Indian Pacing and Electrophysiology Journal 20 (2020) 64–69

Contents lists available at ScienceDirect

Indian Pacing and Electrophysiology Journal

journal homepage: www.elsevier.com/locate/IPEJ

Serum Galectin-3 level and recurrence of atrial fibrillation post-ablation – Systematic review and meta-analysis

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ARTICLE INFO

Article history:
Received 14 November 2019
Received in revised form
15 January 2020
Accepted 13 February 2020
Available online 17 February 2020

Keywords:
Arrhythmia
Atrial fibrillation recurrence
Biomarker
Catheter ablation
Galectin-3

ABSTRACT

Background: Serum galectin-3, a circulating biomarker of fibrosis, has been associated with atrial remodelling. Recent studies investigating serum galectin-3 and AF recurrence post-ablation have shown mixed results. We aimed to analyze the latest evidence on the association between serum galectin-3 and AF recurrence after catheter ablation.

Methods: We performed a comprehensive search on topics that assesses serum galectin-3 and AF recurrence post-ablation up until August 2019.

Results: There were 597 patients from seven studies. The mean difference of serum galectin-3 was similar in both AF recurrence and non AF recurrence group (mean difference 0.78 ng/mL [-0.56, 2.13]; $p = 0.25$; I^2: 69%. Upon removal of a study in sensitivity analysis, the serum galectin-3 became higher in AF recurrence group (mean difference 1.41 ng/mL [0.47, 2.34], $p = 0.003$; I^2: 17%). Serum galectin-3 was associated with a higher risk for AF recurrence (HR 1.25 [1.01, 1.55]; $p = 0.04$; I^2: 76%). Upon removal of a study in sensitivity analysis, HR became 1.45 [1.07, 1.96], $p = 0.02$; I^2: 47%. Meta-analysis of adjusted HR demonstrated that high serum galectin-3 independently predicts AF recurrence (HR 1.15 [1.02, 1.29], $p < 0.02$; I^2: 57%, $p = 0.10$)

Conclusion: Serum galectin-3 is associated with an increased risk of AF recurrence post-ablation. Further studies are required, especially emphasis on the cut-off point should be given, before integrating it in routine risk stratification for AF ablation.

1. Introduction

Atrial fibrillation (AF) is the most prevalent cardiac arrhythmia worldwide, and catheter ablation becomes increasingly used to treat AF [1–3]. Although advances in technology allows a more effective catheter ablation, AF recurrence post-ablation is still frequently encountered [4–6]. Markers that are able to predict AF recurrence allow physicians to risk stratify the patients, weighing the risk and benefits before performing catheter ablation [7,8].

Serum galectin-3 has been associated with the atrial electrical and structural remodelling, and it has been associated with an increased incidence of AF in previous studies [9–11]. Serum galectin-3 has also been shown to be associated with poor prognosis in AF patients [12]. Recent studies investigating serum galectin-3, and AF recurrence post-ablation have shown mixed results. In this systematic review and meta-analysis, we will analyze the latest evidence on the importance of serum galectin-3 and whether they are associated with AF recurrence after catheter ablation.

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Peer review under responsibility of Indian Heart Rhythm Society.

https://doi.org/10.1016/j.ipej.2020.02.002

2. Methods

2.1. Search strategy

We performed a comprehensive search on topics that assess serum galectin-3 and AF recurrence post-ablation with keywords ["galectin-3" and "atrial fibrillation"] and its synonym from inception up until August 2019 through PubMed, EuropePMC, Cochrane Central Database, ClinicalTrials.gov and hand-sampling from potential articles cited by other studies. The records were then systematically evaluated using inclusion and exclusion criteria. We also perform hand-sampling from references of the included studies. Two researchers (R.P and E.Y) independently performed an initial search, discrepancies were resolved by discussion. A Preferred Reporting Items for Systematic Reviews and Meta-Analyses flowchart of the literature search strategy of studies was presented in Fig. 1.

