Cerrahpaşa Med J 2022; 46(3): 230-237 ORIGINAL ARTICLE

The Relationship of Hemoglobin Drop with In-Hospital Mortality and Long-Term Morbidity and Mortality in Patients with Acute Coronary Syndrome

Fuat Polat[1], Nafia İnan Kardelen Ohtaroğlu Tokdil[3], Burçak Kılıçkıran Avcı[2], Bilgehan Karadağ[2], Zeki Öngen[2]

[1]Department of Cardiology, Şırnak State Hospital, Şırnak, Turkey
[2]Department of Cardiology, İstanbul University-Cerrahpaşa, Cerrahpaşa School of Medicine, İstanbul, Turkey
[3]Department of Cardiology, Kanuni Sultan Süleyman Training and Research Hospital, İstanbul, Turkey

Cite this article as: Polat F, İnan Kardelen Ohtaroğlu Tokdil N, Kılıçkıran Avcı B, Karadağ B, Öngen Z. The relationship of hemoglobin drop with in-hospital mortality and long-term morbidity and mortality in patients with acute coronary syndrome. *Cerrahpaşa Med J.* 2022;46(3):230-237.

Abstract

Objective: The use of antithrombotic and anticoagulant drugs and invasive strategies increase the risk of bleeding in patients with acute coronary syndrome. It is not known to what extent the change in hemoglobin level determines the clinical outcome.

Methods: Patients with the diagnosis of ST-elevation myocardial infarction, non-ST-elevation myocardial infarction, or unstable angina pectoris, who underwent coronary angiography, detected acute lesion, and followed in the coronary care unit were included in the study. The primary endpoint of the study was the composite outcome of in-hospital mortality, cardiac mortality, all-cause mortality, revascularization, and stroke.

Results: The median follow-up period of a total of 208 patients was 23 ± 9 (1-34) months, mean age was 58.9 ± 12.6 years, 74.5% (n = 155) of the patients were male, and 74.5% (n = 155) were ST-elevation myocardial infarction. The mean difference between the hemoglobin before the procedure and the lowest hemoglobin until hospital discharge was 1.38 ± 1.37 mg/dL, and the highest difference was 7.3 mg/dL. No statistically significant correlation was found between the drop in hemoglobin and the composite endpoint. A drop of 3.25 mg/dL in hemoglobin affected the composite endpoint with a sensitivity of 11.42% and a specificity of 89.86% (likelihood ratio: 1.2).

Conclusion: No significant relationship was found between the drop in hemoglobin and the composite outcome of in-hospital mortality, cardiac mortality, all-cause mortality, revascularization, and stroke. A low correlation was found between at least 3.25 mg/dL hemoglobin drop and composite outcome.

Keywords: Acute coronary syndrome, hemoglobin drop, mortality

Introduction

Acute coronary syndrome (ACS) patients are treated with intensive antiplatelet, anticoagulant, and in some cases, fibrinolytic therapy, at the time of first admission, during percutaneous intervention and during follow-up. Drugs are initially administered in a high-dose protocol called a loading dose. While intensive medical treatment reduces ischemic events, it increases complications related to bleeding.[1] Hemoglobin is the main component of red blood cells and acts as a carrier for oxygen and carbon dioxide in the blood. The 3 most common main causes of anemia are blood loss, decreased red blood cell production, and high red blood cell destruction. Anemia acts as a cardiovascular disease equivalent in high-risk patients.[2] Approximately half of adults with chronic diseases, including cardiovascular diseases, have anemia.[3] In patients undergoing coronary intervention, drops in hemoglobin levels can be observed in the coronary intensive care unit and service follow-up. The most common complication of ACS interventions is bleeding related to the access site.[4] Additional comorbidities (diabetes mellitus, hypertension, advanced age, chronic kidney failure, etc.) are other causes that increase bleeding.[5] While minor hemorrhages in ACS patients may cause myocardial damage due to decreased coronary blood flow and demand–supply imbalance, major hemorrhages cause an increase in mortality, especially in the first 30 days, in these patients.[6,7] Previously, bleeding severity was classified by bleeding scores such as the Thrombolysis in Myocardial Infarction (TIMI) and Bleeding Academic Research Consortium (BARC) bleeding scores in ACS, and their effects on cardiovascular endpoints were investigated.[8] The aim of this study was to determine the effect of hemoglobin drop on the composite endpoint of in-hospital mortality, cardiac death, all-cause death, need for revascularization, and stroke. We also examined the least drop in hemoglobin that affected the composite endpoint.

