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Five-year survival of patients with left-side heart valve disease who underwent heart valve surgery

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Abbreviations
HR: hazard ratio

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ABSTRACT

Introduction: The mid and long term survival rate is a necessary parameter to evaluate the outcomes of heart valve surgery.
Objectives: To determine the five-year survival of patients who underwent aortic and/or mitral valve surgery, and the variables that could independently predict a lower survival in the follow-up.
Methods: A cohort study was conducted for evaluating 139 patients who underwent a heart valve surgery, in the period 2010-2012, at the Instituto de Cardiología y Cirugía Cardiovascular of Havana, Cuba, all of which survived the postoperative period, and were followed up to five years after the surgery. A Kaplan-Meier curve was performed to determine the survival after surgery. Also, a multivariate Cox regression was carried out to determine the variables that were independently associated with a lower survival rate. The statistical significance level used was $p<0.05$.
Results: The sample was homogeneous according to clinical and demographic variables. The overall survival rate was 93% at the end of the study, with a mean follow up of 5.8 years. The older age (HR=1.15; p=0.001) and the history of perioperative low cardiac output syndrome (HR= 3.54; p=0.037) were the variables independently associated to lower survival in the follow-up.
Conclusions: The patients' survival when concluded the follow-up was high. The older age and the perioperative low cardiac output syndrome were the variables independently associated to lower survival.
Keywords: Left-side heart valve disease, Heart valve surgery, Survival, Survival Analysis

Supervivencia a los cinco años en pacientes con valvulopatías izquierdas operados de cirugía cardíaca valvular

RESUMEN

Introducción: La supervivencia a mediano y largo plazo es un parámetro necesario para evaluar los resultados de la cirugía valvular cardíaca.
Objetivos: Determinar la supervivencia a los cinco años de los pacientes opera-

Authors' Contribution
JEFM y KMPG: Idea conception and design of the research, data collection and interpretation, and manuscript writing..
AMPC, OGG, AGT: Obtaining of the raw data, and helped to draft the manuscript.
EDV y RCP: Data collection and interpretation.
All authors critically reviewed the manuscript and approved the final report.

dos de cirugía cardíaca valvular aórtica, mitral o ambas, y las variables que pueden pronosticar de manera independiente una peor sobrevida en el seguimiento.
Método: Se realizó un estudio de cohorte que evaluó a los 139 pacientes operados de cirugía cardíaca valvular en el trienio 2010-2012, en el Instituto de Cardiología y Cirugía Cardiovascular de La Habana, Cuba, y que fueron egresados vivos del postoperatorio, hasta un período de cinco años posteriores a la intervención. Se realizó una curva de Kaplan Meier para determinar la supervivencia al final del seguimiento, así como un análisis multivariable de Cox para determinar las variables que se asociaron a una menor supervivencia. El nivel de significación estadística empleado fue p<0,05.
Resultados: La muestra resultó homogénea según las variables clínicas y demográficas. La supervivencia al término del seguimiento, que tuvo una media de 5,8 años, fue de un 93%. El incremento de la edad (HR=1,15; p=0,001) y el haber sufrido bajo gasto cardíaco durante el perioperatorio (HR=3,54; p=0,037) se asociaron de manera independiente a una peor sobrevida en el seguimiento.
Conclusiones: La supervivencia de los pacientes al concluir el seguimiento fue elevada. El incremento de la edad y el bajo gasto cardíaco perioperatorio fueron las variables asociadas de manera independiente a una menor sobrevida.
Palabras clave: Valvulopatía izquierda, Cirugía valvular cardíaca, Sobrevida, Análisis de supervivencia

INTRODUCTION

Despite the development of minimally invasive interventional techniques such as percutaneous balloon mitral valvuloplasty and transcatheter aortic valve replacement[1], valvular heart surgery continues to be a common indication globally, with over a quarter of a million patients being operated on annually[2]. It ranks second only to coronary-artery bypass grafting in standard cardiac surgery in Cuba[3].

The survival of patients subjected to heart valve surgery, in the short, mid and long term, is an irreplaceable parameter for assessing the quality of this complex procedure[4]; determined by a set of variables that have been evaluated in various prediction models and which are of unparalleled value for decision-making in each individual patient[5,6].

