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Review

Galectin-3 may serve as a marker for poor prognosis in colorectal cancer: A meta-analysis

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ABSTRACT

Galectin-3 has an important function in the development of tumors. The purpose of this meta-analysis was to explore the relationships between the expression of galectin-3 on clinicopathological features and prognosis of colorectal cancer (CRC). A comprehensive literature search was used to identify eligible studies, and Stata software was conducted using in this meta-analysis. A total of 15 studies, including 1661 cases, were matched in the inclusion criteria. The pooled analysis indicated that galectin-3 expression was related to the poor overall survival (OS) in CRC patients (HR: 1.77, 95% CI: 1.36–2.31, $P < 0.0001$). Our meta-analysis also showed that cancerous tissues have higher levels of galectin-3 expression than normal tissues. Besides, positive galectin-3 expression was also related to advanced TNM stages(III/IV vs. I/II: OR 5.30, 95% CI: 2.42–11.61, $P < 0.0001$), higher Duke's stages (C/D vs. A/B: OR 4.00, 95% CI: 2.22–7.22, $P < 0.0001$), venous invasion (venous invasion vs. not: OR 3.02, 95%CI: 1.75–5.22, $P < 0.0001$) and higher CEA level (CEA ≥ 5 ng/ml vs. ≤ 5 ng/ml: OR 2.09, 95% CI: 1.09–4.03, $P = 0.03$). In summary, our results indicated that overexpression of galectin-3 is significantly related to the tumor progression and could be a efficient in predicting the prognosis of patients with CRC.

1. Introduction

Colorectal cancer, a major health problem worldwide, which is the third and second most common cancer in males and females, the second and third cause of cancer-related deaths among males and females, respectively [1]. The incidence of CRC is increasing in certain countries [2]. In contrast to incidence trends, the CRC mortality rate was decreasing in a large number of countries worldwide. The most likely reason for this was attributed to CRC screening, which reduced prevalence of risk factors, and/or improved treatments [3,4]. However, there are not enough comprehensive prognostic molecular markers to predict CRC prognosis and provide guidance for treatment options. [5]. Consequently, there is an urgent need to find effective and specific biomarkers for CRC diagnosis along with prognosis.

Galectin-3 is a member of the galectin family and is characterized by their binding affinity for β-galactosides, which is located within the cytoplasm and the nucleus but can be transported to the cell surface, extracellular space, and the circulation [6]. Galectin-3 plays important roles in cell proliferation, adhesion, differentiation, angiogenesis, and apoptosis. Besides, there is mounting evidence shows that galectin-3 may act as a mediator of tumor cell transformation, migration, invasion, and metastasis [7].

Research increasingly suggests that galectin-3 level is significantly elevated in cancer tissues and associated with CRC metastasis and prognosis [8–12]. In the present study, we aimed to explore the relationship between galectin-3 expression level and the

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Table 1
Newcastle–Ottawa quality assessments scale.

Study	Selection				Comparability	Exposure			Total
	Adequacy of case definition	Represent-ativeness of the cases	Selection of Controls	Definition of Controls	Comparability of cases and controls on the basis of the design or analysis	Ascertainment of exposure	Same method of ascertainment for cases and controls	Non-Response Rate	
Liu T 2017 [13]	★	★	–	★	★	★	★	★	**7**
Hung ZL 2016 [14]	★	★	–	–	★★	★	★	★	**7**
Lu WQ 2017 [15]	★	★	–	–	★★	–	★	★	**6**
Wu KL 2017 [16]	★	★	–	–	★★	–	★	★	**6**
Vinod G 2016 [17]	★	★	–	–	★★	★	★	★	**7**
Heather D 2013 [18]	★	★	–	–	★★	★	★	★	**7**
Hannah B 2013 [19]	★	★	–	–	★★	★	★	★	**7**
Luciana Z 2011 [20]	★	★	–	–	★	★	★	★	**6**
Harald L 1995 [21]	★	★	–	–	★	★	★	★	**6**
Kazuya E 2005 [22]	★	★	–	–	★	★	★	★	**6**
Xavier S 1997 [23]	★	★	–	–	★★	★	★	★	**7**
Masato N 1999 [24]	★	★	–	–	★	★	★	★	**6**
Wang XL 2015 [25]	★	★	–	–	★	★	★	–	**5**
Yang XZ 2016 [26]	★	★	–	★	★	★	★	–	**6**
Ren LL 2017 [27]	★	–	–	★	★	★	★	★	**6**

