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Risk factors associated with hospital mortality in mitral valve reoperation

Fatores de risco associados à mortalidade hospitalar em reoperação valvar mitral

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A B S T R A C T

Objective: to identify the factors associated with mortality in mitral valve reoperation, to create a predictive model of mortality and to evaluate the EuroSCORE. **Methods:** a total of 65 patients were evaluated from January 2008 to December 2017. It was verified the association of variables with death and a multiple logistic regression model was used to stratify patients. **Results:** hospital mortality was 13.8% and in the Death Group: EuroSCORE was 12.33±8.87 (p=0.017), the left ventricular ejection fraction (LVEF) was 45.33±5.10 (p=0.000), the creatinine was 1.56±0.29 (p=0.002), the prothrombin time (TAP) was 1.64 (p=0.001), pulmonary artery systolic pressure (PSAP): 66.1±13.6 (p=0.002), female: 88% (p=0.000), malnutrition: 77.7% (p=0.007), associated tricuspid disease: 44,4% (p=0.048), presence of ventricular arrhythmia: 77.7% (p=0.005), implantation of a biological prosthesis: 55.5% (p=0.034), bronchopneumonia and sepsis: 33,3% (p=0.048), systemic inflammatory response syndrome (SIRS): 55.5% (p=0.001), low cardiac output syndrome (LCOS): 88.8% (p=0.000). **Conclusion:** the factors associated with mortality were: EuroSCORE, LVEF, creatinine, TAP, PSAP, female, malnutrition, tricuspid disease, ventricular arrhythmia, implantation of biological prosthesis, SIRS, SBDC, bronchopneumonia and sepsis. The explanatory variables of death of the model were: EuroSCORE, creatinine, TAP, LVEF, length of stay in the intensive care unit (ICU), interval between surgeries and presence of ventricular arrhythmia. The high EuroSCORE is related to higher mortality.

Keywords: Mitral Valve. Risk Factors. Reoperation. Hospital Mortality.

INTRODUCTION

The majority of patients undergoing mitral valve surgery should require further surgery at some late period of their survival. Valvular diseases of rheumatic origin remain prevalent in developing countries[1], which causes many patients to undergo surgery very young and often require reoperation.

Mitral valve reoperation presents a high surgical risk, as well as an important late mortality[2]. The factors predisposing to these results are complex and have extremely significant socio-regional characteristics and great variations. In Brazil, the number of reoperations is high, mainly due to the great use of biological prostheses, which have a limited life span due to the structural dysfunction of the prosthetic material[3].

In the international literature[4-6], multivariate analyzes were performed to identify risk factors for morbidity and mortality. In Brazil, data show that mortality during cardiac surgery is still high[7], which can be explained partly by the socioeconomic differences of our population[7-9]. The use of predictors of risk events scores is well established but the difficulty is that the risk models derived and validated in one site usually present lower performance when applied in a different setting, even in the same place over time. In the history of cardiac surgery, the predicted risk model with the greatest impact was EuroSCORE II[10], which is widely used in several heart surgery centers worldwide.

Thus, the objective of this study was to identify factors associated with hospital mortality,

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to create a predictive model of mortality adequate to our reality, and to evaluate the behavior of EurosCORE in a referral hospital.

METHODS

We performed a retrospective analysis of patients over 18 years old who had undergone mitral valve surgery at *Hospital do Coração Nossa Senhora da Salete*, in Cascavel - State of Paraná, Brazil. The Hospital is a tertiary care center, a reference in cardiology for the Unified Health System (SUS) of the 10th Health Region. This work was submitted to the Ethics Committee of the University Hospital of the State University of Western Paraná, with approval number 2042552.

We evaluated 65 consecutive patients operated from January 2008 to December 2017. We defined hospital mortality as any cause of death during hospitalization and up to the 30th postoperative day. To evaluate the predictive factors of the occurrence of death, we verified the association of variables (factors) with death by means of univariate statistical analysis, that is, we calculated the Pearson and Spearman correlation coefficients and the matrices correlation coefficients. Subsequently, we used the variables to fit a multiple logistic regression model, with a significance level of 5%. The software used was the Statgraphics 5.1®. The data available for fitting the multiple logistic regression model were observations of a dichotomous "Y-response" variable, related to deaths, that is, it only assumed one of two values, '1' for the Death Group and '0' for the Survivor Group. The Death Group was formed by nine observations and the Surviving Group, by 56. The fitting was made looking for the variables most correlated with death in the correlation matrices between all variables preliminarily calculated and introduced in the model. Thus, we found the significance of the model based on the corresponding p-value in a deviation analysis test, until seven explanatory variables were obtained, which explained 99.95% of the variance of the variable Y (death). The estimation of the model parameters (coefficients of the variables) was done by the maximum likelihood method using iterative process, and in the logistic regression we tried to maximize the probability of an event occurring.

