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ORIGINAL ARTICLE

Subacute postoperative atrial fibrillation after heart surgery: Incidence and predictive factors in cardiac rehabilitation

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Abstract

Background: Postoperative atrial fibrillation (POAF) is the most common arrhythmia following cardiac surgery (CS). It may occur between the 1st and the 4th postoperative day as acute POAF or between the 5th and the 30th as subacute (sPOAF). sPOAF is associated with higher thromboembolic risk, which consistently increase patients' morbidity. Neutrophil-to-lymphocyte ratio (NLR) is a low-cost inflammatory index proposed as possible POAF predictor. Identification of patients' risk categories might lead to improved postoperative outcomes.

Methods: The aim was to assess the incidence of sPOAF and to identify possible predictors in patients performing cardiovascular rehabilitation (CR) after CS. A single-center cohort study was performed on 737 post-surgical patients admitted to CR on sinus rhythm. Continuous monitoring with 12-lead ECG telemetry was performed. We evaluated the predictive role of anamnestic, clinical, and laboratory data, including baseline NLR.

Results: Subacute POAF was documented in 170 cases (23.1%). At the multivariate analysis, age (OR 1.03; $p=.001$), mitral valve surgery (OR 1.77; $p=.012$), acute POAF (OR 2.97; $p<.001$), and NLR at baseline (OR 1.13; $p=.042$) were found to be independent predictive factors of sPOAF following heart surgery.

Conclusions: sPOAF is common after CS. Age, mitral valve procedures, acute POAF, and preoperative NLR were proved to increase sPOAF occurrence in CR. NLR is an affordable and reliable parameter which might be used to qualify the risk of arrhythmias at CR admission. Identification of new predictors of postoperative atrial fibrillation may allow to improve patients' prognosis.

KEYWORDS
atrial fibrillation, cardiac rehabilitation, cardiac surgery, neutrophil-to-lymphocyte ratio, postoperative complications

Vincenzo Rizza and Francesco Maranta contributed equally to this work.

1 | INTRODUCTION

Atrial fibrillation (AF) is the most common sustained arrhythmia after cardiac surgery (CS).[1,2] Its prevalence ranges from 15% to 60% with the highest rate observed in patients undergoing valvular surgery.[1–4] POAF usually occurs from 2 to 30 days after surgery: it may arise between the 1st and the 4th day after surgery as acute POAF (aPOAF) or between the 5th and the 30th day as subacute POAF (sPOAF).[5] Underlying pathophysiological mechanisms of POAF have not been fully clarified. The role of typical AF risk factors is controversial: while elderly and mitral valve disease seem to be good predictors of atrial arrhythmias following CS, diabetes and hypertension do not correlate with the occurrence of postoperative atrial fibrillation.[6–8] Consistent studies show that preoperative factors such as atrial lesions, left atrial dilatation, or electrolyte imbalances predispose to POAF by inducing dispersion of atrial refractoriness and non-uniform conduction.[9–11] Moreover, surgical procedures cause an increase in cytokines production; the consequent inflammatory milieu and the oxidative stress may facilitate progressive atrial fibrosis which is a well-known trigger for AF.[12,13] Preoperative neutrophil-to-lymphocyte ratio (NLR) is an emerging inflammatory biomarker which has been supposed to predict the incidence of various cardiovascular diseases, including POAF after CS.[14,15]

Subacute POAF is often underdiagnosed as usually patients are discharged from Cardiac Surgery Units without undergoing prolonged monitoring.[16–18] However, the onset of sPOAF should not be neglected as it impacts negatively on patients' prognosis being associated with numerous complications, like stroke, renal failure, and increased post-surgical mortality while aPOAF is usually a self-limited arrhythmia.[19–23]

Therefore, cardiac rehabilitation (CR) may represent the adequate setting to adopt preventive strategies in order to improve patients' clinical outcomes. The identification of clinical predictors of post-surgical arrhythmias in CR might be useful to stratify subjects, improving selection for prophylactic interventions, closer monitoring for complications, and establishing the probability of chronic AF progression.[24]

We designed a retrospective study to identify predictors of subacute postoperative atrial fibrillation (sPOAF) in subjects undergoing a postoperative CR program in our center.

