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ORIGINAL ARTICLE

# Analysis of the SHARPEN Score in the Prediction of In-Hospital Mortality of Patients With Infective Endocarditis Undergoing Cardiac Surgery

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## Abstract

**Background:** The SHARPEN score was developed to predict in-hospital mortality in patients hospitalized for infective endocarditis (IE), undergoing or not undergoing cardiac surgery. A comparison with other available scores has not yet been carried out.

**Objective:** To evaluate the performance of the SHARPEN score in predicting in-hospital mortality in patients hospitalized for IE undergoing cardiac surgery and compare it with that of both nonspecific and IE-specific surgical scores.

**Methods:** Retrospective cohort study including all admissions of patients ≥18 years who underwent cardiac surgery due to active IE (modified Duke criteria) at a tertiary care university hospital between 2007 and 2016. The SHARPEN score was compared to the EuroSCORE, EuroSCORE II, STS-IE, PALSUSE, AEPEI, EndoSCORE and RISK-E scores. Differences P<0.05 were considered statistically significant.

**Results:** A total of 105 hospitalizations of 101 patients (mean age 57.4±14.6 years; 75.2% male) were included. The median SHARPEN score was 11 (9-13) points. The observed in-hospital mortality was 29.5%. There was no statistically significant difference in observed vs. estimated mortality (P = 0.147), with an area under the ROC curve of 0.66 (P = 0.008). In comparison with the other scores, no difference was observed in discriminative ability. The statistics of the SHARPEN score at a cutoff >10 points — positive predictive value (PPV): 38.1%, 95%CI:30.4-46.6; negative predictive value (NPV): 80.0%, 95%CI:69.8-87.4; and accuracy: 58.1%, 95%CI:48.1-67.6 — showed overlapping 95%CIs, indicating no significant difference between scores.

**Conclusions:** The SHARPEN score did not present parameters with a significant difference in relation to the other scores analyzed; despite the easy obtainment of its few variables, it has limited applicability in clinical practice, like other existing scores.

**Keywords:** Endocarditis; Cardiac Surgical Procedures; Hospital Mortality.

## Introduction

Despite advances in its medical and surgical treatment, infective endocarditis (IE) remains associated with severe complications and high mortality. The presentation and course of IE are highly variable, depending on host factors (preexisting heart disease, prosthetic valve, implantable cardiac device), the causative organism, and the adequacy of treatment (antibiotics, surgery). The interaction of these factors results in an in-hospital mortality rate for patients with IE ranging from 15 to 30%.[1] Surgical treatment is required in approximately half of patients with IE due to severe complications. Reasons for considering surgery early in the active phase (while the patient is still receiving antibiotic treatment) are to avoid progressive heart failure and irreversible structural damage caused by severe infection, as well as to prevent systemic embolization. On the other hand, surgical therapy during the active phase of IE is associated with significant risk.[2]

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**Central Illustration: Analysis of the SHARPEN Score in the Prediction of In-Hospital Mortality of Patients With Infective Endocarditis Undergoing Cardiac Surgery**

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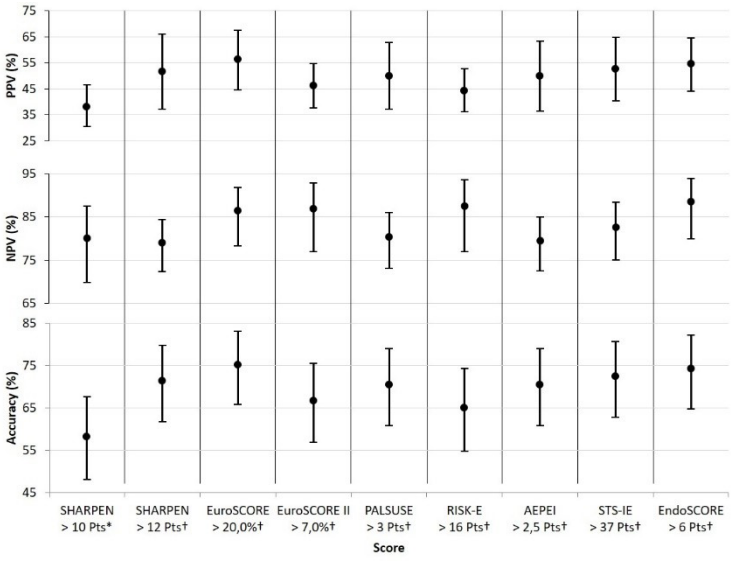


