Journal of Cardiology 65 (2015) 216–223

Contents lists available at ScienceDirect

Journal of Cardiology

journal homepage: www.elsevier.com/locate/jjcc

Original article

Predictors of long-term (10-year) mortality postmyocardial infarction: Age-related differences. Soroka Acute Myocardial Infarction (SAMI) Project

Ygal Plakht (RN, PhD)[a,b,1,*], Arthur Shiyovich (MD)[c,1], Harel Gilutz (MD)[d]

[a] Nursing Research Unit, Soroka University Medical Center, Beer-Sheva, Israel
[b] Recanati School for Community Health Professions, Faculty of Health Sciences, Ben-Gurion University of the Negev, Beer-Sheva, Israel
[c] Department of Internal Medicine E, Rabin Medical Center, Beilinson Hospital, Petah-Tikva, Israel
[d] Department of Cardiology, Soroka University Medical Center, Beer-Sheva, Israel

ARTICLE INFO

Article history:
Received 27 December 2013
Received in revised form 21 April 2014
Accepted 3 June 2014
Available online 30 June 2014

Keywords:
Acute myocardial infarction
All-cause mortality
Prediction
Long-term risk stratification
Age-related differences

ABSTRACT

Background: Cardiovascular diseases are the leading cause of death in elderly people. Over the past decades medical advancements in the management of patients with acute myocardial infarction (AMI) led to improved survival and increased life expectancy. As short-term survival from AMI improves, more attention is being shifted toward understanding and improving long-term outcomes.
Aim: To evaluate age-associated variations in the long-term (up to 10 years) prognostic factors following AMI in "real world" patients, focusing on improving risk stratification of elderly patients.
Methods: A retrospective analysis of 2763 consecutive AMI patients according to age groups: ≤65 years (n = 1230) and >65 years (n = 1533). Data were collected from the hospital's computerized systems. The primary outcome was 10-year postdischarge all-cause mortality.
Results: Higher rates of women, non-ST-elevation AMI, and most comorbidities were found in elderly patients, while the rates of invasive treatment were lower. During the follow-up period, mortality rate was higher among the older versus the younger group (69.7% versus 18.6%). Some of the parameters included in the interaction multivariate model had stronger association with the outcome in the younger group (hyponatremia, anemia, alcohol abuse or drug addiction, malignant neoplasm, renal disease, previous myocardial infarction, and invasive interventions) while others were stronger predictors in the elderly group (higher age, left main coronary artery or three-vessel disease, and neurological disorders). The c-statistic values of the multivariate models were 0.75 and 0.74 in the younger and the elder groups, respectively, and 0.86 for the interaction model.
Conclusions: Long-term mortality following AMI in young as well as elderly patients can be predicted from simple, easily accessible clinical information. The associations of most predictors and mortality were stronger in younger patients. These predictors can be used for optimizing patient care aiming at mortality reduction.

Introduction

Cardiovascular heart disease is the leading cause of death in both men and women older than 65 years [1,2]. Among people who died of ischemic heart disease, more than 80% were ≥65 years of age [3]. Over the past decades medical advancements in the management of patients with acute myocardial infarction (AMI) led to improved survival and increased life expectancy [3]. When placed in the context of current life expectancy, AMI often occurs over a decade before end of life [3]. As short-term survival from AMI continues to improve, more attention is being shifted toward understanding and improving long-term outcomes [4–8].

The elderly, compared with younger individuals, are a unique population presenting with different clinical characteristics and a worse prognosis following AMI [2]. Actually, older age, as a factor we cannot affect, is consistently one of the main negative prognostic values in most trials and mortality following AMI increases steeply with age [2,9,10]. This was suggested to be related, in great part, to increased comorbidities and suboptimal

* Corresponding author at: Nursing Research Unit, Soroka University Medical Center, P.O.B. 151, Beer-Sheva 84101, Israel.
Tel.: +972 8 640 0029; fax: +972 8 624 4343.
E-mail addresses: Plakht@exchange.bgu.ac.il, igalpl@clalit.org.il (Y. Plakht).
[1] These authors contributed equally to this study.

http://dx.doi.org/10.1016/j.jjcc.2014.06.001
0914-5087/

treatment in these high-risk patients [2,11]. Underrepresentation of older patients in clinical trials guiding acute and long-term care coupled with the uncertainty about the benefits and risks associated with advancing age, likely explain this practice [3,12]. Thus, limited information exists regarding the age-associated disparities in the long-term prognostic factors following myocardial infarction in the real world.

The aim of the current study was to evaluate age-associated disparities in the long-term (10-year) prognostic factors following AMI in "real world" unselected patients, focusing particularly on improving risk stratification of elderly patients pointing out targets of potential interventions.

Methods

In this retrospective study, we used the database of the previously published Soroka Acute Myocardial Infarction (SAMI) Project [13,14], including patients who had been admitted for AMI in 2002–2004 and discharged alive. Out of 2773 consecutive patients, 2763 were included, as 10 patients were excluded due to missing age data. The World Heart Organization (WHO) definition was used for creating two groups of patients: younger (≤65 years) and older (>65 years of age) [10].

Data were obtained from the hospital's information systems and included demographic, cardiovascular risk factors and comorbidities, AMI clinical characteristics and interventions, and test results [13]. Grouping of diseases and interventions was based on the International Classification of Disease, Ninth Revision, Clinical Modification (ICD-9-CM) discharge codes as we have previously elaborated [13]. In addition, diagnoses of anemia were grouped together with low hematocrit and low hemoglobin blood levels (for men – hemoglobin <13 g/dL and hematocrit <39%; for women – hemoglobin <12 g/dL and hematocrit <36%, at discharge). The group of diagnoses of renal diseases included high creatinine blood levels (creatinine level ≥1.2 mg/dL, at discharge). Similarly, the diagnosis of dyslipidemia was grouped with abnormal blood lipid levels (low-density lipoprotein cholesterol >130 mg/dL). Diagnosis of diabetes mellitus (DM) was based on the diagnosis of the treating physicians without overruling and was classified as either with complications or without. Diagnoses of DM with renal manifestations were classified as renal diseases; the diagnoses of DM with peripheral vascular manifestations were grouped with peripheral vascular diseases (PVDs). Strokes (both ischemic and hemorrhagic) were included in the category "neurologic disorders". Echocardiography measurements and definitions relating to chamber sizes, mass, and function in addition to valvular function (e.g., mitral regurgitation) were in accordance with the recommendations and reference values of the American Society of Echocardiography (ASE) at that time [15,16].