Received: April 8, 2022 **Accepted:** May 10, 2022 **Publication Date:** July 15, 2022
Corresponding author: Fuat Polat, Department of Cardiology, İstanbul University-Cerrahpaşa, Cerrahpaşa School of Medicine, İstanbul, Turkey
e-mail: drfuatpolat@gmail.com
DOI: 10.5152/cjm.2022.22024

Methods

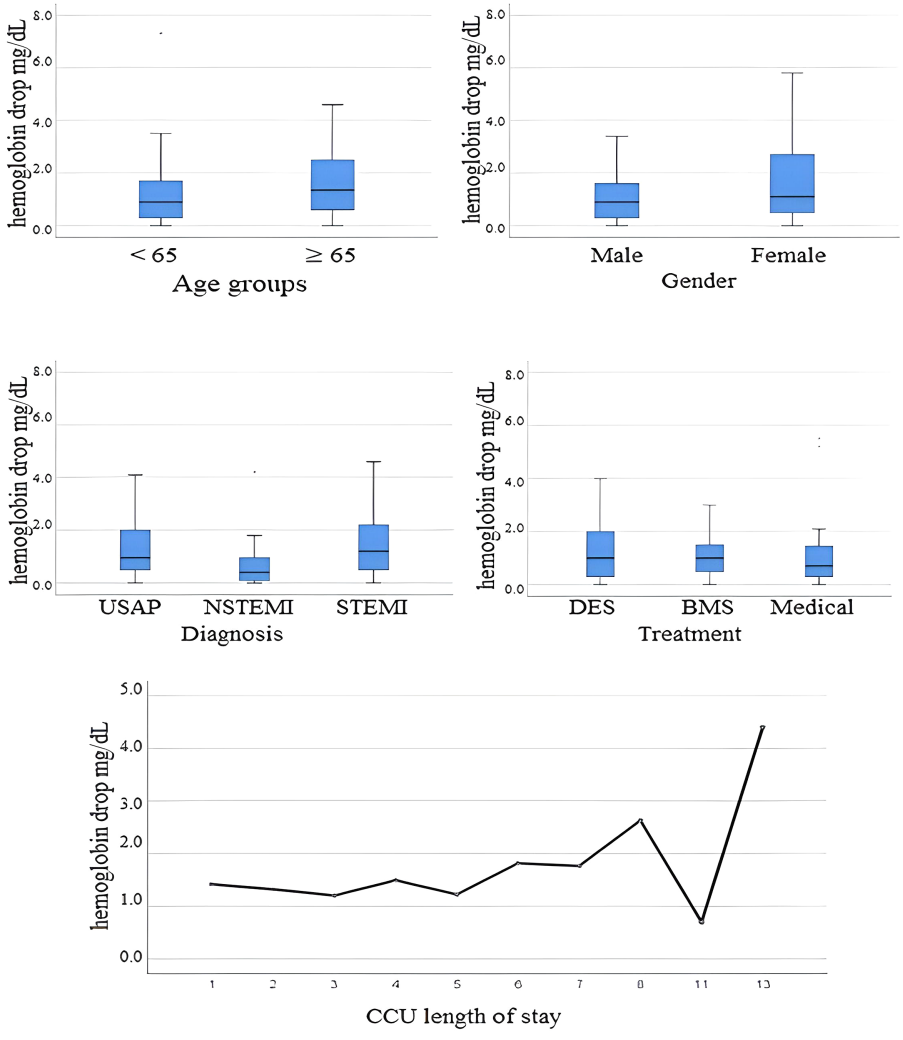
Study Design and Population

The study was designed as prospective, randomized, and observational. The study was initiated after the İstanbul University-Cerrahpaşa, Cerrahpaşa School of Medicine Dean's Office Clinical

Research Ethics Committee approval numbered 30330229-605.99 -57699 on September 14, 2018. Patients aged 18 years or older, who were admitted to the catheter laboratory with the diagnosis of ST-elevation myocardial infarction (STEMI), non-ST-elevation myocardial infarction (NSTEMI), or unstable angina pectoris (USAP), whose acute lesion was detected in coronary angiography and followed in the coronary care unit (CCU) were included in the study. Patients with anticoagulant treatment, bleeding diathesis, non-critical lesion in coronary angiography, advanced liver or kidney failure, and malignancies are not included in the study. The first patient was included in the study in November 2017, and the study end date was determined as October 2020. Data of 208 of 247 patients included in the study were analyzed. The flow chart of the study is shown in Figure 1.

Definitions and Endpoints

Coronary angiography was performed in the first 12 hours in patients with STEMI and in the first 72 hours in patients with NSTEMI and USAP. Hemogram, creatine kinase myocardial band (CK-MB), and troponin tests were taken from all patients before the procedure, during CCU follow-ups, and before discharge. The levels of urea, creatinine, glucose, pro-brain natriuretic peptide (proBNP), glycosylated hemoglobin, low-density lipoprotein, c-reactive protein (CRP), sodium, potassium, aspartate aminotransferase, and alanine aminotransferase were followed during hospitalization. Based on the hemogram examination of the patients at admission, the difference between the lowest hemoglobin values and the value at admission was calculated in the period until discharge. Hemoglobin drop was also classified according to previously determined bleeding scores, The TIMI and BARC bleeding scores. Age, sex, STEMI diagnosis, hemoglobin on admission, CCU duration, troponin peak, CK-MB peak, creatinine, CRP, pro-BNP, ejection fraction (EF), hypertension (HT), diabetes mellitus (DM), atrial fibrillation (AF), chronic heart failure (CHF), chronic renal failure (CRF), ticagrelor, and tirofiban were investigated in terms of its effect on TIMI and BARC bleeding score. In-hospital mortality, cardiac mortality, all-cause mortality, revascularization, and stroke were determined as the composite endpoint, and it was aimed to determine the hemoglobin drop that had a significant effect on the endpoint. Then, the effect of the determined absolute decrease on the endpoint was investigated. In subgroup analyses, the effects of age, sex, CCU duration, MI subtype, antiplatelet and anticoagulant therapy, and interventional therapy on the hemogram drop were examined.