2 | AIM OF THE STUDY

The aim of this study was to evaluate the prevalence of subacute postoperative atrial fibrillation (sPOAF) and to identify sPOAF predictors in patients performing a cardiovascular rehabilitation (CR) program after CS.

3 | MATERIALS AND METHODS

A single-center observational retrospective cohort study was conducted in the Cardiovascular Rehabilitation Unit of San Raffaele Hospital, Milan, Italy. We enrolled 737 patients hospitalized for cardiac rehabilitation after open-heart surgery that was performed in the Cardiac Surgery Unit of the same hospital from March 2011 to April 2014 and from September 2017 to April 2019. Patients with the following criteria were excluded: age < 18 years; non-sinus rhythm at the admission to CR unit; patients undergoing transcutaneous valvular heart replacement or percutaneous revascularization. Both valvular and CABG patients were included in the study population. A single-vessel surgical revascularization or a single valve repair/replacement were considered as simple interventions, while multiple-vessel surgical revascularizations, multiple valve procedures, and combined surgeries were defined as complex interventions. Our study was conducted in accordance with the amended Declaration of Helsinki. Informed consent was obtained from all patients before study began.

All patients underwent continuous 12-lead ECG monitoring during the whole postoperative period in order to detect possible arrhythmias. The occurrence of subacute postoperative atrial fibrillation was diagnosed using current ESC criteria (irregularly irregular R-R intervals, absence of distinct P-waves and irregular atrial activations with a minimum duration of 30 s on the telemetry).[25] Anamnestic, clinical, and laboratory data from the preoperative and postoperative periods were collected, including baseline neutrophil-to-lymphocyte ratio (NLR). Even preoperative 2D-echocardiographic left ventricle ejection fraction (LVEF) and left atrial volume index (LAVi) were recorded. All the patients performed treadmill 6-minute walking test (6MWT) at admission and before discharge. Tailored cardiac aerobic exercises of rehabilitation program were conducted using treadmill and/or cycle ergometer.

4 | STATISTICAL ANALYSIS

All the variables were tested through the Kolmogorov–Smirnov test to assess their gaussian distribution. Non-parametric variables are presented as median and interquartile range (IQR), while gaussian are described as mean and standard deviation. Categorical variables are presented as absolute number and percentage of the total. The Student *t*-test was used to compare parametric variables, while the Mann–Whitney U and the Wilcoxon were adopted to test non-parametric variables, respectively, as independent values and repeated measurements. Frequency distribution was tested using Chi-square test or Fisher's exact test. p-value<.05 was considered statistically significant. Binary logistic regression analysis was performed to assess independent predictors of subacute postoperative atrial fibrillation. All the variables with a univariate p-value<.05 were subsequently entered into the final multivariate model. Results of the regression analysis are presented as odds ratio (OR) with a 95% confidence interval (CI). Multivariate analysis p-values were two-sided and a p-value<.05 was considered statistically significant. All statistical analyses were performed using the SPSS software (version 25.0, SPSS Inc., Chicago, IL, USA).

5 | RESULTS

5.1 | Baseline features of the general population

Descriptive statistics of population are shown in Table 1. Patients were predominantly of male sex (n = 467, 63.4%). Median age was 62 years old, ranging from 52 to 71 years. Arterial hypertension was found in 322 patients (43.7%), dyslipidaemia in 182 (24.7%), diabetes mellitus in 64 (8.7%), family history of coronary artery disease (CAD) in 118 (16%), smoking in 62 (8.4%), history of smoking in 205 (27.8%). Median body mass index (BMI) was 24.8 kg/m^2 with 73 patients (9.9%) categorized as obese (BMI ≥30 kg/mq). Moreover, 105 patients (14.2%) presented chronic kidney disease defined according to KDIGO (eGFR<60 mL/min based on CKD-EPI 2009). Possible CAD was assessed in each case before surgery through coronary angiography as routine clinical practice in our center. One hundred forty-two patients (19.3%) reported history of paroxysmal AF which was more common in sPOAF cases (p < .001). About preoperative echocardiographic parameters, no significant difference was found in terms of LVEF, while the sPOAF group presented higher LAVi values (44.2 mL/mq vs. 36.3, p < .001).

The majority of patients underwent valvular heart surgery (n = 719, 97.6% of the total population): 471 (63.9% of total population) mitral valve repair or replacement, 118 (16%) tricuspid valve repair or replacement, 252 (34.2%) aortic valve replacement, and 56 (14.6%) combined valvular surgery.

