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A systematic review and meta-analysis

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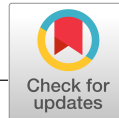
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RESEARCH ARTICLE

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Galectin-3 and risk of atrial fibrillation: A systematic review and meta-analysis

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Abstract

Background: Galectin-3 is an inflammatory marker that is raised in myocardial fibrosis and inflammation. Recent studies have explored its role in predicting atrial fibrillation (AF) outcomes. The aim of this systematic review and meta-analysis is to examine the association between serum concentration of galectin-3 and AF.

Methods: PubMed, EMBASE, and the Cochrane Database were searched. A total of 280 studies were identified, of which 28 studies involving 10 830 patients were included in our meta-analysis.

Results: Galectin-3 is present at higher concentrations in patients with AF than those in sinus rhythm (mean difference [MD] = -0.68 ng/mL, 95% CI: -0.92, -0.44, Z = 5.61, P < .00001). Galectin-3 levels were significantly higher in the persistent AF than in the paroxysmal AF group (MD = -0.94 ng/mL, 95% CI: -1.85, -0.03, Z = 2.04, P = .04). Higher galectin-3 levels were associated with a 45% increase in the odds of developing AF (odds ratio [OR] = 1.45, 95% CI: 1.15, 1.83, Z = 3.11, P = .002) and risk of AF recurrence (hazard ratio [HR] = 1.17, 95% CI: 1.06, 1.29, Z = 3.12, P = .002).

Conclusions: Our meta-analysis found that galectin-3 is significantly higher in patients with persistent AF than in those with paroxysmal AF, and can predict both AF development and recurrence after treatment.

KEYWORDS

atrial fibrillation, galectin-3, meta-analysis, recurrence

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1 | INTRODUCTION

Atrial fibrillation (AF) is the most common arrhythmia observed in clinical practice with a rising prevalence in part due to an aging population. By 2020, AF is expected to affect 10-15 million patients in the United States alone.¹ Patients with AF have increased risks for developing complications such as heart failure, stroke, and premature death. The pathophysiology of AF is complex and is thought to involve pro-inflammatory responses, leading to structural remodeling and in turn tissue fibrosis and electrophysiological remodeling. The end result is a pro-arrhythmic substrate for arrhythmogenesis. As with other disorders, blood markers have been used for risk stratification purposes.²⁻⁷ More recently, galectin-3, which is raised in the context of myocardial fibrosis, inflammation, and immune response activation, has emerged as a promising biomarker for risk stratification.⁸ A recent meta-analysis has demonstrated that galectin-3 provides incremental prognostic value that extends beyond that of traditional risk factors in the context of heart failure.⁹ However, the evidence on AF has been controversial with some studies reporting prognostic values while others have demonstrated little utility. In this study, therefore, we conducted a systematic review and meta-analysis of published studies to evaluate the prognostic value of galectin-3 in the context of AF.

2 | MATERIALS AND METHODS

2.1 | Search strategy

This systematic review and meta-analysis was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) statement. We searched studies that examined association between serum concentration of galectin-3 and atrial fibrillation (AF). Two independent reviewers (MG and AC) systematically and independently searched the electronic databases of PubMed, EMBASE, and the Cochrane Database to identify relevant studies from their inception through June 24, 2018. The search terms used were as follows: (galectin 3 or gal 3) and (atrial fibrillation or AF). There were no restrictions with date of publication or language. The search details of different databases were recorded in Table S1. Excluded studies encompassed duplicate studies or ineligible for our study selection criteria. The disagreement was resolved by discussion with a senior reviewer (TL).

2.2 | Selection criteria

The following inclusion criteria were applied: (a) The study design was a observational study (included prospective cohort, retrospective cohort, and case-control); (b) there were measured serum concentration of galectin-3 at least about two groups in one study; (c) compared groups were AF group and sinus rhythm group, or paroxysmal AF group and persistent AF group, or recurrence AF group and without recurrence AF group; and d) the hazard ratios (HRs)/odds ratio (OR) and the corresponding 95% confidence intervals

(CI) or mean \pm standard deviation (SD) were reported for galectin-3. If the reported data of galectin-3 in some studies can translate to means \pm SD by calculation, we also included. Regarding multiple articles originating from the same cohort and reporting the same event, only those with the largest sample and the longest follow-up duration were included.

