Evaluation of the Relationship Between Hemoglobin Levels and Thrombolysis in Myocardial Infarction Risk Score in Patients with Non-ST Elevation Acute Coronary Syndrome

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ABSTRACT

Introduction: The relationship between hemoglobin (Hb) levels at admission and the thrombolysis in myocardial infarction (TIMI) risk score in patients with non-ST elevation acute coronary syndrome (NSTE-ACS) was investigated.

Patients and Methods: In total, 286 NSTE-ACS patients were included in the study. Hb levels and biochemical parameters were measured at admission. The patients were grouped into the following three groups according to the TIMI risk score: low-intermediate-, and high-risk groups.

Results: Hb levels (in g/dL) at admission in low-, intermediate-, and high-risk groups were 13.5 ± 1.9, 12.5 ± 1.9, and 11.3 ± 1.9, respectively ($p < 0.001$). We found a negative moderate correlation between Hb levels and TIMI risk scores ($r= -0.408$, $p < 0.001$). In univariate regression analysis, it was found that with the increase in the TIMI risk score, Hb levels at admission were significantly reduced (estimate= -0.406; $p< 0.001$; 95% confidence interval; -0.521 to -0.290).

Conclusion: We found that as the TIMI risk score of patients admitted to hospital presenting with NSTE-ACS increased, their Hb levels at admission correspondingly decreased. Thus, the simple and commonly measured Hb level can be a useful parameter in stratifying the risks of patients presenting with NSTE-ACS during admission.

Key Words: Myocardial infarction; hemoglobins; acute coronary syndrome

ST Yükselmesiz Akut Koroner Sendrom Hastalarında TIMI Risk Skoru ile Hemoglobin Değeri Arasındaki İlişkinin Değerlendirilmesi

ÖZET

Giriş: ST yükselmesiz akut koroner sendrom hastalarının geliş hemoglobin seviyesi ile TIMI risk skoru arasındaki ilişki araştırıldı.

Hastalar ve Yöntem: ST yükselmesiz akut koroner sendromlu 286 hasta çalışmaya dahil edildi. Tüm hastaların geliş anında hemoglobin ve biyokimyasal parametreleri çalışıldı. Hastalar TIMI risk skoruna göre düşük, orta ve yüksek risk olarak 3 gruba ayrıldı.

Bulgular: Geliş hemoglobin seviyesi (g/dL) düşük, orta ve yüksek TIMI risk grubunda sırasıyla (13.5 ± 1.9, 12.5 ± 1.9, 11.3 ± 1.9, $p< 0.001$) olarak saptandı. Hemoglobin seviyesi ve TIMI risk skoru arasında orta düzeyde negatif korelasyon bulundu ($r: -0.408$, $p< 0.001$). Tek değişkenli regresyon analizinde TIMI risk skoru artışı ile geliş hemoglobin seviyelerinin önemli derecede düşük olduğu saptandı (Estimate; -0.406, $p< 0.001$, %95 GA[-0.521-(-0.290)].

Sonuç: ST yükselmesiz akut koroner sendrom ile hastaneye yatırılan hastaların risk skoru attıkça geliş hemoglobin seviyelerinin bağlantılı olarak düşük olduğu tespit edildi. Basit ve yaygın bir test olarak kullanılan hemoglobin seviyesi, ST yükselmesiz akut koroner sendrom hastalarının geliş anındaki risk durumunu belirlemede kullanılabilir.

Anahtar Kelimeler: Miyokart infarktüsü; hemoglobinler; akut koroner sendrom

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INTRODUCTION

Non-ST elevation acute coronary syndrome (NSTE-ACS), the most common form of ACS, is a major cause of hospitalization[1]. Risk stratification is recommended for the management of NSTE-ACS treatment. In addition to clinical findings, a combination of various laboratory parameters with risk factors is associated with better risk prediction[2,3].

Anemia, an independent predictor of mortality after ACS, is seen in approximately 15% of patients presenting with ACS, and the incidence goes up to 43% in elderly patients[4,5]. The ACUITY trial demonstrated that the presence of anemia on admission in patients with NSTE-ACS is associated with both short and long-term adverse events and increased 1-year mortality[6].

