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RESEARCH

SEX-RELATED DIFFERENCES ON MORTALITY IN PATIENTS AGED 80 YEARS OR OLDER WITH ACUTE MYOCARDIAL INFARCTION: THERE IS STILL A GAP

Abstract

Introduction: Sex-related differences on cardiovascular mortality in patients with acute coronary syndrome have been debated for decades. Although the gap between the two sexes has begun to close, women still have higher all-cause mortality. However, there is little data with respect to elderly women, particularly for those over 80 years. Therefore, we sought to determine all-cause mortality of elderly women with acute myocardial infarction and to compare it to men.

Materials and Method: This retrospective study evaluated patients 80 years or older who were admitted to the cardiology clinic due to acute myocardial infarction between May 2015 and November 2017. The primary outcomes of the study were in-hospital, 30-day, and long-term all-cause mortality.

Results: Two hundred twenty patients (126 women and 94 men) were included in the final analysis. Median follow-up was eight months. Long-term all-cause mortality of women was significantly higher compared to men [n=52 (41.3%) vs. n=26 (27.7%), respectively; p=0.03]. There was no significant sex difference for both in-hospital and 30-day mortality, although women had more events. Kaplan-Meier analysis revealed lower cumulative survival for women (log-rank: p=0.02), and Cox regression analysis found that female sex was as an independent risk factor for mortality [hazard ratio=1.7 (95% confidence interval=1.06-2.72); p=0.02].

Conclusion: Sex-related differences on mortality continue to be a critical issue, even for elderly patients with acute myocardial infarction. Since women have significantly higher long-term all-cause mortality, they should strictly be treated according to the guidelines and every effort should be made for risk reduction with close follow-up.

Keywords: Acute coronary syndrome; Coronary artery disease; Aged; Aged, 80 and over; Gender identity

ARAŞTIRMA

AKUT MİYOKARD ENFARKTÜSÜ GEÇİREN 80 YAŞ VE ÜZERİ HASTALARDA CİNSİYET İLE İLİŞKİLİ FARKLILIKLARIN MORTALİTE ÜZERİNE ETKİSİ: HALA BİR FARK VAR

Öz

Giriş: Akut koroner sendrom gelişen hastalarda cinsiyet farkının kardiyovasküler mortalite üzerine olan etkisi uzun yıllardır tartışılmaktadır. Her iki cinsiyet arasındaki fark kapanmaya başlamış olsa da, kadınların hala tüm nedenlere bağlı ölüm oranları daha yüksektir. Öte yandan, özellikle 80 yaş üstü yaşlı kadınlarla ilgili çok az veri bulunmaktadır. Bu nedenle bu çalışmada akut miyokard enfarktüsü geçiren yaşlı kadınların tüm nedenlere bağlı mortalitelerin belirlenmesi ve erkeklerle karşılaştırılması amaçlanmıştır.

Gereç ve Yöntem: Bu retrospektif çalışmada, Mayıs 2015-Kasım 2017 tarihleri arasında akut miyokard infarktüsü nedeniyle kardiyoloji kliniğine yatırılan 80 yaş ve üzeri hastalar değerlendirilmiştir. Çalışmanın temel sonlanım noktası hastane içi, 30 günlük ve uzun süreli tüm nedenlere bağlı ölümlerının belirlenmesidir.

Bulgular: Çalışmaya toplam 220 hasta (126 kadın ve 94 erkek) dahil edilmiştir. Ortalama takip süresi 8 aydır. Kadınların uzun dönemde tüm nedenlere bağlı mortalitesi erkeklere göre anlamlı derecede yüksek bulunmuştur [sırasıyla n=52 (% 41.3) ve n=26 (%27.7); p=0.03]. Öte yandan, kadınların gerek hastane içi gerekse 30 günlük mortalitesi daha yüksek olmasına rağmen, istatiksel açıdan cinsiyetler arası fark bulunmamıştır. Kaplan-Meier analizinde kadınların kümülatif sağkalımı daha düşüktür (log-rank: p=0.02) ve Cox regresyon analizi, kadın cinsiyetin mortalite için bağımsız bir risk faktörü olduğunu göstermiştir [tehlike oranı=1.7 (%95 güven aralığı=1.06-2.72); p=0.02].

