



# Predictors of 1-Year Major Cardiovascular Events after ST-Elevation Myocardial Infarction in a Specialized Cardiovascular Center in Western Iran

Parisa Janjani, PhD<sup>1</sup>, Sayeh Motevaseli, MSc<sup>1</sup>, Nahid Salehi, MD<sup>1</sup>, Reza Heidari Moghadam, MD<sup>1</sup>, Soraya Siabani, MD, PhD<sup>2</sup>, Mahdi Nalini, MD, PhD<sup>1\*</sup>

<sup>1</sup>Cardiovascular Research Center, Health Institute, Imam-Ali Hospital, Kermanshah University of Medical Sciences, Kermanshah, Iran.

<sup>2</sup>Department of Health Education and Health Promotion, Kermanshah University of Medical Sciences, Kermanshah, Iran.

Received 28 December 2021; Accepted 20 February 2022

## Abstract

**Background:** Identifying the long-term predictors of recurrent cardiovascular events may help improve the quality of care and prevent subsequent events. We aimed to investigate the predictors of 1-year major cardiovascular events (MACE) in patients discharged after ST-elevation myocardial infarction (STEMI) in a tertiary hospital in Iran.

**Methods:** This registry-based cohort study included consecutive STEMI patients between 2016 and 2019 in Imam-Ali Hospital, Kermanshah, Iran. All patients discharged alive from STEMI hospitalization were followed up for 1 year for MACE, consisting of all-cause mortality, nonfatal MI, and nonfatal stroke. We estimated the hazard ratio (HR) and the 95% confidence interval (95% CI) using Cox proportional-hazard models to evaluate potential predictors, including demographic characteristics, medical history, cardiovascular risk factors, laboratory tests, reperfusion therapy, and medications.

**Results:** During 2187.2 person-years, 21 patients were lost to follow-up (success rate =99.1%). Of 2274 post-discharge STEMI patients (mean age =60.26 y; 21.9% female), 151 (6.6%) experienced MACE, including, all-cause mortality (n=115, 5.1%), nonfatal MI (n=20, 0.9%), and nonfatal stroke (n=16, 0.7%). Independent predictors of MACE were age (HR:1.02; 95% CI: 1.00–1.04), no education vs ≥12 years of formal schooling (HR: 2.07; 95% CI: 1.17–3.67), stroke history (HR: 2.37; 95% CI: 1.48–3.81), the glomerular filtration rate (HR: 0.98; 95% CI: 0.97–1.00), the body mass index (HR: 0.94; 95% CI: 0.89–0.99), peak creatine kinase-MB (HR: 1.00; 95% CI: 1.00–1.002), thrombolysis vs primary percutaneous coronary intervention (HR: 1.85; 95% CI: 1.21–2.81), and left ventricular ejection fraction <35% vs ≥50% (HR: 2.82; 95% CI: 1.46–5.47).

**Conclusion:** Age, education, stroke history, the glomerular filtration rate, the body mass index, peak creatine kinase-MB, reperfusion therapy, and left ventricular function can be independently associated with 1-year MACE.

*J Teh Univ Heart Ctr 2022;17(2):62-70*

**This paper should be cited as:** Janjani P, Motevaseli S, Salehi N, Heidari Moghadam R, Siabani S, Nalini M. Predictors of 1-Year Major Cardiovascular Events after ST-Elevation Myocardial Infarction in a Specialized Cardiovascular Center in Western Iran. *J Teh Univ Heart Ctr 2022;17(2):62-70.*

**Keywords:** Myocardial infarction; Mortality; Morbidity; Risk factors; Stroke

\*Corresponding Author: Mahdi Nalini, Assistant Professor of Research in Clinical Sciences and Epidemiology, Cardiovascular Research Center, Imam-Ali Hospital, Shahid Beheshti Blvd, Kermanshah, Iran. 6715847145. Tel: +98 83 38376525. Fax: +98 83 360043. E-mail: mahdinalini@yahoo.com.





## Introduction

Patients who survive ST-segment–elevation myocardial infarction (STEMI) are at an elevated risk of morbidity and mortality.<sup>1, 2</sup> For instance, in the United States, about one-quarter of annual MI cases are due to recurrent events.<sup>2</sup> The risk of subsequent cardiac events is highest in the first year after MI events, a crucial period for clinical care and secondary prevention.<sup>3</sup> Previous studies, mainly from high-income countries, have indicated that age, diabetes, hypertension, stroke history, reduced renal function, and no revascularization history are among the significant predictors of subsequent fatal and nonfatal cardiovascular events in STEMI patients.<sup>3, 4</sup> The identification of cardiovascular event predictors following MI can help health systems to improve the quality of care and to prevent subsequent events in STEMI patients.<sup>5</sup>

The majority of prior studies are focused on the short-term outcomes of MI<sup>3</sup> or only mortality.<sup>1</sup> Long-term mortality is an important outcome among surviving STEMI patients; however, other nonfatal recurrent cardiovascular events are also crucial because of their high incidence rate and significant impact on patients' quality of life and economic consequences.<sup>2, 6</sup>

In recent years, the burden of ischemic heart disease has declined strikingly in high-income countries,<sup>7</sup> mainly because of advances in health-system infrastructure and guideline-based therapies, including systematic secondary prevention programs.<sup>8, 9</sup> Nonetheless, in low- and middle-income countries (LMICs), accounting for 80% of the world's population,<sup>7</sup> the optimal guideline-based management is unfeasible,<sup>10</sup> and the burden of morbidity and mortality remains elevated.<sup>7</sup> These conditions notwithstanding, data are scarce regarding the management and predictors of the clinical outcomes of STEMI in LMICs.<sup>10</sup> Therefore, in the present study, we aimed to evaluate the predictors of 1-year major cardiovascular events (MACE) of STEMI survivors in Imam-Ali Hospital, western Iran.

