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# Surgical treatment for infective endocarditis and hospital mortality in a Brazilian single-center

## *Tratamento cirúrgico para endocardite infecciosa e mortalidade hospitalar em centro único brasileiro*

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*Abstract*

***Objective:*** **We evaluated patients underwent cardiac valve surgery in the presence of infective endocarditis in an attempt to identify independent predictors of 30-day mortality.**

***Methods:*** **We evaluated 837 consecutive patients underwent cardiac valve surgery from January 2003 to May 2010 in a tertiary hospital in São José do Rio Preto, São Paulo (SP), Brazil. The study group comprised patients who underwent intervention in the presence of infective endocarditis and was compared to the control group (without infective endocarditis), evaluating perioperative clinical outcomes and 30-day all cause mortality.**

***Results:*** **In our series, 64 patients (8%) underwent cardiac valve surgery in the presence of infective endocarditis, and 37.5% of them had surgical intervention in multiple valves. The study group had prolonged ICU length of stay (16%), greater need for dialysis (9%) and higher 30-day mortality (17%) compared to the control group (7%, *P*=0.020; 2%, *P*=0.002 and 9%, *P*=0.038; respectively). In a Cox regression analysis, age (*P* = 0.007), acute kidney injury (*P* = 0.004), dialysis (*P* = 0.026), redo surgery (*P* = 0.026), re-exploration for bleeding (*P* = 0.013), tracheal reintubation (*P* <0.001) and type I neurological injury (*P* <0.001) were identified as independent predictors for death. Although the manifestation of infective endocarditis influenced on mortality in univariate analysis, multivariate Cox regression analysis did not confirm such variable as an independent predictor of death.**

***Conclusion:*** **Age and perioperative complications stand out as predictors of hospital mortality in Brazilian population. Cardiac valve surgery in the presence of active infective endocarditis was not confirmed itself as an independent predictor of 30-day mortality.**

***Descriptors:*** **Bacterial endocarditis. Cardiac surgical procedures. Hospital mortality.**

*Resumo*

***Objetivo:*** **Avaliamos pacientes submetidos à cirurgia valvar em vigência de endocardite infecciosa na tentativa de identificar preditores independentes de mortalidade intra-hospitalar em 30 dias.**

***Métodos:*** **Foram avaliados 837 pacientes consecutivamente submetidos à cirurgia valvar, no período de janeiro de 2003 a maio de 2010, em um hospital terciário de São José do Rio Preto, SP, Brasil. O Grupo de Estudo compreendeu indivíduos submetidos à intervenção em vigência de endocardite infecciosa e foi comparado ao Grupo Controle, considerando complicações clínicas perioperatórias e óbito por todas as causas em 30 dias.**

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| Abbreviations, Acronyms & Symbols | |
|---|---|
| **CG** | Control group |
| **CI** | Confidence interval |
| **CVS** | Cardiac valve surgery |
| **SG** | Study group |
| **EuroSCORE** | European System for Cardiac Operative Risk Evaluation |
| **HR** | Hazard ratio |
| **ICU** | Intensive care unit |
| **IE** | Infective endocarditis |
| **SD** | Standard deviation |

***Resultados:*** **Em nossa casuística, 64 (8%) pacientes foram submetidos à cirurgia valvar em vigência de endocardite infecciosa, sendo 37,5% deles com indicação de intervenção cirúrgica em múltiplas valvas. O Grupo de Estudo apresentou maior permanência em Unidade de Terapia Intensiva (16%), necessidade de diálise (9%) e maior mortalidade em 30 dias (17%) comparado ao Grupo Controle (7%, *P*=0,020; 2%, *P*=0,002 e 9%, *P*=0,038; respectivamente). A análise de regressão de Cox confirmou idade (*P*=0,007), lesão renal aguda (*P*=0,004), diálise (*P*=0,026), reoperação (*P*=0,026), reintervenção por sangramento (*P*=0,013), reintubação orotraqueal (*P*<0,001) e lesão neurológica tipo I (*P*<0,001) como preditores independentes para óbito. Embora a manifestação de endocardite infecciosa influencie na mortalidade na análise univariada, a regressão de Cox não confirmou tal variável como preditor independente de óbito em nossa casuística.**

***Conclusão:*** **Idade e complicações perioperatórias destacam-se como preditores de mortalidade hospitalar em população brasileira. Cirurgia valvar em vigência de infecção ativa não se confirma como preditor independente de óbito nesta casuística.**

***Descritores:*** **Endocardite bacteriana. Procedimentos cirúrgicos cardíacos. Mortalidade hospitalar.**

## INTRODUCTION

Surgical mortality for infective endocarditis (IE), while declining in the last decades, stands out as an important cause of death in native or prosthetic valve interventions [1-3], justifying early diagnosis and appropriate antibiotic therapy as key points to the success of the treatment [4].