2.2. Selection criteria

The inclusion criteria for this study are all studies that assess the serum galectin-3 and AF recurrence after ablation. We include all related clinical researches/original articles and exclude case reports, and review articles.

2.3. Data extraction

Data extraction and quality assessment were done by two independent authors (R.P and V.C) using standardized extraction form which includes authors, year of publication, study design, sample size, patient characteristics, persistent/paroxysmal AF, serum galectin-3 (ng/mL), serum galectin-3 cut-off (ng/mL), follow-up period, and AF recurrence.

2.4. Statistical analysis

To perform the meta-analysis, we used RevMan version 5.3 software (Cochrane Collaboration). We used the hazard ratio (HR) and a 95% CI. We used mean difference and its standard deviation (SD) as a pooled measure for the continuous data and inverse variance method for HR. Inconsistency index (I^2) test, which ranges from 0 to 100%, was used to assess heterogeneity across studies. A value above 50% or $p < 0.10$ indicates statistically significant heterogeneity. We used random-effect model for meta-analysis regardless of heterogeneity. All P values were two-tailed with a statistical significance set at 0.05 or below.

3. Results

We found a total of 420 results. We screened 361 records after removing duplicates. There were 9 relevant titles/abstract. After assessing 9 full-text for eligibility; we excluded 2 because of 1) Group was divided between AF and non-AF (not AF recurrence) 2) Outcome was the response to ablation in heart failure patients. We included seven studies in the qualitative synthesis and seven studies in meta-analysis [13–20]. (Fig. 1; Table 1) Seven studies were prospective cohorts. There was a total of 597 patients from seven studies.

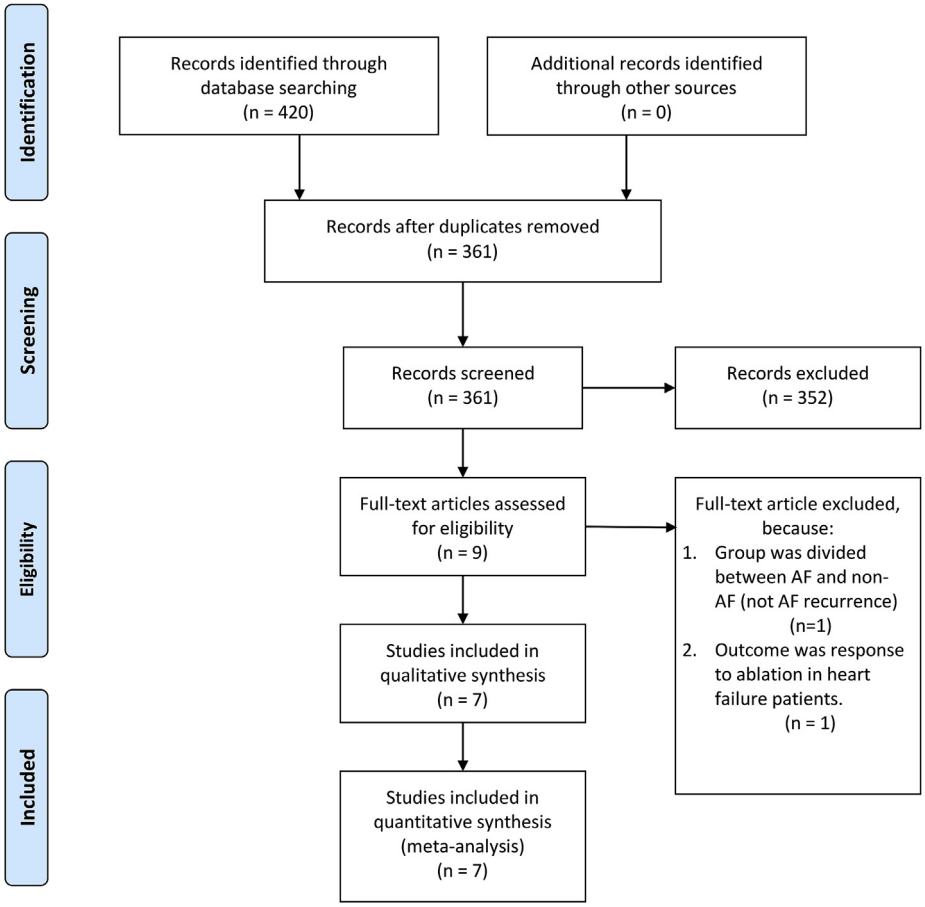

Fig. 1. Study flow diagram. Description: AF = Atrial fibrillation.