Mortality data were obtained from the hospital's mortality database, updated on a weekly basis from the Ministry of the Interior Population Registry. The primary endpoint was post-discharge all-cause mortality during up to 10 years follow-up period. The study protocol conforms to the ethical guidelines of the Helsinki Declaration and was approved by the local ethics committee.

Statistical analysis

Statistical analysis of the data was performed using IBM SPSS Statistics v.20.0 software (IBM, Chicago, IL, USA). Comparisons of the prevalence rates of the investigated parameters between the groups were performed using Chi-square test. Mortality in the whole study population was assessed using Kaplan–Meier approach to survival analysis and comparison between the groups was performed with log-rank test. In addition, we compared survival rates of the study groups with the general population (matched by age, sex, and ethnicity) in Israel (1998–2002), based on the report of the Central Bureau of Statistics [17], provided the estimated annual risk of mortality. The data regarding the general population were considered as expected values; the comparisons were performed using one-sample log-rank test and are presented as standardized mortality ratio (SMR) with 95% confidence interval (CI), as it was proposed in the literature [18,19].

The strength of the association of the investigated variables with death was assessed as hazard ratio (HR) and 95% CI, using Cox proportional hazard models. In addition, for each study variable an interaction model with age group was built.

Multivariate analysis included Cox proportional hazard models. Two similar models were calculated, one model for each age group. The variables included in the models were those that were found to be statistically significant prognostic markers of the endpoint, in the univariate analysis, at least in one age group. Finally, the interaction model was performed by entering the interaction terms for all variables. For each test, p values <0.05 were considered statistically significant. Statistical significance of the interaction variables suggested different strengths of relationship between the age groups.

The accuracy of the multivariable models was assessed using c-statistic, represented by the area under the receiver operating characteristic (ROC) regression in which the follow-up period was included as covariate.

Results

Patient clinical characteristics

The age of the full cohort (n = 2763) was distributed between 25.7 and 101.5 years, mean 66.6 ± 13.3 years. The elder patients comprised 1533 (55.5%) subjects and the younger group 1230 (44.5%). Baseline characteristics according to the age groups are presented in Table 1.

A higher rate of women and non-ST-elevation myocardial infarction (NSTEMI) was found among the elder versus the younger age group. Furthermore, a higher rate of most comorbidities was found among the elders, including comorbidities that required treatment and intervention modifications [renal diseases, anemia, and chronic obstructive pulmonary disease (COPD)], except significantly lower rates of dyslipidemia and smokers. Moreover, clinical complications were more prevalent in the older group [left ventricular (LV) dysfunction, congestive heart failure (CHF), and atrial fibrillation/flutter] and echocardiography parameters representing the aging heart [elevated LV filling pressure, left atrial dilatation, and mitral regurgitation (MR)]. Significant three-vessel or left main coronary artery (LMCA) diseases and lower rates of invasive therapies were found among the elder than the younger group. Lower rates of interventional therapies [e.g., coronary artery bypass surgery (CABG) and percutaneous coronary intervention (PCI)] were found among the older age group as compared to the younger group.

Follow-up and mortality

During the follow-up period (up to 10 years; median 8.2 years), 1298 patients died (cumulative mortality of 46.8%). Cumulative mortality among the elderly was significantly higher compared with the younger group (70.0% versus 19.0%, $p < 0.001$; Fig. 1). In the total cohort, the long-term mortality rates were higher compared to age-, sex-, and ethnicity-matched general population of Israel with SMR of 2.24 (95% CI: 2.10–2.38; $p < 0.001$). Furthermore, the latter differences as compared to matched general population seemed to be somewhat more prominent in

Table 1
Baseline characteristics of the study population by age groups.

