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Prosthesis-Patient Mismatch Causes a Significantly Increased Risk of Operative Mortality in Aortic Valve Replacement

Muhammad Shahzeb Khan,[1] Faizan Imran Bawany,[1] Asadullah Khan,[2] Mehwish Hussain,[1]

MBBS- Dow University of Health Sciences, Karachi, Pakistan[1]; MBBS- Cardiac Surgery Department, Civil Hospital Karachi, Dow University of Health Sciences, Karachi, Pakistan[2]

ABSTRACT

Background: Small aortic prosthesis can lead to prosthesis-patient mismatch (PPM). Implanting such small prosthesis remains a controversial issue. This study was done to investigate whether or not PPM causes an increased operative mortality in aortic valve replacement (AVR).

Methods: Two-hundred-two consecutive patients undergoing primary AVR in a tertiary hospital were included. The sample was grouped according to the aortic valve prosthesis size: ≤21 mm (small) and >21 mm (standard). The effect of variables on outcomes was determined by univariate and multivariable regression analyses.

Results: PPM was found significantly more among patients with AVR ≤ 21mm (P < 0.0001). Moreover, the likelihood of mortality also was significantly higher in these patients (P < 0.0001). Univariate analysis demonstrated small prosthesis size, urgent operation, PPM, female gender, and NYHA Class IV as significant predictors of mortality. Multivariate regression identified female gender, PPM, and urgent operation as the key independent predictors of mortality.

Conclusion: PPM and female gender are significant predictors of mortality. Care should be taken to prevent PPM by implanting larger prosthesis especially in females.

INTRODUCTION

Aortic valve replacement (AVR) is a procedure that remains the most frequent operation among all the cardiac valve surgeries [Sedrakyan 2004]. It is estimated that around 300,000 valves are implanted globally every year [Pibarot 2009]. The outcome of AVR is greatly influenced by valve size and hemodynamic performance [David 1998] making optimal selection of prosthetic valve a key element.

Small prosthesis size in AVR has been linked with bad prognosis [LaPar 2011]. One of the major complications of using a small prosthesis is prosthesis-patient mismatch (PPM). Many studies have shown that PPM can result in higher short-term mortality rates [Rao 2000]. However, a few studies have shown that mortality in AVR is not solely due to PPM associated with small prosthesis size but in fact is linked with other co-morbidities [LaPar 2011].

Implanting small prosthesis in AVR has been a controversial topic. It remains a major debate whether PPM affects short-term mortality or not. This study was done to test the hypothesis that PPM is an independent predictor of mortality in AVR.

METHODS

We included 202 consecutive patients undergoing AVR in a tertiary hospital. All patients with aortic valve disease,

Table 1. Patients Demographic Characteristics and Preoperative Risk Factors

Variable	AVR ≤ 21 (N = 84)	AVR > 21 (N = 118)	P Value
Age (years)	25 (19)	30 (27)	0.113
Gender			
Male	48 (33.8%)	94 (66.2%)	0.001
Female	36 (60%)	24 (40%)	
NYHA			
Class 1	4 (25%)	12 (75%)	0.082
Class 2	18 (40.9%)	26 (59.1%)	
Class 3	36 (37.5%)	60 (62.5%)	
Class 4	26 (56.5%)	20 (43.5%)	
Hypertension			
No	74 (43%)	98 (57%)	0.32
Yes	10 (33.3%)	20 (66.7%)	
Diabetes			
No	72 (43.4%)	94 (56.6%)	0.268
Yes	12 (33.3%)	24 (66.7%)	
Diagnosis			
Aortic stenosis	8 (26.7%)	22 (73.3%)	0.072
Aortic insufficiency	76 (44.2%)	96 (55.8%)	
Ejection Fraction(%)	60 (15)	65 (15)	0.149
LVEDD(mm)	56 (22)	60 (19)	0.086
LVESD(mm)	41 (14)	40 (14)	0.318

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Correspondence: Muhammad Shahzeb Khan, MBBS- Dow University of Health Sciences, 109/2, Main Kha-E-Bane Amirkhusro, Phase 6, DHA, Karachi, Pakistan; mobile number: +0092321-2066743 (e-mail: shahzebkhan@gmail.com).

either stenosis or regurgitation, were included in the study. However, patients with a history of previous coronary artery bypass graft surgery or congenital heart problems were excluded from the sample. Similarly, patients who were undergoing concomitant surgical procedures, such as mitral valve replacement or coronary artery bypass graft surgery, were also excluded from the study.

