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Gender differences in ischemic heart disease among the Middle-Eastern population

Razlike među polovima kod ishemijske bolesti srca u populaciji Bliskog istoka

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Abstract

Background/Aim. Despite substantial improvements in the outcomes of ischemic heart disease (IHD) in women, it continues to be the leading cause of morbidity and mortality. This paper aimed to study the gender-based differences among the Middle-Eastern population presented with IHD. **Methods.** This was a prospectively designed study where IHD patients who had an indicated coronary angiography (CA) performed at the tertiary cardiac center between 1st September 2014 to 1st September 2015 were analyzed. IHD patients were classified into two groups: stable IHD (SIHD) and acute coronary syndrome (ACS). **Results.** A total of 400 IHD patients had completed coronary angiographic data. About 70% of the patients were diagnosed with ACS and 30% with SIHD. Females were older (64 ± 12 years *vs* 59 ± 13 years, $p < 0.004$) and had higher body mass index (34 ± 7 kg/m2 *vs* 29 ± 5 kg/m2, $p < 0.001$) compared to males. Females were more diagnosed with hypertension (87% *vs* 62%, $p < 0.001$) and diabetes mellitus (76% *vs* 58%, $p < 0.001$) compared to males. Among patients with ACS, males tended to have more ST-elevation myocardial infarction (STEMI) (37% *vs* 12%, $p < 0.001$) whereas females presented more with non-STEMI (45% *vs* 17%, $p < 0.001$. **Conclusion.** Middle-Eastern females tended to have more adverse risk factors, presented more with non-STEMI, and had fewer rates of in-hospital complications.

Key words:
cardiac catheterization; coronary angiography; percutaneous coronary intervention; acute coronary syndrome; middle east; gender.

Apstrakt

Uvod/Cilj. Uprkos znatnom poboljšanju ishoda liječenja ishemijske bolesti srca (IBS) kod žena, ona i dalje predstavlja vodeći uzrok mortaliteta i morbiditeta. Cilj je bio ispitati razlike vezane za ishemijsku bolest srca zasnovane na razlikama kod polova u populaciji Bliskog istoka. **Metode.** Prospektivnom studijom analizirani su bolesnici sa IBS kojima je urađena elektivna koronarna angiografija u kardiološkom centru tercijernog nivoa u periodu od 1.9. 2014. do 1.9.2015. godine. Bolesnici sa IBS su bili podeljeni na dve grupe: grupu sa stabilnom ishemijskom bolešću srca (SIBS) i grupu sa akutnim koronarnim sindromom (AKS). **Rezultati.** Ukupan broj bolesnika kod kojih je urađena koronarna angiografija je 400. Oko 70% bolesnika je bilo dijagnostifikovano kao AKS, a 30% kao SIBS. Žene su bile starije (64 ± 12 godina *vs* 59 ± 13 godina, $p < 0,004$) i imale su veći indeks telesne mase (34 ± 7 kg/m² *vs* 29 ± 5 kg/m², $p < 0,001$) u poređenju sa muškarcima. Žene su češće imale povišen krvni pritisak (87% *vs* 62%, $p < 0,001$) i šećernu bolest (76% *vs* 58%, $p < 0,001$). Među bolesnicima sa AKS, muškarci su češće imali infarkt miokarda sa elevacijom ST segmenta (STEMI) (37% *vs* 12%, $p < 0.001$), dok su se žene češće prezentovale sa non-STEMI (45% *vs* 17%, $p < 0,001$). **Zaključak.** Žene sa Bliskog istoka su češće imale faktore rizika, prezentovale se češće sa non-STEMI i imale su manju stopu intrahospitalnih komplikacija.

Ključne reči:
kateterizacija srca; angiografija koronarnih arterija; perkutana koronarna intervencija; akutni koronarni sindrom; bliski istok; pol.

