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Article

Circulating Levels of Ferritin, RDW, PTLs as Predictive Biomarkers of Postoperative Atrial Fibrillation Risk after Cardiac Surgery in Extracorporeal Circulation

Claudia Altieri[1†], Calogera Pisano[1†], Labriola Vincenzo, Maria Sabrina Ferrante[1], Anna Maria Porreca[2], Paolo Nardi[1], Carlo Bassano[1], Dario Buioni[1], Ernesto Greco[3], Giovanni Ruvolo[1] and Carmela Rita Balistreri[4*†]

[1] Department of Cardiac Surgery, Tor Vergata University Rome, 00133 Rome, Italy
[2] Department of Medical Oral Science and Biotechnology, G. D'Annunzio, University of Chieti, Chieti, Italy
[3] Cardiac Surgery Unit, Department of Clinical, Internal Medicine, Anesthesiology and Cardiovascular Sciences, Sapienza University Rome, 00161 Rome, Italy
[4] Cellular and Molecular Laboratory, Department of Biomedicine, Neuroscience and Advanced Diagnostics (Bi.N.D.), University of Palermo, 90134 Palermo, Italy
† These authors contributed equally to this work
*Corresponding author: carmelarita.balistreri@unipa.it

Abstract: **Background**: Postoperative atrial fibrillation (POAF) is the most common arrhythmia after cardiac surgery in conventional extracorporeal circulation (CECC), with an incidence of 15-50%. The POAF pathophysiology is not known, and no blood biomarkers exist. However, an association between increased ferritin levels and increased AF risk, has been demonstrated. Based on such evidence, here, we evaluated the effectiveness of ferritin and other haemato-chemical parameters as a POAF onset biomarker in subjected to cardiac surgery. **Materials and Methods:** We enrolled 90 patients (mean age= 66.9±2.8 years; 40 men and 20 females) with diverse heart pathologies and subjected to cardiothoracic surgery. Their blood samples were collected and used to determine haemato-chemical parameters. The *tree test* approach was used to detect the best data-driven ferritin cuff-off value (=141 ng/ml) to predict POAF risk. **Results:** The data obtained demonstrated significant higher concentrations, absolute values, and percentages, of ferritin, RDW, PLTs, in POAF patients. However, the ferritin resulted to be the independent factor associated with the onset POAF risk. Thus, we detected the ferritin cut-off value, which, when ≥ 141 ng/ml identifies the subjects at the highest POAF risk. **Conclusions:** Ferritin values≥ 141 ng/ml might be used as predictive POAF biomarker.

Keywords: Postoperative atrial fibrillation; cardiac surgery; conventional extracorporeal circulation; circulating ferritin levels; POAF onset biomarker

1. Introduction

Cardiac Postoperative atrial fibrillation (POAF) is a secondary form of AF from the reversible cause [1]. POAF represents, in fact, the most common arrhythmia after thoracic or cardiac surgery, having a prevalence of about the 15% to 50% in patients subjected to coronary artery bypass surgery (CABG) [2], and of 60-80% in patients undergoing valve surgery [3,4]. POAF is associated with diverse severe complications, including stroke, cardiac failure, and cardiovascular death [3,4]. The risk to develop stroke, including stroke severity and mortality from stroke, is particularly frequent in post-cardiothoracic surgery AF patients [5,6]. All these complications need additional treatments, as well as prolonged hospital stays and increased costs [7].

The pathophysiology of POAF is not fully identified, but it appears to have a multifactorial character [1,3,4]. The first factor might be linked to surgery treatment which induces in patients a hypercoagulation, with a high risk of bleeding. Another factor manifests post-surgery and occurs with sympathetic activation, which causes heart rate

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elevation and catecholamine release, leading the myocardium to develop arrhythmia. In addition, post-surgery electrolyte imbalances, transient hypoxemia, and electrophysiological disturbances may also contribute to POAF onset. Furthermore, hypervolemia from intraoperative fluid administration can also induce right atrial stretching, causing an arrhythmia. Circulating increase of levels of elevated C-reactive protein (CRP) and interleukins, and a significative augment of leukocyte count also appear to contribute to the onset and progression of POAF, especially in post-cardiac surgery patients, even if the involved mechanisms are not well-recognized. Open heart surgery and CECC also contribute to evocating local and systemic inflammation. In addition to direct effects on the heart, systemic inflammation may cause diminished visceral blood flow resulting in mucosal ischemia, edema, and impaired mucosal transport. A better understanding of the underlying mechanisms might enable the identification of new therapeutic targets [1,3,4].