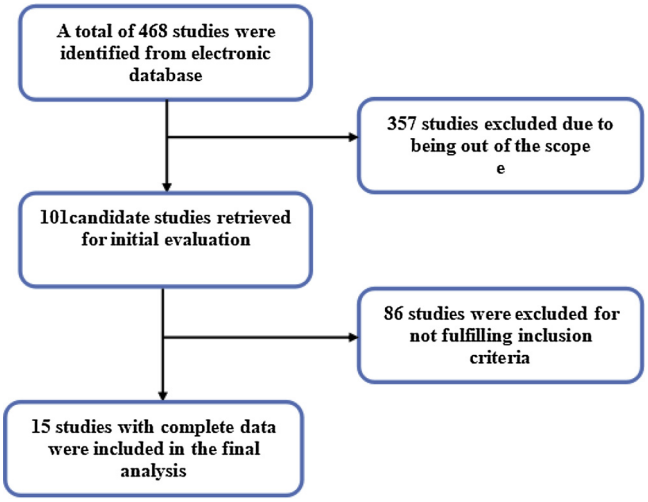


Fig. 1. Flow diagram for selection of studies in the meta-analysis.

clinicopathological parameters of CRC patients, and determine whether galectin-3 could be used as a potential prognostic marker.

2. Materials & methods

2.1. Publication search

Eligible studies related to the expression of galectin-3 and overall survival (OS) in CRC patients were retrieved by searching the following combination terms of PubMed, Web of Science database, EMBASE, Science Direct, CNKI and Wanfang database: ("Galectin-3 or Galectin 3 or Gal-3 or LGALS3") and ("colorectal tumor, colorectal cancer, or colorectal carcinoma") and ("prognostic, prognosis, or survival"). A list of citations related to all studies was used to identify other eligible studies. The last search was performed in November 2018.

2.2. Inclusion & exclusion criteria

The inclusion criteria in our meta-analysis were base on the following aspects: (1) Galectin-3 was examined and evaluated by immunohistochemistry or elisa in human CRC; (2) the relationships between galectin-3 expression and OS or clinicopathological features or prognosis of CRC was obtained; (3) patients were diagnosed with colorectal carcinoma by histopathological examination yet without restriction for region, race, gender and age. (4) valid data about galectin-3 expression and OS and the other clinicopathological features were obtained directly form the original text or could be calculated indirectly. Studies were excluded according to the following criteria: (1) duplicate or similar studies from the original data; (2) Comments, reviews, unpublished data, conference abstracts, letters or case reports; (3) The research without access to full text or extract the outcome indicators. (4) The data of odds ratios (OR), hazard ratio (HR) and a 95% confidence interval (CI) were obtained failure form the original text or would be calculated indirectly. According to the selection, comparability and outcomes of the study cohorts, Total quality score of NOS was ranged from 0 to 9, details were presented in Table 1.

2.3. Data extraction

Two investigators (Wang CY and Zhou XL) extracted data from the eligible studies independently. Disagreement was resolved by the discussion and reached a consensus. The data extracted from each study included: thetumor characteristics, HR and 95% CI of OS. We extracted the data by Engauge Digitizer version 7.2 from Kaplan–Meier curve in some studies which there was no direct HR data. The following information was recorded from each study also included: author's name, publication year, detection method, cut-off value, study location, specimens source, total number of patients included in the study.