Table 1
Summary of the included studies.

Author	Study Design	Patient Characteristics	Sample (n)	Paroxysmal AF (%)	Age (years±SD)	Male (%)	Galectin-3 Cut-off Point (ng/mL)	Follow-up	Galectin-3 Kits
Begg 2018	Prospective Cohort	AF undergoing 1st time ablation	92	67	58.23 ± 20.13	70	N/A	12 months	Elabscience Human Gal-3 ELISA (Beijing, China)
Celik 2018	Prospective Cohort	AF undergoing ablation	50	100	49.84 ± 12.45	56	N/A	12 months	Elabscience Human Gal-3 ELISA (Beijing, China)
Berger 2017	Prospective Cohort	AF undergoing thoracoscopic ablation	98	45	59.8 ± 8.6	76	>14	210 [IQR 184–234] days	Gal-3 ELISA kits from BG Medicin Inc. (Waltham, Massachusetts United States)
Clementy 2016	Prospective Cohort	AF undergoing 1st time ablation	160	55	61 ± 10	71	≥15	12 months	VIDAS Galectin-3 kit (bioMérieux, Marcy-l′ Etoile, France)
Takemoto 2016	Prospective Cohort	AF undergoing 1st time ablation	55	53	62.7 ± 1.1	82	>13.05	12 months	N/A
Kornej 2015	Prospective Cohort	AF undergoing ablation	92	51	62 ± 9	65	N/A	6 months	Hölzel human Galectin-3 ELISA HZ-4858, Cologne, Germany
Wu 2015	Prospective Cohort	Persistent AF without structural heart disease undergoing 1st time ablation	50	0	48.9 ± 7.8	94	>5.83	17 ± 4.1 months	Milliplex MAPKits (Merck Millipore, Germany)

Description: AF = Atrial Fibrillation, N/A = Not Available/Applicable, SD=Standard Deviation.

3.1. Study characteristics

The patients included in this systematic review and meta-analysis was AF undergoing 1st-time ablation in 4 studies, and there were 3 studies that did not mention whether they enroll 1st-time ablation only or they included repeat ablation. Ablation was mostly done by catheter except in one study which reported outcome for thoracoscopic ablation. There were 3 studies that reported 100% paroxysmal AF or 100% persistent AF. Follow-up duration differs but mostly were 12 months. The cut-off for serum galectin differs across studies. There were 3 studies reporting HR Ratio, and one study (Takemoto 2016) reported odds ratio (OR). We consider the OR as HR for the meta-analysis; the study itself did not significantly alter heterogeneity of the pooled HR.

3.2. Serum Galectin-3 and recurrence of atrial fibrillation post-ablation

2 studies showed that serum galectin-3 was higher in AF recurrence group, and 5 other studies did not show a significant difference. The mean difference of serum galectin-3 was similar in both AF recurrence and no AF recurrence group (mean difference 0.78 ng/mL [-0.56, 2.13]; p = 0.25; I^2: 69%, p = 0.007) [Fig. 2A]. On sensitivity analysis by removing one study at a time, we found that upon removal of Kornej et al. study the serum galectin-3 was higher in AF recurrence group (mean difference 1.41 ng/mL [0.47, 2.34], p = 0.003; I^2: 17%, p = 0.30). [Fig. 2B].

