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Circulating galectin-3 on admission and prognosis in acute heart failure patients: a meta-analysis

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Abstract

Changes of serum galectin-3 have been associated with the pathogenesis of many cardiovascular diseases. The aim of the study was to evaluate the prognostic role of serum galectin-3 in patients with acute heart failure (AHF) in a meta-analysis. Follow-up studies evaluating the association between serum galectin-3 on admission and clinical outcomes in AHF patients were identified via search of PubMed and Embase databases. A random effects or a fixed effects model was applied to pool the results depending on the heterogeneity. Subgroup analysis was used to evaluate the influences of study characteristics on the outcomes. Overall, 7057 AHF patients from eighteen follow-up studies were included. Higher serum galectin-3 was associated with higher risks of all-cause mortality (adjusted risk ratio [RR], 1.58; $p < 0.001$), mortality/HF rehospitalization (RR, 1.68; $p < 0.001$), and cardiovascular mortality (RR, 1.29; $p = 0.04$), but not HF rehospitalization (RR, 1.24; $p = 0.25$) in AHF patients. Subgroup analyses showed that study characteristics including study design, sample size, age, gender, left ventricular ejection fraction, galectin-3 variable type, follow-up duration, and adjustment of type B natriuretic peptide did not significantly impact the results. Significant heterogeneities were detected for the outcomes of all-cause mortality and mortality/HF rehospitalization. However, trim-and-fill analyses by including the imputed studies to generate symmetrical funnel plots showed similar significant meta-analysis results. These results suggested that higher serum galectin-3 may be associated with poor prognosis in AHF patients. Further studies are needed to determine the mechanisms underlying the potential prognostic role of galectin-3 in AHF.

Keywords Galectin-3 · Acute heart failure · Mortality · Rehospitalization · Meta-analysis

Introduction

Despite significant improvements in the diagnostic and treatment strategies for heart failure (HF) in recent decades, this disease remains one of the most important causes of morbidity and mortality for people all over the world [1]. Acute HF (AHF) refers to the decompensated status of the cardiac function, which is characterized by the symptom of volume overload and pulmonary edema [2, 3]. Pathologically, AHF could be resulted from acute cardiac events such as myocardial infarction or severe myocarditis, or following the deterioration of cardiac function in chronic HF (CHF) patients induced by risk factors such as infection, arrhythmia, or myocardial ischemia [3–5]. The prognosis in patients with AHF is very poor despite intensive treatments during hospitalization, with a reported composite outcome of mortality or rehospitalization of up to 50% within 3 months after discharge [4, 6]. Therefore, improving the risk stratification strategies for the early identification of AHF patients at higher risk for adverse clinical outcome is important in clinical practice.

Accumulating evidence indicated that galectin-3, a marker of fibrosis, immune response, and inflammation, is involved in the pathogenesis and progression of HF [7, 8]. Clinical studies in patients with CHF showed that higher serum galectin-3 is correlated with poor cardiac systolic function and severity of ventricular remodeling in CHF [7, 8]. Interestingly, epidemiological studies indicated that higher serum galectin-3 may predict poor prognosis in HF patients, mostly in CHF patients [9, 10]. Some studies have been performed to evaluate the association between serum galectin-3 and clinical outcomes in AHF patients, but results of these studies were inconsistent [11–28]. To the best of our knowledge, only one meta-analysis focusing on the prognostic role of serum galectin-3 in AHF patients was performed to date

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[29]. However, only four studies published before 2013 were included in this meta-analysis, and only mortality outcome was reported [29]. Many relevant studies published since then were not included [15–28]. Therefore, an updated meta-analysis was performed in this study to systematically evaluate the potential prognostic role of serum galectin-3 on admission in AHF patients.

Methods

This study was performed in accordance with the MOOSE (Meta-analysis of Observational Studies in Epidemiology) [30] and Cochrane's Handbook [31] guidelines.

Database search

We searched the databases of PubMed and Embase for relevant records, using the combination of the following terms: (1) "galectin-3" OR "galectin 3"; (2) "heart failure" OR "cardiac failure" OR "cardiac dysfunction" OR "cardiac insufficiency"; and (3) "acute" OR "decompensated". We limited the search to human studies published in English. A manual analysis of the reference lists of original and review articles was performed as a supplementation. The final search was performed on May 19, 2019.

Inclusion and exclusion criteria

Studies were included if they met the following criteria: (1) full-length article in English; (2) designed as longitudinal follow-up studies; (3) included AHF patients (de novo AHF or worsening CHF requiring hospitalization); (4) serum galectin-3 was measured on admission as exposure of interest; (5) documented the incidences of at least one of the outcomes: all-cause mortality (ACM), all-cause mortality or HF rehospitalization (ACM/HFR), HF rehospitalization (HFR), or cardiovascular mortality (CVM); and (6) reported the multivariable adjusted risk ratios (RRs) and their corresponding 95% confidence intervals (CIs) for the above outcomes in patients with higher versus lower galectin-3 at baseline. The clinical outcomes were defined in accordance with the definitions used in the original articles. For repeated reports of the same cohort, latest studies with the longest follow-up duration were included.