2.3 | Data extraction

Two blinded reviewers (MG and AC) independently extracted the relevant data from each eligible study using a standard data extraction form and cross-checked. The following data were extracted: first author's last name, publication year, location, study design, number of participants, male ratio, mean age, duration of follow-up, study population, and measurement methods of galectin-3. Any disagreement was resolved by consensus with a senior reviewer (TL). If there was no sinus group and the two groups were different types of atrial fibrillation, we defined paroxysmal AF group as the control group.

2.4 | Quality assessment

To limit heterogeneity secondary to differences among study designs, the methodological quality of included articles was evaluated by two blinded reviewers (MG and AC) applying the Newcastle-Ottawa Score (NOS) checklist. We graded the quality as good (≥ 7 stars), fair (4-6 stars), and poor (<4 stars).

2.5 | Statistical analysis

The demographic characteristics of included patients are provided as mean \pm SD, or median (interquartile range, IQR), or a percentage, as appropriate. All data of galectin-3 were pooled analysis by means \pm SD or HR or OR. The primary outcome was the serum concentration of galectin-3 for different groups. Pooled effect sizes were presented as the mean \pm SD for each study. Since the related data were occasionally absent, we utilized raw data to calculate mean \pm SD. We use the method of translation median and IQR to mean \pm SD by Wan et al¹⁰ and Luo et al¹¹. In brief, q_1 is the first quartile, m is the median, q_3 is the third quartile, n is the sample size, and therefore, mean $\approx (0.7 + 0.39/n)(q_1 + q_3)/2 + (0.3 - 0.39/n)m$.¹¹ When $Q \leq 50$, $SD \approx (q_3 - q_1)/\eta(n)$, $n = 4Q + 1$, we use the numerical values of $\eta(n)$ were given by Wan et al¹⁰; When $Q > 50$, we used the formula that $SD \approx (q_3 - q_1)/1.35$.¹²

Continuous data were expressed as mean difference (MD) and 95% CI, pooled analysis by inverse variance. Statistical heterogeneity across studies was assessed by chi-square test and quantified with the use of the I^2 statistic. An $I^2 > 50\%$ was indicative of at least moderate heterogeneity, and we used random effect model to analyze this result. To assess the effect of individual studies on the estimated relative risk, we also performed a sensitivity analysis by recalculating the pooled relative risk after omitting one study at a time and checking the consistency of the overall effect estimate. Furthermore, publication bias was evaluated by inspecting the funnel plot for each

outcome. Statistical significance was defined as a 2-tailed *P*-value of .05. All statistical analyses were performed with the Review Manager, version 5.3 (RevMan; The Cochrane Collaboration).

3 | RESULTS

A flow diagram of the search procedure is illustrated in Figure 1. A total of 280 studies were identified from PubMed, EMBASE, and Cochrane Library by the initial search. Of these, 57 duplicate citations and 223 ineligible studies were excluded for the following reasons: That the study was an experimental or animal study, review article, or outcome of the study was not related to AF or galectin-3. Among the 38 full-text articles assessed for eligibility, ten were excluded for the following reasons: One study lacked a control group;¹³ one study population was heart failure;¹⁴ four studies lacked available data for further analysis;¹⁵⁻¹⁸ and four reported duplicate data from studies that later published as full text.¹⁹⁻²² Finally, 28 studies involving 10 830 patients were included in our meta-analysis,²³⁻⁵⁰ with their baseline characteristics shown in Tables 1 and 2.

Fourteen studies compared serum concentrations of galectin-3 between the sinus rhythm group and AF group.^{26,28,29,31-33,37,40,42,44,46,47,49,50} Our meta-analysis shows that the AF group had higher concentrations of galectin-3 than the sinus rhythm (SR) group (mean difference [MD] = -0.68 ng/mL, 95% CI: -0.92, -0.44, *Z* = 5.61, *P* < .00001) (Figure 2A). Furthermore, we showed that higher galectin-3 levels were associated with a 45% increase in the odds of developing AF (odds ratio [OR] = 1.45, 95% CI: 1.15, 1.83, *Z* = 3.11, *P* = .002) (Figure 2B). Six studies compared galectin-3 levels between paroxysmal AF and persistent AF patients.^{24,35,37,41,48,50}

The pooled analysis showed that galectin-3 levels were significantly higher in the persistent AF group (MD = -0.94 ng/mL, 95% CI: -1.85, -0.03, *Z* = 2.04, *P* = .04) (Figure 2C).

