ORIGINAL ARTICLE

Gender equality applies (partially) to ST-segment elevation myocardial infarction too

Alexandru Ceamburu[1], Razvan Constantin Serban[1], Ioana Sus[1,2], Eva Katalin Lakatos[1,2], Zoltan Demjen[1], Paul Ciprian Fisca[1,2], Laszlo Hadadi[1,2], Cristina Somkereki[1,2], Alina Scridon[2]

Abstract: **Objectives –** Previous studies reported outcome differences following ST-segment elevation myocardial infarction (STEMI) between genders. We aimed to evaluate gender-related differences in in-hospital post-STEMI outcomes and to identify the substrate of such differences, if present. **Methods –** Cardiovascular risk factors, hemodynamic, electrographic, echocardiographic, angiographic status, and blood parameters at hospital admission were retrospectively assessed for 672 patients presented with STEMI treated by primary percutaneous coronary intervention. In-hospital post-STEMI outcomes were evaluated. All parameters were compared between female and male patients. **Results –** Among all STEMI patients, 30.3% were females. Compared to male patients, women were older and more often had a history of heart failure (p≤0.0001). They were also more frequently hypertensive (p = 0.02) and diabetic (p< 0.001). Post-STEMI, female patients presented more often cardiogen shock (p = 0.01) and required more frequently diuretic therapy (p< 0.001). In-hospital mortality was also higher in female than in male patients (p< 0.01). However, after adjusting for the potential confounders, female gender did not remain an independent predictor of in-hospital mortality (p=0.16). **Conclusions –** Female patients had higher rates of post-STEMI complications and higher in-hospital mortality. However, these gender-related differences appear to be fully explained by the higher cardiovascular risk factors burden in females.
Keywords: female, gender, outcomes, risk factors, ST-segment elevation myocardial infarction.

Rezumat: **Obiective –** Studii anterioare au raportat diferenţe în evoluţia post-infarct miocardic acut cu supradenivelare de segment ST (STEMI) între cele două sexe. Ne-am propus să evaluăm diferenţele în evoluţia intraspitalicească post-STEMI între femei şi bărbaţi şi să identificăm substratul acestor diferenţe, dacă ele există. **Metode –** Factorii de risc cardiovascular, aspectul electrocardiografic, ecocardiografic, angiografic şi parametrii de laborator la prezentare şi evoluţia post-STEMI au fost evaluate la 672 de pacienţi cu STEMI trataţi prin angioplastie coronariană primară. Datele au fost evaluate comparativ între cele două sexe. **Rezultate –** Din cei 672 de pacienţi, 30,3% au fost de sex feminin. Faţă de bărbaţi, femeile au fost mai vârstnice (p<0,0001), mai frecvent hipertensive (p=0,02) şi diabetice (p<0,001) şi au avut mai frecvent antecedente de insuficienţă cardiacă (p=0,0001). Post-STEMI, femeile au prezentat mai frecvent şoc cardiogen (p=0,01), au necesitat mai frecvent tratament diuretic (p<0,001) şi au avut mortalitate intraspitalicească mai ridicată (p<0,01). După corecţia pentru potenţialii factori de confuzie, sexul feminin nu a rămas însă predictor independent de mortalitate intraspitalicească post-STEMI (p=0,16). **Concluzii –** Femeile au prezentat mai frecvent complicaţii şi au avut mortalitate intraspitalicească mai mare post-STEMI. Aceste diferenţe par să se explice însă în totalitate prin încărcătura mai mare cu factori de risc a femeilor.
Cuvinte cheie: evoluţie, factori de risc, femei, infarct miocardic acut cu supradenivelare de segment ST, sex.