Sonuç: Akut miyokard enfarktüsü geçiren hastalarda cinsiyetin mortalite üzerine olan etkisi yaşlılarda da önemini korumaktadır. Kadınların uzun vadede tüm nedenlere bağlı ölüm oranları önemli ölçüde yüksek olduğundan, bu hastalar klavuz önerilerine göre tedavi edilmeli ve yakından takip edilerek risk azaltımı için her türlü çaba gösterilmelidir.

Anahtar sözcükler: Akut koroner sendrom; Koroner arter hastalığı; Yaşlı; Yaşlı, 80 ve üzeri; Cinsiyet kimliği

INTRODUCTION

Numerous studies have found that women with coronary artery disease (CAD) have worse prognoses than men, and this sex-related difference in outcomes was relevant across the spectrum of acute coronary syndromes (ACS) (1,2). The higher morbidity and mortality of women are most likely multifactorial in origin, which include pathophysiological differences of acute myocardial infarction, baseline risk burden, and various clinical presentations that lead to misdiagnosis or treatment delays (3,4). Although this gap has been steadily decreasing the past two decades due to strict implementation of evidence-based therapies, women still experience less favorable outcomes than men, particularly in the context of ACS (5).

However, data is scarce in elderly women with CAD, particularly in those who are very elderly (age 80 years or older) as these patients are either excluded or underrepresented in major clinical trials (6). The underlying pathologies, clinical presentations, and treatment strategies of these patients substantially differ from their younger counterparts (7). First, elderly patients are generally undertreated due to multiple co-morbidities, although recent guidelines recommend the same therapies regardless of age (8). Second, clinical signs and symptoms may be subtle, leading to delays with the appropriate treatment (9). Third, a substantial proportion of patients cannot be fully revascularized because of extensive and severe CAD with heavy calcification, all of which are considered as bad prognostic factors for percutaneous coronary intervention success (10). Besides these age-related differences, sex-related factors that were previously believed to play an important role for the mortality difference between the two sexes are no longer relevant in this age group. Those who are 80 years or older lose the protective effect of estrogen, and the baseline differences in clinical risk factors between the two sexes diminish. Therefore, based on these physiological changes and the lack of available data, it is unclear whether elderly women still have worse mortality compared to elderly men. Thus, in our study, we sought to determine all-cause mortality of elderly women (aged 80 years or older) with ACS, and to compare it to men.

MATERIALS AND METHOD

Patients

In this retrospective cohort study, the data of elderly patients (aged 80 years or older) who were admitted to our cardiology clinic between May 2015 and November 2017 were retrospectively evaluated, and those who had an ACS diagnosis were included. The diagnosis of ACS was based on the presence of at least two of the following: typical chest pain, dynamic electrocardiographic changes, and/or elevated troponin levels consistent with acute ischemia. Patients who underwent elective percutaneous coronary intervention (PCI) due to stable CAD, and those who had end-stage malignancy with a life expectancy of less than one year were excluded. Ethical board approval was obtained from the local ethics committee both for retrospective archive search and for prospective mortality analysis.

Clinical, laboratory, and procedural data were retrieved from hospital records. Clinical evaluation included age, sex, ACS type, heart failure (Killip classification), hypertension, diabetes mellitus, accompanying comorbidities, stroke, history of coronary revascularization, history of coronary revascularization (PCI and/or bypass surgery), and in-hospital medications. Laboratory data included admission creatinine, estimated glomerular filtration rate, maximal creatinine, initial and maximum Troponin I values, and other routine biochemical parameters. When evaluating the PCI findings, final "thrombolysis in myocardial infarction" (TIMI) flow was used as the criteria to assess procedure success – TIMI-3 flow was considered as successful reperfusion. The severity and extent of CAD was analyzed using SYNTAX score (http://www.syntaxscore.com). These calculations were performed by two interventional cardiologists in a blinded fashion. Both pre-procedural and post-procedural (residual) SYNTAX scores were calculated, where appropriate, in order to assess the completeness of revascularization and residual atherosclerotic burden. The diagnosis of acute kidney injury was determined using the Acute Kidney Injury Network criteria, in which an increase of at least 50% in serum creatinine was considered mandatory for diagnosis (11).

