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Journal of Atrial Fibrillation
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Development and Validation of A Simple Clinical Risk Prediction Model for New-Onset Postoperative Atrial Fibrillation After Cardiac Surgery: Nopaf Score

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Abstract

Introduction; Postoperative atrial fibrillation (POAFib) occurs in 20 to 40% of patients following cardiac surgery, and is associated with an increased perioperative morbidity and mortality. We aimed to develop and validate a simple clinical risk model for the prediction of POAFib after cardiac surgery.

Methods; An analytical single center retrospective cohort study was conducted, including consecutive patients undergoing cardiac surgery between 2004 and 2017 with POAFib. To create the predictive risk score, a logistic regression model was performed using a random sample of 75% of the population. Coefficients of the model were then converted to a numerical risk score, and three groups were defined: low risk (≤1 point), intermediate risk (2-5 points) and high risk (≥6 points). The score was validated using the remaining 25% of the patients. Discrimination was evaluated through the area under the curve (AUC) ROC, and calibration using the Hosmer-Lemeshow (HL) test, calibration plots, and ratio of expected and observed events (E/O).

Results; Six thousand five hundred nine patients underwent cardiac surgery: 52% coronary artery bypass grafting (CABG), 20% valve surgery, 14% combined (CABG and valve surgery) and 12% other. New-onset AF occurred in 1222 patients (18.77%). In the multivariate analysis, age, use of cardiopulmonary bypass pump, severe reduction in left ventricular ejection fraction (LVEF), chronic renal disease and heart failure were independent risk factors for POAFib, while the use of statins was a protective factor. The NOPAF score was calculated by adding points for each independent risk predictor. In the derivation cohort, the AUC was 0.71 (CI95% 0.69-0.72), and in the validation cohort the model also showed good discrimination (AUC 0.67 IC 0.64-0.70) and excellent calibration (HL P = 0.24). The E/O ratio was 1 (CI 95%: 0.89-1.12). According to the risk category, POAFib occurred in 5% of low; 11% of intermediate and 27.7% of high risk patients in the derivation cohort (P <0.001), and 5.7%; 12.6%; and 23.6% in the validation cohort respectively (P <0.001)

Conclusion: From a large hospitalized population, we developed and validated a simple risk score named NOPAF, based on clinical variables that accurately stratifies the risk of POAFib. This score may help to identify high-risk patients prior to cardiac surgery, in order to strengthen postoperative atrial fibrillation prophylaxis.

Introduction

Atrial fibrillation (AF) is the most common sustained arrhythmia and one of the most frequent complications after cardiac surgery, with a global prevalence between 20% and 40% depending on the definition and the method used diagnosis [1,2]. Its incidence varies according to the type of surgery, occurring in almost 30% of patients after a coronary artery bypass graft (CABG), and up to 50% after valve surgery, either isolated or combined [3,4].

Postoperative Atrial Fibrillation (POAfib) is associated with increased adverse outcomes, including higher short and long term mortality rates, and increased length of hospital stay which leads to

Key Words

Atrial Fibrillation, Cardiac Surgical Procedures, Thoracic Surgery, Cardiac Arrhythmia.

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greater costs [3, 5-7]. In order to avoid these outcomes, several POAFib prophylactic methods have been studied, but some of them fail to prove net clinical benefit due to potential complications when used routinely. Therefore, the constant effort to find a suitable method to predict POAfib lies in the need of limiting prophylaxis to high-risk patients, so as to minimize the global burden of complications associated with these therapies [8,9]. A method that could accurately identify high risk patients would enable targeted preventive/therapeutic interventions, without exposing the overall population to the risk of antiarrhythmic toxicity or the added drug costs [10].

In this scenario, previous studies have identified multiple clinical risk factors that could influence the occurrence of POAfib [11-13]. The most relevant ones include age, heart failure, rheumatic heart disease, chronic kidney disease (CKD), and chronic obstructive pulmonary disease (COPD) [14].