BACKGROUND

Cardiovascular diseases (CVDs) are the leading cause of death worldwide. According to the *World Health Organization,* an estimated 17.9 million people died from CVDs in 2016[1]. Among CVDs, acute myocardial infarction (AMI) represents one of the most important causes of morbidity and mortality. In Romania, AMI was responsible for 84.2 deaths per 100.000 inhabitants in 2016[2]. Several studies have reported higher in-hospital mortality in women compared with men presenting with ST-segment elevation myocardial infarction (STEMI)[3-6]. The reason for this between-gender difference in post-STEMI outcomes remains unclear. Several hypotheses have been proposed to explain the higher risk of mortality in women, including more serious co-morbidity, longer time to revascularization, or

[1] Emergency Institute for Cardiovascular Diseases and Transplantation, Targu Mures, Romania

[2] University of Medicine, Pharmacy, Science and Technology, Targu Mures, Romania

▼ **Contact address:**
Razvan Constantin Serban
Emergency Institute for Cardiovascular Diseases and Transplantation, 50 Gheorghe Marinescu Street, 540136, Targu Mures, Romania.
E-mail: serbanrazvan1@gmail.com

less likelihood to receive guideline-recommended invasive procedures[4,6]. However, most of these studies were performed in the pre-percutaneous coronary intervention (PCI), or even in the pre-thrombolytic era. Therefore, we aimed to identify the most relevant gender-related differences regarding in-hospital post-STEMI outcomes in patients treated by primary PCI and, if present, to identify the substrate of such differences.

MATERIAL AND METHODS

Study population
The study included consecutive patients treated by primary PCI for STEMI in our center between January 2011 and December 2016. The study complied with the Declaration of Helsinki; the research protocol was approved by the local institutional Ethics Committee. Patients enrolled were older than 18 years, with STEMI (type I) hospital admission, treated by primary PCI within the first 12h after symptoms onset or 12h to 24h after symptoms onset if they presented signs of persistent ischemia. Patients who required thrombolytic treatment prior to PCI were excluded. Patients were also excluded if they presented left bundle branch block or paced rhythm, or if they had a history of coronary artery by-pass graft surgery.

Baseline clinical characteristics
Variables including demographic and cardiovascular risk factors (age, smoking status, arterial hypertension, diabetes mellitus, obesity, heart failure, chronic kidney disease, chronic respiratory diseases, previous MI) and treatment history (beta-blockers, calcium channel blockers, angiotensin converting enzyme inhibitors and/or angiotensin II receptor blockers, statins) were retrospectively collected and analyzed. Chronic kidney disease was defined as an estimated glomerular filtration rate < 60 ml/min/1.73 m^2 on admission according to the Cockroft-Gault equation, as described previously[7]. Data regarding clinical presentation (Killip class), hemodynamic status (blood pressure, heart rate, left ventricular ejection fraction), time from symptoms onset to presentation, and electrocardiographic parameters (sum of ST-segment elevation and ECG localization of STEMI) at hospital admission were also assessed. Angiographic parameters, including the SYNergy between PCI with TAXUS™ and Cardiac Surgery (SYNTAX I) score, pre- and post-PCI Thrombolysis in Myocardial Infarction (TIMI) flow, thrombus aspiration and glycoprotein IIb/IIIa inhibitors

usage, and PCI-related complications such as iatrogenic coronary artery dissection, coronary perforation, angiographic no-reflow, angiographically visible distal embolization, and acute intra-PCI occlusion were also evaluated. All data were compared between female and male patients.

In-hospital post-ST-segment elevation myocardial infarction outcomes
Patients data were evaluated for in-hospital post-STEMI mortality and in-hospital outcomes and complications, including inotropic and diuretics usage, cardiogenic shock, and cardiac arrest. Kidney dysfunction, length of hospital stay, and all-cause mortality were also analyzed. All parameters were compared between female and male patients.

