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Coronary artery bypass grafting in South Asian patients: Impact of gender

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HIGHLIGHTS

- This paper gives an account of coronary artery bypass grafting (CABG) surgery performed in South Asian population with special attention to female gender.
- This is unique study as far as female patients are concerned in this part of the world.
- The female gender itself is a predictor of adverse outcome in terms of mortality.
- These results will help in preoperative counseling and suggests vigilant approach in perioperative care in female patients.
- It is heartening to note that the results are comparable to international standards.

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ABSTRACT

Background: Outcomes following Coronary artery bypass grafting (GABG) vary between genders, with females having a higher postoperative mortality than males. Most of the studies are on Caucasian or mixed population and it is postulated that Asian population and in particular women have higher morbidity and mortality. In this study we have compared outcomes of elective CABG in men and women of South Asian origin in terms of morbidity and mortality.

Methods: From January 2006 to December 2012, 1970 patients underwent isolated elective CABG at the Aga Khan University Hospital, Pakistan were selected. The prospectively collected data was analyzed retrospectively including univariate and multivariate analysis to find the association of morbidity and mortality.

Results: Among the study patients 1664 (85%) were male and 306 (15%) female. Hypertension and diabetes were the most common comorbid conditions seen preoperatively in female patients. Atrial fibrillation and sepsis were the most common postop complications seen in females. In hospital mortality was 3.9% in female underwent CABG as against 0.6% in male. Multivariate analysis showed older age, renal failure, dyslipidemia and prolonged cross clamp time as predictors of postoperative morbidity. Multivariate analysis showed female gender, age and renal failure as predictors of in hospital mortality.

Conclusions: Female gender is an independent risk factor for postoperative mortality following CABG however, female gender is not found to be independent risk factor for morbidity. The trend of higher mortality in female patients was comparable to most studies done on Caucasian patients.

1. Introduction

The outcomes following Coronary artery bypass grafting (CABG) have improved over the years and overall mortality in elective cases is around 1–2%. However when gender differentiation is used there is considerable evidence to suggest that outcome following CABG surgery vary between male and female. The evidence shows that women carry a higher operative mortality than men [1]. In fact they

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are at greater risk of complications and mortality whether the revascularisation is performed surgically or using percutaneous coronary intervention technique [2]. According to The Society of Thoracic Surgeons National Adult Cardiac Surgery Database as cited by Edwards et al. [3] females have an operative mortality of 3.54% compared to 2.15% for men. Investigations searching for potential causes for this difference have shown inconsistent results. Some research indicates female gender as an independent risk factor for operative mortality following CABG surgery [4] and as such several risk models which have been developed to assess operative mortality associated with CABG have included female gender as an important risk factor [5,6]. Others have stated that differences in outcomes between the two genders can be attributed to co-morbid conditions which are more prevalent in females [7] and that female gender itself has not been associated with increased mortality [7]. It has also been suggested that South Asian ethnicity per se is an independent predictor of a poorer outcome after CABG and in particular women have been found to have higher morbidity and mortality [8].

The aim of this study was to investigate the influence of female gender on outcomes in terms of morbidity and mortality after elective CABG surgery as compared to male patients.

2. Materials and methods

All patients undergoing isolated elective CABG procedure at the Aga Khan University Hospital, Pakistan between January 2006 and December 2012 were included in the study. Patients underwent emergency surgery, off pump CABG, redo CABG or other concurrent cardiac surgical procedures were excluded from the study. This was a retrospective review of data, which was prospectively collected in the cardiothoracic surgery computerized database using a standardized tools and definitions.

Our database consisting of patient demographics, pre-operative risk factors, operative information and short-term post-operative outcomes including morbidity and mortality. Patients were divided into two groups by gender. Demographics, pre-operative risk factors and short term outcomes were compared between these two groups.

The short term outcomes analyzed consisted of the following:

a. In hospital or 30 days mortality – defined as death during hospital stay or within 30 days after discharge.
b. Stroke – defined as a new central neurological deficit persisting for more than 24 hours.
c. Deep sternal wound infection – involving muscle and bone – demonstrated during surgical exploration and either positive cultures or requiring treatment with antibiotics.
d. Reopening for any cause.
e. Sepsis – defined as inflammation and evidence/suspicion of microbial process ± organ dysfunction/hypotension.
f. Atrial fibrillation – absence of p waves and irregular rhythm documented on ECG.