TABLE 1 Descriptive statistics of the general population. Two groups were defined according to the occurrence of sPOAF.

Clinical features	Whole population	sPOAF	Non-sPOAF	*p*-value
Baseline characteristics				
Total (*n*, %)	737 (100)	170 (23.1)	567 (76.9)	–
Age in years (median, IQR)	62 (52–71)	66 (56–74)	61 (50–70)	**<.001**
Age > 65 years old (*n*, %)	298 (40.4)	88 (51.8)	210 (37)	**.001**
Male sex (*n*, %)	467 (63.4)	105 (61.8)	362 (63.8)	.622
Smoking (*n*, %)	62 (8.4)	10 (5.9)	52 (9.2)	.175
Previous smoking (*n*, %)	205 (27.8)	45 (26.5)	160 (28.2)	.655
Diabetes mellitus (*n*, %)	64 (8.7)	14 (8.2)	50 (8.8)	.813
Hypertension (*n*, %)	322 (43.7)	77 (45.3)	245 (43.2)	.631
Body mass index (median, IQR)	24.8 (22.3–27.3)	24.4 (22.2–27)	24.9 (22.5–27.4)	.557
Obesity (*n*, %)	73 (9.9)	18 (10.6)	55 (9.7)	.868
Family history of CAD (*n*, %)	118 (16)	27 (15.9)	91 (16)	.958
Dyslipidaemia (*n*, %)	182 (24.7)	46 (27.1)	136 (24)	.415
CAD (*n*, %)	129 (17.5)	26 (15.3)	103 (18.2)	.387
CKD according to KDIGO (*n*, %)	105 (14.2)	28 (16.5)	77 (13.6)	.345
History of AF	142 (19.3)	50 (29.4)	92 (16.2)	**<.001**
LVEF [%] (median, IQR)	55.2 (51.5–59.1)	54.4 (48.6–60.3)	55.6 (52–59.3)	.412
LAVi [mL/mq] (median, IQR)	38.4 (35.3–41.6)	44.2 (39.1–47.9)	36.3 (33.5–39.8)	**<.001**
Cardiac Surgery Unit				
CABG (*n*, %)	44 (6)	8 (4.7)	36 (6.3)	.428
Valvular surgery (*n*, %)	719 (97.6)	167 (98.2)	552 (97.4)	.514
Aortic valve (*n*, %)	252 (34.2)	55 (32.4)	197 (34.7)	.564
Mitral valve (*n*, %)	471 (63.9)	120 (70.6)	351 (61.9)	**.039**
Tricuspid valve (*n*, %)	118 (16)	33 (19.4)	85 (15)	.168
Complex surgery (*n*, %)	276 (37.4)	78 (45.9)	198 (34.9)	**.010**
aPOAF (*n*, %)	265 (36)	99 (58.2)	166 (29.3)	**<.001**

Bold values reached the statistical significace (p-value < 0.05).

Abbreviations: AF, atrial fibrillation; aPOAF, acute postoperative atrial fibrillation; CABG, coronary artery bypass grafting; CAD, coronary artery disease; CKD, chronic kidney disease; KDIGO, kidney disease-improving global outcomes; LAVi, left atrial volume index; LVEF, left ventricle ejection fraction; sPOAF, subacute postoperative atrial fibrillation.

A minority of patients ($n = 44$, 6% of total population) had significant CAD and performed CABG. One hundred fifty-five patients (40.5%) underwent complex CS.

5.2 | Occurence of postoperative atrial fibrillation

Postoperative atrial fibrillation was documented in 336 patients (45.6% of total population). Two hundred sixty-five (36%) experienced acute POAF, 170 (23.1%) had at least one episode of sPOAF during CR while 99 (13.4%) were diagnosed with both.

5.3 | Comparison of lab parameters

Table 2 summarizes the laboratory values of patients before and after CS. At the preoperative time (T0), lymphocytes were lower in the sPOAF subpopulation (1.6×10^9/mL vs. 1.7×10^9, $p = .024$). Consistent with the lymphocytic count, arrhythmic patients showed higher values of T0-neutrophil-to-lymphocyte ratio (2.33 vs. 2.17, $p = .027$; Figure 1). No other statistical differences were found between sPOAF and non-sPOAF group in terms of preoperative variables.

