Clinical Presentation and Outcomes in Real-Life Management of Elderly Patients Aged ≥75 Years Presenting with Acute Myocardial Infarction

ABSTRACT

Background: The aim of this study was to provide insight into the real-life clinical presentation and outcomes of the elderly presenting with acute myocardial infarction from the Turkish Myocardial Infarction registry database.

Methods: TURKMI was a nationwide, multicenter, observational, 15-day snapshot registry conducted to address the management of acute myocardial infarction patients admitted to percutaneous intervention-capable hospitals. The present analysis included the comparison of consecutively enrolled acute myocardial infarction patients aged ≥75 and <75 years.

Results: Of the overall 1930 patients, 362 patients were aged ≥75 years. Elderly patients were more likely to have hypertension and renal failure and less likely to have hypercholesterolemia. Elderly patients were admitted to hospitals almost 1 hour later mainly due to a late call to emergency medical service. At discharge, medical therapies were significantly less prescribed to the elderly. The proportion of patients undergoing coronary angiography was significantly lower in elderly (81.8% vs. 96.4%, $P < .001$). Both in-hospital and 1-year mortality were significantly higher in elderly patients (9.1% vs. 2.7% and 22.7% vs. 5.8%, $P < .001$ respectively). The adjusted risk of 1-year mortality was 4-fold in elderly (hazard ratio and 95% CI 4.0 [2.9-5.6], $P < .001$). In multivariate analysis, every 5-beat/min increase in heart rate increased mortality by 7%. Higher heart rate and use of antiplatelet agents on admission were predictors of mortality in elderly.

Conclusion: In real-life settings, elderly patients presenting with acute myocardial infarction are prone to prolonged total ischemic time and are subjected to less-intensive medical treatment and interventional approaches. Besides age, the increased heart rate could be the major determinant of mortality.

Keywords: Acute myocardial infarction, coronary artery disease, preventive cardiology, PTCA/PCI

INTRODUCTION

Age is an independent risk factor for adverse events after myocardial infarction (MI), and mortality rates gradually increase in elderly patients.[1] However, elderly patients have been often underrepresented in randomized clinical trials.[2] Despite improvements in early revascularization and medical therapy in MI, evidence-based medical treatment and revascularization remain inadequate in elderly MI patients compared to younger patients.[3] Moreover, elderly individuals are subjected to more conservative treatment strategies contrarily to the recommendations of the guidelines.

The course of acute MI in elderly patients includes significant differences from the non-elderly patients. Diagnosis, treatment, and follow-up after discharge include various difficulties. Both the impact of co-morbidities and the real benefits of the interventions are not clear. Elderly is less likely to receive coronary angiography after MI[4]; however, the specific subjects for the less-aggressive approach are not well defined. On the other hand, short-term clinical outcomes were decreased in these elderly patients owing to these less-optimal therapies.[5,6] The aim of our study was to present the course of MI including variations in hospital admissions,

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risk factors, co-morbidities, and antiplatelet regimen in elderly population in a nation-wide real-life clinical data and to determine in-hospital and 1-year mortality in this particular population.

METHODS

Study Population

The present study is generated from the nationwide TURKMI registry[7] which was conducted to assess the management of patients with acute MI. Of note, TURKMI (clinicaltrials.gov NCT04241770) was a national, multicenter, observational study conducted in 50 percutaneous intervention (PCI)-capable cardiology centers selected from the regions according to their sampling weight. Study protocol was approved by the Ethics Committee (No: 2018-46; Date: October 09, 2018). Written informed consent was obtained from all participants. The present analysis included the comparison of those ≥75 years with younger (<75 years [non-elderly group]) consecutively admitted with acute MI to the participating hospitals.

According to TURKMI protocol, inclusion criteria were (1) being hospitalized within 48 hours from the onset of symptoms of the index event; (2) having a final (discharge) diagnosis of acute MI (either ST-elevation MI [STEMI] or non-ST-elevation [NSTEMI]) with positive troponin levels, and (3) signed informed consent. Patients unwilling or unable to consent were excluded. Patient demographic and medical history data, presenting symptoms, admission mode (self-transport, by ambulance, or transfer from other hospitals), in-hospital clinical course including cardiac medications and interventional procedures, and 1-year mortality were obtained prospectively. For the diagnosis of MI, the third universal definition was used, detail regarding MI definition is described elsewhere.[7]

Definitions and Outcomes

All treatment decisions were based according to patients' clinical settings and attending clinicians' decisions. All definitions of risk factors and co-morbidities were described in detail in the design article of the TURKMI study.[7] Hypertension was defined as blood pressure ≥140/90 mm Hg and/or patients taking antihypertensive therapy before MI. Hypercholesterolemia was also termed as fasting total cholesterol ≥200 mg/dL or low-density lipoprotein (LDL)

cholesterol ≥130 mg/dL or taking any cholesterol-lowering drugs. Obesity was described according to the body mass index ≥ 30 kg/m^2. Diabetes mellitus (DM) was defined as the fasting glucose levels ≥ 126 mg/dL, glycated hemoglobin more than 6.5% where available, or a history of diabetes diagnosis/treatment. If the patient ever smoked actively before MI, he or she was termed to be a smoker. Other co-morbidities like atrial fibrillation, chronic kidney disease, peripheral arterial disease, and family history of premature coronary artery disease were defined in detail elsewhere.[7] In-hospital death (cardiovascular or other reasons), non-fatal MI, stroke, coronary or peripheral revascularization, emergency department visit due to chest pain or dyspnea, hospitalization for heart failure was assessed during hospitalization and at the end of the first month. All-cause mortality of the elderly population was also assessed 1 year after the index event.

