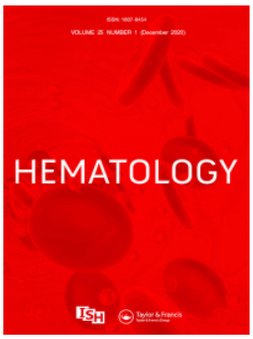

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Association between high galectin expression and poor prognosis in hematologic cancers: a systematic review and meta-analysis

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ABSTRACT

Background: Galectin (Gal) is considered a promising immune checkpoint molecule. More and more studies have shown that high expression levels of galectins in hematologic cancer are positively correlated with poor clinical prognosis. However, the exact prognostic significance of galectins remains unclear.

Methods: PubMed, Embase, Web of Science, and Cochrane Library were searched for studies addressing the correlation of galectin expression levels with prognosis of hematologic cancers. Stata software was used to estimate hazard ratios (HR) and 95% confidence intervals (CI).

Result: Hematologic cancer patients with high galectin expression levels showed poor overall survival (OS, HR = 2.43, 95% CI: 1.95, 3.04), disease-free survival (DFS, HR = 3.29, 95% CI: 1.61, 6.71), and event-free survival (EFS, HR = 2.20, 95% CI: 1.47, 3.29) outcomes. Subgroup analysis revealed that high expression levels of galectins pointed to relatively poor OS in MDS (HR = 5.44, 95% CI: 2.09, 14.18), as compared to AML, CHL and CLL. No correlation was found between galectins and OS in NHL and MM. Among the three galectins, Gal-9 (HR = 3.60, 95% CI: 2.03, 6.38) showed higher correlation with poor prognosis than Gal-1 and Gal-3. In addition, use of peripheral blood (HR = 2.96, 95% CI: 2.07, 4.22) samples and qRT-PCR (HR = 2.80, 95% CI: 1.96, 4.01) method for galectin detection were shown to improve its prognostic correlation in hematologic cancers.

Conclusion: Meta-analysis revealed high expression of galectins was associated with poor prognosis in hematologic cancer patients and galectins can be considered a promising prognostic predictive marker.

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KEYWORDS
Hematologic cancer; galectin; prognosis; systematic review; meta-analysis

1. Introduction

Hematologic cancer is one of the most significant public health concerns and an important cause for mortality worldwide. Its characteristics include rapid progression, high malignancy, systemic dissemination, limited treatment options, and a tendency to form minimal residual disease (MRD) [1–3]. The main types of hematologic cancers include leukemia, malignant lymphoma, multiple myeloma (MM), and myelodysplastic syndrome (MDS). Compared to solid tumors, hematologic cancers are challenging to diagnose and treat, thus leading to significant physical and emotional suffering for affected individuals [4–6].

According to Globocan 2020 data released by the International Agency for Research on Cancer (IARC) of the World Health Organization (WHO), it was estimated that there were 1278362 new cases of hematological cancers to be diagnosed worldwide in 2020, accounting for 6.6% of all cancer cases [7]. This indicates a 7.73% increase in the number of new cancer cases worldwide as compared to 2018, suggesting that the growing incidence of hematologic cancers remains a threat and challenge to public health systems [8]. As the majority of hematologic cancers can't be detected by conventional imaging techniques or treated by surgery, early diagnosis and timely intervention of hematologic cancers are crucial for improving the prognosis. Therefore, it is imperative to develop new biomarkers for the diagnosis and prognosis of hematologic cancers.

Galectin (Gal) is a β-galactose binding protein encoded by LGALS genes. It has high affinity for β-galactose residues on polysaccharides. Belonging to the superfamily of animal lectins, galectins are widely distributed in animals [9]. To date, a total of 16 galectins have been identified since first identification in 1976 [10, 11]. Galectins can be categorized into three types based on the carbohydrate recognition domain (CRD) in the molecule [12]. The first type is prototypic galectin with a single CRD, including Gal-1, Gal-2, Gal-5, Gal-7, Gal-10, Gal-11, Gal-13, Gal-14, Gal-15, and Gal-16. The second type is chimeric galectin, in which the CRD is linked to a collagen-like N-domain and Gal-3 is the only member. The third type is a tandem-repeat galectin comprising two distinct CRDs; its members include Gal-4, Gal-6, Gal-8, Gal-9, and Gal-12.

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Previous studies have demonstrated the vital role of galectins in various biological and pathophysiological processes *in vivo*, including infection, inflammation, angiogenesis, immune escape, and tumor progression [13]. Galectins were observed to be expressed to varying degrees in heart disease [14–17], kidney disease [18–20] and various cancers [21–28]. Studies have shown that galectin can serve as a biomarker for diagnosis and prognosis, as well as a potential therapeutic target in multiple diseases [10]. Gal-3, as an early biomarker for thyroid cancer, is valuable in assisting the clinical diagnosis of thyroid cancer [29]. Gal-1 [30–33], Gal-3 [34–36], Gal-9 [37–39] and Gal-12 [40] also showed prognostic potential in acute myeloid leukemia (AML), chronic lymphocytic leukemia (CLL), classic Hodgkin lymphoma (CHL), non-Hodgkin lymphoma (NHL) and other hematologic cancers. However, a systematic review assessing the effect of galectins in the prognosis of hematologic cancers is still lacking.

For this, our study evaluated the association between galectin overexpression and prognosis of hematologic cancers through meta-analysis, aiming to elucidate the clinical application value of galectins as a prognostic biomarker for hematologic cancers. Our findings provided references for hematology departments to select appropriate biomarkers to estimate the prognosis of hematologic cancers.