The time of CR admission (T1) did not differ between the sPOAF and non-sPOAF group (11 days vs. 10, $p = .519$).

At T1, sPOAF patients showed a lower number of platelets (218×10^3 vs. 232×10^3, $p = .032$), while high-sensitive troponin T (262 ng/L vs. 194.5, $p = .001$), neutrophils (3.9×10^9/mL vs. 3.8×10^9, $p = .021$) as well as NLR (3.57 vs. 3.26, $p = .016$) were significantly higher compared to the non-sPOAF subpopulation. No evident difference was found in terms of peak C-reactive protein (CRP) levels considering both the CS and the CR stay (140.6 mg/L vs. 136.4, $p = .378$) (Figure 2): this result is concordant with the fact that postoperative clinically evident infective complications (pneumonias, gastrointestinal infections, phlebitis, mediastinitis, wound infections, or infective endocarditis not requiring redo heart surgery) had similar incidence in patients with and without sPOAF (9.6% vs. 9.1%; Chi-square = 1.184, $p = .482$).

TABLE 2 Comparison of lab parameters between patients with and without sPOAF.

	Whole population	sPOAF	Non-sPOAF	*p*-value
Lab parameters				
Preoperative (T0)				
WBC [10^9/L] (median, IQR)	6.4 (5.3–7.5)	6.5 (5.2–7.8)	6.4 (5.4–7.5)	.823
Hb [g/dL] (median, IQR)	13.9 (12.5–15)	13.9 (12.6–14.7)	13.9 (12.5–15)	.432
HCT [%] (mean, SD)	39.3 (4.4)	38.5 (4.2)	39.4 (4.5)	.692
Platelets [10^9/L] (mean, SD)	213 (61)	233 (62)	209 (62)	.434
Monocytes [10^9/L] (median, IQR)	0.5 (0.4–0.6)	0.5 (0.4–0.6)	0.5 (0.4–0.6)	.619
Neutrophils [10^9/L] (median, IQR)	3.9 (3–4.8)	3.9 (3.1–5.1)	3.8 (3–4.7)	.148
Lymphocytes [10^9/L] (median, IQR)	1.7 (1.4–2.1)	1.6 (1.4–2)	1.7 (1.4–2.1)	**.024**
Neutrophil-to-lymphocyte ratio [10^9/L] (median, IQR)	2.23 (1.66–2.97)	2.33 (1.84–3.27)	2.17 (1.64–2.87)	**.027**
Creatinine [mg/dL] (median, IQR)	0.87 (0.74–1.02)	0.87 (0.75–1.03)	0.86 (0.74–1.02)	.389
Troponin T [ng/L] (median, IQR)	9.4 (6.8–12.1)	9.2 (6.3–11.9)	9.5 (7–12.2)	.289
eGFR [mL/min] (median, IQR)	83.2 (69.1–98.5)	81.9 (66.4–95.9)	83.9 (70.6–100.6)	.067
Cardiac rehabilitation admission (T1)				
WBC [10^9/L] (median, IQR)	8.2 (6.8–10)	8.3 (6.9–10.3)	8.1 (6.8–9.9)	.217
Hb [g/dL] (median, IQR)	10.5 (9.7–11.5)	10.4 (9.6–11.4)	10.6 (9.7–11.6)	.224
Platelets [10^9/L] (median, IQR)	229 (172–304)	218 (160–282)	232 (178–309)	**.032**
Monocytes [10^9/L] (median, IQR)	0.9 (0.7–1.1)	0.9 (0.7–1.1)	0.9 (0.7–1.1)	.621
Neutrophils [10^9/L] (median, IQR)	5.3 (4.2–6.9)	5.8 (4.4–7.4)	5.2 (4.2–6.7)	**.021**
Lymphocytes [10^9/L] (median, IQR)	1.3 (1.6–2)	1.6 (1.2–2)	1.6 (1.3–2)	.149
Neutrophil-to-lymphocyte ratio [10^9/L] (median, IQR)	3.34 (2.46–4.58)	3.57 (2.68–5)	3.26 (2.41–4.43)	**.016**
Creatinine [mg/dL] (median, IQR)	0.84 (0.71–1.01)	0.86 (0.7–1.02)	0.84 (0.71–1.01)	.903
eGFR [10^9/L] (median, IQR)	86.5 (68.1–99.9)	82.3 (66.3–95)	89.3 (68.6–101.9)	.088
Troponin T [ng/L] (median, IQR)	205.5 (105–353)	262 (134–394)	194.5 (100–336)	**.001**
C-reactive protein [mg/L] (median, IQR)	55.3 (32.6–90.5)	59.1 (37.8–97.8)	54.2 (31.6–88.7)	.072

Bold values reached the statistical significace (*p*-value < 0.05).