3. Surgical strategy

All of the surgeons used a standard operating strategy. After induction of anaesthesia, a median sternotomy approach was used. The conduits were harvested and CPB was established using right atrial and aortic cannulae, following systemic heparinisation (300u/kg). Myocardial protection was achieved with moderate hypothermia (28–32 °C) and blood cardioplegia given anterogradely via the aortic root. This was enhanced with topical cooling. Distal coronary anastomoses were performed on a still heart. After completion of the grafting on coronaries and rewarming, the aortic cross-clamp was removed and the proximal ends of the vein grafts were anastomosed to the aorta under a partially occluding clamp. In selected cases a single clamp technique was used for both distal and proximal anastomoses. Once the reperfusion was established through the grafts, the heart was gradually weaned from the heart lung machine and subsequent chest closure was carried out.

4. Statistical analysis

Statistical analysis of data was performed using SPSS version 20. Results were expressed as mean ± standard deviation (SD) with ranges for all continuous variables and numbers (percentages) for categorical data. Group comparison was performed by using *t*-test for continuous variable and Pearson Chi-Square test for categorical variable wherever appropriate. Univariate and multivariate logistic regression analysis was carried out to investigate predictors of postoperative morbidity and mortality. A p-value <0.05 was considered statistically significant.

5. Results

Between January 2006 and December 2012, 2923 patients underwent elective CABG. One thousand nine hundred and seventy patients fulfilled the inclusion criteria, out of which 306 (15%) were female and 1664 (85%) were male. Mean age of male patients was 57.2 (±SD) 9.51 and for female patients it was 58.8 (±SD) 8.37, ($p = 0.005$). Females were more likely to suffer from diabetes and hypertension compared to men (Table 1). There was no statistically significant difference in the preoperative ejection fraction or the number of vessels involved between the male and female patients (Table 1).

Intra-operative variables are presented in Table 1. Use of internal mammary artery graft, and mean bypass time did not show any statistically significant difference between males and females, however mean cross clamp time was significantly low in females, ($p = 0.036$).

Early postoperative outcomes are documented in Table 2. Overall in hospital mortality was significantly higher for females (3.9%) than males (0.6%), ($p < 0.001$).

Of the post-operative morbidity in this cohort of patients, atrial

Table 1
Preoperative and intraoperative characteristics of patients by gender, n = 1970.

Pre-operative variable	Male 1664 (85%)	Female 306 (15%)	P
Comorbid factors			
Age, mean (±SD)	57.2 (±9.5)	58.8 (±8.4)	0.005
-Age <60 years	981 (59.0)	160 (52.3)	0.030
-Age ≥60 years	683 (41.0)	146 (47.7)	–
Diabetes Mellitus	790 (47.5)	180 (58.8)	<0.001
Hypertension	1141 (68.6)	250 (81.7)	<0.001
Dyslipidemia	882 (53.0)	163 (53.3)	0.932
Renal Insufficiency	123 (7.4)	26 (8.5)	0.502
Ejection fraction			
>50%	909 (54.6)	188 (61.4)	0.084
30-50%	574 (34.5)	88 (28.8)	–
<30%	181 (10.9)	30 (9.8)	–
Vessels involved			
Single	12 (0.7)	2 (0.7)	0.955
Two	192 (11.5)	37 (12.1)	–
Three	1460 (87.7)	267 (87.3)	–
Left main vessel disease ≥50%	242 (14.5)	34 (11.1)	0.127
Intraoperative variables			
Use of LIMA	1608 (96.6)	298 (97.4)	0.600
Cross clamp time (min)	61.2 (±21.6)	58.4 (±19.3)	0.036
Bypass time (min)	98.9 (±29.3)	100.5 (±58.4)	0.475

Table 2
Short term post-operative morbidity and mortality.

Post-operative variables	Male 1664 (85%)	Female 306 (15%)	P
Deep sternal wound infection	2 (0.1)	0	0.544
Sepsis	9 (0.5)	7 (2.3)	0.002
Stroke	3 (0.2)	1 (0.3)	0.601
Atrial fibrillation	190 (11.4)	36 (11.8)	0.861
Reopening	40 (2.4)	6 (2.0)	0.837
Mortality	10 (0.6)	12 (3.9)	<0.001

fibrillation (AF) was found to be the most common; however there was no significant difference in incidence of AF between the female and male groups, ($p = 0.861$). Females were found to have a significantly higher incidence of sepsis 2.3% compared to 0.5% in males.

Univariate predictors of post-operative morbidity found that age, hypertension, dyslipidemia and renal failure were associated with post-operative morbidity (Table 3). Multivariate analysis also showed that increasing age, dyslipidemia and renal failure were independently associated with postoperative morbidity (Table 3) after adjusting for gender, diabetes, hypertension, ejection fraction, left main vessel disease of >50% and cross clamp time of >72 minutes.

Predicting the factors of post-operative mortality, multivariate model showed that female gender, renal failure and increasing cross clamp time were independent risk factors for post-operative mortality after adjusting for age, diabetes, hypertension, dyslipidemia, ejection fraction and left main vessel disease of >50% (Table 4).