No blood biomarkers exist until now for facilitating POAF management [3,4]. However, a recent metanalysis [8] conducted on 35799 male and female individuals from the general Danish population has demonstrated a significant association between the increased ferritin concentration and higher risk of AF in both sexes, even if the effect size appeared to be more pronounced in men. In addition, the authors of such study have evidenced a growing enhancement in AF risk related to a stepwise increasing ferritin concentration, with a peak of the highest AF risk when the ferritin concentration is > 600 μg/L both in men and women [8]. Another study from Sokal and coworkers [9], conducted on 40 patients subjected to the first AF cryoablation procedure and followed for a period of follow-up time of 6 months, has evidenced increased levels of ferritin combined with augmented concentrations of high sensibility-CRP, as optimal AF biomarkers and its usefulness in the evaluation of the efficacy of cryoablation.

Based on such evidence, we tested for the first time the effectiveness of circulating ferritin levels and the other haemato-chemical biomarkers as POAF onset biomarkers in 90 patients (mean age=69.2±8.1 years; 60 men and 30 females) subjected to cardiothoracic surgery.

2. Results

2.1 Demographic and basal clinical characteristics of patients enrolled in the study

They are presented in **Table 1**. Precisely, we selected in the study 90 patients having a mean age of 69.2 (±8.1 SD) years, prevalently constituted by men for the 67%, and affected 80% by hypertension, 15% by diabetes, 30% by dyslipidemia, 22% by COPD, 30% by obesity, and with previous cardiovascular events in the 33%. The 26.7% and the 10% of the patients was respectively subjected to ace-inhibitors and amiodarone treatment. In addition, the 45% of cases was smoker and the 25% ex-smoker. All the cases were subjected to cardiothoracic surgery for coronaropathies (N=22), valvopathies (mitral and/or aortic; N=40), ascending aorta aneurysms (N=22), or for a combined aortopathies (3 with valvopathies and ascending aorta aneurysms; and 3 with coronaropathies and ascending aorta aneurysms).

Of them 30 cases (see Table 1) developed POAF within the 5 postoperative days. They were characterized by being older (mean age: 71.2±9.2; p=0.02 by t test) and prevalently man (70%), and with the highest value of body surface area (BSA) and of percentages of obesity (50%), hypertension (90%), COPD (43%) and previous CVD (53%) (see Table 1).

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Table 1. Demographic and basal clinical characteristics of patients.

Variables	Overall	Without POAF	With POAF	p-value
	N=90	***n= 60***	***n=30***	
Gender, n (%), n (%):				
F	30 (33.0)	21 (35.0)	9 (30.0)	0.81 †
M	60 (67.0)	39 (65.0)	21 (70.0)	
Age (mean ±SD)	69.2±8.1	**66.5±7.8**	**71.2±9.2**	**0.006^**
Body surface area (BSA), (mean± SD)	1.80±3.8	1.83±4.3	1.91 ±5.2	0.46^
IPERTENSION, n (%), n (%):				0.07§
No	18 (20.0)	15 (25.0)	3 (10.0)	
YES	72 (80.0)	45 (75.0)	27 (90.0)	
Smoking, n (%):				0.93†
Ex	22 (25.0)	14 (23.0)	8 (27.0)	
No	27 (30.0)	18 (30.0)	9 (30.0)	
YES	41 (45.0)	28 (47.0)	13 (43.0)	
DIABETES, n (%):				0.44§
No	77 (85.0)	52 (87.0)	25 (83.0)	
YES	13 (15.0)	8 (13.0)	5 (17.0)	
DYSLIPIDEMIA, n (%):				0.11§
No	63 (70.0)	43 (72.0)	20 (67.0)	
YES	27 (30.0)	17 (28.0)	10 (33.0)	
Chronic obstructive pulmonary disease (COPD), n (%):				**0.001§**
No	70 (78.0)	**53 (88.0)**	**17 (57.0)**	
YES	20 (22.0)	**7 (12.0)**	**13 (43.0)**	
OBESITY, n (%):				**0.004§**
No	63 (70.0)	**48 (80.0)**	**15 (50.0)**	
YES	27 (30.0)	**12 (20.0)**	**15 (50.0)**	
Previous cardiovascular diseases (CVD), n (%):				**0.004§**
No	60 (67.0)	**46 (77.0)**	**14 (47.0)**	
YES	30 (33.0)	**14 (33.0)**	**16 (53.0)**	
Amiodarone., n (%):				0.22 §
No	77 (85.0)	53 (88.0)	24 (80.0)	
YES	13 (15.0)	7 (12.0)	6 (20.0)	
ACE-INHIBITORS., n (%):				0.470†
No	63 (70.0)	43 (72.0)	23 (77.0)	
YES	27 (30.0)	17 (28.0)	7 (33.0)	

