Galectin-3 is an independent predictor of postoperative atrial fibrillation and survival after elective cardiac surgery

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BACKGROUND Postoperative atrial fibrillation (POAF) is a frequent complication after heart surgery and is associated with thromboembolic events, prolonged hospital stay, and adverse outcomes. Inflammation and fibrosis are involved in the pathogenesis of atrial fibrillation.

OBJECTIVE The purpose of this study was to assess whether galectin-3, which reflects preexisting atrial fibrosis, has the potential to predict POAF and mortality after cardiac surgery.

METHODS Four hundred seventy-five consecutive patients (mean age 67.4 ± 11.8 years; 336 (70.7%) male) undergoing elective heart surgery at the Medical University of Vienna were included in this prospective single-center cohort study. Galectin-3 plasma levels were assessed on the day before surgery.

RESULTS The 200 patients (42.1%) who developed POAF had significantly higher galectin-3 levels (9.60 ± 6.83 ng/mL vs 7.10 ± 3.54 ng/mL; $P < .001$). Galectin-3 significantly predicted POAF in multivariable logistic regression analysis (adjusted odds ratio per 1-SD increase 1.44; 95% confidence interval 1.15–1.81; $P = .002$). During a median follow-up of 4.3 years (interquartile range 3.4–5.4 years), 72 patients (15.2%) died. Galectin-3 predicted all-cause mortality in multivariable Cox regression analysis (adjusted hazard ratio per 1-SD increase 1.56; 95% confidence interval 1.16–2.09; $P = .003$). Patients with the highest-risk galectin-3 levels according to classification and regression tree analysis (>11.70 ng/mL) had a 3.3-fold higher risk of developing POAF and a 4.4-fold higher risk of dying than did patients with the lowest-risk levels (≤5.82 ng/mL).

CONCLUSION The profibrotic biomarker galectin-3 is an independent predictor of POAF and mortality after cardiac surgery. This finding highlights the role of the underlying arrhythmogenic substrate in the genesis of POAF. Galectin-3 may help to identify patients at risk of POAF and adverse outcome after cardiac surgery.

KEYWORDS Galectin-3; Postoperative atrial fibrillation; Cardiac surgery; Fibrosis; Mortality; Biomarker

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Introduction

Postoperative atrial fibrillation (POAF) within the first days of cardiac surgery occurs in an estimated 20%–50% of patients and is associated with thromboembolic events, hemodynamic instability, heart failure (HF), prolonged hospital stay, and adverse long-term outcomes.[1–3] The mechanisms of POAF are far from being understood, and it is still difficult to identify patients at risk. Preexisting patient factors and intraoperative atrial tissue injury (caused by hypoxia, inflammation, oxidative stress, surgery, etc) increase the risk of POAF as does sympathetic activation.[1,4] Although atrial remodeling and fibrosis are known to cause conduction abnormalities and facilitate the development of atrial fibrillation (AF),[5] the role of preexisting fibrosis in the genesis of POAF remains uncertain[6,7] and the role of the novel biomarker galectin-3 has not yet been assessed.

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Galectin-3, a pleiotropic β-galactoside–binding lectin, is abnormally increased in fibrotic disorders in various organ systems including heart, liver, kidney, and lung and is associated with poor prognosis.[8–10] Galectin-3 is activated in in vitro models of fibrosis[11] and itself promotes the activation of additional profibrotic factors, fibroblast proliferation, and collagen production.[10] In addition to its pivotal role in ventricular fibrosis and HF where it strongly predicts mortality and disease progression,[9,10] galectin-3 is regarded as an upstream mediator of atrial remodeling and atrial fibrogenesis.[12] Furthermore, galectin-3 is independently correlated with the left atrial (LA) volume index and the extent of LA fibrosis[13] and predicts the incidence of AF.[14]

It seems intuitive that galectin-3 might provide additional discriminatory power in the prediction of both POAF and fatal events on an individual patient level in the era of personalized medicine. Therefore, we aimed to assess the value of preoperative plasma levels of galectin-3 for the prediction of POAF and long-term survival in a comprehensive cohort of patients undergoing elective cardiac surgery.

Methods

Study design, setting, and population

This prospective, observational, single-center cohort study was conducted at the Medical University of Vienna (Vienna General Hospital) in Austria, a large university-affiliated tertiary center. Between May 2013 and May 2018, all patients admitted for elective coronary artery bypass graft (CABG) surgery and/or valve surgery (valve replacement or reconstruction) were eligible for inclusion in this study. Exclusion criteria were age less than 18 years, AF at hospital admission or within the last 6 months before admission, nonelective cardiac surgery, planned percutaneous or transapical valve implantation, and refusal to give informed consent. The study adheres to the Declaration of Helsinki as revised in 2013 and was approved by the ethics committee of the Medical University of Vienna (EK No: 1110/2013). All patients provided written informed consent for the participation in the study.

Routine preoperative assessment included electrocardiogram (ECG), echocardiogram, clinical examination, assessment of medical history, and determination of standard laboratory parameters. Participation in the study had no influence on the surgical or postoperative treatment.