2. Materials and methods

2.1. Literature search

Four databases, i.e. PubMed, Embase, Web of Science, and Cochrane Library, were searched from inception to March 7, 2023 to collect studies on the association between high galectin expression and the prognosis of hematologic cancers. Screening was conducted by two reviewers independently based on the titles and abstracts as well as the full texts of articles. Disagreements were resolved by a third reviewer through consensus. The following terms used in literature search were respectively 'galectin', 'leukemia', 'lymphoma', 'multiple myeloma', 'myelodysplastic syndromes', 'prognosis', etc. Only English-language articles were included. This systematic review was conducted following the recommendations of Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) [41] and Meta-analysis of Observational Studies in Epidemiology (MOOSE) [42]. An ethical approval was not required since no human or animal trial was involved in this work.

2.2. Eligibility criteria

The PECOS (population, exposure, comparison, outcome, and study design) format was applied in this review, shown as follows: (1) Population: patients diagnosed with hematologic cancers including leukemia, lymphoma, MM and MDS by cytology and histopathology; (2) Exposure: galectin overexpression at diagnosis; (3) Comparison: comparison between patients with galectin overexpression and those with low expression; (4) Outcome: the hazard ratios (HR) and 95% confidence intervals (CI) of overall survival (OS), disease-free survival (DFS), relapse-free survival (RFS, counted as a distinct form of DFS in this review) and event-free survival (EFS); (5) Study design: observational studies.

The exclusion criteria included: (1) non-English studies; (2) studies with duplicate data already included in this review; (3) studies with incorrect statistical methods; (4) studies exploring the correlation between low galectin expression and prognosis of hematologic cancers; (5) reviews, conference articles, animal studies, case reports and other studies without survival data; (6) studies with HR and 95% CI unavailable. Literature evaluation was independently summarized by two reviewers, and any disagreement was resolved through a consensus judgement by a third reviewer.

2.3. Data extraction

Two reviewers independently extracted the data from eligible articles as follows: author, region, publication year, hematologic cancer type, galectin type, sample size, sample type, galectin detection method, follow-up time, cut-off value of galectins, outcome endpoint. As for studies that did not report HR and 95% CI directly, survival curves were used to calculate them by means of GetData Graph Digitaler 2.25 (GetData Pty Ltd., Kogarah, Australia).

2.4. Quality assessment

Each study was independently scored by two reviewers according to Newcastle-Ottawa Scale (NOS). Studies with NOS scores ≥ 7 were considered of high quality, indicating a low risk of bias. Review Manager 5.4 (The Cochrane Collaboration, Oxford, UK) was utilized to produce a risk of graph and risk of bias summary.

2.5. Data analysis

Stata 15.0 (Stata Corp, College Station, TX, U.S.A.) was applied to analyze the data and generate the forest plots. Pooled HR and 95% CI were used to assess the association between high galectin expression and prognosis of hematologic cancers. Heterogeneity among the included studies was evaluated by the I^2 statistic and an $I^2 < 50\%$ indicated non-significant heterogeneity among studies. If so, the fixed-effects model was then applied for meta-analysis. Otherwise, the random-effects model was applied. A subgroup analysis and a sensitivity analysis were performed to

address studies with significant clinical heterogeneity. Begg's test, Egger's test and funnel plot asymmetry were used to evaluate the publication bias of included studies, and a *p*-value of less than 0.05 was considered funnel plot asymmetry, suggesting statistically significant publication bias.

3. Results

3.1. Literature screening process and results

A total of 1329 articles were identified by literature searching. Among them, 472 articles were removed due to duplication; 285 articles, including reviews, conference articles, animal studies and case reports, were excluded due to absence of survival data. After an exclusion of 536 articles by reason of their irrelevance to this review, there remained 36 articles that underwent further screening for eligibility based on the inclusion criteria. Resultantly, a total of 17 articles, which were published between 2000 and 2022, were included in the systematic review and meta-analysis. Out of these, 6 studies were subject to the qualitative review [21, 30, 33, 35, 37, 39], while 11 studies to the quantitative meta-analysis [31, 32, 34, 36, 38, 43–48]. The flow diagram of the literature screening procedure is shown in Figure 1.

3.2. Basic characteristics and quality assessment

The 11 articles for quantitative meta-analysis comprised 1544 patients from China [34, 44, 45, 47],