Data extraction and quality evaluation

Database search, data extraction, and quality assessment were independently performed by two authors, and discrepancies were resolved by consultation with the corresponding author. Data extracted include (1) first author, location, and design of the study; (2) patient characteristics: number, mean age, gender, proportions of HF with reduced ejection fraction (HFrEF), and baseline left ventricular ejection fraction (LVEF) of the patients; (3) assays for galectin and variable types of galectin presentation; and (4) follow-up durations, outcomes reported, and variables adjusted. Study quality evaluation was performed with the Newcastle-Ottawa Scale [32], which ranges from 1 to 9 stars and judges each study regarding three aspects: the selection of the study groups, the comparability of the groups, and the ascertainment of the outcome of interest.

Statistical analyses

Data of RRs and their corresponding standard errors (SEs) were calculated from 95% CIs or p values, and were logarithmically transformed to stabilize variance and normalized the distribution [31]. The Cochran's Q test and I^2 test were performed to evaluate the heterogeneity among studies [33]. An I^2 test, > 50% indicates significant heterogeneity. A fixed effects model was applied if no significant heterogeneity was detected; otherwise, a random effects model was applied. Sensitivity analyses by removing individual study one at a time were performed to evaluate the stability of the results [34]. Predefined subgroup analyses were performed to evaluate the study characteristics on the results (study design, sample size, age, male proportion, LVEF, galectin-3 variable type, follow-up duration, and adjustment of type B natriuretic peptide [BNP]). For continuous variables, the median was used as cutoff for stratification. Potential publication bias was assessed by funnel plots with the Egger regression asymmetry test [35]. If the funnel plots were asymmetrical, a "trim-and-fill" analysis was performed [31]. To achieve symmetrical funnel plots, this method assumes the existence of the hypothetically unpublished studies with negative results, estimates their RRs, and recalculates the pooled RR after incorporating this "missing" study [31]. RevMan (Version 5.1; Cochrane Collaboration, Oxford, UK) and STATA software (Version 12.0; Stata Corporation, College Station, TX) were used for the statistical analyses.

Results

Results of literature search

The process of database search and study identification is presented in Fig. 1. Briefly, 752 studies were obtained via initial literature search, and 719 were excluded based on title and abstract because they were irrelevant to the study purpose. The remaining 33 studies underwent full-text review. Of them, fifteen were further excluded because one of them was not a follow-up study, three did not include patients with CHF, four did not report outcomes of interest, five were not with

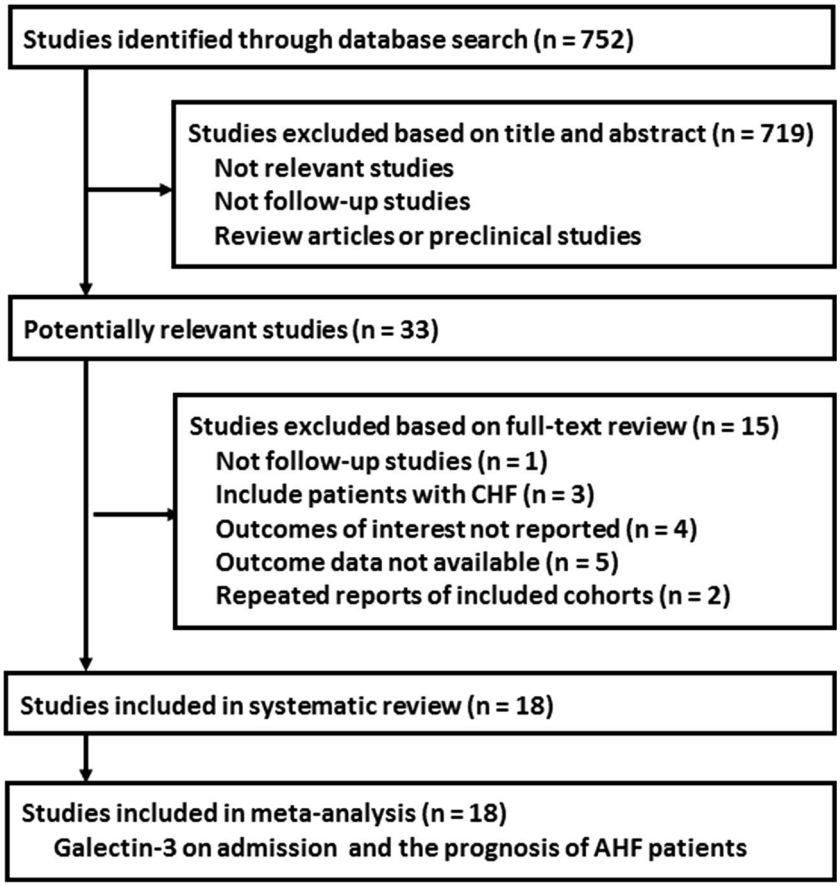

Fig. 1 Flowchart of database search and study identification

available outcome data, and the other two were repeated reports of the included cohorts. Finally, eighteen studies [11–28] were included.

