ORIGINAL ARTICLE

# GENDER-BASED DIFFERENCES IN CLINICAL PROFILE AND OUTCOME OF PRIMARY PERCUTANEOUS CORONARY INTERVENTION IN PATIENTS WITH ST-SEGMENT ELEVATION MYOCARDIAL INFARCTION

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**Objectives:** A conflict of evidence exists regarding the gender-based differences in outcomes after primary percutaneous coronary intervention (PCI), therefore, aim of this study was to compare the clinical characteristics, angiographic findings, and outcome of primary PCI for men and women.

**Methodology:** Data for this study was extracted from a prospectively managed primary PCI database of the National Institute of Cardiovascular Diseases (NICVD), Karachi, Pakistan. We included consecutive patients of either gender with STEMI undergone primary PCI. Data on clinical characteristics, angiographic finding, and post procedure outcomes for female were compared with male group and also with a propensity matched male cohort.

**Results:** A total of 2400 patients were included with 421(17.5%) women. The mean age for the men and women were 54.44±11.16 and 57.17±11.01 years respectively; p<0.001. Women had significantly high prevalence of hypertension (61.0% vs. 39.1%; p<0.001), diabetes (37.1% vs. 23.9%; p<0.001), and obesity (18.5% vs. 13.5%; p=0.008). The median symptom onset to hospital arrival time was 216 [366-124] minutes vs. 180 [310-112] minutes; p=0.001 for women and men. In-hospital mortality rate was 3.8% vs. 2.5%; p=0.147 for female and unmatched male cohort, while it was 3.6% vs. 3.8%; p=0.855 for female and propensity matched male cohort.

**Conclusion:** Gender-based differences persist in clinical profile of the patients with STEMI. Women are likely to be older in age with more diabetes, hypertension, and obesity. Gender-based difference in outcome of primary PCI is appears to be driven by differences in clinical profile as adjusted outcome is not different for men and women.

**Keywords**: cardiovascular diseases, acute myocardial infarction, ST-segment elevation myocardial infarction, primary percutaneous coronary intervention, gender-difference, female, outcome

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## INTRODUCTION

Cardiovascular diseases (CVD) remains a leading cause of death among both male and female, but a significantly different epidemiological landscape has been observed for men and women along with evidence of different clinical expression of atherosclerosis and pathophysiology of disease.[1] The incidence rate of CVD, especial during reproductive years, is significantly lower for women when compared to men population with an almost 10 years of gape in average presentation age. It can be partly attributed to the cardioprotective mechanism of the main female sex circulating hormone, the estrogen.[2,3] Where there is comparatively lower risk of development of diseases, but the clinical evidence suggest that the female gender as an independent prognostic indicator after acute coronary event. Various studies have found female gender to be associated with a significant increased risk of short- and long-term mortality after acute coronary event.[4-13] Nonetheless, there exist a conflict of evidence as ample literature also available suggesting either no gender differences in outcomes or attributing differences in outcomes with differences in baseline characteristics or increased burden of comorbidities in women due to relatively older age at presentation.[14,15]

Studies reporting gender disparities in outcomes postulated various determinants of higher rate of adverse events in women, some studies argued that the atypical clinical presentation is more common among women also pre-hospital delay is more common for females as compared to their male counterpart

resulting in delay in reperfusion therapy.[7, 9, 10, 16-18] It has been also observed that women are less likely to receive aggressive management and guideline directed medical therapy (GDMT).[7-9, 16]

Primary percutaneous coronary intervention (PCI), when performed within 12 hours of window period, is the treatment of choice for the restoration of myocardium in patients with ST-segment elevation myocardial infarction (STEMI).[19, 20] However, a very limited data are available regarding gender-based difference in angiographic profile and outcomes of STEMI patients in Pakistani population. Our center is the largest cardiac care center of the country, therefore, in this study we aimed to compare the clinical characteristics, angiographic findings, and outcome of primary PCI for men and women presented with STEMI.

