ethics Committee, 20.06.2018/006). This retrospective study was performed by screening of the medical records alone; thus, the requirement of obtaining informed consent was from the patients was waived.

The outcome of our study was all-cause mortality. Survival status was assessed using telephone contacts and checked using the National Death Notification System.

Baseline characteristics of patients including patient demographics (age and sex), past medical history (diabetes mellitus and hypertension), smoking status, low-density lipoprotein level, left ventricular ejection fraction (LVEF), hemoglobin levels, glucose and creatinine measurements, medication (acetylsalicylic acid, clopidogrel/ticagrelor, anticoagulants, beta-blockers, statins, and diuretics), angiographic characteristics, and PCI data were identified from the computer database of our institution.

How to cite: Tek M, Çetin MS, Berkalp B, Amasyalı B, Özgeyik M, Çelebi S. Baseline Hemoglobin Levels Predict All-Cause Mortality After Saphenous Vein Graft Interventions. Eur J Ther 2020; 26(2): 102-6.

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Received: 31.05.2019 • **Accepted:** 25.06.2019

Statistical Analysis

Statistical analyses were performed using Statistical Package for the Social Sciences 25 (IBM Corp., Armonk, NY, USA). Categorical variables are displayed as frequencies, and continuous variables are displayed as mean±standard deviation. Univariate Cox regression analysis was used to analyze the association of the variables with mortality, and variables with p<0.1 in the univariate analysis were further analyzed using a multivariate Cox regression model. In addition, to estimate all-cause mortality, receiver operating characteristic (ROC) curve was used to detect the optimal cut-off point of hemoglobin, the Youden index was used for identification of the best cut-off point for hemoglobin. Kaplan–Meier survival curves were used to assess survival times, and the log rank test statistic was used to test survival time differences between the upper and lower cut-off point of hemoglobin. A p-value of <0.05 was considered statistically significant.

RESULTS

During the mean follow-up period of 42.4 months, 12 of 105 patients suffered all-cause mortality. The cause of mortality was reinfarction in two patients, heart failure in four patients, renal insufficiency in one patient, and unknown reasons in remaining. Patients were divided into two groups according to their mortality status. Baseline and procedural characteristics are summarized in Tables 1 and 2. The baseline hemoglobin levels and LVEF were significantly different between groups (13.7±1.5 vs. 11.7±1.0, p=0.005 and 49±10.8 vs. 38.3±12.4, p=0.014, respectively). Furthermore, Cox regression analysis was performed to determine the predictors of mortality and results of the regression analysis are shown in Table 3. Among these parameters, only hemoglobin levels were associated with mortality in multivariate analysis.

According to the ROC analysis, a hemoglobin cut-off value of 12.55 g/dL discriminated all-cause mortality with an accuracy of 85% (sensitivity 83.3%, specificity 76.4%, p<0.001) (Figure 1). In our study group, the hemoglobin value was <12.55 g/dL in 31 patients and >12.55 g/dL in 74. There were 9 (29.0%) mortality events in patients with a hemoglobin value<12.55 g/dL and 3 (4.0%) in those with a hemoglobin value≥12.55 g/dL (p=0.001). During follow up, the mortality rates according to the hemoglobin cut-off value of 12.55 g/dL were estimated using Kaplan–Meier analysis (Figure 2). Survival curve demonstrated a survival benefit of 21 months for patients with a hemoglobin level of >12.55 g/dL (cumulative survival 95.3% vs. 70%, log rank p-value=0.001).

DISCUSSION

In the present study, the main finding was that a low baseline hemoglobin value was independently associated with increased

Table 1. Baseline characteristics of patients according to the mortality status

Variables	Mortality (–) n=93	Mortality (+) n=12	p
Age, years	65.0 (8.8)	67.3±6.4	0.291
Male/female, %	87 /13	83/17	0.661
HT, %	54	83	0.07
DM, %	38	58	0.229
Smoking, %	32	50	0.332
Glucose, mg/dL	140.5 (72.7)	174.6 (64.4)	0.129
Creatinine, mg/dL	1.0 (0.37)	1.5 (1.2)	0.174
LDL, mg/dL	119.9 (42.9)	132.8 (53.6)	0.462
Hemoglobin, g/dL	13.7 (1.5)	11.7 (1.0)	<0.001
LVEF, %	49.0 (10.8)	38.3 (12.4)	0.014
Medications			
ASA, %	90	50	0.873
Clopidogrel, %	87	42	0.341
Ticagrelor, %	4	8	0.292
Varfarin, %	4	0	0.760
NOAC, %	2	0	0.873
Beta–blocker, %	68	42	0.504
ACEI/ARB, %	52	17	0.259
Statin, %	61	25	0.341
Diuretics, %	15	0	0.506

DM: diabetes mellitus; HT: hypertension; LDL: low–density lipoprotein; LVEF: left ventricular ejection fraction; ASA: Acetylsalicylic acid; NOAC: non–VKA oral anticoagulants; ACEI: angiotensin–converting enzyme inhibitor; ARB: angiotensin receptor blocker

Table 2. Procedural characteristics of patients according to the mortality status

