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Predictors of Hospital Mortality and Left Ventricular Function Recovery After Aortic Valve Replacement for Severe and Isolated Aortic Stenosis with Left Ventricular Dysfunction

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Abstract*— Objective: The aim of this study was to evaluate postoperative outcomes of AVR for isolated AS with severe left ventricular dysfunction and to identify predictors of hospital mortality and left ventricular function recovery. Methods: This retrospective bicentric study covers over a 15-year period between January 2000 and April 2016, 61 patients with isolated AS and severe left ventricular dysfunction who underwent AVR were enrolled. Results: Mean age was 58.21 ± 12.50 years. 70.5% of patients were in NYHA class III or IV. The mean left ventricular ejection fraction (LVEF) was 32.9 ± 5.6%, and the mean EuroSCORE was 12.20 ± 4.50. The hospital mortality was 11.50%. Multivariate logistic regression analysis found renal failure (OR = 8.98, CI [1.64; 48.70], p = 0.03) and congestive heart failure (OR = 10.90, CI [2.4; 59.83], p <0.001) as related to the risk of hospital mortality. The median follow-up time was 38 [21; 84] months. Late mortality was 7.7% due to non cardiovascular causes in all cases. The functional status and LVEF were significantly improved. In the multivariate analysis early postoperative LVEF (OR, 0.44; CI [0.14; 0.75]; p=0.006) and transprosthetic gradient (OR, -0.72; CI, [-1.42; -0.02]; p=0.04) influence long term LVEF. Conclusions: Despite a high rate of hospital mortality, long term outcome of AVR for severe and isolated AS with left ventricular dysfunction is excellent. Preoperative renal failure and congestive heart failure are predictors of hospital mortality. Early postoperative LVEF and transprosthetic gradient influence left ventricular function recovery.

***Index Terms*— severe aortic stenosis, aortic valve replacement, left ventricular dysfunction, hospital mortality, left ventricular function recovery.**

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I. Introduction

Aortic stenosis (AS) is the most common type of acquired valvular heart disease [1], Surgical aortic valve replacement (AVR) still represents the gold standard among the therapeutic options in patients with severe symptomatic aortic valve stenosis [2], Dysfunction of the left ventricle (LV) increases the risk of surgery failure significantly but does not constitute a reason to reject these patients [3]. Several risk factors have been reported as associated with hospital mortality [3]-[6]. However, most published series are heterogeneous. Furthermore, the heterogeneity of such factors means that no single or group of factors have been signaled as common base for hospital mortality after AVR in AS with LV dysfunction. The aim of the current study was to evaluate postoperative outcomes of AVR for isolated AS with severe left ventricular dysfunction and to identify predictors of hospital mortality and left ventricular recovery.

II. PATIENTS AND METHODS

A. Patient population

This retrospective bicentric study covers over a 15-year period (between January 2000 and April 2016). It includes 61 patients who underwent isolated AVR for severe AS associated to reduced LV function (LVEF < 40%) in the Cardiovascular Surgery Departments of the Avicenna University Hospital and the Military Hospital, both in Rabat (Morocco).

Inclusion criteria were**:**

- Severe native aortic stenosis with an area < 1 cm^2 or < 0.6 cm^2 / m^2
- Systolic left ventricular ejection fraction (LVEF) <40%

Exclusion criteria were**:**

- Previous aortic valve replacement
- Aortic insufficiency over grade I
- Associated valve disease requiring surgical correction
- Coronary artery disease
- History or clinical evidence of previous acute myocardial infraction
- Less than 18 years old age

The baseline operative risk of the patients was estimated using the logistic EuroSCORE.

B. Methods

Demographic, clinical and operative data were obtained from the individual patient hospital records.
Prospective follow-up of survivors was carried out by a visit, including physical examination, chest X radiogram and echocardiogram.
All patients in our series underwent transthoracic echocardiography (TEE) by an experienced cardiologist. All measurements were made in accordance with the relevant recommendations of the American Society of Echocardiography [7], and those of the European Society of Echocardiography [8].
Measurements of the LV were made on 2D and TM TEE images in parasternal longitudinal axis view, and EF was calculated using Simpson's method. The mean trans-Aortic valve gradient was measured using the modified Bernouilli equation. Aortic valve area was calculated using the continuity equation.
Dobutamine stress echocardiography (DSE) has been performed in 6 cases.
All but one patient underwent coronary angiography —the exceptional patient was operated in extreme emergency after cardiac arrest.