## Methods

Kermanshah Province in the west of Iran had almost 2 million inhabitants in the 2016 census.<sup>11</sup> The eponymous capital city of the province is Kermanshah. Imam-Ali Hospital, affiliated with Kermanshah University of Medical Sciences, is the only specialized tertiary university cardiovascular hospital in the province.

Launched on July 1, 2016, the current registry-based cohort study with a 1-year follow-up enrolled all consecutive STEMI patients (>18 y) admitted to Imam-Ali Hospital and diagnosed by cardiologists based on the fourth universal definition of MI.<sup>12</sup>

This study included all patients discharged alive

from STEMI hospitalization between July 1, 2016, and September 19, 2019. The Ethics Committee of Kermanshah University of Medical Sciences approved the study protocol (ethics registration code: KUMS.REC.1395.252). All the participants in the registry signed written informed consent.

In this registry, trained nurses, using a standard questionnaire, collected data about demographic information, medical history, laboratory test findings, electrocardiography data, reperfusion therapy, and medications at discharge. Demographic data, MI history, stroke history, coronary artery bypass surgery (CABG), smoking, diabetes, and hypertension were recorded based on self-report. These data were obtained by interviewing the patients and/or their first-degree relatives and using medical records. The place of residence was categorized as the city of Kermanshah and other cities or villages of the province. Laboratory findings were measured during the first 24 hours of admission; they included hemoglobin, low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), and serum creatinine. Also recorded were reperfusion therapies, including primary percutaneous coronary intervention (PCI), pharmaco-invasive strategies (ie, thrombolysis followed by angiography and PCI if indicated), thrombolysis alone, and CABG. The body mass index (BMI) was calculated as weight in kilograms divided by the square of height in meters. The glomerular filtration rate (GFR) on admission was estimated using the chronic kidney disease epidemiology collaboration formula,<sup>13</sup> based on age, sex, and baseline serum creatinine. The left ventricular ejection fraction (LVEF) was measured before discharge from the hospital and categorized into 3 groups:  $\leq 35\%$ ,  $35\%–50\%$ , and  $\geq 50\%$ . Information about medication at discharge, including aspirin, P2Y12 inhibitors,  $\beta$ -blockers, angiotensin-converting enzyme inhibitors/angiotensin receptor blockers (ACE-Is/ARBs), and statins, was obtained from medical records. The quality of the data was rechecked and confirmed by trained physicians.

The outcome of this study was MACE, considered a composite of all-cause mortality, nonfatal MI, and nonfatal stroke, during a 1-year follow-up. During admission, the patients' mobile and home phones, as well as 2 phone numbers of their first-degree relatives, were recorded. Twelve months after discharge, the registry's trained nurses collected follow-up data regarding the date of death, MI, and stroke of each patient via in-person interviews or telephone calls. The occurrence of MI and stroke was ascertained through the reviews of the patients' hospitalization documents by trained physicians. The follow-up time was extended from the date of discharge until the date of MACE occurrence, loss to follow-up, or 1 year after discharge, whichever occurred first. For patients with more than 1 incidence of the individual components of MACE, the first event was considered in the analysis.

Continuous variables were expressed as the mean with the standard deviation (SD), and categorical variables were

reported as frequencies (percentages). Cox proportional-hazard modeling was conducted to determine the predictors of the composite of all-cause mortality, nonfatal MI, and nonfatal stroke. The proportionality of hazards was verified by plotting the Schoenfeld residuals versus time and the Schoenfeld global test ( $P=0.511$ ). Candidate variables for inclusion in statistical models were chosen according to previous studies<sup>3,5</sup> and variables of interest. These variables were age, sex (female/male), years of formal schooling (0, <12, and  $\geq 12$  y), place of residence (Kermanshah city/others), MI history, prior stroke, prior CABG, ever smoking, diabetes, hypertension, LDL-C, HDL-C, GFR, hemoglobin, BMI, MI type (anterior wall or left bundle branch block/others), the highest level of CK-MB, reperfusion therapy (primary PCI, pharmaco-invasive strategies, thrombolysis, CABG, and no-reperfusion), LVEF ( $\leq 35\%$ ,  $35\%–50\%$ , and  $\geq 50\%$ ), and medications at discharge (aspirin, P2Y2 inhibitors,  $\beta$ -blockers, ACE-Is/ARBs, and statins). We reported the hazard ratio (HR) with the 95% confidence interval (95% CI) using univariable and fully-adjusted Cox models. In the final model, the strategy of change-in-estimate with a cutoff of 10% was used to identify the independent predictors of the composite outcome,<sup>14</sup> which was validated via stepwise selection methods. In a sensitivity analysis, we evaluated the predictors of all-cause mortality. All the statistical analyses were conducted by using the Stata statistical software (Stata Corp, Release 12, College Station, TX). A statistical significance level of 0.05 was considered (2-tailed).

## Results

A total of 2295 STEMI patients were discharged alive from Imam-Ali Hospital between July 1, 2016, and September 19, 2019. We excluded 21 patients from the study due to loss to follow-up, resulting in the availability of 2274 patients for analysis. The rates of missing data among the covariates were low; they consisted of years of schooling in 96 patients (4.2%), the place of residence in 20 (0.9%), LDL-C in 78 (3.4%), HDL-C in 119 (5.2%), hemoglobin levels in 2 (0.1%), and LVEF in 37 (1.6%).

