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Original Paper

Prognostic Role of High Gal-9 Expression in Solid Tumours: a Meta-Analysis

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Key Words
Gal-9 • Prognosis • Solid tumour • Meta-analysis

Abstract
Background/Aims: Recently, many studies have demonstrated that galectin-9 (Gal-9) exhibits altered expression and has a close association with metastasis and recurrence in various cancers. Therefore, we conducted a meta-analysis to assess the prognostic role of Gal-9 expression in solid tumours. ***Methods:*** We searched PubMed, Embase, and Web of Science until June 2017 and identified fourteen eligible studies containing 2,408 patients to include in the meta-analysis. ***Results:*** The pooled results indicated that higher Gal-9 expression in cancer tissue associated with an improved CSS (HR=0.48, 95% CI 0.39-0.58). In the subgroup analysis, a significant relationship was observed between higher Gal-9 expression and both CSS (HR=0.48, 95% CI 0.39-0.59) and OS (HR=0.62, 95% CI 0.49-0.78) in digestive cancers. ***Conclusions:*** The findings of this meta-analysis highlight the role of Gal-9 as a useful clinical prognostic biomarker, which may facilitate the treatment of patients with solid tumours.

Introduction

Cancer is a primary cause of death across the world and has become a major problem for public health. Although the survival rate of cancer patients has shown a significant improvement recently, approximately 14.1 million new cancer cases and 8.2 million deaths occurred in 2012 worldwide [1]. The successful treatment of cancer depends on early diagnostic methods and suitable therapeutic strategies, the latter of which based on effectively predicting the prognosis of cancers. Therefore, the discovery of better tumour biomarkers is crucial for us to improve the sensitivity and specificity for the detection and prognosis for cancer.

Galectin-9(Gal-9) is the ninth member of the β-galactoside-binding soluble lectin family which exerts their primary biological functions by interacting with specific glycoconjugates. The expression of Gal-9 was initially described as an eosinophil chemoattractant secreted

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by T lymphocytes [2] and plays a significant role in immune regulation [3-5]. Nevertheless, Gal-9 is also involved in diverse biological processes, including cell aggregation, adhesion, chemoattraction, and apoptosis [6]. Recently, several studies have demonstrated that Gal-9 induced apoptosis of Tim-3$^+$ T-cells as the ligand of T cell immunoglobulin- and mucin-domain-containing molecule-3 (Tim-3) [7, 8]. Tim-3 is a member of the receptor family involved in immune-checkpoint functions and is considered to perform a pivotal role in mediating T cell exhaustion in cancers [9].

Compared with Tim-3, the expression of Gal-9 in human solid tumours is more extensive. Many clinical studies have clarified that the expression of Gal-9 has a close association with metastasis and recurrence in solid tumours, including melanoma [10], gastric cancer [11, 12], colon cancer [13], hepatocellular cancer [14-16], pancreatic and ampullary cancer [17], lung cancer [18], bladder cancer [19], breast cancer [20], and clear cell renal cell cancer [21]. However, the consistency and magnitude of the prognostic impact of Gal-9 remains unclear. Thus, we integrated all published evidence systematically in this meta-analysis in order to reveal the association between Gal-9 and the prognosis of patients with various types of solid tumours. We also hope to improve the diagnosis and treatment of cancer targeting Gal-9.

Materials and Methods

Search strategy

This meta-analysis was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [22]. PubMed, Embase and Web of Science databases were searched for literatures predicting the association between expression of Gal-9 and prognosis in various cancers. Keywords employed in our search strategy were "Gal-9 OR galectin9 OR galectin-9 OR half curling element 9" (all fields) AND "tumour OR cancer OR carcinoma" (all fields) AND "prognosis OR prognostic OR survival OR outcome" (all fields). The last search was performed on June 26, 2017. We also screened the references of identified literature for further identification of relevant studies. The database search was conducted by two authors independently (K. Wang and Z. Chen).