C. Surgical Management

Classical aortic valve replacement was performed under general anesthesia and cardiopulmonary bypass (CPB) with the moderate systemic temperature, through median sternotomy. Up to 2002, myocardial protection was based on antegrade intermittent crystalloid cardioplegia (cold saint Thomas II) but since 2003, intermittent hyperkalemia cold blood cardioplegia was employed.

D. Follow- up

Early postoperative stage was defined as 6 months after surgery and the late operative stage was defined as over a year after AVR.
All surviving patients underwent TTE before hospital discharge. During the follow-up, patients were contacted directly and were individually requested to make an appointment with the primary surgeon and referring cardiologist. They were checked during the visit by physical examination, chest X radiogram, ECG and echocardiogram.
Occasionally, the follow-up data were obtained by telephone contact with the referring cardiologist.

E. Statistical analysis

Standard descriptive statistical methods were used for analyses of the data. The normality of the distributions was assessed using the Kolmogorov-Smirnov test. Continuous variables were expressed as means (M) with standard deviation (SD) or medians (MD) with interquartile range (IQR). Student's t-test was used in order to compare and study the relationships between the continuous variables whenever the data was normally distributed, and Non-parametric Mann-Whitney test was used in the others cases. Categorical variables were described as numbers and percentages (%) and analyzed using the $\chi 2$ test or Fisher's exact test, as appropriate. One-way analysis of variance with the post hoc Bonferroni test (for normal distribution with equal variance between groups) or Friedman test (for non normally distributed data) were applied for quantitative variables between paired groups of data.
The mortality risk factors were studied using logistic regression analysis and presented as adjusted OR with 95% CI.
Predictors of left ventricular systolic function recovery were analyzed using linear regression analysis and presented as adjusted OR with 95% CI.
Survival curves for time-to-event variables were constructed on the basis of all the available follow-up data using Kaplan-Meier estimates and were compared with the log rank test. A two-sided α level of 0.05 was used for all superiority testing. A p-value < 0.05 was considered to be significant.
All the analyses were performed with the *Statistical Package for the Social Sciences* (SPSS version 11.5, Chicago, Illinois, USA).

III. Results

A. Baseline Clinical Characteristics

Sixty one patients with left ventricular ejection fraction (LVEF) < 40% were included in this study. All of them met the inclusion criteria and underwent exclusive surgical replacement of the aortic valve during the designated period. The patients had a mean age of 58.21 ± 12.50 years and 83.60 % were men. The mean logistic EUROSCORE was 12.20 with extremes ranging from 4.17 to 67.70. The mean LVEF was 32.90% ± 5.60%. Mean transvalvular gradient was 49.16 mmHg ± 18.44 mmHg, but 16 patients (26.2%) had a severely reduced transvalvular gradient (<40 mmHg). General baseline characteristics for the entire cohort are summarized in Table I

B. Surgical Results

Eleven (18%) biological and 50 (82%) mechanical prosthesis were implanted. The mean diameter was 23 mm. The median duration of CPB was 91 minutes [80; 111], whereas the mean aortic cross-clamp time was 67.31 ± 20.80 minutes. Inotropic support was used during weaning from cardiopulmonary bypass in a total of 56 patients (92%). IABP was used in 2 patients (3.4%).

C. Mortality and Morbidity in the Early Postoperative Period

The 30-day mortality was 11.5% (7/61). The following postoperative complications were observed: low cardiac output in 24 patients (39.3%); third degree atrioventricular block in 2 patients (3.28%), reoperation for bleeding in 1 patient (1.64%), acute renal failure in 2 patients (3.28%), and deep wound infection in 1 patient (1.64%) (Table II). After simple logistic regression analysis, the mortality risk factors were: NYHA functional class (p=.01), renal failure (p=.01), congestive heart failure (p<.001) and prolonged cardiopulmonary bypass duration (p=.01). For every 1% increase in LVEF, the unadjusted risk of death decreased by 14%. After multiple logistic regression analysis, renal failure (OR, 8.98; 95% CI, 1.64 to 48.70; p=.03) and congestive heart failure (OR, 10.90; 95% CI, 2.4 to 59.83; p<.001) were the only predictors of mortality in the immediate

postoperative period. Logistic regression analyses are shown in table III.