## METHODOLOGY

After the approval of the institutional ethical review committee, data for this study was extracted from the prospectively managed primary PCI database of the National Institute of Cardiovascular Diseases (NICVD), Karachi, Pakistan. We included data of consecutive patients, both male and female, presented with STEMI undergone primary PCI at NICVD, Karachi, Pakistan during July 2017 and June 2018. Patients with missing information regarding the study variables such as clinical presentation, angiographic finding, and post-procedure outcomes were excluded from the analysis.

Extracted data were consisted of clinical characteristics, such as age, gender, risk profile, and timing of hospital arrival and procedure, angiographic characteristics, such as diseases burden, infarct related artery (culprit artery), and lesion characteristics and complexity, procedural details and post procedure outcomes and complication. A detailed methodology of data collected is defined elsewhere.[21]

Data analysis were performed with the help of IBM SPSS version 21. Data were stratified by gender and comparative analysis between men and women for clinical characteristics, angiographic characteristics, procedural details, and post procedure outcomes were performed by applying independent sample t-test for continuous variables, such as age, body mass index (BMI), symptom onset to hospital arrival time, hospital arrival to procedure time, total ischemic time, lesion length, fluoroscopic time, and contrast volume, and mean ± standard deviation (SD) and median [interquartile range (IQR)] were computed. Categorical variables were compared by applying the Chi-square test and frequencies and percentages were calculated. The criteria for statistical significance of the difference between men and women was $p \leq 0.05$ throughout the analysis. Considering the statistical implication of female to male ratio of 1:4.7 in our dataset, a propensity matched cohort in 1:1 ratio of female and male was formed. Propensity matching was performed using "MatchIt" package on R software version 3.6.1 and profile variables for matching were age, BMI, co-morbid conditions such as hypertension, diabetes, smoking, prior history of myocardial infarction, duration to hospital arrival after symptom onset, duration to procedure after hospital arrival, and cardiogenic shock at presentation.

## RESULTS

A total of 2400 STEMI patients undergone primary PCI were included in this analysis, 421 (17.5%) were female and remaining 1,979 (82.5%) were male patients. The male STEMI patient cohort was observed to be younger than their female counter part with mean age of 54.44 (± 11.16) years vs. 57.17 (± 11.01) years; $p<0.001$, respectively. Similarly, the premature MI (≤ 40 years) was more commonly observed for the male cohort, 10.7% (211) vs. 5.2% (22); $p<0.001$. Relatively more complex cardiovascular disease risk profile was observed for the female cohort with more hypertension (61.0% vs. 39.1%; $p<0.001$), more diabetes (37.1% vs. 23.9%; $p<0.001$), and more obesity (18.5% vs. 13.5%; $p=0.008$), while smoking was more common for the male cohort, 30.7% vs. 1.9%; $p<0.001$, respectively. The demographic and clinical characteristics of the male and female cohorts are presented in Table 1.

A delay of more than half an hour was observed for female patients, as compared to their male counterpart, in symptom onset to hospital arrival, 216 [366-124] minutes vs. 180 [310-112] minutes; $p=0.001$, and for 42.8% of the female (vs. 35.8% for male) patients the symptom onset to hospital arrival time was more than four hours. Similarly, around 13 minutes of delay was observed for females in hospital arrival to the procedure time, 77 [107-55] minutes vs. 64 [95-42] minutes; $p<0.001$, and hospital arrival to the procedure time exceeds a standard cutoff of 90 minutes for 38.2% of the female (vs. 27.5% for male) patients. Presentation and procedure timing are presented in Table 1.

The angiographic characteristics and in-hospital outcomes of the male and female cohorts are presented in Table 2. Both, male and female, cohorts are found to be alike in angiographic profile such as pre-procedure Thrombolysis in Myocardial Infarction (TIMI) flow grade ($p=0.635$), number of diseased

vessels (p=0.359), and infarct related artery (p=0.232). The post-procedure TIMI flow grade III was not achieved in relatively higher proportion of female patients as compared to male patients, 5.5% vs. 3.2%; p=0.026, respectively. In-hospital mortality rate was also relatively higher for the female cohort, 3.8% (vs. 2.5% for male), however, no statistically significant differences were observed in in-hospital outcomes of both male and female cohorts.