Section criteria

Eligible literature was included in this meta-analysis according to the criteria as follows: (1) Gal-9 expression was detected in cancer tissue; (2) investigation of the association between Gal-9 expression and survival outcome were represented in overall survival (OS), cancer-specific survival (CSS), disease-free survival (DFS), relapse-free survival (RFS) or progression-free survival (PFS); and (3) reported sufficient data to estimate the hazard ratio (HR) and 95% confidence intervals (CI) according to the Gal-9 expression. When the same patient cohort was reported in several studies, we included the complete cohort or the most recent cohort. Letters, editorials, expert opinions, reviews, case reports and non-human trials were excluded. We also excluded studies lacking key data for further analysis or whose sample sizes were smaller than 40. Titles and abstracts of the identified literature were assessed independently by two reviewers and subsequently, those considered irrelevant were excluded. Comprehensive evaluation was carried out to further screen the enrolled articles by viewing the full text carefully. Any disagreement were resolved by consensus.

Data extraction and quality assessment

Two reviewers independently extracted the required information from all eligible studies in line with the following details: surname of the first author, publication year, patients' country of origin, tumour type, sample size, mean or median age, patients' gender, tumour stage, lymph node metastasis and distant metastasis, follow-up time, cut-off value, median or mean follow-up months, detection method, outcome, and HR and 95%CI of the high Gal-9 expression group versus the low one for OS, CSS, DFS, and RFS as applicable. For studies whose HRs were not provided, we extracted the survival data from the original study data (Kaplan-Meier curves or the required data) using the software Engauge Digitizer 4.1 and calculated the estimated survival data by Tierney's method [23].

According to the Newcastle-Ottawa Quality Assessment Scale (NOS), the quality of each study was systematically evaluated by two reviewers independently [24]. A score total of 0 and 9 was considered as the lowest and highest quality, respectively. A study that achieved a score of six or higher would be identified to have high quality.

Statistical analysis

The high expression of Gal-9 was defined on the basis of the cut-off values provided by the authors. Pooled HRs and their 95% CIs were used to describe the relationship between Gal-9 expression and prognosis of patients. Heterogeneity was evaluated using Cochran's Q test and Higgins I-squared statistics. $I^2 > 50\%$ and/or $P < 0.1$ indicated a statistically significant heterogeneity, which would allow the use of a random-effect model. Otherwise, a fixed-effect model was applied. If heterogeneity existed, subgroup analysis would be adopted to further explore its source. We also performed sensitivity analysis by omission of each single study to evaluate stability of the results. The Begg and Egger funnel plot was utilized to estimate publication bias. STATA software version 12.0 (Stata Corporation, College Station, TX, USA) was utilized in this meta-analysis. A P-value < 0.05 was considered to indicate statistical significance.

Results

Study characteristics

According to the searching strategy described in the materials and methods, 261 studies in the literature were initially retrieved. However, 238 of them were excluded by screening the titles, abstracts, publication types and full texts. Among those remaining, 12 articles containing 14 studies were included into the meta-analysis after further evaluation (Fig. 1) [10-21].

The main features of the included studies are summarized in Table 1. A total of 2, 408 patients from China, Netherlands, Japan and Korea were diagnosed with various cancers, including melanoma, gastric cancer, colon cancer, hepatocellular cancer, pancreatic and ampullary cancer, lung cancer, bladder urothelial cancer, breast cancer and clear cell renal cell cancer. All of studies were designed retrospectively and the year published ranged from 2002 to 2017. Ten studies were reported on Asians and four on Caucasians. OS and CSS were reported in seven studies, while RFS and DFS were evaluated in three studies. We selected OS and CSS as the main survival outcome of all eligible studies for our meta-analysis. HRs with their 95%CIs were reported in seven studies directly. In another seven studies, the data was extracted from the graphical survival plots. The cut-off values of Gal-9 varied in different studies.

Quality assessment

According to the Newcastle-Ottawa Quality Assessment Scale, the quality of the 14 eligible studies that were enrolled in our meta-analysis was assessed. Each study showed a selection bias, likely because each study contained only one or two types of cancer. Thus, the whole population of solid