The variables evaluated were age, gender, functional class according to the New York Heart Association, EuroSCORE, malnutrition assessed by the Malnutrition Universal Screening Tool (MUST)[11], time of preoperative hospitalization, diabetes, smoking, associated aortic or tricuspid disease, interval between surgery in years, patient bearer of native valves, bioprosthetic or mechanical valve, number of procedures, serum creatinine (mg/dl), hemoglobin (g/dl), and time of prothrombin activity (PT) at the time of admission expressed by the international normalized ratio (INR). Regarding the heart rhythm, we divided the patients into three groups: sinus rhythm, atrial fibrillation and ventricular arrhythmia. The echocardiographic variables evaluated were left atrium dimension, left ventricular diastolic dimension (LVDD), type of valvular dysfunction; stenosis or insufficiency pulmonary artery systolic pressure (PASP), left ventricular ejection fraction (LVEF) calculated by the Teichholz formula[12], number of the surgery performed, whether it was the second, third or fourth, extracorporeal circulation time (ECT), type of implanted prosthesis, biological or mechanical, length of stay in the intensive care unit (ICU) in days, need of exploratory thoracotomy by bleeding in the immediate postoperative period, bronchopneumonia, sepsis, systemic inflammatory response syndrome (SIRS) and low cardiac output syndrome (LCOS).

The access route was a new sternotomy and the extracorporeal circulation was established by aortic and bicaval cannulation. The femoral region was left exposed, but the femoral vessels were not dissected.

RESULTS

Hospital mortality was 13.8% (9 patients). The mean age was 48±12 years; 49 patients (75%) were female. Table 1 shows the statistical description of the quantitative variables and table 2, the description of the qualitative ones.

The most explanatory variables of death were EuroSCORE, surgery interval, left ventricular ejection fraction, serum creatinine, prothrombin activity time, length of stay in the intensive care unit and presence of ventricular arrhythmia.

The equation of the final regression model is logistic for the sigmoid curve is: death = exp (eta) / (1+exp (eta), where eta corresponds to the best linear combination of variables to explain (predict) the value of the death variable. Thus, the result obtained for the model was: eta= 598.681 - 3.06764 x EuroSCORE - 24,4945 x interval surgery - 7,46427 x LVEF + 53.6369 x creatinine + 23.9337 x PT(INR) - 7.36136 x ICU time - 77.5164 x ventricular arrhythmia.

Tables 3 and 4 show the maximum likelihood estimates of the parameters when fitting the model with only one variable and with the seven variables, respectively.

The deviation analysis showed that the model is significant, since the corresponding value is p<0.05 (5%), that is, there is a significant relationship between death and the seven factors, which explains 99.9567% (52.2583) of the data variance (52.2809), leaving as residue only 0.000433% (0.0226525) of unexplained variance.

Table 1. *Descriptive statistics of the quantitative variables in the survivor and death groups.*

Variable	Survivor group	Death group	p-value
PREOPT*	3.22±3.83	4.33±2.41	0.111
Age (years)	47.2±11.5	52.9±15.1	0.190
EuroSCORE	3.33±2.62	12.33±8.87	0.017
Surgery interval (years)	11.48±3.21	9.78±0.98	0.190
Creatinine (mg/dl)	1.19±0.28	1.56±0.29	0.002
Hemoglobin (mg/dl)	10.31±1.96	10.67±2.0	0.649
PT** (INR)	1.19±0.22	1.64±0.15	0.001
LA*** (mm)	48.75±3.81	49.67±3.91	0.470
LVDD[#] (mm)	58.30±4.84	59.44±3.91	0.115
PASP[##] (mmHg)	51.45±8.61	66.1±13.6	0.002
LVEF[###] (%)	57.64±7.32	45.33±5.10	0.000
ECT[¥] (min)	107.28±33.827	131.1±52.9	0.104
ICUT[¥¥] (days)	2.82±2.05	6.22±5.15	0.193