The mean age of the patients was  $60.26 \pm 12.25$  years, and 21.9% were female. In the present study, 71.7% ( $n=1562$ ) of the patients had low levels of formal schooling: 30.9% had no formal education and 40.9% had less than 12 years of schooling. Moreover, 11.0% of the patients did not receive any reperfusion therapies, and 16.9% received only thrombolysis without subsequent coronary angiography or PCI during the index hospitalization. The baseline characteristics of the patients are presented in Table 1. Patients with the incidence of MACE were more likely to be women and older.

During 798 330 person-days of follow-up, 151 of the 2274 patients (6.6%) experienced MACE: 115 all-cause deaths (5.1%), 20 MIs (0.9%), and 16 strokes (0.7%). Figure 1 shows the association between the categorized independent variables and MACE occurrence.

The results of the unadjusted and fully adjusted models are presented in Table 2. In the unadjusted analyses, older age, the female sex, diabetes, hypertension, LVEF below

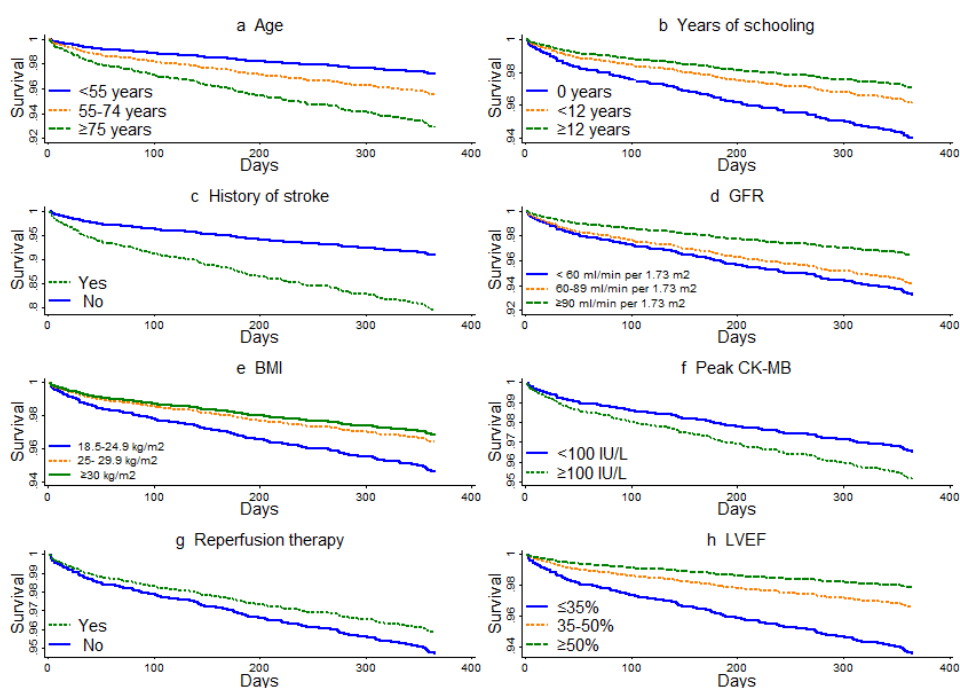


Figure 1. MACE-free survival using the final Cox model based on categorized independent variables, including a; age (<55, 55-74, and  $\geq 75$  years), b; years of formal schooling (0, <12, and  $\geq 12$  years), c; history of stroke; d; GFR (<60, 60-89, and  $\geq 90$  ml/min per 1.73m<sup>2</sup>), e; BMI (18.5-24.9, 25-29.9, and  $\geq 30$  kg/m<sup>2</sup>), f; peak CK-MB (<median  $\geq$ median IU/L), g; reperfusion therapy, and h; LVEF ( $\leq 35\%$ ,  $35\%–50\%$ , and  $\geq 50\%$ ). MACE, major adverse cardiovascular events; GFR, glomerular filtration rate; BMI, body mass index; CK-MB, creatine kinase-MB; LVEF, left ventricular ejection fraction.



Table 1. Baseline characteristics of STEMI patients according to MACE status\*

	All (n=2274)	MACE (+) (n=151)	MACE (-) (n=2123)
Age (y)	60.26±12.25	67.61±13.86	59.74±11.96
Peak CK-MB (IU/L)	128.73±121.20	142.16±130.80	127.77±120.47
Hemoglobin (g/dL)	14.76±1.77	14.22±1.99	14.80±1.75
LDL-C (mg/dL)	105.33±31.22	104.59±36.15	105.38±30.85
HDL-C (mg/dL)	41.38±9.13	40.75±9.87	41.42±9.07
GFR (mL/min per 1.73m <sup>2</sup> )	69.12±17.43	58.72±18.73	69.86±17.10
Body mass index (kg/m <sup>2</sup> )	26.22±4.02	24.94±3.87	26.31±4.02
Sex (female)	497 (21.9)	54 (35.8)	443 (20.9)
Years of Schooling			
0	672 (30.9)	78 (55.7)	594 (29.2)
<12 (y)	890 (40.9)	44 (31.4)	846 (41.5)
≥12 (y)	616 (28.3)	18 (12.9)	598 (29.3)
Place of Residence			
Kermanshah city	1750 (77.6)	105 (72.9)	1645 (77.1)
Others	504 (22.4)	39 (27.1)	465 (22.0)
History of MI	265 (11.7)	21 (13.9)	244 (11.5)
History of stroke	112 (4.9)	23 (15.2)	89 (4.2)
History of CABG	270 (11.9)	15 (9.9)	255 (12.0)
Ever smoking	1127 (49.6)	63 (41.7)	1064 (50.1)
Diabetes mellitus	447 (19.7)	43 (28.5)	404 (19.0)
Hypertension	929 (40.9)	88 (58.3)	841 (39.6)
Anterior MI/ LBBB	1195 (52.6)	90 (59.6)	1105 (52.1)
Reperfusion Therapy**			
Primary PCI	1355 (61.5)	70 (47.1)	1285 (62.4)
Pharmaco-invasive approach	234 (10.6)	7 (4.8)	227 (11.0)
Thrombolysis alone	372(16.9)	38 (26.0)	334 (16.2)
CABG	199 (8.8)	192 (9.0)	7 (4.6)
No reperfusion	243 (11.0)	31 (21.2)	212 (10.3)
LVEF			
<35%	964 (43.1)	96 (64.9)	868 (41.6)
35-50%	893 (39.9)	41 (27.7)	852 (40.8)
≥50%	380 (16.1)	11 (7.4)	369 (17.7)
Medication at Discharge			
Aspirin	2246 (98.8)	148 (98.0)	2098 (98.8)
P2Y12 inhibitors	2199 (96.7)	143 (94.7)	2056 (96.8)
β-blockers	1868 (82.2)	121 (80.1)	1747 (82.3)
ACE-Is/ARBs	1694 (74.5)	117 (77.5)	1577 (74.3)
Statins	2208 (97.1)	145 (96.0)	2063 (97.2)