Variables	Mortality (–) n=93	Mortality (+) n=12	p
Total graft number	2.5 (0,6)	3.0 (0.7)	0.091
Treated graft age, years	10.2 (5.8)	12.9 (5.2)	0.120
Treated graft localization			
Diagonal	73	8	
Circumflex/OM	9	4	0.099
Right coronary/PDA	1	0	
Thrombus presence, yes	5	1	0.570
Stent diameter, mm	2.9 (0.4)	3.0 (0.5)	0.631
Stent length, mm	20.5 (7.2)	25.2 (8.0)	0.089
Stent number	1.5 (0.8)	1.8 (0.9)	0.320
Drug–eluting stent, yes	77	10	0.591
Gp IIb/IIIa inhibitors, yes	8	1	0.683
PCI indication			
Stable angina, %	48	67	
ACS,%	52	33	0.359

Gp: glycoprotein; OM: obtuse marginal branch of circumflex coronary artery; PDA: posterior descending artery; PCI: percutaneous coronary intervention; ACS: acute coronary syndrome

Table 3. Predictors of mortality after saphenous graft interventions

Variables	Univariate		Multivariate	p
Age, years	1.022 (0.934–1.119)	.638		
Male, yes	1.255 (0.151–10.440)	0.834		
HT, yes	1.919 (0.385–9.572)	0.426		
DM, yes	1.480 (0.368–5.947)	0.581		
Smoking, yes	0.953 (0.192–4.725)	0.953		
Glucose, mg/dL	1.003 (0.995–1.011)	0.462		
Creatinine, mg/dL	1.827 (1.130–2.956)	0.014	1.503 (0.788–2.869)	0.216
LDL, mg/dL	1.007 (0.992–1.022)	0.362		
Hemoglobin, g/dL	0.568 (0.373–0.863)	0.008	0.519 (0.324–0.834)	0.007
LVEF, %	0.913 (0.837–0.996)	0.041	0.958 (0.904–1.016)	0.151
Total graft number	3.009 (0.940–9.631)	0.064		
Treated graft age, years	1.049 (0.932–1.182)	0.428		
Treated graft localization		0.056		
Diagonal, yes	4.106 (0.964–17.493)		3.054 (0.622–14.992)	
Other, yes	Ref.		Ref.	0.169
Thrombus, yes	2.425 (0.292–20.151)	0.412		
Stent diameter, mm	1.434 (0.349–5.892)	0.617		
Stent length, mm	1.074 (0.987–1.167)	0.096	1.068 (0.980–1.165)	0.134
Stent number, mm	1.422 (0.721–2.804)	0.309		
Drug-eluting stent, yes	0.676 (0.135–3.376)	0.633		
Gp IIb/IIIa inhibitors, yes	1.425 (0.175–11.631)	0.741		
PCI indication	1.287(0.844–1.964)	0.241		

DM: diabetes mellitus; Gp: glycoprotein; HT: hypertension; LDL: low-density lipoprotein; LVEF: left ventricular ejection fraction; OM: obtuse marginal branch of circumflex coronary artery; PCI: percutaneous coronary intervention; PDA: posterior descending artery

Figure 1. ROC curve analysis according to hemoglobin cut-off 12.55

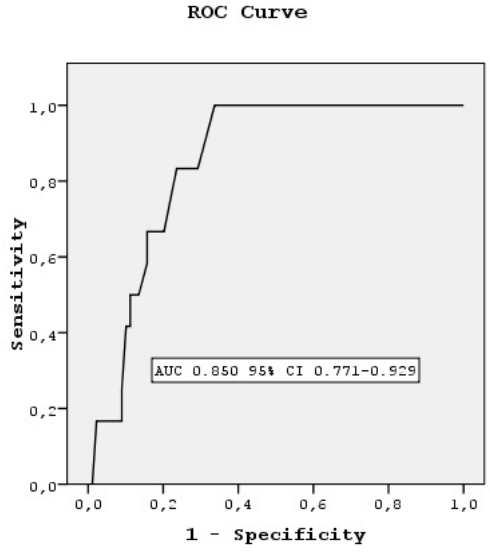
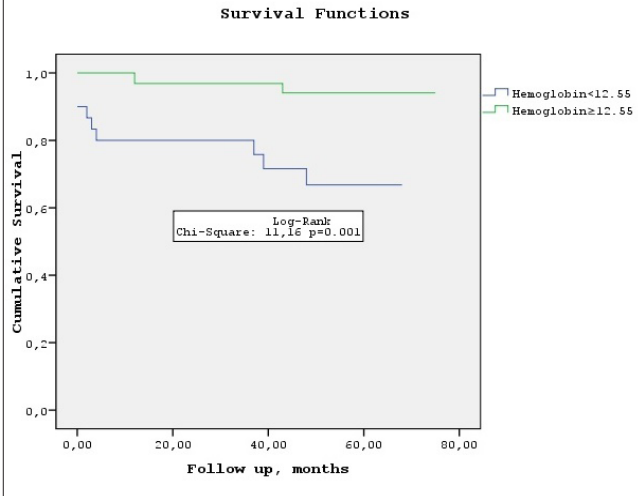


Figure 2. Kaplan-Meier Survival curves according to hemoglobin cut-off 12.55



all-cause mortality in patients undergoing SVG PCI. There was a progressive increase in all-cause mortality as the baseline hemoglobin value decreased below 13.25 g/dL.