Variable	Age ≤65 years $n=1230$	Age >65 years $n=1533$	p
Demographic characteristics			
Age, years (mean; SD)	53.68; 7.55	76.11; 7.15	
Gender, male	1016 (82.6)	858 (56)	<0.001
Ethnicity (4.8% missing or unknown)			<0.001
Jews	938 (84.3)	1400 (92.3)	
Bedouins	175 (15.7)	116 (7.7)	
Cardiovascular risk factors			
Hypertension	512 (41.6)	898 (58.6)	<0.001
Dyslipidemia (14.4% missing)	912 (79.4)	826 (67.9)	<0.001
DM – all forms	373 (30.3)	590 (38.5)	<0.001
DM without recorded renal or peripheral circulation manifestations	326 (26.5)	462 (30.1)	0.036
PVD	117 (9.5)	310 (20.2)	<0.001
Tobacco use disorder	754 (61.3)	331 (21.6)	<0.001
Renal diseases (0.9% missing)	169 (13.9)	569 (37.3)	<0.001
Obesity	292 (23.7)	231 (15.1)	<0.001
Cardiac history			
History of PCI	172 (14)	179 (11.7)	0.07
History of CABG	64 (5.2)	155 (10.1)	<0.001
Previous MI	205 (16.7)	339 (22.1)	<0.001
Other cardiac disorders			
Mitral and aortic valves disorders	126 (10.2)	342 (22.3)	<0.001
Cardiomegaly	69 (5.6)	148 (9.7)	<0.001
CHF	54 (4.4)	235 (15.3)	<0.001
Atrial fibrillation and flutter	65 (5.3)	319 (20.8)	<0.001
Characteristics of AMI event			
STEMI	879 (71.5)	913 (59.6)	<0.001
Results of angiography (n)	952	742	
Coronary artery disease			<0.001
No or nonsignificant	53 (5.6)	25 (3.4)	
Significant one vessel	262 (27.5)	102 (13.7)	
Significant two vessels	278 (29.2)	205 (27.6)	
Significant three vessels or significant LMCA	359 (37.7)	410 (55.3)	
Intervention for AMI			<0.001
Conservative	419 (34.1)	926 (60.4)	
CABG	108 (8.8)	116 (7.6)	
Thrombolytic therapy or/and PCI	703 (57.2)	491 (32)	
Results of echocardiography (n)	1029	1017	
Severe left ventricular dysfunction	75 (7.3)	154 (15.1)	<0.001
Concentric or significant left ventricular hypertrophy	37 (3.6)	67 (6.6)	0.002
LV dilatation	28 (2.7)	48 (4.7)	0.017
Elevated LV filling pressure	78 (7.6)	168 (16.5)	<0.001
Moderate or severe MR	25 (2.4)	86 (8.5)	<0.001
Moderate or severe pulmonary hypertension	12 (1.2)	91 (8.9)	<0.001
Left atrial dilatation	85 (8.3)	225 (22.1)	<0.001
Significant right ventricular dysfunction	118 (11.5)	134 (13.2)	0.24
Moderate or severe tricuspid regurgitation	20 (1.9)	90 (8.8)	<0.001
Results of laboratory tests			
Plasma sodium (0.7% missing), <135 meq./L	248 (20.4)	440 (28.8)	<0.001
Plasma potassium (0.7% missing), >5.1 meq./L	201 (16.5)	428 (28)	<0.001
Other disorders			
Anemia (0.7% missing)	378 (31)	840 (55.1)	<0.001
Gastro-intestinal hemorrhage	17 (1.4)	51 (3.3)	0.001
COPD	57 (4.6)	173 (11.3)	<0.001
Malignant neoplasm	18 (1.5)	85 (5.5)	<0.001
Alcohol or drug addiction	39 (3.2)	17 (1.1)	<0.001
Schizophrenia or psychosis	17 (1.4)	25 (1.6)	0.595
Neurological disorders	15 (1.2)	52 (3.4)	<0.001

Data presented as the number of patients and percent of categories for all investigated variables except age.
SD, standard deviation; DM, diabetes mellitus; PVD, peripheral vascular disease; PCI, percutaneous coronary intervention; CABG, coronary artery bypass graft; LV, left ventricular; MR, mitral regurgitation; AMI, acute myocardial infarction; CHF, congestive heart failure; STEMI, ST-elevation myocardial infarction; LMCA, left main coronary artery; COPD, chronic obstructive pulmonary disease.

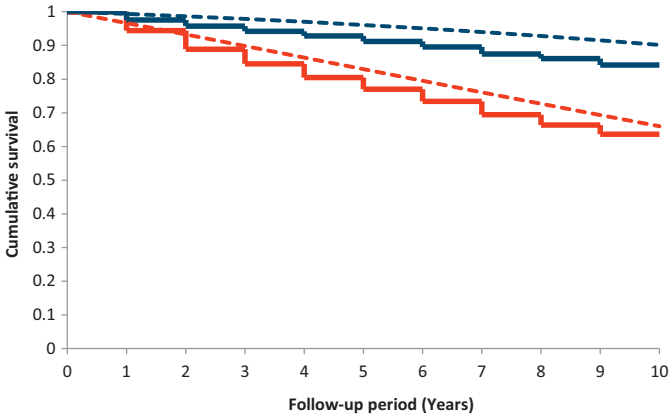

Fig. 1. Cumulative survival functions throughout the follow-up period, in the study cohort (solid lines) and the general population (dashed lines) for younger (blue/black) and older groups (red/gray).

the younger group (SMR = 2.29, 95% CI: 1.96–2.66) than in the elders (SMR = 2.22, 95% CI: 2.08–2.38) ($p < 0.001$ for each) (Fig. 1).

Age-related differences in long-term mortality predictors

A linear association was found between age and long-term mortality; 1-year increase in age was related with OR of 1.08 (95% CI: 1.08–1.09, $p < 0.001$) for mortality. Similarly, the latter linear association was found in each age group (Table 2).

The univariate analysis (Table 2) showed a linear association between age and long-term mortality in each age group. Additionally, disparities in mortality predictors between the groups were found. The association between the following significant predictors and mortality was found to be stronger in the younger than older population: cardiovascular risk factors (DM, PVD, and renal diseases); cardiac history (previous MI, CHF, and atrial fibrillation or flutter); CABG as a treatment of AMI (lower mortality compared to conservative treatment); pathologic results of echocardiography (LV dysfunction and dilatation, MR, and pulmonary hypertension); electrolyte disturbances (hyponatremia and hyperkalemia); and other noncardiovascular comorbidities (anemia, COPD, malignant neoplasm, and schizophrenia or psychosis).

Furthermore, the following characteristics were found to be significant predictors only in the younger group: Arab ethnicity, hypertension, history of CABG, cardiomegaly, and alcohol/drug addiction, while obesity (lower mortality) and significant three-vessel coronary artery or LMCA diseases (compared to no or nonsignificant) predicted long-term mortality only in the older population.

Multivariate analysis

The results of the multivariate analysis are presented in Table 3. For most significant predictors, the association with the risk of mortality was found to be stronger in the younger population, compared with the older population: renal diseases, previous MI, CABG treatment, hyponatremia, anemia, and malignant neoplasm. Furthermore, alcohol or drug addiction and schizophrenia or psychosis were significantly associated with higher risk of death only in the younger age group, while older age, significant three-vessel or LMCA diseases, left atrial dilatation, and neurological disorders only in the older age group.

The *c*-statistics of the multivariate models for 10-year all-cause mortality were 0.75 and 0.74 in the younger and the older groups, respectively. The *c*-statistic of the interaction model was 0.86.