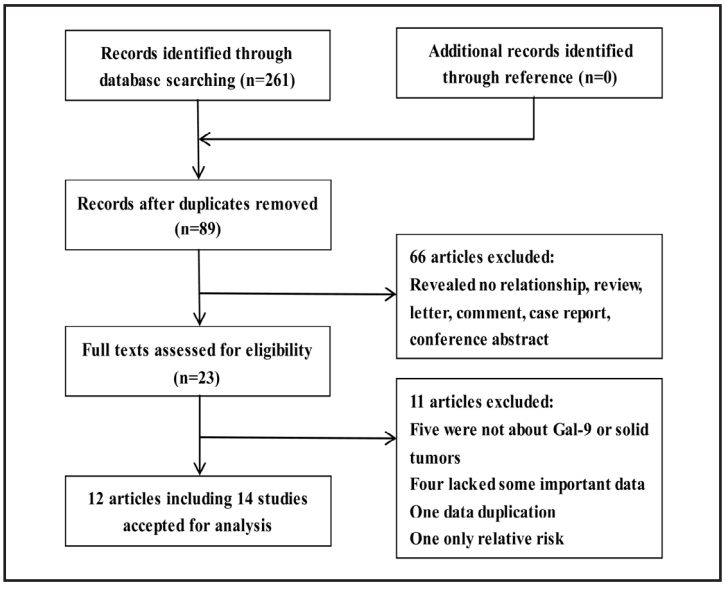

Fig. 1. Flow diagram of the study selection process.

Table 1. Main characteristics of all studies included in the meta-analysis. OS = overall survival; CSS = cancer-special survival; RFS = relapse-free survival; DFS = disease-free survival; NA: not available; SC: survival curve; IRS: immunoreactivity score; IHC: immunohistochemistry; ccRCC: clear cell renal cell carcinoma. [a]Study by Sideras et al. [16] that evaluated the association between Gal-9 expression and CCS/RFS in a cohort of 91 hepatocellular cancer patients. [b]Study by Sideras et al. [16] that evaluated the association between Gal-9 expression and CSS in a cohort of 60 hepatocellular cancer patients. [c]Study by Sideras et al. [17] that evaluated the association between Gal-9 expression and CSS in a cohort of 148 pancreatic cancer patients. [d]Study by Sideras et al. [17] that evaluated the association between Gal-9 expression and CSS in a cohort of 76 ampullary cancer patients

Study	Country	Cancer	NO. of patients	Age(years)	Sex(M/F)	Cancer stage or grade	High expression n (%)	Cut-off value	Follow-up (months)	Multivariate analysis	Survival analysis	HR and 95%CI
Jiang 2013[11]	China	Gastric	305	Median 64	231/74	TNM I-IV	97(31.8%)	H-score>200	Median 40	no	OS	SC
Gu 2013[15]	China	Liver	147	NA	111/36	Grade I-IV	130(88.4)	NA	Mean 34.4	no	OS/DFS	SC
Zhang 2012[14]	China	Liver	200	Median 51	144/56	TNM I-IV	113(56.5%)	IHC >10%	Mean 49.1	no	CSS	SC
Liu 2017[19]	China	Bladder	202	Mean 61.6	167/35	Grade I-III	102(50.5%)	H-score>57	Mean 60.5	yes	CSS/RFS	SC
Irie 2005[20]	Japan	Breast	84	Median 54	0/84	Grade I-III	42(50%)	H-score>80	Median 118	no	DFS	SC
Sideras 2017[a][16]	Netherlands	Liver	91	NA	63/31	Grade I-III	73(80.2%)	IHC>0	Mean 37.2	yes	CSS/RFS	report
Sideras 2017[b][16]	Netherlands	Liver	60	NA	48/12	Grade I-III	46(76.7%)	IHC>0	Mean 31.8	no	CSS	SC
Kageshita 2002[10]	Japan	Melanoma	70	NA	NA	Grade I-III	23(32.9%)	H-score>100	NA	no	OS/DFS	SC
Wang 2016[13]	China	Colorectal	90	Mean 66.5	46/44	TNM I-IV	51(56.7%)	IHC >10%	Mean 64.0	yes	OS	report
Ohue 2016[18]	Japan	Lung	120	Mean 64.1	61/59	TNM I	37(30.8%)	IRS≥3	NA	no	OS	report
Sideras 2017[c][17]	Netherlands	Pancreatic	148	NA	NA	Grade I-III	79(53.3%)	NA	Mean 17.5	no	CSS	report
Sideras 2017[d][17]	Netherlands	Ampullary	76	NA	NA	Grade I-III	41(51.9%)	NA	Mean 17.5	no	CSS	report
Fu 2015[21]	China	ccRCC	196	Median 55	137/59	TNM I-IV	89(45.4%)	H-score>80	Median 106	yes	OS/RFS	report
Choi 2017[12]	Korea	Gastric	619	NA	413/206	TNM I-IV	327(52.8%)	IHC >10%	Mean 65.7	yes	OS	report