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Introduction

Ischemic heart disease (IHD) is the most common cause of morbidity and mortality worldwide [1]. Chest pain is a common presentation of the acute coronary syndrome (ACS). However, women tend to have more atypical symptoms [2, 3]. Studies have shown that men presented more with ST-elevation myocardial infarction (STEMI), whereas women presented more with non-STEMI (NSTEMI) [4]. Symptomatic women undergoing coronary angiography (CA) tend to have less extensive and severe coronary artery disease (CAD), but more adverse prognosis compared to men [4].

The gender differences in mortality after reperfusion are predominantly explained by baseline differences, including advanced age and greater comorbidity in women. Procedural success in percutaneous coronary intervention (PCI) is similar in men and women, although women tend to experience more bleeding complications [5]. Women also face higher mortality from IHD due to their relatively higher prevalence of "female-pattern" IHD [6]. Application of guidelines therapy is improving outcomes in women. However, mechanisms and interventions directed at gender differences in IHD are still a matter for debate [7].

In this prospectively designed study, the CA data registry was used to study the gender-based differences among the Middle-Eastern population presented with IHD in the tertiary interventional cardiac center.

Methods

The study was designed as a prospective observational cohort study. The study subjects were enrolled with ACS, referred to the Chest Diseases Hospital (CDH) from the public sector (Ministry of Health Hospitals) as well as the private hospitals, for an indicated cardiac CA with possible PCI if needed.

Study subjects and data collection

Study subjects were prospectively enrolled from 1st September 2014 to 1st September 2015. According to the inclusion criteria patients with the age of 18 years and above with IHD diagnosis were included in the study.

IHD diagnosis including both stable and ACS variables was based on the American College of Cardiology clinical data standards. Briefly, stable IHD (SIHD) patients were those who had unacceptable ischemic symptoms despite medical therapy and who were amenable to, and candidates for coronary revascularization, or whose clinical characteristics and results of noninvasive testing (exclusive of stress testing) indicated a high likelihood of severe IHD, and who were amenable to, and candidates for coronary revascularization, as well as those who could not undergo diagnostic stress testing, or had indeterminate or non-diagnostic stress tests when there was a high likelihood that the findings would result in important changes to therapy [7].

ACS was defined as a clinical presentation consistent with unstable angina (UA)/NSTEMI or STEMI within 8 days of admission, associated with any one of the following: ECG changes, elevated biomarkers of myocardial necrosis (any one of CPK-MB/troponin-T or troponin-I). STEMI was diagnosed if ECG showed evidence of ST segment elevation in ≥ 2 contiguous leads or a new left bundle branch block in addition to chest pain or elevated cardiac markers. The rest of the cases were labeled as NSTEMI/UA based on the presence of elevated biomarkers of myocardial necrosis with or without chest pain.

The study protocol was approved by the institutional review board, and all patients provided written informed consent, which included consent for the CA. Patients younger than 18 years of age and patients refusing to give consent were excluded from the study.

Statistical methods

Demographic and baseline characteristics, treatment patterns, angiographic status, and in-hospital outcomes were compared between men and women overall and according to ACS status: UA/NSTEMI and STEMI. Since patients often had multiple lesions intervened upon during a single PCI laboratory visit, lesion characteristics were assigned as follows: for each characteristic, the highest risk value of any lesion intervened upon during the index PCI was recorded. Continuous variables were described as medians (with inter-quartile ranges) and categorical variables were described as frequencies. Continuous and ordinal categorical variables were compared using stratum adjusted Wilcoxon rank sum test, whereas nominal categorical variables were compared using stratum adjusted χ^2 test where stratification is done by hospital. User-defined missing values were treated as missing. In examining the relationship between gender and outcomes, as well as gender and medical treatments, comparison adjusting for ACS status alone was initially performed. A *p*-value of 0.05 was established as the level of statistical significance for all tests. All analyses were performed using SAS software (versions 8.2, SAS Institute, Cary, NC).