Study characteristics and quality evaluation

The characteristics of the included studies are presented in Table 1. Overall, our meta-analysis included 7057 AHF patients from eighteen follow-up studies, of which twelve were prospective cohort studies [11–13, 15–17, 21–23, 25, 26, 28], and the other six were retrospective cohorts or post hoc analyses [14, 18–20, 24, 27]. One study included two datasets of patients with HFrEF and HFpEF [19], and another study included two datasets of patients with ischemic HF and non-ischemic HF [28], which were included separately. The mean age of the patients varied between 59 and 79 years, and the proportion of male varied from 39 to 93%. The mean LVEF at baseline varied from 30 to 51%. The follow-up durations varied from 1 to 60 months. When presenting the association between serum galectin-3 and clinical outcomes, demographic factors including age and gender were adjusted for all of the included studies. Besides, cardiovascular risk factors, comorbidities, HF medications, and BNP or N-terminal pro-brain natriuretic peptide (NT-proBNP) were also adjusted to a various extent. The Newcastle-Ottawa scale varied from 7 to 9 for the included studies.

Association between galectin-3 and ACM in AHF patients

Thirteen studies [11–13, 15–17, 19, 21, 24–28] including fifteen datasets reported the association between serum galectin-3 and risk of ACM. Significant heterogeneity was detected (I^2 = 51%, p for Cochran's Q test = 0.01). Pooled results with a random effects model showed that higher serum galectin-3 on admission was independently associated with higher risk of ACM in AHF patients (adjusted RR, 1.58; 95% CI, 1.33 to 1.88; $p < 0.001$; Fig. 2a). Sensitivity analyses by excluding one study at a time retrieved similar results (data not shown). Subgroup analyses indicated that the association between higher serum galectin-3 on admission and higher risk of ACM in AHF patients was not significantly affected by study characteristics including study design, sample size, age, gender, baseline LVEF, variable type of galectin-3, follow-up duration, and adjustment of BNP or NT-proBNP (Table 2).

Table 1 Characteristics of the included studies

Study	Country	Design	No. of patients	Mean age (years)	Male (%)	HFrEF (%)	Baseline LVEF (%)	Gal-3 assay	Gal-3 variable type	Follow-up duration (month)	Outcomes reported	Variables adjusted	NOS
van Kimmenade 2006	the US	PC	209	72.8	51.0	NR	46.5	ELISA	Continuous	2	ACM, ACM/HFR	Age, gender, HTN, DM, CAD, PP, BMI, eGFR, LVEF, TnI, NT-proBNP, and HF medications	9
de Boer 2011	the Netherlands	PC	592	72.0	65.0	81.9	32.3	ELISA	Continuous	18	ACM, ACM/HFR, HFR	Age, gender, BNP, eGFR, DM, and LVEF	9
van der Velde 2013	the Netherlands	Post hoc analyses	324	69.9	60.0	NR	33.0	ELISA	Dichotomized	6	ACM/HFR	Age, gender, NT-pro BNP, eGFR, DM, and LVEF	7
Carrasco-Sánchez 2013	Spain	PC	419	76.2	39.4	0	NR	ELISA	Dichotomized	12	ACM, ACM/HFR	Age, gender, anemia, DM, NYHA classification, serum sodium, NT-proBNP, and BUN	9
Meijers 2015	the Netherlands	PC	285	72.0	67.0	NR	32.0	ELISA	Dichotomized	6	ACM/HFR	Age, gender, DBP, PP, stroke, MI, AF, PAD, DM, LVEF, previous HF hospitalization, serum sodium, SCr, and NT-proBNP	8
Núñez 2015	Spain	PC	264	72.7	49.6	44.7	51.0	ELISA	Dichotomized	24	ACM, HFR	Age, gender, prior admission for AHF, prior history of stroke, wide QRS, SBP, LVEF, eGFR, hs-TnT, NT-proBNP	8
Lala 2016	Romania	PC	79	64.0	73.0	75.0	NR	ELISA	Dichotomized	12	ACM/HFR	Age, gender, HTN, DM, LVEF, eGFR, and NT-proBNP	8
Mueller 2016	Austria	PC	137	76.0	93.0	NR	40.0	ELISA	Dichotomized	12	ACM	Age, gender, SBP, eGFR, LVEF, NYHA classification, and BNP	8
Beltrami 2016	Italy	RC	98	75.0	51.0	54.1	NR	ELISA	Dichotomized	6	ACM/HFR	Age, gender, smoking, DM, HTN, CKD	8
Demissei 2016	the Netherlands	Post hoc analyses	2033	70.2	67.1	71.6	30.0	ELISA	Dichotomized	6	ACM, ACM/HFR, CVM	Age, gender, BMI, SBP, DBP, HR, NYHA classification, medical histories of AF, COPD, stroke, PAD, HTN, DM, hypercholesterolemia, IHD, HF hospitalization, NT-proBNP, and CVD medications	8
Jackson 2016	UK	PC	628	70.8	58.4	77.4	40.1	ELISA	Continuous	34	ACM	Age, gender, BMI, SBP, HR, LVEF, DM, SCr, current smoking, medical histories of AF, COPD, stroke, PAD, and BNP	9
Behnes 2016	Germany	PC	122	73.0	61.0	75.0	39.0	ELISA	Continuous	60	ACM	Age, gender, LVEF, SCr, NYHA classification, DM, CAD, HGB, serum sodium, CVD medications, and NT-proBNP	9
Feola 2016	Italy	RC	83	73.2	80.7	NR	37.2	ELISA	Continuous	12	ACM/HFR	Age, gender, and eGFR	7
Miro 2017	Spain	RC	115	79.0	51.3	NR	46.0	ELISA	Dichotomized	1	ACM	Age, gender, and eGFR	7
van Vark 2017	the Netherlands	PC	496	74.0	63.0	83.0	30.0	ELISA	Continuous	12	ACM, ACM/HFR, HFR, CVM	Age, gender, SBP, DM, LVEF, previous HF hospitalization, CAD, BMI, eGFR, and baseline NT-proBNP	9