Several published studies also examined the value of galectin-3 in predicting patients who will have AF recurrence after different treatments for SR restoration. Our meta-analysis shows that patients with no recurrence had significantly lower galectin-3 levels than those with disease recurrence (MD = -4.23 ng/mL, 95% CI: -6.13, -2.33, *Z* = 4.37, *P* < .0001) (Figure 2D). Furthermore, higher galectin-3 levels were associated with higher risk of AF recurrence (hazard ratio [HR] = 1.17, 95% CI: 1.06, 1.29, *Z* = 3.12, *P* = .002) (Figure 2E).

Funnel plot results suggested that publication bias may be present (Figures S1-S5).

4 | DISCUSSION

AF is the most frequently cardiac arrhythmia observed in clinical practice, with an increasing prevalence due to an aging population and the rising burden of comorbid cardiovascular diseases.⁵¹ It is important at the public health level because of its predisposition to stroke, heart failure, dementia, premature mortality, and disability.⁵² In this condition, there is an ongoing cardiomyopathic process of the atrial myocardium,^{53,54} involving a number of cellular and molecular mechanisms revolving around inflammation.^{55,56} One of the consequences is fibrosis, characterized by increased turnover of the extracellular matrix, producing conduction abnormalities that provide the necessary substrate for arrhythmogenesis.^{57,58} A number of blood biomarkers^{3,5-7,59-62} and electrocardiographic predictors^{54,63,64} have been found in association with AF onset, development, and

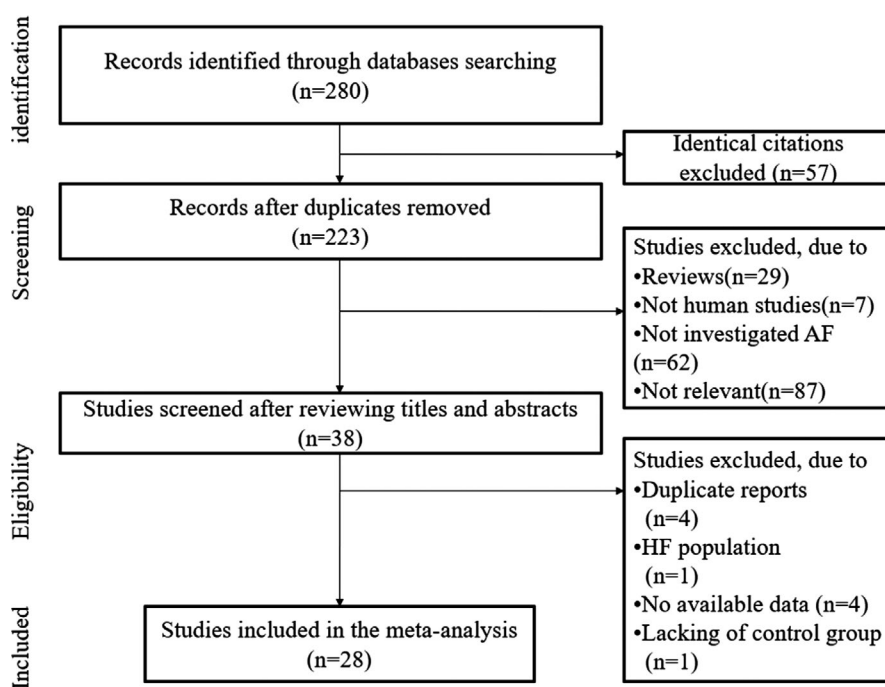


FIGURE 1 Flow diagram of study selection process

TABLE 1 Characteristics of included studies for meta-analysis of association of galectin-3 and AF