Clinical outcomes

The primary outcomes of the study were in-hospital, 30-day, and long-term all-cause mortality. In-hospital mortality was evaluated through the review of hospital records, whereas 30-day and long-term mortality were identified prospectively via the national death notification system.

Statistical analysis

Continuous variables are displayed as mean±standard deviation if normally distributed, or median and interquartile range if not normally distributed. Distribution of data was assessed using the Kolmogorov-Smirnov test. Categorical variables are reported as number and percentage. Continuous variables were compared between groups using independent sample T-test. Categorical data were compared using the chi-squared or Fisher's exact test. Event-free survival curves were generated using the Kaplan-Meier method, and differences in survival curves between the two sexes were assessed using the log-rank test. A two-tailed *p*-value of <0.05 was considered statistically significant.

To assess the independent predictors of mortality, we built a Cox proportional hazards model, which included sex, undergoing coronary angiography, diabetes mellitus, hypertension, acute kidney injury, maximum serum troponin level, total cholesterol, ACS type, , and heart failure Killip classification greater than 1 as covariates. When building the model, covariates that were found to be significant in the univariate analysis ($p<0.10$), or those that were believed to have clinical significance, were entered into the model. To avoid interactions among variables, we checked for correlations using Pearson correlation coefficient test, or chi-squared test for dichotomous variables. Statistical analysis was performed using SPSS 20 software (SPSS Inc., Chicago, IL, USA).

RESULTS

Among 3,450 patients who were screened for eligibility, 220 patients were included in the final analysis (Figure 1). Median follow-up was 8(IQR 2-20) months (maximum 31 months). Baseline clinical characteristics, medications, and outcomes are presented in Table-1. Of the 220 included patients, 126 (57.3%) patients were women. The majority of patients (n=145, 65.9%) had non-ST elevation myocardial infarction. There was no significant sex difference for baseline risk factors, renal function, acute kidney injury, left ventricular ejection fraction, and the rate of coronary angiography. Men had a higher frequency of bypass surgery history than women [n=16 (17.0%) vs. n=7 (5.6%), respectively; p=0.006].

Baseline laboratory findings are presented in Table 2. Women had lower admission hemoglobin (11.8, IQR 10.5-13.0 g/dL vs 12.5, IQR 11.1-14.2 g/dL p=0.005) and higher total cholesterol values (167, IQR 140-203 mg/dl vs 157, IQR 124-189 mg/dL; p=0.02) than men, respectively. Platelet count was also higher in women compared to men (235, IQR 187-295 $x10^3/mm^3$ vs. 210, IQR 164-260 $x10^3/mm^3$, respectively; p=0.002).

Procedural details are presented in Table-3. Overall, 145 (65.9%) patients underwent coronary angiography, and among those, 107 (73.8%) patients underwent PCI. There was no statistical difference between the groups in terms of percentage of patients who underwent coronary angiography, admission and residual SYNTAX scores, post-intervention TIMI flow, and types of implanted stents. The only statistical difference between the groups was the median length of bare metal stents (BMS), which was longer in women than men (30, IQR 18-43 vs. 18, IQR 15-20 mm, respectively; p=0.02).

In terms of clinical outcomes, although women had higher incidence of in-hospital and 30-day mortality, there was no statistical difference between women and men [19 (15.1%) vs. 10 (10.6%), respectively; p=0.33 for in-hospital mortality, and 31 (25.2%) vs. 14 (14.9%), respectively; *p*=0.06 for 30-day mortality]. However, long-term mortality (maximum 31 months), was significantly higher in women than men [52 (41.3%) vs. 26 (27.7%), respectively; *p*=0.03] (Figure-2). Multivariate Cox regression analysis revealed that sex (women) (hazard ratio [HR]=1.7 [95% confidence interval [CI]=1.06-2.72]; *p*=0.02], maximum serum Troponin I values (HR=1.007 [95% CI=1.003-1.011]; *p*=0.02, and heart failure Killip classification greater than 1 (HR=3.58 [95% CI=2.28-5.61]; *p*=0.001) were independent predictors of mortality (Table 4). Kaplan-Meier analysis also showed that women had statistically worse long-term survival than men (log-rank; *p*=0.02) (Figure 3).