§ p-value derived from Fisher exact test

†p-value derived from the Chi-squared test

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^ p-value derived from t test

2.2. Evaluation of circulating Ferritin levels and other haemato-chemical biomarkers in POAF vs. No POAF cases

By comparing the serum levels of haemato-chemical biomarkers in the patients with POAF vs. cases without POAF (**see Table 2**), we detected that POAF cases had significantly lower concentrations of HB and sideraemia than patients without POAF. In addition, POAF patients showed significantly higher concentrations and percentages, of Ferritin and RDW, respectively (**see Table 2**). Besides, the circulating levels of PLT also resulted significantly higher in POAF cases. However, after adjustment for age, previous CVD, obesity, hypertension, COPD, and gender, we assessed significative differences persisting only between the concentrations of Ferritin and the POAF risk (*P*=.002, by a logistic regression analysis). POAF cases also developed postoperative complications (i.e., endotracheal intubation>48h, pericardial and pleural spillage, p=0.059, by Chi squared test; data not shown) than cases without POAF and subjected to cardiothoracic surgery.

Table 2. Preoperative circulating levels of haemato-chemical biomarkers in the patients enrolled in the study.

Variables	Overall	Without POAF	With POAF	p-value^ *(POAF cases vs. cases without POAF)*
	N=90	***N=60***	***N=30***	
Hemoglobin, HB (g/dl) (mean ± SD)	13.4 ± 5.6	**13.8±7.8**	**11±4.6**	**0.036**
PLT $10^3/\mu L$	229.42±12.8	**231±6.7**	**244.8±6.9**	**<0.0001**
CREATININE (mg/dl)	1.31 ±8.9	0.98±8.9	1.49±9.2	0.39
International normalized ratio (INR)	1.10±0.9	1.09±3.8	1.23±5.4	0.45
Mg (mg/dl)	2.02±2.6	1.96±2.1	1.8±4.8	0.42
K (mEq/L)	4.24 ±3.1	4.18±2.9	4.29±3.2	0.44
RDW (%)	14.1±3.6	**12.8 ±4.5**	**15.9±3.1**	**0.0005**
FERRITIN (ng/ml)	217.11±4.9	**237.5±6.9**	**284.2±3.1**	**<0.0001**
SIDERAEMIA	81.5 ±3.6	82 ±4.6	79 ±5.6	**0.01**

^p values detected by t test

2.3. Predictive Role of Ferritin on the POAF risk and outcomes in the patients enrolled

Given the strong action of Ferritin as a variable independent of the POAF risk, as reported above, we calculated through the tree test, the ferritin cut-off value, equal to 141 ng / ml, which allows to identify two subgroups of patients on 90 enrolled (see Figure1): a) **group 1** with basal ferritin values ≥ 141ng/ml, represented by 54.0% (49/90) of the total patients, who developed, when subjected to cardiothoracic surgery, POAF for the 59% (29/49) of cases; b) **group 0,** having basal ferritin values ≤ 141ng/ml, and represented by

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46% of the total patients (41/90), who developed POAF only in 3% of them. Thus, the basal ferritin values ≥ 141ng/ml consent of identifying the cases enrolled with the highest risk of developing POAF. Accordingly, the group 0 with basal ferritin values ≤ 141ng/ml resulted prevalently represented by cases, the 97%, who did not develop POAF after cardiothoracic surgery.