First author	Country	Design	Study population	Number of patients	Follow-up	Measurement methods of galectin-3	Quality score
Szadkowska 2013	Poland	PC	First acute MI treated with pPCI	145	Until discharge	VIDAS Galectin-3 kit	6
Clementy 2014	France	Case-control	Symptomatic AF	187	NA	VIDAS Galectin-3 kit	6
Gurses 2014	Turkey	PC	Lone AF underwent cryoballoon-based PVI	100	12 mo	ELISA	6
Ho 2014	United States	PC	AF and SR	3306	10 y	ELISA	7
Lee 2014	China	PC	AF	96	18 mo	ELISA	6
Sonmez 2014	Turkey	Case-control	AF and SR	85	NA	ELISA	7
Yalcin 2014	Turkey	Case-control	Lone AF and SR	256	NA	ELISA	6
Gurses 2015a	Turkey	Case-control	AF and SR	151	NA	ELISA	8
Gurses 2015b	Turkey	PC	Persistent AF	65	3 mo	ELISA	6
Kornej 2015	Germany	PC	AF underwent catheter ablation	119	6 mo	ELISA	6
Wu 2015	China	PC	Persistent AF and SR	96	17 mo	Milliplex MAP Kits	9
A 2016	Russian	Case-control	Metabolic syndrome with AF and SR	100	NA	ELISA	5
Alexandre 2016	France	PC	SR underwent CABG with/without AVR	137	27 d	ELISA	9
Chen 2016	Australia	Case-control	New onset AF and chronic AF (control)	131	NA	ELISA	7
Clementy 2016	France	PC	Symptomatic AF	160	12 mo	VIDAS Galectin-3 kit	7
Ionin 2016	Russian Federation.	PC	Metabolic syndrome with AF and SR	230	NA	ELISA	5
Mohanty 2016	United States	PC	AF underwent catheter ablation	145	15 mo	NA	6
Takemoto 2016	United States	PC	AF underwent radiofrequency ablation	55	12 mo	ELISA	8
Begg 2017a	UK	PC	Persistent AF and SR	119	383 d	ELISA	8
Begg 2017b	UK	Case-control	Paroxysmal AF underwent catheter ablation and SR	129	NA	ELISA	8
Berger 2017	Netherlands	PC	AF underwent thoracoscopic surgical ablation	98	20.7 mo	ELISA	6
Dzeshka 2017	Belarus	Case-control	Paroxysmal AF and SR	76	NA	ELISA	5
Fashanu 2017	United States	PC	SR	4257	15.7 y	Chemiluminescent microparticle immunoassay	6
Hernandez-romero 2017	Spain	PC	Undergoing CABG without AF	100	Until discharge	ELISA	6
Pavlovic 2017	Serbia	PC	NSTEMI with AF and SR	54	461 d	ELISA	8
Begg 2018	UK	PC	AF underwent radiofrequency ablation	92	1 y	ELISA	7
Kang 2018	China	Case-control	AF underwent radiofrequency ablation and SR	30	NA	ELISA	8
Tang 2018	China	PC	AF	113	NA	ELISA	7

Abbreviations: AVR, aortic valve replacement; CABG, coronary artery bypass graft; ELISA, enzyme-linked immunosorbent assay; PC, prospective cohort; pPCI, Primary percutaneous coronary intervention; PVI, pulmonary vein isolation.