Clinical complications and treatment failure may suggest surgical valve replacement for IE by up to 60% of cases [5-7]. However, due to possible association between increased incidence of postoperative complications and mortality, the real benefit of early surgical intervention on IE remains doubtful [8].

In the absence of adequate treatment, IE can be fatal. Despite the medical and surgical treatment being able to modify the course of disease, mortality remains high, ranging from 17% to 36% of cases according to the population studied [9,10]. In this context, this study evaluated the mortality of patients undergoing cardiac valve surgery (CVS) in the presence of IE in an attempt to identify independent predictors of 30-day mortality in a regional referral center.

## METHODS

This study evaluated 837 patients admitted to the São José do Rio Preto Medical School Cardiac Surgery Postoperative Intensive Care Unit after CVS from January 2003 to May 2010. This Brazilian Hospital is a regional tertiary referral service with 540 beds for a population demand of 1.5 million inhabitants. In this research, patients were divided into two groups: (SG) study group, subjects undergoing CVS in the presence of IE; and (CG) control group, consisting of patients with CVS performed in the absence of IE. The analysis was conducted as a prospectively historical type, including gathering information on the local computer database. The constitution of SG considered the recent recommendations of the American College of Cardiology / American Heart Association for IE surgical approach [11]. This study was approved by the São José do Rio Preto Medical School Ethics Committee (6079/2010) and, because of its observational nature, the informed consent was waived.

We evaluated demographic data, clinical outcomes and complications occurred in the postoperative period, and 30-day all cause mortality. Categorical data are presented as absolute numbers and percentages, and continuous variables as mean ± standard deviation (SD) or median and interquartile, when applicable. Categorical data were compared by chi-square test or Fisher's exact test and continuous variables were compared using the nonparametric Mann-Whitney test. Survival curve was constructed to demonstrate the outcome of 30-day mortality for both groups. The Cox regression analysis was used to determine independent predictors of 30-day mortality. Hazard ratio (HR) and 95% confidence intervals (95% CI) were calculated for predictors of mortality. The analysis was performed with the SPSS software (version 20) and *P* value <0.05 (two-tailed) was considered statistically significant.

## RESULTS

In our series, 64 (8%) patients underwent CVS in the presence of IE, and 37.5% had surgical intervention in multiple valves. In the SG there was predominance of males (67%) lower body mass index (23 kg/m$^2$), greater value for

European System for Cardiac Operative Risk Evaluation (EuroSCORE) (9 points), and greater cardiopulmonary bypass time (100.5 min) compared to CG (47%, $P = 0.002$, 24 kg/m², $P = 0.028$, 90 min, $P = 0.020$ and 4 points, $P < 0.001$, respectively). Table 1 shows the demographic and baseline characteristics of all groups.

The analysis of clinical outcomes demonstrated that the EG had a higher percentage of subjects with prior cardiac valve surgery (47%), higher prolonged intensive care unit (ICU) length of stay (over 14 days) (16%) and need for dialysis (9%) compared to CG (28%, $P = 0.001$; 7%, $P = 0.020$ and 2%, $P = 0.002$, respectively, Table 2). Consequently, patients undergoing CVS in the presence of IE had higher 30-day mortality (17%) compared to those without active infection (9%, $P = 0.038$).