Discussion

The current study evaluated long-term survival and age-related disparities in predictors of all-cause mortality following AMI in unselected "real life" patients. The main findings of the study include: first, significantly higher long-term mortality in older patients compared with younger; moreover, significantly higher long-term mortality of patients discharged alive following AMI compared with age-, gender-, and ethnicity-matched general population (SMR = 2.2), and somewhat greater impact of AMI on mortality in the young than in older patients compared to matched general population; second, long-term all-cause mortality in the older patients as well as in relatively young AMI patients can be accurately predicted from simple, easily accessible clinical information present at the time of initial hospital presentation including a wide variety of noncardiovascular comorbidities; third, differences in risk factors that are significantly associated with long-term mortality between older and younger populations were found.

These differences include many risk factors that are predictive only in the younger group and few that are predictive only in the older group. Moreover, there were significant disparities in the prediction strength of numerous risk factors, most of whom have stronger associations with long-term mortality in the younger group. Although the age used for the definition of older or elderly patients varies among trials from 55 to 80 years [8,20–22], standard WHO definition of 65 years, reflecting also the most common retirement age in Europe, was applied for this study. Baseline characteristics of our entire cohort, the characteristics of the older patients specifically, and the higher prevalence of women, NSTEMI, comorbidities, and risk factors in the older population are consistent with other similar cohorts of "real life" patients, applying similar age definitions [7,10]. Furthermore, the lower rates of mechanical reperfusion and the significantly increased short- and long-term mortality rates after hospital discharge in the elderly are in agreement with previous reports [7,10].

Throughout the years various short- and long-term mortality models have been reported [23–27]. Most of these models were derived from clinical trial databases or specific subgroups of patients with acute coronary syndromes. Patients with complications and comorbidity tend to be excluded from such trials, thus limiting "real world" applicability. However, the database of the current study, that served the development and validation of the recently reported SAMI score [14], is based on an unselected contemporary, "all comer" population.

The well-established GRACE score also has minimal exclusion criteria and spans the whole spectrum of acute coronary syndrome [27,28]. The GRACE score was found to accurately predict mortality at 6 months and in a recent report the score performed well (*c*-statistic 0.77) in predicting long-term mortality (5-year follow-up) after AMI. However, the mean age of the population in the latter study was between 65 and 67 years, whereas in the current and similar reports it is a decade older; hence, the results of the GRACE score is less applicable to older patients [29]. Roe et al. [7] recently reported the CRUSADE long-term mortality model and risk score that were retrospectively derived and validated on patients ≥65 years old with NSTEMI. The CRUSADE long-term mortality risk score comprised 13 most clinically and statistically significant variables from the full model (based entirely on variables from initial hospital presentation) and had comparable discrimination in the derivation and validation samples (*c*-statistics 0.734 and 0.727, respectively) for up to 3-year mortality following AMI. Furthermore, consistent with our findings, the authors found that older patients with NSTEMI still face high mortality rates of approximately 40% within 3 years of their events. However, our

Table 2
Cumulative mortality (percent of categories) according to the investigated variables by the age groups (univariate analysis); *p* values of the interaction models.