ACS: Acute coronary syndrome, BMS: Bare metal stent, CCU: Coronary care unit DES: Drug-eluting stent, NSTEMI: Non-ST elevation myocardial infarction, STEMI: ST elevation myocardial infarction USAP: Unstable angina pectoris.

Figure 1. The effect of age, sex, ACS subgroups, invasive and medical treatment groups, and CCU length of stay on hemoglobin drop.

Statistical Analysis

Baseline characteristics by the prespecified sex and MI categories were compared using the chi-square test and the Fisher exact test when appropriate. The Student's *t*-test was used to compare the means of parametric groups with 2 continuous data and to determine the significant difference. Mann–Whitney *U* test was used to compare the means of non-parametric groups with 2 continuous data and to determine the significant difference. The dependent group *t* test was used for the analysis of continuous and 2 dependent parametric groups. Wilcoxon test was used for the analysis of continuous and 2 dependent nonparametric groups. Kolmogorov–Smirnow normality test was used as normality test for parametric or non-parametric analysis of continuous variables.

Receiver Operating Characteristic (ROC) analysis was performed to detect the drop in hemoglobin affecting the endpoint. Multivariable logistic models for in-hospital mortality and TIMI and BARC bleeding score outcomes were performed. The Cox proportional hazards regression model was used to evaluate the independent contribution of baseline clinical factors to the development of endpoints. A multivariate Cox regression was performed to evaluate the independent significance of all parameters with a *P* value of <.05 in univariate analysis. Kaplan–Meier estimates for endpoints, stratified by hemoglobin reduction category, were determined and statistically evaluated with the log-rank test. The results were evaluated at a 95% CI and the statistical significance level was defined as $P < .05$. All analyses were performed using the International Business Machines (IBM) Statistical Package for Social Sciences-25 (Chicago, Ill, USA) package program.

Results

The median follow-up period of 208 patients followed was 23 ± 9 (1-34) months. The mean age of the patients was 58.9 ± 12.6 years and 74.5% (155) of the patients were male, 74.5% had STEMI (155), and the mean length of stay in the intensive care unit was 3 days. Other characteristic features of all patients are shown in Table 1.

The comparison of male and female sex in terms of patient characteristics is shown in Table 2.

The mean age of men (57) was significantly lower ($P < .001$) compared to women (64.5). No significant difference was found in terms of length of stay in the intensive care unit. In the first blood test at hospitalization, hemoglobin levels were found to be significantly higher in men ($P < .001$), while pro-BNP and CRP levels were found to be higher in women ($P = .05$ for both). Troponin peak and CK-MB peak and creatinine levels were similar between sex. There was no significant difference in terms of EF between the sex in the echocardiography performed before coronary angiography. While DM was more common in women ($P = .02$), HT and AF on admission electrocardiography (ECG) were similar between sex. While the diagnosis of USAP was significantly higher in females ($P = 0.009$), the diagnoses of STEMI and NSTEMI were similar between sex. The left anterior descending coronary artery in men and the right coronary artery in women were more frequently culprit arteries ($P = .002$). Female patients received less-invasive treatment ($P = .003$). Men and women received similar rates of antiplatelet and anticoagulant therapy.

The comparison of ACS diagnoses and patient characteristics of the patients is shown in Table 3.

Mean age was lower in STEMI patients than in USAP and NSTEMI patients ($P = .03$). The duration of stay in the intensive care unit of the ACS groups was similar. Troponin and CK-MB peak levels were higher in STEMI patients ($P < .001$ for both), while pro-BNP and creatinine levels were higher in NSTEMI patients ($P = .02$ and $P = .03$, respectively). C-reactive protein levels were similar between groups. In echocardiography performed before coronary angiography, EF% was lower in STEMI patients ($P < .001$). The diagnoses of HT and DM were similar

Table 1. Patient Characteristics

Characteristics	Patient (n = 208) (%)
Age (year)	58.9 ± 12.6
Sex (male)	155 (74.5)
Diagnosis	
USAP	14 (6.7)
NSTEMI	39 (18.8)
STEMI	155 (74.5)
Treatment	
DES	110 (52.9)
BMS	33 (15.9)
Medical	40 (19.2)
Hypertension	80 (38.5)
DM	80 (38.5)
Hyperlipidemia	38 (18.3)
COPD	8 (3.8)
AF	10 (4.8)
HF	8 (3.8)
CRF	24 (11.5)
CVD	3 (1.4)
Malignancy	6 (2.9)
Smoking (active or past)	83 (39.9)
Alchol (active or past)	13 (6.3)
ASA	207 (99.5)
Clopidogrel	15 (7.2)
Ticagrelor	182 (87.5)
Tirofiban	25 (12)
Anticoagulant	11 (5.3)
EF%	48 ± 9.6
LVEDD (mm)	45.8 ± 6.1
LVESD (mm)	31.2 ± 5.5
RV disfunction	12 (5.8)
Regional wall motion anomaly	125 (60.1)
Mitral regurgitation (modarete or severe)	31 (14.9)

ASA, acetylsalicylic acid; AF, atrial fibrillation; BMS, bare metal stent; COPD, chronic obstructive pulmonary disease; CRF, chronic renal failure; CVD, cerebrovascular disease; DES, drug-eluting stent; DM, diabetes mellitus; EF, ejection fraction; HF, heart failure; LVEDD, left ventricular end-diastolic dimension; LVESD, left ventricular end-systolic dimension; NSTEMI, non-ST elevation myocardial infarction; STEMI, ST elevation myocardial infarction; USAP, unstable angina pectoris.