The following variables were included in the univariate Cox analysis: age (years), male gender, body mass index (kg/m²), readmission to intensive care, diabetes mellitus, CVS in the presence of IE, multiple valve surgery, acute kidney injury, dialysis, left ventricular systolic dysfunction moderate or severe, redo surgery, reoperation for bleeding, tracheal reintubation and type I neurological injury. Table 3 shows the variables associated with 30-day mortality, highlighting age ($P = 0.007$), acute kidney injury ($P = 0.004$), dialysis ($P = 0.026$), redo surgery ($P = 0.026$), reoperation for bleeding ($P = 0.013$), tracheal reintubation ($P < 0.001$) and type I neurological injury ($P < 0.001$) as independent predictors of death determined by multivariate Cox regression model. Cardiac valve surgery in the presence of infective endocarditis was a predictor of death in the non adjusted analysis (HR = 1.96, 95% CI = 1.04 - 3.70, $P = 0.038$, Figure 1). However, after adjustment for predictors in the multivariate model, this variable was not independent ($P = 0.06$).

Table 1. Demographic data and baseline characteristics of patients.

| Baseline Characteristics | All Patients n 837 | Endocarditis ( + ) n 64 | Endocarditis ( - ) n 773 | *P* |
|---|---|---|---|---|
| Age (median, Q1 e Q3) | 52 (40 – 61) | 52,5 (40 – 61) | 52 (40 – 61) | 0.902 |
| Men [n (%)] | 405 (48%) | 43 (67%) | 362 (47%) | 0.002 |
| BMI (median, Q1 e Q3) | 24 (22 – 28) | 23 (20 – 26) | 24 (22 – 28) | 0.028 |
| Diabetes Mellitus [n (%)] | 46 (5%) | 4 (6%) | 42 (5%) | 0.773 |
| Mitral Valve Surgery [n (%)] | 602 (72%) | 43 (67%) | 559 (72%) | 0.380 |
| Aortic Valve Surgery [n (%)] | 374 (45%) | 33 (52%) | 341 (44%) | 0.249 |
| Tricuspid Valve Surgery [n (%)] | 213 (25%) | 17 (27%) | 196 (25%) | 0.831 |
| Multiple Valve Surgery [n (%)] | 300 (36%) | 24 (37,5%) | 276 (36%) | 0.854 |
| LV Dysfunction moderate/severe [n (%)] | 121 (14%) | 10 (16%) | 111 (14%) | 0.782 |
| ECC Time (median, Q1 e Q3) | 91 (76 – 113) | 100,5 (80 – 125) | 90 (75 – 111,5) | 0.020 |
| Additive EuroScore (median, Q1 e Q3) | 5 (3 – 6) | 9 (6 – 11) | 4 (3 – 6) | <0.001 |

*n= number of individuals; Q1 and Q3 in reference to Quartis 25% and 75%; BMI= body mass index; LV= left ventricle; ECC= extracorporeal circulation*

Table 2. Perioperative clinical complications.

| Clinical complication | All Patients n 837 | Endocarditis ( + ) n 64 | Endocarditis ( - ) n 773 | *P* |
|---|---|---|---|---|
| Length of ICU stay (median, Q1 e Q3) | 2 (2 – 4) | 4 (2 – 11) | 2 (2 – 4) | 0.006 |
| ICU Readmission [n (%)] | 47 (6%) | 2 (3%) | 45 (6%) | 0.571 |
| Length of ICU stay > 14 days [n (%)] | 61 (7%) | 10 (16%) | 51 (7%) | 0.020 |
| Reoperation [n (%)] | 246 (29%) | 30 (47%) | 216 (28%) | 0.001 |
| Reintervention for bleeding [n (%)] | 33 (4%) | 0 (0%) | 33 (4%) | 0.168 |
| AF [n (%)] | 78 (9%) | 1 (2%) | 77 (10%) | 0.026 |
| Reintubation for lung complications [n (%)] | 106 (13%) | 9 (14%) | 97 (13%) | 0.726 |
| Acute Renal Failure [n (%)] | 222 (27%) | 20 (31%) | 202 (26%) | 0.373 |
| Dialysis [n (%)] | 19 (2%) | 6 (9%) | 13 (2%) | 0.002 |
| Mediastinitis [n (%)] | 23 (3%) | 0 (0%) | 23 (3%) | 0.248 |
| Neurological disorder type I [n (%)] | 39 (5%) | 2 (3%) | 37 (5%) | 0.761 |
| Death in 30 days [n (%)] | 82 (10%) | 11 (17%) | 71 (9%) | 0.038 |

*n= number of individuals; ICU= Intensive Care Unit; Q1 and Q3 in reference to Quartis 25% and 75%; AF= atrial fibrillation*

Table 3. Independent predictors for hospital mortality in 30 days.

