Biomedicine Advances

Biomedicine Advances. 2024;1(1):20-26
doi: 10.34172/bma.04
https://biomedad.ae

Original Article

Investigation of the impact of iron deficiency anemia on the clinical outcome of hospitalized patients and the 6-month outcome of acute STEMI patients undergoing primary angioplasty

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Summary

Introduction: Acute myocardial infarction (MI), particularly ST-elevation myocardial infarction (STEMI), is a severe form of acute coronary syndrome often resulting from complete coronary artery occlusion. Iron deficiency (ID) is a prevalent nutritional disorder worldwide and may influence cardiovascular outcomes, including in STEMI patients. This study aimed to assess the impact of ID on left ventricular function and clinical outcomes in STEMI patients undergoing primary percutaneous coronary intervention (PPCI).

Methods: This prospective study included 257 patients with acute STEMI admitted to Shahid Madani hospital in Tabriz between October 2020 and October 2022. Patients who presented within 12 hours of chest pain onset and met the inclusion criteria were categorized into two groups based on the presence or absence of ID, defined by serum ferritin levels <100 mg/dL or transferrin saturation <20%. Comprehensive demographic, clinical, and angiographic data were collected. The primary outcomes assessed were the occurrence of major adverse cardiovascular events (MACE), thrombolysis in myocardial infarction (TIMI) flow grading, and enzymatic infarct size during hospitalization and at 6-month follow-up.

Findings: ID was present in 54.4% of the patients. No significant differences were observed between the ID and non-ID groups regarding age, gender, body mass index (BMI), prevalence of comorbidities, or baseline left ventricular ejection fraction (LVEF). Additionally, the incidence of in-hospital and 6-month MACE, TIMI flow after PPCI, and enzymatic infarct size did not differ significantly between the two groups. However, serum iron, transferrin saturation, and ferritin levels were significantly lower in the ID group.

Conclusion: Although ID was common among STEMI patients undergoing PPCI, it did not significantly affect in-hospital or 6-month outcomes. These findings suggest that ID may not be a crucial determinant of prognosis in STEMI patients, but further large-scale studies are needed to corroborate these results.

Keywords: ST-elevation myocardial infarction, Iron deficiency, Percutaneous coronary intervention

Received: June 21, 2024, **Revised:** August 15, 2024, **Accepted:** September 10, 2024, **ePublished:** October 1, 2024

Introduction

Acute myocardial infarction (MI) is one of the diagnoses of acute coronary syndrome, which is divided into two categories with ST-elevation myocardial infarction (STEMI) and no ST-elevation myocardial infarction (NSTEMI) according to the presence or absence of ST-segment elevation in the electrocardiogram (ECG).[1] STEMI generally occurs when coronary blood flow suddenly decreases following thrombotic occlusion of a coronary artery already narrowed by atherosclerosis, leading to complete occlusion of the coronary artery. In contrast, NSTEMI can be caused by a decreased oxygen supply or an increase in oxygen demand in the myocardium that has occurred in the context of coronary obstruction. The main clinical symptom of STEMI is chest pain, typically felt in the area below the sternum or sometimes in the epigastrium.[2] The World Health Organization and the American Heart Association have considered at least two of the following three criteria necessary for the diagnosis of STEMI (acute MI with ST-segment elevation): clinical symptoms characteristic of MI; ECG changes; and typical increases and then decreases in biochemical markers.[1] Iron is both an essential nutrient and an environmental toxin. Iron is necessary for oxygen transfer and cell oxidation.[1] Anemia is one of the most important and widespread public health issues in the world[2] and has an adverse effect on the health of many children and women in developing countries. More than 30% of the world's people suffer from anemia.[3] Iron deficiency (ID) anemia refers to insufficient red blood cells (RBC) due to ID.[4] ID is the most common form of malnutrition in the world, which affects about two billion people. ID Anemia is extremely