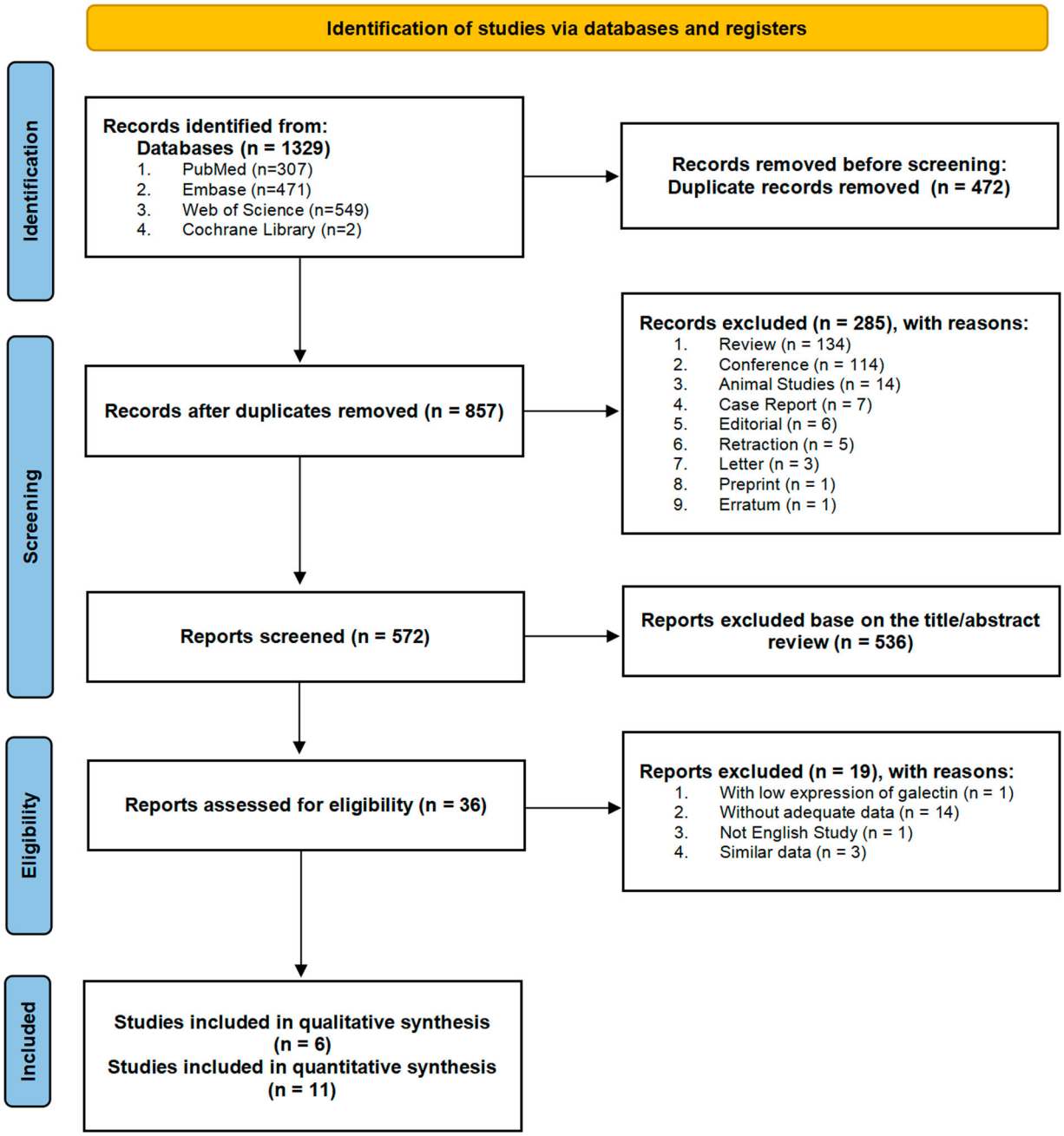

Figure 1. Flow diagram of literature screening procedure in the meta-analysis.

Denmark [31, 32], South Korea [36, 38], the United States [46], Japan [43], and Poland [48] respectively. The patients were diagnosed with AML [34, 44–47], CLL [48], CHL [32, 36], NHL [31], MM [38], and MDS [43], covering the majority of hematologic cancers in clinical practice. The characteristics of the included studies are shown in Table 1. Based on NOS assessment results, the overall quality of the included studies was deemed to be satisfactory for meta-analysis. The risk chart and risk of bias summary are shown in Figure 2.

3.3. Meta-analysis results

3.3.1. OS results

OS data was included in all 11 studies. Results of heterogeneity analysis ($I^2 = 5.6\%$, $p = 0.389$) indicated there was no statistically significant heterogeneity among studies. As shown in Figure 3, the pooled HR was 2.43 (95% CI: 1.95, 3.04), which indicated that high expression levels of galectins were significantly correlated with poor OS. Sensitivity analysis revealed that the pooled HR was not altered via removing one study at a time, indicating the stability and reliability of the results (Figure 4). Begg's test showed a risk of bias ($p = 0.019$) while Egger's test indicated no risk of bias ($p = 0.122$). No publication bias was observed in the funnel plot (Figure 5).

3.3.2. DFS results

Two studies contained DSF data. Non-significant heterogeneity was found in I^2 test analysis ($I^2 = 15.7\%$, $p = 0.305$). As can be seen in Figure 6(A), pooled HR for DFS was calculated to be 3.29 (95% CI: 1.61, 6.71), showing a significant association between high expressions of galectins and poor DFS.

3.3.3. EFS results

Two studies had EFS data. Similar to OS and DFS, non-significant heterogeneity ($I^2 = 14.4\%$, $p = 0.280$) was found between the two studies. Meanwhile, the pooled HR was 2.20 (95% CI: 1.47, 3.29), which also indicated the significant association between high galectin expressions and poor EFS (Figure 6(B)).

3.3.4. Subgroup results

Subgroup analyses were further conducted for cancer types, galectin types, sample types and detection methods based on OS results. The forest plots of subgroup analysis are shown in Figure 7.

Cancer types. The involved hematologic cancers included MDS, AML, NHL, CHL, MM and CLL. Results showed that high galectin expressions were significantly correlated with poor OS in patients with MDS (HR = 5.44, 95% CI: 2.09, 14.18), AML (HR = 2.34, 95% CI: 1.75, 3.13), CHL (HR = 2.26, 95% CI: 1.33, 3.85), and CLL (HR = 2.75, 95% CI: 1.20, 6.30), while no correlation

Table 1. The main characteristics of the eligible literatures included in the meta-analysis ($n = 11$). Studies are ordered by author names.

Study ID	Region	Cancer type	Galectin type	Sample size	Sample type	Detection method	Follow-up (months)	Cut-off value	Outcome end-point	Data sources
Asayama 2017	Japan	MDS	Gal-9	40	PB	ELISA	<25	10 ng/mL	OS	Report in the article
Cheng 2013	China	AML	Gal-3	320	BM	qRT-PCR	<200	50%	OS	Kaplan-Meier curve
Gao 2017	China	AML	Gal-3	106	PB	ELISA	<100	50%	OS + RFS	Kaplan-Meier curve
Gao 2017	China	AML	Gal-3	208	PB	ELISA	<100	50%	OS	Kaplan-Meier curve
Holst 2020	Denmark	NHL	Gal-1	163	Tissue	IHC	<60	90%	OS	Kaplan-Meier curve
Kamper 2011	Denmark	CHL	Gal-1	143	Tissue	IHC	<240	50%	OS + EFS	Report in the article
Koh 2014	South Korea	CHL	Gal-3	110	Tissue	IHC	<240	10%	OS + EFS	Report in the article
Lee 2021	South Korea	MM	Gal-9	109	BM	qRT-PCR	<108	1%	OS	Report in the article
Ruvolo 2019	America	AML	Gal-3	205	PB + BM	Other methods	<156	NA	OS	Kaplan-Meier curve
Wang 2022	China	AML	Gal-3	88	PB	qRT-PCR	<80	5.89 ng/mL	OS + DFS	Kaplan-Meier curve
Wdowiak 2019	Poland	CLL	Gal-3/9	52	PB	Other methods	<50	75%	OS	Kaplan-Meier curve