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*PPV, NPV, and accuracy of the analyzed scores, according to the cutoff point. Observed mortality was 29.5%, except for the RISK-E, which was 29.0%: five cases of pulmonary/tricuspid OE were excluded, as they are not included in the analysis of this score. Error bars denote the 95% CI.*
*NPV: negative predictive value; PPV: positive predictive value; Pts: points.*
**Cutoff point for the high-risk category according to the original score study.*
*†Cutoff point defined according to Youden's J index*

Prognostic scores are a reasonable estimate of the risk of death, which is important in clinical decision-making regarding indications for surgery. Estimates are needed to inform patients and their families about surgical risks, and risk stratification allows for a fair comparison of cardiac surgery outcomes, so that surgeons and hospitals treating high-risk patients do not appear worse off than others.[3] The performance of traditional surgical scores (EuroSCORE and EuroSCORE II) and IE-specific scores (STS-IE, PALSUSE, AEPEI, EndoSCORE, RISK-E) in predicting surgical risk in patients undergoing cardiac surgery for IE was recently evaluated in a Brazilian cohort.[4] In that study, the best performer in terms of predicting mortality risk was the EuroSCORE when taking both discrimination power and calibration (observed-to-estimated mortality ratio) into account. However, previous work showed conflicting results, with the EuroSCORE underperforming compared to an IE-specific score (STS-IE).[5] These differences in the literature support the hypothesis that, to date, no single score has proven to be ideal to identify patients with IE at greater risk for in-hospital mortality.

The SHARPEN score was developed to predict in-hospital mortality in hospitalizations secondary to IE in patients undergoing or not undergoing cardiac surgery.[6] Unlike other scores, the SHARPEN score is composed of clinical variables that are readily obtained, which could facilitate its use in clinical practice. Analysis of SHARPEN in a Brazilian cohort in a tertiary care center showed performance similar to that described in the original cohort.[7] Within this context, the objective of the present study was to evaluate the SHARPEN score as a predictor of in-hospital mortality in hospitalized patients with IE who underwent cardiac surgery, and to compare it with traditional and IE-specific surgical scores – an analysis not performed in the literature yet.

## Methods

Retrospective cohort study including all admissions between 2007 and 2016 of patients aged ≥18 years who underwent cardiac surgery due to active IE at *Hospital de Clínicas de Porto Alegre* (HCPA), a tertiary public teaching hospital in southern Brazil. Only patients with definitive IE, diagnosed according to the modified Duke criteria,[8] were included; those whose electronic medical records were unavailable were excluded. Patients were identified from the surgical booking system and by a keyword search in the

electronic medical record system of HCPA. The present study was approved by the institutional Research Ethics Committee (protocol no. 16-0632).

The SHARPEN score[6] was calculated for each IE admission. Depending on the calculated score, admissions were classified as low- (2 to 6 points), moderate- (7 to 10 points), or high-risk (11 to 20 points). The parameters of interest were:

- **S**ystolic blood pressure <90 mmHg at presentation: 3 points;
- **H**eart failure during hospitalization (Framingham criteria[9]): 2 points;
- **A**ge: <50 years: 2 points; 50-65 years: 4 points; >65 years: 6 points;
- **R**aised serum creatinine at admission (>2.26 mg/dL): 2 points;
- **P**neumonia (≥48 hours after admission): 2 points;
- **E**levated C-reactive protein (peak >200 mg/L during hospitalization): 2 points;
- **N**on-intravenous drug abuser: 3 points.

The performance of the SHARPEN score was compared with that of the logistic EuroSCORE[10] and EuroSCORE II,[11] as well as the IE-specific STS-IE,[12] PALSUSE,[13] AEPEI,[14] EndoSCORE,[15] and RISK-E[16] scores. Any death during hospitalization, regardless of length of stay, was defined as in-hospital mortality. Creatinine clearance (CrCl) was estimated using the Cockcroft–Gault formula.[17]