TABLE 2 Characteristics of included patients in the meta-analysis

First author	Age (years)	Male (%)	Hypertension (%)	Diabetes (%)	LAD (mm)	LVEF (%)
Szadkowska 2013	61.8 ± 10.4	76.3	77.4	24	NR	54.8 ± 9.5
Clementy 2014	62 ± 10	68	50	18	42 ± 7	54 ± 11
Gurses 2014	56.95 ± 11.36	43.8	0	0	39.1 ± 4.7	NR
Ho 2014	58.6 ± 9.2	47	NR	14.5	NR	NR
Lee 2014	NR	NR	NR	NR	NR	NR
Sonmez 2014	70 ± 10	37	63.2	24.2	NR	53.3 ± 12.8
Yalcin 2014	NR	NR	0	0	37.1 ± 4.4	NR
Gurses 2015a	58.1 ± 10.2	47.1	0	0	NR	65.9 ± 3.3
Gurses 2015b	56.09 ± 8.03	46.2	NR	NR	NR	NR
Kornej 2015	61.5 ± 8.6	57.5	NR	NR	NR	NR
Wu 2015	47.6 ± 9.4	94.8	0	0	37.6 ± 4.7	63.2 ± 4.9
A 2016	NR	NR	NR	NR	NR	NR
Alexandre 2016	67.2 ± 10.7	86.7	78.1	38.7	NR	60.5 ± 9.9
Chen 2016	70.3 ± 11.8	59	52.5	26	NR	NR
Clementy 2016	61 ± 10	71	49	17	42 ± 8	54 ± 11
Ionin 2016	50 ± 22.4	NR	NR	NR	NR	NR
Mohanty 2016	NR	69	NR	NR	NR	NR
Takemoto 2016	62.7 ± 1.1	82	NR	NR	44.3 ± 1.1	59.2 ± 0.8
Begg 2017a	62.8 ± 10.0	68.8	52.5	13.2	42.8 ± 6.1	55.7 ± 12.4
Begg 2017b	57.8 ± 11.4	69.4	40.2	11.8	40.1 ± 6.7	58.5 ± 9.2
Berger 2017	59.8 ± 8.6	76	57	7	NR	50.2 ± 10.3
Dzeshka 2017	62.16	57.5	NR	NR	NR	NR
Fashanu 2017	62.7 ± 5.7	41.6	NR	15.5	NR	NR
Hernandez-romero 2017	65.1 ± 9.5	77	70	47	40.71 ± 5.80	NR
Pavlovic 2017	68.1 ± 10.9	60.6	91.6	29.8	NR	55.12 ± 8.9
Begg 2018	58.23 ± 15.47	69.9	33.5	10.15	NR	NR
Kang 2018	62.45 ± 5.14	NR	NR	NR	38.8 ± 3.61	63.25 ± 2.49
Tang 2018	66.7 ± 9.4	50.6	54.1	22.25	38.6 ± 4.9	42.2 ± 9.0

Abbreviations: LAD, left atrium diameter; LVEF, left ventricular ejection fraction; NR, not reported.

recurrence. Of these, galectin-3 plays a key role in acute and chronic pro-inflammatory responses and mediates activation of quiescent fibroblasts and synthesis of collagen.⁶⁵ Previous studies have reported the prognostic value of galectin-3 in cardiovascular pathologies such as acute coronary syndrome,⁶⁶ heart failure,^{67,68} and in the general population.^{16,69} Recently, a meta-analysis examined its prognostic value in the context of heart failure and in the general population,^{9,18} but whether it aids risk stratification in AF remains controversial. Several trends have emerged from this meta-analysis regarding the correlation between galectin-3 concentrations and AF. Firstly, galectin-3 levels are higher in AF patients than those in SR and increased levels are associated with higher odds of AF development. Secondly, galectin-3 levels did significantly differ between AF subtypes. Thirdly, galectin-3 levels are higher in patients with AF recurrence than those with no recurrence after SR restoration.

Galectin-3 was originally discovered in 1982 as Mac-2,⁷⁰ cloned in 1991, and subsequently recognized as a β -galactoside-binding

lectin.⁷¹ It has diverse biological functions such as regulation of cell adhesion,⁷² immunity,⁷³ inflammation,⁷⁴ and fibrosis.⁷⁵ Its pathological role in the heart, specifically heart failure, has been discussed in detail by the excellent review here.⁷⁶ It is upregulated in response to increased stressors such as angiotensin II and pressure overload. It is thought to play a critical role in the transition from compensatory remodeling to decompensation, as originally shown in an animal model.⁷⁷ AF can induce tissue injury, leading to increased synthesis and subsequent release of galectin-3 by macrophages.⁷⁷ Galectin-3 can itself mediate macrophage activation through both classical and alternative pathways,⁷⁸ as well as induce adverse structural and electrophysiological remodeling in the atria.⁴² The latter effect may be independent of heart failure, since galectin-3 is raised in AF patients without structural heart disease.³² The following mechanisms underlying galectin-3-mediated atrial dysfunction have been identified. The extracellular pentameric domain of galectin-3 can interact with pro-fibrotic signals,