MDS = myelodysplastic syndrome, AML = acute myeloid leukemia, NHL = non-Hodgkin lymphoma, CHL = classic Hodgkin lymphoma, MM = multiple myeloma, CLL = chronic lymphocytic leukemia, PB = peripheral blood, BM = bone marrow, NA = not available, OS = overall survival, RFS = relapse-free survival, EFS = event-free survival, DFS = disease-free survival.

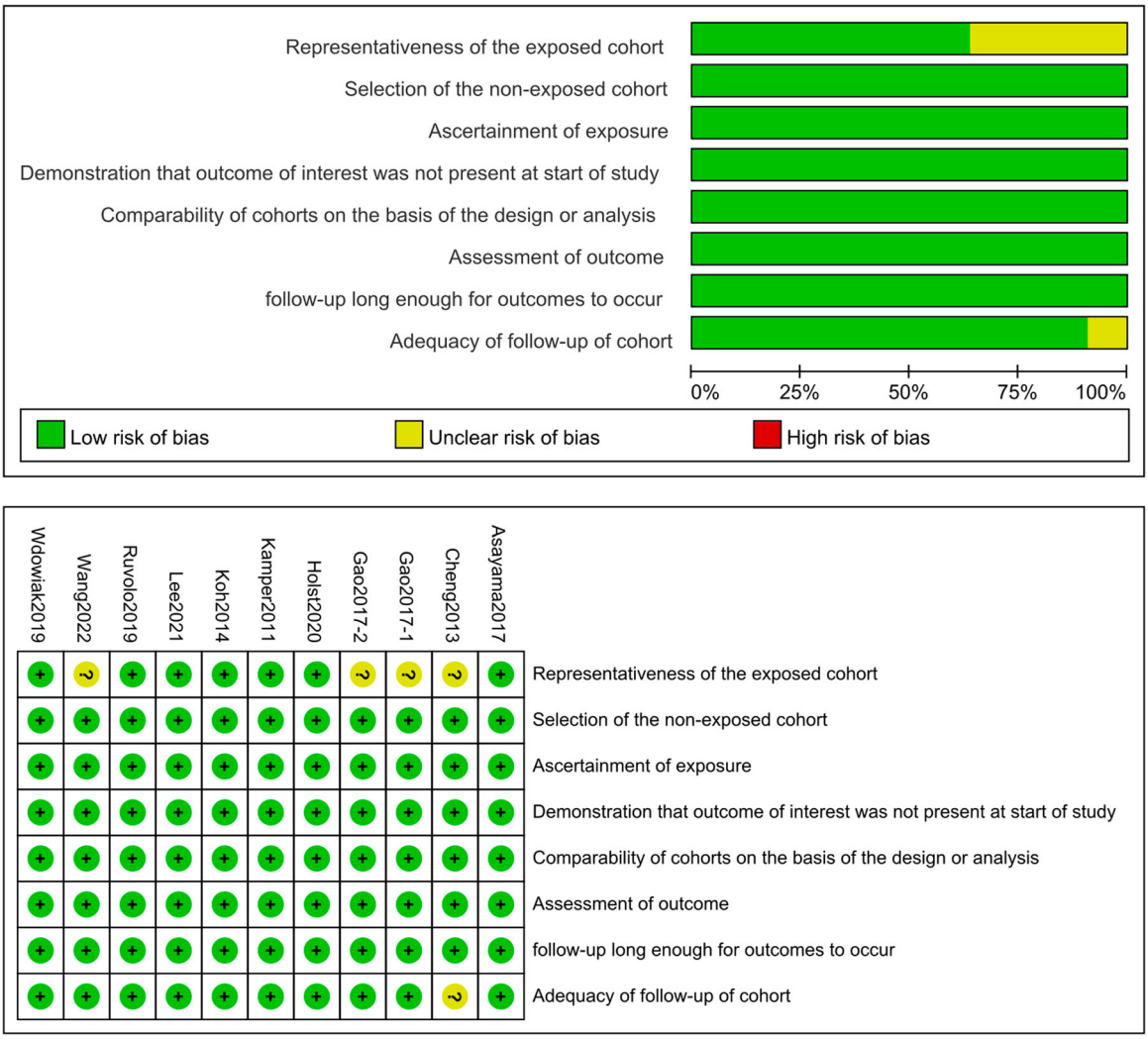

Figure 2. Risk of graph and risk of bias summary of the eligible literatures.

was found in patients with NHL (HR = 2.15, 95% CI: 0.76, 6.10) and MM (HR = 2.08, 95% CI: 0.87, 4.97). This may be attributed to the relatively small number of related studies and presence of a degree of bias for NHL and MM. The pooled HR results indicated that high galectin expressions were of greater value for poor prognosis in MDS than in other hematologic cancers.

Galectin types. Subgroup analysis for galectin types showed that high expression levels of Gal-1, Gal-3, and Gal-9 were significantly correlated with poor OS in patients with hematologic cancers, and Gal-9 (HR = 3.60, 95% CI: 2.03, 6.38) was superior to Gal-1 (HR = 1.89, 95% CI: 1.14, 3.14) and Gal-3 (HR = 2.39, 95% CI: 1.82, 3.15) in its correlation with the outcome in hematologic cancers.