All 4 studies that measured HR for serum galectin-3 showed that it was associated with a higher AF recurrence. Serum galectin-3 was associated with a higher risk for AF recurrence (HR 1.25 [1.01, 1.55]; p = 0.04; I^2: 76%, p = 0.006) [Fig. 3A]. On sensitivity analysis by removing of Clementy et al. study, HR became 1.45 [1.07, 1.96], p = 0.02; I^2: 47%, p = 0.15. [Fig. 3B]. Meta-analysis of adjusted HR demonstrated that high serum galectin-3 independently predicts AF recurrence (HR 1.15 [1.02, 1.29], p < 0.02; I^2: 57%, p = 0.10). [Fig. 3C].

3.3. Publication bias

Contoured funnel-plot analysis was constructed for mean difference (Fig. 4A) between AF recurrence and no AF recurrence and its hazard ratio (Fig. 4B). The funnel plot was asymmetrical in both cases indicating the risk of publication bias. Regression-based Egger test showed for mean difference showed no indication of small-study effects (p = 0.625). However, the presence of small-study effects was statistically significant in the hazard ratio (p < 0.001) and adjusted hazard ratio for AF recurrence (p = 0.015).

4. Discussion

Serum galectin-3 was associated with the increased risk for AF recurrence post-ablation; however, the risk appears to increase on a specific cut-off point, as the difference in mean between the AF recurrence and non-AF recurrence group was not significant. The cut-off point of ≥13–15 ng/mL was shown to be associated with AF recurrence by the studies. The difference in mean became significant if one study is removed to reduce heterogeneity. The association between galectin-3 and AF recurrence seemed to apply in both paroxysmal and persistent AF.

Galectin-3 is one of the pro-fibrotic molecule that might be associated with AF substrate [18,21], it activates and promotes pro-fibrotic factors, fibroblast proliferation, transformation, pro-apoptotic effects, and collagen deposition (especially collagen type I) [22–24]. Galectin-3 did not only play a role in cardiac fibrosis [25], but also in pulmonary, liver, renal, and vascular fibrosis [26–29]. AF itself causes tissue injuries and further promotes Galectin-3 production [23]. Serum galectin-3 level has also been shown to independently correlate with the extent of left atrial fibrosis upon delayed enhanced magnetic resonance imaging [9]. Left atrial fibrosis itself has been shown to correlate independently with AF recurrence [30]. Fibrosis interrupts bundle continuity with consequent conduction abnormality and myofibroblast in fibrotic remodeled myocardium cause ectopic activity [31]. A change in serum galectin-3 upon follow-up has also been shown to be associated with increased risk of AF recurrence [HR 2.91 (1.19–7.15), P = 0.014]; however, investigation exploring in this dynamic is lacking [18]. This is an exciting finding because, galectin-3 can potentially be a marker for therapeutic success; Berger et al. hypothesized that elimination of AF triggers reduces the fibrotic substrate, and consequently decreasing galectin-3 level [18].

The association between galectin-3 and AF recurrence was yet to be explored in heart failure (HF) patients, cardiac remodelling and fibrosis in heart failure itself have been shown to have a positive correlation with galectin-3 [32]. Moreover, cardiac remodelling in HF especially those that involve atria may cause an increased complexity and increased AF recurrence [33]. Clementy et al.