2.4. Major prevalence of risk POAF factors in the Group 1vs. Group 0

In addition, as shown in Table 3, the cases of group 1 were significantly older, and with major factors of risk for POAF (i.e., hypertension 79%, COPD 27%, obesity 31%, previous CVD 41%), than the cases of group 0, even if no significant differences were detected by comparing the values. In addition, they showed to have significant lower levels of HB and sidereamia than the subjects of group 0, and significant higher levels of PTLs and percentages of RDW.

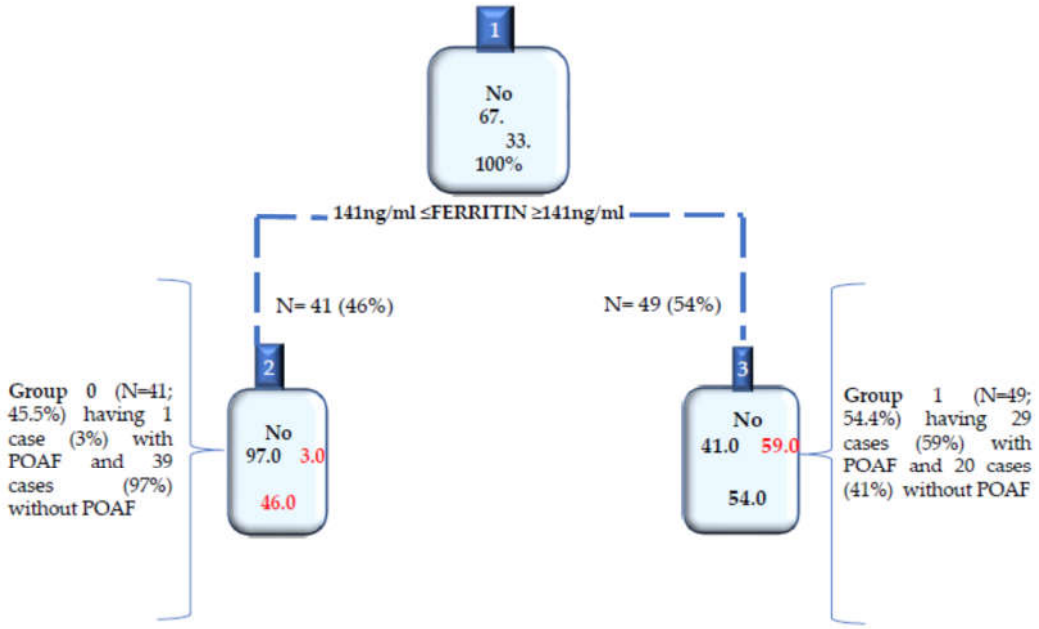

Figure 1. Classification tree (CART) for POAF outcome on 90 patients using ferritin levels as a predictor. Values in nodes represent the percentages of POAF=No. The shows the classification tree analysis. Starting from a situation in which 67% of patients was without POAF and 33% with POAF (see Table 1), it is possible to obtain the maximum decrease in node impurity by "splitting" on basal ferritin variable with a cut-off of ≥141ng/ml. All patients with a basal ferritin level ≥141 ng/ml will go to the right of the split while all others will go to the left of the split.

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Table 3. A and B. Hematological biomarkers, and demographic and clinical features in the two sub-groups obtained by stratifying for the ferritin value of 141ng/ml detected by tree test analysis.

A.

Variables	Group 0	Group 1	p-value^
Hemoglobin, HB (g/dl) (mean ± SD)	**14±5.1**	**12±3.8**	**0.02**
PLT $10^3/\mu L$	**218±5.9**	**239±8.9**	**<0.0001**
CREATININE (mg/dl)	1.02±8.9	1.18±8.1	0.45
International normalized ratio (INR)	1.07±2.1	1.14±5.4	0.42
Mg (mg/dl)	1.87±2.1	1.9±5.8	0.43
K (mEq/L)	4.18±2.9	4.09±3.1	0.45
RDW (%)	**13 ±6.1**	**15.1±5.6**	**0.047**
SIDERAEMIA	87 ±7.1	80 ±6.1	**<0.0001**

B.