Statistical Analysis

Categorical variables were presented as the number and percentage and were compared using the chi-square test, Fisher's exact test, or the Mantel—Haenszel test between the independent groups such as gender and risk categories. These variables were given as the mean ± standard deviation or median and interquartile range and were compared using an independent t-test or the Mann—Whitney U test. The Kolmogorov—Smirnov test was used for the normal distribution of continuous variables. Comparison of the cumulative mortality risk between patients ≥75 years old or younger was made using the Kaplan—Meier method and compared with a log-rank test. Multiple analysis was performed with stratified Cox regression analysis, in which the diagnosis (STEMI or NSTEMI) was included in the model as a stratum. Several models were created. In the first model (baseline characteristics model), age category, sex, history of MI/coronary bypass/PCI, heart rate at admission, the time between symptom onset and arrival at the study center, and acetylsalicylic acid use at baseline were included in the model. To be able to consider the angiographic characteristics, the second and the third models were performed in patients who underwent coronary angiography (n=1808). The second model included the variables of PCI (PCI performed or not performed) and the number of vessels (single vessel or multivessel), along with the variables included in the baseline model. In order to limit the variables included in the model, the number of vessel variables was replaced by the variable of left main involvement in the third model. And the last two models were compared using the Akaike information criterion (AIC). Proportional hazard assumption was assessed with log-minus-log plots and testing the Schoenfeld residuals. Log linearity was assessed by plotting Martingale residuals. Analyses were conducted using Statistical Package for the Social Sciences 18.0 for Windows and Stata, and a P value of <.05 was considered significant.

RESULTS

Of the 1930 patients included in the TURKMI study, 362 patients aged ≥75 years (18.7%) consisted of our study population. Non-ST-elevations were more common both in elderly and non-elderly patients compared to STEMIs (NSTEMI vs.

HIGHLIGHTS

- Elderly patients with acute myocardial infarction (AMI) are prone to prolonged total ischemic time.
- Elderly patients with AMI are subjected to less-intensive medical and interventional treatment.
- The adjusted risk of 1-year mortality is 4-fold in elderly patients with AMI.
- Increased heart rate is a major determinant of mortality in elderly with AMI.
- Late admission is a major determinant of mortality in elderly with AMI.

STEMI: 66.9% vs. 33.1% in the elderly and 60.8% vs. 39.2% in the non-elderly groups, $P < .001$).

Baseline Characteristics
Table 1 depicts the baseline characteristics including the laboratory measurements of the elderly patients in comparison to non-elderly. The proportion of women was higher in the elderly MI patients (46.4% vs. 21.4%, $P < .001$). For risk factors, only the proportion of hypertension was higher in the

elderly, hypercholesterolemia, obesity, smoking, and family history of cardiovascular disease (CVD) were all significantly more frequent in the non-elderly group. The proportion of self-reported diabetes was similar in the 2 groups. Estimated glomerular filtration rate was also higher in the non-elderly group [85.8 (68.1-101.6) vs. 60.1(45.5-78.8), $P < .001$]. Prior diagnosis of coronary artery disease and CVD was similar between the groups except for atrial fibrillation and heart failure which were more frequent in the elderly patients

Table 1. Baseline Characteristics of the Elderly Patients (>75 years of age) in Comparison with the Non-elderly Patients

	Elderly patients (>75 years)	Non-Elderly patients (< 75 years)	P
n	362	1568	
Age, year (mean ± SD)	81 ± 5	58 ± 10	<.001
Female, n (%)	168 (46.4)	336 (21.4)	<.001
BMI (kg/m²) (mean ± SD)	26.74 ± 4.2	27.91 ± 4.19	<.001
Risk factors			
Hypertension, n (%)-Based on patient's self-report	234 (64.6)	721 (46)	<.001
Hypercholesterolemia, n (%)	89 (32.7)	526 (43.7)	.001
Diabetes, n (%)-Based on patient's self-report	123 (34)	531 (33.9)	.967
Obesity (BMI ≥30 kg/m²), n (%)	63 (19)	376 (26.6)	.004
Weight < 60 kg	41 (12.3)	43 (2.7)	<.001
Smoking, n (%)	72 (19.9)	870 (55.5)	<.001
Family history of CV disease, n (%)	24 (6.6)	164 (10.5)	.027
History of CV disease, n (%)			
History of coronary artery disease and/or CABG and/or PCI)	107 (29.6)	443 (28.3)	.620
Myocardial infarction	58 (16)	204 (13)	.132
PCI	55 (15.2)	284 (18,1)	.188
CABG	39 (10.8)	126 (8)	.093
Transient ischemic attack or stroke	8 (2.2)	21 (1.3)	.220
Peripheral arterial disease	4 (1.1)	13 (0.8)	.542
Heart failure	14 (3.9)	31 (2)	.032
Atrial fibrillation	12 (3.3)	11 (0.7)	<.001
Valve surgery	0 (0)	5 (0.3)	.591
Pacemaker/intracardiac defibrillator	3 (0.8)	4 (0.3)	.127
Concomitant disease, n (%)			
Cancer	16 (4.4)	38 (2.4)	.038
Thyroid disease	9 (2.5)	41 (2.6)	.890
Renal failure	32 (8.8)	71 (4.5)	.001
Chronic obstructive lung disease	29 (8)	66 (4.2)	.003
History of bleeding	3 (0.8)	7 (0.4)	.409
Laboratory findings (mean ± SD)			
White blood cell (K/mm³)	10.8 ± 4.3	11.6 ± 20.2	.004
Hemoglobin (g/dL)	12.8 ± 2.1	14.1 ± 2.1	<.001
Blood glucose (mg/dL)	136.8 ± 65.2	131.3 ± 59.2	.174
Creatinine (mg/dL)	1.2 ± 0.7	1.1 ± 1.8	<.001
Total cholesterol (mg/dL)	180.1 ± 47.2	196.9 ± 51.5	<.001
LDL-cholesterol (mg/dL)	113.9 ± 38.7	125.0 ± 42.8	<.001
HDL-cholesterol (mg/dL	42.5 ± 10.5	40.9 ± 10.4	.001
Triglycerides (mg/dL)	123.5 ± 69.7	173.3 ± 127.9	<.001