Statistics
Continuous variables are presented as median and interquartile range. Categorical data are summarized using frequencies and percentages. Fisher's test was used for comparison of categorical data and the Mann-Whitney U test was applied for comparison of continuous variables between the two groups. Multiple logistic regression analysis was used to assess the ability of female gender to independently predict in-hospital post-STEMI mortality; the model included all clinical and cardiovascular risk factors that differed significantly between male and female patients. All tests were two-sided and a *p*-value of less than 0.05 was considered statistically significant. Statistical analyses were performed using the GraphPad Prism 8 software (GraphPad Software, San Diego, CA).

RESULTS

Patients' characteristics according to gender
Out of the total of 672 patients included in the study, 204 (30.3%) patients were of female gender. Compared to male patients, female patients with STEMI (Table 1) were older, were more likely to have a history of arterial hypertension, diabetes mellitus, heart failure, and chronic kidney disease, but they were less likely to be active smokers (all p< 0.05). Female patients also displayed longer time from symptoms onset to presentation than their male counterparts (p< 0.01). In agreement with their higher disease burden, female patients were also more likely to be on ongoing beta-blocker, calcium channel blocker, renin-angiotensin-aldosterone system blocker, and statin therapy (all p< 0.05).

Table 1. Baseline patients' characteristics according to gender

Parameter	Total (n=672)	Male (n=468)	Female (n=204)	p-value
Age (years)	61 (53-71)	59 (51-68)	67 (59-75)	< 0.0001
Active smokers (n, %)	313 (46.5)	250 (53.4)	63 (30.8)	< 0.0001
Arterial hypertension (n, %)	433 (64.4)	289 (61.7)	144 (70.5)	0.02
Diabetes mellitus (n, %)	149 (22.1)	85 (18.1)	64 (31.3)	< 0.001
Body mass index (kg/m^2)	27.6 (24.9-31.1)	27.6 (24.8-31.1)	27.6 (25.1-31.2)	0.92
Heart failure (n, %)	62 (9.2)	29 (6.1)	33 (16.1)	0.0001
Chronic kidney disease (n, %)	68 (10.1)	39 (8.3)	29 (14.2)	0.02
Chronic respiratory disease (n, %)	53 (7.8)	38 (8.1)	15 (7.3)	0.87
Previous MI (n, %)	48 (7.1)	37 (7.9)	11 (5.3)	0.32
Beta-blockers usage (n, %)	139 (20.6)	85 (18.1)	54 (26.4)	0.01
Calcium channel blockers usage (n, %)	59 (8.7)	32 (6.8)	27 (13.2)	0.01
ACEI/ARB usage (n, %)	195 (29.0)	120 (25.6)	75 (36.7)	< 0.01
Statins usage (n, %)	64 (9.5)	37 (7.9)	27 (13.2)	0.04
Time from symptoms onset to presentation (h)	5 (3-8)	5 (3-8)	6 (4-9)	< 0.01

Quantitative data are expressed as median and interquartile range and were compared using the Mann-Whitney U test. Categorical data are expressed using frequencies and percentages and were compared using Fisher's test.
ACEI – angiotensin converting enzyme inhibitor; ARB – angiotensin II receptor blocker; MI – myocardial infarction

Table 2. Clinical and hemodynamic status on admission according to gender

Parameter	Total (n=672)	Male (n=468)	Female (n=204)	p-value
Killip class >II (n, %)	42 (6.2)	25 (5.3)	17 (8.3)	0.16
SBP (mmHg)	130 (112-145)	130 (112-144)	131 (112-148)	0.57
DBP (mmHg)	80 (70-90)	80 (70-90)	80 (70-88)	0.18
HR (bpm)	77 (65-90)	75 (65-89)	80 (66-95)	0.01
LVEF (%)	45 (40-47)	45 (40-50)	45 (40-45)	0.14

Quantitative data are expressed as median and interquartile range and were compared using the Mann-Whitney U test. Categorical data are expressed using frequencies and percentages and were compared using Fisher's test.
DBP – diastolic blood pressure; HR – heart rate; LVEF – left ventricular ejection fraction; SBP – systolic blood pressure

Clinical and hemodynamic status at admission according to gender

There was no significant difference between males and females regarding the Killip class on admission. Compared to male patients, female patients with STEMI had higher heart rates on admission (p = 0.01), but presented similar blood pressure with their male counterparts (both p >0.05) (Table 2).