Several studies have analyzed the results of heart valve surgery in different contexts, mainly in the immediate period, which is undoubtedly the one with the highest risk of mortality given the characteristics of this stage: anesthesia, cardiopulmonary bypass, mechanical ventilation, among others[7,8]. However, studies with longer-term follow-up –five to ten years after surgery– are less frequent[4]. In our field there are few studies that analyze the results of this type of surgery at mid and long term.

Therefore, it was considered of interest to conduct a study in patients who had mitral and aortic valve surgery, or both; with the aim of determining survival at five years after surgery, as well as the variables that can independently predict lower survival at follow-up.

METHOD

A cohort study was carried out, which evaluated all patients with valvular surgery (mitral or aortic repair or replacement, or both) at the Institute of Cardiology and Cardiovascular Surgery of Havana, who were discharged alive from the postoperative period, up to a period of 5 years after surgery. The patients included in the study were operated on during the three-year period from January 1, 2010 to December 31, 2012, so the follow-up was completed on December 31, 2017.

By reviewing medical records, perioperative data defined by the variables of interest were collected and patients were subsequently followed up by telephone communication with them or their relatives, as appropriate, to determine whether they were still alive or had died; if so, the date of death was specified.

The study was conducted in accordance with the guidelines proposed in the Declaration of Helsinki and was approved by the Ethics Committee of our institution.

Exclusion criteria

Patients with concomitant coronary disease who also required myocardial revascularization, those in whom, for any reason, sufficient preoperative information could not be obtained, and those who could not be reached during follow-up, were excluded.

Study variables

Follow-up event of interest: patient's death during follow-up and time of death. Those who did not present this event of interest were considered alive and were followed up until December 31, 2017. The average follow-up time was 5.8 years (range 1.5-6.6 years).

Patient status at follow-up (dependent variable): living or deceased.

Independent variables

General: age, sex, body surface area (Du Bois)[9], personal pathological history (diabetes mellitus, high blood pressure, chronic obstructive pulmonary disease, chronic atrial fibrillation), smoking, rheumatic or non-rheumatic etiology, New York Heart Association (NYHA) functional class III/IV.

Perioperative variables: type of surgery (mitral, aortic or mitro-aortic), of cardiopulmonary bypass time, hospital stay, low cardiac output in the perioperative period (defined by the need for inotropic support for more than 12 hours with or without the use of an intra-aortic balloon pump, associated with a diuretic rhythm of less than 0.5 ml/kg/h).

Preoperative laboratory variables: hemoglobin, uric acid, glomerular filtrate calculated by CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration).

Preoperative echocardiogram: left ventricular ejection fraction (LVEF), right ventricular dysfunction (when the tricuspid annular plane systolic excursion [TAPSE] was less than 12 mm) and pulmonary hypertension, considered when mean pressure in the pulmonary artery was greater than 35 mmHg, calculated by the Maham regression equation (79 - 0.45 × pulmonary acceleration time)[10].

Statistical analysis

The SPSS program for Windows version 15.0 was used for the statistical analysis. Patients were divided into two groups: one was made up of the 128 operated patients who were still alive when follow-up was completed and the other was made up of the 11 patients who died during follow-up. Qualitative variables were expressed in absolute and relative frequencies, to which the Chi-square test for homogeneity was applied, as well as the Fisher test for those with expected frequencies less than five. For quantitative variables, the Kolmogorov-Smirnov normality test was used and then the t-Student test was applied to those with normal distribution, as well as the Mann-Whitney U test for those without normal distribution; these variables were expressed as mean ± standard deviation. The significance level considered was $p<0.05$.

The overall survival of patients at the end of follow-up was calculated by the Kaplan-Meier method. Subsequently, the corresponding individual curves were generated with the variables that, in the univariate analysis, showed significant differences between the groups ($p<0.05$), which were compared using the log rank test. Hazard ratios (HR) were calculated using the Cox equation. Multivariate Cox regression was finally performed, where the variables that presented a value of $p<0.20$ in the univariate analysis were included, being carried out step by step to calculate the value, which could independently have on mortality during follow-up, the significance value used was also $p<0.05$. Some quantitative variables were grouped by ranges for processing.