BMI, body mass index; LDL, low-density lipoprotein; HDL, high-density lipoprotein; CV, cardiovascular; CABG, coronary artery bypass grafting; PCI, percutaneous coronary intervention.

compared to non-elderly. For concomitant disease, elderly patients were more likely to have renal failure, chronic obstructive pulmonary disease, and cancer.

Of the laboratory evaluation on admission, creatine levels were significantly higher in elderly patients with MI compared to the non-elderly patients (1.21 ± 0.7 vs. 1.09 ± 1.81, $P < .001$). However, white blood cell count and LDL-cholesterol levels were higher in a non-elderly group.

Admission Symptoms, Mode of Admission, and Timings
Variables related to hospital admissions including symptoms and timings are given in Table 2. Among the admission symptoms, dyspnea was reported significantly more in the elderly patients than non-elderly (30.1% vs. 15.1%, $P < .001$), whereas all other symptoms and admission systolic blood pressure did not differ between the groups. However, heart rate was significantly higher in the elderly group on admission (84.75 ± 19 vs. 81.8 ± 19 bpm, $P = .001$). The mode of admission did not differ between the groups. In elderly patients with STEMI, median total ischemic time was 86 minutes longer than non-elderly population. This delay was mainly due to the late call of the emergency medical services (EMS). In the STEMI patients, door to balloon time was similar between the groups. Also, all the timings of patients with NSTEMI did not differ between the groups.

Electrocardiographic Findings on Index Admission
Comparisons of the groups according to electrocardiogram (ECG) findings on index admission are presented in Supplementary Table 1. Abnormal ECG findings such as left bundle branch block, right bundle branch block, non-Q wave MI, non-specific ST/T abnormalities, and higher heart rates were more frequent in elderly patients. Although T wave inversion was similar in both groups, ST-depression in 2 adjacent derivations of ≥ 1 mm was more common in the elderly group (50.8 % vs. 42.2% $P = .003$). Atrial fibrillation was also more common in the elderly group compared to younger patients (12.7% vs. 4.1% $P < .001$).

Medications Before Admission and Prescribed at Discharge
All medications before admission and prescribed at discharge are summarized in Table 3. Before hospital admission of the index event, almost 1/3 of the elderly patients were already on acetylsalicylic acid therapy. The proportion of elderly patients on treatment including beta-blockers, Ca

Table 2. Variables Related to Hospital Admissions Including Symptoms and Timings

	Elderly Patients (Age >75 Years)	Non-elderly Patients (Age < 75 Years)	P
n	362	1568	
Symptoms on admission, n (%)			
- Angina pectoris	344 (95)	1489 (95)	.959
- Dyspnea	109 (30.1)	236 (15.1)	<.001
- Palpitation	18 (5)	62 (4)	.381
- Cardiac arrest	5 (1.4)	30 (1.9)	.494
- Syncope	7 (1.9)	26 (1.7)	.715
- Other	22 (6.1)	107 (6.8)	.608
Hemodynamic variables on admission (mean $\pm$ SD)			
- Systolic blood pressure (mm Hg)	135.17 ± 26.6	134.37 ± 26.07	.669
- Heart rate (per minute)	84.75 ± 18.91	81.8 ± 18.63	.001
Mode of hospital admission, n (%)			
Self-transport	171 (47.24)	760 (48.47)	.451
By ambulance	41 (11.33)	181 (11.54)	
Transfer from other hospital	136 (37.57)	590 (37.63)	
Other**	14 (3.87)	37 (2.36)	
Time intervals Median (Q1-Q3) of the hospital admissions for the index event			
For ST-elevation MI			
From symptom onset to EMS call (minutes)	67.5 (50-230)	30 (12-105)	.025
From symptom onset to hospital arrival (minutes)	141.5 (60-399)	84 (40-185)	<.001
Door-to-balloon time (minutes)	38 (29-70)	36 (25-65)	.202
Total ischemic time (minutes)	270 (150-489)	184 (106-315)	<.001
For Non-ST-elevation MI			
From symptom onset to EMS call (minutes)	100 (10-282.5)	60 (20-290)	.993
From symptom onset to hospital arrival (minutes)	199 (60-420)	150 (60-420)	.316

**Transfer from other departments of the same hospitals or myocardial infarction detected during the examinations in the outpatient clinics of the same hospitals.
MI, myocardial infarction; EMS, emergency medical service.

antagonists, nitrates, and angiotensin-converting enzyme (ACE) inhibitors were significantly higher compared to those non-elderly patients at baseline (Table 3). However, the use of lipid-lowering medications was similar between the groups.