Electrocardiographic and angiographic parameters and percutaneous coronary intervention-related complications according to gender

There were no significant between-groups differences regarding the sum of ST-segment elevation (p = 0.19) (Table 3). Anterior STEMI was also similarly common in male and female patients (p = 0.86). Also, there was no significant difference between the two groups regarding the angiographic parameters or the occurrence of PCI-related complications (all p >0.05).

In-hospital evolution according to gender

Female patients presented more often cardiogen shock, kidney dysfunction, and required more frequently diuretic therapy (all p< 0.05) (Table 4). Cardiac arrest was also more common in female than in male patients (p = 0.03). Similarly, length of hospital stay was higher in female compared to male patients (p< 0.01) and female patients presented higher in-hospital mortality compared to their male counterparts (OR 2.56 [95%CI 1.34-4.92], p< 0.01). However, when corrected for the potential confounders, female gender did not prove to be an independent predictor of in-hospital mortality (p = 0.16) (Table 5).

DISCUSSION

Despite the major advances made in STEMI management over the past decades, particularly with the widespread usage of primary PCI, mortality rates remain considerable, with an overall rate of in-hospital

Table 3. Electrocardiographic and angiographic parameters and percutaneous coronary intervention-related complications according to gender

Parameter	Total (n=672)	Male (n=468)	Female (n=204)	p-value
Sum of ST-segment elevation (mm)	8.5 (5.0-14.0)	8.5 (5.0-14.0)	8.0 (4.0-13.2)	0.19
Anterior STEMI (n, %)	280 (41.6)	194 (41.4)	86 (42.1)	0.86
SYNTAX I score (points)	17 (11-24)	16.5 (11.0-23.5)	17.0 (11.7-24.2)	0.48
Pre-PCI TIMI score	0 (0-1)	0 (0-1)	0 (0-1)	0.49
Post-PCI TIMI score	3 (3-3)	3 (3-3)	3 (3-3)	0.75
Thrombus aspiration (n, %)	300 (44.6)	218 (46.5)	82 (40.1)	0.12
Glycoprotein IIb/IIIa inhibitors usage (n, %)	397 (59.0)	279 (59.6)	118 (57.8)	0.67
Coronary artery dissection (n, %)	32 (4.7)	20 (4.2)	12 (5.8)	0.43
Coronary perforation (n, %)	2 (0.2)	0 (0.0)	2 (0.9)	0.09
Angiographic no-reflow (n, %)	117 (17.4)	82 (17.5)	35 (17.1)	1.00
Distal embolization (n, %)	74 (11.0)	53 (11.3)	21 (10.2)	0.78
Acute intra-PCI occlusion (n, %)	12 (1.7)	8 (1.7)	4 (1.9)	0.76

Quantitative data are expressed as median and interquartile range and were compared using the Mann-Whitney U test. Categorical data are expressed using frequencies and percentages and were compared using Fisher's test.
PCI – percutaneous coronary intervention; STEMI – ST-segment elevation myocardial infarction; SYNTAX – SYNergy between PCI with TAXUS™ and Cardiac Surgery; TIMI – Thrombolysis in Myocardial Infarction

Table 4. In-hospital evolution according to gender

Parameter	Total (n=672)	Male (n=468)	Female (n=204)	p-value
Inotropic agents (n, %)	92 (13.6)	56 (11.9)	36 (17.6)	0.05
Diuretic agents (n, %)	199 (29.6)	120 (25.6)	79 (38.7)	< 0.001
Cardiogenic shock (n, %)	57 (8.4)	31 (6.6)	26 (12.7)	0.01
Cardiac arrest (n, %)	78 (11.6)	46 (9.8)	32 (15.6)	0.03
Kidney dysfunction (n, %)	111 (16.5)	63 (13.4)	48 (23.5)	< 0.01
Length of hospital stay (days)	8 (7-11)	8 (7-11)	9 (8-12)	< 0.01
In-hospital mortality (n, %)	39 (5.8)	19 (4.0)	20 (9.8)	< 0.01

Quantitative data are expressed as median and interquartile range and were compared using the Mann-Whitney U test. Categorical data are expressed using frequencies and percentages and were compared using Fisher's test.