After surgery, all patients were initially treated in the intensive care unit and transferred to intermediate care units or normal cardiac/cardiothoracic hospital wards thereafter. Patients were continuously ECG monitored via ECG telemetry during their hospital stay to detect arrhythmia. If patients developed AF, 12-lead ECG was performed. Stored ECG data were analyzed for the presence of AF by trained medical study personnel in all patients.

Study end points

The primary study end point *POAF* was defined as AF occurring during the postoperative hospital stay. *AF* was defined in accordance with the guidelines of the European Society of Cardiology[15] as atrial arrhythmia with absolutely irregular R-R intervals without discernible, distinct P waves lasting for at least 30 seconds. The secondary study end point of all-cause mortality was determined by screening the Austrian register of death (Statistics Austria; https://www.statistik.at/en).

Blood sampling and laboratory analysis

Peripheral venous blood samples were collected on the day before heart surgery. Samples were centrifuged immediately at 3000 rpm (4°C) for 20 minutes, and ethylenediaminetetraacetic acid plasma was stored at −80°C until analysis. Galectin measurements were performed at 1 single time point after a storage duration of 2.9 ± 1.4 years. There was no significant correlation ($r = 0.08$) between the duration of sample storage and measured galectin-3 levels. Ethylenediaminetetraacetic acid plasma levels of galectin-3 were analyzed by enzyme-linked immunosorbent assay (Quantikine, R&D Systems Inc., Minneapolis, MN). Intra- and interassay coefficients of variation for galectin-3 were ≤3.8% and ≤6.3%, respectively. The minimum detectable concentration was 0.016 ng/mL. The measurement and analysis of galectin-3 were performed by a laboratory technician who was not involved in other study activities and was blinded to clinical data. We did not exclude any galectin-3 values from the analysis.

Statistical methods

Categorical data are reported as count and percentage. Associations between categorical data and tertiles (and risk categories) of galectin-3 were analyzed using a test for linear association (Mantel-Haenszel χ^2 test). Continuous data are presented as mean ± SD, and comparison between tertiles (and risk categories) of galectin-3 was performed using the Kruskal-Wallis test. The Spearman correlation coefficient ρ was used to assess correlations between continuous variables. Continuous and categorical variables were compared between the POAF and non-POAF groups by using the Mann-Whitney *U* test and χ^2 test, respectively. Univariate and multivariate binary logistic regression was applied to assess the association between POAF and galectin-3 (and galectin-3 risk categories). Continuous variables were log-transformed before entering regression analysis. In multivariable analysis, we adjusted for the following variables: EuroSCORE II,[16] age, gender, body mass index, coronary artery disease (CAD), arterial hypertension, valvular heart disease, chronic HF, LA diameter index, severity of mitral regurgitation, history of AF, history of cardiac surgery, baseline C-reactive protein and creatinine levels, aortic cross-clamp time, type of surgery (combined procedure [CABG plus valve surgery] vs single procedure [either CABG or valve surgery]), peak lactate and peak noradrenalin dose in the intensive care unit after surgery. The association between the secondary end point all-cause mortality and galectin-3 (and galectin-3 risk categories) was assessed by univariate

