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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

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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: $\leq$65 years ($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 $\geq$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

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[*] 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.

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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 ($\leq$65 years) and older ($>$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 $\geq$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