RESULTS

The population in this study consisted of 139 patients who were able to complete the follow-up, which averaged 5.8 years after surgical treatment. Eleven patients died during this period, for an overall survival of 93% (**Figure 1**) and mortality of 7%. The sample was generally homogeneous according to the variables studied. Significant differences were only found between those who died and those who did not in terms of age ($p<0.0001$), which was higher

in the deceased; preoperative glomerular filtration rate (p<0.0001), which was also lower in this group; as well as the presence of low cardiac output during the perioperative period (p=0.012) that was proportionally higher among the deceased (**Table 1**).

Preoperative glomerular filtration rate of less than 75 ml/min was found to be significantly associated with reduced survival at follow-up. This decrease in survival basically started after a year and a half of follow-up, with an HR of 4.32 (p=0.01) (**Figure 2**). Another variable associated with reduced survival was the presence of low cardiac output during the perioperative period. This difference also began to become noticeable after a year and a half of follow-up, with an HR of 4.15 and a value of p=0.001 (**Figure 3**).

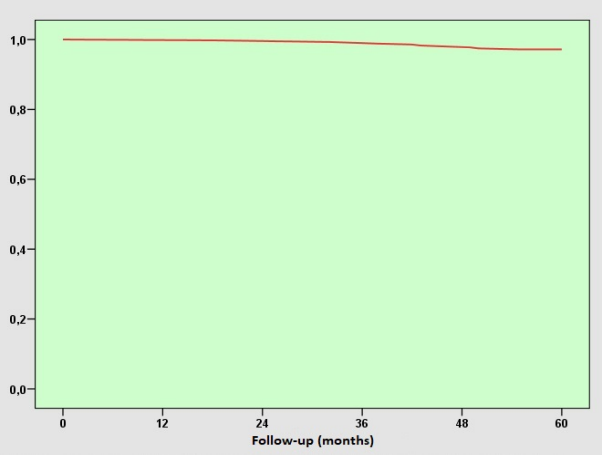

Figure 1. Kaplan-Meier curve of overall survival of patients 5 years after surgery.

Table 1. Characterization of the patients studied.

Variables	Total (N=139)	Living (n=128)	Deceased (n=11)	p value
Age (years)	54.57±11.61	53.48±11.21	67.18±8.65	**<0.0001**
Female	64 (43.9)	57 (44.5)	4 (36.4)	0.55
Body area (m^2)	1.75±0.21	1.76±0.22	1.76±0.20	0.49
Isolated mitral surgery	61 (43.9)	57 (44.5)	4 (36.4)	0.60
Isolated aortic surgery	64 (54.1)	58 (45.3)	6 (54.5)	0.55
Dual valve replacement	14 (10.1)	13 (10.2)	1 (9.1)	0.91
Rheumatic etiology	43 (30.9)	42 (32.8)	1 (9.1)	0.10
Functional class III/IV	107 (77.1)	98 (76.5)	9 (81.8)	0.69
High blood pressure	62 (44.6)	55 (43.1)	7 (63.6)	0.18
Diabetes mellitus	16 (11.5)	15 (11.7)	1 (9.1)	0.79
COPD	9 (6.5)	8 (6.3)	1 (9.1)	0.71
Chronic atrial fibrillation	25 (18.0)	22 (17.2)	3 (27.3)	0.40
Smoking	38 (27.3)	37 (28.9)	1 (9.1)	0.15
Hyperuricemia	30 (21.6)	26 (20.3)	4 (36.4)	0.21
Hemoglobin (g/l)	13.24±1.49	13.27±1.85	12.55±1.39	0.23
Pulmonary hypertension	55 (39.6)	49 (38.1)	6 (54.5)	0.29
Glomerular filtration rate (ml/min/m^2)	93.50±30.53	95.71±30.52	67.3±13.84	**<0.0001**
Right ventricular dysfunction	20 (14.4)	17 (13.3)	3 (27.3)	0.20
Reduced FEVI (≤ 40%)	9 (6.5)	9 (7.1)	0 (0)	0.36
CPB time (min)	146.05±71.31	140.31±68.63	129.64±16.77	0.35
Hospital stay (days)	14.07±10.62	14.64±10.74	17.45±10.63	0.13
Perioperative LCOS	33 (23.7)	27 (21.1)	6 (54.5)	**0.012**

Values are expressed in n (%) and mean ± standard deviation.
CPB, cardiopulmonary bypass; COPD, chronic obstructive pulmonary disease; LCOS, low cardiac output syndrome; LVEF, left ventricular ejection fraction.