2.4. Statistical analysis

This meta-analysis was analyzed by Review Manager (RevMan) software. HR and 95% CI were used to assess the relationships between galectin-3 positive expression with the prognosis and clinicopathological factors of CRC. I^2 test were used to statistical heterogeneity, if $I^2 > 50\%$ did show considerable heterogeneity, a random effects model is used for meta-analysis, otherwise fixed-effects model was used. The total result was described as HR or OR with 95% CI. Meanwhile, 95% CI included 1 was considered insignificant. A P-value represented the overall effect, and $P < 0.05$ was statistically significant.

3. Results

3.1. Study characteristics

The initial search had 486 studies, and a total of 15 studies were matched in the inclusion criteria, after checking and carefully reading the article title, abstract, and full text, the details of the selection process was shown in Fig. 1. Altogether, these 15 studies included 1661 cases provided data about galectin-3 expression in CRC, meanwhile its

Table 2
Characteristics of studies included in the meta-analysis.

First author (year)	Region	Cases	Treatment	Cut-off value (positive expression)	HR estimate	Specimens source	Method	Outcome of patients
Liu T 2017 [13]	China	84	Surgery	≥2 scores	2.1 (1.05,4.17)	Tissue	IHC	OS
Hung ZL 2016 [14]	China	129	Surgery Chemotherapy	≥4 scores	2.37 (0.88,6.39)	Tissue	IHC	OS
Lu WQ 2017 [15]	China	57	Surgery	≥2 scores	2.02 (0.96,4.23)	Tissue	IHC	OS
Wu KL 2017 [16]	China	120	Surgery	> 1.2 ng/ml	2.05 (1.15,3.65)	Serum	ELISA	OS
Vinod G 2016 [17]	Australia	201	Surgery	≥2 scores	2.4 (1.38, 4.19)	Tissue	IHC	OS
Heather D 2013 [18]	Germany	101	Surgery Chemotherapy	Median value	0.52 (0.27,0.98)	Tissue	IHC	OS
Hannah B 2013 [19]	England	51	Surgery	Median value	1.16 (0.62,2.16)	Serum	ELISA	OS
Luciana Z 2011 [20]	Brazil	75	Surgery Chemotherapy	Positive cells ≥50%	0.21(0.037,1.202)	Tissue	IHC	OS
Harald L 1995 [21]	American	153	Surgery	≥2 scores	1.44 (0.92,2.25)	Tissue	IHC	OS
Kazuya E 2005 [22]	Japan	121	Surgery	Positive cells ≥20%	2.73(0.72,10.28	Tissue	IHC	OS
Xavier S 1997 [23]	Spain	190	Surgery	≥2 scores	2.83 (0.92,8.74)	Tissue	IHC	OS
Masato N 1999 [24]	Japan	117	Surgery	Positive cells ≥66.7%	3.1 (1.9,5.16)	Tissue	IHC	OS
Wang XL 2015 [25]	China	80	Surgery	Positive cells ≥26%	1.84 (1.03,3.28)	Tissue	IHC	OS
Yang XZ 2016 [26]	China	64	Surgery Chemotherapy	≥4 scores	2.09 (1.09,3.79)	Tissue	IHC	OS
Ren LL 2017 [27]	China	118	Surgery	≥2 scores	2.24(1.12,4.5)	Tissue	IHC	OS

IHC: immunohistochemistry staining; ELISA: enzyme-linked immunosorbent assay; OS: overall survival; R: reported in text; HR: hazard ratio.