Table 1 Patient characteristics

Characteristic	Entire cohort (N = 475)	POAF group (n = 200)	No POAF group (n = 275)	*P*
Galectin-3 level (ng/mL)	8.15 ± 5.32	9.60 ± 6.83	7.10 ± 3.54	<.001
Age (y)	67.4 ± 11.8	70.6 ± 9.5	65.0 ± 12.6	<.001
Male gender	336 (70.7)	130 (65.0)	206 (74.9)	.019
Body mass index (kg/m^2)	27.5 ± 5.1	27.8 ± 5.8	27.3 ± 4.4	.872
Heart rate (beats/min)	71.2 ± 11.7	71.2 ± 10.8	71.2 ± 12.4	.744
Systolic blood pressure (mm Hg)	130.9 ± 17.8	131.2 ± 17.8	130.7 ± 17.9	.965
Diastolic blood pressure (mm Hg)	71.7 ± 12.9	70.9 ± 12.9	72.4 ± 12.9	.409
Coronary artery disease	290 (61.1)	124 (62.0)	166 (60.4)	.718
History of myocardial infarction	125 (26.3)	54 (27.0)	71 (25.8)	.802
Valvular heart disease	335 (70.5)	157 (78.5)	178 (64.7)	.001
Chronic heart failure	265 (55.8)	125 (62.5)	140 (50.9)	.013
Left atrial diameter (mm)	57.0 ± 3.8	57.7 ± 3.6	56.5 ± 3.9	.001
Left atrial diameter index (mm/m^2)	29.9 ± 3.9	30.4 ± 3.9	29.5 ± 3.8	.003
Mitral regurgitation				.002
Normal or trace	101 (21.3)	35 (17.5)	66 (24.0)	
Mild	250 (52.6)	100 (50.0)	150 (54.5)	
Moderate	62 (13.1)	33 (16.5)	29 (10.5)	
Severe	62 (13.1)	32 (16.0)	30 (10.9)	
Hypertension	384 (80.8)	169 (84.5)	215 (78.2)	.089
Type 2 diabetes mellitus	141 (29.7)	65 (32.5)	76 (27.6)	.252
Chronic lung disease	63 (13.3)	34 (17.0)	29 (10.5)	.041
Serum creatinine level (mg/dL)	1.15 ± 0.91	1.32 ± 1.29	1.02 ± 0.43	.009
Baseline C-reactive protein level (mg/dL)	0.69 ± 1.79	0.81 ± 1.98	0.60 ± 1.63	.026
Baseline leukocyte count (10^9/L)	7.39 ± 2.04	7.41 ± 2.01	7.37 ± 2.07	.462
History of cardiac surgery	26 (5.5)	6 (3.0)	20 (7.3)	.041
History of atrial fibrillation	46 (9.7)	26 (13.0)	20 (7.3)	.037
EuroSCORE II (points)	4.3 ± 5.6	5.0 ± 6.3	3.7 ± 5.1	<.001
Surgery				
Type of surgery				.004
CABG	157 (33.1)	55 (27.5)	102 (37.1)	
Valve surgery	199 (41.9)	80 (40.0)	119 (43.3)	
Valve surgery plus CABG	119 (25.1)	65 (32.5)	54 (19.6)	
Aortic cross-clamp time (min)	92.3 ± 40.3	98.7 ± 44.1	87.7 ± 36.7	.011
Cardiopulmonary bypass time (min)	136.4 ± 55.8	148.6 ± 63.7	127.4 ± 47.4	.001
Postsurgical intensive care unit				
Peak noradrenalin dose (μg/(kg·min))	0.14 ± 0.22	0.15 ± 0.23	0.13 ± 0.21	.015
Peak lactate level (mmol/L)	2.86 ± 1.90	3.09 ± 1.81	2.69 ± 1.95	<.001
Medication on admission				
β-Blocker	268 (56.4)	118 (59.0)	150 (54.5)	.334
RAAS inhibitor	270 (56.8)	116 (58.0)	154 (56.0)	.664
ACE inhibitor	143 (30.1)	64 (32.0)	79 (28.7)	.443
ARB	131 (27.6)	55 (27.5)	76(27.6)	.974
Statin	299 (62.9)	120 (60.0)	179 (65.1)	.257
Aldosterone receptor antagonist	59 (12.4)	26 (9.5)	33 (16.5)	.022
Loop diuretic	113 (23.8)	54 (19.6)	59 (29.5)	.013
Thiazide diuretic	97 (20.4)	58 (21.1)	39 (19.5)	.671

Categorical data are presented as count (percentage) and continuous data as mean ± SD.

ACE = angiotensin-converting enzyme; ARB = angiotensin II receptor blocker; CABG = coronary artery bypass graft; POAF = postoperative atrial fibrillation; RAAS = renin-angiotensin-aldosterone-system.

and multivariable Cox regression analysis. The above-mentioned variables and POAF were assessed in univariate analysis. Because of the smaller number of events, only variables with $P < .05$ in univariate analysis (galectin-3/galectin-3 risk categories, EuroSCORE II, age, CAD, baseline C-reactive protein and creatinine levels, type of surgery, POAF, and peak lactate and peak noradrenalin dose in the intensive care unit) were included in the final multivariable Cox regression model. Furthermore, we created an additional multivariable logistic regression model and an additional Cox regression model to adjust for diverse drug groups as specified in the Results section.

Classification and regression tree (CART) analysis was used to create galectin-3 risk categories. Cumulative survival

according to galectin-3 risk categories was examined using Kaplan-Meier curves (log-rank test). SPSS version 26.0 (IBM Corporation, Armonk, IL) was used for statistical analyses. A P value of $\leq$.05 (2-sided) was considered statistically significant.

Results

A total of 480 consecutive patients admitted to the Vienna General Hospital for elective cardiac surgery were initially included in the study. Galectin-3 levels were available in 475 patients, who comprised the final study population. The patient characteristics of the entire final study population with additional subcategorization according to those who did and did not develop POAF are listed in Table 1. Patients were predominantly male (n = 336 [70.7%]) and were 67.4 ± 11.8 years old. The study cohort comprised 157 patients (33.1%) receiving CABG, 199 (41.9%) receiving valve surgery, and 119 (25.1%) receiving CABG plus valve surgery. A total of 233 patients (49.1%) underwent aortic valve surgery, 105 (22.1%) mitral valve surgery, 25 (5.3%) tricuspid valve surgery, and 7 (1.5%) pulmonary valve surgery (including patients with multivalve surgery). The median aortic cross-clamp time and cardiopulmonary bypass time were 92.3 ± 40.3 and 136.4 ± 55.8 minutes, respectively.