**PREOPT: preoperative time; **PT (INR): prothrombin activity time (International Normalized Ratio); ***LA: left atrium; [#]LVDD: left ventricular diastolic diameter; [##]PASP: pulmonary artery systolic pressure; [###]LVEF: left ventricular ejection fraction; [¥]ECT: extracorporeal circulation time; [¥¥]ICUT: time in the intensive care unit.*

Table 2. *Descriptive statistics of the qualitative variables in the survivor and death groups.*

Variable	Survivor group	Death group	p-value
Gender			
Women	41 (73%)	8 (88%)	0.000
Men	15 (26.7%)	1 (11.1%)	0.433
NYHA class*			
II	46 (82.1%)	7 (77.7%)	0.865
III	9 (16%)	2 (22.2%)	0.932
I	1 (1.7%)	0 (0%)	1.000
MUST** nutrition			
Nourished	40 (71.4%)	2 (22.2%)	0.047
Malnourished	16 (28.5%)	7 (77.7%)	0.007
Smoking	10 (17.8%)	2 (22.2%)	0.667
Diabetes	3 (5.35%)	1 (11.1%)	0.077
Nº of surgery			
2nd surgery	52 (92.8%)	5 (55.5%)	0.553
3rd surgery	4 (7.14%)	3 (33.3%)	0.155
4th surgery	0 (0%)	1 (11.1%)	0.327
Native valva	11 (19.6%)	1 (11.1%)	0.185
Biological prosthesis	43 (76.7%)	8 (88.8%)	0.333
Mechanical prosthesis	2 (3.56%)	0 (0%)	1.000
Sinus rhythm	17 (30.3%)	2 (22.2%)	1.000
Atrial fibrillation	39 (69.9%)	7 (77.7%)	1.000
Ventricular arrhythmia	7 (12.5%)	7 (77.7%)	0.005
Type of valve dysfunction			
Stenosis	43 (76.7%)	8 (88.8%)	0.185
Insufficiency	13 (23.3%)	1 (11.1%)	0.670
Type of implanted prosthesis			
Biological	11 (19.6%)	5 (55.5%)	0.034
Mechanical	45 (80.3%)	4 (44.5%)	1.000
Associated disease			
Tricuspid	11 (19.4%)	4 (44.4%)	0.048
Aortic	7 (12.5%)	0 (0%)	1.000
Exploratory thoracotomy	1 (1.78%)	2 (22.2%)	0.365
Bronchopneumonia	0 (0%)	3 (33.3%)	0.048
Sepsis	0 (0%)	3 (33.3%)	0.048
SIRS***	0 (0%)	5 (55.5%)	0.001
LCOS#	0 (0%)	8 (88.8%)	0.000

**NYHA: New York Heart Association; **MUST: Malnutrition Universal Screening Tool; ***SIRS: systemic inflammatory response syndrome; #LCOS: low cardiac output syndrome.*

Table 3. *Regression models estimated by maximum likelihood for one variable and constant.*

Parameter	Estimate	Default error of the estimate	Percentage explanation	p-value	Chance ratio
Constant	-3.50934	0.714399			
EuroSCORE	0.282525	0.2925050	33.4227%	0.00000	1.33009
Surgery interval	-0.23926	0.157969	5.3638%	0.09400	0.78720
LVEF*	-0.347234	0.112105	43.2946%	0.00000	0.70664
Creatinine	3.34958	1.2349	17.8830%	0.0022	28.49080
PT (INR)**	4.87934	1.67042	28.4254%	0.0001	131.5440
ICUT***	0.274311	0.102693	14.6581%	0.0056	1.3156
VA#	-4.19971	1.1452	44.5967%	0.00000	0.0150

**LVEF: left ventricular ejection fraction; **PT (INR): prothrombin activity time (International Normalized Ratio); ***ICUT: length of stay in the intensive care unit; #VA: ventricular arrhythmia.*

Table 4. *Regression model estimated by maximum likelihood for the seven variables.*