The included patients were observed for a period of 30 days. Preoperative profile, operative, and postoperative variables were gathered for the sample. Preoperative profile included variables such as age, gender, blood group, and New York Heart Association (NYHA) classification. Aortic valve prosthesis size, PPM, wound infection, and atrial fibrillation were some of the key operative and postoperative variables. The sample was grouped according to the aortic valve prosthesis size: ≤21 mm (small) and >21 mm (standard). Prosthesis selection was done according to the surgeon's preference. All the patients were operated using the standard surgical technique and no aortic annular enlargement procedures were done. A 0.85 cm^2/m^2 value of effective orifice area index (EOAI) was taken as the cut off for PPM. EOAI was calculated by dividing the effective orifice area (EOA) of the valve by the patient's body surface area. We used the in vitro EOA values provided by the manufacturer for the above purpose.

All mortalities that occurred during the hospital stay and those that occurred after discharge, but within 30 days of the valve replacement, were defined as operative mortality. However, deaths which had no association with the operation were not included in operative mortalities. Informed written consent was taken from each patient. This study was conducted after the approval from the institutional review board of Dow University of Health Sciences.

IBM SPSS 21 was used for analyzing the data. Continuous variables were found to be skewed while examining by the

Table 2. Postoperative Variables and Mortality Status of Patients

Variable	AVR ≤ 21 (N = 84)	AVR > 21 (N = 118)	*P* Value
Patient prosthesis mismatch			
No	40 (28.2%)	102 (71.8%)	<0.0001
Yes	44 (73.3%)	16 (26.7%)	
Wound infection			
No	82 (41.4%)	116 (58.6%)	>0.999†
Yes	2 (50 %)	2 (50%)	
Stroke			
No	80 (41.2%)	114 (58.8%)	0.721†
Yes	4 (50%)	4 (50%)	
Atrial fibrillation			
No	76 (42.2%)	104 (57.8%)	0.599
Yes	8 (36.4%)	14 (63.6%)	
Expired			
No	64 (36%)	114 (64%)	<0.0001
Yes	20 (83.3%)	4 (16.7%)	

†*P* Value was obtained from Fisher Exact Test

Table 3. Association of Different Factors Between Alive and Expired Patients

Variable	Alive	Expired	*P* Value
Age (years)	26 (26)	28 (28)	0.498
Gender			
Male	132 (93%)	10 (7%)	0.001
Female	46 (76.7%)	14 (23.3%)	
NYHA class			
Other classes	148 (94.9%)	8 (5.1%)	<0.0001
Class 4	30 (65.2%)	16 (34.8%)	
Blood group			
Other than B blood group	102 (81%)	24 (19%)	<0.0001
Blood group B	76 (100%)	0 (0%)	
Hypertension			
No	150 (87.2%)	22 (12.8%)	0.541†
Yes	28 (93.3%)	2 (6.7%)	
Diabetes			
No	144 (86.7%)	22 (13.3%)	0.262†
Yes	34 (94.2%)	2 (5.6%)	
Ejection Fraction	65 (16)	63 (10)	0.483
AVR			
≤21mm	64 (76.2%)	20 (23.8%)	<0.0001
>21mm	114 (96.6%)	4 (3.4%)	
Operative status			
Elective	126 (96.9%)	4 (3.1%)	<0.0001
Urgent	52 (72.2%)	20 (27.8%)	
Patient prosthesis mismatch			
No	134 (94.4%)	8 (5.6%)	<0.0001
Yes	44 (73.3%)	16 (26.7%)	
Wound infection			
No	176 (88.9%)	22 (11.1%)	0.07†
Yes	2 (50%)	2 (50%)	
Stroke			
No	170 (87.6%)	24 (12.4%)	0.6†
Yes	8 (100%)	0 (0%)	
Atrial fibrillation			
No	160 (88.9%)	20 (11.1%)	0.306†
Yes	18 (81.8%)	4 (18.2%)	