Table 1. Baseline characteristics, medications and mortality rates of the study patients according to their sex.

		Total (n=220)	Women (n=126 57.3%)	Men (n=94 42.7%)	p
Age (years)		85±3.6	85±3.3	85±3.8	0.20
NSTEMI		145(65.9%)	89(70.6%)	56(59.6%)	0.08
Hypertension		149(67.7%)	92(73.0%)	57(60.6%)	0.052
Diabetes mellitus		60(27.4%)	35(27.8%)	25(26.9%)	0.88
Prior	PCI	33(15.1%)	15(12.0%)	18(19.4%)	0.13
	CABG	23(10.5%)	7(5.6%)	16(17.0%)	**0.006**
	STROKE	18(8.3%)	9(7.3%)	9(9.6%)	0.53
	CHF	29(13.3%)	17(13.7%)	12(12.8%)	0.83
CRF (eGFR<60 ml/min)		107(49.1%)	68(54.8%)	39(41.5%)	0.051
Acute kidney injury		40(18.3%)	28(22.6%)	12(12.8%)	0.06
Coronary angiography		145(65.9%)	80(63.5%)	65(69.1%)	0.38
LVEF		43.1±11.4	43.8±11.3	42.3±11.7	0.35
Heart failure Killip>1		55(25.0%)	37(29.4%)	18(19.1%)	0.08
Inotropic support		31(14.1%)	21(16.7%)	10(10.6%)	0.20
ASA		201(91.8%)	117(93.6%)	84(89.4%)	0.25
Clopidogrel		179(81.7%)	107(85.6%)	72(76.6%)	0.08
Ticagrelor		13(5.9%)	3(2.4%)	10(10.6%)	**0.01**
Anticoagulants		24(11.1%)	16(13.0%)	8(8.5%)	0.29
In-hospital mortality		29(13.2%)	19(15.1%)	10(10.6%)	0.33
30-day mortality		45(20.7%)	31(25.2%)	14(14.9%)	0.06
Long-term mortality		78(35.5%)	52(41.3%)	26(27.7%)	**0.03**

NSTEMI, non ST elevation myocardial infarction; PCI, percutaneous coronary intervention; CABG, Coronary artery bypass grafting; CHF, congestive heart failure; CRF, chronic renal faiure; eGFR, estimated glomerular filtration rate; LVEF, left ventricular ejection fraction.

Table 2. Baseline laboratory findings of the study patients.

Variable	Women (n=126 57.3%) Median (IQR 25-75)	Men (n=94 42.7%) Median (IQR 25-75)	p
Glucose (mg/dl)	144(117-211)	135(107-177)	0.09
Leukocyte (x10^3)	9.8(7.8-13.2)	9.4(7.4-12.1)	0.16
Platelet count(x10^3/mm^3)	235(187-295)	210(164-260)	**0.002**
Hemoglobin (gr/dl)	11.8(10.5-13.0)	12.5(11.1-14.2)	**0.005**
Urea (mg/dl)	48.9(36.5-71.8)	50.6(39.0-69.5)	0.66
Creatinine (mg/dl)	1.0(0.7-1.3)	1.1(0.9-1.5)	0.41
eGFR (ml/min)	55.9(39.4-79.6)	65.6(44.4-80.3)	0.18
Admission Troponin I ng/ml	1.7(0.3-7.1)	0.6(0.1-3.0)	0.052
Maximum Troponin I ng/ml	7.4(1.6-26.3)	10.8(1.1-38.8)	0.71
Total cholesterol (mg/dl)	167(140-203)	157(124-189)	**0.02**
LDL cholesterol (mg/dl)	93(71-121)	93(69-120)	0.36
HDL cholesterol (mg/dl)	45(33-52)	40(32-47)	0.06
Triglyceride (mg/dl)	108(84-143)	101(74-134)	0.14
ALT (mg/dl)	16(10-30)	14(12-26)	0.34
AST (mg/dl)	26(19-58)	25(17-60)	0.84
CRP (mg/L)	9.7(3.5-33.6)	7.4(2.1-29.5)	0.67