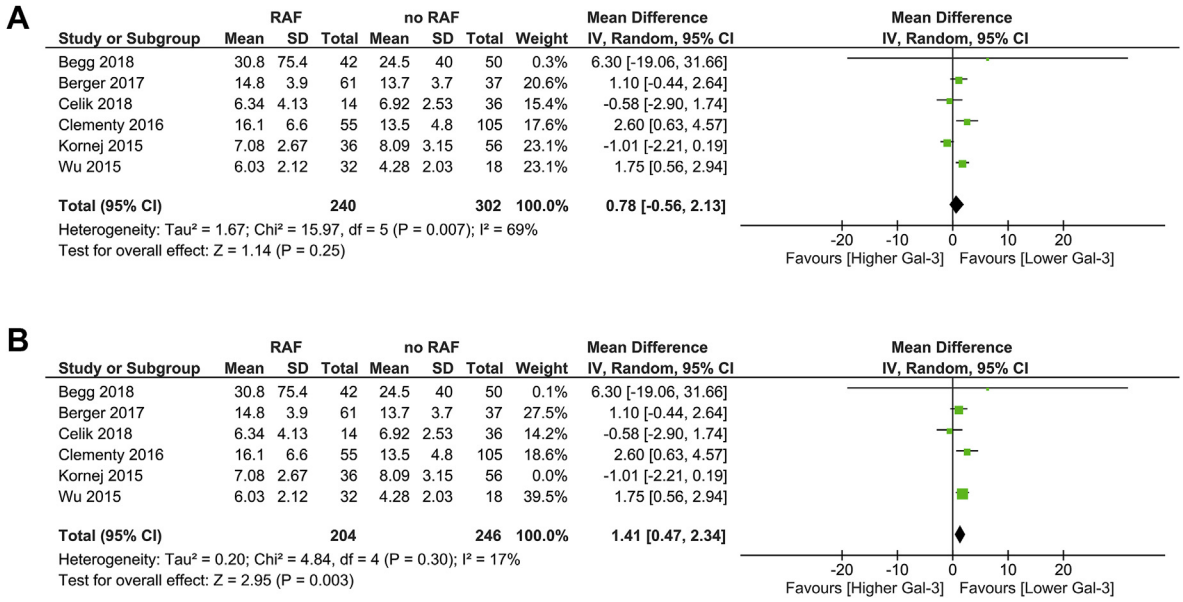

Fig. 2. Mean difference in serum galectin-3 level and atrial fibrillation recurrence. Fig. 2A showing no significant difference between serum galectin-3 in RAF which became significant upon removal of a study (higher in RAF group), as shown in Fig. 2B. Description: RAF = Recurrent AF.