†*P* Value was obtained from Fisher Exact Test

Table 4. Crude and Adjusted Relationship of Risk Factors with Mortality of Patients

Factors	COR	95% CI for OR		*P* Value	AOR	95% CI for OR		*P* Value
Age	1.014	0.985	1.043	0.346				
Female gender	4.017	1.669	9.668	0.002	13.011	1.941	87.233	0.008
NYHA Class 4	9.867	3.873	25.133	<0.0001				
Hypertension	0.487	0.108	2.189	0.348				
Diabetes	0.385	0.086	1.717	0.211				
Ejection fraction	1.021	0.985	1.06	0.259				
AVR (≤ 21 mm)	8.906	2.917	27.196	<0.0001				
Urgent operation	12.115	3.949	37.172	<0.0001	68.883	5.472	867.043	0.001
Patient prosthesis mismatch	6.091	2.441	15.199	<0.0001	35.436	4.753	264.187	0.001
Wound infection	8	1.072	59.674	0.043				
Atrial fibrillation	1.778	0.547	5.779	0.339				

COR: Crude Odds Ratio by Univariate Logistic Regression
AOR: Adjusted Odds Ratio by Stepwise Multivariable Logistic Regression
CI: Confidence Interval

Shapiro-Wilk test. Thus, these variables were presented as median (interquartile range). The test of comparison between the two groups was done by Mann-Whitney U test. Categorical variables were expressed as frequency (percentage). Comparative analysis of these variables was executed by Chi-square test. Fisher's exact test was used when assumption of cell count for chi-square was not fulfilled. For effect measure of risk factors of mortality, univariate logistic regression was run and crude odds ratio were obtained. Factors with P value at most 10% in univariate analysis were put in multivariable logistic regression model to compute the adjusted odds ratio. Stepwise method was employed at this multivariable stage.

RESULTS

Eighty-four patients out of 202 received small aortic valve prosthesis. Age distribution was similar in patients with small or standard aortic valve prosthesis. However, gender distribution was significantly different in both the groups ($P = 0.001$). Ejection fraction, left ventricular end-systolic diameter (LVESD) and left ventricular end-diastolic diameter (LVEDD) were similar in small and standard aortic valve prosthesis. Table 1 shows the patient demographic and preoperative variables stratified according to size of aortic valve prosthesis.

PPM was found significantly more among patients with aortic valve prosthesis size of ≤ 21 mm ($P < 0.0001$). Moreover, the likelihood of mortality also was significantly higher in patients with small aortic valve prosthesis ($P < 0.0001$). The incidence of atrial fibrillation and wound infections were similar in both the groups.

Table 3 describes the association of different factors with mortality of the patients. Seven percent ($N = 10$) of the males expired in our study as compared with 23.3% ($N = 14$) females ($P = 0.001$). The proportion of mortality was about five folds higher in NYHA Class IV ($P < 0.0001$). None of the patients with blood group B expired. Nineteen percent ($N = 24$) of the patients with blood group other than B expired ($P < 0.0001$). Hypertension, ejection fraction, and diabetes were not significantly associated with mortality of patients. Out of the 24 patients who expired, 20 had urgent operative status and 16 had PPM. Stroke and atrial fibrillation were not significantly associated with mortality of patients.

Table 4 displays the crude and adjusted analyses to assess risk factors of mortality in our setup. Age, hypertension, diabetes, ejection, and atrial fibrillation were not significant factors for mortality. Female gender had 4.02 times higher chances of death. Patients classified as NYHA Class IV had almost 10 times higher chances of death. Similar likelihood of mortality ($OR = 8.91$) was observed in patients with small aortic valve prosthesis. Patients who underwent urgent operation had 12 folds the chances of death whereas presence of PPM increased the chances of mortality by six times. Adjusted model depicted that in the presence of other significant factors in crude model, NYHA classification, AVR, and wound infection were sorted out to be insignificant. Among all the other factors, urgent operation was the riskiest factor for mortality in our setup. It caused about 69 times higher chances of death. Risks of mortality in presence of PPM and in female gender were 35.44 and 13.01 times, respectively.