Table 2. Comparison of Patient Characteristics by Male and Female Sex

Characteristics	Male (155)	Female (53)	*P*
Age (year)	57.0	64.5	<.001*
CCU hospitalization time (day)	3.6	4.0	.08
Hemoglobin (mg/dL)	13.9	12.1	<.001*
hsTn-T (peak) pg/mL	1100.0	1600.0	.32
CK-MB (peak) U/L	78.0	66.0	.16
proBNP (peak) pg/mL	289	517	.05*
Creatinine (mg/dL)	1.0	0.88	.23
CRP mg/dL	11.5	24.0	05*
EF%	48.3	47.1	.43
HT	36.1	45.3	.24
DM	33.5	52.8	.02*
AF	5.2	3.8	.69
Diagnosis			.034*
USAP	3.9	15.1	.009*
NSTEMI	19.4	17.0	.92
STEMI	76.8	67.9	.20
IRA			.006*
LMCA	1.9	1.9	1
LAD	47.7	34	.30
CX	23.2	15.1	.22
RCA	20.6	41.5	.002*
Treatment			.036*
DES	55.5	45.3	.78
BMS	17.4	11.3	.50
Medical	14.8	32.1	.003*
ASA	99.4	100.0	.56
Clopidogrel	6.5	9.4	.12
Ticagrelor	89.0	83.0	.20
Tirofiban	13.5	7.5	.19
Anticoagulant	5.2	5.7	.89

ASA, acetylsalicylic acid; AF, atrial fibrillation; CCU, coronary care unit; CK-MB, creatine kinase myocardial band; CRP, C-reactive protein; CX, circumflex artery; DES, drug-eluting stent; DM, diabetes mellitus; EF, ejection fraction; hsTn-T, high-sensitivity troponin-T; IRA, infarct-related artery; LAD, left anterior descending coronary artery; LMCA, left main coronary artery; NSTEMI, non-ST elevation myocardial infarction; proBNP, pro-brain natriuretic peptide; RCA, right coronary artery; STEMI, ST elevation myocardial infarction; USAP, unstable angina pectoris.

between the ACS groups. While AF was not observed in the admission ECG in USAP patients, it was similar in NSTEMI and STEMI patients. Clopidogrel was used more frequently in USAP patients (P = .003); on the other hand, ticagrelor was more frequently used in NSTEMI and STEMI patients compared to USAP (P = .027). Tirofiban and the anticoagulant were never used in USAP patients, whereas they were used at a similar rate in NSTEMI and STEMI patients.

Table 3. Comparison of the Characteristics of USAP, NSTEMI, and STEMI Patients

Characteristics	USAP	NSTEMI	STEMI	*P*
Age (year)	63.6	62.5	57.6	.03*
CCU hospitalization time (day)	4.0	3.3	3.7	.21
Hemoglobin (mg/dL)	13.5	13.1	13.5	.58
hsTn-T (peak) pg/mL	13	123	3460	<.001*
CK-MB (peak) U/L	30	41	104	<.001*
proBNP (peak) pg/mL	157	449	322	.02*
Creatinine (mg/dL)	0.83	1.25	0.90	.03*
CRP (mg/dL)	12.1	15.3	14.7	.93
EF%	54.6	52	46.4	<.001*
Hypertension	21.4	48.7	37.4	.17
DM	28.5	33.3	40.6	.52
AF	0.0	2.5	5.8	.48
ASA	100.0	97.0	100.0	.11
Clopidogrel	21.2	2.8	1.2	.003*
Ticagrelor	67.5	91.2	94.6	.027*
Tirofiban	0	12.8	12.9	.36
Anticoagulant	0	5.1	5.0	.65

AF, atrial fibrillation; CCU, coronary care unit; CK-MB, creatine kinase myocardial band; CRP, C-reactive protein; DM, diabetes mellitus; EF, ejection fraction; hsTn-T, high-sensitivity troponin-T; NSTEMI, non-ST elevation myocardial infarction; proBNP, pro-brain natriuretic peptide; RCA, right coronary artery; STEMI, ST elevation myocardial infarction; USAP, unstable angina pectoris.

The mean difference between the hemoglobin before the procedure and the lowest hemoglobin until hospital discharge was 1.38 ± 1.37 mg/dL, and the highest difference was 7.3 mg/dL. Hemoglobin difference was compared according to age, sex, ACS groups, duration of intensive care, invasive and medical treatment.