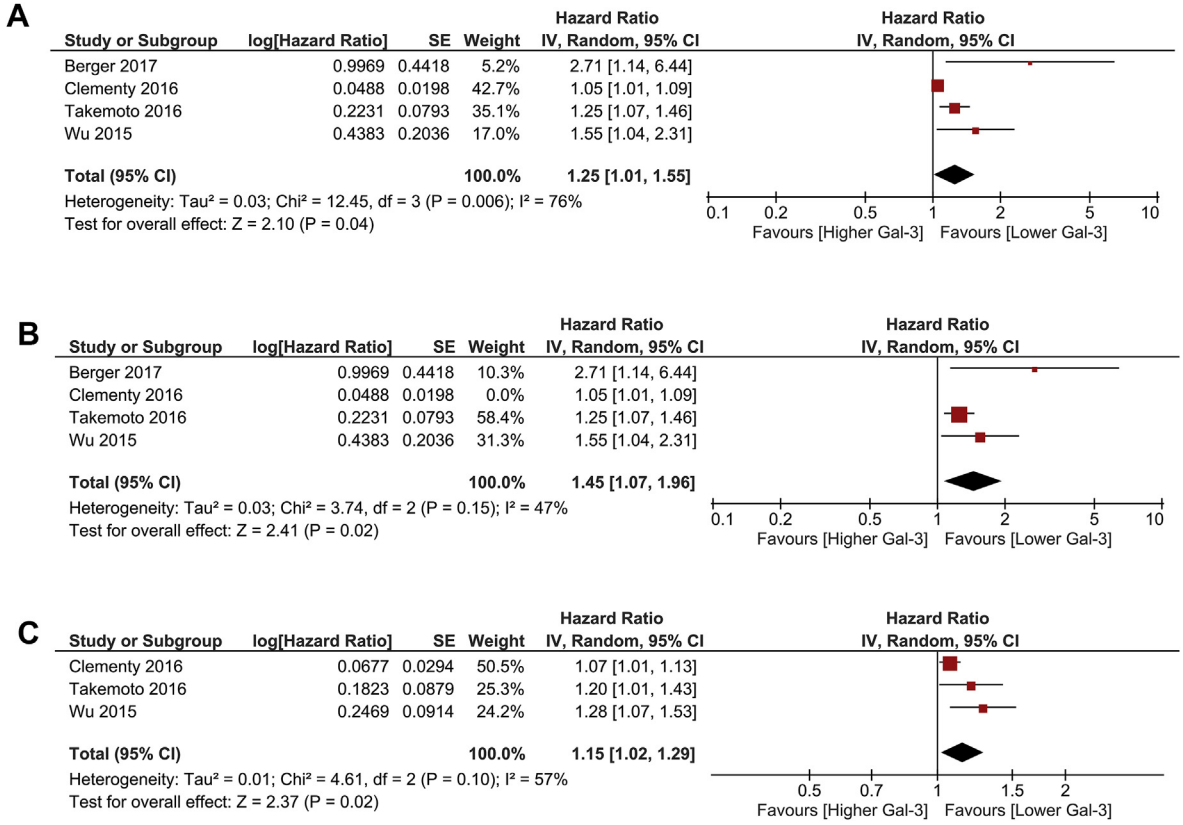

Fig. 3. Serum galectin-3 level and atrial fibrillation recurrence. Fig. 3A showing that increased serum galectin-3 was associated with increased RAF and became more significant along with low heterogeneity upon removal of a study, as shown in Fig. 3B. Fig. 3C showed that serum galectin-3 was independently associated with increased RAF in a pooled adjusted hazard ratio. Description: RAF = Recurrent AF.

showed that HF is one of the factors associated with AF recurrence, they perform subgroup analysis in patients without HF, it would be interesting to know whether galectin-3 is a predictor of AF recurrence in HF subgroup. They reported that galectin-3 is an independent predictor of AF recurrence after adjustment to several factors, including HF [20].

The clinical implication of this result is that serum galectin-3 is a potential biomarker to risk-stratify and identify patients at risk for