Sample types. Peripheral blood (PB), bone marrow (BM) and solid tissue samples were utilized for the single or/and combined detection of galectins. Except for the PB and BM-combined detection, all single detection results revealed a statistically significant correlation between high galectin expressions and inferior OS in patients with hematologic cancer. Meanwhile, compared with BM (HR = 2.43, 95% CI: 1.60, 3.68) and tissue (HR = 2.23, 95% CI: 1.39, 3.59), PB-derived galectins (HR = 2.96, 95% CI: 2.07, 4.22) showed superior potential for prognosis prediction.

Detection methods. ELISA (enzyme-linked immunosorbent assay), qRT-PCR (quantitative real-time PCR), IHC (immunohistochemistry) and other methods were used to assess the galectin expressions. The pooled HRs were calculated to be 2.57 for ELISA (95% CI: 1.59, 4.14), 2.80 for qRT-PCR (95% CI: 1.96, 4.01), 2.23 for IHC (95% CI: 1.39, 3.59) and 1.82 for other methods(95% CI: 1.06, 3.13). This means that all methods were considered effective in evaluating correlation of high galectin expressions with poor OS in hematologic cancers, and qRT-PCR was deemed as the optimal detection method.

4. Discussion

The global cancer burden remains on the rise [49]. Compared to solid tumors, hematologic cancers often pose a challenge in terms of early diagnosis due to the limitations of traditional diagnostic methods such as non-specific symptoms like fever,

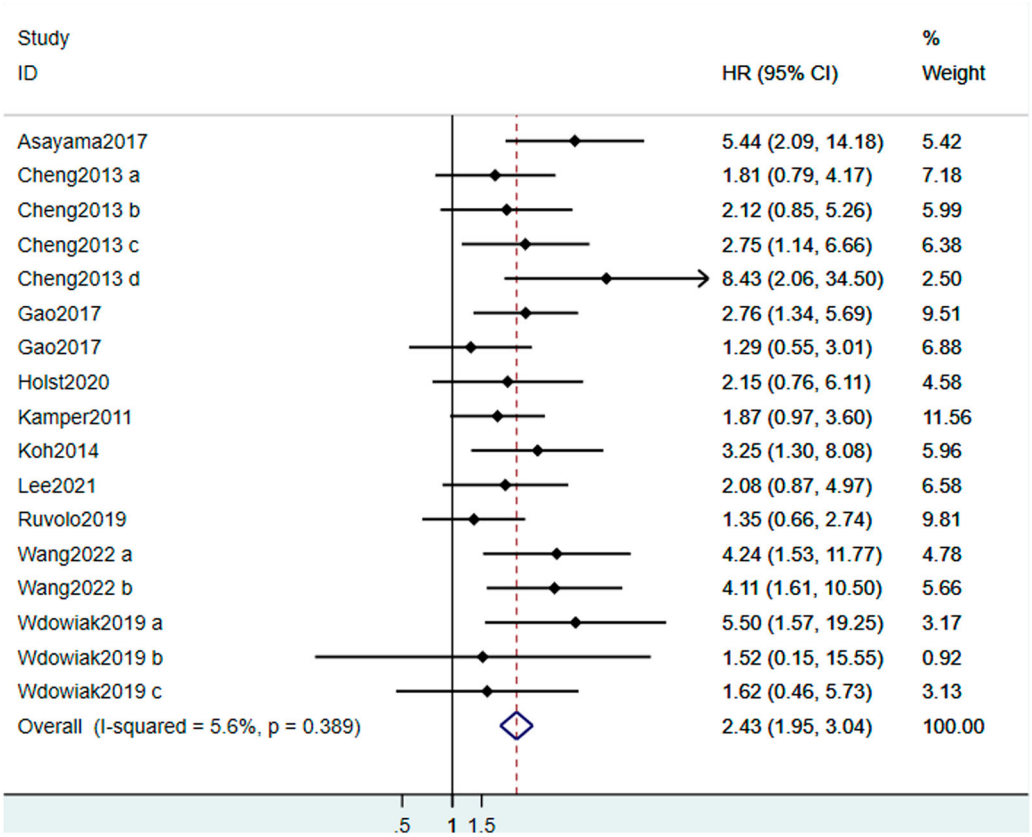

Figure 3. Forest plots of the association between galectin expression with overall survival (OS). HR stands for hazard ratio, while CI indicates confidence interval.

anemia, fatigue, and bone pain [50, 51], as well as the inability for CT or MRI to locate lesion sites [52]. Therefore, new effective biomarkers are urgently needed to improve the early diagnosis and prognosis of hematologic cancers. A growing number of studies have shown that high expressions of Gal-1, Gal-3, Gal-9 and other molecules are positively correlated with poor prognosis in patients with hematologic cancer, suggesting that galectins might be a prognostic biomarker for hematologic cancers. Our work is the first systematic review and meta-analysis to evaluate the association between over-expression of galectins and poor prognosis of hematologic cancers. Our results revealed a significant correlation of high galectin expressions with poor prognosis in hematologic cancers.