When the age groups were determined as under 65 years old and 65 years and over, more hemoglobin drop was observed in patients 65 years and older but did not reach statistical significance (P = .14). Hemoglobin drop was more pronounced in women (P = .002). More hemoglobin drop was detected in STEMI patients than in NSTEMI patients (P = .002). Hemoglobin drop was higher in patients who were hospitalized in the coronary care unit for 6 days or more than those who stayed 5 days or less (P = .008). The rate of hemoglobin drop was similar in patients who received drug-eluting stent, bare-metal stent, and medical treatment (Figure 2).

The effect of demographic and clinical data on TIMI and BARC bleeding scores was analyzed using multivariate logistic regression analysis. Female sex, STEMI diagnosis, and coronary intensive care unit duration were determined as factors increasing TIMI bleeding

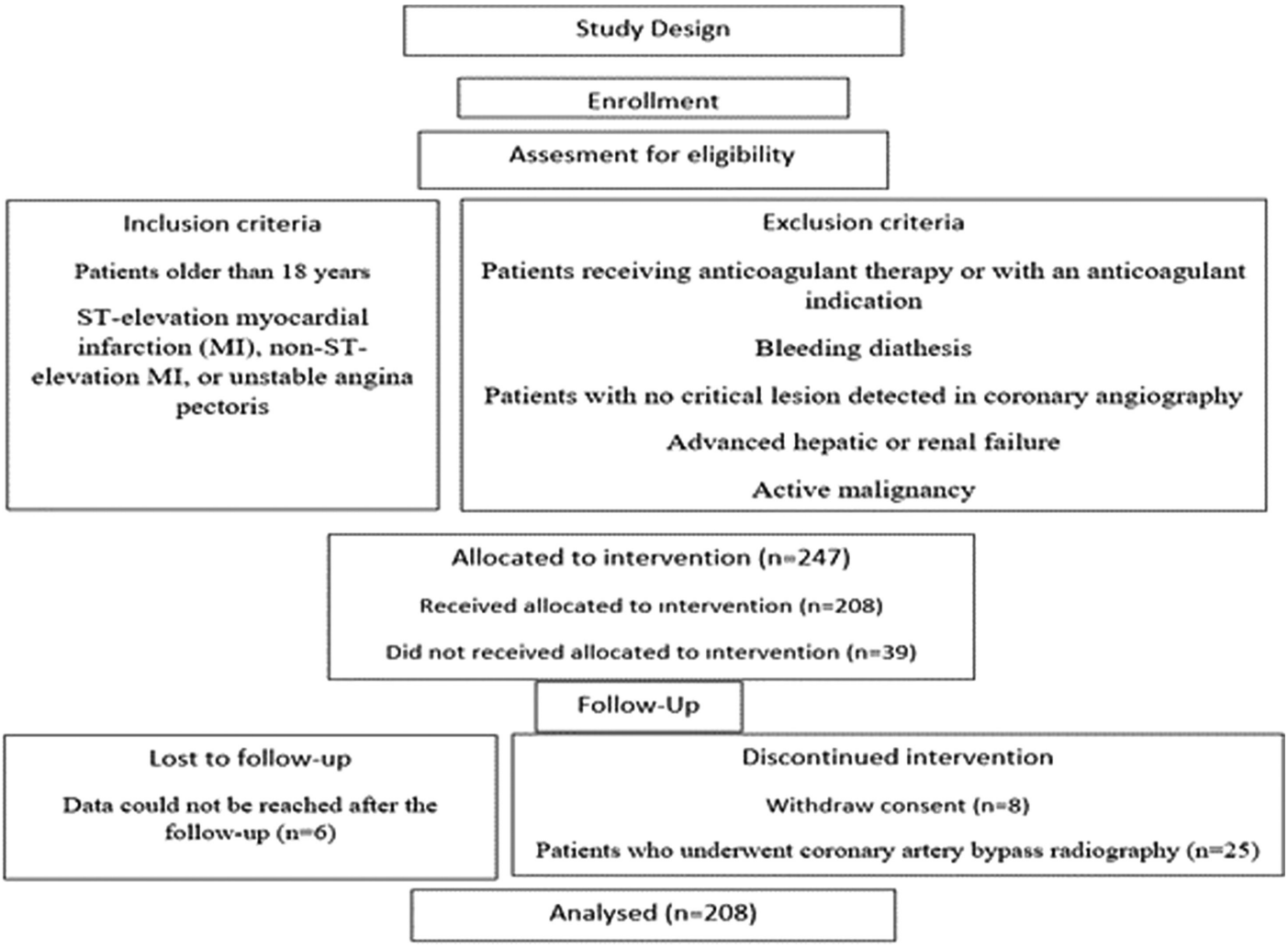


Figure 2. The flow chart of the study population.

score (P = .028, .002, and .003, respectively). Age (>65), female sex, STEMI diagnosis, and coronary intensive care unit duration were determined as factors increasing BARC bleeding score (P = .026, .006, .011, and .004, respectively).

ROC analysis was performed to determine the drop in hemoglobin affecting the composite endpoint of in-hospital mortality, cardiac mortality, all-cause mortality, revascularization, and stroke. Although no statistically significant correlation was found between the drop in hemoglobin and the composite endpoint, the highest LR value (1.2) was reached when there was a decrease of 3.25 mg/dL in hemoglobin. A drop in hemoglobin of 3.25 mg/dL affected the composite endpoint with a sensitivity of 11.42% and a specificity of 89.86% (Figure 3).