IQR, interquartile range; eGFR, estimated glomerular filtration rate; LDL, Low-density cholesterol; HDL, High-density cholesterol; ALT, alanine transaminase; AST, aspartate aminotransferase; CRP, C reactive protein

Table 3. Angiographic and procedural characteristics of very elderly patients according to their sex.

Variable	Overall n=145	Women n=80	Men n=65	p
Number of PCI	107(73.8%)	57(71.2%)	50(76.9%)	0.44
Admission Syntax Score	20(27-10)	20(26-9)	22(28-12)	0.35
Residual Syntax Score	6(18-0)	5(20-0)	6(16-2)	0.68
Mean BMS length (mm)	20(39-18)	30(43-18)	18(20-15)	**0.02**
Mean DES length (mm)	28(38-18)	26(33-18)	28(45-19)	0.20
Timi-3 flow post-PCI	77(72.0%)	37(64.9%)	40(80.0%)	0.08
3-vessel disease	77(53.1%)	41(51.2%)	36(55.4%)	0.62
BMS	42(39.3%)	25(43.9%)	17(34.0%)	0.29
DES	40(37.4%)	20(35.1%)	20(40.0%)	0.60
BMS PLUS DES	10(9.3%)	6(10.5%)	4(8.0%)	0.74

BMS, bare metal stent; DES, drug eluting stent; PCI, percutaneous coronary intervention; TIMI, thrombolysis in myocardial infarction

Table 4. Cox logistic regression analyses of variables related to mortality.

Variable	Univariate analysis			Multivariate analysis		
	HR	95% CI	p	HR	95% CI	p
Gender (women)	1.70	1.06-2.72	**0.02**	1.61	1.005-2.59	**0.04**
Undergoing coronary angiography	0.74	0.47-1.16	0.19			
Diabetes mellitus	0.97	0.59-1.58	0.90			
Hypertension	1.04	0.64-1.69	0.85			
Acute kidney injury	1.96	1.19-3.24	**0.008**			
Maximum Troponin I	1.007	1.003-1.011	**0.001**	1.005	1.001-1.009	**0.02**
Total cholesterol	0.99	0.99-1.00	0.22			
ACS type (STEMI)	1.73	1.10-2.73	**0.01**			
Prior revascularization	0.71	0.40-1.25	0.24			
Killip>1	3.58	2.28-5.61	**<0.001**	3.34	2.11-5.28	**0.001**

HR, hazard ratio; CI, Confidence interval; ACS, acute coronary syndrome; STEMI, ST elevation myocardial infarction

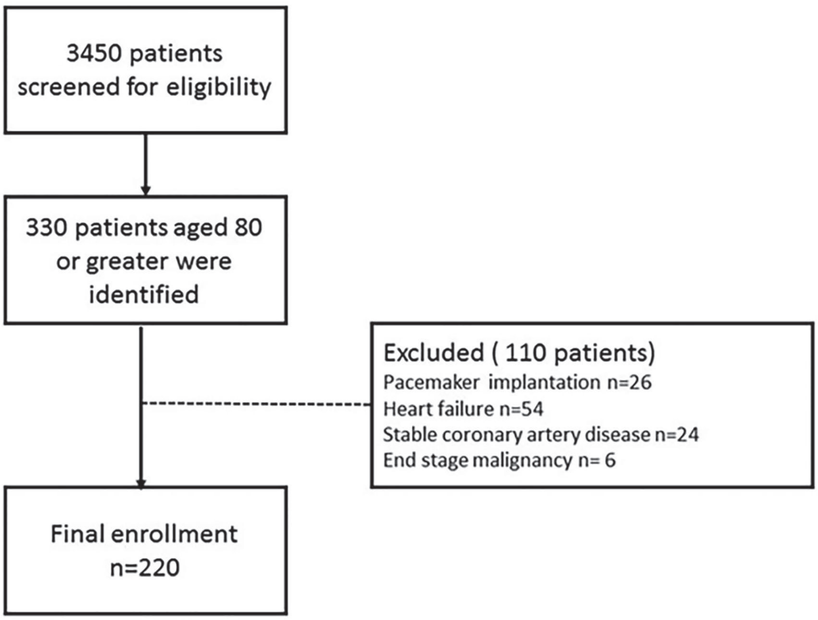

Figure 1. Patient inclusion flow chart.