Table 2. The pooled associations between Gal-9 expression and the prognosis of solid tumours. OS = overall survival; CSS = cancer-special survival; RFS = relapse-free survival; DFS = disease-free survival; HR = hazard ratio; CI = confidence interval

Outcome subgroup	Outcome	No. of studies	No. of patients	HR (95%CI)	P value	Model	Heterogeneity	
							I^2(%)	P value
All	OS	7	1547	0.80(0.52,1.23)	0.311	Random	75.2	<0.001
	CSS	7	1396	0.48(0.39,0.58)	<0.001	Fixed	0.0	0.852
	RFS/DFS	6	790	0.58(0.30,1.10)	0.097	Random	79.9	<0.001
Tumour type								
Digestive System	OS	4	1161	0.62(0.49,0.78)	<0.001	Fixed	9.9	0.344
	CSS	6	1194	0.48(0.39,0.59)	<0.001	Fixed	0.0	0.758
Others	OS	3	386	1.30(0.58,2.93)	0.525	Random	67.8	0.045
	CSS	1	202	0.46(0.26,0.81)	-	-	-	-
Ethnicity								
Asian	OS	7	1547	0.80(0.52,1.23)	0.311	Random	75.2	<0.001
	CSS	3	1021	0.46(0.36,0.58)	<0.001	Fixed	0.0	0.81
Caucasian	OS	0	0	-	-	-	-	-
	CSS	4	375	0.51(0.37,0.70)	<0.001	Fixed	0.0	0.596
Analysis type								
Univariate	OS	7	1547	0.73(0.45,1.19)	0.205	Random	81.4	<0.001
	CSS	7	1396	0.47(0.39,0.57)	<0.001	Fixed	0.0	0.769
Multivariate	OS	3	905	1.03(0.47,2.23)	0.945	Random	83.6	0.002
	CSS	2	293	0.42(0.26,0.67)	<0.001	Fixed	0.0	0.531
HR obtained method								
Reported in text	OS	4	1025	1.09(0.61,1.95)	0.764	Random	77.0	0.005
	CSS	3	315	0.53(0.38,0.74)	<0.001	Fixed	0.0	0.515
Data extrapolated	OS	3	522	0.53(0.39,0.72)	<0.001	Fixed	0.0	0.672
	CSS	4	1081	0.45(0.35,0.57)	<0.001	Fixed	0.0	0.876

tumour cannot be represented by any one study included. The quality of the eligible studies ranged from 5 to 7, with a mean of 6.6. A higher value showed better methodology. As a consequence, each one of the studies mentioned above was enrolled into the subsequent analysis.

Meta-analysis results

The main results of this meta-analysis are listed in Table 2. In our analysis, we merged RFS and DFS together considering the similarities between them. For seven studies evaluating CSS, there was no obvious statistical heterogeneity (I^2=0.0%, P=0.852). The fixed-effects model was used to pool the HRs and 95% CIs. Compared with the low Gal-9 expression, high

expression level of Gal-9 in cancer tissue was associated with an improved prognosis (HR=0.48, 95% CI 0.39-0.58, P<0.001) (Fig. 2A). The random-effects model was employed because obvious heterogeneity was found in OS (I^2=75.2%, P<0.001; HR=0.80, 95% CI 0.52-1.23, P=0.311) and RFS/DFS (I^2=79.9%, P<0.001; HR= 0.58, 95% CI 0.30-1.10, P=0.097), and a weak improved prognosis was observed among participants with high Gal-9 expression (Fig. 2B,2C).