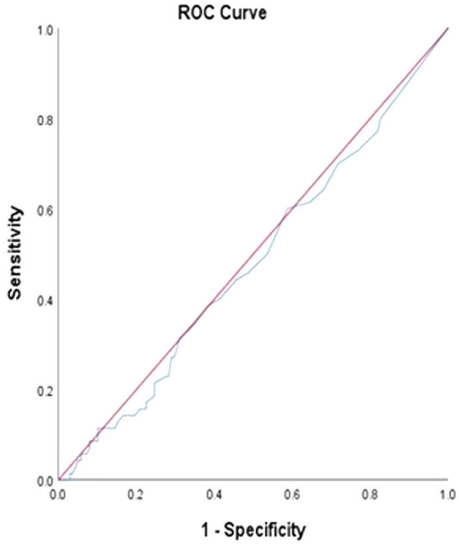
The effects of hemoglobin drop on mortality due to cardiac causes, mortality due to non-cardiac causes, revascularization, and stroke were investigated separately. There was no significant relationship between hemoglobin drop and endpoints. The results are shown in the forest plot graphic (Figure 4).

Discussion

In the study, it was concluded that the decrease in in-hospital hemoglobin in patients with ACS was not significantly effective in the in-hospital mortality, cardiac mortality, all-cause mortality, revascularization, and stroke composite endpoints. A weak correlation was detected between the hemoglobin drop and the composite endpoint, and this correlation was present when the hemoglobin decrease was at least 3.25 mg/dL.

Hemoglobin decline is generally associated with poor clinical outcomes. However, hemoglobin drop was not consistently shown to have a significant effect on the composite endpoints of in-hospital bleeding, death, myocardial infarction, and stroke.[9] Therefore, the relationship between in-hospital bleeding and long-term mortality and morbidity is not clear. In clinical trials investigating different antithrombotic therapies in ACS patients, multiple bleeding risk scores have been developed to appropriately assess the risk–benefit ratio for bleeding and thrombosis.[8] Current bleeding risk scores have similar predictive power in patients receiving both invasive and medical therapy.[10] In our study, 208 patients were followed up with the diagnosis of USAP, NSTEMI, and STEMI. There was no significant effect of hemoglobin drop on the primary endpoint of in-hospital mortality, cardiac mortality, all-cause mortality, revascularization, and stroke composite endpoint. In addition, there was no significant association between individual endpoints and hemoglobin drop.

In the ACS process, there may be bleeding due to intense antiplatelet and anticoagulants, as well as complications of the access tract, and therefore a drop in hemoglobin value. However, intensive fluid therapy can also cause dilutional hemoglobin reduction. As demonstrated in our study, bleeding causing a minor decrease in hemoglobin level did not have a significant effect on major clinical



Risk Factor	AUC (95% CI)	Cutoff	P value	Sensitivity (%)	Spesificity (%)	LR
Hemoglobin drop (mg/dl)	0.48 (0.40-0.56)	3.25	0.62	11.42	89.86	1.2

LR: Likelihood ratio

Figure 3. Areas Under the ROC curve (AUC), sensitivity and specificity by the optimized cutoff points for hemoglobin drop in composite endpoint

endpoints. The impact of progression of bleeding complications and more severe reductions in hemoglobin on major clinical endpoints is controversial. One reason to explain the association of bleeding with adverse outcomes is that the risk factors for bleeding overlap too much with the risk factors for ischemic events. Some conditions that act as a marker for increased ischemic risk contribute to the risk of bleeding and therefore death.[11] In our study, a weak correlation was found between the decrease in hemoglobin of 3.25 mg/dL and above and major clinical events. Another factor that is as important as the severity of the bleeding is the bleeding site. The deleterious impact of access and non-access site bleeding on outcomes is established, but the impact on mortality appears greater for non-access site bleeding.[12] In this respect, gastrointestinal hemorrhages and intracranial hemorrhages that cause the same level of hemoglobin decrease may cause different results. In our study, the cause of hemoglobin decrease was not examined.

It has been shown that advanced age, female sex, invasive strategy, low body weight, anemia, renal failure, bleeding history, use of glycoprotein inhibitors, and oral anticoagulants may increase the risk of bleeding in ACS patients.[13] In another study designed for NSTEMI, pretreatment, age, sex, and procedural variables were found useful in predicting bleeding risk.[14] It has been shown that some biochemical variables can be used to predict bleeding in ACS patients. In a study, it was shown that CK peak level is associated with non-fatal and fatal bleeding in NSTEMI patients.[15] In our study, the effects of age, sex, sub diagnosis of ACS (STEMI, NSTEMI, USAP), duration of coronary care unit, and invasive and medical treatment on hemoglobin drop were investigated. A significant correlation was found between female sex, STEMI diagnosis, intensive care unit duration of 6 days or more, and hemoglobin drop. In our study, age, sex, STEMI diagnosis, hemoglobin on admission, coronary intensive care unit duration,