Abbreviations: eGFR, estimated glomerular filtration rate; Hb, hemoglobin; HCT, hematocrit; sPOAF, subacute postoperative atrial fibrillation; WBC, white blood cells.

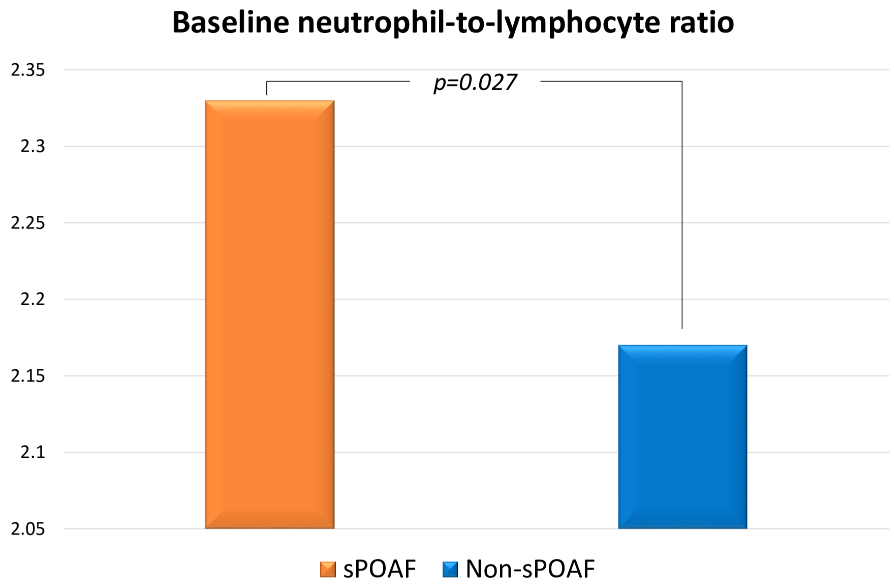

FIGURE 1 Baseline neutrophil-to-lymphocyte ratio values in patients with and without sPOAF.

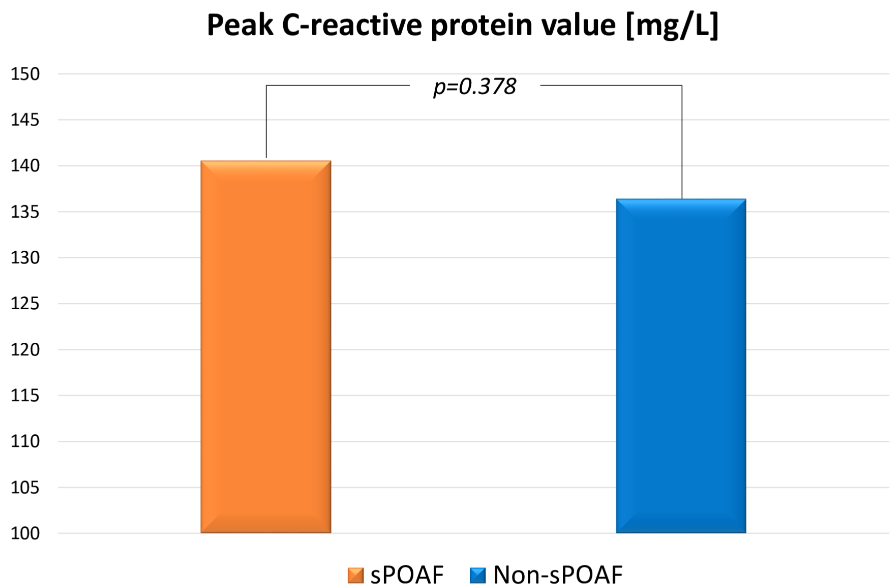

FIGURE 2 Peak C-reactive protein values in patients with and without sPOAF.