The mean galectin-3 level on hospital admission was 8.15 ± 5.32 ng/mL. Associations between galectin-3 and other clinical parameters are presented in Online Supplemental Table 1. Patients with higher galectin-3 levels were more likely to be older, female, and diabetic and were more likely to have chronic lung disease, chronic HF, a history of myocardial infarction and renal dysfunction ($P < .05$ for all). Correspondingly, higher galectin-3 levels were observed in patients treated with loop diuretics, aldosterone receptor antagonists, and β-blockers ($P < .05$ for all) (Online Supplemental Table 1). Furthermore, galectin-3 was weakly but significantly associated with baseline C-reactive protein levels, baseline leukocyte count, LA diameter index, and EuroSCORE II ($P < .05$ for all) (Online Supplemental Table 1). As expected, LA diameter index was significantly associated with the severity of mitral regurgitation ($r = 0.26$; $P < .001$) and the necessity of mitral valve surgery ($r = 0.19$; $P < .001$).

Galectin-3 and POAF

A total of 200 patients (42.1%) developed POAF at 3.1 ± 2.0 days after surgery. Preoperative galectin-3 levels were significantly higher in the POAF group (9.60 ± 6.83 ng/mL) than in patients who did not develop POAF (7.10 ± 3.54 ng/mL; $P < .001$). No correlation was found between galectin-3 levels and time until the onset of POAF ($r = 0.06$; $P = .391$).

Galectin-3 levels significantly predicted POAF in univariate binary logistic regression analysis (odds ratio [OR] per 1-SD increase 1.50; 95% confidence interval [CI] 1.22–1.84; $P < .001$) (Figure 1) and remained a significant predictor of POAF after multivariable adjustment (OR per 1-SD increase 1.44; 95% CI 1.15–1.81; $P = .002$) (Figure 1). Of note, galectin-3 was not only a significant predictor of POAF in the subgroup of patients with HF (OR per 1-SD change 1.51; 95% CI 1.14–1.99; $P = .004$) but also in those without HF (OR per 1-SD increase 1.46; 95% CI 1.08–1.99; $P = .015$) as assessed by subgroup analysis. The effect of

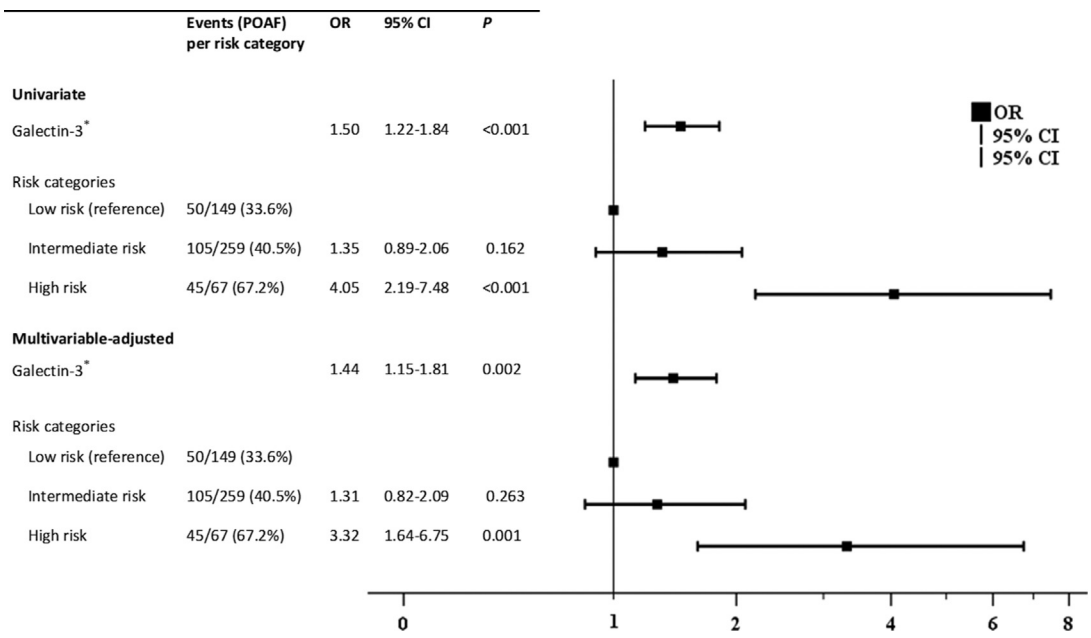

Figure 1 Forest plot showing the association between POAF and preoperative galectin-3 levels/risk categories. Multivariable adjustment was performed for the following variables: EuroSCORE II, age, gender, body mass index, coronary artery disease, arterial hypertension, valvular heart disease, chronic heart failure, left atrial diameter index, severity of mitral regurgitation, history of atrial fibrillation, history of cardiac surgery, baseline C-reactive protein and creatinine levels, aortic cross-clamp time, type of surgery, and peak lactate and peak noradrenalin dose in the intensive care unit after surgery. CI = confidence interval; OR = odds ratio; POAF = postoperative atrial fibrillation. *Per 1-SD increase.