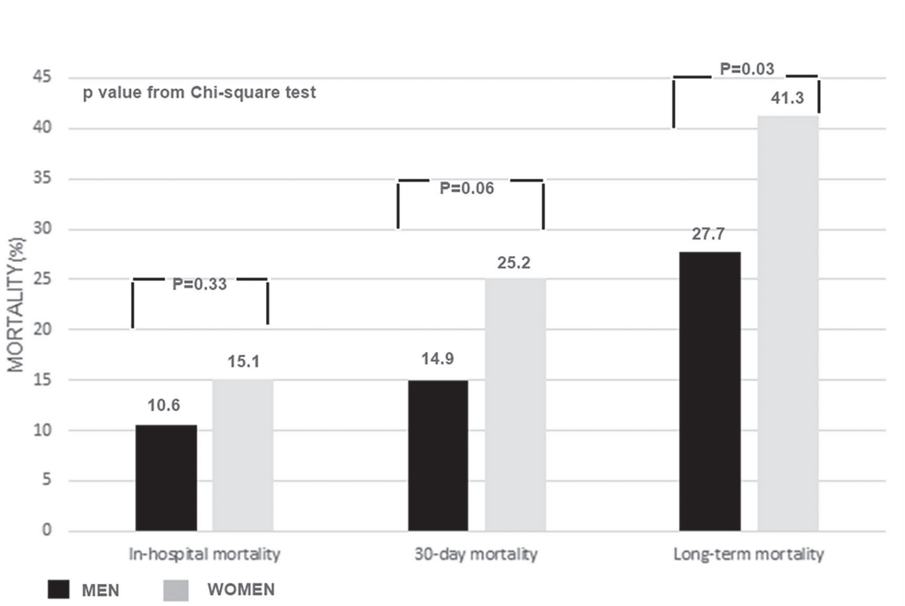

Figure 2. In-hospital, 30-day, and long-term mortality rates of patients according to sex.

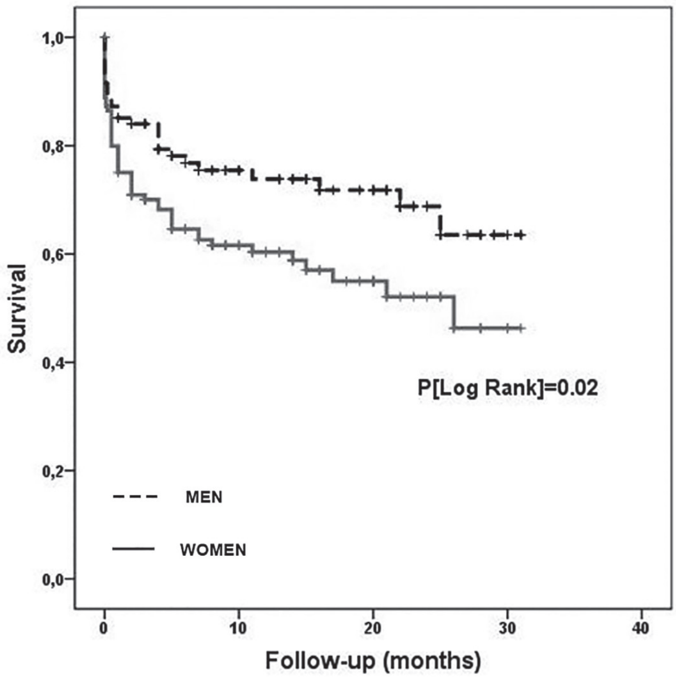

Figure 3. Kaplan-Meier survival plot for men and women with acute myocardial infarction.