Variable	Value(s)	Age ≤65 years			Age >65 years			Interaction
		Cumulative mortality	HR	95% CI	Cumulative mortality	HR	95% CI	*p*
Demographics								
Age, years	1-Year increase		1.06***	(1.04; 1.08)		1.07***	(1.06; 1.08)	0.435
Gender	Female/male	24.8/17.3	1.49*	(1.1; 2.02)	72.9/67.2	1.16	(1.03; 1.3)	0.133
Ethnicity	Arabs/Jews	26.3/17.9	1.52*	(1.10; 2.1)	63.8/70.4	0.86	(0.68; 1.09)	0.006
Cardiovascular risk factors								
Hypertension	Yes/no	22.9/15.6	1.5**	(1.15; 1.94)	68.7/71.2	0.91	(0.8; 1.02)	0.001
Dyslipidemia	Yes/no	16.2/21.2	0.72*	(0.52; 0.99)	63.3/70.8	0.78**	(0.68; 0.91)	0.61
DM – all forms	Yes/no	33.5/12.2	3.15***	(2.43; 4.09)	77.6/64.8	1.45***	(1.28; 1.63)	<0.001
DM without recorded renal or peripheral circulation manifestations	Yes/no	28.8/14.9	2.09***	(1.6; 2.72)	74.2/67.8	1.2**	(1.05; 1.36)	<0.001
PVD	Yes/no	45.3/15.8	3.63***	(2.67; 4.94)	83.5/66.2	1.57***	(1.36; 1.8)	<0.001
Smoking	Yes/no	15.8/23.1	0.65***	(0.5; 0.84)	65.3/71.0	0.84*	(0.73; 0.98)	0.089
Renal diseases	Yes/no	47.9/13.7	4.51***	(3.43; 5.93)	81.2/63	1.7***	(1.5; 1.92)	<0.001
Obesity	Yes/no	18.1/20.2	1.1	(0.82; 1.48)	61.5/71.2	0.72***	(0.61; 0.86)	0.018
Cardiac history								
History of PCI	Yes/no	23.8/17.8	1.37	(0.98; 1.92)	68.7/69.9	0.92	(0.76; 1.11)	0.045
History of CABG	Yes/no	43.7/17.2	3.12***	(2.09; 4.62)	76.8/68.9	1.13	(0.93; 1.36)	<0.001
Previous MI	Yes/no	32.7/15.8	2.36***	(1.77; 3.13)	76.4/67.8	1.34***	(1.17; 1.54)	<0.001
Mitral and aortic valves disorders	Yes/no	31.7/17.1	2.05***	(1.46; 2.88)	76.0/67.9	1.21**	(1.05; 1.39)	0.005
Cardiomegaly	Yes/no	37.7/17.5	2.42***	(1.61; 3.64)	70.9/69.6	1.03	(0.84; 1.26)	<0.001
CHF	Yes/no	53.7/17.0	4.25***	(2.88; 6.28)	87.3/66.6	1.89***	(1.62; 2.2)	<0.001
Atrial fibrillation and flutter	Yes/no	41.5/17.3	2.81***	(1.88; 4.2)	82.4/66.4	1.5***	(1.3; 1.72)	0.004
Characteristics of AMI event, type of AMI	STEMI/NSTEMI	17.6/21.1	0.813	(0.62; 1.07)	68.9/71.0	0.92	(0.81; 1.04)	0.44
Coronary angiography findings, coronary artery disease	No or nonsignificant	18.9	1		36	1		
	Significant one vessel	9.2	0.46*	(0.22; 0.96)	42.2	1.18	(0.58; 2.42)	0.073
	Significant two vessels	15.5	0.8	(0.4; 1.59)	51.2	1.61	(0.81; 3.17)	0.156
	Significant three vessels or significant LMCA	16.7	0.88	(0.5; 1.71)	63.4	2.28*	(1.17; 4.43)	0.047
Intervention for AMI	Conservative	31.1	1		80	1		
	CABG	6.5	0.17***	(0.08; 0.37)	52.6	0.41***	(0.32; 0.54)	0.033
	Thrombolytic therapy or/and PCI	12.9	0.36***	(0.28; 0.47)	54.4	0.47***	(0.41; 0.54)	0.087
Echocardiography findings								
Severe LV dysfunction	Yes/no	46.7/14.3	4.16***	(2.87; 6.03)	84.4/61.8	2.12***	(1.75; 2.57)	0.002
Concentric or significant LV hypertrophy	Yes/no	32.4/16.0	2.14*	(1.19; 3.85)	85.1/63.8	1.96***	(1.49; 2.57)	0.788
LV dilatation	Yes/no	53.6/15.6	4.64***	(2.73; 7.89)	83.3/64.3	1.79***	(1.3; 2.47)	0.003
Elevated LV filling pressure	Yes/no	42.3/14.5	1.52***	(1.34; 1.72)	79.8/62.3	1.17***	(1.09; 1.24)	0.152
Moderate or severe MR	Yes/no	56.0/15.6	5.54***	(3.2; 9.57)	74.4/64.3	1.47**	(1.14; 1.9)	<0.001
Moderate or severe pulmonary hypertension	Yes/no	50.0/16.2	3.83**	(1.7; 8.65)	82.4/63.5	1.88***	(1.48; 2.39)	0.001
Left atrial dilatation	Yes/no	23.5/16.0	1.25	(0.99; 1.58)	77.8/61.6	1.24***	(1.14; 1.35)	0.929
Significant right ventricular dysfunction	Yes/no	28.0/15.1	1.43***	(1.18; 1.73)	76.9/63.4	1.22***	(1.1; 1.36)	0.159
Moderate or severe tricuspid regurgitation	Yes/no	70.0/15.6	7.29***	(4.21; 12.62)	78.9/63.9	1.65***	(1.29; 2.1)	<0.001
Results of laboratory tests								
Plasma sodium, meq./L	<135/≥135	28.6/15.9	1.98***	(1.5; 2.63)	77.5/66.8	1.36***	(1.2; 1.55)	0.017
Plasma potassium, meq./L	>5.1/≤5.1	29.9/16.2	2.02***	(1.51; 2.72)	77.3/67	1.35***	(1.18; 1.53)	0.013
Other disorders								
Anemia	Yes/no	28.6/14.1	2.28***	(1.76; 2.96)	77.1/61.3	1.59***	(1.4; 1.8)	0.013
Gastro-intestinal hemorrhage	Yes/no	29.4/18.5	1.84	(0.76; 4.46)	88.2/69.1	1.68***	(1.25; 2.27)	0.484
COPD	Yes/no	52.6/17.0	3.97***	(2.7; 5.83)	85.0/67.8	1.86***	(1.56; 2.21)	<0.001
Malignant neoplasm	Yes/no	61.1/18.0	4.81***	(2.62; 8.82)	85.9/68.8	1.94***	(1.53; 2.46)	0.006
Alcohol or drug addiction	Yes/no	51.3/17.5	4***	(2.55; 6.38)	82.4/69.6	1.39	(0.82; 2.36)	0.003
Schizophrenia or psychosis	Yes/no	52.9/18.1	4.08***	(2.09; 7.94)	52.9/69.4	1.62*	(1.07; 2.45)	0.021
Neurological disorders	Yes/no	20.0/18.6	1.07	(0.34; 3.35)	68.8/96.2	2.53***	(1.09; 3.37)	0.152

HR, hazard ratio; CI, confidence interval; DM, diabetes mellitus; PVD, peripheral vascular disease; PCI, percutaneous coronary intervention; CABG, coronary artery bypass graft; AMI, acute myocardial infarction; MR, mitral regurgitation; CHF, congestive heart failure; STEMI, ST-elevation myocardial infarction; NSTEMI, non-ST-elevation myocardial infarction; LMCA, left main coronary artery; LV, left ventricular; COPD, chronic obstructive pulmonary disease.
* $p < 0.05$.
** $p < 0.01$.
*** $p < 0.001$.

Table 3
Mortality risk according to the investigated variables by age groups (multivariate analysis); *p* values of the interaction model.