Currently, a widely accepted risk model for POAfib prediction is lacking, several models were created to predict new-onset AF after cardiac surgery [15-20]. We aimed to develop and validate a simple clinical model for the prediction of new-onset Atrial Fibrillation after cardiac surgery, in order to help physicians identify patients at high risk of developing POAFib.

Methods

We conducted a single-center cohort study, performing a retrospective analysis of prospectively collected data.

The study included consecutive patients undergoing cardiac surgery between January 2004 and December 2017 who developed postoperative atrial fibrillation. Patients with previous AF or other atrial arrhythmias were excluded.

Table 1: Baseline characteristics of the derivation and validation cohort

	Derivation cohort (n=4881)	Validation cohort (n= 1628)	P
Age (mean ± SD)	65±11.2	66±11.5	0.1
Male sex (%)	3782 (77.5%)	1223 (74.1%)	0.07
EUROSCORE (Median Pc 25-75)	4 (2-6)	4 (2-6)	0.9
Smoking (%)	611 (12.5%)	207 (12.7%)	0.83
Diabetes mellitus (%)	1070 (21.9%)	361 (22.2%)	0.83
Hypertension (%)	3514 (72%)	1174 (72.1%)	0.92
CKD (GFR <15) (%)	304 (6.2%)	98 (6%)	0.76
COPD (%)	251 (5.1%)	93 (5.7%)	0.37
Cerebrovascular disease (%)	209 (4.2%)	74 (4.5%)	0.69
LVEF <35% (%)	281 (5.8%)	86 (5.3%)	0.47
Type of surgery			0.74
CABG (%)	839 (51.5%)	2574 (52.7%)	
Valvular (%)	363 (22.3%)	1000 (20.5%)	
CABG + Valvular (%)	230 (14.1%)	681 (14%)	
Others (%)	196 (12.1%)	626 (12.8%)	

CKD: Chronic kidney disease. COPD: Chronic Obstructive Pulmonary Disease. CABG: Coronary artery bypass grafting. GFR: Glomerular Filtration Rate. LVEF: Left ventricular ejection fraction

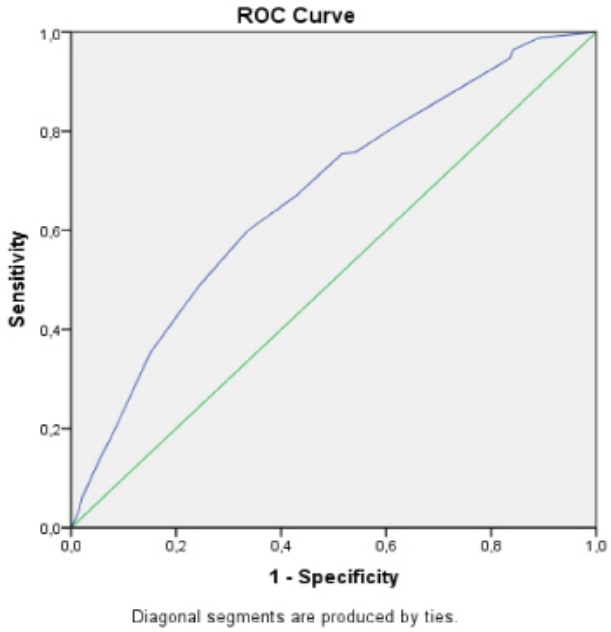

Figure 1: Area under the curve-receiver operating characteristic for NOPAF score

The aim of the study was to create and afterwards validate a simple risk score model that could appropriately predict the occurrence of postoperative AF.

POAFib was defined as in previous studies, as any documented AF episode lasting > 30 seconds recorded either by continuous telemetry throughout hospitalization or on a twelve-lead electrocardiogram performed daily, and when the patient referred symptoms. All patients had continuous telemetry monitoring at least during the first 48 hours by an off-site central monitor unit and, once identified, every arrhythmic event was confirmed by a cardiologist. The definition of heart failure was a prior history of heart failure diagnosed during routine clinical practice, regardless left ventricular ejection fraction.