6. Discussion

It has been well established that the risk profile of women undergoing CABG differs to that of men [3]. The evidence in the literature is conflicting with regards to female gender being an independent risk factor for operative mortality following CABG surgery. What has been consistently shown is that the incidence of operative mortality and morbidity is higher in females [2,9]. Some argue that this is due to an independent association between female gender and the increased prevalence and incidence of morbidity and mortality in females [9]. In addition to this, it has also been observed that Asian population has a higher mortality and morbidity compared to Caucasian population particularly in women where mortality has been reported as high as 5.8% [8]. Risk calculators such as Euroscore II, which look at pre-operative variables to predict operative mortality, include female gender as an independent risk factor [10].

Our current study finds that even after adjusting for the risk factors, women undergoing CABG have a higher risk of operative mortality. Univariate and multivariate analysis showed that female gender is an independent risk factor for increased post CABG mortality. Despite the improvements in operative outcomes for CABG surgery [11], disparity in women's outcomes relative to men remains distinct. Our findings are consistent with other large scale studies including Blankstein et al. [4] who analyzed data from 31 hospitals and compared outcomes between 5,023 women and 10,417 men. They found that part of the increased operative mortality in female patients undergoing CABG can be explained by their higher incidence of comorbidities, even after adjusting for identifiable risk factors, female gender came up as an independent predictor of peri-operative mortality. Bukkapatnam et al. [9] who compared outcomes between 10,708 females and 29,669 males who had CABG surgery performed between 2003 and 2004 using multivariate models and concluded that women were at higher risk of operative mortality than men. With respect to pre-operative risk factors, our study showed that there was a significant disparity between men and women. Women were more likely to suffer from diabetes and hypertension compared to men. These findings are consistent with the published literature [9]. It has been shown that the risk of death post CABG surgery is independently linked to the degree of perioperative hyperglycemia. Some researchers believe that the true risk factor is not diabetes but hyperglycemia which causes the increased risk of post CABG mortality [12,13]. This hypothesis however requires further investigation.

Our results showed a point of interest when assessing intra-operative variables. We found that the use of IMA graft did not show any statistically significant variation between males and females. This is an indicator of quality as previous studies have shown that women receive fewer arterial grafts, particularly with respect to IMA grafts [14]. Bruce and colleagues studied the use of IMA in 21,873 patients undergoing isolated CABG and concluded that in addition to its well documented patency and long-term beneficial effect the LIMA grafting has a strong protective effect on perioperative mortality [15]. The same study has shown that although the use of IMA was low in women (81% vs. 89%) however, those who received IMA had lower mortality. The arterial grafts has a higher patency than saphenous venous grafts [16] and its use is associated with long term survival as well as lower in hospital mortality. It has previously debated that the lower rates of IMA use in women could be associated with the differences in surgical outcomes between the genders [14,16]. Our study however did not support this idea, as our incidences of IMA use in males and females did not show any significant variation, yet mortality rates were still higher for the female gender. Another very important factor responsible for adverse outcome is said to be the small coronaries in female patients corresponding to their small body size and surface area,

Table 3
Crude and adjusted odds ratio and 95% CI for pre-operative morbidity in isolated CABG patients.

Variables	Crude OR (95% CI)	P	Adjusted[b] OR (95% CI)	P
Age ≥60 years	1.95 (1.52, 2.55)	<0.001	1.78 (1.36, 2.34)	<0.001
Gender (Female)	1.04 (0.73, 1.48)	0.826	0.95 (0.65, 1.38)	0.790
Type 2 Diabetes	1.21 (0.93, 1.56)	<0.167	1.06 (0.81, 1.40)	0.667
Hypertension	1.78 (1.30, 2.44)	<0.001	1.31 (0.94, 1.83)	0.108
Dyslipidemia	1.56 (1.20, 2.04)	0.001	1.51 (1.14, 2.00)	0.004
Renal failure	6.99 (4.91, 9.96)	<0.001	6.13 (4.26, 8.84)	<0.001
Ejection fraction[a]				
30–50%	0.95 (0.61, 1.47)	0.948	0.884 (0.53, 1.34)	0.471
<30%	1.08 (0.82, 1.43)	0.575	1.05 (0.78, 1.41)	0.746
Left main vessel disease ≥50%	1.40 (1.00, 1.98)	0.052	1.27 (0.88, 1.83)	0.207
Cross Clamp Time ≥72 min	1.33 (0.69, 2.58)	0.397	1.16 (0.85, 1.58)	0.341

[a] Ejection fraction ≥50% reference.
[b] Adjusted for all variables in the model.

Table 4
Crude and adjusted odds ratio and 95% CI for post-operative mortality in isolated CABG patients.