Variable	Value(s)	Age ≤65 years		Age >65 years		Interaction
		AdjHR	95% CI	AdjHR	95% CI	*p*
Demographics						
Age, years	1-Year increase	1.02	(1; 1.04)	1.06***	(1.05; 1.07)	0.001
Cardiovascular risk factors						
DM without recorded renal or peripheral circulation manifestations	Yes/no	1.59***	(1.19; 2.12)	1.37***	(1.2; 1.57)	0.348
PVD	Yes/no	2.15***	(1.51; 3.06)	1.37***	(1.19; 1.57)	0.065
Renal diseases	Yes/no	2.52***	(1.86; 3.41)	1.51***	(1.31; 1.75)	<0.001
Previous MI	Yes/no	1.88***	(1.38; 2.57)	1.18*	(1.02; 1.36)	0.006
Coronary angiography findings, coronary artery disease (compared to no or nonsignificant)	Significant one vessel	0.83	(0.37; 1.89)	1.56	(0.75; 3.28)	0.258
	Significant two vessels	0.95	(0.44; 2.04)	2	(0.99; 4.05)	0.155
	Significant three vessels or significant LMCA	0.83	(0.4; 1.71)	2.24*	(1.13; 4.45)	0.048
Intervention for AMI (compared to conservative)	CABG	0.1***	(0.04; 0.22)	0.46***	(0.34; 0.63)	0.001
	Thrombolytic therapy or/and PCI	0.48***	(0.33; 0.71)	0.75*	(0.6; 0.93)	0.053
Echocardiography findings						
Severe LV dysfunction	Yes/no	1.57*	(1.02; 2.39)	1.49***	(1.22; 1.82)	0.814
Moderate or severe MR	Yes/no	2.14**	(1.21; 3.81)	1.16	(0.89; 1.51)	0.06
Left atrial dilatation	Yes/no	0.97	(0.76; 1.25)	1.24***	(1.13; 1.35)	0.075
Results of laboratory tests						
Plasma sodium, meq./L	<135/≥135	1.74***	(1.29; 2.35)	1.2**	(1.05; 1.37)	0.027
Other disorders						
Anemia	Yes/no	1.89***	(1.42; 2.51)	1.38***	(1.21; 1.57)	0.045
COPD	Yes/no	2.64***	(1.76; 3.97)	2.01***	(1.68; 2.4)	0.211
Malignant neoplasm	Yes/no	3.35***	(1.74; 6.47)	1.57***	(1.23; 2)	0.036
Alcohol or drug addiction	Yes/no	3.7***	(2.27; 6.02)	1.48	(0.87; 2.53)	0.013
Schizophrenia or psychosis	Yes/no	3.01**	(1.44; 6.29)	1.47	(0.96; 2.25)	0.096
Neurological disorders	Yes/no	0.44	(0.11; 1.81)	2.31***	(1.75; 3.1)	0.023

AdjHR, adjusted hazard ratio; CI, confidence interval; DM, diabetes mellitus; PVD, peripheral vascular disease; PCI, percutaneous coronary intervention; CABG, coronary artery bypass graft; AMI, acute myocardial infarction; MR, mitral regurgitation; CHF, congestive heart failure; LMCA, left main coronary artery; LV, left ventricular; COPD, chronic obstructive pulmonary disease.
* $p < 0.05$.
** $p < 0.01$.
*** $p < 0.001$.

results further extend the findings of the latter study due to the longer follow-up period, inclusion of noncardiovascular risk factors and comorbidity, the applicability to all types of AMI and the comparison of the discriminating factors and strength of prediction between the older and the younger population, thus pointing out specific targets of potential intervention for the older group. Kala et al. [10] evaluated age-related differences in treatment strategies, results of PCI procedures and long-term mortality (5 years) of patients with all types of AMI. Although, for the most part not statistically significant, the authors report that initial signs of heart failure (Killip II–IV), the presence of DM and previous MI, final thrombolysis in myocardial infarction flow, and the infarct-related artery are significant long-term negative predictors but do not play an important role in the older group (>65 years) as they do in the younger. In addition, age was found to be a stronger predictor in the older age group. These findings of tendency toward stronger long-term prediction of risk factors and other comorbidities, in the younger population are consistent with our findings. However, more parameters were found to be significantly associated with the outcome in our study, possibly due to the longer follow-up period. Although we have not elaborately evaluated results of the coronary angiography or the PCI procedures (except the number of arteries significantly involved), that are not usually easily accessible after discharge, PCI was found to be significantly associated with reduced mortality in our study, consistently with the findings of Kala et al. [10]. However, contrary to our findings of borderline increased protective effect in the younger versus the older age group, Kala et al. reported that PCI in the older patients seems to be even more important (had a stronger protective effect) than in younger patients. This inconsistency could stem from the much higher rate of PCI in both age groups in their study compared to ours and possibly from advances in the instruments, the technique, and periprocedural and secondary prevention treatments over the years (our patients were treated approximately 5 years earlier). Alternatively, it is possible, but less likely, that the additive protective effect of PCI in the older group diminishes over time (between 5 and 10 years).

The age-related disparities in the prognostic factors found in the current study could be attributed to the following reasons. Age-related fundamental changes in the anatomy and physiology of the aging heart and cardiovascular system included among others: decreased vascular compliance, endothelial dysfunction, ventricular hypertrophy and remodeling, fibrosis leading to diastolic dysfunction, and diminished response to adrenergic stimulation [2,30–32]. Moreover, physiological aging of other systems included alterations in renal, pulmonary, and hepatic function, altered coagulation, and fibrinolytic activity (increased factor VIII, fibrinogen, and plasmin/antiplasmin complex) [2]. These age-related changes could influence the natural history and the distribution of the mortality causes and hence contribute to the age-related differences in the discriminating ability of various risk factors (e.g., left atrial dilatation, a known contributor to atrial fibrillation, was independently associated with long-term

mortality, mostly in the older group; it is possible that the association is mediated through cerebrovascular events, which are known to be more common among older patients with atrial fibrillation as evident in the CHADS score) [33].

In our study the older group differs demographically from the younger group; a lower rate of male gender and minorities were found, which are known to have a different long-term risk profile [34,35].

Although we did measure comorbidities that are not typically collected in large cardiovascular studies (e.g., malignancies, psychiatric, and neurological disorders), it is highly possible that other nonmeasured parameters such as frailty status, post-discharge management, and lifestyle issues have much stronger influence on long-term mortality in older compared to younger patients with AMI [7,36].

There are acute and long-term differences in treatment, and success rates of treatments in the older versus younger patients [37]. Elderly patients are often subjected to more conservative treatment strategies, which at times diverge significantly from recommendations in accepted guidelines [2]; thus, various insufficiently managed risk factors (e.g., hypertension, renal diseases, and dyslipidemia) could alter mortality rates and causes in the elderly.