Preoperative critical status was defined as the presence of one of the following during the same hospitalization: ventricular tachycardia/fibrillation or aborted sudden death, cardiopulmonary resuscitation, mechanical ventilation before induction of anesthesia, administration of inotropic agents, use of intra-aortic balloon pump/ventricular assist device before induction of anesthesia, or acute kidney injury (anuria or oliguria [urinary output <10 mL/h]).[11] Active IE (still on antibiotics at the time of surgery), chronic lung disease, extracardiac arteriopathy, reduced mobility (severe mobility impairment secondary to neuro-musculoskeletal dysfunction), recent myocardial infarction (≤90 days), severe pulmonary artery hypertension (systolic pulmonary artery pressure >55 mmHg), severe kidney injury (CrCl <50 mL/min), and urgency of surgery were also defined according to the EuroSCORE II criteria.[11]

## Statistical analysis

Data were collected directly from patients' electronic medical records and analyzed using IBM SPSS 21.0, MedCalc 12.5, and OpenEpi 3.01.16 software. Qualitative data were described as absolute and relative frequencies; mean (standard deviation) or median (interquartile range, IQR) were used for quantitative data as appropriate, depending on the normality of distribution, as determined by the Shapiro-Wilk test. In-hospital mortality was compared between groups using the chi-square test or Fisher's exact test, as appropriate. The optimal cut-off point for continuous scores was defined using the highest Youden's J index, as calculated by the equation "(sensitivity + specificity) – 1". Calibration (expressed as the observed-to-estimated [O/E] mortality ratio, *i.e.*, the standardized mortality ratio [SMR]) and the discriminative ability (expressed by the area under the receiver operating characteristic curve [AUC-ROC]) of the scores were evaluated. The mid-p exact test with Miettinen's modification was used to calculate the SMR with a 95% confidence interval (CI). AUC-ROC comparisons were performed using the DeLong test. P-values <0.05 were considered significant.

## Results

We studied 105 hospitalizations of 101 patients (four patients had two hospitalizations each) for active IE, who underwent cardiac surgery, between 2007 and 2016. Of the 107 hospitalizations initially retrieved, two (1.9%) were excluded due to unavailability or inaccessibility to the electronic medical record. Characteristics of the sample are described in Table 1. Hemodialysis before surgery was performed in 22 hospitalizations (21.0%): 14 (13.3%) for chronic kidney disease (CKD), six (5.7%) for acute kidney injury, and two (1.9%) for acute-on-CKD.

The leading indication for surgery was heart failure (n = 49; 46.7%); the main procedures performed were mechanical aortic valve replacement (n = 24; 22.9%), biological aortic valve replacement (n = 22; 21.0%), and biological mitral valve replacement (n = 22; 21.0%). The median (IQR) time between prescription of antibiotics and surgery was 13 (6-22) days.

The median (IQR) SHARPEN score was 11 (9-13) points. The prevalence of each score component is described in detail in Table 2. Overall, 10 admissions (9.5%) were characterized as low-risk, 40 (38.1%) as moderate-risk, and 55 (52.4%) as high-risk.

The observed in-hospital mortality was 29.5% (95%CI: 20.8-38.2%); 20.0% in admissions stratified as low or moderate risk and 38.1% in high-risk admissions (P = 0.068). Low- and moderate-risk admissions were pooled for this analysis due to the limited representativeness of the former.

**Table 1 – Baseline characteristics of the sample**

| Variable | n = 105 |
|---|---|
| Age (years) | 57.4 ± 14.6 |
| Male sex | 79 (75.2) |
| Hypertension | 58 (55.2) |
| NYHA functional class III/IV | 52 (49.5) |
| Valve abscess | 39 (37.1) |
| Previous heart surgery | 33 (31.4) |
| Severe PAH (>55mmHg) | 30 (28.6) |
| Prosthetic valve IE | 29 (27.6) |
| Severe renal failure (CrCl <50 mL/min)* | 23 (21.9) |
| Hemodialysis | 22 (21.0) |
| Preoperative critical status | 20 (19.0) |
| Thrombocytopenia | 19 (18.1) |
| LVEF ≤50% | 16 (15.2) |
| IDDM | 13 (12.4) |
| Previous IE | 10 (9.5) |
| Extracardiac arteriopathy | 8 (7.6) |
| Previous MI | 8 (7.6) |
| Reduced mobility | 7 (6.7) |
| Chronic lung disease | 6 (5.7) |
| Recent MI | 3 (2.9) |
| CCS class IV angina | 1 (1.0) |
| **Site of IE** | |
| Aortic valve | 45 (42.9) |
| Mitral valve | 35 (33.3) |
| Aortic + mitral valves | 20 (19.0) |
| Tricuspid valve | 4 (3.8) |
| Tricuspid + mitral valves | 1 (1.0) |
| Causative pathogen identified | 70 (66.7) |
| *Streptococcus viridans* | 19 (18.1) |
| *Enterococcus sp.* | 10 (9.5) |
| *Staphylococcus aureus* | 9 (8.6) |
| **Urgency of procedure** | |
| Urgent | 96 (91.4) |
| Emergent | 9 (8.6) |
| CABG | 8 (7.6) |
| On-pump time (min) | 83 (63-110) |
| Ischemic time (min) | 64 (51-84) |
| Logistic EuroSCORE | 14.8 (8.1-29.5) |
| EuroSCORE II | 6.9 (3.3-13.6) |