Results

A total of 400 IHD patients had completed coronary angiographic data. Their mean age was 61 ± 12 years, and 64% were males. About 70% of the patients were diagnosed with ACS, and 30% were diagnosed with SIHD. Females were much older (64 ± 12 years *vs* 59 ± 13 years, $p < 0.004$) and had higher body mass index (34 kg/m^2 ± 7 *vs* 29 ± 5 kg/m^2, $p < 0.001$) compared to males. Females tended to have more adverse risk factors. Hypertension was diagnosed in 87% females and 62% males ($p < 0.001$), and diabetes mellitus was diagnosed in 76% females and 58% males ($p < 0.001$) (Tables 1 and 2).

Table 1

Demographics and gender differences among patients with IHD

Patients	All patients (n = 400)	ACS (group A) (n = 279)	SIHB (group B) (n = 121)	*p*
Sex, n (%)				
male	256 (64)	177 (63.4)	79 (65.3)	0.724
female	144 (36)	102 (36.6)	42 (34.7)	
Age (years), mean ± SD				
total population	60.8 ± 12.5	60.5 ± 12.5	61.7 ± 12.0	0.004
male	58.9 ± 12.6	58.8 ± 12.8	59.1 ± 12.1	male *vs* female (group A)
female	64.2 ± 11.7	63.3 ± 12.1	66.4 ± 10.3	
Marital status, n (%)				
single	6 (1.5)	2 (0.7)	4 (3.3)	
married	330 (82.5)	230 (82.4)	100 (82.6)	0.268
widowed	53 (13.3)	39 (14)	14 (11.6)	
divorced	11 (2.8)	8 (2.9)	3 (2.5)	
Height (cm), mean ± SD				
total population	164.6 ± 8.9	164.6 ± 8.5	164.5 ± 9.6	0.917
male	168.9 ± 6.8	168.9 ± 6.2	168.8 ± 7.9	0.926
female	157 ± 6.7	157.2 ± 6.6	156.4 ± 7	0.544
Weight (kg), mean ± SD				
total population	83.3 ± 16.7	83.3 ± 16.2	83.4 ± 17.8	0.978
male	83.2 ± 15.7	82.7 ± 14.9	84.3 ± 17.4	0.446
female	83.5 ± 18.3	84.3 ± 18.2	81.5 ± 18.7	0.402
BMI (kg/m^2), mean ± SD				
total population	30.8 ± 6.3	30.9 ± 6.4	30.8 ± 6.2	0.936
male	29.1 ± 5	29 ± 4.8	29.5 ± 5.3	0.000
female	33.9 ± 7.2	34.6 ± 7.3	33.2 ± 6.9	male *vs* female (group A)
BMI classification, n (%)				
underweight	6 (1.5)	5 (1.8)	1 (0.8)	
normal	63 (15.8)	41 (14.7)	22 (18.2)	0.890
overweight	137 (34.3)	98 (35.1)	39 (32.2)	
obese	194 (48.5)	135 (48.4)	59 (48.8)	
Waist circumference (cm), mean ± SD				
total population	104.3 ± 16.3	104.8 ± 15.5	103.1 ± 18.1	0.355
male	101.8 ± 14.2	101.7 ± 13	102.1 ± 16.6	0.000
female	108.6 ± 18.8	110.1 ± 17.9	105 ± 20.5	male *vs* female (group A)

IHD – ischemic heart disease; ACS – acute coronary syndrome; SIHD – stable IHD; BMI – body mass index; SD – standard deviation.