A number of risk scores are used for risk stratification and treatment planning in ACS (e.g., TIMI, PURSUIT, FRISC, and GUSTO). The thrombolysis in myocardial infarction (TIMI) risk score is among the most commonly used risk score in ACS, but anemia is not included in this score[7,8].

In the present study, we investigated the relationship between hemoglobin (Hb) levels and TIMI risk scores in patients with NSTE-ACS.

PATIENTS and METHODS

Patient Inclusion and Exclusion

A total of 286 patients with NSTE-ACS were enrolled between September 2009 and October 2010 in this study.

The inclusion criteria included the presence of ischemic chest pain and/or typical electrocardiography (ECG) changes (including new-onset ST-segment depression or T-wave inversion in two contiguous leads) and/or elevated troponin T levels (> 0.1 ng/dL). The exclusion criteria included patients with ST elevation, new onset left bundle branch block, previous known bleeding diathesis and anemia, malignancy, infection, and secondary conditions precipitating angina (e.g., fever and thyrotoxicosis). Clinical, demographic, laboratory test, and angiographic results were recorded. An automated analyzer was used for hematologic parameters. Age, gender, coronary risk factors, ongoing medical therapy, and history of coronary artery disease and heart failure (HF) were recorded. Two-dimensional echocardiogram (2D Echo) with Doppler examination was performed according to the guidelines of the American Society of Echocardiography. All patients received standard therapy, including acetylsalicylic acid (ASA), clopidogrel, low-molecular-weight heparin, glycoprotein IIb/IIIa inhibitors, angiotensin-converting enzyme inhibitor (ACEI), beta-blockers, and statins, as recommended by the current guidelines. Patients underwent coronary angiography and percutaneous coronary intervention (PCI) according to the decision of the treating physician. Angiographic data were recorded. The study protocol was approved by the local ethics committee, and written informed consent was obtained from all patients.

TIMI Risk Score

The TIMI risk score was calculated from presenting laboratory and ECG findings. Seven parameters, namely age more than 65 years, presence of more than three coronary artery disease (CAD) risk factors, known CAD (≥ 50 stenosis), aspirin use in the past 7 days, ST deviation ≥ 0.5 mm, at least two angina episodes in the last 24 h, and elevated cardiac markers were used for calculating the TIMI risk score. Because all seven variables have the same magnitude, the result for each patient is the simple arithmetic sum of the number of variables present[8]. TIMI 1 was the low-risk group with scores of 0-2, TIMI 2 was the intermediate-risk group with scores of 3-4, and TIMI 3 was the high-risk group with scores of 5-7.

Statistical Analysis

Mean ± standard deviation and median and range were used for expressing continuous variables, and percentage was used for categorical variables. For testing of normally distributed continuous variables, one way analysis of variance (ANOVA) (Tukey's test for post hoc analysis) was used. Normal distribution was tested with one-sample Kolmogorov–Smirnov test. Kruskal-Wallis test was performed for variables that did not show normal distribution. Pearson's chi-square test was used for testing categorical variables. Pearson's correlation test was used for determining correlation between normally distributed variables. Univariate ordinal regression analysis was used for testing the relationship between TIMI risk scores and Hb levels. A p value of < 0.05 was considered significant for all tests. The Statistical Package for the Social Sciences (SPSS version 11.0, SPSS Inc., Chicago, IL, USA) was used for the analyses.

RESULTS

Demographic characteristics of the patients according to TIMI risk scores are shown in Table 1. Age (55 ± 9.68 ± 10.73 ± 8; $p< 0.001$), hypertension (68%, 86%, and 87%, respectively; $p= 0.001$), and diabetes (15%, 31%, and 62%, respectively; $p< 0.001$) were significantly different between the groups. Drug use for each groups were: statin (9%, 35%, and 55%, respectively; $p< 0.001$), beta-blockers (23%, 55%, and 73%, respectively; $p< 0.001$), ACEI (34%, 63% and 78%, respectively; $p< 0.001$), ASA (20%, 44%, and 78%, respectively; $p< 0.001$), and diuretics (1%, 10%, and 10%, respectively; $p= 0.02$). The prevalence of previous revascularization, myocardial infarction (MI), and HF for each TIMI groups were statistically significant: HF (8%, 18% and 30%, respectively; $p= 0.001$), history of MI (8%, 18% and 37%, respectively; $p< 0.001$), previous PCI (4%, 17% and 39%, respectively; $p< 0.001$), and previous coronary bypass operation (0%, 12% and 25%, respectively; $p< 0.001$). The