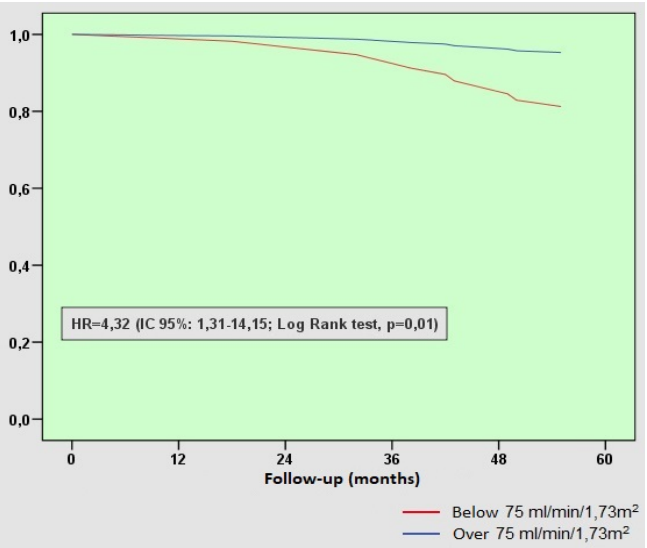

Figure 2. Kaplan-Meier survival curve at 5 years, based on preoperative glomerular filtration rate (ml/min/1,73m^2).

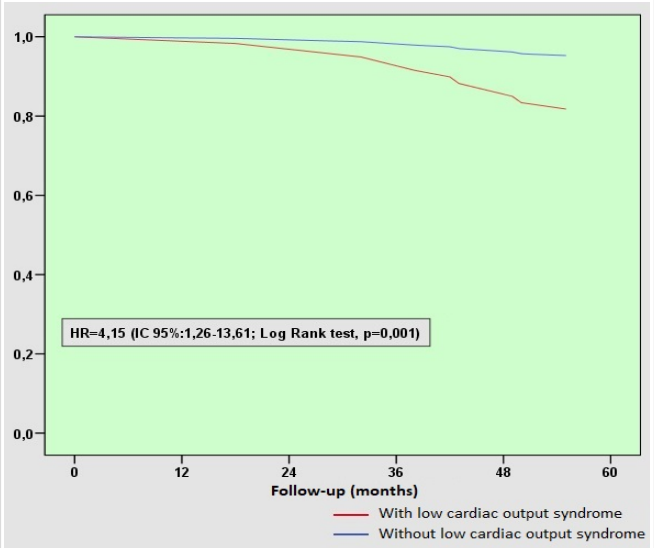

Figure 3. Kaplan-Meier survival curve at 5 years, based on the presence of perioperative low cardiac output syndrome.

Age over 65 years was the most significant variable (HR=23.25; p<0.0001) in relation to lower survival, a difference that was observed from the very beginning of follow-up (**Figure 4**).

Finally, the multivariate analysis showed how the two variables that were independently found to be associated with higher mortality (or, in other words, lower survival) at follow-up were: older age and history of low perioperative cardiac output. In this case, age, analyzed as a continuous variable, increases by 6 to 25% the probability of dying during follow-up for each year of increase prior to surgical treatment (HR=1.15; p=0.001). Patients with low cardiac output were 3.5 times more likely to die over the 5 years after surgery than those who did not have this perioperative complication. With a statistical significance value of p=0.037 (**Table 2**).

DISCUSSION

The results indicate how much a patient with heart valve disease, requiring surgical treatment, may do better after treatment. Considering that the overall survival at the end of follow-up was 93%, the result is good and comparable to other studies analyzing postoperative survival[4,7,11].