Table 5. Crude and adjusted effect of clinical variables on in-hospital mortality

Variable	Unadjusted OR (95%CI)	Adjusted OR (95%CI)
Female gender	2.56 (1.34-4.92)**	1.69 (0.80-3.56)
Age >58 years	5.37 (1.88-15.32)*	5.16 (1.43-18.61)**
Active smoking	0.38 (0.18-0.81)**	0.73 (0.30-1.76)
Arterial hypertension	0.65 (0.34-1.27)	0.35 (0.16-0.77)**
Diabetes mellitus	2.06 (1.04-4.08)***	1.21 (0.52-2.84)
Heart failure	3.60 (1.61-8.06)**	2.83 (1.14-7.04)***
Chronic kidney disease	2.68 (1.17-6.15)***	1.50 (0.56-3.96)
Time from symptoms onset to presentation >7.3 h	1.99 (1.03-3.83)***	1.82 (0.88-3.73)

* – p<0.001; ** – p< 0.01; *** – p< 0.05
Cutoff values for age and time from symptoms onset to presentation were established by receiver operating characteristic analysis. The model included all clinical and cardiovascular risk factors that differed significantly between male and female patients.

STEMI-related mortality of 5.8% in the present study. These results are in line with those from previous studies conducted in patients treated by primary PCI for STEMI[8,9], including with the data from the national ROmanian ST-Elevation Myocardial Infarction registry (RO-STEMI)[10].

Although female patients appear to experience STEMI less frequently than males, females often display worse prognosis, more in-hospital post-STEMI com-plications, and higher short- and long-term mortality rates following STEMI[3-6,11-14]. In accordance with these data, female patients represented less than one third of the total population of STEMI patients included in the present study. They also had higher rate of post-STEMI complications and higher in-hospital mortality rates compared to males.

Nevertheless, the contribution of female gender itself to the higher post-STEMI mortality observed

in numerous studies, including ours, remains controversial. Although female gender has generally been identified as a predictor of post-STEMI mortality in univariate analysis, its ability to independently predict in-hospital post-STEMI mortality remains unclear. In a meta-analysis including 35 studies on patients with STEMI treated by PCI, female gender was identified as an independent predictor of in-hospital and long-term mortality, even after multivariate adjustment.[15] However, whereas some studies identified female gender as an independent predictor of in-hospital mortality[13,16], in others, after adjusting for age, cardiovascular risk factors, or various comorbidities, the association between female gender and increased post-STEMI mortality was either considerably reduced or even entirely lost[17]. These inter-studies differences are most likely due to the different inclusion criteria, different size of the study populations, and different treatment strategies used in the various studies[15,17,18]. Furthermore, many of these data originate from the thrombolytic era, or they were obtained in unselected populations with myocardial infarction both with and without ST-segment elevation or even in patients with the entire spectrum of acute coronary syndromes[3,4,6,14,16]. Meanwhile, few studies have addressed this issue in the specific population of STEMI patients treated by primary PCI[13,19].

In line with these data[13,19], the present study recorded females as having worse post-STEMI outcomes and higher in-hospital mortality rates compared to their male counterparts. Females presented more often cardiogenic shock and required more frequently diuretic therapy; they had more often post-STEMI kidney dysfunction, and had longer hospital stay. The tendency of women to develop fewer collateral vessels has been proposed to explain the increased risk of post-AMI hemodynamic complications observed in females[20]. Cardiogenic shock, the most frequent cause of death among patients hospitalized with AMI, has also been associated with increased comorbidities burden[21], and female gender has been identified as a strong predictor of mortality among patients with AMI and cardiogenic shock[12].