Table I: Preoperative patients characteristics.

Variables	n = 61
Age* (years)	58.2 ± 12.5
Sex‡ Male/Female	51/10 (83.6 %)
BSA†	1.76 ± 0.15
NYHA‡	
-II	18 (29.5%)
-III	27 (44.3%)
-IV	16 (26.2%)
Angina pectoris‡	20 (32.8%)
Syncope‡	5 (8.20%)
Congestive heart failure‡	10 (16.4%)
Etiologies‡	
-Degenerative	39 (64%)
-Rhuematic	20 (33%)
-Congenital	2 (3%)
Comorbidities ‡	
-Hypertension	18 (29.5%)
-Diabetes	8 (13.1%)
-Renal failure	11 (18%)
-AIS	1 (1.6%)
CT index†	0.6 [0.58 ; 0.63]
Aortic valve area*	0.62 ± 0.18
Preoperative LVEDD (mm)*	63.6 ± 9.2
Preoperative LVESD (mm)*	50.2 ± 8.8
Preoperative LVEF * (%)	32.9 ± 5.6
Mean transvalvular gradient * (mmHg)	49.2 ± 18.4
SPAP * (mmHg)	47.6 ± 22.3
Logistic regression Euroscore *	12.2 ±4.5

*: expressed as means standard deviation (SD); †: expressed as medians with interquartile range (IQR); ‡: described as numbers and percentages (%).BSA: body surface area;
AIS: Acute *ischemic* stroke; CT: cardio-thoracic; LVEDD: left ventricular end diastolic diameter; LVESD: left ventricular end systolic diameter; LVEF: left ventricular ejection fraction; SPAP: systolic pulmonary arterial pressure.

D. Mortality during Long-term Follow-up

In addition to the 7 patients who died within the early postoperative period, 3 patients (7.7%) died during a median follow-up period of 38 [21-84] months. Fifteen patients (27.77%) ceased to respond to the follow-up enquiries. The 3 deaths that occurred during the follow-up were due to non cardiovascular causes (hemorrhagic stroke in one patient and cancer in the remaining two). Figure 1 illustrates the Kaplan-Meier survival for the entire cohort.

E. Improvement in Functional Class and Ventricular Function

There was a symptomatic improvement in FC in all patients who survived surgical AVR and were long term followed up. No patient remained in FC IV and only 2 (5.55%) patients were in class III. 29 (80.6%) patients improved to class I (Table IV).

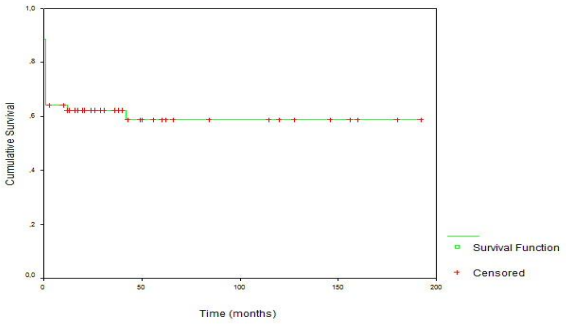
Postoperative echocardiograms were available for 54 patients, and long-term echocardiographic follow-up was available for 36 patients. There was a real improvement in terms of LVEF, left ventricular end diastolic diameter (LVEDD) and left ventricular end systolic diameter (LVESD) when comparing baseline characteristics to early and late postoperative stage (Table V). In the univariate analysis, the following variables predicted absence of improvement of LVEF during long-term follow up: low LVEF before surgery and in the immediate postoperative period (p<.001), low aortic valve area (p<.001), high transprosthetic gradient (p=.005) and elevated LVESD in early postoperative period (p=.006). In the multivariate analysis only early postoperative LVEF (OR, 0.44; 95% CI, 0.14 to 0.75; p=.006) and transprosthetic gradient (OR, -0.72; 95% CI, -1.42 to -0.02; p=.04) influence long term LVEF (Table VI).

Table II: Operative and early postoperative data.