Table 1. Demographic characteristic of the patients according to the TIMI risk scores

	TIMI I n= 91	TIMI II n= 106	TIMI III n= 89	p
Age	55 ± 9	68 ± 10	73 ± 8	< 0.001
Sex Male (%)	70	62	59	0.28
Hypertension (%)	68	86	87	0.01
Diabetes (%)	15	31	62	< 0.001
Smoking (%)	35	24	23	0.14
Statin (%)	9	35	55	< 0.001
Beta Blocker (%)	23	55	73	< 0.001
ACEI (%)	34	63	78	< 0.001
ASA (%)	20	44	78	< 0.001
CCB (%)	20	17	14	0.54
Diuretic (%)	1	10	10	0.02
EF (%)	59 (40-69)	55 (25-69)	49 (20-65)	< 0.001
Cr (mg/dL)	0.9 (0.6-2.4)	1.05 (0.4-7.4)	1.4 (0.6-7)	< 0.001
BNP (pg/mL)	76 (11-4263)	162 (10-5028)	489 (15-5000)	< 0.001
WBC (103/μL)	8.2 ± 2.2	8.8 ± 2.5	9 ± 0.32	0.009
Hb (g/dL)	13.5 ± 1.9	12.5 ± 1.9	11.3 ± 1.9	< 0.001
Htc (%)	39 ± 5.3	36 ± 5.3	33 ± 6	< 0.001
MPV (FL)	8.5 ± 1.3	8.5 ± 1.17	8.7 ± 1.6	0.62
RDW (%)	13.6 (122.1-19.5)	14 (7.1-21.9)	14.4 (12.4-22.3)	0.001
Plt (103/μL)	236 (35-416)	240 (79-484)	224 (64-887)	0.51
CHF (%)	8	18	30	0.001
MI (%)	8	18	37	< 0.001
PTCA (%)	4	17	39	< 0.001
CABG (%)	0	12	25	< 0.001

ACEI: Angiotensin-converting enzyme inhibitor; ASA: Acetyl salicylic acid; BNP: Brain natriuretic peptide; CABG: Coronary artery bypass graft; CCB: Calcium channel blocker, CHF: Congestive heart failure; Cr: Creatinin; EF: Ejection fraction; Hb: Hemoglobin; Htc: Hematocrit, MI: Myocardial infarction; MPV: Mean platelet volume; Plt: Platelet count; PTCA: Percutaneous transluminal coronary angioplasty; RDW: Red blood cell distribution width; WBC: White blood cell count.

Table 2. With the increase in TIMI risk scores, the Hb levels were found to significantly decrease

	Estimate	Standard error	p	95% CI
Hb	-0.406	0.59	< 0.001	-0.521 to -0.290

significantly different parameters were ejection fraction (median: 59, 55, and 49, respectively; p< 0.001), creatinine (median: 0.9, 1.05, and 1.4, respectively; p< 0.001), B-type natriuretic peptide (BNP) (median: 76, 162, and 489, respectively; p< 0.001), Hb (13.5 ± 1.9, 12.5 ± 1.9 and 11.3 ± 1.9, respectively; p< 0.001), hematocrit (Htc) (39 ± 5.3, 36 ± 5.3 and 33 ± 6, respectively; p< 0.001), white blood cells (WBCs) (8.2 ± 2.2, 8.8 ± 2.5 and 9 ± 0.32, respectively; p= 0.009), and red cell distribution width (RDW) (median: 13.6, 14, and 14.4, respectively; p= 0.001). When the correlation between Hb levels and TIMI risk scores was tested, a negative moderate correlation was found (r= -0.408, p< 0.001) (Figure 1). In univariate regression analysis, Hb values and TIMI risk scores were analyzed. Through post hoc analysis by Tukey's test, pairwise comparisons showed significant differences for Hb levels [TIMI 1 vs. TIMI 2 (p= 0.001), TIMI 1 vs. TIMI 3 (p< 0.001), and TIMI 2 vs. TIMI 3 (p< 0.001)]. With the increase in the TIMI risk score, Hb levels were found to significantly decrease (Estimate: -0.406; p< 0.001; 95% confidence interval, -0.521 to -0.290) (Table 2).

