ORIGINAL ARTICLE

Internal Validation of a Risk Score for Prediction of Postoperative Atrial Fibrillation after Cardiac Surgery

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Abstract

Background: Postoperative atrial fibrillation (POAF) after cardiac surgery has great clinical and economic implications. Many attempts have been made to identify risk factors aiming at a better evaluation of prophylactic treatment strategies.

Objective: To perform an internal validation of a risk score for POAF.

Methods: A prospective cohort of 1,054 patients who underwent myocardial revascularization and/or valve surgery was included. The risk score model was developed in 448 patients, and its performance was tested in the remaining 606 patients. Variables with a significance level of 5% in the cohort were included and subjected to a multiple logistic regression model with backward selection. Performance statistics was performed using the c-statistic, the chi-square and the Hosmer-Lemeshow (HL) goodness-of-fit, Pearson's correlation coefficient.

Results: Four variables were considered predictors of outcome: age (≥ 70 years), mitral valve disease, the non-use or discontinuation of beta-blockers and a positive water balance (> 1,500 mL). The ROC curve was 0.76 (95% confidence interval [CI]: 0.72-0.79). The risk model showed a good ability according to the performance statistics– HL test $x^2 = 0.93$; $p = 0.983$ and $r = 0.99$ (Pearson's coefficient). There was an increase in the frequency of POAF with the increase of the score: very low risk = 0.0%; low risk = 3.9%; intermediate risk = 10.9%; and high risk = 60.0%; $p < 0.0001$.

Conclusion: The predictive variables of POAF allowed us to construct a simplified risk score. This scoring system showed good accuracy and can be used in routine clinical practice. (Int J Cardiovasc Sci. 2020; 33(2):158-166)

Keywords: Atrial Fibrillation; Myocardial Revascularization; Heart Valves/surgery; Perioperative Care; Risk Score; Prevention and Control.

Introduction

Atrial fibrillation (AF) remains the most prevalent event in perioperative period of cardiac surgery, with an incidence varying from 20 to 50%, according to the electrocardiographic or cardiac monitoring method used.[1-4] Its incidence has continuously increased over recent decades despite advances of surgical and anesthetic techniques.[3] Postoperative AF (POAF) is associated with worse clinical outcomes, with great impact on health care costs.[1,4-10]

Given the repercussions of AF, many investigations have been conducted to identify factors associated with the pathophysiology of AF, and thereby enable the development of preventive measures, guide the treatment of patients at greater risk, minimize the side effects of antiarrhythmic drugs and maximize the cost-benefit of the therapy.[6,11-13]

Our group has previously published a study on risk factors for the development of POAF, including age over 70 years, mitral disease, non-use of beta-blocker therapy

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in the perioperative period and a positive water balance greater than 1,500 mL in the 48 after surgery.[14]

To this end, we sought to create and validate a risk stratification score of POAF, using preoperative and early postoperative indicators in patients undergoing cardiac surgery.

Material And Methods

Population and sample

The present study consists of a prospective analysis of 1,054 patients at the Institute of Cardiology of Rio Grande do Sul/University Foundation of Cardiology (*Instituto de Cardiologia do Rio Grande do Sul/Fundação Universitária de Cardiologia* - ICIFUC). Study sample consisted of patients who underwent valve surgery and/or myocardial revascularization at the ICIFUC, and was collected during two periods, between 2002 and 2005 (n = 448 patients) and between 2010 and 2011 (n = 606 patients).

Study design

This was an observational prospective cohort study.

Inclusion criteria

Patients aged 18 years or older who underwent valve surgery (mitral and/or aortic valve replacement) and/or myocardial revascularization surgery were included. Patients who underwent additional procedure associated with any of these surgeries were also included.

Exclusion criteria

Patients who underwent emergency procedures, and patients with AF (detected by standard electrocardiography and 24-h ambulatory electrocardiographic monitoring) were excluded.

Study variables

The following variables were evaluated in the validation cohort: gender, age, presence of mitral valve disease (severe regurgitation and/or severe stenosis), use of beta-blockers in the preoperative period, discontinuation of beta-blocker therapy in the postoperative period, presence of a positive water balance greater than 1,500 mL within 48 hours after surgery, duration of hospitalization and in-hospital mortality.