DISCUSSION

In our study, we found that elderly women with acute myocardial infarction had a higher incidence of long-term all-cause mortality compared to men. This difference persisted after adjusting for multiple confounding factors, and thus, female sex appears to be an independent risk factor. On the other hand, although women had more in-hospital and 30-day events, there was no statistically significant difference between sexes.

The underlying factors related to our study results seem to be multifactorial. Generally, the higher mortality of women has been attributed to differences in baseline risk factors between the two sexes (12). Since women develop CAD later in life, particularly after menopause, they have much more comorbidities that increase the incidence of long-term cardiovascular events (13). Besides this, Poon et al. showed that cardiovascular risk in women is generally underestimated, which is typically attributed to atypical symptoms and presentations which lead to delays in hospital admission and thus under treatment and increased mortality (14,15). Historically, women tended to receive less thrombolytic therapy, PCI, and thionopiridines, all of which are possible factors leading to increased mortality (16). Of note, one recent registry demonstrated that women still had an increased risk of adverse clinical outcomes with ACS, even if they underwent an early invasive strategy and coronary revascularization (17). Moreover, women also have issues with secondary prevention. For example, EUROASPIRE IV study showed that women were less likely to receive evidence-based therapy and reach target lipid or blood pressure levels (18). The reason behind this observation remains to be established.

On the other hand, elderly patients, especially those over 80 years, have specific problems that are confined to this age group. For example, these patients are generally reluctant to undergo invasive procedures and do not receive contemporary evidence-based therapy. In addition, the burden of CAD is typically greater, which makes complete revascularization more challenging. Further, the vagueness of symptoms which applies to both sexes is frequent and as demonstrated in numerous previous trials, this leads to a significant delay to the appropriate therapy particularly for octogenarians (8).

In our study, although the rate of coronary angiography and subsequent revascularization were low in both sexes, there was no statistical difference between the groups. In addition, there was no sex difference with respect to baseline risk factors and admission and residual SYNTAX scores. Therefore, the previously proposed mechanism suggesting that baseline clinical risk burden increases the mortality of women with ACS may not be relevant in very elderly patients. The Italian Elderly ACS Study investigated sex-related outcomes in elderly patients with ACS and found similar baseline risk factors and in-hospital mortality for both sexes (19).

Another important finding from our study was the percentage of BMS implantation, which was approximately 40%. The type of stent implantation was based on the operators' discretion, and this rate is far greater than the expected rate for younger patients. Moreover, in our study, women received more BMSs than men, and the median length of the implanted BMSs were longer. This difference might have affected our study results; because it is evident that drug-eluting stents decrease both stent restenosis and major adverse cardiac events, as long as the patient complies with dual antiplatelet therapy (20). Furthermore; acute and chronic renal failure, killip class>1 heart failure, and post-PCI slow flow was also more frequent in women, although it did not reach statistical significance.

Due to the retrospective design of our study, one important factor that we were unable to take into account was the patients' frailty, which may have impacted overall survival (21). In addition, secondary prevention efforts and adherence to medications may have also played a role. Nevertheless, elderly women appeared to have higher mortality incidence particularly in the long-term and this survival difference was most likely related to many factors including socio-economic status, and co-morbid conditions.

There were some limitations for our study. First, this was a single-center retrospective study although it included an underrepresented, real world population. Second, none of the patients underwent bypass surgery, which was mainly due to patients' refusal to undergo the surgery, and this might have affected our results. Third, although we evaluated all-cause mortality, which was a hard endpoint, we did not assess for major adverse cardiac events separately. Finally, the lack of out of hospital medication and adherence was also a limitation.

In conclusion, elderly women (age 80 years or older) with acute myocardial infarction have a higher incidence of long-term all-cause mortality compared to men. This sex-related difference remained significant, even after adjusting for multiple confounding factors. Previously proposed mechanisms for increased mortality of relatively younger women may not apply in this decade of life. Therefore, elderly women with CAD should be followed up closely and treated aggressively according to the guideline recommendations.

Conflict of interest

The authors declare that there is no conflict of interest associated with this work.

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