\*Data are presented as mean±SD or numbers (%).

STEMI, ST-segment-elevation myocardial infarction; MACE, Major adverse cardiovascular events; CK-MB, Creatine kinase-MB; LDL-C, Low-density lipoprotein cholesterol; HDL-C, High-density lipoprotein cholesterol; GFR, Glomerular filtration rate; MI, Myocardial infarction; CABG, Coronary artery bypass surgery; LBBB, Left bundle branch block; PCI, Percutaneous coronary intervention; LVEF, Left ventricular ejection fraction; ACE-Is/ARBs, Angiotensin-converting enzyme inhibitors or angiotensin receptor blockers.

\*\*Seventy-three patients with primary PCI, 29 patients with pharmaco-invasive strategies, and 27 patients with thrombolysis alone finally received CABG during the index hospitalization.

35%, low GFR, a history of stroke, low hemoglobin levels, no formal schooling, and thrombolytic and no reperfusion therapies vs primary PCI increased the incidence of MACE significantly. Ever smoking and a high BMI were protective

factors of MACE in the unadjusted analyses; however, after adjustments for all the variables, the significant association of ever smoking disappeared.

Table 3 shows the independent predictors of MACE and

Table 2. Risk factors associated with 1-year MACE of STEMI patients

	Crude Model HR (95% CI)	P	Fully Adjusted HR (95% CI)	P
Age (y)	1.05 (1.04-1.07)	<0.001	1.02 (1.00-1.05)	0.018
Female sex	2.05 (1.47-2.86)	<0.001	1.04 (0.64-1.68)	0.878
Years of schooling (Reference: 12 y)	1		1	
<12 y	1.70 (0.98-2.95)	0.057	1.37 (0.74-2.53)	0.317
0	4.16 (2.49-6.95)	<0.001	1.88 (0.99-3.57)	0.055
Place of residence (others)	1.29 (0.90-1.87)	0.167	1.12 (0.75-1.68)	0.565
History of MI	1.22 (0.77-1.94)	0.395	0.86(0.50-1.49)	0.594
History of stroke	3.78 (2.42-5.89)	<0.001	2.12 (1.28-3.53)	0.004
History of CABG	0.82 (0.48-1.39)	0.461	0.75 (0.36-1.58)	0.451
Ever Smoker	0.72 (0.52-0.99)	0.045	0.99 (0.66-1.49)	0.978
Diabetes mellitus	1.65 (1.16-2.35)	0.005	1.32 (0.87-2.00)	0.199
Hypertension	2.08 (1.51-2.88)	<0.001	1.36 (0.91-2.03)	0.131
LDL-C	1.00 (0.99-1.00)	0.753	1.00 (1.00-1.01)	0.340
HDL-C	0.99 (0.97-1.01)	0.403	0.98 (0.96-1.00)	0.122
GFR	0.97 (0.96-0.97)	<0.001	0.99 (0.98-1.00)	0.057
Hemoglobin	0.84 (0.77-0.91)	<0.001	0.96 (0.86-1.08)	0.514
Body mass index	0.91(0.88-0.95)	<0.001	0.94 (0.89-0.99)	0.017
Anterior MI/ LBBB	1.36 (0.98-1.88)	0.065	1.06(0.70-1.60)	0.799
Peak CK-MB	1.00 (1.00-1.002)	0.147	1.00 (1.00-1.002)	0.047
Reperfusion therapy (Reference: Primary PCI)	1		1	
Pharmaco-invasive approach	0.57 (0.26-1.24)	0.158	0.74 (0.34-1.64)	0.462
Thrombolysis	2.03 (1.37-3.01)	<0.001	1.89 (1.21-2.95)	0.005
CABG	1.40 (0.56-3.47)	0.468	1.85 (0.58-5.91)	0.302
No reperfusion	2.58 (1.69-3.93)	<0.001	1.65 (0.99-2.76)	0.053
LVEF (Reference: 50%)	1		1	
35-50%	1.61 (0.83-3.12)	0.163	1.63(0.78-3.44)	0.197
<35%	3.59 (1.92-6.70)	<0.001	2.94(1.39-6.19)	0.005
Medication at Discharge				
Aspirin	0.60(0.19-1.87)	0.375	0.89 (0.23-3.44)	0.861
P2Y12 inhibitors	0.59(0.29-1.21)	0.152	0.58 (0.26-1.33)	0.198
β-blockers	0.87(0.58-1.30)	0.501	0.68 (0.44-1.05)	0.085
ACE-Is/ARBs	1.18(0.81-1.73)	0.387	1.07 (0.70-1.63)	0.759
Statins	0.71 (0.31-1.61)	0.416	0.68 (0.28-1.63)	0.385