Variables	n = 61
X clamp time* (mn)	67.3 ± 20.8
CPB time† (mn)	91 [80 ; 111]
Prosthesis size* (mm)	23 [21 ; 23]
Use of positive inotropic agents‡	56 (92%)
IABP‡	2 (3.4%)
Mechanical ventilation time† (h)	9 [7 ; 18]
ICU stay* (h)	72.8 ± 24.8
Early postoperative LVEDD* (mm)	61.4 ± 8.9
Early postoperative LVESD* (mm)	46.8 ± 8.8
Early postoperative LVEF‡ (%)	38.2± 9.3
Mean transprosthesis gradient[1] (mmHg)	12.11 ± 3.5
Complications	
-Bleeding* (ml)	429 ± 16
-Low output syndrome‡	24(39.3%)
-Third-degree AV block‡	2 (3.3%)
-Reoperation for bleeding‡	1 (1.6%)
-Acute renal failure‡	2 (3.3%)
-Wound infection‡	1 (1.6%)
Hospital mortality[3]	7(11.5%)

*: expressed as means standard deviation (SD); †: expressed as medians with interquartile range (IQR); ‡: described as numbers and percentages (%). X clamp: cross clamping; CPB: cardiopulmonary bypass; IABP: intra-aortic balloon pump; ICU: intensive care unit; LVEDD: left ventricular end diastolic diameter; LVESD: left ventricular end systolic diameter; LVEF: left ventricular ejection fraction ; AV: atrioventicular.

Figure 1: Survival Estimate Function
(Kaplan -Meier)



IV. DISCUSSION

Patients with LV dysfunction represent up to 26% of patients with AS [9]. Their spontaneous prognosis is severe [10].

Back in the 1970s, Smith et al were the first to demonstrate the benefit of AVR for severe AS, clinical heart failure and LV dysfunction in a cohort of 19 patients [11]. Later, the benefit of AVR, despite the presence of LV dysfunction, has been confirmed in a larger cohort of 154 patients with an elevated transvalvular gradient (TVG) who underwent AVR [3].

In our study, the 30-day mortality was 11.5%; it displayed a statistically significant association with NYHA functional class, renal failure, congestive heart failure, the degree of preoperative LVEF and cardiopulmonary bypass time. In the multivariate analysis, only renal failure and congestive heart failure were associated with 30-day mortality.

Several risk factors for 30-day mortality were reported including: advanced age, small aortic prosthesis size, prior myocardial infarction, coronary artery disease, reduced preoperative cardiac output, renal disease and cardiothoracic ratio > 0.6 [3],[4],[12]-[14]. Hence, these risk factors seem to be heterogeneous and related to distinct conditions (heterogeneous groups).

Patients with degenerative AS and LV systolic dysfunction have an increased risk of developing acute coronary syndrome (ACS) [15]. That explains why many published reports which included patients with coronary lesions found prior acute myocardial infarction (AMI), concomitant coronary artery bypass graft surgery and untreated coronary lesions as significant risk factors of hospital mortality [3]-[5].Other reports included patients with mitral valve regurgitation (MR) [6] and concluded that preoperative MR is an independent risk factor impacting both hospital mortality, long term survival and long-term functional outcome. The particularity of our study is that we included only patients with isolate severe aortic stenosis and low LVEF. In fact, the present *study is* —to *our knowledge— the second* to analyze results of AVR in these kind of patients and is the largest.

Late mortality occurred in 3 (7.7%) patients after a median follow-up of 38 [21; 84] months. We could not determine relevant factors that might relate to these cases of late mortality since the three deaths had non-cardiac origin. Rabus et al demonstrated that diabetes mellitus and intraaortic balloon pump use were predictors for late mortality in patients who underwent aortic valve replacement in isolated severe aortic stenosis with left ventricular dysfunction [16].More globally, the factors that are known to relate to late mortality after valve operation in patients with left ventricular dysfunction are preoperative use of diuretics, male sex, reoperation, age exceeding 60 years and aortic regurgitation [17].

In our study, LVEF, LVEDD and LVESD evolved favorably during both early and late postoperative periods, LVEF increased by 5.3 points in the immediate post operative period ($p < 0.001$) and then by 12.1 points in the late postoperative period ($p < 0.001$). LVEDD and LVESD decreased respectively by 2.2 mm and 3.4 mm during the early postoperative period ($p < 0.001$) and then by 7.4 mm and 6.8 mm during the late postoperative one ($p < 0.001$).

The left ventricle relays on compensatory mechanisms in order to adapt to the increase in after-load and ensure adequate cardiac output. However, when the after-load reaches a certain level, these compensatory mechanisms are no longer sufficient and dysfunction is established.