TABLE 3 Comparison of functional parameters on the first CR day (T1) between patients with and without sPOAF.

Cardiac rehabilitation admission (T1): Functional performance parameters				
	Whole population	sPOAF	Non-sPOAF	*p*-value
6MWT distance [m] (median, IQR)	270 (200–360)	250 (180–320)	275 (210–370)	**.015**
METs [mL O2/kg/min] (median, IQR)	2.6 (2.21–3.05)	2.52 (2.13–2.90)	2.6 (2.21–3.13)	**.028**

Bold values reached the statistical significace (*p*-value < 0.05).

Abbreviations: 6MWT, 6-minute walking test; METs, metabolic equivalents of task; sPOAF, subacute postoperative atrial fibrillation.

5.4 | Parameters of functional performance

Even parameters of physical performance at CR admission showed some differences as sPOAF patients covered a shorter distance (250 m vs. 275; $p = .015$) and had a worse exercise tolerance (2.5 Metabolic Equivalents of Task vs. 2.6; $p = .028$) when compared to non-arrhythmic subjects. (Table 3).

5.5 | Assessment of predictors of subacute postoperative atrial fibrillation

We performed binary logistic regression to determine independent predictors of sPOAF in patients attending cardiac rehabilitation (Table 4). At univariate analysis, age (OR 1.036; 95% CI 1.022–1.052; $p < .001$), preoperative LAVi (OR 1.223; 95% CI

TABLE 4 Binary logistic regression analysis for predictors of sPOAF.

Univariate and multivariate analysis for predictors of sPOAF				
	Univariate logistic regression		Multivariate logistic regression	
	OR (95% CI)	*p*-value	Adj. OR (95% CI)	*p*-value
Age	**1.036 (1.022–1.052)**	**<.001**	**1.030 (1.012–1.048)**	**.001**
Sex (Male)	1.060 (0.751–1.498)	.740		
Body mass index (BMI)	0.981 (0.941–1.022)	.365		
Obesity	1.049 (0.598–1.841)	.868		
Smoking	0.619 (0.307–1.246)	.179		
Previous smoking	0.916 (0.622–1.348)	.656		
Diabetes mellitus	0.928 (0.500–1.723)	.813		
Hypertension	1.088 (0.771–1.536)	.631		
Dyslipidaemia	1.176 (0.796–1.735)	.415		
Coronary artery disease (CAD)	0.813 (0.509–1.300)	.388		
CAD family history	0.988 (0.618–1.578)	.958		
CKD according to KDIGO	0.870 (0.470–1.611)	.658		
History of AF	**2.151 (1.444–3.204)**	**<.001**	1.543 (0.984–2.419)	.059
Preoperative LVEF	1.086 (0.854–1.421)	.572		
Preoperative LAVi	**1.223 (1.075–1.459)**	**.039**	1.128 (0.806–1.755)	.299
Valvular surgery	1.513 (0.433–5.288)	.517		
Aortic valve surgery	0.898 (0.624–1.294)	.564		
Mitral valve surgery	**1.477 (1.019–2.140)**	**.039**	**1.769 (1.131–2.767)**	**.012**
Tricuspid valve surgery	1.366 (0.876–2.130)	.169		
CABG	0.728 (0.332–1.599)	.429		
Complex surgery	**1.580 (1.116–2.237)**	**.010**	1.220 (0.807–1.844)	.345
aPOAF	**3.368 (2.363–4.801)**	**<.001**	**2.969 (2.012–4.383)**	**<.001**
Postoperative infections	1.261 (0.658–1.996)	.197		
T0-WBC	0.986 (0.911–1.066)	.720		
T0-Hb	1.0004 (0.9104–1.0993)	.994		
T0-Hct	0.952 (0.754–1.203)	.683		
T0-platelets	1.007 (0.990–1.023)	.422		
T0-Neutrophils	1.030 (0.986–1.075)	.187		
T0-Lymphocytes	1.007 (0.900–1.125)	.908		
T0-Neutrophil-to-lymphocyte ratio	**1.151 (1.039–1.275)**	**.007**	**1.127 (1.004–1.265)**	**.042**
T0-Creatinine	0.904 (0.648–1.262)	.554		
T0-eGFR	**0.9928 (0.9859–0.9998)**	**.045**	1.001 (0.992–1.010)	.872
T1-CRP	1.0003 (0.9986–1.0020)	.770		
T1-troponin T	**1.0007 (1.0001–1.0013)**	**.027**	1.0002 (0.9996–1.0009)	.481
T1-WBC	1.021 (0.960–1.085)	.509		
T1-Hb	1.012 (0.988–1.037)	.318		
T1-platelets	**0.9981 (0.9963–0.9999)**	**.042**	0.999 (0.997–1.001)	.234
T1-Neutrophils	1.015 (0.989–1.042)	.253		
T1-Lymphocytes	1.044 (0.950–1.148)	.373		
T1-Neutrophil-to-lymphocyte ratio	1.066 (0.993–1.143)	.077		
T1-Creatinine	0.881 (0.619–1.255)	.483		
T1-eGFR	0.996 (0.990–1.002)	.195		
Peak C-reactive protein	1.312 (0.756–2.004)	.178		
T1-6MWT distance	**0.997 (0.996–0.999)**	**.002**	0.999 (0.997–1.001)	.531
T1-METs	**0.739 (0.570–0.958)**	**.022**	1.074 (0.661–1.746)	.773