Statistical analysis

Quantitative data were expressed as mean ± SD and were compared with 2-sample t tests for independent samples, whereas dichotomous variables were reported as absolute values and proportions. Differences in proportion were compared using an x2 test or Fisher's exact test, as appropriate. Ordinal data and continuous variables inconsistent with normal distribution were expressed as median and interquartile range (IQR), and were compared with the U Mann–Whitney test. A p value of< 0.05 was considered statistically significant.

Using the derivation cohort, we conducted univariate analyses. Variables significantly associated with postoperative AF (P<0.05) were analyzed in a multivariable logistic regression model with a conditional forward approach in order to identify the independent predictors of postoperative AF and to estimate their relative predictive weights (coefficients). Variables that were independently associated with postoperative AF were presented as odds ratios (ORs) along with the 95% confidence intervals (CIs). An OR was considered statistically significant if its CI 95% exceeded 1, with a P value < 0.05. We converted

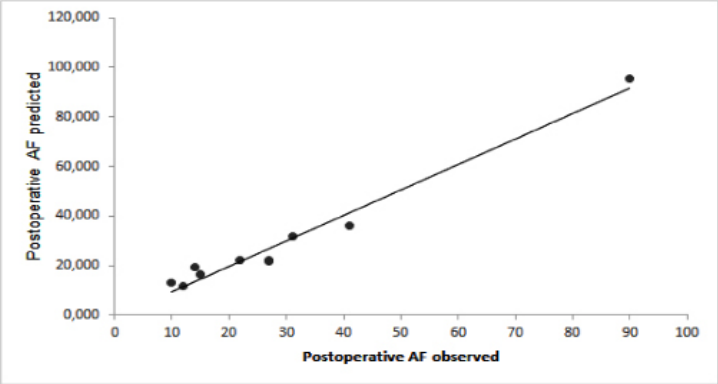

Figure 2: Calibration plot for NOPAF score

the coefficients for the independent predictors into a simplified risk score system [21]. Specifically, we calculated the number of points assigned to each variable by dividing its regression coefficient by the smallest coefficient in the model, then rounded this quotient to the nearest whole number. We then calculated each subject's risk score by summing up the points of all variables present on admission.

We randomly divided the study population into two groups using a numerical assignment with random sequence: one for model derivation (75% of the population) and the other for model validation (the remaining 25%).

Calibration was assessed using the Hosmer-Lemeshow (HL) goodness-of-fit test, which evaluates the difference between the real rate observed and the rate predicted by the model in different risk groups. A P value > 0.05 indicates that the model fits best for the data and, thus, predicts the probability of developing postoperative AF. We calculated the area under the curve (AUC)-ROC to assess the score's predictive value. Youden's index was used to establish the best cut-off point.

Ethical considerations

Committee on Ethics and Research approval was obtained with waiver of consent for retrospective review of previously collected de-identified data.

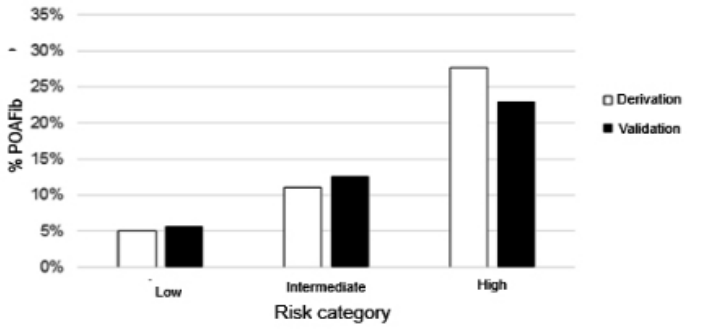

Figure 3: Observed rates of POAFib by risk stratification for the derivation and validation cohorts (P<0.001)

Results

A total of 6509 consecutive patients undergoing cardiac surgery between 2007 and 2017 were included: 4881 (75%) in the derivation group and 1628 (25%) in the validation group.