Table 1 (continued)

Study	Country	Design	No. of patients	Mean age (years)	Male (%)	HFrEF (%)	Baseline LVEF (%)	Gal-3 assay	Gal-3 variable type	Follow-up duration (month)	Outcomes reported	Variables adjusted	NOS
Zhang 2018	China	PC	1020	59.0	70.5	46.7	40.0	ELISA	Continuous	12	ACM	Age, gender, DM, SBP, NYHA classification, LVEF, HGB, serum sodium, CRP, eGFR, NT-proBNP, and CVD medications	9
Testa 2018	Italy	RC	84	77.5	75	71.4	37.8	ELISA	Dichotomized	16	ACM, ACM/HFR, HFR	Age, gender, LVEF, eGFR, DM, and Barthel Index	7
Lala 2018	Romania	PC	69	64.7	48.0	NR	30.0	ELISA	Dichotomized	18	ACM	Age, gender, NYHA classification, DM, COPD, AF	8

Gal-3, galectin-3; *HFrEF*, heart failure with reduced ejection fraction; *LVEF*, left ventricular ejection fraction; *NOS*, the Newcastle-Ottawa Scale; *US*, United States; *UK*, United Kingdom; *PC*, prospective cohort; *RC*, retrospective cohort; *ELISA*, enzyme-linked immunosorbent assay; *ACM*, all-cause mortality; *HFR*, heart failure rehospitalization; *ACM/HFR*, all-cause death or heart failure rehospitalization; *CVM*, cardiovascular mortality; *HTN*, hypertension; *DM*, diabetes mellitus; *CAD*, coronary artery disease; *MI*, myocardial infarction; *AHF*, acute heart failure; *AF*, atrial fibrillation; *COPD*, chronic obstructive pulmonary disease; *eGFR*, estimated glomerular filtrating rate; *HGB*, hemoglobin; *SCr*, serum creatinine; *LVEF*, left ventricular ejection fraction; *TnI*, troponin I; *NYHA*, New York Heart Association; *SBP*, systolic blood pressure; *PP*, pulse pressure; *CRP*, C-reactive protein; *IHD*, ischemic heart disease; *CVD*, cardiovascular diseases; *CKD*, chronic kidney disease; *BMI*, body mass index; *BNP*, type B natriuretic peptide; *NT-proBNP*, N-terminal pro-brain natriuretic peptide

Association between galectin-3 and ACM/HFR in AHF patients

Meta-analysis of eleven studies [11–15, 18–20, 22, 25, 27] with thirteen datasets showed that higher serum galectin-3 on admission was independently associated with higher risk of ACM/HFR in AHF patients (adjusted RR, 1.68; 95% CI, 1.33 to 2.13; $p < 0.001$; $I^2 = 82\%$; Fig. 2b). Sensitivity analyses by excluding one study at a time retrieved similar results (data not shown). Subgroup analyses also did not show significant impact of the predefined study characteristics on the association between galectin-3 and ACM/HFR in AHF patients (Table 2). However, the association between galectin-3 and risk of ACM/HFR was not significant in studies with follow-up durations > 12 weeks (two studies, RR = 1.72, $p = 0.15$).

Association between galectin-3 and HFR or CVM in AHF patients

Meta-analysis including four studies [12, 16, 25, 27] showed that higher serum galectin-3 on admission was not independently associated with higher risk of HFR in AHF patients (adjusted RR, 1.24; 95% CI, 0.86 to 1.78; $p = 0.25$; $I^2 = 54\%$; Fig. 3a). Pooled results of two studies [19, 25] indicated that higher serum galectin-3 on admission was independently associated with higher risk of CVM in these patients (adjusted RR, 1.29; 95% CI, 1.01 to 1.65; $p = 0.04$; $I^2 = 0\%$; Fig. 3b).