The angiographic profile and in-hospital outcomes for the females were found to be not statistically significant from that of a propensity matched male cohort. Conversely in-hospital mortality rate was found slightly higher in male cohort as compared to female with mortality rates of 3.8% vs. 3.6%; p=0.855 for male and female respectively. The angiographic profile and in-hospital outcomes for female and male matched cohorts are presented in Table 3.

**Table 1: Demographic and clinical characteristics stratified by gender**

| Characteristics | Total | Gender | | P-value |
|---|---|---|---|---|
| | | Male | Female | |
| **Total (N)** | **2400** | **1979** | **421** | **-** |
| **Age (mean ± SD years)** | 54.92 ± 11.18 | 54.44 ± 11.16 | 57.17 ± 11.01 | <0.001 |
| ≤ 40 years | 233 (9.7%) | 211 (10.7%) | 22 (5.2%) | <0.001 |
| 41 to 65 years | 1745 (72.7%) | 1445 (73%) | 300 (71.3%) | |
| > 65 years | 422 (17.6%) | 323 (16.3%) | 99 (23.5%) | |
| **BMI (kg/m$^2$)** | 26.09 ± 4.46 | 26.11 ± 4.37 | 25.99 ± 4.85 | 0.665 |
| ≤ 18.5 kg/m$^2$ | 51 (2.1%) | 32 (1.6%) | 19 (4.5%) | <0.001 |
| 18.5 to 25 kg/m$^2$ | 982 (40.9%) | 815 (41.2%) | 167 (39.7%) | |
| 25 to 30 kg/m$^2$ | 1021 (42.5%) | 864 (43.7%) | 157 (37.3%) | |
| > 30 kg/m$^2$ | 346 (14.4%) | 268 (13.5%) | 78 (18.5%) | |
| **Risk factors** | | | | |
| Hypertension | 1031 (43%) | 774 (39.1%) | 257 (61%) | <0.001 |
| Diabetes | 629 (26.2%) | 473 (23.9%) | 156 (37.1%) | <0.001 |
| Smoking | 615 (25.6%) | 607 (30.7%) | 8 (1.9%) | <0.001 |
| Family history of CAD | 82 (3.4%) | 70 (3.5%) | 12 (2.9%) | 0.481 |
| Past history of myocardial infarction | 153 (6.4%) | 142 (7.2%) | 11 (2.6%) | <0.001 |
| **Symptom onset to hospital arrival time (minutes)** | | | | |
| Median [IQR] | 185 [323.5-115] | 180 [310-112] | 216 [366-124] | 0.001 |
| ≤ 120 minutes | 682 (28.4%) | 579 (29.3%) | 103 (24.5%) | 0.021 |
| 121 to 240 minutes | 829 (34.5%) | 691 (34.9%) | 138 (32.8%) | |
| > 240 minutes | 889 (37%) | 709 (35.8%) | 180 (42.8%) | |
| **Hospital arrival to procedure time (minutes)** | | | | |
| Median [IQR] | 65 [97-43] | 64 [95-42] | 77 [107-55] | <0.001 |
| ≤ 90 minutes | 1695 (70.6%) | 1435 (72.5%) | 260 (61.8%) | 0.021 |
| > 90 minutes | 705 (29.4%) | 544 (27.5%) | 161 (38.2%) | |
| **Cardiogenic shock (CS)** | | | | |
| No | 2327 (97%) | 1922 (97.1%) | 405 (96.2%) | 0.318 |
| Yes | 73 (3%) | 57 (2.9%) | 16 (3.8%) | |
| **Pre-procedure serum creatinine (mg/dL)** | 0.87 ± 0.76 | 0.86 ± 0.65 | 0.87 ± 1.13 | 0.897 |
| **Hemoglobin (g/dL)** | 11.06 ± 5.35 | 11.26 ± 5.48 | 10.11 ± 4.54 | <0.001 |

*CAD = coronary artery diseases, SD = standard deviation, BMI = body mass index, IQR = interquartile range*