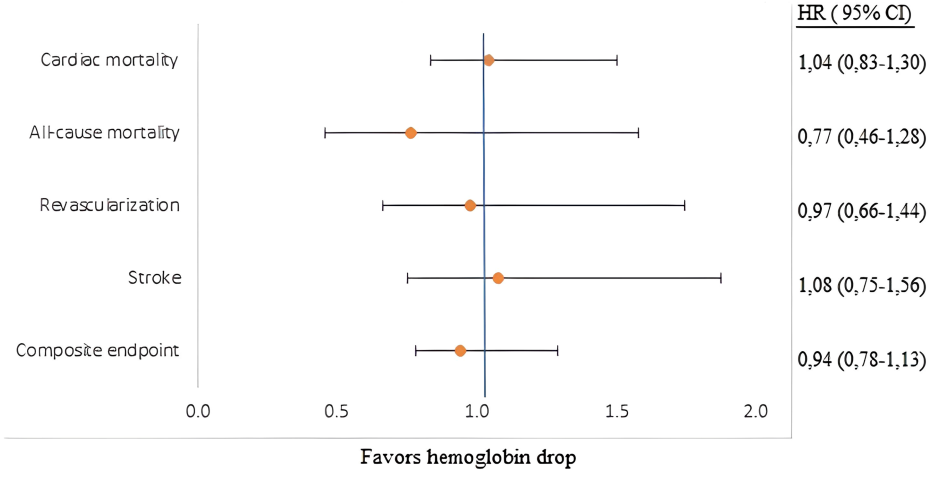


Figure 4. The effect of hemoglobin drop on the endpoints in the forest plot graph.

troponin peak, CK-MB peak, creatinine, CRP, pro-BNP, EF, HT, DM, AF, CHF, CRF, ticagrelor, and tirofiban were investigated in terms of its effect on TIMI and BARC bleeding score. Female sex, STEMI diagnosis, and coronary intensive care unit duration were determined as factors increasing TIMI bleeding score. Age (>65), female sex, STEMI diagnosis, and coronary intensive care unit duration were determined as factors increasing BARC bleeding score.

There are important dissimilarities in clinical presentation, aggregation of comorbidities, cardiovascular risk factors, and the quality of delivery of medical care among men and women with ACS.[5] When patients with ACS are compared by sex, women are older, more fragile, presenting later, and receiving less-invasive interventions than men may explain the higher bleeding risk of women.[16] In our study population, women were older, had lower hemoglobin at admission, and higher proBNP and CRP values. Diabetes mellitus was more common in women and received less invasive treatment. The diagnosis of USAP was more common in women and the responsible lesion was more in the left anterior descending artery in men, while the right coronary artery lesion was more common in women.

ST-segment elevation myocardial infarction patients tend to use more intensive antiplatelet and anticoagulant therapy. More intensive treatment not only increases ischemic complications but also increases the risk of minor and major bleeding. Similar intensities of antiplatelet and anticoagulant therapy are used in the process of ACS in men and women. Due to the lower body mass of women, the blood drug level can be determined more intensely. Another explanation may be that women are given more medical treatment and men more invasive treatment.[17] Anemia is more common in patients with multicomorbidity and the duration of stay in the intensive care unit is longer in these patients. The risk of procedure complications, including bleeding, increases with increased comorbidity.

In ACS, NSTEMI patients are more likely to have comorbidity and are usually older. While in-hospital mortality is higher in STEMI patients, long-term mortality is higher in NSTEMI patients. In our study, age, proBNP, and creatinine values were found to be higher in NSTEMI patients.

Park et al[9] compared clopidogrel and ticagrelor treatment in terms of efficacy and safety in patients with ACS. Although bleeding outcomes were more pronounced with clopidogrel, no difference was observed between the groups in terms of death, MI, and stroke. In our study, all patients received clopidogrel or ticagrelor treatment. Hemoglobin drop was found to be similar in both groups.

Non-vitamin K oral anticoagulant therapy added to dual antiplatelet therapy in patients with ACS increased clinically significant bleeding but did not significantly affect the outcome of MI, stroke, and mortality.[18] In our study, patients who received anticoagulation before the procedure were not included in the study. Periprocedural atrial fibrillation was similar between STEMI–NSTEMI and male and female patient groups. There was no new diagnosis of AF in USAP patients.

The results of this study show that hemoglobin reduction alone does not have a significant effect on major clinical endpoints and that with added risk factors, both bleeding and morbidity and mortality outcomes may be affected. The importance of evaluating the medical treatment and approach to bleeding in patients with ACS on a patient-specific basis was emphasized once again in the study.

There are several limitations of the study. First of all, the small number of patients and the short follow-up period reduce the reliability of the study results. Secondly, the reasons for the hemoglobin drop are not specified. While gastrointestinal hemorrhages can be resolved with simple medical intervention, intracranial hemorrhages can be mortal.

Conclusion

Hemoglobin drop did not significantly affect the composite endpoint of in-hospital mortality, cardiac mortality, all-cause mortality, stroke, and revascularization in patients with acute coronary syndrome. A weak correlation was detected between a minimum drop of 3.25 mg/dL in hemoglobin and the composite endpoint. Hemoglobin drop was significantly higher in female sex, patient with STEMI diagnosis, and intensive care unit duration of 6 days or more.

Ethics Committee Approval: Ethical committee approval was received from the Ethics Committee of İstanbul University-Cerrahpaşa University (Date: September 14, 2018, Approval numbered 30330 229-6 05.99-5769 9).