Publication bias

The funnel plots for the associations between galectin-3 on admission and ACM or ACM/HFR were asymmetrical on visual inspection, indicating significant publication biases. Moreover, results of the Egger's regression tests also indicated the significant publication biases ($p = 0.038$ and 0.022, respectively). For the meta-analysis of the associations between galectin-3 and ACM, trim-and-fill analyses included four imputed studies to generate symmetrical funnel plots, and the results of meta-analysis incorporating these four studies showed similar results (adjusted RR, 1.47; 95% CI, 1.23 to 1.76; $p < 0.001$; Fig. 4a). Similarly, trim-and-fill analyses included six imputed studies to generate symmetry funnel plot for the association between galectin-3 and ACM/HFR, and the results of meta-analysis incorporating these six studies showed similar results (adjusted RR, 1.33; 95% CI, 1.10 to 1.61; $p < 0.001$; Fig. 4b). Publication biases for the meta-analyses of the associations between galectin-3 and HFR or CVM were difficult to estimate because limited studies were included for each outcome.

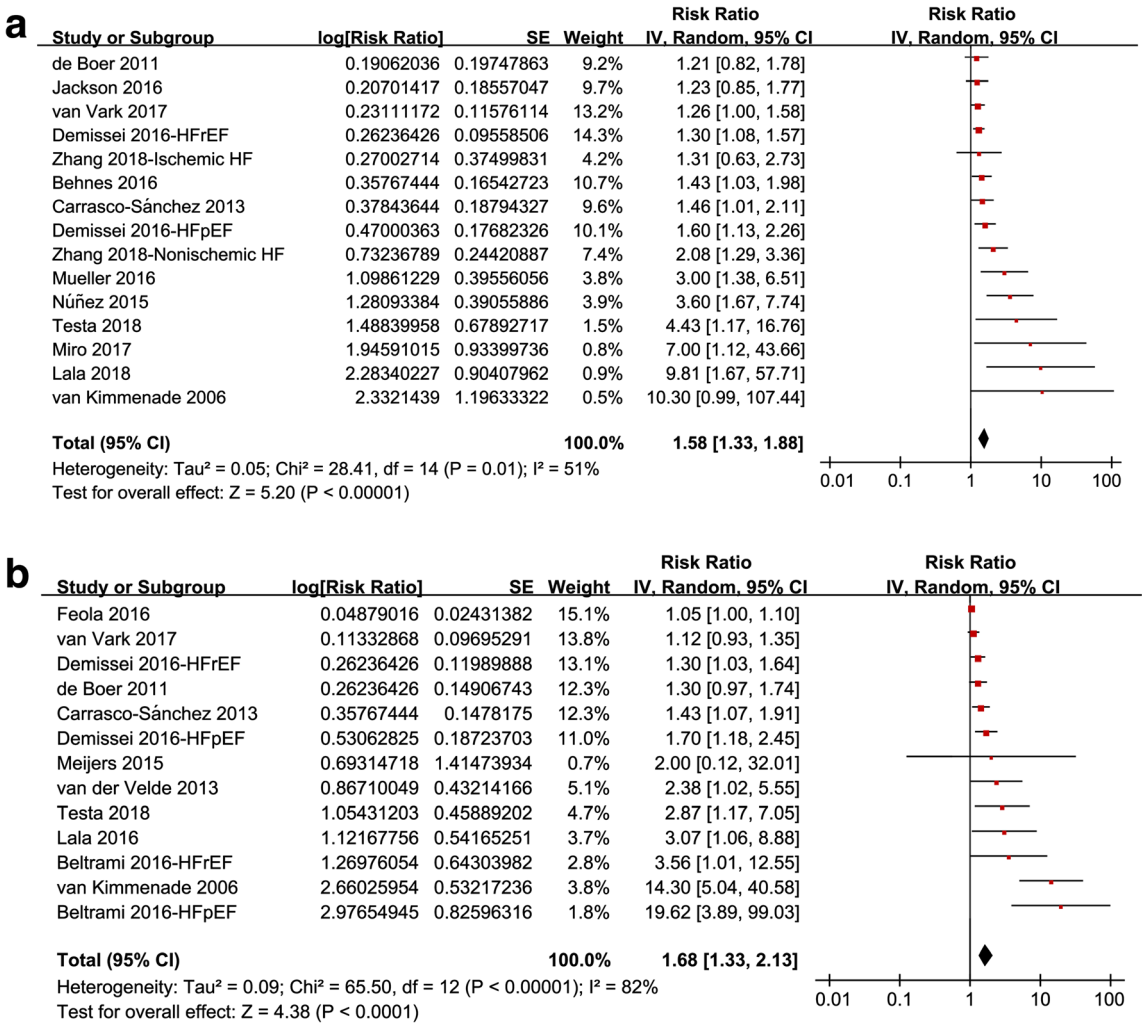

Fig. 2 Forest plots for the meta-analyses of the association between serum galectin-3 and clinical outcomes in AHF patients. **a** Risk of ACM. **b** Risk of ACM/HFR