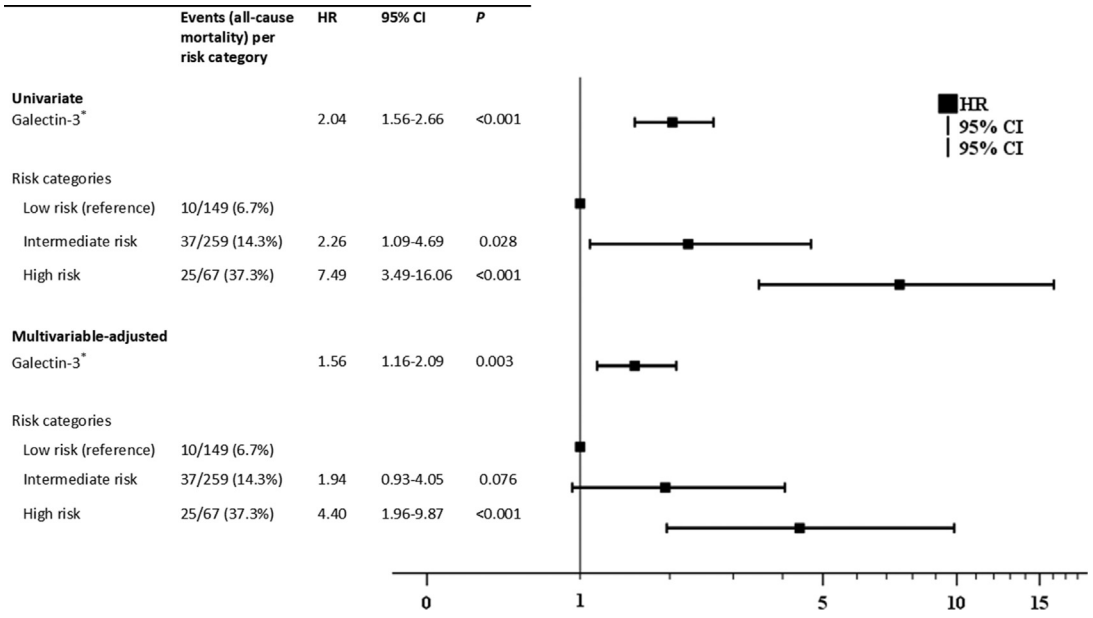

Figure 2 Forest plot showing the association between all-cause mortality and preoperative galectin-3 levels/risk categories. The final multivariable Cox regression model included all variables with $P < .05$ in univariate analysis (galectin-3/galectin-3 categories, EuroSCORE II, age, baseline C-reactive protein and creatinine levels, coronary artery disease, type of surgery, postoperative atrial fibrillation, and peak noradrenalin and peak lactate dose after surgery). CI = confidence interval; HR = hazard ratio. *Per 1-SD increase.

galectin-3 on POAF was not significantly modified by HF as assessed by interaction term analysis ($P = .892$). The association between galectin-3 and POAF was also independent of renin-angiotensin-aldosterone system inhibitors, β-blockers, statins, aldosterone receptor antagonists, loop diuretics, and thiazide diuretics at hospital admission as assessed in a second multivariable logistic regression model (OR per 1-SD increase 1.46; 95% CI 1.17–1.81; $P = .001$).

Galectin-3 and postsurgical survival

During a median follow-up of 4.3 years (interquartile range 3.4–5.4 years), 11 patients (2.3%) required redo cardiac surgery and 72 patients (15.2%) died. Galectin-3 levels were significantly lower in surviving patients (7.65 ± 4.79 ng/mL) than in those who died (10.98 ± 7.04 ng/mL; $P < .001$), and galectin-3 was significantly associated with all-cause mortality in univariate Cox regression analysis (hazard ratio [HR] per 1-SD increase 2.04; 95% CI 1.56–2.66; $P < .001$). This association remained significant after multivariable adjustment (HR per 1-SD increase 1.56; 95% CI 1.16–2.09; $P = .003$) (Figure 2). The association between galectin-3 and all-cause mortality was also independent of renin-angiotensin-aldosterone system inhibitors, β-blockers, statins, aldosterone receptor antagonists, loop diuretics, and thiazide diuretics at hospital admission as assessed in a separate multivariable Cox regression model (HR per 1-SD increase 1.87; 95% CI 1.39–2.51; $P < .001$).

Galectin-3 risk categories

CART analysis yielded 3 galectin-3 risk categories: low risk, ≤5.82 ng/mL; intermediate risk, 5.83–11.70 ng/mL; and high risk, >11.70 ng/mL (see Online Supplemental Table 2 for patient characteristics). Figures 1 and 2 show univariate- and multivariable-adjusted associations between galectin-3 risk categories and study end points. Compared with the galectin-3 low-risk category, the adjusted OR for POAF was 3.32 (95% CI 1.64–6.75) in the high-risk category ($P = .001$) (Figure 1) and the adjusted HR for death was 4.40 (95% CI 1.96–9.87) in the high-risk category ($P < .001$) (Figure 2). Figure 3 shows Kaplan-Meier survival curves stratified according to galectin-3 risk categories.