**Table 2: Angiographic findings and in-hospital outcomes of primary PCI stratified by gender**

| Characteristics | Total | Gender | | P-value |
|---|---|---|---|---|
| | | Male | Female | |
| **Total (N)** | **2400** | **1979** | **421** | **-** |
| **Pre-procedure Thrombolysis in Myocardial Infarction (TIMI) flow grade** | | | | |
| TIMI 0 | 1391 (58%) | 1141 (57.7%) | 250 (59.4%) | 0.635 |
| TIMI I | 231 (9.6%) | 192 (9.7%) | 39 (9.3%) | |
| TIMI II | 465 (19.4%) | 392 (19.8%) | 73 (17.3%) | |

| | | | | |
|---|---|---|---|---|
| TIMI III | 313 (13%) | 254 (12.8%) | 59 (14%) | |
| **Number of vessels involved** | | | | |
| None | 16 (0.7%) | 12 (0.6%) | 4 (1%) | 0.359 |
| Single vessel disease (SVD) | 800 (33.3%) | 667 (33.7%) | 133 (31.6%) | |
| Two vessels disease (2VD) | 689 (28.7%) | 556 (28.1%) | 133 (31.6%) | |
| Three vessels disease (3VD) | 534 (22.3%) | 437 (22.1%) | 97 (23%) | |
| Data not available | 361 (15%) | 307 (15.5%) | 54 (12.8%) | |
| **Infarct related artery** | | | | |
| Left anterior descending artery (LAD) | 1304 (54.3%) | 1093 (55.2%) | 211 (50.1%) | 0.232 |
| Right coronary artery (RCA) | 795 (33.1%) | 638 (32.2%) | 157 (37.3%) | |
| Left circumflex artery (LCX) | 258 (10.8%) | 210 (10.6%) | 48 (11.4%) | |
| Pulmonary descending artery (PDA) | 19 (0.8%) | 18 (0.9%) | 1 (0.2%) | |
| Ramus | 9 (0.4%) | 7 (0.4%) | 2 (0.5%) | |
| Left main artery (LM) | 15 (0.6%) | 13 (0.7%) | 2 (0.5%) | |
| **Lesion Complexity** | | | | |
| Non-High/Non-C Lesion | 1344 (56%) | 1101 (55.6%) | 243 (57.7%) | 0.434 |
| High/C Lesion | 1056 (44%) | 878 (44.4%) | 178 (42.3%) | |
| **Bifurcation lesion** | 632 (26.3%) | 524 (26.5%) | 108 (25.7%) | 0.727 |
| **Lesion length (mm)** | 18.92 ± 8.18 | 18.98 ± 8.2 | 18.66 ± 8.06 | 0.462 |
| **Fluoroscopy time (minutes)** | 14.07 ± 8 | 14.12 ± 8.16 | 13.85 ± 7.2 | 0.53 |
| **Contrast volume (ml)** | 138.45 ± 46.64 | 138.42 ± 46.41 | 138.57 ± 47.79 | 0.953 |
| **Stent type** | | | | |
| POBA | 160 (6.7%) | 131 (6.6%) | 29 (6.9%) | 0.107 |
| Drug Eluting Stent (DES) | 1239 (51.6%) | 1041 (52.6%) | 198 (47%) | |
| Bare Metal Stent (BMS) | 1001 (41.7%) | 807 (40.8%) | 194 (46.1%) | |
| **Post-procedure Thrombolysis in Myocardial Infarction (TIMI) flow grade** | | | | |
| TIMI 0 | 14 (0.6%) | 13 (0.7%) | 1 (0.2%) | 0.022 |
| TIMI I | 16 (0.7%) | 12 (0.6%) | 4 (1%) | |
| TIMI II | 57 (2.4%) | 39 (2%) | 18 (4.3%) | |
| TIMI III | 2313 (96.4%) | 1915 (96.8%) | 398 (94.5%) | |
| **Post-procedure in-hospital outcomes** | | | | |
| Mortality | 66 (2.8%) | 50 (2.5%) | 16 (3.8%) | 0.147 |
| Re-infarction | 11 (0.5%) | 11 (0.6%) | 0 (0%) | 0.125 |
| Cardiogenic shock (CS) | 33 (1.4%) | 29 (1.5%) | 4 (1%) | 0.41 |
| Heart failure (HF) | 28 (1.2%) | 25 (1.3%) | 3 (0.7%) | 0.339 |
| Cerebrovascular accident | 3 (0.1%) | 2 (0.1%) | 1 (0.2%) | 0.472 |
| Bleeding | 16 (0.7%) | 14 (0.7%) | 2 (0.5%) | 0.595 |
| Dialysis | 4 (0.2%) | 2 (0.1%) | 2 (0.5%) | 0.088 |
| Transfusion | 3 (0.1%) | 2 (0.1%) | 1 (0.2%) | 0.472 |