Outcome

The diagnosis of POAF was considered an outcome in the perioperative period. POAF was desfined as an episode of arrhythmia, with electrocardiographic tracing with an irregular baseline secondary to disorganized atrial activity, which is referred to as the so-called "f" waves generating variable RR cycles. Episodes of POAF lasting longer than 15 minutes or requiring medical intervention were considered in the study due to the symptomatology or hemodynamic instability. Patients were monitored continuously for 72 hours, and daily electrocardiograms were obtained during hospitalization. In case of cardiovascular symptoms, additional monitoring was performed.

Procedures

Anesthesia and cardiopulmonary bypass (CPB) were performed according to local standard protocols. After cardiac surgery (immediate postoperative period), the patient remaining for 48 hours or longer in the intensive care unit.

Statistical analysis

Continuous variables with normal distribution were described as means and standard deviations. The hypothesis of normality was verified by the Kolmogorov-Smirnov test. Categorical (or categorized continuous) variables were described as counts and percentages and compared using the chi-square test or Fisher's exact test, when necessary. For construction of the risk score, a derivation cohort was collected between 2002 and 2005, and a validation cohort was collected during 2010-2011. Multivariate analysis with backward selection was applied. Statistical significance was set at $p < 0.05$.

Preliminary model of the risk score

Variables used for analysis were selected based on biological plausibility (association with POAF) and data from literature on POAF. A total of 67 variables were studied in the derivation cohort[14] of 448 patients included between 2002 and 2005.

Variables associated with POAF were selected in a multiple logistic regression model with backward selection, and those with p-values close to 0.05 in the model were maintained. Then, b coefficient of the logistic equation was used for construction of a weighted risk score; when transformed into odds ratios, the values were rounded to compose the score.

Validation

The preliminary risk score (obtained in the derivation cohort) was applied in the validation cohort, and the following performance statistics were applied: C statistics (area under the receiver operating characteristic [ROC] curve), the chi-square of goodness-of-fit of Hosmer-Lemeshow (HL) and consequently Pearson›s correlation coefficient between the observed events and those predicted by the model.

Values for the area under the ROC curve greater than 0.70 indicate that the model has good discriminatory power. A chi-square of HL with $p > 0.05$ indicates good calibration of the model. A Pearson correlation coefficient $r \geq 0.7$ indicates a strong association between observed and predicted values.

Obtaining the final risk score

After obtaining adequate performance in the validation, both databases (derivation and validation) were combined for the formulation of the final score. The variables were the same as those previously studied to achieve more accurate statistics for the coefficients. Performance statistics were obtained as described above.

In addition to the final score, a logistic model (formula below) was generated, which allows direct estimates of the probability of outcome occurrence. The use of a mathematical model is considered by some authors to be more appropriate for obtaining event estimates since a complex formula would limit the use among physicians. In individuals considered to be at high risk in the additive model, the use of the logistic model is the most adequate in determining the individual occurrence of the clinical outcome.[15]

P (event) = 1 {1 + exp (- ([30 + (31x1 +... + kak))

Data were processed and analyzed using the Statistical Package for the Social Sciences (SPSS), version 22.0.

Ethical considerations

This research project was submitted to the Research Ethics Committee of the ICIFUC (registration number 2345902).

Results

Characteristics

In the total sample (n = 1,054), 272 patients had POAF (25.7%). When considering only myocardial revascularization surgeries (63.8%), the POAF rate was 20.3%. In cases of valve intervention alone (23.9%), the frequency of POAF was 34.3% and, in combined surgeries (7.3%), the highest prevalence was observed – 36.6%.

Mean age of the patients was 60.1 ± 12.1 years old, and 26.6% of the patients were 70 years old or older. Most of the patients (65.2%) were men (Table 1).

POAF was associated with longer hospital stay compoared with patients without POAF (median of 10 days vs. 7 days, respectively, $p < 0.05$) and increased in-hospital mortality (5.5% vs. 1.0%, respectively; $p < 0.001$). In addition, with a mean follow-up of five years, we observed higher late mortality rate for patients with POAF compared with those without POAF (6.5% vs 1.4%, respectively, $p = 0.002$).

Development of the risk model (derivation cohort)

The multivariate analysis of the predictors in the derivation cohort (n = 448) is described in Table 2. Based on their statistical significance, the predictors selected for the construction of the score included age (≥ 70 years), mitral valve disease, the non-use or discontinuation of beta-blocker therapy and a positive water balance greater than 1500 mL.

Points were assigned to each variable according to the odds ratio obtained (Table 2).

The area under the ROC curve of the obtained model was 0.77 (95% confidence interval [CI] 0.73 to 0.81).