Fifty-two percent underwent coronary artery bypass graft (CABG) surgeries, 20% valve replacement, 14% combined procedures (revascularization-valve surgery) and 12% other procedures (e.g aortic surgery, septal myectomy or pulmonary endarterectomy). Cardiopulmonary bypass (CPB) was used in 45.7% of the procedures, and only in 1.85% (n=62) of CABG surgeries. Baseline characteristics of the population are described in Table 1. No statistically significant differences were found between the baseline characteristics of the derivation and validation group.

Eighteen percent of patients presented with postoperative AF, , 19.1% in the derivation cohort and 17.8% in validation cohort (p = 0.22).

Table 2: Characteristics of study participants with and without AF in the derivation cohort

	With postoperative AF (n=897)	Without postoperative AF (n=3948)	p
Age1 (mean±SD)	70.6 (±9.2)	63.7 (±11.6)	<0.001
Male sex (%)	673 (72.1%)	3113 (78.9%)	<0.001
Additive European system for cardiac operative risk evaluation score (median, IQR 25-75)	6 (4-8)	4 (2-6)	<0.001
European system for cardiac operative risk evaluation High score	358 (38.4%)	736 (18.6%)	<0.001
Current smoker (%)	73 (7.8%)	538 (13.6%)	0.007
Diabetes (%)	216 (23.2%)	854 (21.6%)	0.3
Hypertension (%)	698 (74.8%)	2816 (71.3%)	0.02
Previous cardiac surgery (%)	52 (5.6%)	194 (4.6%)	0.4
CKF (%)	98 (10.5%)	206 (5.2%)	0.1
COPD/Asthma (%)	66 (7.1%)	185 (4.7%)	<0.001
Cerebrovascular disease (%)	46 (4.9%)	163 (4.1%)	0.4
LVEF < 30 (%)	83 (8.9%)	198 (5%)	<0.001
HF (%)	124 (13.3%)	231 (5.9%)	<0.001
Statin (%)	419 (44.9%)	2051(52%)	<0.001
Beta Blocker (%)	581(62.3%)	2544(64.4%)	0.2
ACEI/ARB (%)	386 (41.4%)	1632 (41.3%)	0.9
Previous IABP (%)	5 (1.7%)	20 (1.5%)	0.2
Urgent surgery (%)	300 (32.2%)	1213 (30.7%)	0.3
Type of surgery			<0.001
CABG (%)	346 (37.1%)	2228 (56.4%)	
Valve surgery (%)	272 (29.2%)	728 (18.4%)	
CABG + valve surgery (%)	201 (21.5%)	480 (12.5%)	
Thoracic aorta (%)	59 (6.3%)	233 (5.9%)	
Other (%)	55 (5.9%)	279 (7.1%)	
CPB (%)	585 (62.7%)	1646 (41.7%)	<0.001
Surgery No-CABG (%)	346 (37.1%)	2228 (56.4%)	<0.001

CKF: Chronic kidney failure. COPD: Chronic obstructive pulmonary disease. LVEF: Left ventricular ejection fraction. HF: Heart failure IABP: Intraaortic balloon pump. CPB: Cardiopulmonary bypass. ACEI: Angiotensin-Converting Enzyme Inhibitor. ARB: Angiotensin Receptor Blocker (ARB). 1: Years

Table 3: Multivariable model and risk score for postoperative atrial fibrillation after cardiac surgery

Risk Factor	OR (IC 95%)	P	B Coefficient	Risk score weight
Age				
60-69 years	2.94 (2.3-3.7)	<0.001	1.08	5
70-79 years	4.7 (3.74-6)	<0.001	1.555	8
>80 years	6.5 (4.8-8.7)	<0.001	1.868	10
Heart Failure	1.48 (1.13-1.92)	0.004	0.392	2
Severe LVSF	1.46 (1.07-1.98)	0.015	0.379	2
CKD	1.47 (1.12-1.93)	0.005	0.388	2
CBP	1.97 (1.68-2.31)	<0.001	0.679	4
Statin use	0.82 (0.70-0.96)	0.014	-0.194	-1

COPD: Chronic obstructive pulmonary disease. LVSF: Left ventricular systolic function <35%, CKD: Chronic kidney disease (CrCl <60). CBP: Cardiopulmonary bypass. Note: We used the method described by Sullivan et al. to calculate the risk score weight. We divide each regression coefficient by the smallest coefficient in the model (Statin use).