Parameter	Estimate	Default error of the estimate	Odds Ratio	Contribution of the variable for the model	Explanation of the model with only the variable	p-value
Constant	598.681	296.324				
EuroSCORE	-3.06764	12.1711	0.0465307	33.4227%	33.4227%	0.9791
Surgery interval	-24.4945	7.6586	2.30243E-11	3.4240%	5.3638%	0.0000
LVEF*	-7.46427	3.9079	0.000573203	33.374%	43.2946%	0.0000
Creatinine	53.6369	100.806	1.96893E23	3.159%	17.8830%	0.9126
PT**	23.9337	40.4968	2.4791E10	2.8966%	28.4254%	0.7829
ICUT***	-7.36136	10.3726	0.000635334	2.0128%	14.6581%	0.7698
VA#	-77.5164	37.0168	2.16297E-34	6.0527%	44.5967%	0.0002

**LVEF: left ventricular ejection fraction; **PT: prothrombin activity time; ***ICUT: length of stay in the intensive care unit; #VA: ventricular arrhythmia.*

Table 5 shows the results of the likelihood ratio test for the parameters. Although only three had p-value below 0.05, the set of variables was the one that best fit, producing an explanation degree of 99.9567%.

The model can be used to predict the response using information from each line of the data file (patient). So if the predicted value is greater than that of the cut line chosen by the researcher, the predicted response is to be true and if this predicted value is smaller, the response is predicted to be false. At the cutoff of 0.4 one gets 100% of all true answers correctly predicted as true, and 100% of all false correctly predicted to be false. In the present case, true means death and false means no death, and the value predicted by the model is the estimated probability of death, that is, P (death =1). Figure 1 demonstrates the predictability of the model.

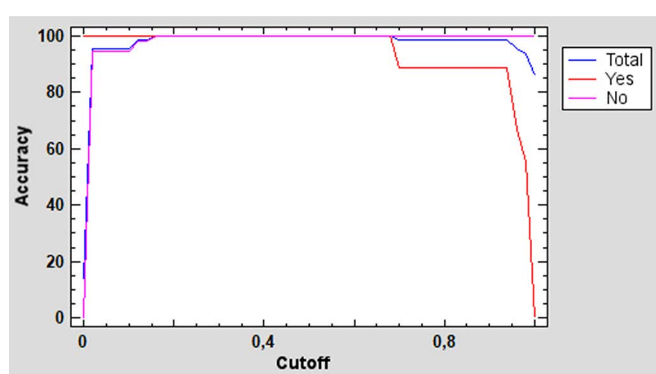

Figure 1. *Model's death prediction capacity.*

Table 5. *Proof of likelihood ratio for parameters.*

Factor	Chi-square	Degrees of freedom	p-value
Interval surgery	16.7415	1	0.0000
EuroSCORE	0.000684113	1	0.9791
LVEF*	19.1658	1	0.0000
Creatinine	0.0120421	1	0.9126
PT**	0.0759345	1	0.7829
ICUT***	0.0856041	1	0.7698
VA#	13.4505	1	0.0002

**LVEF: left ventricular ejection fraction; **PT: prothrombin activity time; ***ICUT: length of stay in the intensive care unit; #VA: ventricular arrhythmia.*

In the 'Box-and-whisker-plot' of the distribution of frequencies of the EuroSCORE variable for the 65 patients, the value of the EuroSCORE with the mean and SD are 4.58±5.05, showing that 80% have values less than or equal to 4.73684. Thus, 25% of the values are less than 2.21 (1st Quartile) and 75% are less than 3.82 (3rd Quartile) so that 25% are higher than 3.82. In the Survivor Group, the value of the EuroSCORE, mean and SD were 3.33±2.62, showing that 25% of the values are less than 2.21 (1st Quartile) and 75% are lower than 3.365 (3rd Quartile), and that 25% is greater than 3.365. In the Death Group, Mean and SD were 12.3278±8.86, therefore 77.78% have values greater than 5,0, 25% of the values are less than 5.3 (1st Quartile) and 75% are less than 20.31 (3rd Quartile), so that in this group 25% are superior to 20.31. There were no outliers in the Death Group.

Thus, considering the frequency distribution of the EuroSCORE, the following criterion can be used in the prediction of death: EuroSCORE <4: probably no death; between 4 and 5: difficult to predict; and >5: probable death.