Bold values reached the statistical significace (p-value < 0.05).

Abbreviations: 6MWT, 6-minute walking test; AF, atrial fibrillation; aPOAF, acute postoperative atrial fibrillation; CABG, coronary artery bypass grafting; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; Hb, hemoglobin; HCT, hematocrit; KDIGO, kidney disease-improving global outcomes; LAVi, left atrial volume index; LVEF, left ventricle ejection fraction; METs, metabolic equivalents of task; sPOAF, subacute postoperative atrial fibrillation; WBC, white blood cells.

1.075–1459; $p = .039$), mitral valve procedures (OR 1.477 95% CI 1.019–2.140, $p = .039$), complex surgery (OR 1.580; 95% CI 1.116–2.237; $p = .010$), history of paroxysmal AF (OR 2.151; 95% CI 1.444–3.204; $p < .001$), acute postoperative AF (OR 3.368 95% CI 2.363–4.801; $p < .001$), T0-NLR (OR 1.151 95% CI 1.039–1.275; $p = .007$) and T1-troponin T (OR 1.0007; 95% CI 1.0001–1.0013; $p = .027$), T0-eGFR (OR 0.9928 95% CI 0.9859–0.9998; $p = .045$), T1-platelets (OR 0.9981 95% CI 0.9963–0.9999; $p = .042$), distance covered on T1-6MWT (OR 0.997; 95% CI 0.996–0.999; $p = .002$), and T1-Metabolic Equivalents of Task (OR 0.739; 95% CI 0.570–0.958; $p = .022$) resulted associated to sPOAF. Variables with a univariate p-value<.05 were subsequently entered into the final multivariate model. The multivariate analysis showed age (OR 1.030; 95% CI 1.012–1.048, $p = .001$), mitral valve procedures (OR 1.769 95% CI 1.131–2.767; $p = .012$), acute postoperative AF (OR 2.969; 95% CI 2.012–4.383; $p < .001$), T0-NLR (OR 1.127; 95% CI 1.004–1.265; $p = .042$) as independent predictors of sPOAF (Chi-square = 6.619; Hosmer-Lemeshow test $p = .578$; Nagelkerke's $R^2 = .158$; percentage of accuracy = 76.9%; AUC-ROC curve = 0.721; 95% CI 0.680–0.762; $p < .001$).

6 | DISCUSSION

AF was confirmed as a very common arrhythmia presenting in more than half of patients after CS. The present study is one of the first to describe specifically the frequency of subacute postoperative atrial fibrillation which is a potentially life-threatening condition.[22,23] Subacute POAF occurred in almost one fourth of patients in cardiac rehabilitation (CR), with higher incidence in older subjects, in those with known history of atrial fibrillation, and after mitral valve or complex surgical procedures.