common in developing countries. However, even in developed countries, in which other forms of malnutrition have nearly disappeared, this problem still remains.[5] ID anemia reduces the capacity of RBCs to deliver oxygen to the body's tissues and cells and causes clinical symptoms such as conjunctivitis, pale color, shortness of breath, dizziness, and weakness.[6] Determination of serum ferritin is an important measurement index.[7,8] Functional ID is associated with left ventricular (LV) dysfunction in patients with chronic heart failure (CHF).[9] Intravenous iron therapy can improve CHF symptoms in patients by reducing LV ejection fraction even in the absence of anemia which increases the possibility that ID instead of hemoglobin (Hb) deficiency is one of the primary concerns in heart failure.[10] Red blood cell distribution width (RDW) indicates the variation in the size of circulating RBCs.[11] Increased RDW has been shown to be a strong independent predictor of increased morbidity and mortality in patients with acute coronary syndrome, even in non-anemic patients.[12-14] Iron is essential for many biological processes, especially in the mitochondria, where it catalyzes enzymatic reactions and plays a role in regulating oxidative stress. Heart tissue is rich in mitochondria which makes iron especially important for heart function.[15] Several lines of evidence have shown that anemic patients have worse outcomes after acute MI.[16-18] However, few studies have fully investigated whether serum iron concentration affects LV function after primary angioplasty and the prognosis of these patients or not.

Methods

This was a prospective study that included 257 patients with acute STEMI who visited Shahid Madani Hospital in Tabriz between October 2020 and October 2022 and underwent primary percutaneous coronary intervention (PPCI). Inclusion criteria were visiting the hospital in the first 12 hours after the onset of chest pain, elevation of the ST segment in the ECG upon presentation, age above 18 years, consent to participate in the study, and completeness of file information. Exclusion criteria were a history of thalassemia hemochromatosis or known anemia, age less than 18 years, history of receiving erythropoietin, iron intake 6 weeks before the study, blood transfusion 6 weeks before the study, patients with any severe bleeding, liver failure and end-stage renal disease patients, malignant tumors, unstable angina, lack of consent to participate in the study, and incompleteness of file information. Venous blood was taken from all participants at the beginning of admission to measure serum ferritin, iron concentration, transferrin, and Hb. The complete history of the patients including demographic information (age, weight, history of blood pressure, history of diabetes, smoking, kidney failure, history of heart surgery, duration of disease, medications taken by the patient, and type of treatment) and angiographic information (infarcted vessels, coronary vessels, dimensions, vessels stent length, and stent size TIMI [thrombolysis in myocardial infarction] flow at baseline and after PPCI) were recorded. Then the patients were divided into two groups with ID anemia and without ID anemia and the characteristics of the two groups including in-hospital major adverse cardiovascular events (MACE) and 6 months TIMI flow at baseline and after PPCI and enzymatic infarct size were compared with one another.

ID was measured based on serum ferritin level or transferrin saturation. Ferritin level less than 100 mg/dL or transferrin saturation less than 20% was considered as ID. Serum ferritin concentration was measured by the immunoassay method. To measure serum iron concentration, color analysis (colorimetry) was performed. Troponin I was also measured by the ELISA method.

Statistical analysis

Statistical analysis of the study data was done by SPSS version 23 software. Quantitative data of the study were presented in the form of mean ± standard deviation or median interquartile range (IQR) in the frequency table. Qualitative data were displayed as frequency and percentage. After checking the normality of the distribution using the Kolmogorov-Smirnov test, one of the independent *t* tests, or the Mann-Whitney U test was used to compare the quantitative variables between the studied groups. The chi-square test was used to compare qualitative variables between groups. A *P* value less than 0.05 was considered significant.

Results

The demographic information of the studied patients is shown in Table 1. The average age in patients without ID was 57.68 years and in the ID group was 58.44 years. No significant difference was observed between the two groups regarding age ($P=0.578$). 101 of the patients without ID and 116 of the patients in the ID group were male. The difference observed in terms of gender between patients was not statistically significant ($P=0.445$). The average weight of patients without ID was 81.02 kg and in the ID group was 78.79 kg. No difference was observed between the two groups ($P=0.151$). The average body mass index (BMI) of the patients without ID was 27.96 and in the group of ID group was 27.21. This difference was also not clinically significant ($P=0.139$). The difference in prevalence of diabetes, hypertension, hyperlipidemia, chronic renal failure (CRF), history of MI, history of PCI, and smoking between the two groups was not statistically significant ($P>0.05$). Moreover, there was no significant difference in terms of medication usage such as Aspirin, statins, beta-blockers, ACEi/ARBs, and clopidogrel between the two groups ($P>0.05$).