Limitations

The data collection of baseline characteristics was retrospective. The endpoint was all-cause mortality, which limited the possibility of evaluating disparities in cause-specific mortality between the elderly and the young, as an explanation for disparities in predictors. The current study evaluated variables from initial hospital presentation and did not assess disparities in subsequent management, procedures, events, and compliance.

Conclusions

Differences in risk factors significantly associated with long-term (10-year) all-cause mortality following AMI between older and younger populations were found. These findings can be used for more accurate risk stratification of elderly patients, for prioritizing targets of potential postdischarge interventions and mortality reduction in these high-risk patients, and for measurements and comparisons of providers' outcomes.

Conflict of interest

No conflict of interest is reported.

References

[1] Murray CJ, Lopez AD. Mortality by cause for eight regions of the world: Global Burden of Disease Study. Lancet 1997;349:1269–76.

[2] Carro A, Kaski JC. Myocardial infarction in the elderly. Aging Dis 2011;2:116–37.

[3] Alexander KP, Newby LK, Cannon CP, Armstrong PW, Gibler WB, Rich MW, Van de Werf F, White HD, Weaver WD, Naylor MD, Gore JM, Krumholz HM, Ohman EM, American Heart Association Council on Clinical Cardiology, Society of Geriatric Cardiology. Acute coronary care in the elderly. Part I: Non-ST-segment-elevation acute coronary syndromes: a scientific statement for healthcare professionals from the American Heart Association Council on Clinical Cardiology: in collaboration with the Society of Geriatric Cardiology. Circulation 2007;115:2549–69.

[4] Bueno H, Armstrong PW, Buxton MJ, Danchin N, Lubsen J, Roland E, Verheugt FW, Zalewski A, Jackson N, Komajda M, Steg PG, Cardiovascular Round Table Clinical Trials ThinkTank Participants. The future of clinical trials in secondary prevention after acute coronary syndromes. Eur Heart J 2011;32:1583–9.

[5] D'Ascenzo F, Biondi-Zoccai G, Moretti C, Bollati M, Omede P, Sciuto F, Presutti DG, Modena MG, Gasparini M, Reed MJ, Sheiban I, Gaita F. TIMI, GRACE and alternative risk scores in Acute Coronary Syndromes: a meta-analysis of 40 derivation studies on 216,552 patients and of 42 validation studies on 31,625 patients. Contemp Clin Trials 2012;33(3):507–14.

[6] Biondi-Zoccai G, Lotrionte M, Agostoni P, Abbate A, Romagnoli E, Sangiorgi G, Angiolillo DJ, Valgimigli M, Testa L, Gaita F, Sheiban I. Adjusted indirect comparison meta-analysis of prasugrel versus ticagrelor for patients with acute coronary syndromes. Int J Cardiol 2011;150:325–31.

[7] Roe MT, Chen AY, Thomas L, Wang TY, Alexander KP, Hammill BG, Gibler WB, Ohman EM, Peterson ED. Predicting long-term mortality in older patients after non-ST-segment elevation myocardial infarction: the CRUSADE long-term mortality model and risk score. Am Heart J 2011;162. 875–83.e1.

[8] Cho YW, Jang JS, Jin HY, Seo JS, Yang TH, Kim DK, Kim DI, Lee SH, Cho YK, Kim DS. Relationship between symptom-onset-to-balloon time and long-term mortality in patients with acute myocardial infarction treated with drug-eluting stents. J Cardiol 2011;58:143–50.

[9] Gharacholou SM, Lopes RD, Alexander KP, Mehta RH, Stebbins AL, Pieper KS, James SK, Armstrong PW, Granger CB. Age and outcomes in ST-segment elevation myocardial infarction treated with primary percutaneous coronary intervention: findings from the APEX-AMI trial. Arch Intern Med 2011;171:559–67.

[10] Kala P, Kanovsky J, Rokyta R, Smid M, Pospisil J, Knot J, Rohac F, Poloczek M, Ondrus T, Holicka M, Spinar J, Jarkovsky J, Dusek L. Age-related treatment strategy and long-term outcome in acute myocardial infarction patients in the PCI era. BMC Cardiovasc Disord 2012;12:31.

[11] Avezum A, Makdisse M, Spencer F, Gore JM, Fox KA, Montalescot G, Eagle KA, White K, Mehta RH, Knobel E, Collet JP, GRACE Investigators. Impact of age on management and outcome of acute coronary syndrome: observations from the Global Registry of Acute Coronary Events (GRACE). Am Heart J 2005;149:67–73.

[12] Gurwitz JH, Col NF, Avorn J. The exclusion of the elderly and women from clinical trials in acute myocardial infarction. JAMA 1992;268:1417–22.

[13] 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;154:173–9.

[14] Plakht Y, Shiyovich A, Weitzman S, Fraser D, Zahger D, Gilutz H. Soroka acute myocardial infarction (SAMI) score predicting 10-year mortality following acute myocardial infarction. Int J Cardiol 2013;167:3068–70.

[15] Zoghbi WA, Enriquez-Sarano M, Foster E, Grayburn PA, Kraft CD, Levine RA, Nihoyannopoulos P, Otto CM, Quinones MA, Rakowski H, Stewart WJ, Waggoner A, Weissman NJ, American Society of Echocardiography. Recommendations for evaluation of the severity of native valvular regurgitation with two-dimensional and Doppler echocardiography. J Am Soc Echocardiogr 2003;16:777–802.

[16] Lang RM, Bierig M, Devereux RB, Flachskampf FA, Foster E, Pellikka PA, Picard MH, Roman MJ, Seward J, Shanewise JS, Solomon SD, Spencer KT, Sutton MS, Stewart WJ, Chamber Quantification Writing Group. et al. Recommendations for chamber quantification: a report from the American Society of Echocardiography's Guidelines and Standards Committee and the Chamber Quantification Writing Group, developed in conjunction with the European Association of Echocardiography, a branch of the European Society of Cardiology. J Am Soc Echocardiogr 2005;18:1440–63.

[17] Central Bureau of Statistics. Complete life tables of Israel, 1997–2001, 1998–2002; June 2004 Jerusalemwww.cbs.gov.il/publications/mortality/2001/intlifee.pdf.