In this meta-analysis, the pooled HR and 95% CI of OS, DFS and EFS indicated the correlation of high

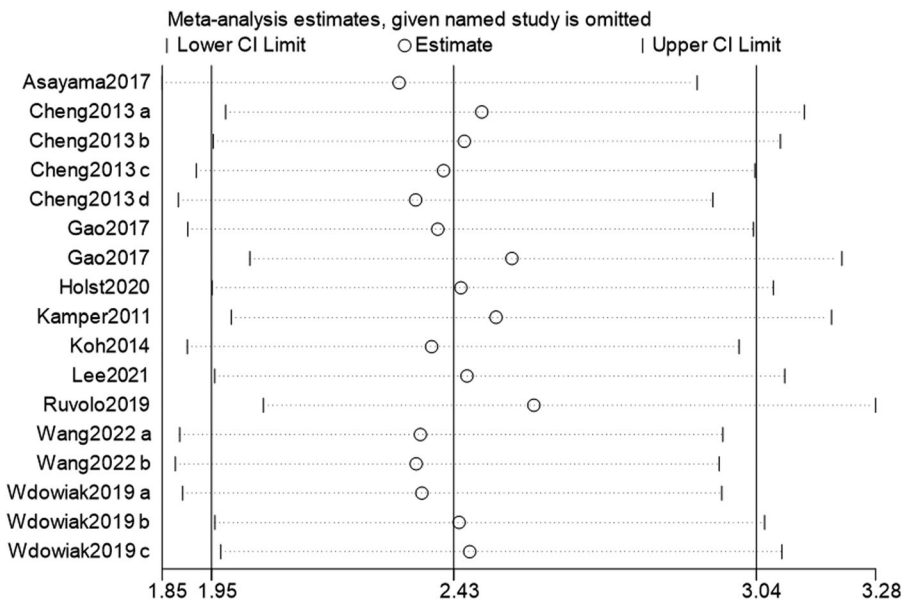

Figure 4. Sensitivity analysis for OS in this meta-analysis.

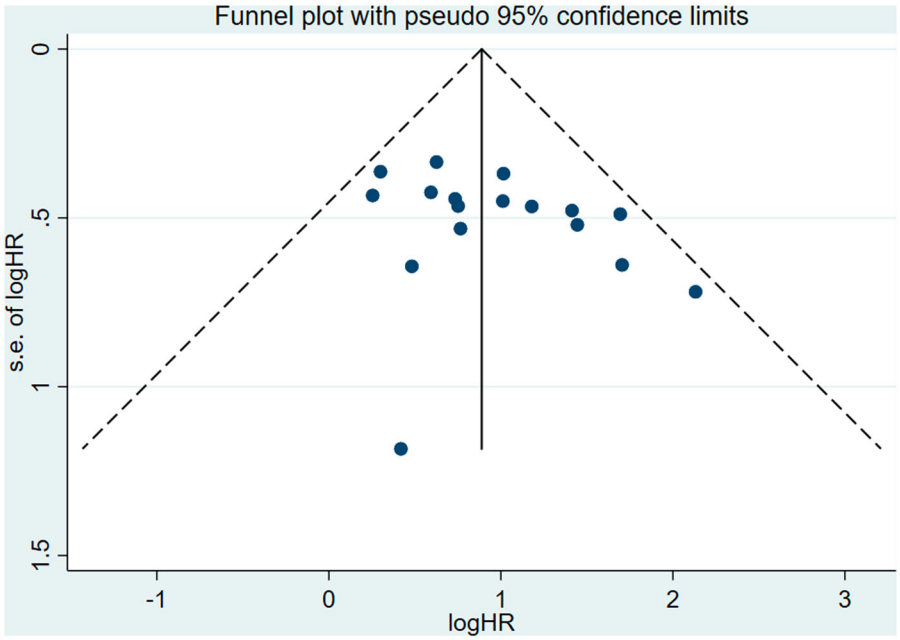

Figure 5. Funnel plot of publication bias of included studies.

galectin expressions with poor outcome in hematologic cancers. All included studies were considered of high quality according to NOS. There was no statistically significant heterogeneity of publication bias in-between studies.

In subgroup analysis, we found that high galectin expressions had better correlation with poor prognosis in MDS than in other tumors, while no correlation was observed in NHL and MM. In a NHL study included the present review, the authors observed a significant difference in OS between Gal-1 high and low expression groups in the CD30-positive subcohort instead of the entire cohort [31]. Similarly, in a MM study included, there was no statistical difference in OS between the gal-9 positive and negative groups in the whole cohort. However, in PD-L1 overexpression subcohort, patients with gal-9 positivity had significantly worse OS than the galectin-negative compartment [38]. Therefore, we inferred that galectins' correlation with OS was context-dependent in NHL and MM. Or, other factors than galectins, like CD30 and PD-L1, affected OS as well, thus obscuring the real OS- correlation of galectins. Zhang *et al.* discovered a positive correlation between gal-9 and proteasome subunit beta type-8 (PSMB8). Meanwhile, these two biomarkers had a synergistic effect on the survival of cells, cell signaling, and the progression of AMLs [53]. This indicates that combined detection of galectin and other molecules (PSMB8) will contribute to better prognosis prediction for hematologic cancers.

Gal-9 exhibited better correlation with poor prognosis than Gal-1 and Gal-3 in this review, indicating the superior prognosis potential of Gal-9 in hematologic cancers. In recent years, there have been several reports underlying the mechanisms of Gal-9/Tim-3 signaling up-regulation in hematologic cancers. TIM-3 was over-expressed in bone marrow-resident T cells of AML patients with treatment failure, leading to increased number of Gal9^{+} CD34^{-} T cells, as compared with AML patients with complete response [54]. Additionally, gal-9 was found to stimulate TIM-3 to co-activate NF-κB and β-catenin signaling pathways in the microenvironment of leukemia, thus accelerating the leukemia progression through TIM-3/Gal-9 autocrine rings [55]. Similarly, the Gal-9/TIM-3 signaling pathway was also activated in CLL, which promoted Treg cell-mediated immune escape through inhibiting CD4^{+} T cells [56]. On the other hand, inhibition of the Gal-9/TIM-3 axis in combination with chemotherapy suppressed the inflammatory response and proliferation of tumor tissues, thus delaying the recurrence of AML [57]. Besides, inhibition of Gal-9 alone or in combination with other antibodies (anti-PD-L1, anti-GITR) could suppress tumor proliferation and prolong OS in varying degrees in syngeneic tumor mice models [58]. All these supported our finding that Gal-9 was significantly correlated with poor outcome in patients with hematologic cancers, affirming the prognosis prediction value of Gal-9. So far, only Gal-1, Gal-3, and Gal-9 have been extensively studied. Whether expressions of other galectins affect the prognosis of hematologic cancers and the underlying mechanism require to be further investigated.

