Original Articles

Gender Differences in Clinical, Angiographic and Procedural Profiles between Young Patients with Acute Coronary Syndrome undergoing Percutaneous Coronary Intervention

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Key words: *Ischaemic heart disease, Acute coronary syndrome, gender, young patients.*

Abstract:

Background: *Acute coronary syndrome (ACS) is increasingly prevalent among young patients, particularly in South Asia, where young patients are known to present with multiple risk factors and gender-based differences in angiographic profiles. This study aimed to compare gender differences in clinical, angiographic and procedural profiles between young patients with ACS undergoing percutaneous coronary intervention (PCI).*

Methods: *This prospective observational study was done at the National Institute of Cardiovascular Diseases (NICVD) from April 2016 to March 2017. 190 young patients with ACS undergoing PCI were included. Clinical, angiographic and procedural variables were compared and statistically analyzed.*

Results: *The mean age of young females and males was 43.8±6.9 years and 40.1±4.3 years respectively (p<<0.001). Young women had significantly more risk factors of hypertension (62.1% vs 33.7%, p<0.001) and diabetes (57.9% vs 31.6%, p<0.001) in comparison to young men. Smoking was significantly greater among young males (70.5% vs 0%, p<0.001). Young females had significantly better mean ejection fraction (EF) (48.4±9.3% vs 45.1±10.4%, p=0. 02). Left main coronary artery (3.2% vs. 1.1%, p=0.61) and left anterior descending artery (51.6% vs. 45.3%, p=0.38) were more frequently involved among young females. Young males showed angiographically more severe CAD and greater frequency of multivessel CAD with higher DVD (22.1%vs 18.9%, p=0.58) and TVD (18.9%vs 11.6%, p=0.15).*

Conclusion: *Significantly more young women with ACS presented with hypertension and diabetes than young males. However, they had better ejection fraction and less severe angiographic profiles.*

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Introduction:

Acute coronary syndromes (ACS) is increasingly prevalent at a younger age, ranging from 2 to 10% based on studies conducted from different countries around the world.[1] The prevalence of ACS among young women has also increased.[2] Coronary Artery Disease (CAD) among young patients is particularly higher among those of South Asian ethnicity, in whom a 2-4-fold higher prevalence, increased severity, extreme prematurity and greater mortality has been observed.[3]

The term "young" in relation to ACS or "Premature" CAD has been defined, in various studies as having an age of onset varying from ≤40 to ≤55 years.[4-7] This disparity in the definition of young CAD in the literature largely stems from the fact that cardiovascular disease develops 7 to 10 years later in women than in men,[8] leading to a difference in the definition of the "young" ACS patient for each gender, chiefly due the fundamental differences in the physiology of women and a protective effect of endogenous oestrogens against CAD. In keeping with this theory and some prior studies, in this study too, we defined young ACS as females <55 years of age, and males <45 years of age.[4-7]

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ACS among younger patients are better understood as a rapidly progressive form of the disease.[7] Younger CAD patients have been observed to have high prevalence of risk factors, different clinical presentations, coronary angiographic profiles, plaque composition and clinical outcomes.[5,9,10] However, although comprising only between a quarter to one third of young ACS patients,[11-13] women present with a significantly heightened ischaemic risk profiles compared with their male counterparts,[12,14] and are prone to adverse in-hospital outcomes despite less obstructive coronary artery disease.[12,15]This has translated to younger, but not older, women having higher rates of adverse cardiovascular outcomes after acute coronary syndromes or intervention procedures than men.[16-18]

Multiple well-designed studies have found that, in comparison to age-matched men, women less than 50 to 55 years may be at higher risk for more adverse short-term outcomes and cardiovascular events particularly following PCI.[14, 18-21]The highest risk for women has been observed up to the age of 50- 60 years.[20]

Younger women have shown greater prevalence of hypertension, diabetes mellitus, cerebrovascular disease, renal impairment and congestive heart failure in comparison to men.[5,12,15,19,21] The use of oral contraceptives among young females have also been implicated in the greater incidence of MI, and subsequent adverse outcomes.[22] Diabetes mellitus is a particularly strong risk factor for CAD in women[14] and is associated with a heightened cardiovascular mortality particularly in women <55 years. Diabetes may also negate the protective effects of estrogen on vascular function, and increase the risks of post PCI complications.[23,24]