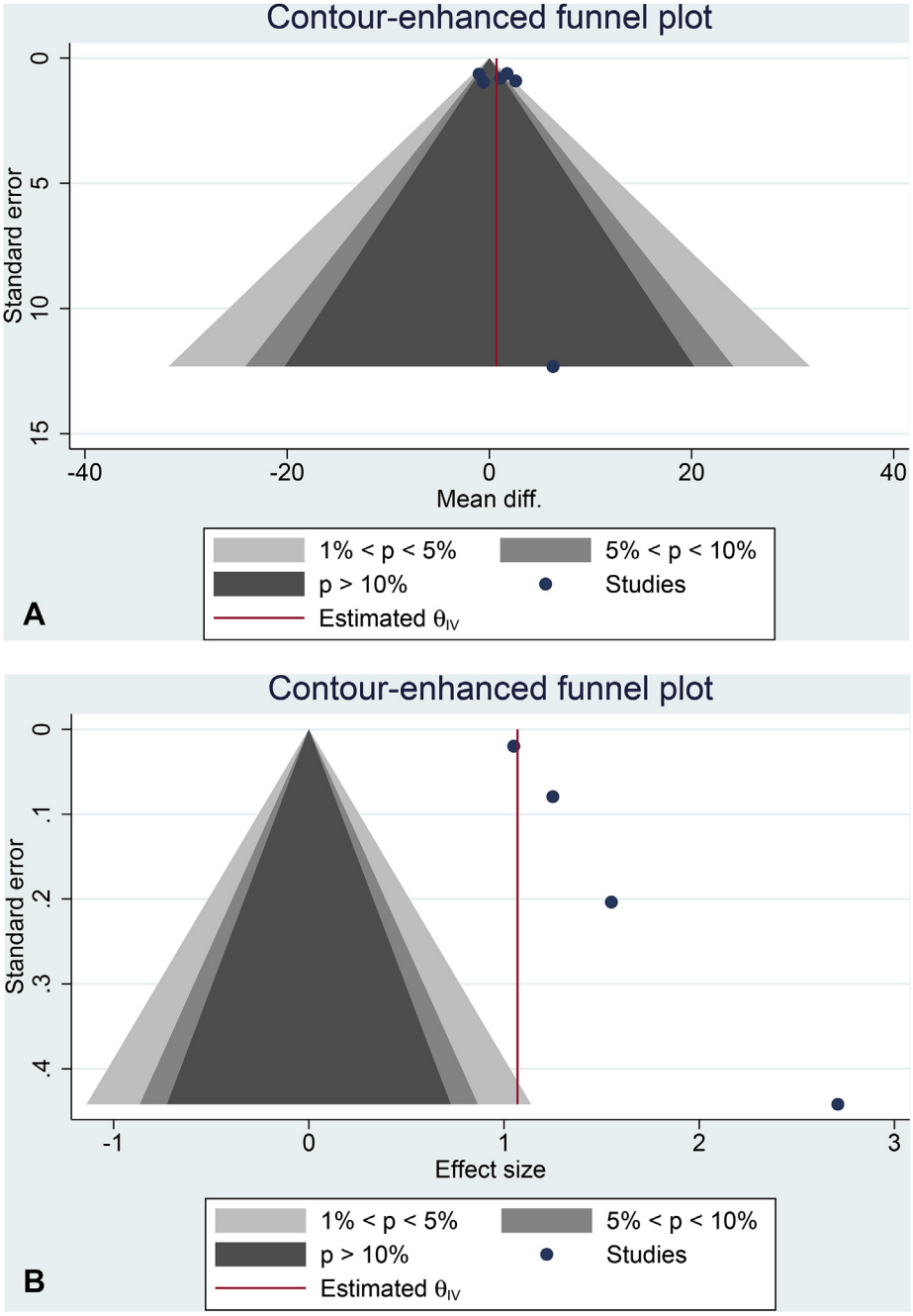

Fig. 4. Contour enhanced funnel plot analysis showing asymmetrical funnel plot for both Mean difference of galectin between AF recurrence and no AF recurrence (4A) and its hazard ratio (4B).

AF recurrence. A cut-off point of ≥13–15 ng/mL might be ideal, although more studies are needed. Galectin-3 can also be integrated into a risk predicting model along with other factors that might be associated with AF recurrence for future studies.

Limitation of this systematic review includes publication bias in which galectin-3 might not be reported by studies if it is not significant. This was indicated by the asymmetrical funnel plot and also the presence of small-study effects. The cut-off point for the serum galectin-3 differs across the studies, this heterogeneity might be due to different labs may have varying protocols for the assay and varying cut-offs. The study and samples were limited in size; hence, we cannot perform multiple subgroup analysis. We consider an odds ratio to be a HR in one study, however, the study did not significantly cause heterogeneity. Future studies are needed before making recommendation on this matter.

5. Conclusion

Serum galectin-3 is associated with an increased risk of AF recurrence post-ablation. However, further studies are needed to confirm these findings. Future studies also have to set a specific cut-off point, preferably between 13 and 15 ng/mL to ensure a uniform cut-off point prior to integration into clinical practice. Also, studies on the change of serum galectin-3 post-ablation should be explored to investigate the possible use of galectin-3 as a marker of therapeutic success.

Authors contribution

Raymond Pranata conceived and designed the study and drafted the manuscript. Raymond Pranata and Emir Yonas acquired the data and drafted the manuscript. Raymond Pranata and Veresa Chintya interpreted the data and performed extensive research for the manuscript. Alexander Edo Tondas and Sunu Budhi Raharjo critically revise the manuscript. All authors contributed to the writing of the manuscript. Raymond Pranata analyzed the data statistically.

Funding

None.

Declaration of competing interest

The authors declare that they have no conflict of interests.

Acknowledgements

None.

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