To explore the heterogeneity among these studies, subgroup analysis was further performed based on four main features, including tumour type, ethnicity, analysis type and HR obtained method. The first subgroup analysis was evaluated according to tumour type. We observed that upregulation of Gal-9 in digestive cancers was related to both better CSS (HR=0.48, 95% CI 0.39-0.59, P<0.001; fixed-effects model) and OS (HR=0.62, 95% CI 0.49-0.78, P<0.001; fixed-effects model), with no heterogeneity in the data (I^2=0.0%, P=0.758; I^2=9.9%, P=0.344, respectively) (Table 2 and Fig. 3). Combined data from the other three studies showed no association between high Gal-9 expression and a good OS (HR= 1.30, 95% CI 0.58-2.93, P=0.525; random-effects model) and with significant statistical heterogeneity (I^2=67.8%, P= 0.045). Only one study reported that higher Gal-9 expression was correlated with better CSS in patients with bladder cancer (HR=0.46, 95% CI 0.26-0.81, P=0.007).

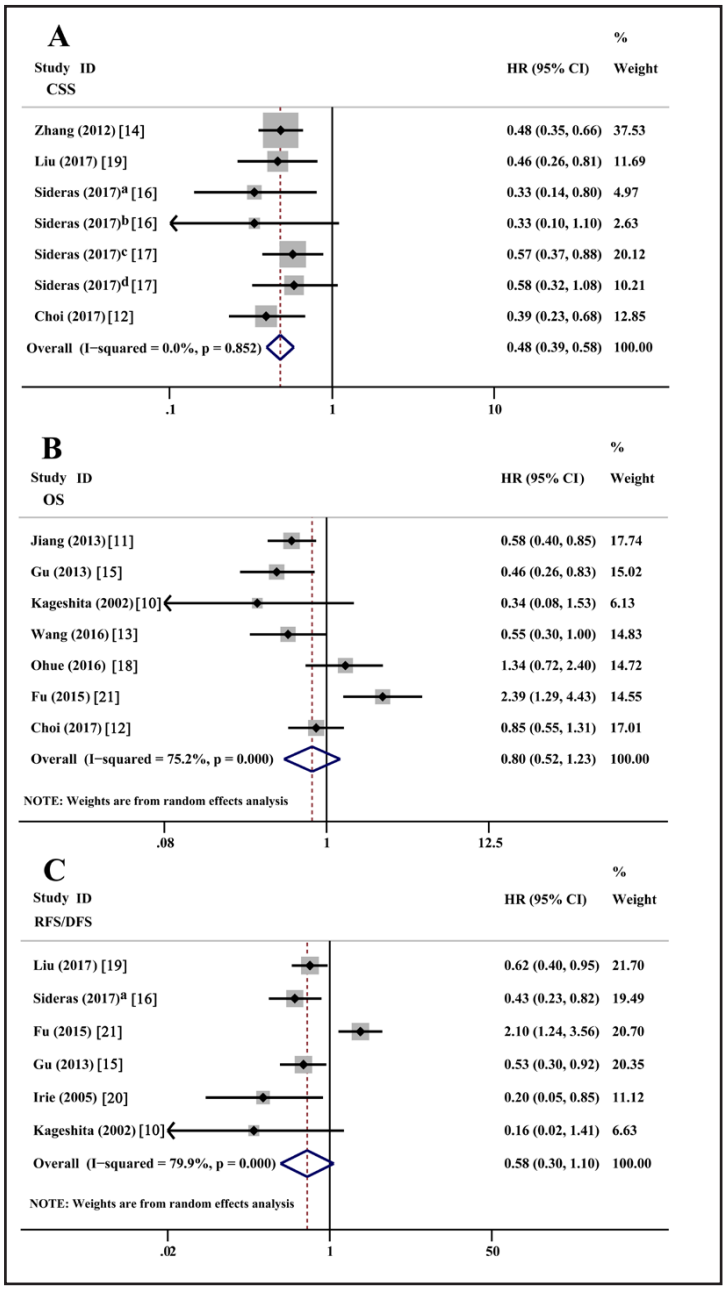

Fig. 2. Forest plots of studies evaluating hazard ratios of high Gal-9 expression for solid tumours. (A) High Gal-9 expression was associated with improved cancer-specific survival in solid tumours; (B) High Gal-9 expression was associated with weak improved overall survival in solid tumours; (C) High Gal-9 expression was also associated with weak improved relapse-free survival/progression-free survival in solid tumours.