Despite a greater prevalence of risk factors, young women <50 years presenting with ACS are known to have better left ventricular (LV) ejection fraction (EF),[12,19,25] and most notably, less severe/ extensive angiographic CAD.[5,19,21]Up to 50% of women presenting with ACS may have angiographically non-obstructive or non-atherosclerotic coronary artery disease that does not translate to favourable outcomes.[26] In most studies, women were less likely to have multi-vessel disease, ulcerated plaque overlying thrombus,[20,21] ACC/AHA type B2/C lesions,[12,21] or bypass graft lesion than men.[5,20]The present study was done to compare the gender-based differences of clinical, angiographic and procedural profiles among young patients with ACS undergoing PCI.

Methods:

This prospective observational study was conducted over a period of 1 year from April 2016 to March 2017 at the Department of Cardiology, National Institute of Cardiovascular Diseases, Dhaka. The study complied with the Declaration of Helsinki. Prior ethical approval was obtained from the ethical review committee of NICVD. Informed written consent was taken from each patient.

Young patients were defined as males <45 years and females <55 years in accordance with the literature. A total of 190 young patients presenting with ACS, and undergoing PCI during index hospitalisation at NICVD were selected by purposive sampling technique, based on predefined enrollment criteria. Patients with prior MI, mechanical complications of MI, cardiogenic shock, valvular heart disease, congenital heart disease and cardiomyopathy were excluded. Study subjects were divided into two groups on the basis of gender. Group I comprised of young females and group II comprised of young males.

The demographic characteristics, risk factors, ACS type and location of MI in case of STEMI, and left ventricular ejection fraction were recorded. Coronary angiography was performed by conventional method (right femoral access) by routine operators. Coronary angiographic variables including Gensini Score, ACC/ AHA lesion type of culprit lesion, number of diseased vessels (single, double, triple) and culprit vessel were noted. In case of angiographically significant stenosis, ad hoc PCI to culprit artery was done. PCI variables including stent type [(drug eluting stent (DES) or bare metal stent (BMS)], stent diameter and length and angiographicsuccess were noted. Data were processed and analyzed using software using SPSS 16.0 (Statistical Package for the Social Sciences by SPSS Inc.,

Chicago, IL, USA, 2007). The test statistics used to analyze the data were descriptive statistics, Chi-squared Test (χ^2), unpaired t-Test and Fisher's Exact Test.

Results:

A total of 190 patients were studied, including 95 young females and 95 young males. The overall mean age was 41.3±5.6 years (range 18-54 years). The mean age of young females was 43.8±6.9 years and young males was 40.1±4.3 years (Table I). Among young females, the highest percentage were in the range of 45- 54 years (50.5%) and lowest in age group of <25 years (3.2%). In contrast, among young males, the majority (83.1%) were in the age group of 35-44 years.A total of 52.6% STEMI, 26.3% NSTEMI and 21.1% UA patients were included with equal distribution between the two genders. Among STEMI patients, 70% were of anterior and 30% were of inferior MI, and they were equally distributed between the two groups.

Table II shows the distribution of risk factors for CAD between the groups. Young females with ACS showed greater prevalence of all risk factors, except smoking, which was significantly greater among young males (70.5% vs 0%, p<0.001). However 8.4% of women reported the use of smokeless tobacco. Hypertension (62.1% vs 33.7%, p<0.001) and diabetes (57.9% vs. 31.6%, p<0.001) were significantly more prevalent among young females. History of dyslipidemia and family history of CAD were found to be greater among young females, although not statistically significant.

Fig 1 shows the distribution of young female patients by menopausal status. Among the 95 young females, majority (74%) were pre-menopausal, while 26% of them were post-menopausal.

Fig 2 shows the distribution of pre-menopausal patients by oral contraceptive pill (OCP) use. Among the 70 pre-menopausal females in this study, 63% had history of taking OCP.

Table-I

Distribution of study patients by age.

Age in years	Young females (n= 95)		Young males (n = 95)		p value
<25	3	3.2	2	2.1	0.65
25 – 34	5	5.3	14	14.8	0.02
35 – 44	39	41.1	79	83.1	<0.001
45 – 54	48	50.5	0	0.0	<0.001
Mean±SD	43.8±6.9		40.1±4.3		<0.001
(Range)	(18-54)		(22-44)		

Table-II

Comparison of risk factors for CAD between young females and males.