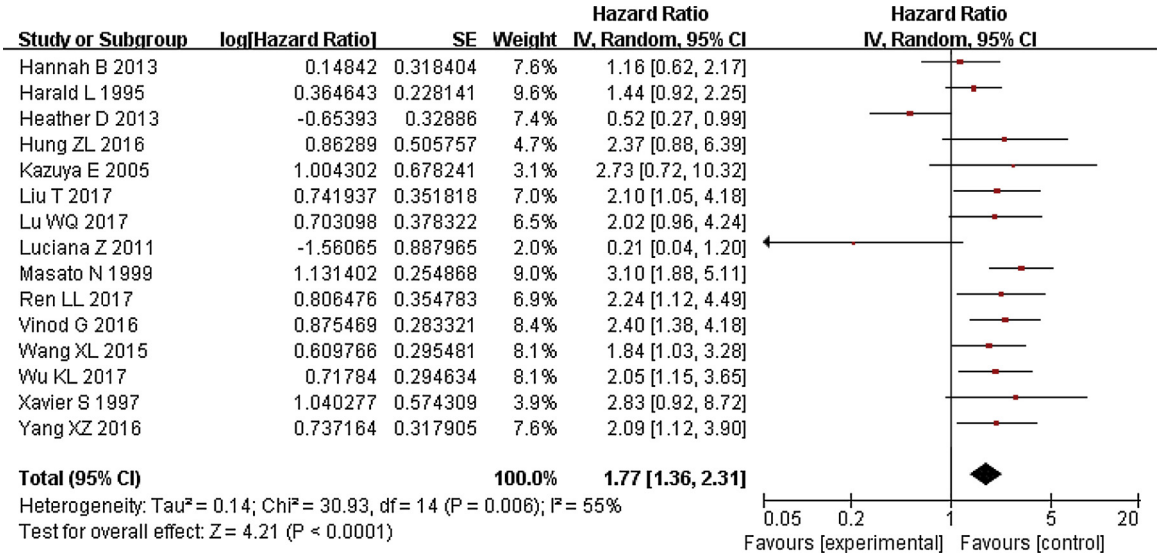


Fig. 2. Forest plots for the association between Galectin-3 and OS (A) of CRC patients. **Note:** Weights are from random or fixed effects analysis. Abbreviations: OS: overall survival; CRC: colorectal cancer; SE: standard error; CI: confidence interva.

prognostic value and clinicopathological features were evaluated in quantitative analysis. Immunohistochemistry or elisa methods was used in all studies for galectin-3 protein expression. All data of the main characteristics were shown in Table 2.

3.2. Impact of Galectin-3 expression on OS in colorectal cancer patients

The association between the expression level of galectin-3 and CRC was performed. Fig. 2 shows the results of a forest plot and meta-analysis of individual HR estimates. In general, the risk of death from galectin-3 positive expression was significantly increased compared to negative galectin-3 expression (HR: 1.77, 95% CI: 1.36–2.31, P < 0.0001)(Fig. 2A). However, considerable heterogeneity was come to under observation (I^2 = 55%, P = 0.006). In order to explain the this heterogeneity, we performed further subgroup analysis by the specimens, ethnicity, cut-off value and treatment method.

Subgroup analysis showed a significant relationship between galectin-3 expression and OS by tissue and serum (pooled HR: 1.81, 95% CI: 1.33–2.46, I^2 = 58%, P = 0.0001; pooled HR: 1.56, 95% CI:0.89-2.87, I^2 = 42%, P = 0.12; respectively) (Fig. 3A). Cut-off value ≥2scores, ≥4scores, positive cells and others (pooled HR: 1.83, 95% CI: 1.23–2.73, I^2 = 45%, P = 0.03; pooled HR: 2.17, 95% CI: 1.28–3.67, I^2 = 0%, P = 0.04; pooled HR: 2.40, 95% CI: 1.73–3.32, I^2 = 0%, P < 0.00001; pooled HR: 1.08, 95% CI:0.50-2.37, I^2 = 79%, P = 0.84; respectively)(Fig. 3B); Asia and non-Asia (pooled HR: 2.25, 95% CI: 1.80–2.82, I2 = 0%, P < 0.00001; pooled HR:1.19, 95% CI: 1.80–2.82, I2 = 0%, P = 0.54; respectively) (Fig. 3C). Surgery treatment and surgery + chemotherapy (pooled HR: 2.00, 95% CI: 0.68–2.09, I2 = 0%, P < 0.00001; pooled HR: 0.99, 95% CI: 0.37–2.63, I2 = 80%, P = 0.98; respectively) (Fig. 3D). These findings suggested that galectin-3 expression involved in the above factors and may have an adverse effect on the prognosis of CRC. Other factors failed to alter significant prognostic effects of galectin-3 expression (Table 3).