Variables	Group 0	Group 1	p-value
Gender, n (%), n (%):			
F	12 (29.0)	19 (39.0)	0.23 †
M	29 (71.0)	30 (61.0)	
Age (mean ±SD)	**68±8.1**	**72±8.2**	**0.002^**
Body surface area (BSA), (mean± SD)	1.84±4.9	1.90 ±5.6	0.46^
IPERTENSION, n (%), n (%):			0.07§
No	15 (37,0)	10 (21.0)	
YES	26 (63.0)	39 (79.0)	
Smoking, n (%):			0.83†
Ex	10 (0.0)	12 (24.0)	
No	15 (37.0)	7(15.0)	
YES	26 (63.0)	30 (61.0)	
DIABETES, n (%):			0.21§
No	33 (80.0)	44 (90.0)	
YES	8 (20.0)	5 (10.0)	
DYSLIPIDEMIA, n (%):			0.07§
No	24 (72.0)	39 (79.5.)	
YES	17 (28.0)	10 (20.5)	
Chronic obstructive pulmonary disease (COPD), n (%):			0.20§

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No	34 (88.0)	36 (73.0)	
YES	7 (12.0)	13 (27.0)	
OBESITY, n (%):			0.53§
No	29 (70.0)	34 (69.0)	
YES	12 (30.0)	15 (31.0)	
Previous cardiovascular diseases (CVD), n (%):			0.07§
No	31 (76.0)	29 (59.0)	
YES	10 (24.0)	20 (41.0)	
Amiodarone., n (%):			0.21 §
No	33 (80.0)	45 (92.0)	
YES	8 (20.0)	4 (8.0)	
ACE-INHIBITORS., n (%):			0.0001
No	22 (54.0)	44 (90.0)	
YES	19 (46.0)	5 (10.0)	

3. Discussion

Molecular biomarkers permit to apply individual decisions in the complex management of a pathology, such as POAF, and their identification constitutes a fundamental phase for achieving the important object to develop personalized therapies [10, 11]. Precisely, predictive POAF biomarkers could permit to reduce the hospital stays, the related costs and to guaranty a better life quality to patients subjected to cardiothoracic surgery by applying preventive personalized treatments. Consistent with such observation and the recent evidence, in our study, we evaluated, for the first time, the effectiveness of the circulating levels of ferritin and the other haemato-chemical biomarkers as POAF onset biomarkers in 90 patients (mean age=69.2±8.1 years; 60 men and 30 females) subjected to cardiothoracic surgery. The data obtained demonstrated that POAF patients showed significantly higher concentrations, absolute values, and percentages, of ferritin, RDW, PLTs, respectively. However, after adjustment for other risk POAF variables, the ferritin resulted to be the independent factor associated with the onset POAF risk. Such interesting result led us to detect the ferritin cut-off value, which, when equal to or greater than the value of 141 ng/ml, identifies the subjects at the highest risk of developing POAF. The high-risk POAF group was defined by us *group 1,* for deafferenting it by the *group 0*, having values of ferritin ≤ 141ng/ml. The subjects of group 1 were significantly older, and with major factors of risk for POAF (i.e., hypertension 79%, COPD 27%, obesity 31%, previous CVD 41%), than the cases of group 0, even if no significant differences were detected by comparing the values. In addition, they showed to have significant lower levels of HB and sideraemia than the subjects of group 0, and significant higher levels of PTLs and percentages of RDW. No other differences were, however, detected between the two groups.