Risk Factors	Young females		Young males		p value
	n	%	n	%	
Smoking	0	0.0	67	70.5	<0.001
Smokeless tobacco	8	8.4	3	3.2	0.21
Hypertension	59	62.1	32	33.7	<0.001
Diabetes mellitus	55	57.9	30	31.6	<0.001
Dyslipidaemia	59	62.1	50	52.6	0.18
Family H/O CAD	41	43.2	33	34.7	0.23

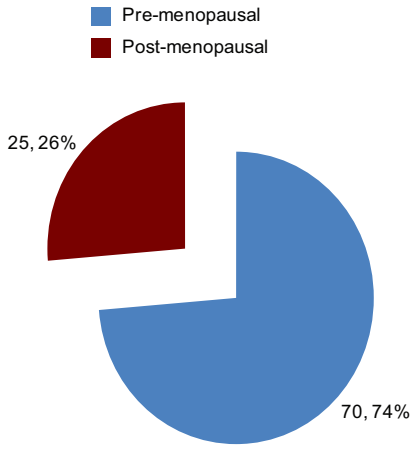

Fig.-1: *Distribution of young female patients by menopausal status (n=95).*

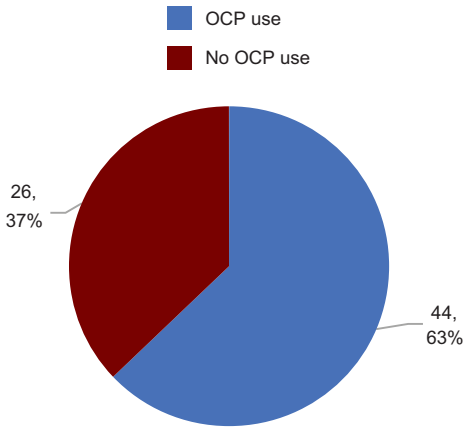

Fig.-2: *Distribution of pre-menopausal young female patients by use of OCP (n=70).*

The mean percent of EF of study patients was 46.8±10.0. Mean ejection fraction (%) was 48.4±9.3 for young females, who had a significantly better EF in comparison to young males, who had a mean EF (%) of 45.1±10.4 (Table III). Among both groups, the majority of patients had mild LV systolic dysfunction (48.4% and 41% of young females and males respectively). There was statistically significant difference among the two groups in the moderate LV dysfunction category, with significantly more young males demonstrating moderate LV dysfunction than young females (p=0.04).

Table IV shows the comparison of angiographic characteristics between the two groups. LMCA (3.2% vs. 1.1%, p=0.61) and LAD (51.6% vs. 45.3%, p=0.38) were more frequently involved among young females. Young males demonstrated angiographically more severe CAD, with significantly higher numbers of ACC/AHA lesion type B2 (40% vs 25.3%, p=0.03) and C (20% vs 9.47%, p=0.03), while type A lesions were significantly more frequent among young females (40% vs. 14.7%, p<0.001).Young males also had greater frequency of multivessel CAD with higher DVD (22.1%vs 18.9%, p=0.58 for young males and females respectively) and TVD (18.9%vs 11.6%, p=0.15 for young males and females respectively).

Table V shows CAD severity by means of the Gensini Score among the study patients. Moderate to severe CAD defined as Gensini Score ≥36 points was found in 51.6% and 41.1% ofyoung males and females respectively, although not statistically significant (p=0.14). Overall mean Gensini score was also greater among young males (44.0±32.4 vs. 39.3±27.6, p=0.27).

Table VI details the PCI procedural characteristics between the two groups. Mean stent diameter was significantly smaller in young females (2.7±0.3 vs. 2.9±0.4 mm, p=0.02), but no

Table-III

Comparison of left ventricular (LV) ejection fraction (EF) between two groups (n=190).

LV EF (%)	Young females		Young males		Total		p value
	n	%	n	%	n	%	
≤30 (Severe)	3	3.2	5	5.3	8	4.2	0.46
31-44 (Moderate)	23	24.2	35	36.8	58	30.5	0.04
45-54 (Mild)	46	48.4	39	41.0	85	44.7	0.30
≥55 (Normal)	23	24.2	16	16.8	39	20.5	0.20
Mean ± SD(Range)	48.4±9.3(30-78)		45.1±10.4(32-65)		46.8±10.0(30-78)		0.02

Table-IV

Comparison of angiographic characteristics between young females and males (n=190).