Patients with POAFib were older (70.6 ±9.2 vs. 63.7±11,6 years; p< 0.001) and had more comorbidities (Aditive EuroSCORE 6 vs. 4, p < 0.001) compared with those without the arrhythmia, and the presence of hypertension, COPD, left ventricular dysfunction (LVD) and heart failure (HF) was more frequent. The rate of current smokers and male sex was lower (7.8% vs. 13.6%, p < 0.007 and 72% vs. 78%, p <0.001, respectively).

The use of preoperative beta blockers was similar in both groups (p = 0.2), while statins usage was lower among patients without the arrhythmia. POAfib occurred more frequently in surgeries other than CABG and surgeries with CBP (Table 2).

In the multivariate analysis, age, surgery using CBP, LVD, chronic renal disease (Creatinine clearance<60), and HF were independent risk factors for POAFib, while use of statins was a protective factor (Table 3).

The score was calculated by adding points for each independent predictor.

In the derivation cohort, the model showed very good discrimination with an AUC of 0.70 (CI 95% 0.68-0.72). In the validation cohort, the AUC was 0.67 (CI 95% 0.64-0.70), similar to the derivation cohort (p = 0.09).

The model also showed excellent calibration (HL p = 0.55) (Figure 2). The expected/observed ratio was 1 (CI 95%: 0.89-1.12) (Table 4). The best cutoff point was 5, with a sensitivity of 75% (95% CI 70-90%) and a negative predictive value of 90% (95% CI 95-91%).

According to the risk category, POAFib occurred in 5% of the population with low risk; 11% with intermediate risk and 27.7% of the high risk group in the derivation cohort (p <0.001), and 5.7%, 12.6%, and 23.6% in the validation cohort groups respectively (p <0.001) (Figure 3).

Discusión

In this study, from one of the largest cohorts on the prediction of postoperative atrial fibrillation, we developed and validated a simple risk score called NOPAF, based only on preoperative variables that accurately stratified the risk of POAFib. The risk prediction model showed good discrimination and excellent calibration to predict this arrhythmia.

Several models were created to predict new-onset AF after cardiac surgery, like CHADS VASC, POAF, HATCH, Multicenter Study of Perioperative Ischemia (McSPI) AFRisk and Atrial Fibrillation Risk Index. Moreover, the CHADS VASC score, originally created to predict the risk of thromboembolism in patients with AF, was both prospectively and retrospectively validated for the prediction of POAFib [22,23]. Kashani et al. [24] made a retrospective evaluation of 2385 patients who underwent CABG surgery or valve surgery. At multiple regression analysis, high-risk patients (score≥2) had a significantly greater probability of developing postoperative AF as compared with the low-risk group (OR 5.21; p <0.0001), with an area under the curve of 0,65. Finally, Yin L et al evaluated (25) this score system only in cardiac valve surgery, and under a multivariate regression analysis CHA_2DS_2-VASc score was a significant predictor of AFCS, with a similar a AUC ROC curve found in our study, of 0.765 (95%CI, 0.723–0.807).

The POAF score is a scoring system that was created and validated to predict postoperative AF in patients undergoing CABG surgery or valve surgery using 7 variables identified in a multivariable analysis, the discriminative ability of the score was moderate, with an area under the curve of 0.66 in the original cohort and of 0.65 in the validation cohort [20].