3.3. Correlation of galectin-3 with clinicopathological features

The association between galectin-3 and several clinicopathological features is illustrated in Table 4. As Fig. 4 shows, we evaluated 4 studies to determine the relationship between cancer tissues and normal tissues. Cancer tissues showed higher positive galectin-3 expression as compared to normal tissues(cancer tissues vs normal tissues: OR 12.22, 95% CI: 7.11–21.01, P < 0.00001) (Fig. 4A). Positive expression of galectin-3 in stage III/IV patients was higher than that in stage I/II patients(III/IV vs. I/II: OR 5.30, 95% CI: 2.42–11.61, P < 0.0001) (Fig. 4B). The higher positive galectin-3 expression Positive expression of galectin-3 in stage C/D patients than that in stage A/B patients (C/D vs. A/B: OR 4.00, 95% CI: 2.22–7.22, P < 0.0001) (Fig. 4C). Patients which CEA ≥ 5 ng/ml showed higher galectin-3 expression levels as compared to patients which CEA ≤ 5 ng/ml. (CEA ≥ 5 ng/ml vs. ≤ 5 ng/ml: OR 2.09, 95% CI: 1.09–4.03, P = 0.03) (Fig. 4D). Patients have venous invasion showed higher galectin-3 expression levels as compared to patients haven't (venous invasion vs. not: OR 3.02, 95%CI: 1.75–5.22, P < 0.0001) (Fig. 4E). However, galectin-3 expression was not obviously associated with gender (Male vs. Female: OR: 1.00, 95% CI: 0.73–1.37, P = 0.18) (Fig. 4B), age (> 50vs ≤ 50: OR: 0.95, 95% CI: 0.50–1.80, P = 0.87) (Fig. 4C), degree of tumor differentiation (Poor differentiation vs. Moderate/high differentiation: OR: 1.85, 95% CI: 0.80–4.30, Z = 1.34, P = 0.15) (Fig. 4D), tumor sites (Rectal vs. Colon: OR: 0.65, 95% CI: 0.38–1.12, P = 0.12) (Fig. 4E), tumor size (≥ 5 cm vs. < 5cm: OR: 1.41, 95% CI: 0.57–3.50, P = 0.45) (Fig. 4F), distant metastases (Positive vs. Negative: OR: 3.42, 95% CI: 0.56–20.68, P = 0.18) (Fig. 4J), lymph node metastases (Positive vs. Negative: OR: 2.08, 95% CI: 0.75–5.77, P = 0.16) (Fig. 4K). The subgroups including analysis model pooled OR (95% CI), studies, cases were conducted explain the heterogeneity (Table 4). There was no significant inter-study heterogeneity in differentiation grade, tumor size, distant metastases, and lymph node metastases did not show evident inter-study heterogeneity, while other histological features showed heterogeneity (supplementary material).

3.4. Publication bias

The shapes of the funnel plots for OS did indicated a moderate publication bias (Fig. 5). Heterogeneity may result from different scoring systems, antibodies, and researchers. Relevant summary data were presented in Table 2. To exclude publication bias, we used the clinically relevant parameters and random-effects model.