Angiographic characteristics	Young females		Young males		Total		p value
	n	%	n	%	n	%	
Culprit artery							
LMCA*	3	3.2	1	1.1	4	2.1	0.61
LAD*	49	51.6	43	45.3	92	48.4	0.38
LCX*	17	17.9	21	22.1	38	20.0	0.46
RCA*	24	25.3	30	31.6	54	28.4	0.33
Ramus Intermedius	2	2.1	0	0.0	2	1.1	0.47
Number of diseased vessels							
Single	66	69.5	56	58.9	122	64.2	0.13
Double	18	18.9	21	22.1	39	20.5	0.58
Triple	11	11.6	18	18.9	29	15.3	0.15
ACC/ AHA lesion type							
A	38	40.0	14	14.7	52	27.4	<0.001
B1	24	25.3	24	25.3	48	25.3	1.00
B2	24	25.3	38	40.0	62	32.6	0.03
C	9	9.47	19	20.0	28	14.7	0.03

*LMCA: Left main coronary artery; *LAD: Left anterior descending; *LCX: Left circumflex; *RCA: Right coronary artery.

Table-V

Distribution of the study patients according to CAD severity by Gensini Score (n=190).

CAD severity by Gensini Score	Young females		Young males		p value
	n	%	n	%	
Moderate to severe (≥36 points)	39	41.1	49	51.6	0.14
Normal to mild (<36 points)	56	58.9	46	48.4	
Mean ± SD	39.3±27.6		44.0±32.4		0.27^{ns}

Table-VI

Comparison of PCI Procedural characteristics between young females and males (n=190).

Procedural characteristics	Young females		Young males		Total		p value
	n	%	n	%	n	%	
Stent diameter (mm)							
2.25	12	12.6	9	9.5	21	11.1	0.48
2.5	32	33.7	16	16.8	48	25.3	0.007
2.75	15	15.8	34	35.8	49	25.8	0.002
3.0	30	31.6	19	20.0	49	25.8	0.06
3.5	6	6.3	14	14.7	20	10.5	0.04
4.0	0	0.0	3	3.2	3	1.6	0.08
Mean diameter	2.7±0.3		2.9±0.4		2.8±0.4		0.02
Stent length (mm)							
<20 mm	31	32.6	22	23.2	63	27.9	0.14
>20 mm	64	67.4	73	76.8	137	72.1	
Mean±SD	25.0±9.6		26.6±9.2		25.8±9.4		0.26
Stent type							
BMS	18	18.9	3	3.2	21	11.1	0.001
DES	77	81.1	92	96.8	169	88.9	
Angiographic success	91	95.8	94	98.9	185	97.4	0.36

significant difference in mean stent length (26.6±9.2 vs. 25.0±9.6 mm, p=0.26) was seen between the two groups. Among young females, the highest number of stents implanted was of the 2.5mm diameter (33.7% of females), while the highest number of stents implanted among young males were of 2.75mm diameter (35.8%).

Discussion:

This prospective observational study presents the comparison of clinical, angiographic and procedural characteristics of young ACS patients undergoing PCI. The mean age of young females was significantly higher than young males (43.8±6.9 vs 40.1±4.3 years, p=0.001), similar to the observations in a study of young Bangladeshi ACS patients by Moniruzzaman et al.[27] and Patted et al.[28], who studied young Indian ACS patients. However, our patients were younger than the patient population of the PROMETHEUS study (48.6±5.6 years vs. 48.1±6.0 years).[12] The younger mean age in this study possibly reflects the earlier onset of premature atherosclerosis among South Asian populations in comparison to Western populations.[3]

There were no differences in terms of ACS types among the subjects as equal numbers of all presentations across the spectrum of ACS were taken from both groups in order to ensure matching. The majority of this young ACS population undergoing PCI presented with ST segment elevation myocardial infarction (STEMI), accounting for 52.6% of all subjects. Anterior MI was more frequent than inferior MI. These findings concur with those of an Indian study, in which an overwhelming majority of patients underwent PCI due to STEMI.[28] In contrast, however, Chandrasekhar et al.[29] observed in the PROMETHEUS study,[12] that unstable angina (UA) comprised almost half of the study population (approximately 46%) and STEMI comprised only approximately one quarter.