Variables	Crude OR (95% CI)	P	Adjusted[b] OR (95% CI)	P
Age ≥60 years	2.99 (1.21, 7.36)	0.017	2.24 (0.88, 5.69)	0.091
Gender (Female)	6.75 (2.89, 15.77)	<0.001	8.26 (3.33, 20.52)	<0.001
Type 2 Diabetes	1.71 (0.71, 4.09)	<0.230	2.26 (0.89, 5.67)	0.083
Hypertension	2.66 (0.78, 9.02)	0.117	1.80 (0.48, 6.74)	0.384
Dyslipidemia	1.90 (0.78, 4.71)	0.160	1.65 (0.64, 4.26)	0.298
Renal failure	7.32 (3.02, 17.75)	<0.001	5.92 (2.26, 15.48)	<0.001
Ejection fraction[a]				
30-50%	1.04 (0.23, 4.78)	0.960	1.12 (0.23, 5.40)	0.471
<30%	1.67 (0.69, 4.03	0.256	1.92 (0.76, 4.86)	0.166
Left main vessel disease ≥50%	1.82 (0.66, 4.97)	0.243	2.44 (0.83, 7.16)	0.106
Cross Clamp Time ≥72 min	2.59 (1.11, 6.04)	0.027	2.88 (1.17, 7.05)	0.022

[a] Ejection fraction ≥50% reference.
[b] Adjusted for all variables in the model.

however Stuart and colleague demonstrated that the coronaries in women are small independent of body size suggesting intrinsic gender effect on lumen [17]. Moreover they recommended further studies to investigate the mechanism that may help to broaden the therapeutic options.

Previous studies have indicated that female gender is actually independently associated with a reduced risk of several morbidities including deep sternal wound infection with a potential explanation for this being the lower use of IMA grafts in women [14]. Our study may support this hypothesis as we have found that there is no reduced risk of deep sternal wound infection when the use of IMA is equal between males and females. We did however find that the incidence of sepsis was significantly higher in females as compared to males. This may be associated with the high incidence of diabetes in women undergoing CABG, as the adverse clinical impact of diabetes is more distinct in diabetic females than males [18]. We found that atrial fibrillation was the most common postoperative complication within this cohort (11.6%) which was much lower than reported in previous studies (27.5%) mainly due to new or worsened diastolic dysfunction after CABG surgery that is associated with an increased incidence of postoperative AF [19].

Multivariate analysis of our data showed that increasing age, dyslipidemia and renal failure are independent predictors of postoperative morbidity. This is consistent with published studies already discussed. Multivariate analysis of our data showed that female gender, cross clamp time and renal failure, all are independent predictors of postoperative mortality. This is in accordance with published literature and risk calculators for predicting postoperative mortality after CABG surgery which uses these variables in the regression model [10]. Increased age was found to be linked to increased morbidity and mortality [20]. In our sample, increasing age was independently associated with morbidity, however lost its significance in mortality model after adjustment for confounders. Renal dysfunction is known to be an important risk factor for postoperative morbidity and mortality. The mortality rate in those with preoperative renal dysfunction has been reported to be three times compare to those who have normal renal function, similarly, patients with acute postoperative renal failure have 10 times more risk of dying [21].

7. Strengths and limitations

The strength of this study is that it is the first study to our knowledge that is looking at differences in outcomes following CABG surgery between male and female gender in the South Asian country like ours. This study have some limitations; due to its retrospective review design, the selection bias likely to introduce that may influence on the outcomes between the two genders. Other limitations include the small proportion of females enrolled in this study. We attempted using propensity scoring for matching in this study however owing to low numbers of events and sparse data, its utility could not be justified [22]. This happens to other study as well referred earlier [7]. However, it may be worth analyzing the data from a wider time range and also extending the study to include multiple institutions which would more likely reflect real world practice more accurately. Other limitations include no long term follow up of patients, which would have provided more information on the long term outcomes following CABG.

8. Conclusion

Our study demonstrates the differences in short term outcomes between male and female patients following CABG surgery. Females were found to have a significantly higher risk of mortality following surgery but the pattern of morbidity was comparable in gender. Although female patients are more likely to have comorbid factors, which may contribute to the increase in mortality, but female gender itself is a predictor for postoperative mortality after surgery. Further investigation is necessary in the Asian population to determine if the outcomes are indeed related to female gender itself or if other as yet un-investigated risk factors are present.

Ethical approval

Not Applicable.

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Author contribution

The study was conceptualised, designed and supervised by Shahid A. Sami. Jamal Khan and Sheema Khan did manuscript writing, Gulshan Bano and Shiraz Hashmi performed statistical analysis. Shahabuddin wrote the protocol, organized the data and critically reviewed the manuscript.

Conflicts of interest

None.

Guarantor

Syed Shahabuddin.
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