DISCUSSION

Risk stratification in ACS plays an important role in selecting an appropriate management strategy. Clinical status on presentation, ECG, and laboratory values are the basic parameters used in calculating risk scores. Although anemia is an independent predictor of risk in ACS, frequently used risk scores such as TIMI and The Global Registry of Acute Coronary Events (GRACE) do not include Hb level as one of the parameters[5]. Sabatine et al studied 40.000 patients from multiple trials and concluded that patients with NSTC-ACS and baseline Hb levels < 11 g/dL had an increased risk of recurrent ischemia and death[9]. The Controlled Abciximab and Device Investigation to Lower Late Angioplasty Complications

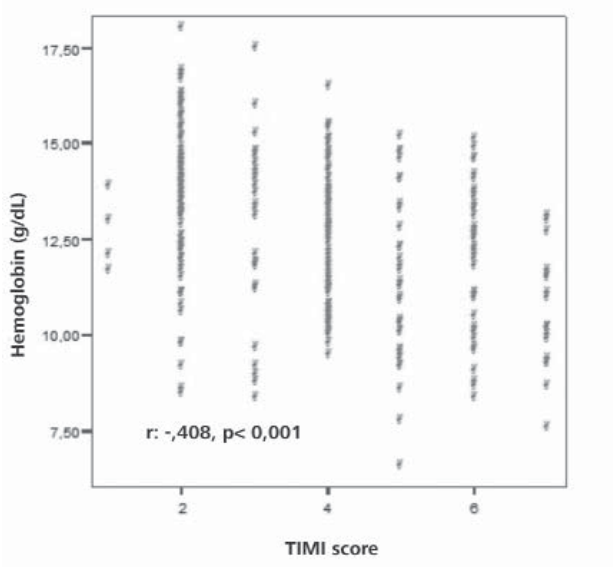

Figure 1. When the correlation between Hb levels and TIMI risk scores was tested, a negative moderate correlation was found (r= -0.408, p< 0.001).

(CADILLAC) trial showed that anemia increased in-hospital mortality by four times and that even after 1 year, the risk remained more than two times higher[10]. Anemia can increase the morbidity and mortality of ACS by two mechanisms: by decreasing oxygen supply to the myocardium and increasing oxygen consumption by elevating the adrenergic discharge[11]. Moreover, anemia stimulates cytokine and erythropoietin release, and thus, by raised inflammatory response, increases endothelial dysfunction, accelerates atherosclerotic process, disturbs the stabilization of atherosclerotic plaque, and triggers the procoagulant process[12]. In the CADILLAC trial, anemia was found to be related with increased age, chronic renal failure, and HF. In the REPLACE-2 trial, anemic patients were found to be older, had lower body weight and higher creatinine clearance, and were more often females[13]. Similar to other studies in the literature, the occurrence of diabetes, hypertension, and renal failure was found to increase with the increase in the risk score in elderly patients. This can explain the high prevalence of anemia in patients with high TIMI risk scores. It is known that anemia is an independent predictor of mortality in patients with HF, and anemic patients present with higher Killip class and cardiogenic shock more often[14,15]. In a previous study, the use of ASA, beta-blockers, and statins was found to be lower in anemic patients, which may contribute to the higher ischemic incidence in these patients[16]. In addition, the use of some drugs such as ASA can increase minor bleeding and thus, the rate of anemia. It is also known that ACEI could accelerate the metabolism of erythropoietin[17]. In our study, we observed that the use of ASA and ACEI was more common in patients with high TIMI risk scores. They may have been partly responsible for the increased rate of anemia. Although the exact mechanism is unclear, bleeding is more frequent in anemic patients[18,19]. Baseline Hb values are predictors of bleeding risk[20]. Anemic patients with ACS also tend to bleed more. The treatment of an anemic patient with bleeding is blood transfusion, which is an additional risk in this patient population[21]. In a meta-analysis by Rao et al, which included 24111 ACS patients from three studies, the 30 day mortality, rate of MI, and composite death and MI in patients with and without transfusion were 8% vs 3.08% (p= 0.001), 25.16% vs 8.16% (p= 0.001) and 29.24% vs 10.02% (p= 0.001), respectively[22]. Wu et al. showed that blood transfusion in elderly acute MI patients decreased mortality when Htc was < 33% but increased mortality when hematocrit was > 36%[23]. Observation studies showed that transfusion should be avoided if Htc is ≥ 25%[24].