Older age is one of the variables with the greatest negative influence on short, mid and long term results in cardiac surgery[4,12]. The continuous aging of our population and the reduction of rheumatic valve

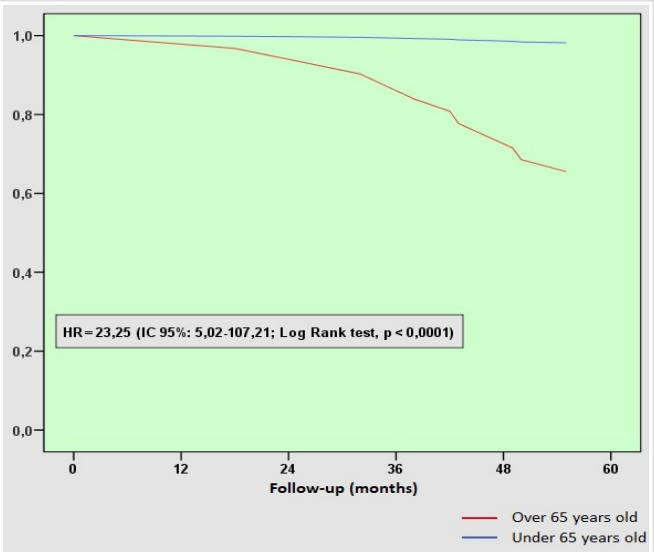

Figure 4. Kaplan-Meier survival curve at 5 years, based on age at the time of surgery.

Table 2. Independent predictive variables of mortality at 5 years after surgery (Cox regression).

Variables	B ± ST	Wald	HR	CI 95%	p value
Older age	0.14±0.43	11.15	1.15	1.06-1.25	0.001
Low perioperative cardiac output	1.26±0.60	4.35	3.54	1.08-11.63	0.037

B, Cox regression coefficient; CI, confidence interval; HR, hazard ratio; SE, standard error.

diseases[3], however, have significantly increased the age of patients diagnosed with mitro-aortic valve disease with indication for heart valve surgery. Which is a huge challenge for the medical team[12]. In this study we found that age, at the time of surgery, was the most important variable in decreasing survival during follow-up, observing a reduction in survival in those over 65 years from the very beginning of the postoperative period. However, it is not possible to evaluate old age as a reason for not indicating surgical treatment, given that the benefits are also high, since this study shows that overall survival at five years of follow-up −in this particular group− was 70%, much higher than the expected survival if no surgery had been performed, which may be around 30% in that time[13]. Furthermore, there are studies that not only propose the improvement of survival in the elderly, but also the favorable impact on their quality of life after surgery[14].

Preoperative renal failure, to any degree, is one of the variables related to discrete surgical outcomes, both immediately and over longer periods of time[15,16]. In the follow-up, a preoperative glomerular filtration rate below 75 ml/min was associated with a shorter survival; which began to decrease a year and a half after surgery. Although Cox's multivariate analysis did not reach statistical significance to be considered a factor with independent value, the authors believe that other studies specifically designed to evaluate it might be carried out.

Low cardiac output is one of the most frequent perioperative complications occurring in patients attending cardiac surgery, which significantly increases perioperative mortality[15,17]. Several risk factors favor its development, including age over 65 years at the time of surgery, renal failure, diabetes, prolonged periods of cardiopulmonary bypass, among others[18].

The patients' follow-up revealed that those with low cardiac output had a lower survival rate, which began to be noticed after a year and a half of the intervention. In the literature available only one study was found that related low cardiac output to lower long-term survival in heart valve surgery[19].

Lastly, the two variables that presented an independent value after Cox regression were older age and low cardiac output during the perioperative stage. Age is recognized as a risk factor for perioperative complications and its increase is associated to lower survival rates in the mid and long term[1,4,5,14,] hence this result confirms what has been reported in the literature. In turn, low cardiac output is recognized as a complication that significantly increases short-term mortality[15,17]. However, there is poor evidence that it influences longer-term survival as only one study was found where this aspect was recognized[19]. For the patients studied, however, its occurrence in the perioperative period reduced survival at follow-up, which could also be associated with other risk factors such as age, diabetes, renal failure, among others, which are shared by patients who suffer it most frequently[18].

The main limitation of this study was that it was conducted in a single facility and, consequently, the number of patients is not high. However, it addresses a complex issue such as surgical outcomes beyond the perioperative period. Therefore, we suggest that a well-designed study be carried out, involving all or most of the institutions in our setting that perform this type of surgery, which results would help the decision making process.

CONCLUSIONS

Patients studied five years after surgical treatment showed high survival. The main variables that were independently associated with a decrease in surviv-

al were older age and the occurrence of low perioperative cardiac output.

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