The evaluation of medications prescribed at discharge revealed that clopidogrel was preferred in 71.2% of elderly patients, while almost half of the non-elderly patients have prescribed ticagrelor (45%). At discharge, beta-blockers, ACE inhibitors, and anti-lipid drugs were significantly less prescribed to the elderly patients compared to those non-elderly. However, calcium antagonists, nitrates, and diuretics were prescribed in the elderly more often. The dual antiplatelet strategy was prescribed less frequently to the elderly group than non-elderly (91.4% vs. 94.5%, $P = .032$).

Coronary Angiography and Percutaneous Coronary Intervention

The proportions of elderly patients either evaluated by coronary angiography or underwent primary PCI were significantly lower than non-elderly (81.8% vs. 96.4%, $P < .001$ and 33.7% vs. 41.2%, $P = .01$, respectively) (Table 4). thrombolysis in myocardial infarction (TIMI)-0 flow after PCI was more frequent in the elderly (5.6% vs. 2.2%, $P = .009$).

Complications After the Myocardial Infarction

All adverse events were more frequently observed in the older age group. Cardiogenic shock, arrhythmias including sustained ventricular tachycardia, and ventricular fibrillation leading to cardiac arrest were observed more in the elderly patients with MI than non-elderly patients (Table 4).

Table 3. Medications Before Admission and Prescribed at Discharge

	Aged >75 years, n = 362	Aged < 75 years, n = 1568	P
Medications before admission, n (%)			
Antiplatelet agents			
Acetyl salicylic acid	112 (34.8)	422 (28.8)	.033
Clopidogrel	37 (10.2)	148 (9.4)	.649
Ticagrelor	0 (0.0)	1 (0.1)	–*
Prasugrel	0 (0.0)	3 (0.2)	–*
Beta blockers	103 (32)	294 (20.0)	<.001
Calcium antagonists	61 (18.9)	182 (12.4)	.002
Nitrates	29 (9.0)	41 (2.8)	<.001
Anti-lipid agents	39 (12.1)	217 (14.8)	.214
ACE inhibitors	65 (20.2)	219 (14.9)	.019
Medications prescribed at discharge, n (%)			
Anti-platelet agents			
Acetyl salicylic acid	322 (98.8)	1508 (99.5)	.243
Clopidogrel	232 (71.2)	698 (46.0)	<.001
Ticagrelor	68 (20.9)	682 (45.0)	<.001
Prasugrel	1 (0.3)	57 (3.8)	.001
Dual antiplatelet	298 (91.4)	1433 (94.5)	.032
Anti-coagulants	25 (6.9)	43 (2.7)	–*
Warfarin	8 (2.3)	20 (1.3)	–*
Dabigatran	2 (0.6)	5 (0.3)	–*
Rivaroxaban	4 (1.1)	5 (0.3)	–*
Apiksaban	9 (2.6)	11 (0.7)	–*
Edoxaban	2 (0.6)	2 (0.1)	–*
Beta blockers	274 (78.1)	1272 (82.5)	.053
Calcium antagonists	62 (17.7)	184 (11.9)	.004
Anti-lipid agents	300 (92.6)	1456 (97.1)	<.001
Diuretics	75 (21.4)	223 (14.5)	.001
ACE inhibitors	165 (47.0)	897 (58.2)	<.001
Angiotensin receptor blockers	32 (9.1)	112 (7.3)	.237
Digitalis	2 (0.6)	7 (0.5)	.676
Anti-arrhythmic	8 (2.3)	16 (1.0)	.067
Nitrates	44 (12.5)	109 (7.1)	.001
Anti-diabetic agents	34 (9.7)	174 (11.3)	.388

*not analyzed
ACE, angiotensin converting enzyme

Table 4. Coronary Angiography, Percutaneous Coronary Intervention, and Adverse Events in Groups During the In-Hospital Period of the Index Event

		Aged >75 Years n =362	Aged < 75 Years n=1568	P
Coronary angiography and percutaneous coronary intervention in groups				
Patients underwent coronary angiography n (%)		296 (81.8)	1512 (96.4)	<.001
Primary PCI, n (%)		122 (33.7)	647 (41.2)	.010
Rescue PCI, n (%)		0 (0.0)	7 (0.4)	.360
Elective PCI, n (%)		95 (27.3)	449 (29.3)	.456
TIMI flow after PCI	0	12 (5.6)	26 (2.2)	.009
	I	6 (2.8)	15 (1.3)	
	II	13 (6.0)	57 (4.8)	
	III	185 (85.6)	1080 (91.7)	
In-hospital adverse events and mortality				
Atrial fibrillation n (%)		4 (1.1)	10 (0.6)	.313
Cardiogenic shock n (%)		13 (3.6)	23 (1.5)	.007
Arrest − VF, n (%)		17 (4.7)	24 (1.5)	<.001
Sustained VT, n (%)		7 (1.9)	9 (0.6)	.019
Mechanical complication, n (%)		0 (0.0)	2 (0.1)	-
AV block, n (%)		2 (0.6)	1 (0.1)	-
Acute renal failure, n (%)		24 (6.6)	38 (2.4)	<.001
Bleeding, n (%)		9 (2.5)	18 (1.1)	.051
Infection, n (%)		8 (2.2)	24 (1.5)	.362
In-hospital mortality, n (%)		33 (9.1)	42 (2.7)	<.001

VF, ventricular fibrillation; VT, ventricular tachycardia; AV, atrioventricular block, PCI, percutaneous coronary intervention.