*CABG: coronary artery bypass grafting; CCS: Canadian Cardiovascular Society; HF: heart failure; IDDM: insulin-dependent diabetes mellitus; IE: infective endocarditis; LVEF: left ventricular ejection fraction; MI: myocardial infarction; min: minutes; NYHA: New York Heart Association; PAH: pulmonary artery hypertension; IV: intravenous.*
** Patients undergoing hemodialysis preoperatively (n = 22; 21.0%) and those for whom body weight data were not available (n = 11; 10.5%) were excluded which made it impossible to calculate the CrCl.*
*Data are expressed as n (%), mean ± standard deviation, or median (interquartile range).*

There was no statistically significant difference in observed vs. estimated mortality in the overall analysis, nor in moderate-risk hospitalizations. Conversely, the observed mortality for low-risk hospitalizations was higher than estimated, while that of high-risk hospitalizations was lower than estimated (Figure 1). There was wide variability in estimated mortality among the analyzed scores (Figure 2). Besides the SHARPEN score, only EuroSCORE, PALSUSE, and RISK-E did not present a statistically significant difference between observed and estimated mortality (Table 3).

The AUC-ROC for the SHARPEN score was 0.66 (95%CI: 0.54-0.79; P = 0.008) (Figure 3). In comparison with the other scores (Table 3), there was no significant difference in discrimination, with only a trend for discriminative ability to be lower than that of the logistic EuroSCORE (P = 0.098) and EndoSCORE (P = 0.110).

Statistics for the SHARPEN score, and for the other scores analyzed, are shown in the Central Figure. An increase in positive predictive value (PPV) and in accuracy can be observed when adopting a cutoff of >12 points, defined according to Youden's J statistic, instead of the threshold used in the original study (>10 points). Using the original threshold, mortality was significantly higher (51.7 vs. 21.0%, P = 0.004). However, the CIs of these statistics – as well as those of the negative predictive value (NPV) – overlap, indicating absence of a statistically significant difference between them.

## Discussion

In this cohort of patients, the SHARPEN score was calibrated (P = 0.147), with no statistically significant difference in discriminative power (AUC-ROC = 0.66;

**Table 2 – Description of the SHARPEN score and patients' (n = 105) distribution by the variables**

| Acronym | Score component | Number (%) |
|---|---|---|
| S | SBP <90mmHg (at presentation) | 11 (10.5) |
| H | Heart failure* (during hospitalization) | 78 (74.3) |
| A | Age (years) | |
| | <50 years | 29 (27.6) |
| | 50-65 years | 41 (39.0) |
| | >65 years | 35 (33.3) |
| R | Creatinine >2.26 mg/dL (at admission) | 23 (21.9) |
| P | Pneumonia (≥48 hours after admission) | 20 (19.0) |
| E | CRP >200 mg/L (during hospitalization) | 36 (34.3) |
| N | Non-IV drug user | 100 (95.2) |

*IV: intravenous; SBP: systolic blood pressure; CRP: C-reactive protein. *According to Framingham criteria.[9]*