More importantly, the present study shows that the increased post-STEMI in-hospital mortality seen in women is not related to the female gender per se, but rather to the higher cardiovascular risk factors burden displayed by this population. Compared to males, female patients with STEMI were older, were more frequently hypertensive and diabetic, and had

more often a history of heart failure and chronic kidney disease. Meanwhile, females were less likely than men to be active smokers, and indicators of infarct size and severity, such as maximum ST-segment elevation, myocardial enzymes levels, and left ventricular ejection fraction on admission, were similar between the two genders. These data are in line with those from larger previous studies, which also showed women with STEMI to be elder and to have more often arterial hypertension, diabetes mellitus, heart failure, and chronic kidney disease than male patients[3,4,14,22]. This clinical setting is not surprising, given that arterial hypertension has been shown to be more common in females than in males after the age of 55 years[23]. Moreover, registry data have indicated an increased likelihood of hypertensive patients with AMI of being older and having higher prevalence of comorbidities[3-5,14]. At its turn, the higher prevalence of cardiovascular conditions such as arterial hypertension and diabetes mellitus in the post-menopause increases the risk of chronic kidney disease and promotes acceleration of atherosclerosis, contributing to the increased risk of coronary events in females with advancing age[24-26]. In addition, in accordance with previous studies[3,5], time from symptoms onset to presentation was longer in females than in their male peers. Several hypothesis have been proposed to explain the delayed presentation to hospital of female patients with STEMI, including the more advanced age and the often atypical symptoms in females[3,5,27]. The more advanced age and the more prevalent diabetes mellitus could further affect the way in which female patients with STEMI perceive their symptoms and could delay their presentation to hospital[27].

In the present study, similarly to female gender, neither the time from symptoms onset to presentation, nor a history of diabetes or chronic kidney disease, were independent predictors of in-hospital post-STEMI mortality in the multiple regression analysis. In fact, the only independent predictors of mortality that could explain the higher risk of mortality in females were advanced age (>58 years) and history of heart failure, whereas the presence of arterial hypertension was associated with lower risk of in-hospital mortality. Increased risk of mortality among women with STEMI has also been linked to females' more advanced age and more complex comorbidities in previous studies. In a recent study performed in 19 Serbian centers, the authors reported significantly higher post-STEMI in-hospital mortality rates in female com-

pared to male patients[11]. In the overall study cohort, mortality rates were shown to increase with advancing age[11]. Meanwhile, a diagnosis of arterial hypertension appears to paradoxically decrease mortality in the post-AMI period. The more frequent prescription of angiotensin converting enzyme inhibitors or angiotensin II receptor blockers in female compared to male patients (36.7% versus 25.6%), related to the higher prevalence of hypertension among females, may explain, at least partially, this reduced-mortality paradox in hypertensive patients with STEMI[28,29].

Potential limitations

A number of potential limitations to our study are worth considering. First, this was an observational, retrospective, single-center study. Thus, our results should be regarded as hypothesis-generating and should ideally be validated in larger, prospective, multicenter studies. Second, in the present study, mortality was only assessed during hospital stay; long-term post-STEMI mortality was not evaluated. Thus, our results should not be extrapolated to long-term outcomes.

CONCLUSIONS

Female patients represented less than one third of the total study population. They presented higher incidence of STEMI-related complications, longer hospital stay, and higher in-hospital mortality rates than their male counterparts. However, after adjusting for the potential confounders, female gender did not remain an independent predictor of in-hospital mortality. The excess in mortality observed in female patients with STEMI treated by primary PCI appears to be due not to the female gender itself, but rather to females' more important cardiovascular risk factors burden (i.e., more advanced age and higher prevalence of heart failure).

Conflict of interest: none declared.

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