Numerous studies evaluated the predictive role of clinical and laboratory findings in terms of postoperative arrhythmic risk,[26–35] but only few papers integrated both preoperative and postoperative data.[33,34] Mariscalco et al. derived and validated the so-called "POAF score", which was able to predict postoperative AF and its related or accompanying complications in patients undergoing CS; however, the score did not distinguish aPOAF from sPOAF and, secondly, it did not consider most of laboratory data (i.e. postoperative troponin or NLR).[36]

The occurrence of sPOAF should not be neglected as it has a stronger prognostic impact in comparison to aPOAF, being associated with several complications like stroke, renal failure, and increased post-surgical mortality.[19–23]

In this context, we decided to set up a cohort study in order to assess sPOAF predictors in CR. We evaluated the role of three-time spread predictive factors: preoperative (clinical anamnesis and baseline biochemistry), intraoperative (type of cardiac intervention), and postoperative (infective complications and CR biochemistry). In our population, sPOAF could be predicted using patient's age, type of heart surgery, episodes of acute POAF in Cardiac Surgery Unit, and baseline NLR values.

Older age, mitral disease, and aPOAF predispose to subacute arrhythmias because they stimulate atrial degeneration and electromechanical remodeling.[8,25,29,35] NLR, instead, is a well-known inflammation biomarker. Baseline NLR has been shown to be a good predictor of cardiovascular mortality in patients undergoing CABG,[35] while the association with postoperative AF remains controversial. Some authors proved that higher preoperative NLR increases the POAF risk,[29,33,34] while others did not obtain the same results.[37,38] A systematic review incorporating 12 studies reports that elevated preoperative NLR predicts POAF with a pooled OR of 1.42 (95% CI 1.16–1.72),[34] which is slightly higher than our result about sPOAF (OR 1.127; 95% CI 1.004–1.265). Inflammation is an important trigger for AF, but only chronic baseline inflammation seems to be related to the occurrence of POAF in the subacute phase. Preoperative cytokines background may represent the pathological substrate over which the surgical injury is responsible of the sPOAF onset even in naïve patients without additional risk factors. This may explain why colchicine exerts a protective effect over POAF, as demonstrated in COPPS trial[39] and confirmed by a recent metanalysis.[40]

Although further studies are necessary to fully understand the etiology of postoperative arrhythmias, the entity of surgical trauma and the subsequent inflammation as well as the grade of preoperative inflammatory status have a role in the sPOAF pathogenesis as for other postoperative complications.[41]

History of paroxysmal AF and complex surgery were more frequent among arrhythmic patients ($p = .010$); however, they both did not produce an increase of sPOAF occurrence during cardiac rehabilitation ($p = .059$ and $p = .345$, respectively), maybe due to the limited dimension of the study population. Similarly, troponin T measured on the first CR day was statistically associated with sPOAF but only at the univariate analysis. So, we cannot exclude that even the severity of cardiac damage might predispose to post-surgical arrhythmias.

Infections are common complications following CS and another well-known trigger of AF due to the release of several pro-inflammatory cytokines, like interleukin (IL)-6, IL-8.[42] The similar incidence of postoperative infective complications in patients with and without sPOAF as the non-significant association between infections and sPOAF at the binary logistic regression analysis contributes to give value to the predictive power of baseline NLR.

Interestingly, even preoperative LAVi did not result as a predictive factor of sPOAF: this evidence reflects the controversial data of the recent literature regarding a possible association between preoperative left atrial dimensions and postoperative atrial fibrillation.[43–45]

Thus, as atrial fibrillation has a negative prognostic impact, it is becoming increasingly important to identify arrhythmic predictors in order to stratify post-surgical patients into different risk categories. The definition of new predictors would allow the cardiologist to address high-risk patients to specific tailored programs of prolonged ECG monitoring, rehabilitation sessions, and even pharmacological prophylaxis. Personalized surveillance may facilitate the detection of post-surgical arrhythmias, possibly preventing severe complications like ischemic stroke and improving patients' prognosis.

7 | CONCLUSIONS

Atrial fibrillation is a very common postoperative arrhythmia following CS. It has a strongly negative impact in terms of morbidity, in-hospital stay, and postoperative mortality. Subacute postoperative atrial fibrillation is frequently diagnosed during the cardiac rehabilitation period. Older age, mitral valve surgical procedures, acute postoperative AF, and baseline neutrophil-to-lymphocyte ratio have been associated with sPOAF. The identification of arrhythmic predictors might be useful to stratify patients' risk in order to tailor treatment strategies and improve their prognosis during the postoperative phase.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

CLINICAL TRIAL REGISTRATION

N/A.

PATIENT CONSENT STATEMENT

Informed consent was obtained from all patients at admission.

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