MACE, Major adverse cardiovascular events; STEMI, ST-segment–elevation myocardial infarction; HR: Hazard ratio; CI, Confidence interval; MI, Myocardial infarction; CABG, Coronary artery bypass surgery; LDL-C, Low-density lipoprotein cholesterol; HDL-C, High-density lipoprotein cholesterol; GFR, Glomerular filtration rate; LBBB, Left bundle branch block; CK-MB, Creatine kinase-MB; PCI, Percutaneous coronary intervention; LVEF, Left ventricular ejection fraction; ACE-Is/ARBs, Angiotensin-converting enzyme inhibitors or angiotensin receptor blockers

all-cause mortality based on the multivariable analysis. In this model, age, a history of stroke, LVEF, GFR, peak CK-MB, BMI, education, and types of reperfusion were associated with the occurrence of MACE. In addition, LVEF <35% versus ≥50% was associated with an almost 3-fold higher risk for MACE (HR: 2.82, 95% CI: 1.46–5.47; P=0.002). BMI per 1 kg/m<sup>2</sup> was an independent predictor for the low incidence of MACE (HR: 0.94, 95% CI: 0.89–0.99; P=0.012). In the sensitivity analysis, the independent predictors of all-cause mortality were similar to those in our main analysis.

## Discussion

In the present study, we investigated the risk factors associated with 1-year MACE among STEMI survivors, which is essential for identifying high-risk patients and secondary prevention. The results indicated that older age, no formal schooling, stroke history, peak CK-MB, thrombolytic therapy vs primary PCI, and LVEF <35% vs ≥50% were associated with the increased incidence of MACE, while a high GFR and a high BMI were predictors of a reduced incidence rate of MACE.



Table 3. Multivariable analysis of factors associated with 1-year MACE and all-cause mortality in STEMI patients

	MACE		All-Cause Mortality	
	HR (95% CI)	P	HR (95% CI)	P
Age (y)	1.02 (1.00-1.04)	0.032	1.03 (1.01-1.05)	0.011
Years of schooling (Reference: 12 [y])	1		1	
<12 (y)	1.32 (0.75-2.34)	0.336	1.04 (0.52-2.08)	0.918
0	2.07 (1.17-3.67)	0.013	2.12 (1.08-4.15)	0.028
History of stroke	2.37 (1.48-3.81)	<0.001	2.61 (1.56-4.40)	<0.001
GFR	0.98 (0.97-1.00)	0.009	0.98 (0.97-1.00)	0.013
Body mass index	0.94 (0.89-0.99)	0.012	0.94 (0.88-0.99)	0.019
Peak CK-MB	1.00 (1.00-1.002)	0.038	1.00 (1.00-1.002)	0.035
Reperfusion therapy (Reference: Primary PCI)	1		1	
Pharmaco-invasive approach	0.68 (0.31-1.48)	0.330	0.84 (0.36-1.97)	0.682
Thrombolysis	1.85 (1.21-2.81)	0.004	1.75 (1.06-2.90)	0.030
CABG	1.34 (0.54-3.33)	0.533	1.09 (0.34-3.50)	0.889
No reperfusion	1.58 (0.98-2.56)	0.061	1.78 (1.05-3.03)	0.033
LVEF (Reference: $\geq 50\%$ )	1		1	
35-50%	1.55 (0.77-3.13)	0.218	1.49 (0.68-3.27)	0.322
<35%	2.82 (1.46-5.47)	0.002	2.41 (1.14-5.07)	0.021

MACE, Major adverse cardiovascular events; STEMI, ST-segment-elevation myocardial infarction; HR: Hazard ratio; CI, Confidence interval; GFR, Glomerular filtration rate; CK-MB, Creatine kinase-MB; PCI, Percutaneous coronary intervention; CABG Coronary artery bypass surgery; LVEF, Left ventricular ejection fraction

Survivors of MI are at an elevated risk of death and nonfatal recurrent cardiovascular events in the future.<sup>1, 2</sup> A systematic review of post-MI patients showed that the risk of subsequent events was at least 30% higher than that of the general population in the long term.<sup>4</sup> In our study, the 1-year post-discharge MACE and all-cause mortality rates among hospital survivors of STEMI were 6.6% and 5.1%, respectively. In line with our results, the 1-year STEMI mortality rate after hospital discharge was 5.2% in a prospective multicenter registry from 5 major cities in Iran.<sup>15</sup> Other studies have also indicated a high incidence rate of recurrent cardiovascular events,<sup>3, 5</sup> although this rate varies considerably between high-income countries and LMICs, based on their health system infrastructure.<sup>16</sup>

In our adjusted analyses, patients with fewer years of formal education had a higher risk of MACE incidence. Several studies have revealed associations between education and mortality and morbidity after cardiac events.<sup>5, 17</sup> By way of example, Yusuf et al,<sup>18</sup> in a large international study (n=155 722), showed that low education was the single largest risk factor compared with other risk factors such as tobacco smoking, hypertension, and diabetes, with the highest population attributable fraction for mortality. A study in China using data from a large-scale nationwide cohort of MI patients showed that lower educational attainment was associated with a 68% increase in the risk of 1-year cardiovascular events.<sup>17</sup> Some studies have shown that lower education levels are accompanied by a high occurrence rate of cardiovascular risk factors such as diabetes, hypertension, and smoking.<sup>19, 20</sup> Education level as a substitute for economic

status<sup>9</sup> affects diverse domains of life, including exposure to healthier social and working environments, better access to health services, and social support.<sup>18</sup> Moreover, poorly educated patients are less likely to have a deep understanding of their disease, clinicians' recommendations,<sup>21</sup> and good adherence to medications.<sup>9</sup>