| Independent predictors for hospital mortality | B | Wald | HR | CI 95% | *P* Value |
|---|---|---|---|---|---|
| Univariate analysis | | | | | |
| Infective endocarditis | 0.673 | 4.318 | 1.96 | 1.04 – 3.70 | 0.038 |
| Age (years) | 0.035 | 18.339 | 1.04 | 1.02 – 1.05 | <0.001 |
| Men | -0.135 | 0.372 | 0.87 | 0.57 – 1.35 | 0.542 |
| BMI (kg/m$^2$) | -0.018 | 0.554 | 0.98 | 0.94 – 1.03 | 0.457 |
| Readmission in ICU | 0.954 | 8.668 | 2.60 | 1.38 – 4.90 | 0.003 |
| Diabetes Mellitus | 0.641 | 2.969 | 1.90 | 0.92 – 3.94 | 0.085 |
| Multiple valve surgery | 0.493 | 9.644 | 1.64 | 1.20 – 2.23 | 0.002 |
| Acute renal failure | 1.767 | 57.483 | 5.85 | 3.71 – 9.24 | <0.001 |
| Dialysis | 2.419 | 63.101 | 11.24 | 6.19 – 20.41 | <0.001 |
| LV Dysfunction Moderate/Severe | 0.197 | 0.452 | 1.22 | 0.69 – 2.17 | 0.501 |
| Reoperation | 0.927 | 17.597 | 2.53 | 1.64 – 3.89 | <0.001 |
| Reintervention for bleeding | 1.943 | 46.110 | 6.98 | 3.98 – 12.23 | <0.001 |
| Reintubation | 2.162 | 95.180 | 8.69 | 5.63 – 13.41 | <0.001 |
| Neurological dysfunction type I | 1.885 | 49.689 | 6.59 | 3.90 – 11.12 | <0.001 |
| | | | | | |
| Multivariate analysis | | | | | |
| Age | 0.024 | 7.214 | 1.03 | 1.01 – 1.04 | 0.007 |
| Acute renal failure | 0.806 | 8.389 | 2.24 | 1.30 – 3.86 | 0.004 |
| Dialysis | 0.771 | 4.946 | 2.16 | 1.10 – 4.27 | 0.026 |
| Reoperation | 0.528 | 4.937 | 1.70 | 1.06 – 2.70 | 0.026 |
| Reintervention for bleeding | 0.769 | 6.217 | 2.16 | 1.18 – 3.95 | 0.013 |
| Reintubation | 1.076 | 16.580 | 2.93 | 1.75 – 4.92 | <0.001 |
| Neurological dysfunction type I | 1.093 | 14.531 | 2.98 | 1.70 – 5.24 | <0.001 |

*HR=Hazard Ratio; CI= Confidence Interval; BMI= body mass index; k=kilogram; m=meter; ICU= intensive care unit*

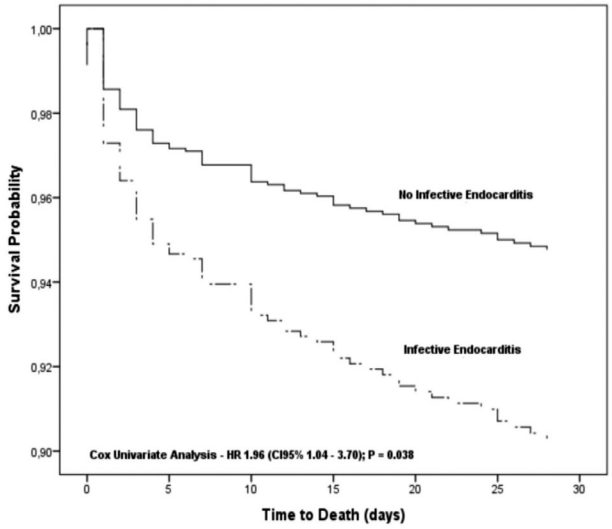


*Fig. 1 – In-hospital survival curve following 30 days*

## DISCUSSION

Despite the current knowledge including prevention, diagnosis and treatment, IE remains a not rare cause of hospitalization with high morbidity and mortality [12,13]. In our analysis, we found 8% of valve-related surgery approaching to IE, percentage similar to that observed in national, North American and European casuistic [14-16]. Moreover, we confirmed high 30-day mortality (17%) for patients undergoing CVS in the presence of active infection, as recently reported by Prendergast & Tornos (ranging from 6% to 25%) [17]. However, the surgical approach in the presence of IE wasn't confirmed as an independent predictor of death in our series.