Discussion

In this meta-analysis, by pooling the results of all available follow-up studies, we found that higher serum galectin-3 on admission is independently associated with higher incidence of ACM, ACM/HFR, and CVM. Subsequent sensitivity analyses by omitting one study at a time did not significantly affect the results. Moreover, subgroup analyses further confirmed that study characteristics, including study design, sample size, age, gender, LVEF, galectin-3 variable type, follow-up duration, and adjustment of BNP did not significantly influence the results, suggesting the robustness of the findings. Although high risks of publication biases were detected for outcomes of ACM and ACM/HFR, trim-and-fill analyses by incorporating the imputed studies to generate symmetrical funnel plots also showed significant associations between higher serum galectin-3 on admission and higher risk of ACM and ACM/HFR. Taken together, these results indicated that higher serum galectin-3 may be associated with poor prognosis in AHF patients. Further studies are needed to determine the mechanisms underlying the potential prognostic role of galectin-3 in AHF.

The prognostic role of serum galectin-3 for HF patients has been evaluated in three previous meta-analyses [9, 10, 29]. The first study published included eleven follow-up studies of CHF or AHF patients and showed that higher serum galectin-3 predicts CVM in overall HF population [9]. However, no subgroup analyses were performed in AHF patients [9]. Moreover, although high risk of publication bias was detected, no further analyses were performed [9]. Similarly, another updated meta-analysis included thirteen follow-up studies with patients of CHF or AHF also showing the similar association between higher serum galectin-3 and ACM in HF patients [10]. However, subgroup analyses focusing on AHF patients were not performed, and significant publication bias was also detected [10]. The third meta-analysis is the only study focusing on the prognostic role of serum galectin-3 in AHF patients. However, only four studies

Table 2 Subgroup analyses

Study characteristics	All-cause mortality					All-cause mortality/HF rehospitalization				
	Dataset number	RR (95% CI)	I^2	*p* for subgroup effect	*p* for subgroup difference	Dataset number	RR (95% CI)	I^2	*p* for subgroup effect	*p* for subgroup difference
Study design										
PC	12	1.65 [1.32, 2.07]	54%	< 0.001		6	1.80 [1.19, 2.75]	81%	0.006	
RC or post hoc analyses	3	1.49 [1.07, 2.07]	51%	0.02	0.61	7	1.78 [1.24, 2.54]	82%	0.002	0.96
Sample size										
< 300	9	2.31 [1.58, 3.38]	54%	< 0.001		7	3.92 [1.47, 10.47]	88%	0.006	
≥ 300	6	1.32 [1.18, 1.49]	0%	< 0.001	0.006	6	1.33 [1.15, 1.52]	26%	< 0.001	0.03
Mean age (years)										
< 72	6	1.49 [1.19, 1.88]	44%	< 0.001		6	2.26 [1.41, 3.63]	69%	< 0.001	
≥ 72	9	1.75 [1.32, 2.32]	59%	< 0.001	0.40	7	1.46 [1.11, 1.92]	83%	0.006	0.12
Male (%)										
< 60	9	1.45 [1.24, 1.69]	32%	< 0.001		4	3.06 [1.26, 7.42]	75%	0.01	
≥ 60	6	2.41 [1.37, 4.26]	68%	< 0.001	0.09	9	1.51 [1.19, 1.92]	82%	< 0.001	0.13
Baseline LVEF (%)										
< 40	9	1.44 [1.22, 1.70]	37%	< 0.001		8	1.29 [1.09, 1.52]	64%	0.004	
≥ 40	5	2.85 [1.37, 5.95]	70%	0.005	0.07	1	14.30 [5.04, 40.58]	–	< 0.001	< 0.001
Gal-3 variable type										
Continuous	7	1.36 [1.16, 1.60]	15%	< 0.001		4	1.39 [1.00, 1.92]	89%	0.05	
Dichotomized	8	2.06 [1.46, 2.90]	65%	< 0.001	0.03	9	1.93 [1.42, 2.64]	56%	< 0.001	0.15
Follow-up duration (months)										
≤ 12	9	1.54 [1.27, 1.86]	43%	< 0.001		11	1.72 [1.32, 2.24]	83%	< 0.001	
> 12	6	1.77 [1.20, 2.62]	65%	0.004	0.53	2	1.72 [0.82, 3.60]	63%	0.15	0.99
BNP or NT-proBNP adjusted										
Yes	12	1.47 [1.27, 1.71]	39%	< 0.001		9	1.63 [1.25, 2.12]	73%	< 0.001	
No	3	6.16 [2.46, 15.46]	0%	< 0.001	0.003	4	3.17 [1.03, 9.76]	86%	0.04	0.26