Prothrombotic effect and proinflammatory cytokine release related to blood transfusion are also associated with additional risk. Infection, hemolytic reaction, and volume overload are the other risk-increasing factors.

In our study, we showed that the TIMI risk score is increased in patients with low Hb values. This may be caused by increased age, more frequent renal failure, HF, diabetes, hypertension, and the wider use of ASA and ACEI in patients with increased TIMI risk scores. Hb is not included in the calculation of commonly used risk scores for NSTE-ACS. In the current study, we found that Hb could be an independent predictor of risk in NSTE-ACS patients.

CONCLUSION

In our study, we found a negative moderate correlation between TIMI risk scores and Hb levels in patients with NSTE-ACS. Regression analysis also showed that Hb levels significantly decreased with increasing TIMI risk scores. Being a simple and commonly used laboratory parameter, Hb values could be used as a risk predictor on patient presentation; however, further studies are needed for its use in prediction of short and long-term mortality.

Study Limitations

The present study has several limitations. First, it was a single-center study. Second, the patient population was relatively small, and further studies with a large sample size are required.

CONFLICT of INTEREST

The authors declared no conflict of interest during the stage of drafting and publishing this article.

AUTORSHIP CONTRIBUTIONS

Concept/Design: ÇG, EG, AME
Analysis/Interpretation: ÇG, GBG, AME, NK
Data acquisition: ÇG, AE, EG
Writing: ÇG, ÖE,
Critical revision: AME, HZA, HMG, OK
Final approval: All of authors