The optimal sample source for galectins was PB, compared to BM and tissue. This is surprising, as we thought BM-derived galectins would be more convincing for prognosis prediction since most hematologic cancers are BM-originated. However, galectins are known to be produced and secreted by diverse cell types including cancer cells (melanoma, prostate

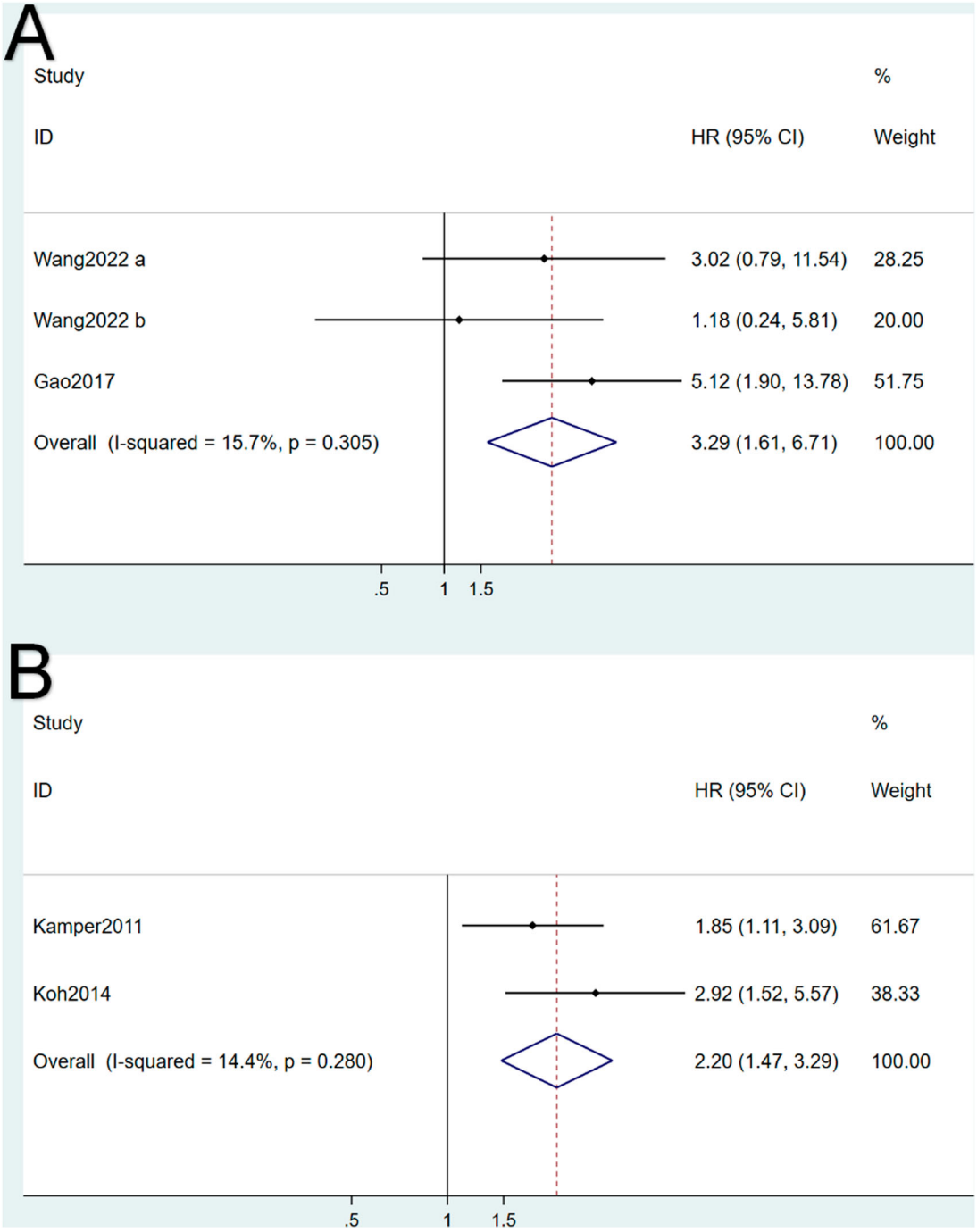

Figure 6. Forest plots of the association between galectin expression with (A) disease-free survival (DFS) and (B) event-free survival (EFS).

cancer, ovary carcinomas, AML, etc.) [59] and non-cancer cells (monocytes, T cells, B cells, DCs, macrophages, stroma cells, etc.) [60, 61]. Additionally, they function both intercellularly and extracellularly [62–64]. Therefore, we speculated that both medullary and extramedullary-sourced galectins, which contributed to its enrichment in PB, participated in the malignant progress of hematologic cancers [65], leading to the better prognosis correlation of PB-derived ones. Still, further large-scale observational studies and mechanism research are required to verify this result. In this review, qRT-PCR was found to be the best method for galectin detection, compared to IHC, ELISA, and other methods. Despite highly sensitive, qRT-PCR reflect the transcriptional levels of galectin expression while ELISA and IHC detect the proteins levels. Because galectins function in the protein form, such methods as ELISA was necessary for detection of galectin protein levels.