Mortality

In-hospital mortality was 3 times higher in elderly patients compared to non-elderly patients (9.1% (n=33) vs. 2.7% (n=42), $P < .001$). Among 362 elderly patients, 82 (22.7%) patients died during the 1-year follow-up. The incidence rate of mortality was higher in the elderly in both NSTEMI and STEMI (for NSTEMI patients aged <75 years 1.79 per 10 000 and patients aged ≥75 years 7.61 per 10 000; for STEMI patients aged <75 years 1.62 per 10 000 and patients aged ≥75 years 8.34 per 10 000). Figure 1 shows the cumulative risk of 1-year mortality in patients with STEMI and NSTEMI.

Univariate comparison of patients who died or survived among the elderly population according to baseline characteristics is presented in Table 5. The patients who died were older, had a higher heart rate, and lower blood pressure during the index event compared to those survived elderly patients. Although the predominant symptom was chest pain, the proportion of dyspnea was relatively higher in non-survived patients. Prior history of renal disease and being on acetylsalicylic acid therapy before the index event and depressed baseline left ventricular ejection fraction were significantly associated with increased 1-year mortality in the elderly group.

In the multiple model 1 (adjusted for baseline characteristics), the risk of 1-year mortality was 4 times higher in the elderly group (HR and 95% CI 4.00 [2.86-5.59]; $P < .0001$). Also, higher heart rate, late hospital admission, and antiplatelet use on admission were significantly associated with higher mortality when the whole study population was taken into the analysis (Table 6a). In patients who underwent
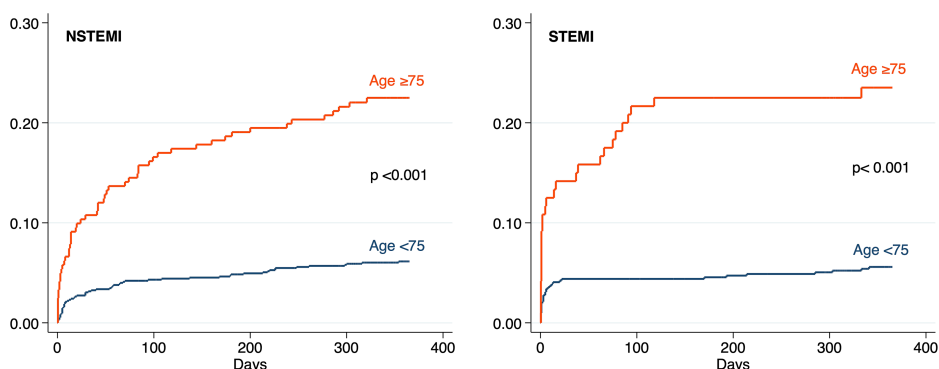

Figure 1. Cumulative risk of 1-year mortality in both NSTEMI and STEMI. STEMI, ST-elevation MI; NSTEMI, non-ST-elevation MI.

Table 5. Univariate Predictors of 1-Year Mortality in Elderly Patients

	Survived Elderly n = 280 (77.3%)	Died Elderly n = 82 (22.7%)	P
Age, mean (SD)	80.65 (4.67)	82.02 (5.19)	.023
Male gender, n (%)	154 (55.0)	40 (48.8)	.321
Weight, mean (SD)	73.38 (11.37)	71.49 (14.55)	.235
STEMI, n (%)	92 (32.9)	28 (34.1)	.827
Anterior STEMI localization, n (%)	44 (48.4)	14 (50)	.879
Angina on admission, n (%)	271 (96.8)	73 (89.0)	.004
Dyspnea on admission, n (%)	69 (24.6)	40 (48.8)	.0001
Mode of hospital admission, n (%)			
Self-transport	142 (50.7)	29 (35.4)	.037
By ambulance	26 (9.3)	15 (18.3)	
Transfer from other hospital	101 (36.1)	35 (42.7)	
Other*	11 (3.9)	3 (3.7)	
History of hypercholesterolemia, n (%)	33 (11.8)	7 (8.5)	.409
History of diabetes, n (%)	91 (32.5)	32 (39.0)	.273
History of smoking, n (%)	56 (20.0)	16 (19.5)	.922
Family history of CVD, n (%)	11 (3.9)	3 (3.7)	.911
History of AF, n (%)	9 (3.2)	3 (3.7)	.843
History of renal disease, n (%)	20 (7.1)	12 (14.6)	.036
Prior acetyl salicylic acid use, n (%)	77 (30.9)	35 (47.9)	.007
HR (bpm) on admission, mean (SD)	83.40 (17.4)	89.42 (22.9)	.011
Systolic BP (mm Hg) on admission, mean (SD)	138.1 (25.3)	124.8 (28.3)	.0001
Coronary angiography and/or PCI, n (%)	238 (85.0)	56 (68.3)	.001
LVEF**, % mean (SD)	46.1 (10.9)	41.2 (11.8)	.003
Acute renal failure, n (%)	11 (3.9)	13 (15.9)	.0001
Major bleeding, n (%)	1 (0.4)	3 (3.7)	.012

*Transfer from other departments of the same hospitals or myocardial infarction detected during the examinations in the outpatient clinics of the same hospitals. **Data for ejection fraction was available for 78.5% of the elderly population.
STEMI, ST-elevation myocardial infarction; CVD, cardiovascular disease; AF, atrial fibrillation; HR, heart rate; BP, blood pressure; PCI, percutaneous coronary intervention; LVEF, left ventricle ejection fraction.

coronary angiography, the addition of the multivessel disease (model 2) or left main coronary artery involvement (model 3) improved the statistical model (based on the AIC values), however, provided similar results for elderly people (HR and 95% CIs were 3.94 [2.64-5.88], and 4.11 [2.76-6.13]; P values < .001) (Table 6a). As a sensitivity analysis, patients with a history of cancer were excluded from the analysis. Hazard ratio and 95% CIs for the elderly group were 4.35 (3.06-6.17) in model 1, 4.44 (2.93-6.73) in model 2, and 4.62 (3.05-6.98) in model 3 (P values < .001).