Validation of the risk model

External validation was performed in 606 patients of the validation cohort. The risk model had an accuracy of 0.78 (95% CI 0.73 to 0.82) measured by the area under the ROC curve, thus exhibiting a good discriminatory ability. Good correlation was noted between expected and observed POAF: r = 0.99, with chi-square = 1.73 (p = 0.94) (Hosmer-Lemeshow test).

Risk model in the total sample (n = 1,054)

The model was then edited using a combination of the developed score and data from the derivation

Table 1 - Characteristics of the sample and univariate analysis

Variable	Total (n = 1054)	POAF (n = 272)	Non-POAF (n = 782)	RR	95% CI	p
Age ≥ 70 years	281 (26.8%)	141 (41.9%)	167 (21.2%)	2.67	1.99-3.59	< 0.0001
Mean age ± SD	60.1 ± 12.1					
Male	690 (65.2%)	182 (66.9%)	508 (64.6%)	1.1	0.82-1.48	0.507
Type of surgery						
Revascularization	675 (63.8%)	141 (51.8%)	534 (67.9%)	1		
Valve surgery	306 (28.9%)	105 (38.6%)	201 (25.6%)	1.98	1.45-2.70	< 0.001
Combined	77 (7.3%)	26 (9.6%)	51 (6.5%)	1.93	1.11-3.28	0.14
Mitral valve disease	109 (10.3%)	46 (16.9%)	63 (8%)	2.33	1.55-3.51	< 0.001
Absence of beta-blocker	454 (42.9%)	197 (72.4%)	257 (32.7%)	5.40	3.98-7.33	< 0.001
Water balance > 1,500 mL	685 (64.7%)	203 (74.6%)	482 (61.3%)	1.85	1.36-2.52	< 0.001

**p-values: Fisher's exact test; POAF: postoperative atrial fibrillation; CI: confidence interval.*

Table 2 - Logistic regression and multivariate risk score (derivation – n = 448)

Variable	B	p	RR	95% CI	Points
Age ≥ 70 years	0.96	< 0.001	2.67	1.59-4.48	2
Mitral valve disease	0.77	0.03	2.18	1.08-4.35	1
Absence of beta-blocker	0.91	< 0.001	2.49	1.53-4.03	1.5
Water balance > 1,500 ml	0.5	0.06	1.65	0.96-2.83	0.5
Constant	-2.471	< 0.001	0.08		

and validation cohorts. Using the variables described, multiple logistic regression was performed, resulting in a recalibrated risk score based on the importance of the coefficient β of the logistic equation (Table 3). Variables related to the development of POAF included age (≥ 70 years), mitral valve disease, the non-use or discontinuation of beta-blockers and a positive water balance greater than 1500 mL.

The area under the ROC curve of the obtained model was 0.76 (95% Cl 0.72- 0.79) (Figure 1).

Table 4 and Figure 2 present the risk of POAF according to the score and the classification of this risk (additive score). There was a progressive increase in the proportion of the event, exhibited by an increase in the score: very low risk (score 0) = 0.0%; low risk (score 1 and 2) = 3.9%; intermediate risk (score 3 to 5) = 10.9%; and high risk (score 6 to 8) = 60.0%; $p < 0.0001$. The logistic equation should be used for risk assessment in the development of POAF individually (Table 3).

In the total sample, 46.8% of the operated patients had low and medium risk. The score predicted POAF in 7.4% of individuals at low risk and 11.7% of those at medium risk; 17% of the total sample was classified as very high risk. To test the calibration of the final score, the observed POAF was compared with that predicted in each of the four classification intervals of the score, resulting in a predicted/observed correlation coefficient of 0.99 with $x^2 = 0.98$ ($p = 0.98$) (Hosmer-Lemeshow test) (Figure 3).

Table 3 - Logistic regression and multivariable risk scores of the total sample (n = 1,054)

Variable	B	P	RR	95% CI	Points
Age ≥ 70 years	0.93	< 0.001	2.55	1.84-3.53	2
Mitral valve disease	0.53	0.01	1.70	1.09-2.65	1
Absence of beta-blocker	1.61	< 0.001	5.04	3.67-6.90	4
Water balance > 1,500 ml	0.43	0.01	1.53	1.1-2.15	1
Constant	-2.56	< 0.001	0.07		

*Logistic equation: Prob(POAF) = 1 / (1 + exp (- (-2.56 + [0.93 * age ≥ 70] + [0.53 * mitral valve disease] + [1.61 * non-use and/or discontinuation of beta-blockers] + [0.43 * Water balance > 1500 mL]))).*