DISCUSSION

The most crucial finding of our study is that PPM is an independent predictor of mortality after AVR. There is a blend of opinions in previous literature with some studies supporting the notion [Blais 2003; Tasca 2006; Walther

2006] and others negating it [Medalion 2000; Frapier 2002; Flameng 2006; Moon 2006; Monin 2007; Nozohoor 2007; Mascherbauer 2008; Howell 2006]. Therefore, the effect of PPM on mortality has remained controversial [Urso 2009]. Such difference in findings may be due to varying cut-off values for PPM and different EOA values used. Some medical professionals use in vivo EAO values [Tasca 2006], whereas others use the in vitro manufacturer's EAO values [Howell 2006]. In our study, we used the in vitro EAO values provided by manufacturers, as in vitro values are constant and widely accessible for every type of prosthetic valve. We believe that it is very important for surgeons to have constant information of all prosthetic valves presently available. Manufacturer's EAO charts give this information, and surgeons may use these charts to ascertain the likelihood of PPM.

Concistrè et al have shown that PPM does not affect mortality in elderly patients who have undergone AVR with small prosthesis [Concistrè 2013]. On the other hand, our study suggests that PPM is a strong predictor of mortality in AVR. Such discrepancy in findings may be due to the different age population in both the studies; none of the patients in our study was older than 65 years of age. This means that younger patients undergoing AVR with small prosthesis may be at an increased risk of mortality due to PPM. Similar to our findings, a previous study [LaPar 2011] also confirms that PPM is significantly more in patients with small prosthesis. It should be noted that our results indicate that small prosthesis increases the chances of mortality only through univariate analysis and has no effect on mortality after application of multivariate analysis. This suggests that small prosthetic valve may be a substitute for the effects of other factors on compromised results after AVR. This is similar to a previous study [LaPar 2011] that also highlights the same influence of small prosthesis on operative mortality after application of univariate and multivariate analysis. Furthermore, our study tells us through multivariate analysis that female gender and urgent operation also are independent predictors of mortality following AVR. In contrast to our multivariate regression findings, previous literature tells us that female gender is not an independent predictor of mortality [LaPar 2011].

Our study also highlights that hypertension and diabetes mellitus are not associated with operative mortality (< 30 days); however, it is suggested diabetes is an independent predictor of late mortality [Koene 2013]. Therefore, it is crucial to assess the long-term effects of diabetes in our setup. Similar to a previous report [Tjang 2007], our study shows that urgent operation is an independent predictor of mortality. We also highlight another potential risk factor for post AVR mortality; that is blood group. Our findings indicate that none of the blood group B patients expired after AVR, pointing toward the notion that blood group B patients may have hidden advantages in AVR. Therefore, more studies involving larger sample size should focus on the effect of blood group on patients' outcome after AVR. Unfortunately, our findings indicate that operative mortality was very high, that is 11.9%. In contrast, a previous study on 4,621 patients indicates an operative mortality of 3.7% [LaPar 2011]. Therefore, it is crucial for cardiac surgeons in our setup to have a deep knowledge of the potential predictors of mortality after aortic valve replacement.

There are several limitations to our study. First, the study was limited to short term (only 30 days post operatively) and did not include data for intermediate or long-term follow-up. Second, our study did not inspect the quality of life following AVR. Moreover, depending on the type of prosthetic valve used, different EOAI, or other valve properties may give rise to different meanings for small prosthetic valve. We also would like to mention that due to the high prevalence of rheumatic heart disease in our country at young age, Manoungian annulus enlargement plasty was not used as majority of the small prosthesis were according to the body surface area and weight of the young sample population. However in some cases, the tilting disc valve was used. Nevertheless, larger sample size and analyzing nationwide data may improve the accuracy of the findings. Other operative and postoperative factors such as cardiopulmonary bypass time, ventilation time, and intensive care unit or hospital length of stays may also be used to study the effect of prosthetic valve size.

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