*PCI= percutaneous coronary intervention, POBA = plain old balloon angioplasty*

**Table 3: Angiographic findings and in-hospital outcomes of primary PCI stratified by gender for matched cohort**

| **Characteristics** | **Gender** | | **p-value** |
|---|---|---|---|
| | **Male** | **Female** | |
| **Total (N)** | **421** | **421** | **-** |
| **Pre-procedure Thrombolysis in Myocardial Infarction (TIMI) flow grade** | | | |
| TIMI 0 | 244 (58%) | 250 (59.4%) | 0.141 |
| TIMI I | 42 (10%) | 39 (9.3%) | |
| TIMI II | 93 (22.1%) | 73 (17.3%) | |
| TIMI III | 42 (10%) | 59 (14%) | |
| **Number of vessels involved** | | | |
| None | 1 (0.2%) | 4 (1%) | 0.344 |

| | | | |
|---|---|---|---|
| Single vessel disease (SVD) | 114 (27.1%) | 133 (31.6%) | |
| Two vessels disease (2VD) | 137 (32.5%) | 133 (31.6%) | |
| Three vessels disease (3VD) | 105 (24.9%) | 97 (23%) | |
| Data not available | 64 (15.2%) | 54 (12.8%) | |
| **Infarct related artery** | | | |
| Left anterior descending artery (LAD) | 227 (53.9%) | 211 (50.1%) | 0.274 |
| Right coronary artery (RCA) | 141 (33.5%) | 157 (37.3%) | |
| Left circumflex artery (LCX) | 42 (10%) | 48 (11.4%) | |
| Pulmonary descending artery (PDA) | 7 (1.7%) | 1 (0.2%) | |
| Ramus | 2 (0.5%) | 2 (0.5%) | |
| Left main artery (LM) | 2 (0.5%) | 2 (0.5%) | |
| **Lesion Complexity** | | | |
| Non-High/Non-C Lesion | 235 (55.8%) | 243 (57.7%) | 0.578 |
| High/C Lesion | 186 (44.2%) | 178 (42.3%) | |
| **Bifurcation lesion** | 111 (26.4%) | 108 (25.7%) | 0.814 |
| **Lesion length (mm)** | 19.56 ± 8.72 | 18.66 ± 8.06 | 0.118 |
| **Fluoroscopy time (minutes)** | 14.97 ± 9.17 | 13.85 ± 7.2 | 0.05 |
| **Contrast volume (ml)** | 140.96 ± 47.8 | 138.57 ± 47.79 | 0.467 |
| **Stent type** | | | |
| POBA | 23 (5.5%) | 29 (6.9%) | 0.337 |
| Drug Eluting Stent (DES) | 218 (51.8%) | 198 (47%) | |
| Bare Metal Stent (BMS) | 180 (42.8%) | 194 (46.1%) | |
| **Post-procedure Thrombolysis in Myocardial Infarction (TIMI) flow grade** | | | |
| TIMI 0 | 2 (0.5%) | 1 (0.2%) | 0.667 |
| TIMI I | 4 (1%) | 4 (1%) | |
| TIMI II | 12 (2.9%) | 18 (4.3%) | |
| TIMI III | 403 (95.7%) | 398 (94.5%) | |
| **Post-procedure in-hospital outcomes** | | | |
| Mortality | 15 (3.6%) | 16 (3.8%) | 0.855 |
| Re-infarction | 2 (0.5%) | 0 (0%) | 0.157 |
| Cardiogenic shock (CS) | 7 (1.7%) | 4 (1%) | 0.363 |
| Heart failure (HF) | 6 (1.4%) | 3 (0.7%) | 0.315 |
| Cerebrovascular accident | 2 (0.5%) | 1 (0.2%) | 0.563 |
| Bleeding | 3 (0.7%) | 2 (0.5%) | 0.654 |
| Dialysis | 1 (0.2%) | 2 (0.5%) | 0.563 |
| Transfusion | 1 (0.2%) | 1 (0.2%) | >0.999 |