Obesity is known as an important risk factor for cardiovascular disease and death.<sup>22</sup> However, there are conflicting data on the association between BMI and adverse cardiovascular events among MI patients.<sup>23, 24</sup> Some studies have indicated that obesity is associated with poor survival among MI patients.<sup>23</sup> By contrast, some post-MI studies, in line with our results, have reported that a high BMI has a protective effect on short- and long-term mortality (a phenomenon often termed "the obesity paradox").<sup>24, 25</sup> Our study showed that a high BMI was related to a decreased incidence of MACE and all-cause mortality, even after adjusting for other covariates and excluding patients with a BMI value below 18.5 kg/m<sup>2</sup>. These findings chime in with a study by Plakht et al,<sup>25</sup> who showed that after adjustments for age, LVEF, reperfusion therapy, renal dysfunction, and anemia, the obesity paradox persisted. In a large-scale cohort study of the Iranian population, BMI was a poor predictor of cardiovascular mortality.<sup>26</sup> Researchers argued that BMI could not differentiate between fat mass, muscle, or bone density and could not reflect fat distribution in the body.<sup>26</sup>

Our results showed that appropriate reperfusion therapy was an independent predictor of the incidence of MACE and mortality. According to guidelines, primary PCI, when implemented in a timely manner (<120 min), is the best

strategy in the treatment of STEMI patients and is associated with lower risks of death and adverse outcomes.<sup>27</sup> However, in LMICs, inadequate infrastructure is a major barrier to the optimal treatment of STEMI patients, and a small proportion of these patients receive primary PCI.<sup>16</sup> Multiple studies have suggested that the pharmaco-invasive approach may be a realistic alternative when it is not possible to perform a timely primary PCI.<sup>28</sup> In our study, among 919 patients without primary PCI, only 25.5% received pharmaco-invasive therapy, whereas in some high-income countries, using well-organized STEMI networks, almost all non-primary PCI-treated patients undergo pharmaco-invasive therapy.<sup>29</sup> We found that the pharmaco-invasive approach had a lower rate of MACE incidence than primary PCI, although the difference was statistically nonsignificant. Similar findings concerning the incidence of MACE and mortality in the pharmaco-invasive approach compared with primary PCI have been reported in some other studies.<sup>28</sup>

We showed that old age, stroke history, a low GFR, peak CK-MB, and left ventricular dysfunction also had significant associations with the incidence of MACE, which is similar to the findings of other studies.<sup>3-5</sup> We found that a lower LVEF (<35% vs ≥50%), with a risk ratio of nearly 3.0, was the strongest independent predictor of adverse events. In agreement with our study, some studies have reported that a lower LVEF is one of the most powerful predictors of mortality and morbidity.<sup>5</sup> In addition, in our final model, peak CK-MB, independent of LVEF, was significantly associated with the incidence of MACE, indicating the significance of the extent of infarction in recurrent cardiovascular events. Our results demonstrated that an increased GFR was independently associated with a low incidence rate of MACE, which is consistent with prior findings among STEMI patients.<sup>30</sup> Some other studies have indicated that renal dysfunction is a major risk factor for adverse cardiovascular events.<sup>5,31</sup>

To our knowledge, this is the first large registry-based study with a 1-year follow-up of STEMI patients to rigorously adjudicate predictors of fatal and nonfatal recurrent cardiovascular events in western Iran. Our findings should be interpreted in the context of the following limitations. Although participation in secondary prevention programs such as cardiac rehabilitation and lifestyle modification programs could improve the survival rate and quality of life of STEMI patients, we did not have data on such programs in this study. Given that our study is observational, the findings may be influenced by unmeasured confounding variables. In addition, similar to any observational study, there is a possibility of information bias, especially in self-reported variables. Our results are based on data from a tertiary cardiovascular hospital with primary PCI capability; therefore, they cannot be generalized to the entire province or country. Finally, small numbers of nonfatal MI and stroke events precluded separate analyses of the individual

components of MACE.

## Conclusion

In the present study, among ST-segment–elevation myocardial infarction survivors, age, formal schooling, stroke history, glomerular filtration rate, body mass index, peak CK-MB, reperfusion therapy, and left ventricular ejection fraction were associated with the occurrence of major cardiovascular events during a 1-year follow-up. Our findings highlight the importance of reperfusion therapy, especially the pharmaco-invasive approach, in the incidence of cardiovascular events in our population. These results also indicate that investment in education can improve the long-term health conditions of these patients. Identifying the long-term predictors of recurrent cardiovascular events can improve the quality of clinical care and secondary prevention programs.

## Acknowledgments

The authors thank those who participated in this study. Further, we wish to deeply appreciate our hardworking colleagues Dr Hossein Siabani, who provided data collection quality control, and Ms. Leila Zamzam, Mrs. Hanyeh Charejo, and Ms. Elaheh Mohammadi, who collected the data. This study was approved and supported by Kermanshah University of Medical Sciences, Kermanshah, Iran.