AVR reduces ventricular after-load and would lead to increased EF and symptomatic improvement unless myocardial damage, especially a scar or irreversible myocardial fibrosis, exists.

Improvement of the ventricular function displayed a statistically significant association with preoperative LVEF, aortic valve area, early postoperative LVEF, early postoperative LVESD, and mean transprosthetic gradient. In the multivariate analysis, only increased early postoperative LVEF and low mean transprosthetic gradient were associated with improvement in ventricular function. Vaquette et al demonstrated that early postoperative recovery of LV function was associated with significantly greater relief of symptoms and longer survival [14] and Ruel et al showed that a prosthesis–patient mismatch affects primarily patients with impaired preoperative left ventricular function and results in decreased survival, lower freedom from heart failure, and incomplete left ventricular mass regression. Patients with impaired left ventricular function represent a critical population for whom prosthesis–patient mismatch should be avoided at the time of aortic valve replacement [18].

Table III: Univariate and Multivariate analysis of risk factors of hospital mortality

Variables	**Univariate Analysis**			**Multivariate Analysis**		
	0R	**95% IC**	**p-Value**	**0R**	**95% IC**	**p-Value**
Age	1.03	[0.96 ; 1.10]	0.41			
Sex	0.83	[0.89 ; 7.78]	0.87			
Renal failure	**8.94**	**[1.64 ; 48.70]**	**0.01***	**8.98**	**[1.64 ; 48.70]**	**0.03***
CHF	**10.66**	**[1.90 ; 59.61]**	**<0.001***	**10.90**	**[2.4 ; 59.83]**	**<0.001***
NYHA	**7.21**	**[1.48 ; 35.12]**	**0.01***	34.69	[0.5 ; 2059.70]	0.09
CT index	151631	[0.009 ; 2 10^{27}]	0.16			
Etiologies	1.92	[0.39 ; 9.38]	0.41			
Preoperative LVEF	**0.86**	**[0.77 ; 0.96]**	**<0.001***	1.01	[0.84 ; 1.22]	0.87
Preoperative LVEDD	0.98	[0.89 ; 1.07]	0.68			
Preoperative LVESD	1.02	[0.93 ; 1.12]	0.57			
Mean transvalvular gradient	1.01	[0.96 ; 1.04]	0.69			
Aortic valve area	0.39	[0.005 ; 29.55]	0.67			
SPAP	1.02	[0.98 ; 1.05]	0.37			
X clamp time	1.00	[0.96 ; 1.04]	0.94			
CPB time	**1.02**	**[1.00 ; 1.04]**	**0.01***	1.02	[0.99 ; 1.06]	0.90
Bleeding	0.99	[0.99 ; 1.01]	0.53			

OR: odds ratio; CI: confidence interval; CHF: congestive heart failure; CT: cardio-thoracic; LVEDD: left ventricular end diastolic diameter; LVESD: left ventricular end systolic diameter; LVEF: left ventricular ejection fraction; SPAP: systolic pulmonary arterial pressure. X clamp: cross clamping; CPB: cardiopulmonary bypass; IABP: intra-aortic balloon pump.
*p-value < 0.05 was considered to be significant.

Table IV : Long-term outcomes

Variables	n = 54
Controlled patients	n = 39
Follow up period† (months)	38 [21 ; 84]
Late death‡	3 (7.7 %)
NYHA‡	
-I	29 (80.6%)
-II	5 (13.9%)
-III	2 (5.6%)
Use of digitalo-diuretic treatment	12 (32.4%)
Late complications	
-Cerebrovascular accident	2 (5.1%)
-Congestive heart failure	2 (5.1%)
Late postoperative LVEDD (mm)*	54 ± 8
Late postoperative LVESD (mm)*	40 ± 7.5
Late postoperative LVEF* (%)	50.3 ± 9.6

*: expressed as means standard deviation (SD); †: expressed as medians with interquartile range (IQR); ‡: described as numbers and percentages (%).LVEDD: left ventricular end diastolic diameter; LVESD: left

ventricular end systolic diameter; LVEF: left ventricular ejection fraction.