Discussion

The present study clearly demonstrates for the first time that circulating galectin-3 levels at hospital admission are independently predictive of POAF in patients undergoing elective cardiac surgery. This finding is in line with the observations of Alexandre et al,[17] who measured galectin-3 levels in a

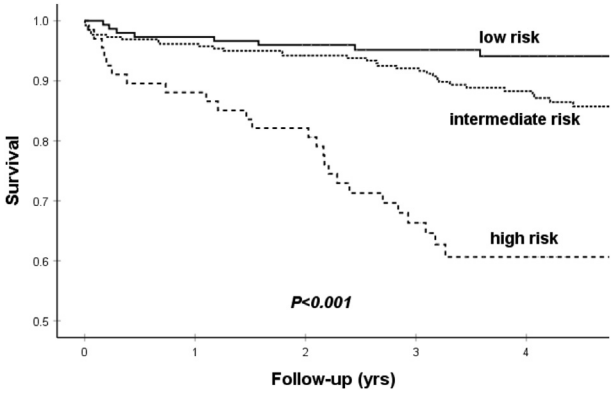

Figure 3 Kaplan-Meier plots showing the crude cumulative survival according to galectin-3 risk categories.

subgroup of 29 patients in the ALDOsterone for Prediction of Post-Operative Atrial Fibrillation study and found higher galectin-3 levels in patients with POAF than in those without POAF. In distinction to this prior study, we have now examined the association between galectin-3 levels and POAF in a cohort of 475 patients with elective CABG and/or valve surgery and showed that galectin-3 remains predictive after adjusting for a comprehensive set of potential confounders. CART analysis yielded a galectin-3 low-risk category (≤5.82 ng/mL), intermediate-risk category (5.83–11.70 ng/mL), and high-risk category (>11.70 ng/mL). The risk of POAF after surgery was 3.3-fold higher in the high-risk group than in the low-risk group. In addition, galectin-3 predicted all-cause mortality after cardiac surgery with a 4.4-fold higher risk in the galectin-3 high-risk group than in the low-risk group.

The present study extends current knowledge of galectin-3 and AF as well as of the pathogenesis of POAF in general. Galectin-3 levels are known to be elevated in patients with AF compared with control subjects and are particularly high in patients with persistent AF,[18] LA enlargement,[18] and advanced atrial fibrosis.[13] Galectin-3 levels also predict future AF[14] as well as the recurrence of AF after catheter ablation[19,20] and after electrical cardioversion.[21] It is highly expressed by fibroblasts, macrophages, other inflammatory cells, and also by cardiomyocytes in the failing or stressed heart.[12,22] Although galectin-3 initially even exerts protective antiapoptotic and antinecrotic actions, in the long term it serves as an upstream mediator of atrial and ventricular remodeling and fibrosis via multiple mechanisms.[12,23–26] Prolonged galectin-3 expression induces cardiac fibroblast proliferation, activation, and transformation of quiescent fibroblasts into matrix-producing myofibroblasts.[23,26] Furthermore, galectin-3 promotes macrophage and mast cell infiltration and the release of proinflammatory and profibrotic mediators such as transforming growth factor β1 and interleukin 1 and 2 and is involved in the activation of the transforming growth factor β1/SMAD signaling pathway, which is a key pathway in fibrosis.[12,27] In addition, galectin-3 promotes the nuclear translocation of transcription factors for collagen transcription such as β-catenin.[26] All these actions lead to synthesis and deposition of collagen type I and other fibrotic extracellular matrix components impairing the homeostasis between type I and type III collagen and consequently depressing myocardial function.[23,26] Galectin-3 further favors structural remodeling by its inhibition of metalloproteinases, which are essential for extracellular matrix degradation.[26] Galectin-3 also promotes atrial electrical remodeling[13] in terms of conduction abnormalities and other unfavorable electrical processes, which facilitate the initiation and maintenance of AF.[5,12]

The strong association of galectin-3 with POAF emphasizes the importance of a preexisting atrial proarrhythmogenic substrate in the multifactorial genesis of POAF. This hypothesis is also supported by previous studies linking POAF to LA enlargement, the extent of LA fibrosis, and to poor LA function—all of which are also associated with elevated galectin-3.[6,7,28,29] Moreover, POAF has been linked to other biomarkers of fibrosis and collagen synthesis, such as procollagen I carboxyterminal propeptide and procollagen III amino terminal propeptide, as well as to tissue levels of transforming growth factor β1 and collagen I and III in atrial biopsies.[6]

Although galectin-3 levels might be an easily measurable biomarker of atrial fibrosis and risk of POAF, galectin-3 does not exclusively reflect fibrosis in the atrial chambers. It also reflects fibrosis in the ventricular chambers,[8,9] as seen in chronic HF, and in extracardiac organs, such as the kidney, liver, and lung.[10] Despite the lack of specificity for atrial tissue, galectin-3 predicted POAF in the present study and remained predictive after adjustment for multiple other disorders that could be accompanied by fibrosis (eg, chronic HF, valvular heart disease, hypertension, and CAD).[8,9]