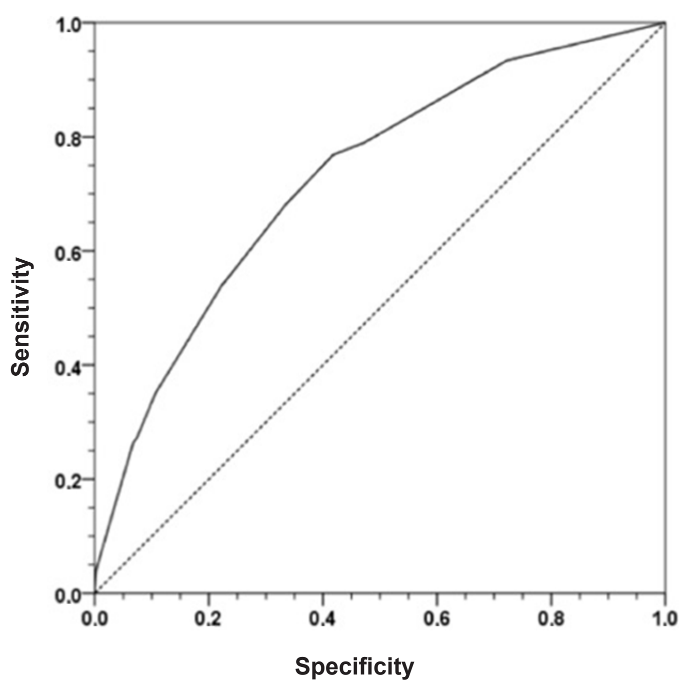

Figure 1 - Area under the ROC curve for the occurrence of postoperative atrial fibrillation: c = 0.76 (95% confidence interval 0.72 - 0.79) in the final model (n = 1,054).

Discussion

Despite advances in surgical techniques and postoperative management, POAF continues to be a very frequent complication. Alhough many factors associated with the occurrence of POAF have been reported, there are few prediction models available.[16-19]

Our study identified four predictors for POAF that comprised: age ≥ 70 years, mitral valve disease, the non-use of beta-blockers in the preoperative period or their discontinuation in the postoperative period and a positive water balance greater than 1,500 mL within 48 hours after the surgery. Thus, an easy-to-apply and clinically useful tool was used to calculate the POAF risk. The selection of the variables was made based on the experience of the department of cardiac surgery of the ICIFUC and available literature.[14,20] When using predictive risk models, we evaluate the possibility of the risk of occurrence of POAF in a sample rather than individually.[21]

The incidence of POAF in this study was 25.7%, and when only valve surgeries combined with revascularization were considered, this number was 34.3%. This incidence is similar to the means reported in the literature.[3,22,23] It is worth mentioning that we used continuous monitoring only in the period of intensive therapy and after intermittent electrocardiography, which may have underestimated the cases of asymptomatic POAF. Few studies[24,25] used continuous monitoring and reported prevalence rates of 44% to 64%. Therefore, the literature demonstrates a high prevalence of asymptomatic POAF that is generally greater than 25%, underscoring the need for indetifying factors that contribute to POAF, which was the main objective of this study.

Table 4 - Risk scores and frequency of postoperative atrial fibrillation (n = 1,054)

Score	Sample (n = 1058)	POAF (n)	POAF (%)	Risk category
0	189	14	7.4	Low
1 and 2	307	36	11.7	Medium
3 to 5	382	181	30.9	High
6 to 8	180	104	57.8	Very high

The findings of longer hospitalization and increased early and late mortality associated with the occurrence of postoperative arrhythmia are consistent with the findings reported in the literature that strongly suggest that the prognosis of POAF patients is compromised in the long term.[7,25-27]

Age greater than 70 years was an important predictor of POAF in this study, adding two points to the score. Age as a predictor of POAF was reported to stratify the risk factors associated with arrhythmia.[16,28] Mathew et al.[26] demonstrated that a one-decade increase in age leads to a 75% increase in the risk of developing POAF; the authors also reported that patients older than 70 years were at high risk regardless of other clinical characteristics. Zaman et al.[28] showed that patients over 60 years of age have a 3.8-fold increased risk for development of AF compared with the population under 60 years, and such risk is likely related to atrial dysfunction and fibrosis. These factors are linearly