Table V: Evolution of LVEF, LVEDD and LVESD in preoperative, early postoperative and late postoperative period

Variables	Preoperative (G1)	Early postoperative period (G2)	Late postoperative period (G3)	P Value
LVEF	32.9 ± 5.6	38.2 ± 9.3	50.3 ± 9.6	G2 Vs G1 p < 0.001* G3 Vs G2 p < 0.001* G3 Vs G1 p < 0.001*
LVEDD	63.6 ± 9.2	61.4 ± 8.9	54 ± 8	G2 Vs G1 p < 0.001* G3 Vs G2 p < 0.001* G3 Vs G1 p < 0.001*
LVESD	50.2 ± 8.8	46.8 ± 8.8	40 ± 7.5	G2 Vs G1 p < 0.001* G3 Vs G2 p < 0.001* G3 Vs G1 p < 0.001*

LVEDD: left ventricular end diastolic diameter; LVESD: left ventricular end systolic diameter; LVEF: left ventricular ejection fraction.
*p-value < 0.05 was considered to be significant.

Table VI: Predictors of LVEF improvement

Variables	Univariate Analysis			Multivariate Analysis		
	β	**95% CI**	**P-Value**	**Adjusted β**	**95% CI**	**P-Value**
Preoperative LVEF	**0.89**	**[0.49 ; 1.29]**	**<0.001***	0.30	[-1,33 ; 0.72]	0.17
Preoperative LVEDD	-0.20	[-0.66 ; 2.44]	0.36	-	-	-
Preoperative LVESD	-0.33	[-0.72 ; 0.05]	0.09	-	-	-
Mean transvalvular gradient	-0.14	[-0.29 ; 0.02]	0.09	-	-	-
aortic valve area	**31.20**	**[17.43 ; 44.94]**	**<0.001***	7.30	[-7.36 ; 21.96]	0.32
SPAP	-0.12	[-0.26 ; 0.02]	0.08	-	-	-
Early Postoperative LVEF	**0.72**	**[0.48 ; 0.96]**	**<0.001***	**0.44**	**[0.14 ; 0.75]**	**0.006***
Early Postoperative LVEDD	-0.26	[-0.73 ; 0.21]	0.26	-	-	-
Early Postoperative LVESD	**-0.54**	**[-0.92 ;-0.17]**	**0.006***	-6 10^{-2}	[-0.36 ; 0.24]	0.68
Prosthesis size	0.60	[-1.35 ; 2.51]	0.54	-	-	-
Mean transprosthesis gradient	**-0.13**	**[-2.12 ; -0.40]**	**0.005***	**-0.72**	**[-1.42 ; -0.02]**	**0.04***

CI: Confidence interval; LVFE: left ventricular ejection fraction, LVEDD: left ventricular end-diastolic diameter, LVESD : left ventricular end-systolic diameter, SPAP: systolic pulmonary artery pressure.
*p-value < 0.05 was considered to be significant

LV contractile reserve is known to be a predictor for operative mortality in low-gradient AS [19],[20]. Dobutamine stress echocardiography (DSE) has emerged as an important non invasive clinical tool for evaluating left ventricular contractile reserve [21]. On the other hand, DSE is also used for the diagnosis of relative AS, defined as primary LV dysfunction with non severe AS [22], [23]. Thus, DSE may identify patients who are most likely to benefit from surgery [20-23]. Since 2012, we started using DSE in patients with low gradient. However, we used it thus far in the cases of 3 (19%) patients only. Hence, although all these patients had a contractile reserve, their number is low and does not allow us to draw any statistics-based conclusion.
Finally, although the results of AVR for severe and isolated aortic stenosis with left ventricular dysfunction are encouraging, Transcatheter Aortic Valve Implantation (TAVI) seems to be a serious alternative. Accordingly, in the Clavel et al series, the hospital mortality for TAVI was only 16%, while average EurSocore was 34%, and after one year of follow-up, 58% of patients recovered a LVEF > 50%, versus 20% for AVR [24].In Conclusion, the long term outcome of AVR for severe and isolated AS with left ventricular dysfunction is excellent as evidenced by: Better survival (although the rate of hospital mortality is still for further improving), decreased left ventricular diameters and improvement in left ventricular function and functional class.

V. STUDY LIMITATION

Although the data were collected prospectively, our study is prone to the biases of its retrospective nature. Although, to our knowledge, this is the largest study of its nature, the still small sample size might decrease the weight of the statistical results. Additionally, the young age of our patients and their heterogeneous etiologies could influence the results. All ours conclusion should be considered in that context.

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