## References

1. Tu JV, Austin PC, Walld R, Roos L, Agras J, McDonald KM. Development and validation of the Ontario acute myocardial infarction mortality prediction rules. *J Am Coll Cardiol* 2001;37:992-997.
2. Virani SS, Alonso A, Aparicio HJ, Benjamin EJ, Bittencourt MS, Callaway CW, Carson AP, Chamberlain AM, Cheng S, Delling FN, Elkind MSV, Evenson KR, Ferguson JF, Gupta DK, Khan SS, Kissela BM, Knutson KL, Lee CD, Lewis TT, Liu J, Loop MS, Lutsey PL, Ma J, Mackey J, Martin SS, Matchar DB, Mussolino ME, Navaneethan SD, Perak AM, Roth GA, Samad Z, Satou GM, Schroeder EB, Shah SH, Shay CM, Stokes A, VanWagner LB, Wang NY, Tsao CW; American Heart Association Council on Epidemiology and Prevention Statistics Committee and Stroke Statistics Subcommittee. Heart disease and stroke statistics-2021 update: a report from the American Heart Association. *Circulation* 2021;143:e254-e743.
3. Jernberg T, Hasvold P, Henriksson M, Hjelm H, Thuresson M, Janzon M. Cardiovascular risk in post-myocardial infarction patients: nationwide real world data demonstrate the importance of a long-term perspective. *Eur Heart J* 2015;36:1163-1170.
4. Johansson S, Rosengren A, Young K, Jennings E. Mortality and morbidity trends after the first year in survivors of acute myocardial infarction: a systematic review. *BMC Cardiovasc Disord* 2017;17:53.
5. Wang Y, Li J, Zheng X, Jiang Z, Hu S, Wadhwa RK, Bai X, Lu