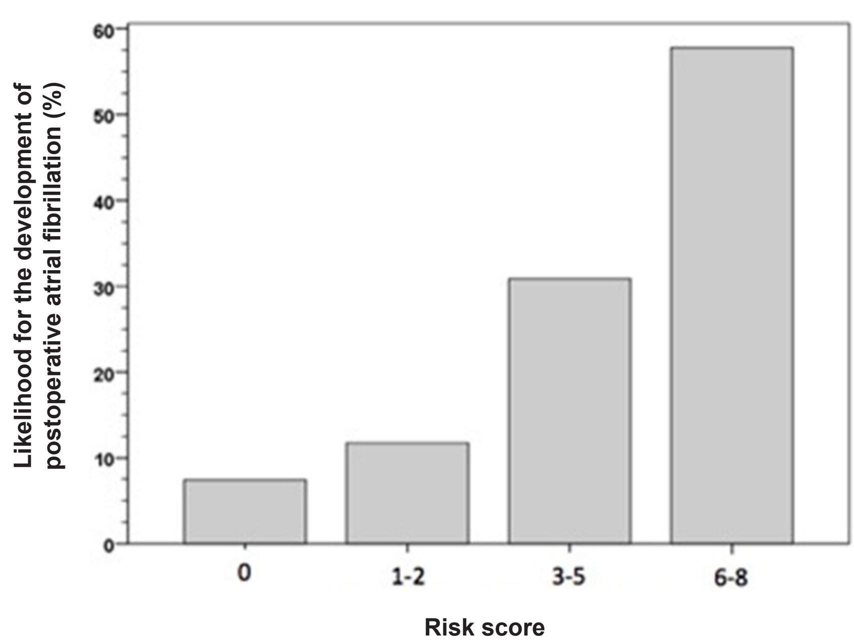

Figure 2 - Increase in the risk (expressed in %) for development of postoperative atrial fibrillation according to the score.

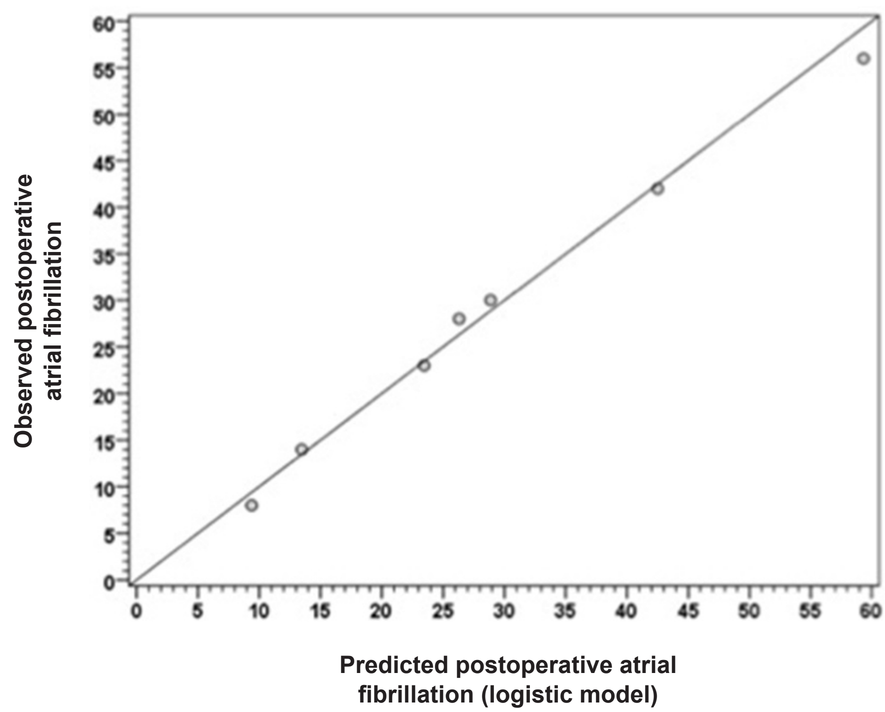

Figure 3 - Dispersion of points representing predicted postoperative atrial fibrillation (POAF) (by logistic model) and observed POAF among the patients (n = 1,054, events = 272 POAF). The Pearson coefficient was r = 0.99 m with x^2 (Hosmer-Lemeshow) = 0.98 (p = 0.986), indicating good performance of the final risk score model.

associated with age and consequently associated with a reduction of atrial electric conduction velocity, generating an arrhythmogenic substrate.[28]