The characteristics related to MI among patients are shown in Table 2. The prevalence of anterior STEMI

Table 1. The demographic information of the studied patients

Feature	Lacking iron deficiency (n = 117)	Having iron deficiency (n = 140)	Total (n = 257)	P value
Demographic information				
Age	57.68 ± 10.63	58.44 ± 11.12	58.09 ± 10.88	0.578
Gender				0.445
Male	101 (86.3%)	116 (82.9%)	217 (84.4%)	
Female	16 (13.7%)	24 (17.1%)	40 (15.6%)	
Weight (kg)	81.02 ± 12.13	78.79 ± 12.95	79.83 ± 12.61	0.151
BMI	27.96 ± 4.92	27.21 ± 4.07	25.55 ± 4.06	0.139
Medical history				
Diabetes	38 (32.5%)	39 (27.9%)	77 (30%)	0.421
Hypertension	52 (44.4%)	70 (50%)	122 (47.5%)	0.374
Hyperlipidemia	24 (20.5%)	21 (15.0%)	45 (17.5%)	0.247
CRF	3 (2.6%)	5 (3.6%)	8 (3.1%)	0.731
MI	11 (9.4%)	12 (8.6%)	23 (8.9%)	0.816
History of PCI	16 (13.7%)	19 (13.6%)	35 (13.6%)	0.981
History of anemia	1 (0.9%)	18 (12.9%)	19 (7.4%)	< 0.001
Smoking	64 (57.4%)	61 (43.6%)	125 (48.6%)	0.075
Drug history				
Aspirin	18 (15.4%)	33 (23.6%)	51 (19.8%)	0.101
Statins	10 (8.5%)	23 (16.4%)	33 (12.8%)	0.060
Beta blockers	17 (14.5%)	18 (12.9%)	35 (13.6%)	0.697
ACEi/ARB	30 (25.6%)	41 (29.3%)	71 (27.6%)	0.515
Clopidogrel	0 (0%)	3 (2.1%)	3 (1.2%)	0.253
Characteristics of myocardial infarction				
Anterior STEMI, n (%)	61 (52.1%)	79 (56.4%)	140 (54.5%)	0.491
LVEF, mean (SD), %	37 ± 7.09	36.94 ± 6.41	36.97 ± 6.72	0.941
Door to balloon time, min	71.84 ± 63.13	64.09 ± 42.12	67.62 ± 52.76	0.242
Total ischemic time, min	374.02 ± 258.65	318.89 ± 237.77	322.42 ± 247.03	0.802
Length of stay, day	4.35 ± 2.24	4.6 ± 2.99	4.49 ± 2.67	0.461
Laboratory findings				
Hb, g /dL	15.16 ± 1.57	14.42 ± 1.80	14.76 ± 1.74	< 0.001
MCV, fl	89.31 ± 5.96	89.57 ± 6.16	89.45 ± 6.06	0.729
SI, mic /dL	101.94 ± 36.66	72.52 ± 36.2	85.91 ± 39.19	< 0.001
TS, %	38.17% ± 14.31	24.5 ± 12.53	30.72 ± 14.98	< 0.001
Ferritin, ng/mL	235.57 ± 157.7	115.87 ± 139.86	170.37 ± 159.56	< 0.001
Cr, mg /dL	1.10 ± 0.29	1.84 ± 0.44	1.5 ± 0.23	0.341
BS, mg /dL	186.55 ± 95.41	159.57 ± 77.34	170.03 ± 86.94	0.012
CTNI peak	18.13 ± 12.71	18.02 ± 11.51	18.07 ± 12.05	0.943
Vital signs				
HR, beat/min	77.15 ± 16.18	78.19 ± 17.67	77.72 ± 16.99	0.626
SBP, mm Hg	139.22 ± 25.04	138.88 ± 22.51	139.04 ± 23.65	0.908
DBP, mm Hg	84.32 ± 17.48	85.5 ± 14.46	84.96 ± 15.88	0.553

BMI, body mass index; CRF, chronic renal failure; MI, myocardial infraction; PCI, percutaneous intervention; ACEi, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; BS, blood sugar; Cr, creatinine; CTINI, cardiac troponin I; MCV, mean corporate volume; Hb, hemoglobin SI, serum iron; TS, transferrin saturation; HR, heart rate; SBP, systolic blood pressure; DBP, diastolic blood pressure.
The numeric data are presented in median [IQR] or mean ± SD, based on the normality of distributions, and nominal data are presented in number (percentage).