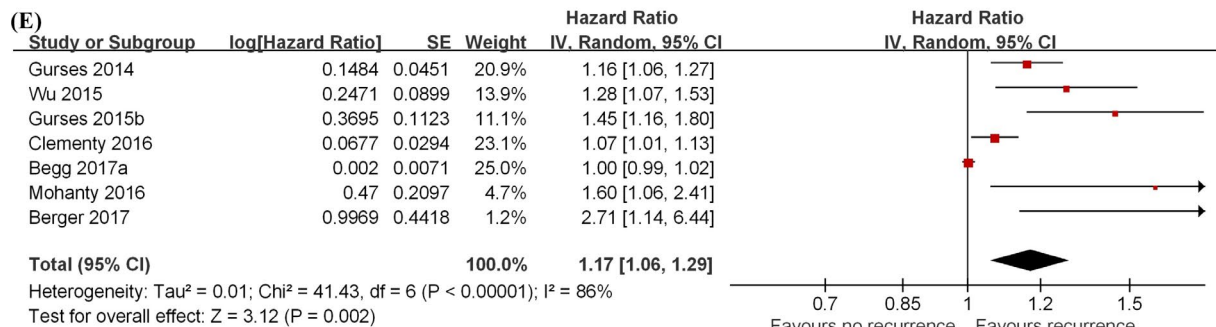
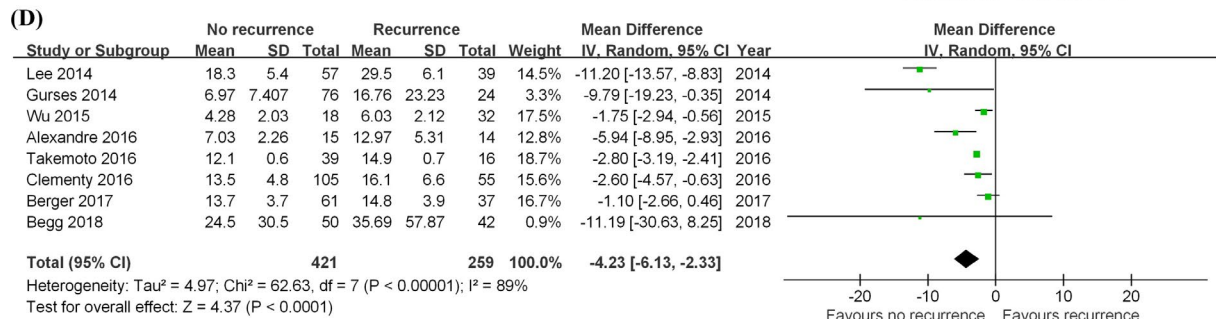
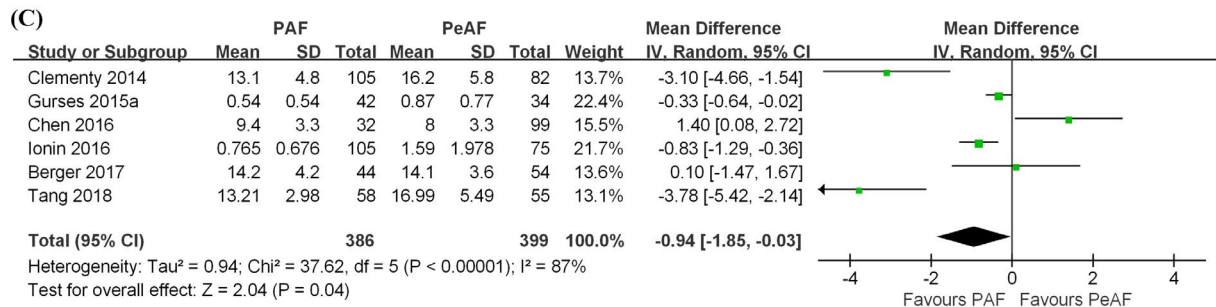
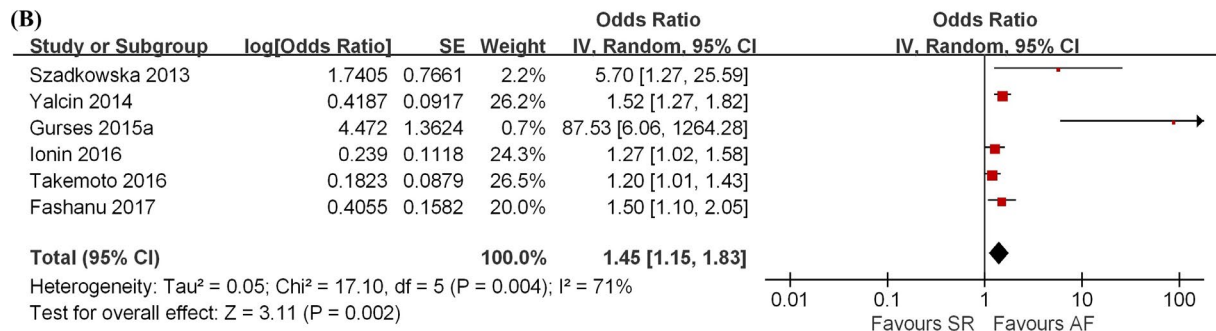
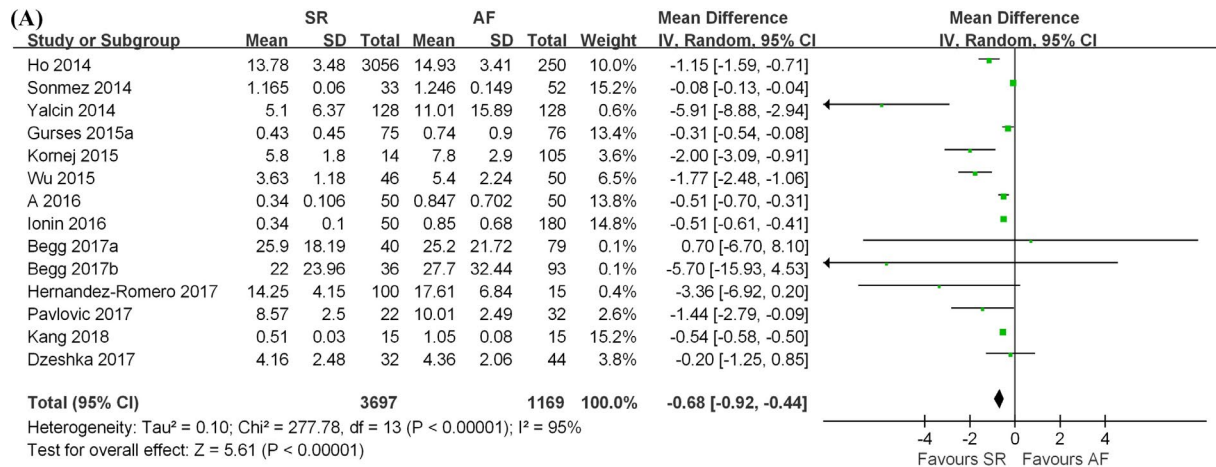