4. Discussion

CRC ranks third and second in the world in terms of morbidity and cancer-related mortality, respectively. [1]. Since the rates for early diagnosis and high inmortality in patients with advanced colorectal cancer, it is urgently needed to develop promising biomarkers for

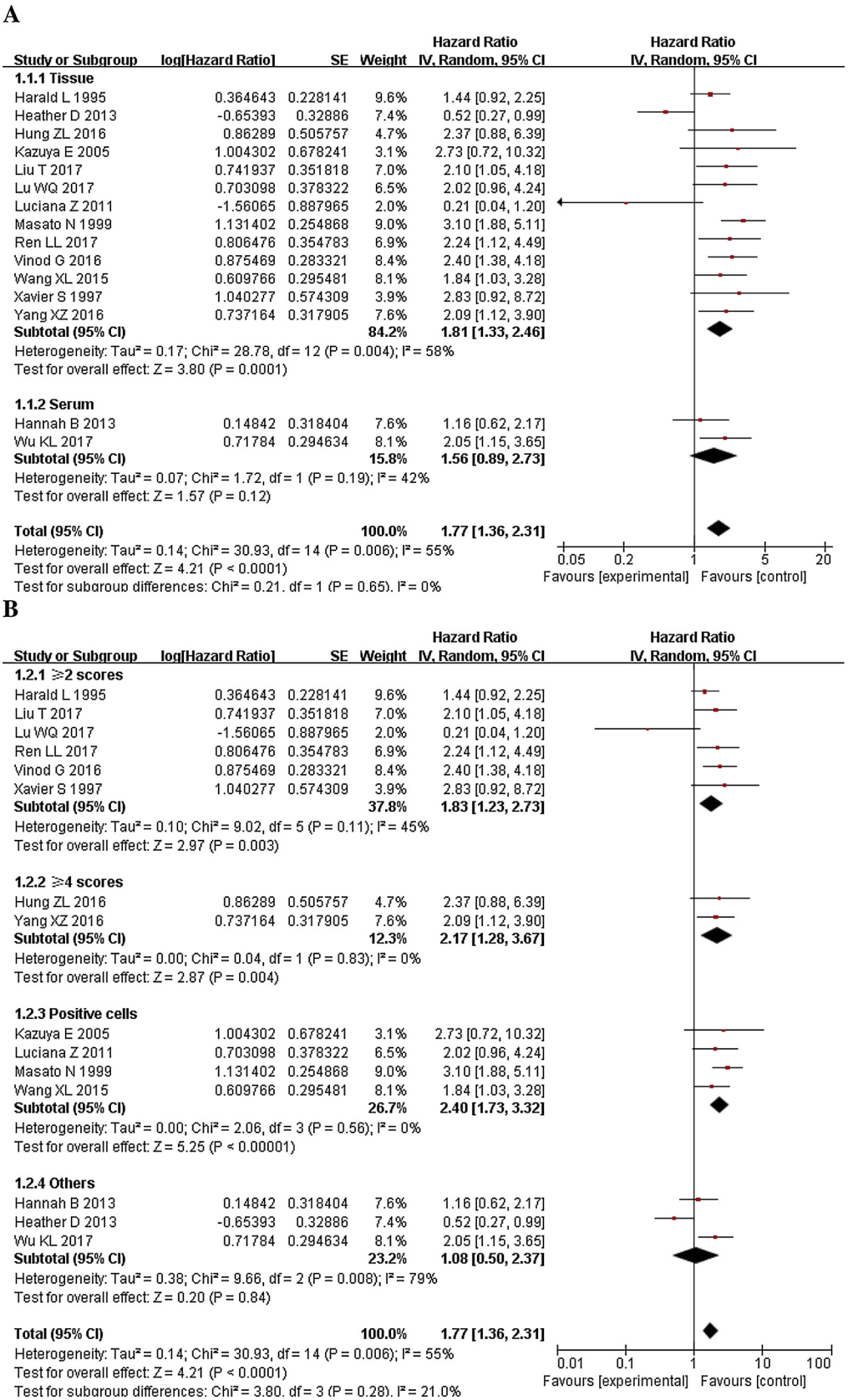
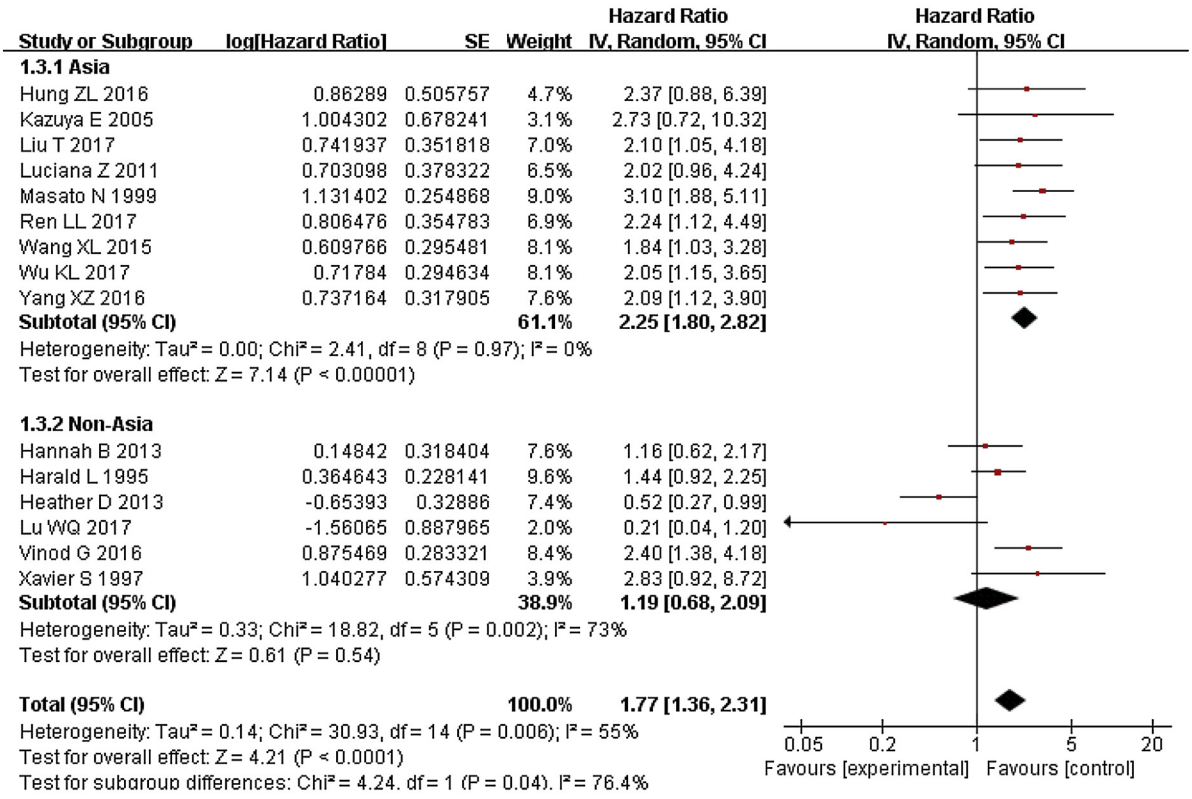