Table 2. Characteristics related to MI among patients

Characteristic	Individuals Without Iron Deficiency (n = 117)	Individuals With Iron Deficiency (n = 140)	Total individuals (n = 257)	*P* value
In-hospital mortality	0 (0.0%)	2 (1.4%)	2 (0.8%)	0.502
Heart failure requiring diuretics	21 (17.9%)	33 (23.6%)	54 (21.0%)	0.271
Ventricular arrhythmia	14 (12.0%)	11 (7.9%)	25 (9.7%)	0.268
Stroke	0 (0%)	0 (0%)	0 (0%)	-
Recurrent MI	0 (0%)	3 (2.1%)	3 (1.2%)	0.253
AVB	8 (6.8%)	4 (2.9%)	12 (4.7%)	0.132
Gastrointestinal bleeding	0 (0%)	3 (2.1%)	3 (1.2%)	0.253
Vascular complications	5 (4.3%)	3 (2.1%)	8 (3.1%)	0.475
Hematuria	2 (1.7%)	1 (0.7%)	3 (1.2%)	0.593
6-Month mortality	1 (0.9%)	0 (0%)	1 (0.4%)	0.455
Heart failure requiring hospitalization	1 (0.9%)	1 (0.7%)	2 (0.8%)	1.000
6-Month recurrent MI	2 (1.7%)	2 (1.4%)	4 (1.6%)	1.000
Stroke	0 (0%)	0 (0%)	0 (0%)	-

AVB, atrioventricular block; MI, myocardial infraction.
Nominal data are presented in numbers (percentages).

among patients without ID was 52.1% and among patients with ID was 56.4%, no significant difference was observed between the two groups ($P = 0.491$). The average left ventricular ejection fraction (LVEF) among patients without ID was 37 and among patients with ID was 36.94, which were not significantly different ($P = 094$). The average door-to-balloon time among patients without ID was 71.84 minutes and among patients with ID was 64.09 minutes, the average total ischemic time was 374.02 minutes among patients without ID and in patients with ID it was 318.89 minutes. The average length of hospitalization between non-iron-deficient and iron-deficient patients with 104.5 hours versus 110.44 hours was not significantly different from each other ($P = 461.0$). Hb, serum iron level (SI), transferrin saturation (TS), ferritin level, and blood sugar levels were significantly different between the two groups. The average SI among patients without ID was 101.94 and among patients with ID was 72.52 ($P < 0.01$). The average TS among patients without ID was 38.17 and among patients with ID was 24.5 ($P < 0.01$). The average ferritin among patients without ID was 235.57 and among patients with ID was 115.87 ($P < 0.01$). The average blood sugar among patients without ID was 186.55 and among patients with ID was 159.57 ($P < 0.01$). There was no significant difference in terms of vital signs including heart rate (HR), systolic blood pressure (SBP), and diastolic blood pressure (DBP) between the two groups ($P > 0.05$). The average HR among the patients without ID was 77.15 per minute and among the patients with ID was 78.19 per minute. The average SBP and DBP among the patients without ID were 139.2 and 84.3 mm HG respectively, and among patients with ID were 138.8 and 85.5 mm HG respectively.

The findings related to angiography among patients are shown in Table 3. There was no significant difference in terms of any of these findings between the patients of the two groups ($P > 0.05$). Regarding the number of vessels involved, patients were divided into two categories: single vessel disease (SVD) and multi-vessel disease (MVD). There was no significant difference between the patients of the two groups. The TIMI score was evaluated among the patients at baseline and after PPCI. None of the patients had a TIMI score equal to zero after PPCI. However, there was no significant difference in terms of these findings between the patients of the two groups ($P = 0.882$ and $P = 0.831$, for TIMI score before and after spontaneous PPCI.) Spontaneous recanalization was found In 22.2% of patients without ID and in 23.6% of patients with ID ($P = 0.798$)). 15.4% of the patients in the group without ID and 14.3% of the patients with ID were no-reflow ($P = 805.0$). The use of IABP was performed in only two patients, both of whom had ID. A significant difference from There was no opinion on stent size and length between patients ($P = 0.243$ and 0.924 according to education).