FIGURE 2 Forest plots of meta-analysis. A, Serum concentrations of galectin-3 between the SR group and AF group. B, The odds of concentrations of galectin-3 developing AF. C, Serum concentrations of galectin-3 between PAF group and PeAF group. D, Serum concentrations of galectin-3 between AF recurrence group and sinus rhythm restoration group. E, The hazard ratio of concentrations of galectin-3 in AF recurrence. SR, sinus rhythm; AF, atrial fibrillation; CI, confidence interval; M-H, Mantel-Haenszel; SD, standard deviation; IV, Inverse Variance

such as transforming growth factor- β /SMAD, which can initiate fibrosis.³⁹ Furthermore, galectin-3 can form complexes, which can cross-link glycosylated ligands to form a lattice.⁷⁹ This lattice could potentially trap transforming growth factor- β receptors to amplify the pro-fibrotic signaling pathways in the atria. It should be noted that AF may further induce galectin-3 release from macrophages, producing a vicious cycle that can perpetuate AF progression.⁸

There are several strengths of this meta-analysis. Firstly, this study adhered to PRISMA guidelines, which ensured the quality of the systematic evaluation and minimization of bias. Secondly, a large sample size of 10 830 patients from a total of 28 studies was included, meaning that we are confident. Finally, galectin-3 levels were determined using enzyme-linked immunosorbent assay (ELISA) in 21 of the studies, and therefore, we can be confident that the values provided are comparable. However, some limitations must be noted. Firstly, only 14 of the 28 included studies had quality scores of 7 or above, suggesting quality of the remaining 14 studies requires cautious interpretation. Secondly, attempts were made to identify the origin of the high heterogeneity. There are several reasons as to why this may be the case, for example, differing characteristics of the study groups, such as acute myocardial infarction, metabolic syndrome, or after coronary artery bypass grafting surgery or ablation procedures; possible variable contributions from confounders such as heart failure and other comorbid conditions; different follow-up periods; and different study designs.

5 | CONCLUSIONS

Our meta-analysis found that galectin-3 is significantly higher in patients with persistent AF than in those with paroxysmal AF and can predict both AF development and recurrence after treatment.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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