The relationship between high Gal-9 expression and prolonged CSS was also considered to have statistical significance in other subgroups with no heterogeneity, including Asians

(HR=0.46, 95% CI 0.36-0.58, P<0.001; fixed-effects model), Caucasians (HR=0.51, 95% CI 0.37-0.70, P<0.001; fixed-effects model), univariate analysis (HR=0.47, 95% CI 0.39-0.57, P<0.001; fixed-effects model), multivariate analysis (HR=0.42, 95% CI 0.26-0.67, P<0.001; fixed-effects model), reported in text (HR=0.53, 95% CI 0.38-0.74, P<0.001; fixed-effects model), data extrapolated (HR=0.45, 95% CI 0.35-0.57, P<0.001; fixed-effects model). Nevertheless, high Gal-9 expression only correlated to an extended OS in data extrapolated subgroup (HR=0.53, 95% CI 0.39-0.72, P<0.001; fixed-effects model) and with no heterogeneity (I^2=0.0%, P= 0.672). In other subgroups, high Gal-9 expression showed no association with a good OS, including Asians (HR=0.80, 95% CI 0.52-1.23, P=0.311; random-effects model; I^2=75.2%, P<0.001), univariate analysis (HR=0.73, 95% CI 0.45-1.19, P=0.205; random-effects model; I^2=81.4%, P<0.001), multivariate analysis (HR=1.03, 95% CI 0.47-2.23, P= 0.945; random-effects model; I^2=83.6%, P= 0.002), and reported in text (HR=1.09, 95% CI 0.61-1.95, P= 0.764; random-effects model; I^2=77.0%, P= 0.005).

Sensitivity analysis

We performed sensitivity analysis to evaluate the effect of each study on the synthetic results of CSS and OS by omitting each single study sequentially. The fixed-effects model was used and the study of Fu et al. displayed an apparent influence on the overall results [21] (Fig. 4). An outlier of heterogeneity was shown in our forest plot of OS above [21]. When we excluded this study from our analysis, a significant HR and 95%CI was obtained (HR=0.68, 95% CI 0.54-0.84, P<0.001) and heterogeneity was reduced greatly (I^2=48.2%, P=0.085).

Publication bias

Both Begg's funnel plot and Egger's test were used to assess the publication bias for OS and CSS. The funnel plots figures did not show any unsymmetrical evidence (Fig. 5). The P-values of Egger's and Begg's tests were all over 0.05 (CSS, P=0.368 for the Begg's test, P=0.231 for the Egger's test; OS, P=0.230 for the Begg's test, P=0.894 for the Egger's test). Hence, no significant publication bias exists in this meta-analysis.

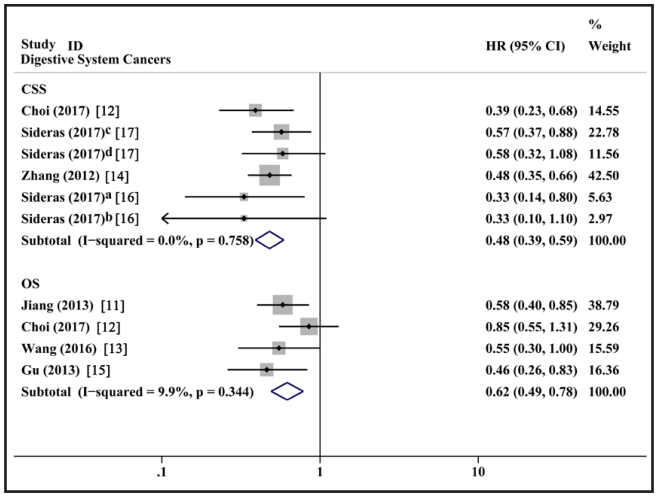

Fig. 3. Forest plots of studies evaluating hazard ratios of high Gal-9 expression for digestive tumours.