The present study also observed an association between galectin-3 and poor long-term survival after elective heart surgery. This finding is in line with previous studies describing an association between galectin-3 levels and increased mortality after CABG[30] and transapical aortic valve implantation.[31] These associations are unsurprising, as galectin-3 has established its role as a reliable predictor of mortality in diverse cardiovascular disorders, such as in HF and CAD, as well as in the general population.[10,26]

Clinical implications

The present data aid in understanding the pathogenesis of POAF, which is associated with numerous adverse outcomes and complications such as acute cardiovascular events, congestive HF, renal failure, future AF, and mortality.[1,3] A better understanding of the underlying pathogenesis might help to develop future preventive strategies. Galectin-3 might also be a target for intervention to prevent atrial or ventricular fibrogenesis and remodeling.[19,32] In this respect, Yu et al[33] was able to attenuate ventricular fibrosis, left ventricular dysfunction, and subsequent HF development in galectin-3 knockout mice and by pharmacological inhibition of galectin-3. Pharmacological inhibition of galectin-3 in a sheep model reduced atrial fibroblast proliferation and beneficially influenced electrical remodeling, leading to a decrease in AF inducibility and a reduction in overall AF burden.[19] Furthermore, it was possible to limit or entirely prevent the induction of fibrosis in extracardiac organs, such as the liver and kidney in animals lacking galectin-3.[10,32] Despite these promising preliminary results in animal studies, large interventional trials in humans assessing the therapeutic potential of galectin-3 modulation to treat fibrosis have not been performed.

Of most importance, in the era of personalized medicine, the measurement of galectin-3 may also improve preoperative risk assessment and help to identify patients who need closer monitoring in the postoperative period in terms of individualized patient care.

Limitations

The present study is a single-center study, and future studies are required to validate the present results. However, we might have overcome a potential selection bias via enrolling a large sample size of consecutive patients in the entire Viennese catchment area. The present study also included patients with a history of AF, provided there were no AF episodes during the 6 months before surgery. To control for potential confounding, we included "history of AF" in the multivariable regression analysis, and as an exploratory secondary analysis, we also excluded the 46 patients with a history of AF from analysis and found no difference in results (data not shown). Furthermore, changes in treatment/medication during the follow-up period were not recorded and may have influenced all-cause mortality. LA volume index data were not available; therefore, LA diameter index was used as a surrogate marker of LA size.

Conclusion

Preoperative galectin-3 plasma levels have an independent value for predicting POAF and reduced survival after elective cardiac surgery. Galectin-3 levels may reflect the degree of atrial fibrosis, which is a predisposing factor for the development of POAF. The present study extends the knowledge of the pathogenesis of POAF and might help to design future studies aiming to prevent POAF and accompanied unfavorable health outcomes. The easily applicable cutoff values for risk categories that this study has identified could be used to flag patients at increased risk of POAF and adverse outcomes who need special attention and might serve as a useful prognostic parameter in a multimodal risk assessment approach in the era of personalized medicine.

Appendix

Supplementary data

Supplementary data associated with this article can be found in the online version at https://doi.org/10.1016/j.hrthm.2022.06.019.