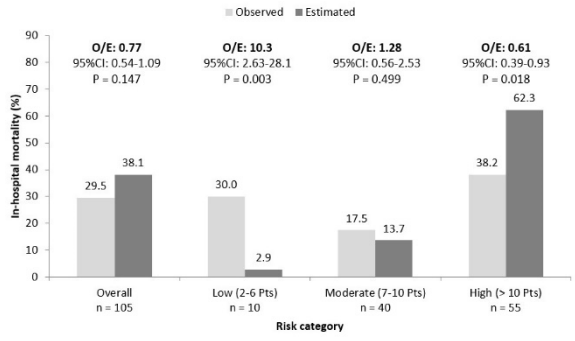


**Figure 1 – Observed/estimated in-hospital mortality and overall mortality by SHARPEN risk categories.**
*CI: confidence interval; O/E: observed/estimated; Pts: points.*

P = 0.008) in relation to the other tested scores. Likewise, the PPV, NPV, and accuracy of SHARPEN were not significantly different from those of the other scores included in this analysis. Compared to the original cohort,[6] there was a difference in O/E mortality ratio between the low- and high-risk groups, especially in the former (O/E: 10.3; P = 0.003). This difference may be explained by the fact that, while in the original study the proportion of patients undergoing cardiac surgery was 38.3%, our cohort was composed exclusively of surgical patients.

The possibility of using a tool that yields reliable prognostic information based on clinical variables alone is a potential advantage of this new score. In addition, these are objective variables, hence easy to obtain and standardize, which facilitates outcome measurement across different populations. In addition, the SHARPEN score does not include microbiological variables (which may be affected by issues such as difficult confirmation or slow-growing pathogens), unlike other STS-IEs, such as the STS-IE,[12] PALSUSE,[13] EndoSCORE,[15] and RISK-E.[16] However, as it incorporates two variables that can only be identified late in the admission (nosocomial pneumonia and peak C-reactive protein >200 mg/L), it may have limited value in early risk estimation.

In the original study cohort including 233 patients with an in-hospital mortality of 23.2%, of which only 51 (21.9%) underwent cardiac surgery, the score showed an AUC-ROC of 0.86 (95%CI: 0.80-0.91).[6] In the only study that validated the SHARPEN score in Brazil,[7] including 179 hospitalizations for IE in a public hospital, with an in-hospital mortality rate of 22.3% and cardiac surgery performed in 68 patients (38.0%), the score showed an AUC-ROC of 0.76 (95%CI: 0.67-0.85); 0.77 when only clinical treatment was performed and 0.72 in those requiring cardiac surgery. In this study, there was no analysis of specific mortality in the high-risk group (>10 points).

A key strength of the present analysis was the evaluation of the score performance in a cohort of exclusively hospitalizations in which cardiac surgery was performed, unlike the original cohort[6] and the subsequent Brazilian study that also evaluated the performance of the score.[7] Furthermore, while in the original study only 26.2% of admissions were categorized as high risk, in the present series they represented 52.4% of the total. On the other hand, while the feared *S. aureus* was the main etiologic agent in the original cohort (48.1%), in this cohort it was the cause of only 8.6% of hospitalizations. In the present study, we observed a nonsignificant increase in score accuracy when we adopted a higher cutoff point, raising the hypothesis that, perhaps, for high-risk surgical patients, the cutoff point should be higher; this will need to be confirmed in future cohorts.

Unlike previous studies and comparative studies, we chose to analyze the score statistics starting from a

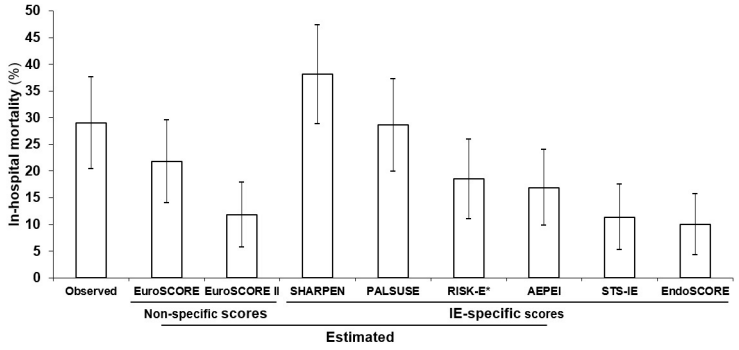


**Figure 2 – Observed and estimated in-hospital mortality according to the tested scores. *Observed mortality was 29.5%, except for the RISK-E, which was 29.0% (five cases of pulmonary/tricuspid IE were excluded, as they are not included in the analysis of this score). Error bars denote the 95% CI.**
*IE: infective endocarditis*