This study observed that young females had higher frequencies of baseline risk factors, particularly hypertension and diabetes. Several other studies have made similar observations. Moniruzzaman et al.[27] also observed higher prevalence of hypertension (55% vs.34.7%) and diabetes (50% vs. 25.3%) among young Bangladeshi females.Hypertension and diabetes were also significantly more prevalent among young women in the study by Chandrasekhar et al.[12] Diabetes is a particularly strong risk factor for coronary artery disease (CAD) in women and is associated with a heightened cardiovascular mortality particularly in women <55 years.[14] Some studies suggest that diabetes may also negate the protective effects of estrogen on vascular function, and increase the risks of post PCI complications.[23,24]

Smoking, however, was observed exclusively among young males (70.5%). While no females reported cigarette smoking, 8.4% of them gave a history of taking smokeless tobacco. These findings concur with Bangladeshi,[27]Indian populations[28] and some Western studies in which fewer females were known to be smokers.[14,16] They differ from more recent studies where smoking was significantly more frequently observed among young females.[12,19,21]

Another significant observation in terms of risk factors is the fact that almost two-thirds of pre-menopausal females in our study gave a history of OCP use, which is an additional risk factor for CAD. Furthermore, the hormone oestrogen, traditionally known to exert a protective effect on vascular endothelial function in pre-menopausal women, has also been suggested as a possible reason for the increased risk of vascular injury complications in younger women by some authors.[20] Estrogen may increase the level of various coagulation factors and inflammatory markers and affects vascular endothelial function and its reaction to circulating vasoactive factors. Alternatively, the protective influence of estrogen may be over-ridden by the presence of risk factors, particularly diabetes, resulting in worse outcomes for young women with ACS compared with young men.[20] Further studies on the presence of specific estrogen receptors and their relationship with CAD among women are warranted.

Young females had significantly better LV systolic function than young males, an observation that has been reported across many studies globally.[12,27,28] Young women also had

angiographically less severe CAD, as reflected by less frequency of multivessel disease (30.5% vs 41% for young females vs males respectively) and lesser Gensini scores.These findings concur with previous studies, wherein a majority of young females have had SVD, with more males having DVD and TVD. [12,19,27,28]This is further confirmed by the fact that young males in our study had more complex culprit lesion in terms of ACC/ AHA lesion types B2 and C, with similar observations reported in other studies as well.[12,19]Despite angiographically less severe CAD, young women in our study had greater LMCA involvement as culprit artery in comparison to young males. Interestingly, studies from Bangladesh[27] and overseas[12,28] also reported greater LMCA involvement among young females with ACS and CAD.

Young women required a significantly smaller mean stent diameter in this study, in comparison to young males. Chandrasekhar et al.[12] also observed similar stent profiles between the two genders, with no statistically significant differences in stent length. Smaller stent size implies a small coronary artery diameter, which could make them prone to more peri-procedural complications such as dissection. Prior studies have reported that intracoronary stents have been used less frequently among young women with ACS, although the use of DES has been more frequent among females or comparable among both genders.[12,21] On the contrary, in our study, significantly fewer young females received a DES (81.1% vs 96.8%, p=0.001), possibly due to financial constraints. Despite this, women have been shown to derive greater benefit from DES due to reduced intimal hyperplasia and as such, a greater use of DES should be advocated.[29]

There are many differences in mechanisms of ACS and plaque characteristics between young males and females that may be attributed to differences in angiographic severity and outcome.[29] These biological differences in atherosclerosis between men and women have not been entirely clarified, and further studies using intravascular ultrasound (IVUS) and optical coherence tomography (OCT) may be helpful in defining gender differences in angiographic profiles and lesion characteristics among young patients undergoing PCI.

Conclusion:

Young females with ACS are known to present with a greater clustering of risk factors for CAD, particularly hypertension and diabetes, in comparison to young males. However, despite this, young females were found to have better ejection fraction, and less severe CAD on angiography. They have smaller vessel diameters. The fact that young women have more risk factors could also mean that the presentation of ACS itself is more often than not, complicated by these co-morbidities in young women, leading to adverse outcomes.

Study limitations:

This study was not without limitations. The study was a relatively small, single center study. Furthermore, the study population only included those patients who underwent PCI. Sampling method was non-random, so there was risk of selection bias.

Conflict of Interest - None.

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