Limitations of our work: (1) the retrospective nature of the included studies may generate recall, measurement, and reporting biases in the study design; (2) there was a small number of DFS- or/and EFS-related studies, and more studies are required for better evaluation of galectins' prognostic value in hematologic cancers; (3) due to the lack of the original HR and

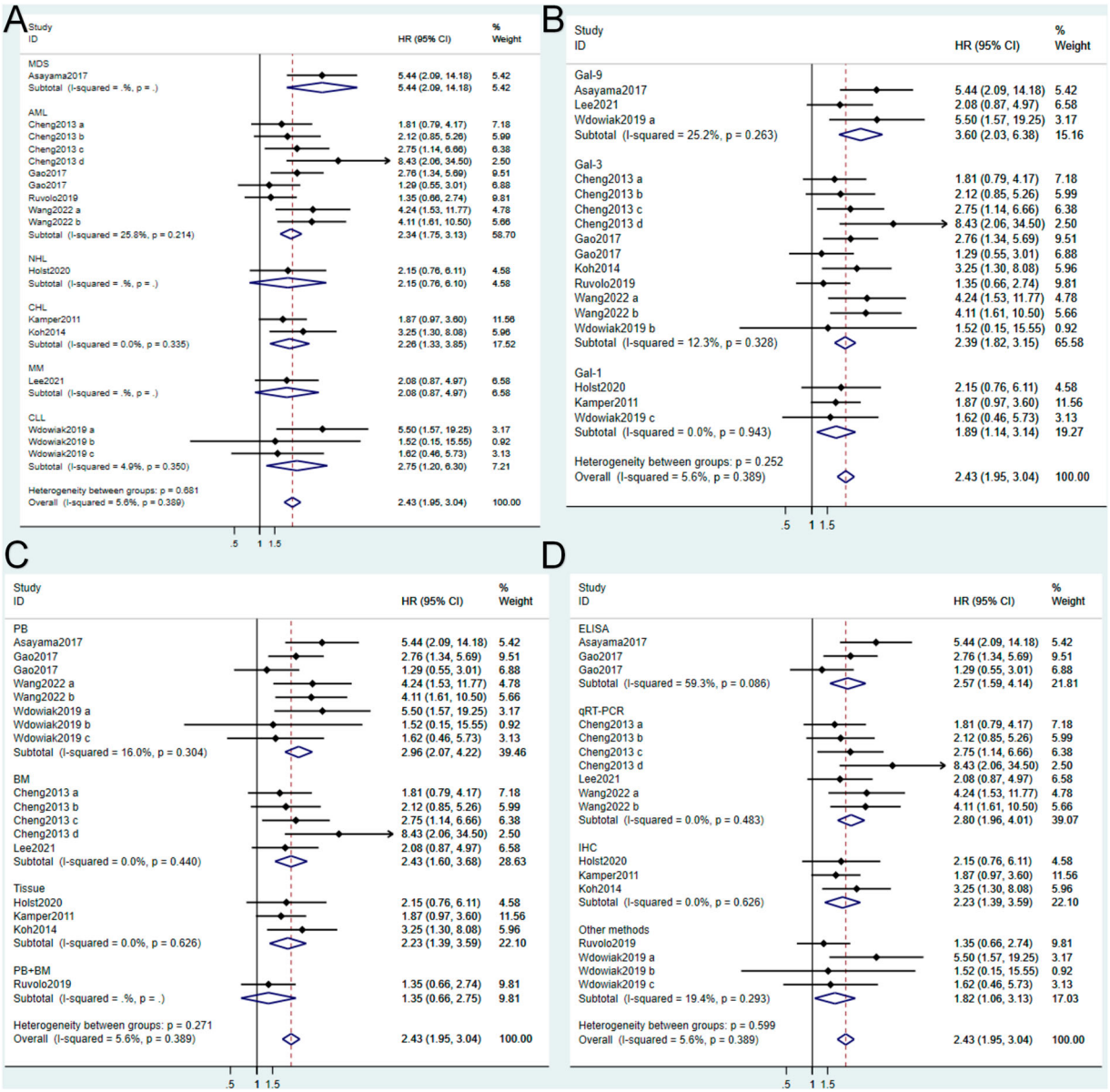

Figure 7. Forest plots of the subgroup analysis of cancer types (A), galectin types (B), sample types (C) and detection methods (D). MDS: myelodysplastic syndrome, AML: acute myeloid leukemia, NHL: non-Hodgkin lymphoma, CHL: classic Hodgkin lymphoma, MM: multiple myeloma, CLL: chronic lymphocytic leukemia, PB: peripheral blood, BM: bone marrow.

95% CI data in 7 of the 11 cohort studies, we extracted related data and calculate HR and 95% CI based on the survival curve, during which errors might be inevitably caused; (4) different cut-off values were set for galectins in different studies, which could affect the accuracy of correlation analysis; (5) there was lack of correlation analysis between high galectin expressions and other prognostic factors like cytogenetic and molecular abnormalities.

In summary, Our results suggested that high expression levels of galectins were associated with poor OS, DFS and EFS in hematologic cancer patients. Subgroup analysis showed that galectins had the greatest prognostic value in MDS, with Gal-9 exhibiting optimal prognostic correlation. Meanwhile, the use of PB samples and qRT-PCR method for galectin detection contributed to its prognostic correlation. All these findings may be helpful for the departments of hematology to select appropriate biomarkers for prognosis prediction. In the next step, we will confirm the correlations of high Gal-9 expression with poor prognosis in AML using clinical samples and animal models. In the meantime, we are hoping to identify new prognosis-related biomarkers in AML. On the other hand, an association analysis will be conducted between galectin expressions and molecular abnormalities in AML using online databases, followed by experimental validation using clinical samples.

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Haotian Liu and Tiantian She designed the study. Qiuying Dai and Yixian Li conducted literature search. Zhenfei Tang and Qiuying Dai performed the data collection. Haotian Liu was in charge of using the software. Haotian Liu and Tiantian

She analyzed the data and composed the final version. This work was supported by Tianjin Municipal Education Commission [Grant No.2021KJ262].

Disclosure statement

No potential conflict of interest was reported by the author (s).

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Data availability

The data could be obtained by contacting corresponding author.

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