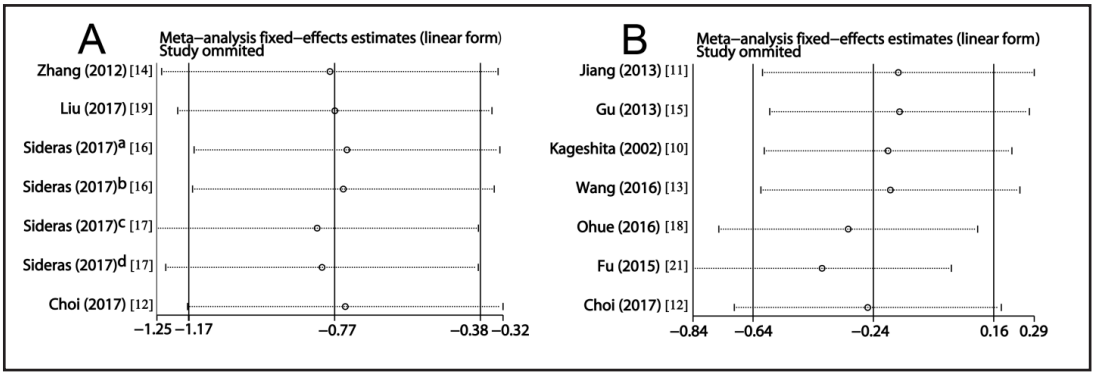

Fig. 4. Sensitivity analysis on the relationships between Gal-9 expression and outcome in solid tumours patients. Survival data are reported as (A) Cancer-specific survival; (B) Overall survival.

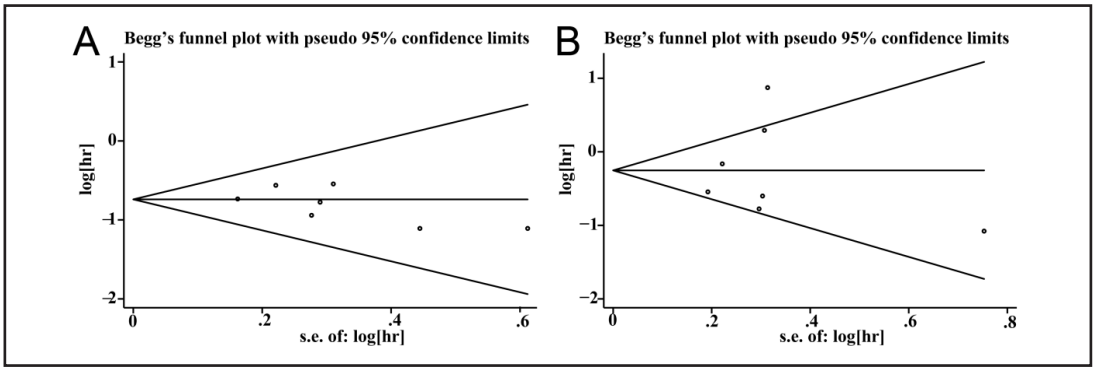

Fig. 5. Funnel plots for the evaluation of potential publication bias. (A) Cancer-specific survival for solid tumours; (B) Overall survival for solid tumours.

Discussion

To the best of our knowledge, this report describes the first meta-analysis to analyse the association between the level of Gal-9 and the prognosis of patients in solid tumours comprehensively and systematically. In this study we show that high expression of Gal-9 in cancer tissue is associated with an improved CSS in cancer patients (HR=0.48, 95% CI 0.39-0.58, P<0.001). Weak improved OS (HR=0.80, 95% CI 0.52-1.23, P=0.311) and DFS/RFS (HR= 0.58, 95% CI 0.30-1.10, P=0.097) were observed among patients who were considered to have high Gal-9 expression. Generally, in the subgroup analysis, elevated Gal-9 expression was an important prognostic marker in cancer patients for CSS, regardless of tumour type, ethnicity, analysis type and HR obtained method. A significant association was found between digestive cancers and both CSS (HR=0.48, 95% CI 0.39-0.59, P<0.001) and OS (HR=0.62, 95% CI 0.49-0.78, P<0.001). These results indicated that Gal-9 might serve as a positive prognostic biomarker for solid tumours especially of digestive origin.