HF, heart failure; *RR*, risk ratio; *CI*, confidence interval; *PC*, prospective cohort; *RC*, retrospective cohort; *LVEF*, left ventricular ejection fraction; *Gal-3*, galectin-3; *BNP*, type B natriuretic peptide; *NT-proBNP*, N-terminal pro-brain natriuretic peptide

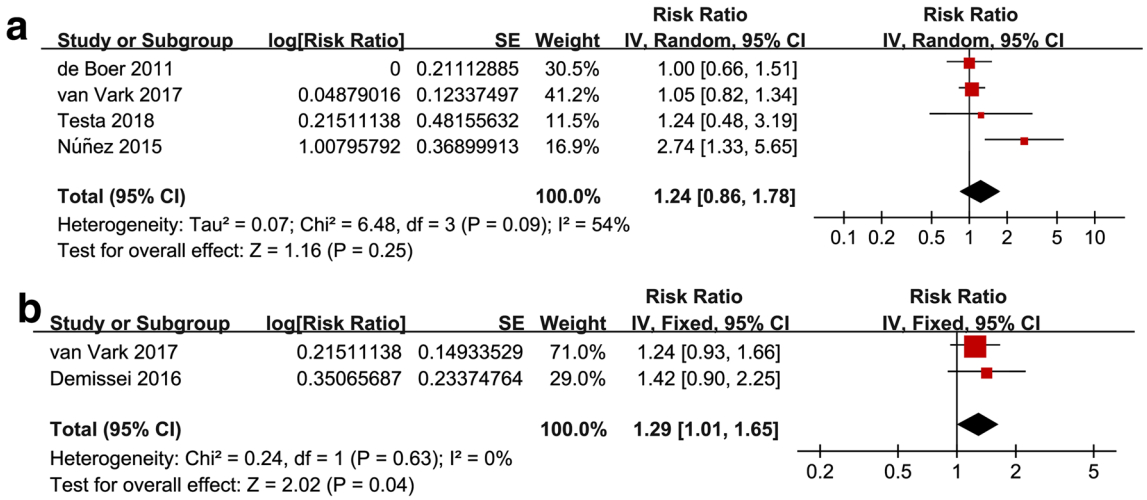

Fig. 3 Forest plots for the meta-analyses of the association between serum galectin-3 and clinical outcomes in AHF patients. **a** Risk of HFR. **b** Risk of CVM