Our series of patients considered subjects with high severity disease transferred from other hospitals for surgery treatment with established diagnosis of IE, justified by the infection refractory to medical treatment. In this context, factors such as age, comorbidities, clinical presentation and surgical technique used in valve approach can influence the postoperative results [18,19]. Although there is no statistical difference between the groups in age, this variable was found as an independent predictor of 30-day mortality in patients with IE, reinforcing results of Murdoch et al. [20]. Furthermore, in contrast to data of Chirillo et al. [21], the prevalence of diabetes mellitus was similar between the groups do not representing a risk factor for poor clinical outcome in patients with active IE

undergoing CVS. Although evidenced greater proportion of male gender and lower body mass index in EG, these parameters were not associated with worse postoperative prognosis. The higher cardiopulmonary bypass duration in this group may reflect the greater surgical difficulty for a complete removal of the cardiac valve in patients with IE [17].

The International Collaboration on Endocarditis-Prospective Cohort Study [20] reported 17.7% of overall in-hospital mortality for patients with IE, while Wallace et al. [22] reported 15% mortality in the group undergoing medical treatment and 22% for those who underwent additional surgery. Still, the hospital mortality in patients with valvular abscess due to complications of IE has been reported as 19.2% in Brazilian patients [23]. Similarly, the present study found a hospital mortality rate of 17% at 30 days for patients undergoing CVS due to IE and prolonged ICU length of stay, probably reflecting the severity of sepsis in these individuals [24-26]. However, the anatomical location of the valve infection was similar among the groups, confirming the absence of its association with clinical complications, including mortality, reflecting results previously presented by Rostagno et al. [13].

In this context, the presence of signs of heart failure, persistent infection, acute kidney injury, thrombocytopenia, paravalvular abscess at echocardiography and need for urgent surgery are indicated as predictors of hospital mortality [27-29]. Several studies have associated renal dysfunction with worse prognosis in the evolution and treatment of IE, reporting sepsis, lesions in glomerular architecture and antibiotic toxicity as etiologic factors [22,30,31]. Results of this analysis confirmed the acute kidney injury requiring dialysis as independent predictors of hospital mortality.

This study demonstrated that reoperation, including re-exploration due to postoperative bleeding, was also a predictor of 30-day mortality. Attempting to decrease perioperative mortality for valve replacement surgery in the presence of IE, Musci et al. [32] recently proposed valvuloplasty as an effective alternative in previously selected cases, with consequent reduction in the need for reoperation and recurrent infections, but this surgical modality was not evaluated in this analysis. Besides these factors, the type I neurological injury and tracheal reintubation stood out as predictors of mortality in patients undergoing CVS in the presence of IE, in agreement with previous studies [33,34]. In this case, the manifestation of encephalopathy due to cardiovascular surgical procedure or severe sepsis, characterized by altered mental status or focal neurological deficit without evidence of impairment in anatomical imaging methods may have contributed definitely to returning to invasive mechanical ventilation and consequent high risk of in-hospital deaths.

**Study limitations**

Studies related to IE approach are limited by its low relative frequency, the huge variability of the population affected and their underlying risk factors, represented mostly by series of case reports or single centers experience. In our sample, due to the small number of valve involvement by IE, there was limitation in demonstrating the relationship between prognosis, native or prosthetic valve involvement and etiologic agent identified in blood cultures, a fact worsen by the wide range of pathogens involved in its manifestation, affecting the scope and statistical power to draw definitive conclusions. Further investigations are needed to evaluate whether more sensitive prognostic markers may improve the detection of high-risk patients for whom aggressive surgical valve treatment during an IE can really contribute to the reduction of in-hospital mortality.

## CONCLUSION

Although hospital mortality rate for patients undergoing cardiac valve surgery due to refractory infective endocarditis remains high in the Brazilian population, the surgical approach during an active infection is not confirmed as an independent predictor of death in our series.

In this case, age, acute kidney injury, dialysis, redo surgery, re-exploration for bleeding, tracheal reintubation and type I neurological injury stand out as predictors of in-hospital mortality (30 days) in this population.

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