Table 2

Risk factors and gender differences among patients with IHD

Category	All patients (n = 400)	Total population male (n = 256)	Total population female (n = 144)	*p*	ACS (group A) (n = 279)	SIHD (group B) (n = 121)	*p*
Hypertension	284 (71)	159 (62.1)	125 (86.8)	0.000	196 (70.3)	88 (72.7)	0.617
Dyslipidemia	209 (52.3)	133 (52)	76 (52.8)	0.874	147 (57.2)	62 (51.2)	0.791
Diabetes mellitus	257 (64.3)	148 (57.8)	109 (75.7)	0.000	184 (65.9)	73 (60.3)	0.283
Smoking history							
non-smoker	208 (52)	75 (29.3)	133 (92.4)		150 (53.8)	58 (47.9)	
previous smoker (stopped > 1 year ago)	48 (12)	46 (18)	2 (1.4)	0.000	28 (10)	20 (16.5)	
recent smoker (stopped 1 year, 1 month ago)	8 (2)	4 (1.6)	4 (2.8)		6 (2.2)	2 (1.7)	0.738
current smoker	136 (34)	131 (51.2)	5 (3.5)		95 (34.1)	41 (33.9)	
Prior MI	128 (32)	86 (33.6)	42 (29.2)	0.364	82 (29.4)	46 (38)	0.090
Prior PCI	82 (20.5)	59 (23)	23 (16)	0.093	49 (17.6)	33 (27.3)	0.027
Prior CABG	25 (6.3)	18 (7)	7 (4.9)	0.391	15 (5.4)	10 (8.3)	0.274
Prior HF	38 (9.5)	16 (10.2)	12 (8.3)	0.552	28 (10)	10 (8.3)	0.580
Prior stroke	38 (9.5)	24 (9.4)	14 (9.7)	0.910	32 (11.5)	6 (5)	0.041
Peptic ulcer	25 (6.3)	19 (7.4)	6 (4.2)	0.198	19 (6.8)	6 (5)	0.484
Chronic renal failure	28 (7)	19 (7.4)	9 (6.3)	0.660	20 (7.2)	8 (6.6)	0.842
on dialysis	6 (1.5)	5 (2)	1 (0.7)	0.379	3 (1.1)	3 (2.5)	0.204
Chronic lung disease	39 (9.8)	18 (7)	21 (14.6)	0.014	23 (8.2)	16 (13.2)	0.124

IHD – ischemic heart disease; ACS – acute coronary syndrome; SIHD – stable ischaemic heart disease; MI – myocardial infarction; PCI – percutaneous coronary intervention; CABG – coronary artery by-pass grafting; HF – heart failure.

Gender differences among patients with ACS

Of the 279 ACS patients, 60 patients were diagnosed with UA (32 males and 28 females), 122 were diagnosed with NSTEMI (34 males and 89 females), and 97 patients were diagnosed with STEMI (74 males and 23 females). Females presented more with NSTEMI (45% females *vs* 17% males, $p < 0.001$), whereas males presented more with STEMI (37% males *vs* 12% females, $p < 0.001$). There were no statistically significant differences between males or females concerning UA (16% males *vs* 14% females, $p = 0.57$) (Table 3).

Coronary angiography and gender difference

Of the 400 IHD patients, CA was diagnosed as normal in 30%. Of these, females had less normal coronaries (36 females *vs* 85 males). About 24% had single-vessel disease (54 males *vs* 40 females), 95 had double-vessel disease (60 males *vs* 35 females), and 57 had triple-vessel disease (36 males *vs* 21 females). Left main disease was diagnosed in 3 patients (1 male *vs* 2 females) (Table 4).

Table 3

Gender differences among patients with ACS

Characteristics	All patients n (%)	Male n (%)	Female n (%)	*p*
Unstable angina at presentation	60 (15)	32 (16)	28 (14)	0.570
NSTEMI at presentation	122 (31)	34 (17)	89 (45)	< 0.001
STEMI at presentation	97 (24)	74 (37)	23 (12)	< 0.001
Positive EET	96 (24)	50 (25)	46 (23)	0.640
Abnormal nuclear	140 (35)	62 (31)	78 (39)	0.090
Prior PCI	46 (12)	22 (11)	24 (22)	0.752
Prior CABG	38 (98)	24 (12)	14 (7)	0.081
Pre-procedural aspirin	390 (98)	196 (98)	194 (97)	0.521
Pre-procedural clopidogrel	372 (93)	191 (96)	181 (91)	0.051

NSTEMI – non-ST-elevation myocardial infarction; STEM – myocardial infarction with ST-elevation; ACS – acute coronary syndrome; PCI – percutaneous coronary intervention; CABG – coronary artery by-pass grafting; EET – treadmill exercise test.