Although CABG has been shown to increase survival, 25% of the vein grafts were occluded after 5 years and 50% of them were occluded after 10 years (7). Redo CABG is associated with greater morbidity and mortality but is not always associated with a satisfactory relief of symptoms (8). Therefore, a large number of patients are currently treated with PCI. In addition, compared with PCI of the native vessels, SVG PCI has been associated with higher rates of in-stent restenosis, target vessel revascularization, myocardial infarction, and death. Poor outcomes are associated with the nature of SVG atherosclerosis, which is characterized by diffuse, concentric, and friable plaques with absent or thin fibrous caps and high thrombotic burden. The survival rates of SVG PCI are poor, and clinical factors associated with long-term mortality remain elusive (9-10).

Anemia is a common comorbidity that adversely affects the cardiovascular system. It is associated with various types of cardiovascular diseases, such as heart failure or ACS. Anemia results in a significant reduction in oxygen supply to the myocardium and triggers myocardial ischemia in the presence of a limited coronary reserve (2).

The prognostic significance of low baseline hemoglobin levels has been reported in a variety of demographic groups and clinical settings including various cardiovascular diseases. Sabatine et al. (11) examined the baseline hemoglobin levels of about 40,000 patients with ACS and reported that cardiovascular mortality increased as hemoglobin levels decreased below 14 g/dL in patients with ST-elevation myocardial infarction and a higher mortality rate was observed in patients with ACS with hemoglobin levels below 11 g/dL. Arant et al. (12) found that hemoglobin was an independent predictor of adverse cardiovascular outcomes, with a 20% increased risk for each 1 g/dL decrement in hemoglobin level in women presenting with ischemic-type symptoms. In a study conducted by Brener et al. (13) on 16.000 patients, it was reported that baseline hemoglobin and anemia were independent predictors of major bleeding and death. The association between hemoglobin levels and mortality rate has also been shown across a broad range of indications for PCI (5, 6, 14). Kitai et al. (15) demonstrated that in patients who underwent elective PCI, even mild anemia was associated with significantly higher risk for major adverse cardiac events. Lee et al. (16) and Poludasu et al. (6) investigated the prognostic impact of mild anemia in patients undergoing PCI. Stahli et al. (17) reported that anemia was associated with increased all-cause mortality in patients undergoing chronic total occlusion PCI. Multiple mechanisms have been proposed for higher mortality in patients with anemia undergoing PCI. Increased myocardial oxygen demand (18), increased catecholamine levels, and worsening of myocardial ischemia in the presence of a limited coronary reserve (2) are considered major possible mechanisms. Procedure-related blood loss, higher degrees of inflammation, and comorbidities associated with anemia are the other possible explanations for increased mortality rate.

In our study, we assessed the effect of the baseline hemoglobin levels on all-cause mortality in patients undergoing SVG PCI. Similar to PCI of the native vessel, the baseline hemoglobin levels were found to be associated with mortality. To our knowledge, our study is the first to show this association. In a study conducted by Nikolsy et al. (19) including patients who underwent SVG PCI, the impact of anemia on outcomes of patients undergoing PCI was investigated, but no subgroup analysis was performed to assess the relation between anemia and mortality. Clinical factors associated with long-term mortality after SVG PCI have been reported in very few studies (10, 20); however, in these studies, the effect of hemoglobin levels has not been assessed or demonstrated.

Patients who underwent CABG have more extensive disease. Therefore, procedural blood loss and ischemia induced by balloon inflation during PCI may be less tolerated in the presence of anemia. Additionally, these patients have higher levels of markers of inflammation associated with thrombotic events. These mechanisms may contribute to the poor outcomes of anemic patients undergoing SVG PCI.

Our study has several limitations. This was a retrospective single-center study with a relatively small sample size. We did not collect information regarding the cause or the predisposing factors of anemia. Moreover, we did not record hemoglobin levels at discharge or changes in hemoglobin levels during hospitalization, which were reportedly associated with mortality. Hemoglobin levels at admission may fluctuate according to hydration status. Furthermore, we could not analyze the influence of dual antiplatelet therapy duration after SVG PCI.

CONCLUSION

The baseline hemoglobin levels may predict all-cause mortality in patients undergoing SVG PCI. In the future, prospectively designed trials should evaluate the value of correcting anemia before the procedure.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of TOBB ETÜ Hospital (20.06.2018/006).

Informed Consent: Due to the retrospective design of the study, informed consent was not taken.

Author Contributions: Concept – B.B.; Design - B.B., M.T.; Supervision - E.D., B.A.; Data Collection and/or Processing - S.Ç., M.Ö.; Analysis and/or Interpretation - M.S.Ç.; Literature Search - B.A.; Writing - M.T.; Critical Reviews - E.D.
Peer-review: Externally peer-reviewed.

Conflict of Interest: The **a**uthors have no conflicts of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

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