These findings demonstrate, for the first time, the importance to detect the ferritin values, and if ≥141 ng/ml in our case, in the individuals to subject to cardiothoracic surgery, given the high probability of developing POAF after the surgery treatment in CECC. This evaluation is always underestimated, as well as the screening of total iron parameters. They can evidence not only an iron deficiency status accompanied by clinical symptoms (i.e., fatigue, which is not specific and often confused with the symptoms of primary diseases), but they can also provide information about the clinical status of a patient, an individual, related to degree of systemic inflammation. It is well recognized, indeed, that

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the status of iron deficiency is recurrent in patients with chronic inflammatory diseases (such as chronic cardiovascular diseases [12-14], i.e., coronaropathies, valvopathies, and ascending aorta aneurysms, affecting the patients of our study), that significantly correlates with their severity. Iron deficiency is mediated by high systemic levels of cytokines, which evocate a parallel increase of hepcidin concentrations. In turn, hepcidin causes the sequestration of iron in cells of the reticuloendothelial system, determining the onset of a functional iron deficiency, even without anemia. The development of iron deficiency, even if functional, exacerbates underlying chronic diseases, alters erythropoiesis, and represents an independent factor of morbidity and mortality. In daily practice, the the iron body status is evaluated by detecting ferritin concentrations, because it reflects the iron body storage and transferrin saturation, which reproduces the transport of iron [12, 13]. The serum concentration of ferritin is usually augmented in cases with a systemic inflammatory body condition likely related to diverse chronic inflammatory diseases, even if there is still not a scientific and clinical consensus on a threshold value to be used in chronic inflammatory conditions [14]. However, international guidelines define the iron deficiency condition when the serum ferritin values are <100 μg/L related or not to a transferrin saturation <20% and suggest to attention the condition of iron depletion. In addition, it has been reported that high serum ferritin levels correlate with aging process [15]. Accordingly, we detected that the patients of group 1 were older and with a worse clinical history than the patients of group 0, and with the highest levels of ferritin, which suggested in the complex a severer inflammatory status and clinical conditions than the components of group 0. They also had lower levels of HB and higher percentages and levels of RDW and PTLs, as abovementioned, which evidenced a severity grade of the inflammatory status and clinical conditions. Such erythropoiesis disturbances have been showed to be likely determined by the iron sequestration in the macrophages. Two recent studies [16, 17] have, indeed, demonstrated significant associations between RWD, the sensitive marker of increased red cells turnover [18,19], and AF in general populations. In addition, Topal and coworkers [20] have recently proved that the median values of white blood cell, platelet, neutrophil, neutrophil/lymphocyte ratio, platelet/lymphocyte ratio, resulted significantly greater in cases with AF and undergoing off-pump coronary artery bypass grafting than in those in the non- AF group. Likewise, Sayin and coworkers [21] have also documented that PLT counts accompanied by the evaluation of other immune-inflammatory indexes can predict new onset AF in cases affected by acute coronary syndrome. Guzelburc and colleagues [22] have also detected a significant relationship between preoperatively calculated Platelet max index (PMI) and POAF, concluding that PMI may be used to predict patients at high risk of developing POAF. No studies there are until now in literature on the significant relationship between preoperatively calculated ferritin concentration and POAF. The limited number of studies, precisely represented by two works, have examined this association with AF only in general population. Of note is, however, the metanalysis conducted on 35799 male and female individuals from the general Danish population [8], as well as the study from Sokal and coworkers [9], conducted on 40 patients subjected to the first AF cryoablation procedure. This evidences the necessity to validate our date in a larger number of cases and to perform prospective studies than retrospective investigations, such as our study, that suffers of this limitation, as well as a relatively reduced number of cases, to include in the evaluation other immune and inflammatory parameters.

4. Materials and Methods

4.1. Study population and design

The study was started once approval was obtained from the local ethics committee. This was a retrospective observational cohort study and conducted on patients, having a mean age of 69.2 (±8.1 SD) years, prevalently constituted by men for the 67%, and affected 80% by hypertension, 15% by diabetes, 30% by dyslipidemia, 22% by COPD, 30% by obesity, and with previous cardiovascular events in the 33%. They were subjected to elective

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cardiothoracic surgery for coronaropathies (N=22), valvopathies (mitral and/or aortic; N=40), ascending aorta aneurysms (N=22), or for a combined aortopathies (3 with valvopathies and ascending aorta aneurysms; and 3 with coronaropathies and ascending aorta aneurysms). In addition, they were selected by the team of Cardiac surgery Unit from Tor Vergata University, between January 2021 and March 2022. Patients were also divided into two groups, namely, group 1 and group 0, according to the occurrence of POAF during the postoperative period (after 5 days) and the ferritin cut-off values. Patients' preoperative baseline clinical characteristics, comorbid conditions, laboratory parameters, intraoperative data, postoperative outcomes, and complications were screened through the computerized medical database of the hospital, recorded, and compared between the groups (see Tables 1-3). Thus, the predictive risk factors and perioperative results of POAF after cardiothoracic surgery were determined. Patients with a history of previous AF or other cardiac dysrhythmias, those undergoing emergency and re-operative operations were excluded from the study.