However, when only patients aged >75 years were taken into account, the multivariate analysis revealed that higher heart rate and use of antiplatelet agents on admission were the 1-year mortality predictors in patients presenting with acute MI (Table 6b). Additionally, every 5-beat increase per minute in heart rate increased mortality by 7% when we considered only the elderly population (Table 6b).

DISCUSSION

Our contemporary data showed that the risk of in-hospital and 1-year mortality was 3.4 and 4 times higher in the elderly patients (aged ≥ 75 years) with MI compared to those aged <

75 years, respectively. Increased heart rate and antiplatelet use on admission were the major determinants of mortality in elderly patients with MI. Elderly patients are admitted to the hospitals almost 1 hour later mainly due to late calls to EMS leading to prolonged total ischemic time compared to patients aged < 75 years. Moreover, elderly patients are still less treated with coronary invasive strategies and evidence-based medical therapies including dual antiplatelet therapies, anti-hyperlipidemia drugs, and renin-angiotensin system (RAS) blockers compared to those younger than 75 years.

In accordance with the previous data, our study showed that the elderly patients were more likely to have NSTEMIs (66.9% vs. 60.8%, P = .032) as compared to the non-elderly patients.[8] Mortality after MI tends to increase progressively with aging, and the risk of death especially during hospitalization or within the first month after acute coronary events increase with advanced age.[9-11] The prevalence of conventional CVD risk factors in the elderly was different from non-elderly in the present database. According to a previous study, although the mortality of women with STEMI was found to be higher than that of men,[12] this may be explained by the advanced age of women presenting with STEMI. In our

Table 6a. Baseline Characteristics of Fully Adjusted Model of Whole Study Population

Characteristics	Adjusted HR, CI	*P*
Model 1#		
Being aged ≥75 years	4.0 (2.86-5.59)	.0001
Male	0.96 (0.68-1.37)	.828
Heart rate*	1.09 (1.05-1.14)	.000
Time from symptom-onset to hospital arrival**	1.01 (1.0-1.03)	.022
Acetyl salicylic acid use at baseline	1.32 (0.90-1.93)	.158
Model 2##		
Being aged ≥75 years	3.94 (2.64-5.88)	.0001
Male	0.97 (0.64-1.48)	.886
Heart rate*	1.11 (1.06-1.15)	.0001
Time from symptom onset to hospital arrival**	1.01 (1.0-1.03)	.102
Acetyl salicylic acid use at baseline	1.08 (0.67-1.73)	.747
Percutaneous coronary intervention	0.72 (0.45-1.14)	.161
Multi vessel disease	1.71 (0.97-3.04)	.066
Model 3###		
Being aged ≥75 years	4.11 (2.76-6.13)	.0001
Male	0.97 (0.64-1.49)	.905
Heart rate*	1.11 (1.06-1.16)	.000
Time from symptom-onset to hospital arrival**	1.01 (1.0-1.03)	.100
Acetyl salicylic acid use at baseline	1.07 (0.66-1.71)	.793
Percutaneous coronary intervention	0.74 (0.46-1.19)	.219
Left main coronary artery involvement	1.56 (1.03-2.35)	.034

Cox proportional hazard regression model, significance at *P* < .01.
Stratified by diagnosis.
#Adjusted for age, gender, history of myocardial infarction, coronary bypass, percutaneous coronary intervention, heart rate at admission, time between symptom onset and arrival at the study center, and acetylsalicylic acid use at baseline.
*Every 5 beats increase per minute in heart rate.
**Every 30 minutes delay from symptom-onset to hospital arrival.
Adjusted for age, gender, history of myocardial infarction, coronary bypass, percutaneous coronary intervention, heart rate at admission, time between symptom onset and arrival at the study center, and acetylsalicylic acid use at baseline, percutaneous coronary intervention at any time, multivessel disease.
Adjusted for age, gender, history of myocardial infarction, coronary bypass, percutaneous coronary intervention, heart rate at admission, time between symptom onset and arrival at the study center, and acetylsalicylic acid use at baseline, percutaneous coronary intervention at any time, left main coronary artery involvement.

elderly population, the effect of gender on 1-year mortality of MI could not be demonstrated. As expected, elderly were more likely to have risk factors like hypertension, heart failure, and renal failure which are known to increase with age, whereas the elderly were less likely to have hypercholesterolemia, smoking, obesity, and family history of CVD. Patients with higher lipid levels and family history of CVD who could be more likely to have familial hypercholesterolemia or those with higher life-long CVD risk would probably not live long till the older ages. As the cumulative effect of LDL cholesterol leads to CVD events in early ages, hypercholesterolemia may not be a strong predictor of CVD in the elderly as in young adults. However, SCORE risk charts developed for older people (SCORE-OP) revealed that even though hypercholesterolemia and other traditional risk factors do not strongly predict CVD risk as in the younger population, more effective management of these risk factors such as LDL-cholesterol lowering with statins and blood pressure treatment is still effective in terms of lowering CVD events in the elderly.[13-15] Of note, SCORE-OP was developed for the age group of 65-80 years from the SCORE-risk calculation model and validated to predict CVD mortality better than the standard risk scales.[16] It is clear that risk estimation by taking into account the older individuals such as in SCORE OP reduces excessive use of medication in the elderly population by decreasing the overestimation of the risk. However, in our elderly population with a mean age of 81 ± 5 years, smoking and hypercholesterolemia were no longer presented as risk factors for 1-year mortality. Therefore, in this late elderly group, the attenuation of the association between traditional risk factors and CVD risk might be more pronounced probably due to increased co-morbidities as in our elderly MI patients.