- J, Wang Q, Li Y, Wu C, Xing C, Normand SL, Krumholz HM, Jiang L. Risk factors associated with major cardiovascular events 1 year after acute myocardial infarction. *JAMA Netw Open* 2018;1:e181079.
6. Timmis A, Townsend N, Gale CP, Torbica A, Lettino M, Petersen SE, Mossialos EA, Maggioni AP, Kazakiewicz D, May HT, De Smedt D, Flather M, Zuhlik L, Beltrame JF, Huculeci R, Tavazzi L, Hindricks G, Bax J, Casadei B, Achenbach S, Wright L, Vardas P; European Society of Cardiology. European Society of Cardiology: Cardiovascular disease statistics 2019. *Eur Heart J* 2020;41:12-85.
  7. Finegold JA, Asaria P, Francis DP. Mortality from ischaemic heart disease by country, region, and age: statistics from World Health Organisation and United Nations. *Int J Cardiol* 2013;168:934-945.
  8. Tunstall-Pedoe H, Vanuzzo D, Hobbs M, Mähönen M, Cepaitis Z, Kuulasmaa K, Keil U. Estimation of contribution of changes in coronary care to improving survival, event rates, and coronary heart disease mortality across the WHO MONICA Project populations. *Lancet* 2000;355:688-700.
  9. Yusuf S, Islam S, Chow CK, Rangarajan S, Dagenais G, Diaz R, Gupta R, Kelishadi R, Iqbal R, Avezum A, Kruger A, Kutty R, Lanan F, Lisheng L, Wei L, Lopez-Jaramillo P, Oguz A, Rahman O, Swidan H, Yusuf K, Zatonski W, Rosengren A, Teo KK; Prospective Urban Rural Epidemiology (PURE) Study Investigators. Use of secondary prevention drugs for cardiovascular disease in the community in high-income, middle-income, and low-income countries (the PURE Study): a prospective epidemiological survey. *Lancet* 2011;378:1231-1243.
  10. Chandrashekar Y, Alexander T, Mullasari A, Kumbhani DJ, Alam S, Alexanderson E, Bachani D, Wilhelmus Badenhorst JC, Baliga R, Bax JJ, Bhatt DL, Bossone E, Botelho R, Chakraborty RN, Chazal RA, Dhaliwal RS, Gamra H, Harikrishnan SP, Jeilan M, Kettles DI, Mehta S, Mohanan PP, Kurt Naber C, Naik N, Ntsekhe M, Otieno HA, Pais P, Piñeiro DJ, Prabhakaran D, Reddy KS, Redha M, Roy A, Sharma M, Shor R, Adriaan Snyders F, Weii Chieh Tan J, Valentine CM, Wilson BH, Yusuf S, Narula J. Resource and infrastructure-appropriate management of ST-segment elevation myocardial infarction in low- and middle-income countries. *Circulation* 2020;141:2004-2025.
  11. Statistical Centre of Iran. Estimation of population in Iran by province and year. <https://rb.gy/vgedij> (1 January 2021).
  12. Thygesen K, Alpert JS, Jaffe AS, Chaitman BR, Bax JJ, Morrow DA, White HD; Executive Group on behalf of the Joint European Society of Cardiology (ESC)/American College of Cardiology (ACC)/American Heart Association (AHA)/World Heart Federation (WHF) Task Force for the Universal Definition of Myocardial Infarction. Fourth universal definition of myocardial infarction (2018). *J Am Coll Cardiol* 2018;72:2231-2264.
  13. Levey AS, Stevens LA, Schmid CH, Zhang YL, Castro AF, 3rd, Feldman HI, Kusek JW, Eggers P, Van Lente F, Greene T, Coresh J; CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration). A new equation to estimate glomerular filtration rate. *Ann Intern Med* 2009;150:604-612.
  14. Greenland S, Pearce N. Statistical foundations for model-based adjustments. *Annu Rev Public Health* 2015;36:89-108.
  15. Kassaian SE, Masoudkabar F, Sezavar H, Mohammadi M, Pourmoghaddas A, Kojuri J, Ghaffari S, Sanaati H, Alaeddini F, Pourmirza B, Mir E; IPACE2 Registry Investigators. Clinical characteristics, management and 1-year outcomes of patients with acute coronary syndrome in Iran: the Iranian Project for Assessment of Coronary Events 2 (IPACE2). *BMJ Open* 2015;5:e007786.
  16. Xavier D, Pais P, Devereaux PJ, Xie C, Prabhakaran D, Reddy KS, Gupta R, Joshi P, Kerkar P, Thanikachalam S, Haridas KK, Jaison TM, Naik S, Maity AK, Yusuf S; CREATE registry investigators. Treatment and outcomes of acute coronary syndromes in India (CREATE): a prospective analysis of registry data. *Lancet* 2008;371:1435-1442.
  17. Huo X, Khera R, Zhang L, Herrin J, Bai X, Wang Q, Lu Y, Nasir K, Hu S, Li J, Li X, Zheng X, Masoudi FA, Spertus JA, Krumholz HM, Jiang L. Education level and outcomes after acute myocardial infarction in China. *Heart* 2019;105:946-952.
  18. Yusuf S, Joseph P, Rangarajan S, Islam S, Mentz A, Hystad P, Brauer M, Kutty VR, Gupta R, Wielgosz A, AlHabib KF, Dans A, Lopez-Jaramillo P, Avezum A, Lanan F, Oguz A, Kruger IM, Diaz R, Yusuf K, Mony P, Chifamba J, Yeates K, Kelishadi R, Yusufali A, Khatib R, Rahman O, Zatonka K, Iqbal R, Wei L, Bo H, Rosengren A, Kaur M, Mohan V, Lear SA, Teo KK, Leong D, O'Donnell M, McKee M, Dagenais G. Modifiable risk factors, cardiovascular disease, and mortality in 155 722 individuals from 21 high-income, middle-income, and low-income countries (PURE): a prospective cohort study. *Lancet* 2020;395:795-808.
  19. Kubota Y, Heiss G, MacLehose RF, Roetker NS, Folsom AR. Association of educational attainment with lifetime risk of cardiovascular disease: the atherosclerosis risk in communities study. *JAMA Intern Med* 2017;177:1165-1172.
  20. Schultz WM, Kelli HM, Lisko JC, Varghese T, Shen J, Sandesara P, Quyyumi AA, Taylor HA, Gulati M, Harold JG, Mieres JH, Ferdinand KC, Mensah GA, Sperling LS. Socioeconomic status and cardiovascular outcomes: challenges and interventions. *Circulation* 2018;137:2166-2178.
  21. Dennison CR, McEntee ML, Samuel L, Johnson BJ, Rotman S, Kieley A, Russell SD. Adequate health literacy is associated with higher heart failure knowledge and self-care confidence in hospitalized patients. *J Cardiovasc Nurs* 2011;26:359-367.
  22. Lavie CJ, Milani RV, Ventura HO. Obesity and cardiovascular disease: risk factor, paradox, and impact of weight loss. *J Am Coll Cardiol* 2009;53:1925-1932.
  23. Rana JS, Mukamal KJ, Morgan JP, Muller JE, Mittleman MA. Obesity and the risk of death after acute myocardial infarction. *Am Heart J* 2004;147:841-846.
  24. Nigam A, Wright RS, Allison TG, Williams BA, Kopecky SL, Reeder GS, Murphy JG, Jaffe AS. Excess weight at time of presentation of myocardial infarction is associated with lower initial mortality risks but higher long-term risks including recurrent reinfarction and cardiac death. *Int J Cardiol* 2006;110:153-159.
  25. Plakht Y, Shiyovich A, Weitzman S, Fraser D, Zahger D, Gilutz H. A new risk score predicting 1- and 5-year mortality following acute myocardial infarction Soroka Acute Myocardial Infarction (SAMI) project. *Int J Cardiol* 2012;154:173-179.
  26. Nalini M, Sharafkhan M, Poustchi H, Sepanlou SG, Pourshams A, Radmard AR, Khoshnia M, Gharavi A, Dawsey SM, Abnet CC, Boffetta P, Brennan P, Sotoudeh M, Nikmanesh A, Merat S, Etemadi A, Shakeri R, Malekzadeh R, Kamangar F. Comparing anthropometric indicators of visceral and general adiposity as determinants of overall and cardiovascular mortality. *Arch Iran Med* 2019;22:301-309.
  27. Fazel R, Joseph TI, Sankardas MA, Pinto DS, Yeh RW, Kumbhani DJ, Nallamothu BK. Comparison of reperfusion strategies for ST-segment-elevation myocardial infarction: a multivariate network meta-analysis. *J Am Heart Assoc* 2020;9:e015186.
  28. Sim DS, Jeong MH, Ahn Y, Kim YJ, Chae SC, Hong TJ, Seong IW, Chae JK, Kim CJ, Cho MC, Rha SW, Bae JH, Seung KB, Park SJ; Korea Acute Myocardial Infarction Registry (KAMIR) Investigators. Pharmacoinvasive strategy versus primary percutaneous coronary intervention in patients with ST-segment-elevation myocardial infarction: a propensity score-matched analysis. *Circ Cardiovasc Interv* 2016;9:e003508.
  29. Huber K, Goldstein P, Danchin N, Fox KA, Welsh R, Granger CB, Henry T, Gersh BJ. Enhancing the efficacy of delivering reperfusion therapy: a European and North American experience with ST-segment elevation myocardial infarction networks. *Am Heart J* 2013;165:123-132.
  30. Salehi N, Motevaseli S, Janjani P, Bahremand M, Heidari Moghadam R, Rouzbahani M, Siabani S, Tadbiri H, Nalini M. Reperfusion therapy and predictors of 30-day mortality after ST-segment elevation myocardial infarction in a university medical center in western Iran. *Arch Iran Med* 2021;24:796-803.
  31. Sarnak MJ, Amann K, Bangalore S, Cavalcante JL, Charytan DM, Craig JC, Gill JS, Hlatky MA, Jardine AG, Landmesser U, New-





by LK, Herzog CA, Cheung M, Wheeler DC, Winkelmayr WC, Marwick TH; Conference Participants. Chronic kidney disease and coronary artery disease: JACC state-of-the-art review. *J Am Coll Cardiol* 2019;74:1823-1838.