*PCI= percutaneous coronary intervention, POBA = plain old balloon angioplasty*

## DISCUSSION

To the best of our knowledge this is the largest study conducted in Pakistani population assessing gender-based differences in angiographic findings and outcomes of primary PCI in patients with STEMI. We observed that female patients comprises of less than 1/5th of clinical burden of STEMI patients. Premature MI (≤ 40 years) is less common among female and female patients are relatively older than male counterpart due to which women are more likely to be diabetic, hypertensive, and obese as compared to men, but less likely to be smokers. These observations regarding female patients were concord with the past studies, with average age difference between female and male patients is reported to be ranging from 5 to 10 years.[4-9, 12, 13, 15, 22, 23]

In this study we have also observed that the STEMI management timeline for women is different as compared to men, female patients had significant higher time lapse between onset of symptoms to hospital arrival as well as hospital arrival to the procedure, resulting in aggregate delay in timely restoration of myocardium. Similar observations were made by some of the previous studies.[4, 9, 23] Pre-hospital delay in patients with acute myocardial infarction (AMI) is one of important predictors of adverse outcomes and complications, it has been reported that with every 30 minutes of delay in reperfusion after AMI, risk of 1-year mortality and complication increases by 7.5 times.[24] Bugiardini R et al.[25] conducted a comparative study of male and female 6022 patients with STEMI registered from 41 hospitals participated in the International Survey of

Acute Coronary Syndromes in Transitional Countries (ISACS-TC) registry and observed that female patients are more exposed to prolonged untreated ischemia, further, higher rate of mortality among women found to be associated with pre-hospital delay even after adjusting for the baseline characteristics.

In this study we observed that the angiographic findings, such as number of diseases vessels, infarcted related artery, and pre-procedure TIMI flow grade, in female patients were not different from that of male. But post-procedure outcomes and complications such as no reflow and in-hospital mortality rate were relatively higher among female patients. Studies of various nature have also reported the same observation of relatively or significantly higher rate of adverse outcomes among women.[4, 5, 8, 9, 12, 13, 15, 22, 25] However, differences in outcomes was suspected to be driven by the fact that female patients had more high risk clinical profile as compared to male patients, which included older age, more diabetic, more hypertensive, more obese, and prolonged exposure to the untreated ischemia. Therefore, female patients were compared to the propensity matched cohort of male patients which showed that the apparent difference by gender in in-hospital mortality rate diminished. A similar observation of no difference in outcome of primary PCI in male and female patients after adjusting for the baseline risk profile was evident in various studies from the past.[12, 15, 22, 25]

Even though, to the best of our knowledge this is the largest study of its kind based on a single center based registry maintained by the largest cardiac care center of the Pakistan, our studies has limitations, data regarding only post-procedure in-hospital outcomes were available, therefore, no inferences can be made regarding role of female gender in short- and long-term outcomes after primary PCI. Even though it was based on prospectively maintained registry, but exclusion of cases with missing information on study variables may introduce a selection bias.

## CONCLUSION

In conclusion, female patients comprises of less than one-fifth of the total clinical burden of STEMI. Women with STEMI are more likely to be older, hypertensive, diabetic, and obese. The angiographic findings are likely to be similar for both genders but the differences in outcomes after primary PCI may persist. The differences in outcomes may likely to be driven by the differences in clinical profile, once adjusted for the clinical profile the difference in outcomes diminishes.

## AUTHORS' CONTRIBUTION

SMA, TA, and MK: Concept and design, data acquisition, interpretation, drafting, final approval, and agree to be accountable for all aspects of the work. ASM, MK, KFA, AA, and NAS: Data acquisition, interpretation, drafting, final approval and agree to be accountable for all aspects of the work.

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