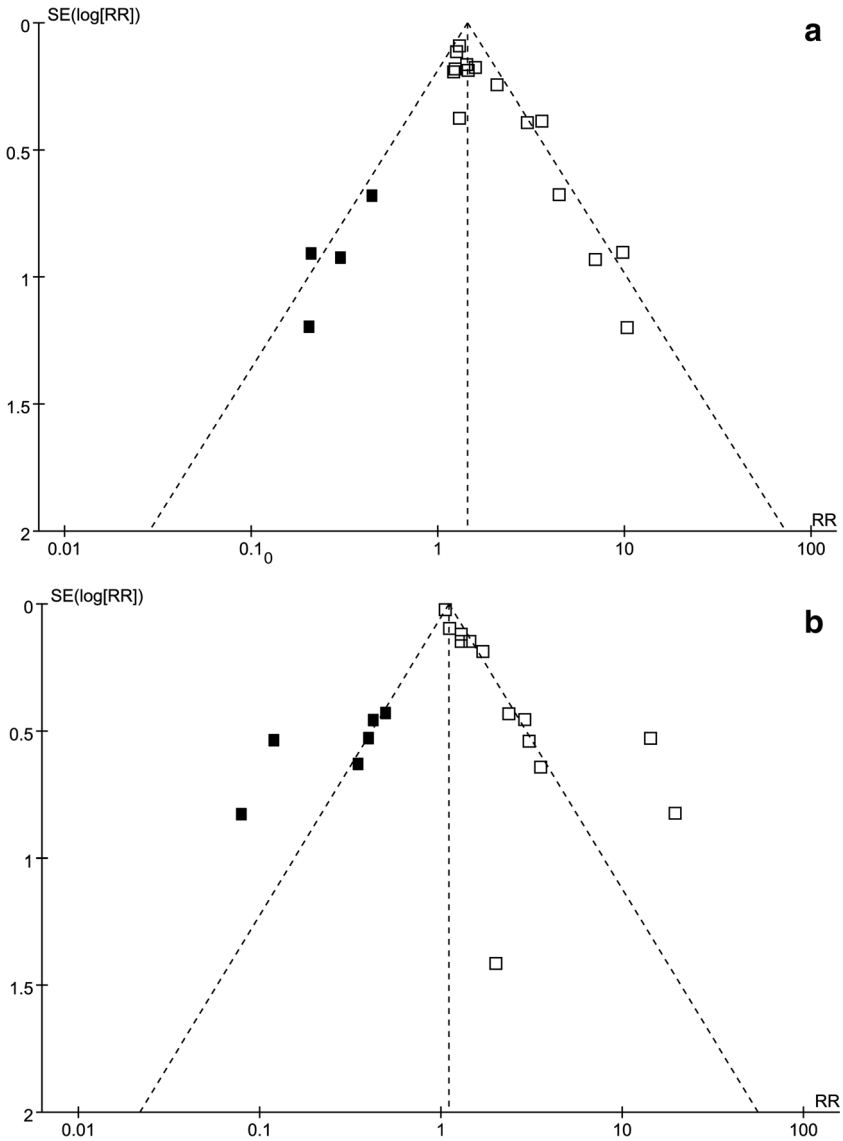

Fig. 4 Funnel plots with trim-and-fill analyses for the association between serum galectin-3 and clinical outcomes in AHF patients. **a** Risk of ACM. **b** Risk of ACM/HFR. The white square indicates the included studies in meta-analysis for each outcome, while the black square indicates the imputed studies so as to generate symmetrical funnel plots

published before 2014 were included, and the results need to be validated and updated. Comparing with previous meta-analyses, our study has significant strengths. Firstly, we included up-to-date studies that included AHF patients only to reduce the potential heterogeneity introduced by including studies with CHF patients. Secondly, eighteen follow-up studies with more than 7000 AHF patients were included. The large sample size of the overall population allows us to come to a more reliable conclusion. Thirdly, we evaluated the predictive efficacy of serum galectin-3 for various clinical outcomes in AHF patients, including HF rehospitalization and CVM, which were rarely investigated in previous meta-analyses. Fourthly, sensitivity analyses and subgroup analyses were performed to evaluate the study characteristics on the results, and consistent results were retrieved, indicating the stability of the findings. Finally, we performed trim-and-fill analyses to further analyze the influence of the publication biases detected for outcomes of ACM or ACM/HFR. Since the publication biases were probably due to missing unpublished studies with negative results, the meta-analysis results were not significantly affected by including the imputed studies into the meta-analysis, which further validate the findings. Overall, the result of our study provided the state-of-the-art evidence that higher serum galectin-3 is an independent predictor of poor prognosis in AHF patients.

Our study has some important clinical implications. Firstly, we included studies in which serum galectin-3 was measured on admission. Our findings supported use of serum galectin-3 measurement as a factor for AHF risk stratification. Secondly, only multiple variable adjusted results were included, which suggested the independent prognostic efficacy of serum galectin-3 in AHF. Moreover, the prognostic role of BNP or NT-proBNP in AHF patients has been well observed [36]. Interestingly, results of subgroup analyses showed that the prognostic role of serum galectin-3 for AHF remained significant in studies that BNP or NT-proBNP were adjusted. These findings indicated the serum galectin-3 has additional prognostic value to BNP or NT-proBNP in AHF patients. Currently, the potential mechanisms underlying the potential prognostic role of galectin-3 in AHF remain unclear. Pathophysiologically, galectin-3 is a beta-galactoside–binding lectin that can be secreted by macrophages, monocytes, and epithelial cells [37]. Galectin-3 has been confirmed to mediate myocardial fibrosis, ventricular remodeling, and cardiac oxidative stress and ischemia-related damages induced by hypertension, diabetes, and coronary artery diseases [38–40]. In cardiomyocytes and animal models of cardiovascular diseases, inhibition of galectin-3 was shown to exert therapeutic efficacy by attenuation of ventricular remodeling and myocardial apoptosis [41, 42]. However, few of these experimental studies were performed in models of AHF. Whether therapeutic inhibition of galectin-3 has beneficial hemodynamic effect in animal models of AHF deserves further investigation.

Our study has limitations which should be considered when interpreting the results. Firstly, significant heterogeneity remained underlying the meta-analyses for the outcomes of ACM or ACM/HFR. Since data were limited regarding the LVEF status and etiologies of HF, we were unable to determine whether the association between galectin-3 and prognosis was similar in AHF patients with reduced or preserved LVEF, and in those with ischemic or non-ischemic AHF. Secondly, although we pooled the multivariable adjusted RR, due to the nature of meta-analysis of observational studies, we could not exclude the possibility of the influence of potential confounding factors for the association between galectin-3 and prognosis in AHF. Thirdly, a causative association between higher galectin-3 and poor prognosis could not be retrieved from the current study because this is a meta-analysis of observational studies. Moreover, we only observed the association between serum galectin-3 on admission and prognosis in AHF patients. Further research is required to assess the optimal cutoff points for galectin-3 on admission, as well as the values of serial measurements, changes following admission, and discharge levels of galectin-3 to improve risk stratification in AHF patients.

In conclusion, higher serum galectin-3 may be associated with poor prognosis in AHF patients. Further studies are needed to determine the mechanisms underlying the potential prognostic role of galectin-3 in AHF.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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