REFERENCES

1. Rosamond W, Flegal K, Furie K, Go A, Greenlund K, Haase N, et al. American Heart Association Statistics Committee and Stroke Statistics Subcommittee. American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Heart disease and stroke statistics–2008 update: a report from the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Circulation 2008;117:e25-e146.
2. Tello-Montoliu A, Marín F, Roldán V, Mainar L, López MT, Sogorb F, et al. Multimarker risk stratification approach to non-ST elevation acute coronary syndrome: implications of troponin T, CRP, NT pro-BNP and fibrin D-dimer levels. J Intern Med 2007;262:651-8.
3. Guler E, Gecmen C, Guler GB, Karaca O, Agus HZ, Gunes HM, et al. Adding lipoprotein (a) levels to the GRACE score to predict prognosis in patients with non-ST elevation acute coronary syndrome. Kardiol Pol 2013;71:695-701.
4. Alexander KP, Chen AY, Wang TY, Rao SV, Newby LK, LaPointe NM, et al. Transfusion practice and outcomes in non–ST-segment elevation acute coronary syndromes. Am Heart J 2008;155:1047-53.
5. Lipsic E, Van Der Horst IC, Voors AA, van der Meer P, Nijsten MW, van Gilst WH, et al. Hemoglobin levels and 30 day mortality in patients after myocardial infarction. Int J Cardiol 2005;100:289-92.
6. Kunadian V, Mehran R, Lincoff AM, Feit F, Manoukian SV, Hamon M, et al. Cox DA. Effect of anemia on frequency of short- and long-term clinical events in acute coronary syndromes (from the Acute Catheterization and Urgent Intervention Triage Strategy Trial). Am J Cardiol 2014;114:1823-9.
7. Fox KA, Dabbous OH, Goldberg RJ, Pieper KS, Eagle KA, Van de Werf F, et al. Prediction of risk of death and myocardial infarction in the six months after presentation with acute coronary syndrome: prospective multinational observational study (GRACE). BMJ 2006;333:109.
8. Antman EM, Cohen M, Bernink PJ, McCabe CH, Horacek T, Papuchis G, et al. The TIMI risk score for unstable angina/non-ST elevation MI: a method for prognostication and therapeutic decision making. JAMA 2000;284:835-42.
9. Sabatine MS, Morrow DA, Giugliano RP, Burton PB, Murphy SA, McCabe CH, et al. Association of hemoglobin levels with clinical outcomes in acute coronary syndromes. Circulation 2005;111:2042-9.
10. Nikolsky E, Aymong ED, Halkin A, Grines CL, Cox DA, Garcia E, et al. Impact of anemia in patients with acute myocardial infarction undergoing primary percutaneous coronary intervention: analysis from the Controlled Abciximab and Device Investigation to Lower Late Angioplasty Complications (CADILLAC) trial. J Am Coll Cardiol 2004;44:547-53.
11. Levy PS, Quigley RL, Gould SA. Acute dilutional anemia and critical left anterior descending coronary artery stenois impairs end organ oxygen delivery. J Trauma 1996;41:416-23.
12. Mazzone A, Cusa C, Mazzucchelli I, Vezzoli M, Ottini E, Pacifici R, et al. Increased production of inflammatory cytokines in patients with silent miyocardial ischemia. J Am Coll Cardiol 2001;38:1895-901.
13. Lincoff AM, Bittl JA, Harrington RA, Feit F, Kleiman NS, Jackman JD, et al. Bivalirudin and provisional glycoprotein IIb/IIIa blockade compared with heparin and planned glycoprotein IIb/IIIa blockade during percutaneous coronary intervention: REPLACE-2 randomized trial. JAMA 2003;289:853-63.
14. Sharma R, Francis DP, Pitt B, Poole-Wilson PA, Coats AJ, Anker SD. Haemoglobin predicts survival in patients with chronic heart failure: a substudy of the ELITE II trial. Eur Heart J 2004;25:1021-8.
15. Dauerman HL, Goldberg RJ, White K, Gore JM, Sadiq I, Gurfinkel E, et al. GRACE Investigators. Revascularization, stenting and outcomes of patients with acute myocardial infarction complicated by cardiogenic shock. Am J Cardiol 2002;90:838-42.
16. Breddin K, Loew D, Lechner K, Oberla K, Walter E. The German-Austrian aspirin trial: a comparison of acetylsalicylic acid, placebo and phenprocoumon in secondary prevention of myocardial infarction. On behalf of the German-Austrian Study Group. Circulation 1980;62:V63-72.
17. López-Sendón J, Swedberg K, McMurray J, Tamargo J, Maggioni AP, Dargie H, et al. Expert consensus document on angiotensin converting enzyme inhibitors in cardiovascular disease - The Task Force on ACE inhibitors of the European Society of Cardiology. Eur Heart J 2004;25:1454-70.
18. Spencer FA, Moscucci M, Granger CB, Gore JM, Goldberg RJ, Steg PG, et al. GRACE Investigators. Does comorbidity account for the excess mortality in patients with major bleeding in acute myocardial infarction? Circulation 2007;116:2793-801.
19. Stone GW, Witzenbichler B, Guagliumi G, Peruga JZ, Brodie BR, Dudek D, et al. HORIZONS-AMI Trial Investigators. Bivalirudin during primary PCI in acute myocardial infarction. N Engl J Med 2008;358:2218-30.
20. Bassand JP, Afzal R, Eikelboom J, Wallentin L, Peters R, Budaj A, et al. Relationship between baseline haemoglobin and major bleeding complications in acute coronary syndromes. Eur Heart J 2010;31:50-5.
21. McKechnie RS, Smith D, Montoye C, Kline-Rogers E, O'Donnell MJ, DeFranco AC, et al. Blue Cross Blue Shield of Michigan Cardiovascular Consortium (BMC2). Prognostic implication of anemia on in-hospital outcomes after percutaneous coronary intervention. Circulation 2004;110:271-7.
22. Rao SV, Jollis JG, Harrington RA, Granger CB, Newby LK, Armstrong PW, et al. Relationship of blood transfusion and clinical outcomes in patients with acute coronary syndromes. JAMA 2004;292:1555-62.
23. Wu WC, Rathore SS, Wang Y, Radford MJ, Krumholz HM. Blood transfusion in elderly patients with acute myocardial infarction. N Engl J Med 2001;345:1230-6.
24. Alexander KP, Chen AY, Wang TY, Rao SV, Newby LK, LaPointe NM, et al. Transfusion practice and outcomes in non-ST-segment elevation acute coronary syndromes. Am Heart J 2008;155:1047-53.