[18] Finkelstein DM, Muzikansky A, Schoenfeld DA. Comparing survival of a sample to that of a standard population. J Natl Cancer Inst 2003;95:1434–9.

[19] Massachusetts General Hospital (MGH). MGH biostatistic; 2014, http://hedwig.mgh.harvard.edu/biostatistics/node/30 (accessed 21.06.14).

[20] Shelton RJ, Crean AM, Somers K, Priestley C, Hague C, Blaxill JM, Wheatcroft SB, McLenachan JM, Greenwood JP, Blackman DJ. Real-world outcome from ST elevation myocardial infarction in the very elderly before and after the introduction of a 24/7 primary percutaneous coronary intervention service. Am Heart J 2010;159:956–63.

[21] Schiele F, Meneveau N, Seronde MF, Descotes-Genon V, Oettinger J, Ecarnot F, Bassand JP. Changes in management of elderly patients with myocardial infarction. Eur Heart J 2009;30:987–94.

[22] de Bruyne MC, Mosterd A, Hoes AW, Kors JA, Kruijssen DA, van Bemmel JH, Hofman A, Grobbee DE. Prevalence, determinants, and misclassification of myocardial infarction in the elderly. Epidemiology 1997;8:495–500.

[23] Boersma E, Pieper KS, Steyerberg EW, Wilcox RG, Chang WC, Lee KL, Akkerhuis KM, Harrington RA, Deckers JW, Armstrong PW, Lincoff AM, Califf RM, Topol EJ, Simoons ML. Predictors of outcome in patients with acute coronary syndromes without persistent ST-segment elevation. Results from an international trial of 9461 patients. The PURSUIT Investigators. Circulation 2000;101:2557–67.

[24] Morrow DA, Antman EM, Giugliano RP, Cairns R, Charlesworth A, Murphy SA, de Lemos JA, McCabe CH, Braunwald E. A simple risk index for rapid initial triage of patients with ST-elevation myocardial infarction: an InTIME II substudy. Lancet 2001;358:1571–5.

[25] Kim HK, Jeong MH, Ahn Y, Kim JH, Chae SC, Kim YJ, Hur SH, Seong IW, Hong TJ, Choi DH, Cho MC, Kim CJ, Seung KB, Chung WS, Jang YS, et al. A new risk score system for the assessment of clinical outcomes in patients with non-ST-segment elevation myocardial infarction. Int J Cardiol 2010;145:450–4.

[26] Antman EM, Cohen M, Bernink PJ, McCabe CH, Horacek T, Papuchis G, Mautner B, Corbalan R, Radley D, Braunwald E. The TIMI risk score for unstable angina/non-ST elevation MI: a method for prognostication and therapeutic decision making. JAMA 2000;284:835–42.

[27] Eagle KA, Lim MJ, Dabbous OH, Pieper KS, Goldberg RJ, Van de Werf F, Goodman SG, Granger CB, Steg PG, Gore JM, Budaj A, Avezum A, Flather

MD, Fox KA, GRACE Investigators. A validated prediction model for all forms of acute coronary syndrome: estimating the risk of 6-month postdischarge death in an international registry. JAMA 2004;291:2727–33.
[28] Granger CB, Goldberg RJ, Dabbous O, Pieper KS, Eagle KA, Cannon CP, Van De Werf F, Avezum A, Goodman SG, Flather MD, Fox KA, Global Registry of Acute Coronary Events Investigators. Predictors of hospital mortality in the global registry of acute coronary events. Arch Intern Med 2003;163:2345–53.
[29] Fox KA, Carruthers KF, Dunbar DR, Graham C, Manning JR, De Raedt H, Buysschaert I, Lambrechts D, Van de Werf F. Underestimated and under-recognized: the late consequences of acute coronary syndrome (GRACE UK-Belgian Study). Eur Heart J 2010;31:2755–64.
[30] Burns TR, Klima M, Teasdale TA, Kasper K. Morphometry of the aging heart. Mod Pathol 1990;3:336–42.
[31] Nixon JV, Hallmark H, Page K, Raven PR, Mitchell JH. Ventricular performance in human hearts aged 61 to 73 years. Am J Cardiol 1985;56:932–7.
[32] Ornato JP, Peberdy MA, Tadler SC, Strobos NC. Factors associated with the occurrence of cardiac arrest during hospitalization for acute myocardial infarction in the second national registry of myocardial infarction in the US. Resuscitation 2001;48:117–23.
[33] Gage BF, Waterman AD, Shannon W, Boechler M, Rich MW, Radford MJ. Validation of clinical classification schemes for predicting stroke: results from the National Registry of Atrial Fibrillation. JAMA 2001;285:2864–70.
[34] Sonel AF, Good CB, Mulgund J, Roe MT, Gibler WB, Smith Jr SC, Cohen MG, Pollack Jr CV, Ohman EM, Peterson ED. Racial variations in treatment and outcomes of black and white patients with high-risk non-ST-elevation acute coronary syndromes: insights from CRUSADE (Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes With Early Implementation of the ACC/AHA Guidelines?). Circulation 2005;111:1225–32.
[35] Plakht Y, Gilutz H, Shiyovich A, Zahger D, Weitzman S. Gender and ethnic disparities in outcome following acute myocardial infarction among Bedouins and Jews in southern Israel. Eur J Public Health 2011;21:74–80.
[36] Ekerstad N, Swahn E, Janzon M, Alfredsson J, Lofmark R, Lindenberger M, Andersson D, Carlsson P. Frailty is independently associated with 1-year mortality for elderly patients with non-ST-segment elevation myocardial infarction. Eur J Prev Cardiol 2013 [Epub ahead of print].
[37] Wenaweser P, Ramser M, Windecker S, Lutolf I, Meier B, Seiler C, Eberli FR, Hess OM. Outcome of elderly patients undergoing primary percutaneous coronary intervention for acute ST-elevation myocardial infarction. Catheter Cardiovasc Interv 2007;70:485–90.