Informed Consent: Written informed consent was obtained from all participants who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – F.P., K.O.T.; Design – F.P., Z.Ö.; Supervision – Z.Ö., B.K.; Funding – F.P., K.O.T.; Materials – F.P.; Data Collection and/or Processing – F.P., K.O.T.; Analysis and/or Interpretation – B.K.A., F.P.; Literature Review – F.P.; Writing – F.P.; Critical Review – Z.Ö., B.K., B.K.A.

Declaration of Interests: The authors have no conflicts of interest to declare.

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

References

1. Steg PG, Huber K, Andreotti F, et al. Bleeding in acute coronary syndromes and percutaneous coronary interventions: position paper by the Working Group on Thrombosis of the European Society of Cardiology. *Eur Heart J*. 2011;32(15):1854-1864. [CrossRef]
2. Kengne AP, Czernichow S, Hamer M, Batty GD, Stamatakis E. Anaemia, haemoglobin level and cause-specific mortality in people with and without diabetes. *PLOS ONE*. 2012;7(8):e41875. [CrossRef]
3. Duman TD, Aktas G, Meryem Atak B, Kocak MZ, Kurtkulagi O, Bilgin S. General characteristics of anemia in postmenopausal women and elderly men. *Aging Male*. 2019, 1-5. [CrossRef]
4. Jolly SS, Yusuf S, Cairns J, et al. Radial versus femoral access for coronary angiography and intervention in patients with acute coronary syndromes (RIVAL): a randomised, parallel group, multicentre trial. *Lancet*. 2011;377(9775):1409-1420. [CrossRef]
5. Breen K, Finnegan L, Vuckovic K, Fink A, Rosamond W, DeVon HA. Multimorbidity in patients with acute coronary syndrome is associated with greater mortality, higher readmission rates, and increased length of stay: a systematic review. *J Cardiovasc Nurs*. 2020;35(6):E99-E110. [CrossRef]
6. Shah RM, Patel D, Molnar J, Ellenbogen KA, Koneru JN. Cardiac-re synchronization therapy in patients with systolic heart failure and QRS interval ≤130 ms: insights from a meta-analysis. *Europace*. 2015;17(2):267-273. [CrossRef]
7. Eikelboom JW, Mehta SR, Anand SS, Xie C, Fox KAA, Yusuf S. Adverse impact of bleeding on prognosis in patients with acute coronary syndromes. *Circulation*. 2006;114(8):774-782. [CrossRef]
8. Fortuni F, Crimi G, Morici N, et al. Assessing bleeding in acute coronary syndrome using the Bleeding Academic Research Consortium definition. *J Cardiovasc Med (Hagerstown)*. 2019;20(12):818-824. [CrossRef]
9. Park DW, Kwon O, Jang JS, et al. Clinically significant bleeding with ticagrelor versus clopidogrel in Korean patients with acute coronary

syndromes intended for invasive management: a randomized clinical trial. *Circulation*. 2019;140(23):1865-1877. [CrossRef]
10. Marquis-Gravel G, Neely ML, Valgimigli M, et al. Long-term bleeding risk prediction with dual antiplatelet therapy after acute coronary syndromes treated Without revascularization. *Circ Cardiovasc Qual Outcomes*. 2020;13(9):e006582. [CrossRef]
11. Steg PG, Huber K, Andreotti F, et al. Bleeding in acute coronary syndromes and percutaneous coronary interventions: position paper by the working group on Thrombosis of the European Society of Cardiology. *Eur Heart J*. 2011;32(15):1854-1864. [CrossRef]
12. Verheugt FWA, Steinhubl SR, Hamon M, et al. Incidence, prognostic impact, and influence of antithrombotic therapy on access and non-access site bleeding in percutaneous coronary intervention. *JACC Cardiovasc Interv*; 2011:4:191-197.
13. Choi SS, Sergie Z, Mehran R. Impact of in-hospital major bleeding on outcomes in acute coronary syndromes. *Curr Opin Cardiol*. 2012;27(6):669-674. [CrossRef]
14. Widimsky P, Motovska Z, Bolognese L, et al. Predictors of bleeding in patients with acute coronary syndromes treated with prasugrel. *Heart*. 2015;101(15):1219-1224. [CrossRef]
15. Brewster LM, Fernand J. Creatine kinase during non-ST-segment elevation acute coronary syndromes is associated with major bleeding. *Open Hear*. 2020;7(2). [CrossRef]
16. Mehilli J, Presbitero P. Coronary artery disease and acute coronary syndrome in women. *Heart*. 2020;106(7):487-492. [CrossRef]
17. Mohamed MO, Rashid M, Timmis A, et al. Sex differences in distribution, management and outcomes of combined ischemic-bleeding risk following acute coronary syndrome. *Int J Cardiol*. 2021;329:16-22. [CrossRef]
18. Khan SU, Arshad A, Riaz IB, Talluri S, Nasir F, Kaluski E. Meta-analysis of the safety and efficacy of the oral anticoagulant agents (apixaban, Rivaroxaban, dabigatran) in patients with acute coronary syndrome. *Am J Cardiol*. 2018;121(3):301-307. [CrossRef]