Discussion

Iron acts as a key enzymatic factor in the mitochondrial respiratory chain. Therefore, iron is crucial for the homeostasis of every cell, especially cardiomyocytes which require a high amount of energy.[19] Mitochondrial dysfunction is recognized as the primary mechanism of myocardial ischemia-reperfusion injury.[20] Hence, the hypothesis that ID may exacerbate myocardial damage is proposed. Study by Jenča et al suggested that lower serum iron levels are associated with an increase of mortality in MI patients.[21] Free iron has also been cited as a catalyst for the

Table 3. Demographic information of the studied patients

Characteristic			Individuals without iron deficiency (n=117)	Individuals with iron deficiency (n=140)	Total individuals (n=257)	*P* value
Culprit lesion	Proximal LAD		27(23.1%)	46 (32.9%)	73 (28.4%)	0.230
	Non-proximal LAD		36 (30.8%)	38 (27.1%)	74 (28.8%)	
	OM/LCX		13 (11.1%)	19 (13.6%)	32 (12.5%)	
	PLB/PDA/RCA		41 (35.0%)	37 (26.4%)	78 (30.4%)	
Arteries	SVD		43 (36.8%)	55 (39.3%)	98 (38.1%)	0.677
	MVD		74 (63.2%)	85 (60.7%)	159 (61.9%)	
TIMI flow	Baseline	0	86 (73.5%)	94 (67.1%)	180 (70.0%)	0.882
		1	5 (4.3%)	13 (9.3%)	18 (7.0%)	
		2	4 (3.4%)	9 (6.4%)	13 (5.1%)	
		3	22 (18.8%)	24 (17.1%)	46 (17.9%)	
	Post-PPCI	1	2 (1.7%)	1 (0.7%)	3 (1.2%)	0.831
		2	16 (13.7%)	19 (13.6%)	35 (13.6%)	
		3	99 (84.6%)	120 (85.7%)	219 (85.2%)	
Spontaneous recanalization			26 (22.2%)	33 (23.6%)	59 (23.0%)	0.798
No-reflow			18 (15.4%)	20 (14.3%)	38 (14.8%)	0.805
GP IIb/IIIa Inhibitor			66 (56.4%)	72 (51.4%)	138 (53.7%)	0.426
Thrombosis grade	low		27 (23.1%)	39 (27.9%)	66 (25.7%)	0.382
	High		90 (76.9%)	101 (72.1%)	191 (74.3%)	
Use of AIBP			0 (0.0%)	2 (1.4%)	2 (0.8%)	0.502
Stent Size			3.21±0.45	3.15±0.44	3.18±0.44	0.243
Stent length			23.02±6.65	23.10±7.03	23.06±6.85	0.924
Total STE (ST-elevation)	Baseline		10.36±8.16	10.14±7.86	10.24±7.98	0.829
	Post-PPCI		3.66±3.29	4.08±5.13	3.89±4.38	0.443
STR>50%			85 (72.6%)	112 (80.0%)	197 (76.7%)	0.365

The numeric data are presented in median [IQR] or mean ± SD, based on the normality of distributions, and nominal data are presented in number (percentage).

LAD: Left anterior descending artery, OM: Obtuse Marginal Artery, LCX: Left Circumflex Artery, PLB: Posterior Lateral Branch of the coronary arteries, PDA: Patent Ductus Arteriosus, RCA: Right Coronary Artery, SVD: Single-vessel disease, MVD: Multi-vessel disease, TIMI: Thrombolysis in Myocardial Infarction, PPCI: Primary Percutaneous Coronary Intervention, AIBP: Intra-Aortic Balloon Pump, STR: Secondary Tricuspid Regurgitation

production of free radicals in ischemic myocardial injury. At high iron concentrations of serum, iron accumulates in cells, which leads to oxidative stress and cardiomyocyte necrosis. In contrast, at low concentrations, iron enhances cell survival processes by increasing nitric oxide production.[22] In the study of Cosentino et al, patients with ID were shown to have higher levels of high-sensitivity troponin as well as larger areas at risk of infarction however; they showed less reperfusion injury, resulting in similar infarct sizes. Therefore, it seems that iron plays both an exacerbating and protective role during acute ischemia and against reperfusion injury.[23] On the other hand, ferritin which is an acute-phase reactant, is suggested to be associated with disease severity and worse prognosis.[24] Diagnosing ID in inflammatory conditions is challenging and the results of multiple studies on the impact of ID on outcomes in STEMI patients are varied. These differences could be due to variations in study methodologies, the prevalence of ID and ID anemia, different definitions of ID, differences in ischemic time, initial LVEF, and the prevalence of anterior MI in these studies. The present study aimed to investigate the effect of ID on hospital and 6-month clinical outcomes in patients with acute STEMI who underwent PPCI. Results showed that the occurrence of MACE, TIMI flow grading for presentation and after PPCI, and enzymatic infarct size were not significantly associated with ID. However, in a study by Cosentino et al, with a 56% prevalence of ID among STEMI patients, the results indicate that ID is coupled with a greater ischemic injury while it is associated with better in-hospital outcomes.[23] In another similar study by Zeller et al, with a lower prevalence of ID (29.1%), the data was indicative of a strong association of ID with adverse outcomes in patients with acute coronary syndrome.[25] In this study there was no significant difference in the prevalence of diabetes, hypertension, hyperlipidemia, history of CRF, history of MI, history of PCI, and smoking between the two groups. Besides, when anterior STEMI, average LVEF,