Galectin-9 (Gal-9) is a member of the galectin family of carbohydrate-binding proteins. Based on the presence of one to three conserved carbohydrate-recognition domains (CRD), all galectin family members can be classified into three subgroups, including proto-type galectins, tandem-repeat galectins and chimaera-type galectins [25]. Gal-9 is recognized as a so-called tandem-repeat galectin containing an N-terminal CRD (N-CRD) and a C-terminal CRD (C-CRD). Recent studies indicate that the C-CRD of Gal-9 is responsible for receptor recognition and T-cell death, while the N-CRD is more potent in activation of dendritic cells (DCs) [26]. A critical role of Gal-9 has been reported in infectious disease, autoimmune disease and cancer [27]. One identified binding partner of various glycoproteins interacting with Gal-9 is Tim-3, which is expressed on specific T-cell subsets and cells of the innate immune system, including macrophages, monocytes, and DCs [8, 28]. Nagahara et al., found that Gal-9 enhanced $CD8^+$T-cell-mediated antitumour immunity via Tim-3 dependent interactions between DCs and $CD8^+$ T cells, and the quantity of IFN-γ was produced accordingly though Gal-9 induces apoptosis in $CD4^+$ Th1 cells [29]. A meta-analysis conducted by Zhang et al., demonstrated a positive association between high Tim-3 expression and poor prognosis in patients with solid tumours [30]. Meanwhile, $Tim\text{-}3^+CD8^+$ T cells were found to impair IFN-γ production which suppressed the cytotoxic activity of functional T cells [31]. Additionally, endothelial cell-expressed Tim-3 can facilitate metastasis of melanoma cells [32] and the progression of lymphoma via mediating immune evasion [33]. However, these processes were not mediated by Gal-9. Consequently, the expression of Gal-9 might block Tim-3 competitively on endothelial cells to inhibit metastases and the progression of cancer cells [33]. Decreased Gal-9 and increased Tim-3 expression were observed to be associated with poor prognosis in gastric cancer [11] and this finding was consistent with our results.

Therefore, the protein of Gal-9 performs an important role in augmenting antitumour immunity via the Gal-9/Tim-3 pathway. Furthermore, Su et al. found that the effects of Gal-9 on T cells were independent of Tim-3 [34]. This means that the antitumour activities of Gal-9 may be exerted by additional receptors apart from Tim-3.

The ability of Gal-9 to inhibit metastasis has recently been reported in several studies. For instance, Gal-9 induced both cell aggregation and apoptosis of melanoma cells [10], while most patients with distant metastasis lacked Gal-9 expression in breast cancer [20]. In an adhesion assay, an increased cellular adherence ratio was observed in Gal-9 overexpressing oral squamous carcinoma cells, suggesting that this lectin was correlated with anti-metastatic activity in oral cancer [35]. Similar results were also observed in gastric cancer [11] and hepatocellular carcinoma [14]. It has been proposed that both attachment and invasion of tumour cells are inhibited by Gal-9 through interference with cell adhesion molecules binding to ligands on the vascular endothelium and the extracellular matrix [36]. Treating with recombinant Gal-9 was shown to decrease metastasis of cancer in several studies [37-39]. Nevertheless, Irie et al.., reported that overexpression of Gal-9 in breast cancer cells exhibited a reduced adhesion to the extracellular matrix [20]. Meanwhile, Zhang et al.., reported that Gal-9 isoforms differentially regulated the adhesion of LoVo cells to the extracellular matrix *in vitro* [40]. The contradiction in these studies may be attributed to the differences in cell origins.

There are several limitations in this paper. First, this meta-analysis included only 14 studies and 2, 408 patients, which lead to relatively insufficient data in the subgroup analyses. Second, different cut-off values were applied in these studies, because of the lack of uniform cut-off values in Gal-9 expression. This may influence the validity of Gal-9 as a predictive marker in cancer prognosis. Third, several HRs with 95% CIs were calculated by digitizing and extracting the data from the Kaplan-Meier curves, which inevitably brought minor statistical deviations. Finally, the significant heterogeneity among these studies might have been caused by variation in patient origin, publication year, tumour type, tumour stage, experimental method, follow-up time and cut-off values. In consideration of the limitations of the present analysis, more well-designed studies with more tumour types and larger sample sizes are needed.

Conclusion

Gal-9 seems not only to be regarded as a prognostic marker for solid tumours but also as an important new therapeutic target. This conclusion should be regarded with caution due to the limitations of the current analysis. Considering the sparse data, further researches with respect to Gal-9 is warranted.

Acknowledgements

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Disclosure Statement

The authors declare no conflicts of interest concerning this article.

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