The Multicenter Study of Perioperative Ischemia (McSPI) AFRisk [15] had an area under the ROC curve of 0.77., but it is much complex model that requires pre-, intra-, and postoperative data

Regarding the HATCH score, a recent study aimed to investigate the association between HATCH score and AFCS after isolated CABG, showed that HATCH score (OR 1.334; 95% CI 1.022 to 1.741, P=0.034) was an independent predictor of AF after CABG surgery, but with a poor discriminative ability to predict AFCS with

Table 4: Contingency table for Hosmer-Lemeshow test

Deciles	Postoperative Atrial Fibrillation				Total
	No		Yes		
	Observed	Expected	Observed	Expected	
1	210	206,908	10	13,092	
2	148	146,481	15	16,519	
3	92	92,449	12	11,551	
4	168	173,192	27	21,808	
5	105	99,850	14	19,150	
6	101	101,058	22	21,942	
7	139	138,444	31	31,556	
8	81	86,063	27	21,937	
9	87	91,957	41	36,043	
10	208	202,599	90	95,401	
Total	1339	1339	289	289	

an AUC ROC of 0.57 [26].

More recently Waldron et al compared the predictive ability of multiple perioperative atrial fibrillation risk indices in cardiac surgery patients, and they also found limited ability to predict AFCS with AUC of the ROC curve of 0.77 for McSPI AFRisk index, 0.58 and 0.66 for CHA_2DS_2-Vasc score and POAF score clinical risk prediction model, respectively [27].

The Atrial Fibrillation Risk Index, a retrospectively derived and prospectively validated score, uses 4 clinical variables to predict AF in only CABG surgery, with had adequate discriminatory power, with a concordance index of 0.68 [28].

The predictive ability of the POAF score, the CHA_2DS_2-VASc, and the Atrial Fibrillation Risk Index was also compared in patients undergoing nonemergent CABG surgery or valve surgery. The incidence of postoperative AF was remarkably higher, near 34%, with poor discrimination and calibration for the 3 scoring systems, with AUC-ROC for prediction of postoperative AF<0.6 [29].

The primary strength of this study is the prospective collected data, the large number of variables included and the size of the cohort. Additionally, Our final predictive model, includes only six simple variables that can be collected in the preoperative consultation, with similar discrimination ability previously reported in the literature for other risk scores. In contrast to other published studies [20,23,27,29], this cohort had lower risk of atrial fibrillation after cardiac surgery, It occurred in 18% of patients in this study. An explanation for this could be that most of the surgeries included in our study were CABG, and less than 2% of these were performed with CPB, compared with other studies where its use was significantly higher [15,18,24].

With this novel information, physicians might be able to appropriately discriminate patients who would benefit from an intense prophylactic treatment from those who could only develop unnecessary side effects. Moreover, with further research, this risk prediction model could help to improve postoperative ambulatory follow-up in those patients who developed transient POAfib, offer better antithrombotic treatment and promote the design of individualized management strategies.

Future studies are necessary to determine the generalizability of our results to larger populations, and should not only focus on developing better predictive models but also on identifying effective prophylaxis strategies taking into account the individual POAfib risk.

Considering limitations of this study, we should mention the retrospective nature and the fact that as it was conducted in a high-complexity cardiovascular center, with the vast majority of CABG were performed without CPB the sample may not be representative of the reality of other centers, as it was conducted in a monovalent highly complex cardiovascular center. However, the results can be extrapolated due to the size of the cohort and the number of variables included. Another limitation is that not all patients had the same time of continuous telemetry; all having at least 48 hours but those severely ill patients continued monitoring for longer. Therefore, we may have underdiagnosed asymptomatic atrial fibrillation, especially in those patients who required less monitoring time.

Conclusion

From a large hospitalized population, we developed and validated a simple risk score based on preoperative variables that accurately stratified the risk of atrial fibrillation after cardiac surgery. This score could help with patients risk stratification prior to surgery, identifying precisely those at high risk. Future validations are necessary in our environment, preferably with larger studies of prospective design.

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