4.2. Postoperative monitoring

During the postoperative first 48 h in ICU, electrocardiogram (ECG), invasive central venous and arterial pressures, and oxygen saturation of the patients were continuously monitored, and arterial blood gas analyses were performed regularly every 2–4 h. Cardiac rhythms of patients were assessed by obtaining standard 12-lead ECGs every day for the remaining days until discharge. In addition, heart rate and rhythm were assessed by palpation of the radial pulse at least once in every 4 h. An additional 12-lead ECG was obtained and analyzed in case of tachycardia, palpitation, or a suspicion of an irregular cardiac rhythm. POAF was diagnosed with the existence of an irregular RR interval and an absence of P wave on the ECG.

4.3. Laboratory analysis

Blood samples were taken from a peripheral vein after a 6–8-h fasting period. The samples were placed into sterile tubes containing a standard amount of anticoagulant and were quickly delivered to the laboratory for the analysis. To determine preoperative values of the haemato-chemical parameters, the samples were studied in an automatic CBC analysis device (Beckman Coulter Inc., CA, USA). The studied and derived CBC parameters for this study were hemoglobin (HB), Red cell distribution width (RDW) and platelet (PLT) counts, expressed among the patients as mean ± standard deviation. Furthermore, concentrations of ferritin (immunochemical method) and sideraemia (immunochemical method) were determined in standard way in hospital laboratory using Roche Diagnostics reagents according to the manufacturer instructions.

4.4. Statistical Analysis

Normality distribution for quantitative variables was assessed by the Shapiro-Wilk. The Mann–Whitney U test was computed to compare continuous clinical variables expressed as mean± standard deviation, while chi-square tests or the Fisher's exact test (count <5) were used to compare categorical ones. Multiple explanatory variable logistic regression analysis was performed to determine the risk factors/covariates for POAF. A classification tree (CART) [23] was grown using binary recursive partitioning to predict the POAF outcome detecting the best partition (cut-off) for the ferritin basal level. Recursive partitioning is a statistical tool used to separate a group into 2 subgroups, repeatedly, given some risk factors of interest. This is a data-driven approach to explore the data to search for optimal split variables, builds a decision tree structure and finally classify all subjects into subgroups that are homogeneous with respect to the outcome of interest [24].During the CART analysis, first, the entire study population, and thereafter, all newly defined subgroups, were investigated at every step of the analysis to determine which variable at what cut-off point yielded the most significant division into two prognostic subgroups that were as homogeneous as possible with respect to estimates of FAPO

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outcome. The rule of splitting is based on the minimization of the Gini Index [25]. Subgroups resulting from a minimum split criterion chose to be at least 30 patients. The resulting final subgroups were most homogeneous with respect to the probability of having POAF. All statistical analyses were performed using R Statistical Software (version 3.5.3; R Foundation for Statistical Computing, Vienna, Austria). All tests were two-tailed, and a p-value ≤ 0.05 was considered indicative of a statistically significant association.

5. Conclusions

This is the first study to investigate and demonstrate significant association between plasma ferritin concentration, as a biomarker of functional iron deficiency, and chronic inflammation, or better predictive of POAF. Our data, consequently, suggest the relevance to clearly recommend the screening of the iron parameters, and particularly of ferritin, and the use of appropriate preoperative anti-inflammatory treatments in patients with values of ferritin superior of 141ng/ml to subject to surgery treatments for reducing the post-operative complications, such as POAF, and improving the clinical features and consequently the life quality, as well as the surgery success associated with the reduction of prolonged hospital stays and increased costs.

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