Table 4

Coronary angiography findings among patients with IHD

Category	All patients (n = 400)	Male (n = 256)	Female (n = 144)	*p*
Vessel disease status, n (%)				
Normal	121 (30.3)	85 (33.3)	36 (25)	
SVD	94 (23.5)	54 (21.1)	40 (27.8)	
DVD	95 (23.8)	60 (23.4)	35 (24.7)	
TVD	57 (14.2)	36 (14.1)	21 (14.6)	0.471
LM	3 (0.3)	1 (0.4)	2 (1.4)	
LM + DVD	18 (4.5)	14 (5.5)	4 (2.8)	
LM + TVD	12 (3)	6 (2.3)	6 (4.2)	
Vessel classifications, n (%)				
LM stenosis	21 (5.3)	10 (3.9)	11 (7.6)	0.109
LAD stenosis	210 (52.5)	128 (50)	82 (56.9)	0.183
LCX stenosis	152 (38)	99 (38.7)	53 (36.8)	0.713
RCA stenosis	154 (38.5)	99 (38.7)	55 (38.2)	0.925
Treatment options, n (%)				
Medical	153 (38.3)	106 (41.4)	47 (32.6)	
PCI	196 (49)	120 (46.9)	76 (52.8)	0.095
CABG	51 (12.8)	30 (11.7)	21 (14.6)	
PCI, n (%)				
BMS used	20 (10.2)	9 (7.5)	11 (14.5)	0.117
DES used	176 (89.8)	111 (92.5)	65 (85.5)	0.117
PCI to ISR	2 (0.5)	2 (0.8)	0	0.270
PCI to bifurcation	4 (1)	3 (1.2)	1 (1.3)	0.570
Average waiting period for PCI/CABG, n (%)				
1 day	389 (97.3)	249 (97.3)	140 (97.2)	0.980
2 days	11 (2.8)	7 (2.7)	4 (2.8)	

IHD – ischemic heart disease: SVD – single-vessel disease; DVD – double-vessel disease; TVD – triple-vessel disease; LM – left main coronary artery disease; LAD – left anterior descending coronary artery; Lcx – left circumflex artery; RCA – right coronary artery; PCI – percutaneous coronary intervention; CABG – coronary artery bypass grafting; BMS – bare metal stents;
DES – drug-eluting stents; ISR – in-stent restenosis.

In-hospital outcomes

Stent thrombosis tended to be more frequent in males than females (3% *vs* 0%), but females had more heart failure than males (4% vs 1%). The most significant complication differences were in acute kidney injury. Males tended to have more frequent kidney injuries than females (5% *vs* 1%), while women had more fever compared to males (8% *vs* 3%) (Table 5).

Table 5

In-hospital outcomes (PCI complications) among IHD population

Characteristics	All patients n (%)	Male n (%)	Female n (%)	*p*
Failure of PCI	2 (1)	1 (1)	1 (1)	0.990
Bifurcation Stenting	10 (3)	4 (2)	6 (3)	0.052
PCI of ISR	6 (2)	3 (2)	3 (2)	0.990
Stent thrombosis	3 (1)	3 (2)	0 (0)	0.080
Heart Failure	10 (3)	2 (1)	8 (4)	0.050
CIN	10 (3)	9 (5)	1 (1)	0.010
VT/VF	6 (2)	3 (2)	3 (2)	0.990
Infection (fever)	20 (5)	5 (3)	15 (8)	0.020
Pseudo aneurysm	6 (2)	3 (2)	3 (2)	0.990
Groin hematoma	10 (3)	6 (3)	4 (2)	0.520
Retroperitoneal bleeding	2 (1)	1 (1)	1 (1)	0.990
MI as a complication	9 (2)	3 (2)	6 (3)	0.50
CVA	3 (1)	0 (0)	3 (2)	0.240
Death	1 (1)	0 (0)	1 (1)	0.990