The presence of mitral valve disease was a predictor of POAF in our sample, adding one point to the score, and increasing by 2.3-fold the risk for POAF. This factor alone had not been described by other authors in studies on POAF and differs from the classic association with AF. As a pathophysiological mechanism, stenosis and mitral insufficiency cause atrial dysfunction due to left atrial pressure and volume overload with consequent atrial dysfunction and arrhythmic substrate. We emphasize that pathophysiological changes at the cellular level in valve disease have been poorly described in the literature. In addition, surgical manipulation of the atria may be associated with the development of POAF. The diameter of the left atrium alone was not a predictor of POAF.[14,29]

The absence of beta blockers or their discontinuation in the postoperative period had an important contribution (possibly four points) to the score developed in our study. Previous studies, including meta-analyses, have described this strong association. In a meta-analysis including 28 studies and 4,074 patients, Crystal et al.,[30] reported an OR of 0.35 (95% CI 0.26-0.49) associated with this finding. Andrews et al.,[31] analyzing 24 studies, reported that patients with ejection fractions greater than 30% were associated with an OR of 0.28 (95% CI 0.21-0.36). The worst clinical scenario would be the non-use of beta-blokers during the pre- and postoperative periods.

The only postoperative factor per se, namely, the presence of a positive water balance greater 1,500 mL in 48 hours after surgery, was a predictor of POAF in our cohort, contributing one point to the score. The mechanism was likely related to atrial dilatation during this critical inflammatory period, which has been described by Kalus et al.[32] High risk scores for the other variables in the preoperative period could guide a restrictive strategy in the management of postoperative hydration if there is no clinical contraindication.

The area under the ROC curve was 0.76 (95% CI 0.72 - 0.79), reflecting the discriminating power of the model. Regarding the calibration, an HL test of r = 0.99, x^2 = 0.98

(p = 0.986) was obtained, indicating good performance of the model. The only POAF prediction score that had a similar discrimination was reported by Mathew et al.,[26] in which an area under the ROC curve of 0.77 was obtained after the definition of 10 pre-, intra- and postoperative predictor variables.[26] Previously reported prediction scores had lower discrimination values compared with our risk score.[11,12,26,33-35] The absence of a perfect discrimination can be explained by the multifactorial origin of the POAF, pathophysiological mechanisms that have not been fully characterized to date, and heterogeneity of heart diseases.

Our risk model was developed and validated in one center, and several studies have suggested that the scores have a lower efficacy when applied in different patients from those used to construct the model. Therefore, external validation is fundamental to determine the clinical relevance of this risk model. However, as with any risk stratification score, this tool should be reassessed in the long term regarding existing variables and incorporation of new variables.

It is important to highlight that, since these results were obtained from a clinical database, caution is needed when extrapolating them to the general population. This is the first clinical predictive score for POAF developed in a Brazilian population.

Conclusion

In summary, we detected four risk variables for the development of POAF during the postoperative period of heart valve surgery and/or revascularization in a Brazilian sample. Using these risk variables, it was possible to construct a score that had a good predictive ability for the outcome occurrence. In addition, this model enables the appropriate classification of patients with a low, medium, high or very high risk of developing POAF.

Author contributions

Conception and design of the research: Ronsoni RM, Leiria TLL, Pires LM, Kruse ML, Pereira E, Silva RG, Lima GG. Acquisition of data: Ronsoni RM, Leiria TLL, Pires LM, Kruse ML, Pereira E, Silva RG, Lima GG. Analysis and interpretation of the data: Ronsoni RM, Leiria TLL, Pires LM, Kruse ML, Pereira E, Silva RG, Lima GG. Statistical analysis: Ronsoni RM, Leiria TLL, Pires LM, Kruse ML, Pereira E, Silva RG, Lima GG. Obtaining financing: Ronsoni RM, Leiria TLL, Pires LM, Kruse ML, Pereira E, Silva RG, Lima GG. Writing of the manuscript: Ronsoni RM, Leiria TLL, Pires LM, Kruse ML, Pereira E, Silva RG, Lima GG. Critical revision of the manuscript for intellectual content: Ronsoni RM, Leiria TLL, Pires LM, Kruse ML, Pereira E, Silva RG, Lima GG.

Potential Conflict of Interest

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

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Study Association

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Ethics approval and consent to participate

This study was approved by the Ethics Committee of the ICIFUC under the protocol number 2345902. All the procedures in this study were in accordance with the 1975 Helsinki Declaration, updated in 2013. Informed consent was obtained from all participants included in the study.

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