total ischemic time, door-to-balloon time, and length of stay were evaluated, there were no significant differences between the two groups. Some of our findings differ from similar studies. In this study, the average ischemic time was 350 minutes, while in a study by Cosentino et al, the average time was 180 minutes and their LVEF was 53% while in this study it was 37%. Additionally, the prevalence of Anterior MI and multi-vessel involvement, particularly proximal LAD, was higher in the present study compared to the study by Cosentino et al.[23] This study demonstrated that the incidence of in-hospital and 6-month post-discharge MACE did not differ significantly between patients with and without ID. The evaluated in-hospital complications in this study include; in-hospital death, heart failure requiring diuretics, ventricular arrhythmia, stroke, recurrent MI, AV block, gastrointestinal bleeding, vascular complications, and hematuria. The evaluation of 6-month MACE included death, heart failure requiring hospitalization, recurrent MI within 6 months, and stroke. In a study by Cosentino et al, the occurrence of the primary endpoint was lower in patients with ID who had STEMI compared to those without (10% vs. 18%).[23] Another study by Huang et al showed that serum iron concentration, but not Hb, was associated with the TIMI risk score and 6-month left ventricular function following primary angioplasty for acute MI and multiple linear regression in Huang and colleagues' study showed that baseline serum iron concentration could predict 6-month LV systolic function following primary angioplasty for acute MI even after adjusting for traditional prognostic factors.[26] In a study by Zeller et al, it was found that ID was associated with an increased severity of non-fatal MI and cardiovascular mortality with a hazard ratio of 1.25.[25] In another study by Duarte et al, patients in the first tertile of serum iron (≤40 mcg/dL) had higher rates of adverse events both in-hospital and after 1 year. Meanwhile, in the same study, lower and higher levels of ferritin (less than or equal to 110 ng/mL as the first tertile and more than 219 ng/mL as the third tertile) were associated with higher rates of heart failure during hospitalization and death within one year. Ferritin levels greater than 316 ng/mL, were identified as an independent risk factor for one-year mortality.[27] In this study, CTNI tests were used to evaluate the enzymatic infarct size, and this factor also showed no significant difference between the two groups while, in another study, patients with ID had higher levels of high-sensitivity troponin and mitochondrial DNA at the time of admission compared to patients without ID.[23]

Limitations of the study

The differences between the results of the present study and previous studies can be attributed to several factors. Firstly, the small number of patients studied and the low number of MACE events that occurred may have impacted the findings. Secondly, the longer total ischemic time in our study compared to similar studies could obscure the potential effect of ID on patient outcomes. Thirdly, the higher prevalence of anterior MI and multi-vessel and proximal LAD involvement in our study compared to previous studies, might affect the overall outcomes and ultimately eliminate the differences between patients with and without ID. Additionally, the limitations of the present study include its single-center nature, the small sample size, the low number of MACE events, the use of ferritin to define ID given that ferritin is an acute-phase reactant, and the lack of patient follow-up beyond six months.

Conclusion

Although ID anemia can be common among STEMI patients, it cannot perform as a suitable prognostic factor for STEMI patients undergoing PPCI. it did not significantly affect in-hospital or 6-month outcomes.

Acknowledgments

The research protocol was approved and supported by the Student Research Committee, Tabriz University of Medical Sciences (grant number: 66928). We would like to appreciate the cooperation of the clinical research development unit of Shahid Madani Hospital, Tabriz, Iran in the conduction of this research.

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Competing Interests

The authors report no relationships that could be construed as a conflict of interest.

Ethical Approval

The ethics committee of the Tabriz University of Medical Science reviewed and approved the study protocol (Ethical Code: IR.TBZMED.REC.1400.017).

Funding

This research project was funded by a grant from the Research Vice-Chancellor, Tabriz University of Medical Sciences (Grant number: 66928).

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