References

1. Maisel WH, Rawn JD, Stevenson WG. Atrial fibrillation after cardiac surgery. Ann Intern Med 2001;135:1061–1073.
2. Mathew JP, Fontes ML, Tudor IC, et al. A multicenter risk index for atrial fibrillation after cardiac surgery. JAMA 2004;291:1720–1729.
3. Ahlsson A, Fengsrud E, Bodin L, Englund A. Postoperative atrial fibrillation in patients undergoing aortocoronary bypass surgery carries an eightfold risk of future atrial fibrillation and a doubled cardiovascular mortality. Eur J Cardiothorac Surg 2010;37:1353–1359.
4. Bidar E, Maesen B, Nieman F, Verheule S, Schotten U, Maessen JG. A prospective randomized controlled trial on the incidence and predictors of late-phase postoperative atrial fibrillation up to 30 days and the preventive value of biatrial pacing. Heart Rhythm 2014;11:1156–1162.
5. Olsen FJ, Bertelsen L, de Knegt MC, et al. Multimodality cardiac imaging for the assessment of left atrial function and the association with atrial arrhythmias. Circ Cardiovasc Imaging 2016;9:e004947.
6. Swartz MF, Fink GW, Sarwar MF, et al. Elevated pre-operative serum peptides for collagen I and III synthesis result in post-surgical atrial fibrillation. J Am Coll Cardiol 2012;60:1799–1806.
7. Ozben B, Akaslan D, Sunbul M, et al. Postoperative atrial fibrillation after coronary artery bypass grafting surgery: a two-dimensional speckle tracking echocardiography study. Heart Lung Circ 2016;25:993–999.
8. de Boer RA, Voors AA, Muntendam P, van Gilst WH, van Veldhuisen DJ. Galectin-3: a novel mediator of heart failure development and progression. Eur J Heart Fail 2009;11:811–817.
9. Ho JE, Liu C, Lyass A, et al. Galectin-3, a marker of cardiac fibrosis, predicts incident heart failure in the community. J Am Coll Cardiol 2012;60:1249–1256.
10. Sciacchitano S, Lavra L, Morgante A, et al. Galectin-3: one molecule for an alphabet of diseases, from A to Z. Int J Mol Sci 2018;19:379.
11. Nishi Y, Sano H, Kawashima T, et al. Role of galectin-3 in human pulmonary fibrosis. Allergol Int 2007;56:57–65.
12. Clementy N, Piver E, Bisson A, et al. Galectin-3 in atrial fibrillation: mechanisms and therapeutic implications. Int J Mol Sci 2018;19:976.
13. Yalcin MU, Gurses KM, Kocyigit D, et al. The association of serum galectin-3 levels with atrial electrical and structural remodeling. J Cardiovasc Electrophysiol 2015;26:635–640.
14. Ho JE, Yin X, Levy D, et al. Galectin 3 and incident atrial fibrillation in the community. Am Heart J 2014;167:729–734.
15. Hindricks G, Potpara T, Dagres N, et al. 2020 ESC Guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS). Eur Heart J 2021;42:373–498.
16. Nashef SA, Roques F, Sharples LD, et al. EuroSCORE II. Eur J Cardiothorac Surg 2012;41:734–744. discussion 744–735.
17. Alexandre J, Saloux E, Chequel M, et al. Preoperative plasma aldosterone and the risk of atrial fibrillation after coronary artery bypass surgery: a prospective cohort study. J Hypertens 2016;34:2449–2457.
18. Gurses KM, Yalcin MU, Kocyigit D, et al. Effects of persistent atrial fibrillation on serum galectin-3 levels. Am J Cardiol 2015;115:647–651.
19. Takemoto Y, Ramirez RJ, Yokokawa M, et al. Galectin-3 regulates atrial fibrillation remodeling and predicts catheter ablation outcomes. JACC Basic Transl Sci 2016;1:143–154.
20. Clementy N, Garcia B, Andre C, et al. Galectin-3 level predicts response to ablation and outcomes in patients with persistent atrial fibrillation and systolic heart failure. PLoS One 2018;13:e0201517.
21. Gurses KM, Yalcin MU, Kocyigit D, et al. Serum galectin-3 level predicts early recurrence following successful direct-current cardioversion in persistent atrial fibrillation patients. Turk Kardiyol Dern Ars 2019;47:564–571.
22. Bivona G, Bellia C, Lo Sasso B, et al. Short-term changes in Gal 3 circulating levels after acute myocardial infarction. Arch Med Res 2016;47:521–525.
23. Sharma UC, Pokharel S, van Brakel TJ, et al. Galectin-3 marks activated macrophages in failure-prone hypertrophied hearts and contributes to cardiac dysfunction. Circulation 2004;110:3121–3128.
24. Lin YH, Lin LY, Wu YW, et al. The relationship between serum galectin-3 and serum markers of cardiac extracellular matrix turnover in heart failure patients. Clin Chim Acta 2009;409:96–99.
25. McCullough PA, Olobatoke A, Vanhecke TE. Galectin-3: a novel blood test for the evaluation and management of patients with heart failure. Rev Cardiovasc Med 2011;12:200–210.
26. Blanda V, Bracale UM, Di Taranto MD, Fortunato G. Galectin-3 in cardiovascular diseases. Int J Mol Sci 2020;21:9232.
27. Liu YH, D'Ambrosio M, Liao TD, et al. *N*-Acetyl-seryl-aspartyl-lysyl-proline prevents cardiac remodeling and dysfunction induced by galectin-3, a mammalian adhesion/growth-regulatory lectin. Am J Physiol Heart Circ Physiol 2009;296:H404–H412.
28. Hakala T, Hedman A, Turpeinen A, Kettunen R, Vuolteenaho O, Hippelainen M. Prediction of atrial fibrillation after coronary artery bypass grafting by measuring atrial peptide levels and preoperative atrial dimensions. Eur J Cardiothorac Surg 2002;22:939–943.
29. Kim SH, Behnes M, Natale M, et al. Galectin-3 reflects left atrial function being assessed by cardiac magnetic resonance imaging. Clin Lab 2017;63:1701–1710.
30. Parker DM, Owens SL, Ramkumar N, et al. Galectin-3 as a predictor of long-term survival after isolated coronary artery bypass grafting surgery. Ann Thorac Surg 2020;109:132–138.
31. Zhang HL, Song GY, Zhao J, et al. Preprocedural circulating galectin-3 and the risk of mortality after transcatheter aortic valve replacement: a systematic review and meta-analysis. Biosci Rep 2020;40:BSR20202306.
32. Slack RJ, Mills R, Mackinnon AC. The therapeutic potential of galectin-3 inhibition in fibrotic disease. Int J Biochem Cell Biol 2021;130:105881.
33. Yu L, Ruifrok WP, Meissner M, et al. Genetic and pharmacological inhibition of galectin-3 prevents cardiac remodeling by interfering with myocardial fibrogenesis. Circ Heart Fail 2013;6:107–117.