DISCUSSION

Mitral reoperations present a higher risk of adverse events when compared with first surgeries which may compromise survival. Mortality in this study was 13.8%, the most common cause being low cardiac output syndrome. This rate has been similar in recent studies[4,6,13]. This situation demonstrates that these patients still require more attention. The shorter interval between surgeries in the Death Group was considered explanatory by the model. Studies have shown that the mortality rate in patients who are reoperated within less than the usual time intervals present higher mortality, usually due to the presence of heart failure due to paravalvular reflux or to the injury of cardiac structures during the new sternotomy[14,15]. Likewise, patients submitted to a higher number of reoperations also present higher mortality due to the risk of cardiac lesions (right ventricle and innominate vein)[4]. Decreased left ventricular ejection fraction was associated with higher mortality in the univariate analysis and highly explanatory of death in the model. The published studies demonstrate that this is the most consistent factor in explaining mortality in mitral reoperation and warn of the need for reoperating patients before deterioration of the ventricular function[6,13,14,16]. Vohra *et al.*[13] reported that patients with left ventricular ejection fraction <50% had EuroSCORE II of 12±4, thus showing their high risk. The association of this variable also shows good consistency, as demonstrated in our model.

Likewise, increased creatinine was associated with death in the univariate analysis and was explanatory in the model, consistent with the literature, as described by several authors as an independent predictor of death[6,13,14,16]. High pulmonary artery pressure is a clinical and hemodynamic syndrome, which is a serious clinical situation, usually associated with mitral stenosis. During surgery, the right ventricle is significantly dilated and the trunk of the pulmonary artery is tense, death occurring due to ventricular failure[17]. High pulmonary artery pressure was associated with death in the univariate analysis but did not present a good explanation in the model. On the other hand, in the multivariate analyzes it was predictive of death when associated with tricuspid valve reflux[17,18].

The length of stay in the intensive care unit (ICUT) was explanatory for death in the model. These patients are those who require prolonged mechanical ventilation, pulmonary infections and have received greater transfusion of hemoderivatives that may cause pulmonary inflammatory response in mitral valve reoperations[6,18]. Longer hospital stay was also associated with higher mortality by other authors[13,14]. Prothrombin time (PT) was an explanatory factor of death in our study. Changing PT indicates depletion of vitamin K dependent factors. In Brazil, Brandão *et al*.[9] reported that decreased prothrombin activity was associated with hospital mortality in valve reoperations in univariate analysis. Decreased prothrombin activity was found mainly in patients who had heart failure demonstrated by functional class III and IV (NYHA). These patients had an increased mortality rate, probably due to altered liver function[4]. It is also worth noting that reoperations do not increase the risk of bleeding in the postoperative period[19], but when there was a need for greater transfusion of blood products, mortality increased[14]. In the univariate analysis, women presented higher mortality, but there was no explanation for death in the model, as described in other studies[13,18].

The presence of ventricular arrhythmia (extrasystole) was associated with death in the univariate analysis and was explanatory of death in the model. We believe that its presence is a sign of ventricular dysfunction. Fukunaga *et al*.[20] reported that arrhythmias were a factor associated with hospital mortality in valve reoperations. The presence of ventricular extrasystoles (VES)>5VES/min is also considered an isolated preoperative risk factor in non-cardiac, elective surgeries and may also be related to myocardiopathy[21]. The prognosis of arrhythmia is related to the clinical manifestations of heart failure manifested by NYHA class III and IV, where myocardial injury due to valve dysfunction has usually occurred[4]. The presence of tricuspid reflux was associated with death in our series in the univariate analysis, but it was not explanatory of death in the model. However, Fukunaga *et al*.[22] suggest that the correction of severe tricuspid reflux should be performed to improve hospital mortality. Teman *et al*.[23] suggest that patients who will undergo mitral reoperation and have tricuspid reflux should be corrected prophylactically because they present lower mortality when the condition is less severe. The biological prosthesis implant was associated with higher mortality, but was not explanatory in the model. In routine reoperations, we prefer mechanical prosthesis implantation in young patients, in order to reduce the number of surgeries.

Thus, when the mechanical prosthesis is not performed, it is due to technical difficulties such as a calcified or small orifice ring, where there may be difficulty in the proper functioning of the prosthesis. Another situation that impairs the mechanical prosthesis implantation is the valve ring lesion or lesion of cardiac structures, usually the atrioventricular disjunction, when the mortality is high[20]. It is noteworthy that in these cases there was increased ECT, renal insufficiency, cardiac lesions, situations related to higher mortality[6,15,18,20]. The risk of severe malnutrition was associated with death, but it was not explanatory in our model.