Recently, the SCORE2-OP model covering the age interactions for risk factors was introduced. This new model also highlighted the necessity to improve the accuracy of risk prediction in elderly patients, due to the wide distribution of 10-year CVD event risk in these patients.[17] Likewise, low body weight (<60 kg) was significantly more common in our elderly patients compared to those younger aged. It is well known that being underweight is associated with

Table 6b. Multiple Analysis of 1-Year Mortality Predictors in Patients Aged >75 Years Presenting with Acute Myocardial Infarction

Characteristics	Adjusted HR, CI	P
Model-1[#]		
Male	0.93 (0.58-1.51)	.776
Heart rate*	1.07 (1.00-1.14)	.041
Time from symptom-onset to hospital arrival**	1.01 (1.0-1.03)	.105
Acetyl salicylic acid use at baseline	1.89 (1.13-3.15)	.015
Model-2[##]		
Male	0.73 (0.41-1.32)	.299
Heart rate*	1.10 (1.02-1.19)	.016
Time from symptom-onset to hospital arrival**	1.01 (0.99-1.04)	.193
Acetyl salicylic acid use at baseline	1.62 (0.84-3.10)	.147
Percutaneous coronary intervention	0.62 (0.31-1.22)	.166
Multi vessel disease	1.23 (0.48-3.18)	.669
Model-3[###]		
Male	0.73 (0.41-1.32)	.299
Heart rate*	1.10 (1.02-1.19)	.016
Time from symptom-onset to hospital arrival**	1.02 (0.99-1.04)	.182
Acetyl salicylic acid use at baseline	1.58 (0.83-3.04)	.165
Percutaneous coronary intervention	0.67 (0.34-1.33)	.248
Left main coronary artery involvement	1.51 (0.81-2.78)	.191

Cox proportional hazard regression model, significance at *P* < .01.
Stratified by diagnosis.
[#]Adjusted for age, gender, history of myocardial infarction, coronary bypass, percutaneous coronary intervention, heart rate at admission, time between symptom-onset and arrival at the study center, and acetylsalicylic acid use at baseline.
*Every 5 beats increase per minute in heart rate.
**Every 30 minutes delay from symptom-onset to hospital arrival.
[##]Adjusted for age, gender, history of myocardial infarction, coronary bypass, percutaneous coronary intervention, heart rate at admission, time between symptom-onset and arrival at the study center, and acetylsalicylic acid use at baseline, percutaneous coronary intervention at any time, multivessel disease.
[###]Adjusted for age, gender, history of myocardial infarction, coronary bypass, percutaneous coronary intervention, heart rate at admission, time between symptom-onset and arrival at the study center, and acetylsalicylic acid use at baseline, percutaneous coronary intervention at any time, left main coronary artery involvement.

both poor outcomes and also with increased risk of frailty in the elderly,[18,19] and addition of frailty indices or at least low body weight could improve the CVD risk estimation in the elderly patients.

Another important finding of our analysis was the late arrival of the elderly patients. Both in STEMI and NSTEMIs, the elderly were almost 60 min and 50 min, respectively, late to admit compared to those younger than 75 years of age. The major component of late arrival was the late EMS call after symptom onset in our cohort. Late admissions due to delayed contact with EMS especially in the elderly patients with STEMI could lead to increased total ischemic time which is directly related to mortality. Elderly patients who were admitted to the hospital during the index event by self-transport rather than ambulance and/or transferring from another hospital were reported to survive more after 1-year follow-up. This was probably due to more preference for self -transportation by less severe patients.

Our real-life data showed that elderly patients are still subjected to more conservative treatment strategies, despite the evidence-based recommendations in the guidelines. Although elderly patients were more aggressively treated with beta-blockers and ACE inhibitors compared to non-elderly patients before MI, after the infarction the proportion of patients prescribed beta-blockers, ACE inhibitors, and lipid-lowering agents were less in the elderly patients. These results could be due to reduced renal functions, higher risk of drug interactions, and higher risk of drug-induced adverse effects in elderly patients. Moreover, the use of clopidogrel was significantly higher in our elderly group (71.2% vs. 46.0%, *P* < .001), while almost half of the non-elderly patients have prescribed ticagrelor (45%) at discharge from the hospital. Nevertheless, selecting the antiplatelet therapy and tailoring the dosage of the antithrombotic therapy is of importance in the elderly considering the increased bleeding risk and reduced renal functions. Considering the risk of bleeding in the elderly, clopidogrel, a less potent drug, might have been preferred naturally in this group. Indeed, the low use of dual antiplatelet strategy in the elderly supported this idea. The higher rates of co-morbidities including atrial fibrillation and renal failure might have also affected the antiplatelet drug choice.

In our study, elderly patients underwent coronary angiography and primary PCI less than non-elderly. This might be due to a higher proportion of multivessel disease, left main disease, comorbidities, and late admission in the elderly.

Though merge at the end of 1 year, the course of mortality curves differed according to the type of MI. The cumulative risk of 1-year mortality was increased steeply during the first 3 months then followed by a plateau in STEMI patients. Meanwhile, mortality has increased gradually in the NSTEMI. Mortality curves came closer in 1-year in patients with STEMI and NSTEMI (Figure 1). A rapid increase in the cumulative risk of mortality in the early period after STEMI could be explained by a higher frequency of mechanical complications and arrhythmias in the first 3 months, and the more depressed myocardium in the early period after STEMI.