PCI – percutaneous coronary intervention; IHD – ischemic heart disease; ISR – in-stent restenosis; CIN – contrast-induced nephropathy; VT/VF – ventricular tachycardia/ventricular fibrillation; MI – myocardial infarction; CVA – cerebrovascular accidents.

Discussion

Techniques of treatment should be custom designed for each gender, as our registry revealed lesser high-risk angiographic features but more in-hospital complication rates in females than in males. This should not only be instrumental in reducing post-intervention complications but shall also aid to improve the appropriate antiplatelet therapy adherence and efficacy.

In our study, patients were admitted to general hospitals for non-invasive cardiology services. This indicates low referral rates for invasive strategies. The same is in harmony with the results of the recent ACS registry published in Kuwait, which shows the rates of in-hospital coronary angiography cases as significantly lower (21% for NSTEMI, 17% for STEMI, and 15% for UA [8]) as compared to the Global Registry of Acute Coronary Events (GRACE) rate of 53% for NSTEMI, 55% for STEMI, and 42% for UA [9]. In Kuwait, there was an acute lack of onsite cardiac cath-labs in general hospitals which was stretching the capacity of the sole invasive cardiac centre, which was our site. This might have been a major cause for the lesser number of in-hospital coronary angiograms, the theory which was also proposed worldwide by Fox et al. [10]. In addition, there may be many intrinsic biological mechanisms that require more studies, specifically at the basic level.

The rate of women presenting with UA/NSTEMI and having atypical symptoms was significantly higher compared to men, which was similar to the findings in Global Use of Strategies to Open Occluded Coronary Arteries (GUSTO) IIb study, which attributed this to the differences in anatomy, the pathophysiology of CAD, and clinical characteristics in the two genders [11]. However, this might also be due to lesser utilization of the acute antiplatelet therapy on admission in females and due to unnoticed reasons, even though it was proven in other trials [12, 13], as well as our own, that women with ACS are older and have more co-morbidities. Nevertheless, as opposed to the findings of Blomkalns et al. [14] that women with ACS present more often with both prior and current signs of congestive heart failure, we found similar or better left ventricular functions in terms of ejection fraction (EF) in women.

Chest pain was not a common finding in elderly males or females, and if found, it was milder or more often absent in females than in their male counterparts , possibly owing to the higher comorbidities like diabetes mellitus. However, even though chest pain incidences were predominant in many cases of those below 55 years of age, regardless of the ACS type, women in the same group seemed to have higher asymptomatic presentation rates [3]. Although there were high similarities between our patient cohort and those of the Euro Heart Survey II [15], our survey into the treatment and short-term prognosis revealed some noticeable differences.

Even though women mostly presented with atypical cases and Killip I (as against Killip III for males), and were mostly diagnosed as NSTEMI, most males could be managed by PCI while women had higher CABG rates.

Given the information that the results of PCI may be inferior to CABG, most subjects did not defer from choosing PCI over surgery. Higher mortality rates of post-PCI in females have been decreasing [16–19], and as for the National

Heart, Lung and Blood Institute, registries have slumped from 2.6% in 1985 to 1.5% in 1994 (*p*-value not significant) [20].

Variations in procedural outcomes owing to differences from presentation, diagnosis, management, and treatment in the two genders were identified. However, more work needs to be done to identify and explain these based on inherent biological differences between males and females [21].

Conclusion

In this single-centre cohort study, it was found that among the Middle-Eastern population, females tended to have more adverse risk factors, presented more with non-STEMI, and had fewer rates of in-hospital complications than males.

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