The incidence of high-risk patients classified by MUST[11] was 77% in the Death Group. These patients are generally associated with higher mortality, prolonged use of antibiotics, low cardiac output, greater use of inotropes and positive blood cultures[24]. MUST was the preferred score for stratifying the risk of malnutrition in the population with indication for cardiac surgery[25]. The greatest cause of death was low cardiac output syndrome in eight patients, and one patient died due to occlusion of the tracheostomy cannula by secretion. Other causes associated with death in the univariate analysis were: bronchopneumonia, sepsis, SIRS, which can be considered terminal phases, as described in other studies[6,16,20], but in the model they were not explanatory.

Prediction in cardiac surgery adopts a score based on factors considered as predictors of death or complications, but the literature is still not consensual about the best predictive system to be used[26]. Currently there are more than 20 models of risk scores in cardiac surgery[27]. Among them, the most well-known and used is the EurosCORE II (European System For Cardiac Operative Risk)[10]. However, EuroSOCORE was designed for an older population with a low incidence of rheumatic disease and is not specific for valve surgery. This heterogeneity reported in the studies is a great problem in comparing the results in smaller centers[13]. On the other hand, Onorati *et al*.[6] described the first multicenter European study, in which eight centers participated. Similarly, they found limitations, such as retrospective information recording, surgical routine different from each participating center, and differences among the population, but it would be closer to reality. Hence, we devised a score appropriate to our local population, trying to estimate hospital mortality more accurately. The deviation analysis showed that the model is significant ($p<0.0000$) and the seven variables explained 99.95% of the data variance. Factors that affect patient outcomes are numerous and often confound the rigor of the analyzes, so the result of the score should be evaluated in conjunction with the benefit of the procedure given by scientific knowledge, with team and patient autonomy in making decision and discussion of ethical principles. However, for validation, the score should be tested in a prospective multicenter study and compared to other prediction models. The description of the frequency of the EuroSCORE is another tool that can aid decision making.

We conclude that the identification of risk factors and the creation of a predictive risk model appropriate to our reality, associated to the performance of the EuroSCORE, are important tools in improving survival in mitral reoperation.

R E S U M O

Objetivo: *identificar os fatores associados à mortalidade em reoperação valvar mitral, criar um modelo preditivo de mortalidade e avaliar o EuroSCORE.* **Métodos:** *foram avaliados 65 pacientes submetidos à reoperação de valva mitral no período de janeiro de 2008 a dezembro de 2017. Foi verificada a associação das variáveis com o óbito e criado um modelo de regressão logística múltiplo para estratificar os pacientes.* **Resultados:** *a mortalidade hospitalar foi de 13,8% e, neste grupo, o EuroSCORE foi de 12,33±8,87 (p=0,017), a fração de ejeção do ventrículo esquerdo (FEVE) foi de 45,33±5,10 (p=0,000), a creatinina foi 1,56±0,29 (p=0,002), o tempo de atividade da protrombina (TAP): 1,64±0,15 (p=0,001), pressão sistólica da artéria pulmonar (PSAP): 66,1±13,6 (p=0,002), sexo feminino: 88% (p=0,000), desnutrição: 77,7% (p=0,007), doença tricúspide associada: 44,4% (p=0,048), presença de arritmia ventricular: 77,7% (p=0,005), implante de prótese biológica: 55,5% (p=0,034), broncopneumonia e sepse: 33,3% (p=0,048), síndrome da resposta inflamatória sistêmica (SIRS): 55,5% (p=0,001), síndrome do baixo débito cardíaco: 88,8% (p=0,000).* **Conclusão:** *os fatores associados à mortalidade foram: EuroSCORE, FEVE, creatinina, TAP, PSAP, sexo feminino, desnutrição, doença tricúspide, arritmia ventricular, implante de prótese biológica, SIRS, SBDC, broncopneumonia e sepse. As variáveis explicativas de óbito do modelo foram: EuroSCORE, creatinina, TAP, FEVE, tempo de internamento na unidade de terapia intensiva (UTI), intervalo entre cirurgias e presença de arritmia ventricular. O EuroSCORE elevado está relacionado à maior mortalidade.*

Descritores: *Valva Mitral. Fatores de Risco. Reoperação. Mortalidade Hospitalar.*

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