Although in-hospital mortality was higher in elderly patients in our study (9.1%) compared to non-elderly patients (2.7%), it is obvious that the cut-off age for defining the elderly affects the mortality rates following MI in this population. In Euro-Heart ACS Survey, in-hospital death was 16.8% in patients aged > 85 years.[20] In a recent study of STEMI, although the primary PCI was performed in 78% of the patients, overall, in-hospital mortality was 24% in the elderly aged ≥90 years.[21] In another study[22] including both STEMI and NSTEMI patients, 10.2% of patients aged 80 years old died during the index hospitalization, and it was comparable with 9.1% in-hospital mortality in our elderly acute MI patients aged > 75 years. Defining the cut-off age for the determination of the elderly age limit could be a matter of debate. Although many guidelines do not define elderly by any specific age criteria, studies mostly describe patients aged 65 years or older as elderly patients and those aged > 75 years as "late elderly patients." However, currently, it is proposed to change the definition of elderly to those over 75 years of age instead of the current 65 years in accordance with the aging of the population.[23] Therefore, the 75 years we used in our database is currently the most preferred cutoff, whereas older data suggested lower cutoffs, such as 65 years.[24]

In the China Acute Myocardial Infarction (CAMI) registry, primary PCI was safe and effective with a reduction of mortality in patients ≥75 years old.[25] In our study, 81.8% of the elderly patients with MI underwent coronary angiography and 33.7% underwent primary PCI. Likewise, in KAMIR-NIH registry, PCI was performed in 87.4% of elderly patients, and in-hospital and 1-year mortality were much lower (3.9% and 4.3%, respectively).[26] It is obvious that invasive revascularization in the geriatric population is more complicated and challenging due to the increased frequency of multi-vessel disease, left main coronary involvement, calcified lesions, and decreased left ventricular systolic functions with age.[27] The proportion of TIMI flow rate of zero was reported more in our elderly group, and it could be related with increased in-hospital mortality rates in this population. This finding could be the result of late hospital admissions and longer total ischemic times in our elderly patients. On the other hand, it should be noted that PCI was not associated with mortality in a multivariate model. The risk of 1-year mortality was 4 times higher in the elderly group. Besides from being elderly, increased heart rate and late hospital admission were the major drivers for mortality. All of these findings could trigger each other and complicate the picture of the MI. Late hospital admissions which are more frequent in the elderly MI patients could lead to increased myocardial damage and acute heart failure, resulting with increased heart rates. Especially, in elderly patients with late presentations, increased heart rates could be the important indicator of mortality.

Strengths and Limitations

The major strength of the present study is representation of a nationwide real-life clinical practice for the management of elderly patients with acute MI. The prospective enrollment of MI patients consecutively within a 2-week period is another strength. As the elderly patients are mostly excluded from the clinical trials, our study is of importance to fill the gap by depicting the impact of the implementation of the latest guideline-recommended treatments in the elderly population.

Our study has several limitations. First, we enrolled only primary PCI-capable hospitals and assumed that all the patients with acute MI are eventually directed to these sites. Consequently, in these primary PCI-capable hospitals, the elderly patients with MI mostly underwent coronary angiograms contrary to the previous data. We did not include patients who died before admission to the study centers. The elderly patients who died (n = 82) represent a relatively small group and multiple analyses should be carefully evaluated accordingly.

CONCLUSION

Our nationwide real-life data with a prospective enrollment of MI patients revealed important information about the management of acute MI in elderly patients. Both in-hospital and 1-year mortality rates are higher in elderly patients compared to non-elderly patients. Mortality determinants for in-hospital and 1-year follow-up periods could differ among the elderly and the non-elderly patients with MI, in terms of baseline patient characteristics, prior comorbidities and medications, admission features, and treatment strategies. Elderly patients with acute MI admit to hospitals with longer total ischemic times and are still subjected to less-intensive medical therapies including dual antiplatelet therapies. Increased heart rate is an important determinant of survival in elderly patients presenting with MI. Related to the aging population, it is crucial to understand the risk factors and clinical presentations of elderly patients to develop appropriate primary and secondary prevention strategies for these high-risk individuals.

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Supplementary Table 1. Comparison of the Elderly and Non-elderly Patients According, Electrocardiography Findings on Index Admission

Electrocardiography Findings on Admission, n (%)	Elderly patients (Age 75 years)	Non-Elderly patients (Age < 75 years)	*P*
Sinus rhythm	307 (84.8)	1455 (92.8)	<0.001
Atrial fibrillation / Flutter	46 (12.7)	64 (4.1)	<0.001
Pace-maker	2 (0.6)	3 (0.2)	0.237
Ventricular fibrillation / Flutter	1 (0.3)	8 (0.5)	1.000
Others	4 (1.1)	19 (1.2)	1.000
New LBBB, n (%)	24 (6.8)	44 (2.9)	<0.001
New RBBB n (%)	12 (3.4)	22 (1.5)	0.013
AV Block, n (%)	11 (3.1)	33 (2.2)	0.302
ST segment elevation in 2 adjacent derivations ≥1mm, n (%)	126 (35.1)	626 (40.7)	0.052
ST segment depression in 2 adjacent derivations ≥1mm, n (%)	181 (50.8)	648 (42.2)	0.003
T wave inversion, n (%)	98 (27.6)	379 (24.8)	0.266
Non-specific ST / T changes, n (%)	95 (26.8)	336 (22.0)	0.057

LBBB, Left Bundle Branch Block; RBBB, Right Bundle Branch Block; AV, Atrioventricular Block