**Table 3 – Observed-to-estimated mortality ratio and ROC curve analysis for the studied scores**

| Score | O/E Mortality* | 95%CI | P | AUC-ROC | 95%CI | P |
|---|---|---|---|---|---|---|
| SHARPEN | 0.77 | 0.54-1.09 | 0.147 | 0.66 | 0.54-0.79 | 0.008 |
| Nonspecific scores | | | | | | |
| EuroSCORE | 1.37 | 0.94-1.91 | 0.094 | 0.77 | 0.67-0.87 | <0.001 |
| EuroSCORE II | 2.56 | 1.77-3.59 | <0.001 | 0.70 | 0.59-0.81 | 0.001 |
| IE-specific scores | | | | | | |
| PALSUSE | 1.04 | 0.72-1.46 | 0.790 | 0.71 | 0.60-0.82 | 0.001 |
| RISK-E | 1.20 | 0.82-1.71 | 0.320 | 0.71 | 0.61-0.82 | 0.001 |
| AEPEI | 1.76 | 1.22-2.47 | 0.004 | 0.65 | 0.53-0.77 | 0.014 |
| STS-IE | 2.58 | 1.79-3.62 | <0.001 | 0.68 | 0.57-0.80 | 0.003 |
| EndoSCORE | 2.98 | 2.06-4.18 | <0.001 | 0.77 | 0.66-0.87 | <0.001 |

*AUC-ROC: area under the ROC curve; CI: confidence interval; IE: infective endocarditis; O/E: observed-to-estimated mortality; STS-IE: IE-specific score. *Observed mortality was 29.5%, except for the RISK-E, which was 29.0%: five cases of pulmonary/tricuspid IE were excluded, as they are not included in the analysis of this score*

defined cutoff point, as we believe this information is more useful in daily clinical practice, and then define the best threshold through the optimal sensitivity and specificity ratio (Youden's index). Using the AUC-ROC allowed us to determine the overall accuracy of the score based on the analysis of all points in the score. Given a specific score, and the score of a given patient, patients can be placed in low- or high-risk groups, yielding an estimate (within a 95%CI) of the associated mortality.

The present study has limitations. The sample was relatively small and restricted to a single tertiary care center. The long period of analysis means that both clinical and surgical management of these patients may have changed over time. Finally, retrospective data collection can compromise the quality of the data obtained.

## Conclusions

Several research groups have been searched for the optimal prognostic score for risk stratification in cardiac

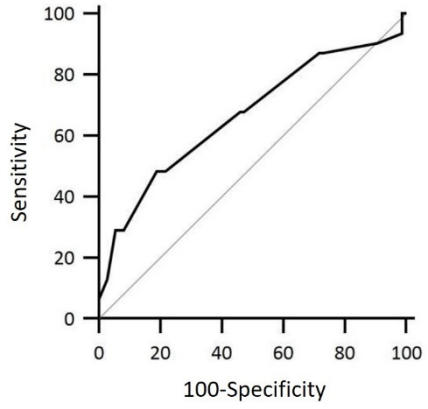


**Figure 3 – SHARPEN score ROC curve**

surgery in IE, although no one score has proven superior to others for this purpose.[18] The findings obtained in the present cohort corroborate this statement, since none of the tested scores could be considered ideal, with AUC-ROCs considered reasonable at best (0.7 < AUC-ROC ≤ 0.8), with maximum accuracy of 75.2%. Specifically in relation to the SHARPEN score, its properties did not differ significantly from those of the other analyzed scores; despite the easy obtainment of its few variables, it has limited applicability in clinical practice, like other existing scores.

## Author Contributions

Conception and design of the research: Gus M, Pivatto Júnior F; acquisition of data: Lech MC, Stefani J, Fabra LC, Pivatto Júnior F; analysis and interpretation of the data, writing of the manuscript and critical revision of the manuscript for intellectual content: Lech MC, Stefani J, Fabra LC, Gus M, Pivatto Júnior F; statistical analysis: Pivatto Júnior F.

### Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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There were no external funding sources for this study.

### Study Association

This study is not associated with any thesis or dissertation work.

### Ethics Approval and Consent to Participate

This study was approved by the Ethics Committee on Animal Experiments of the Hospital de Clínicas de Porto Alegre (HCPA) under the protocol number 16-0632.

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