Fig. 3. Forrest plot of the hazard ratio for the association of Galectin-3 expression with OS by subgroup analysis. Subgroup analysis was performed by Specimens (A), Cut-off value (B), Ethnicity (C) and method of therapy (D).

Note: Weights are from random effects analysis.

Abbreviations: OS: overall survival; CI: confidence interva.

C



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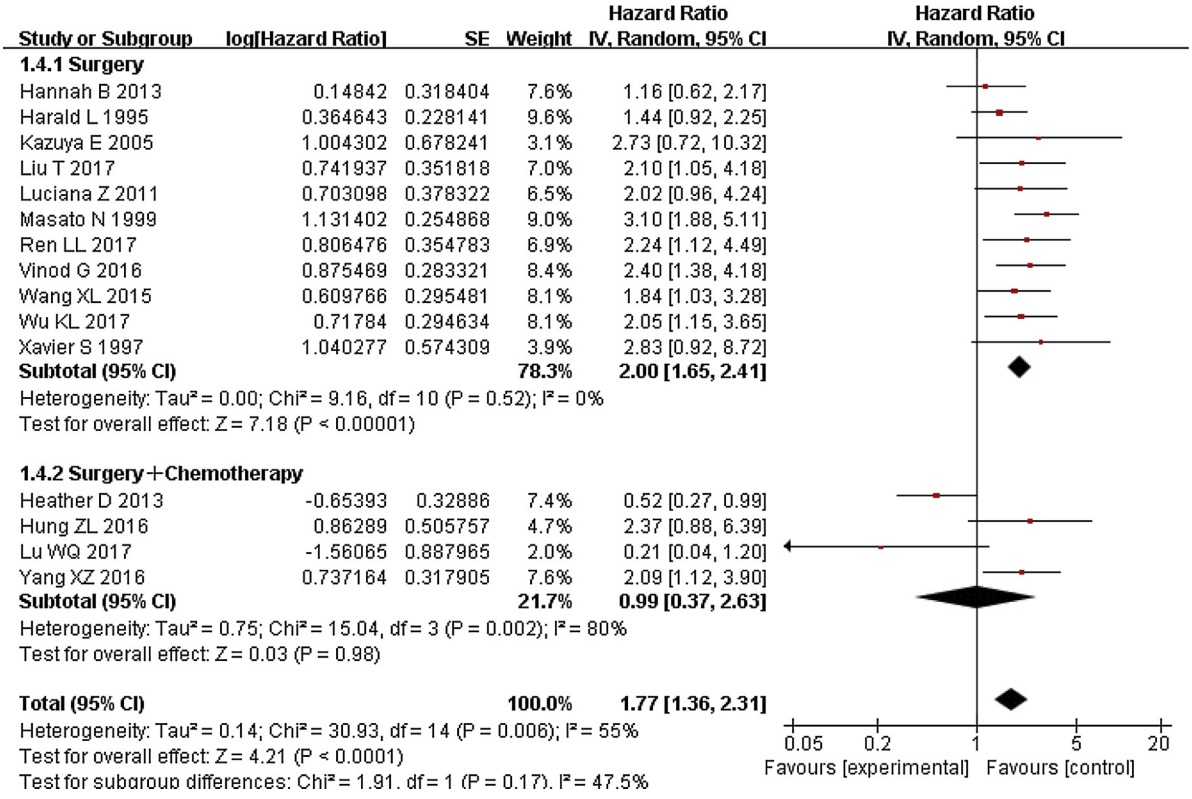

Fig. 3. (*continued*)

patients with colorectal cancer. As a member of the lectin family, Galectin-3 were considered as a potential prognostic biomarkers of tumor and is involved in physiological and pathological processes for its unique structure and functions.[28,29]. Galectin-3 has been studied in a number of neoplasms with different results. Among these, the information regarding colorectal cancer is controversial. Therefore, this

Table 3
Stratified analysis of pooled hazard ratios.

Subgroup analysis	Studies (N)	Analytical model	HR	95% CI	P value for HR	P value/I^2 (%) for heterogeneity
Overall effect	**15**	**REM**	**1.77**	**1.36-2.31**	**< 0.0001**	**0.006 (55%)**
Specimens						
Tissue	**13**	**REM**	**1.81**	**1.33-2.46**	**0.0001**	**0.004 (58%)**
Serum	**2**	**REM**	**1.56**	**0.89-2.73**	**0.12**	**0.19 (42%)**
Cut-off value						
≥2 scores	**6**	**REM**	**1.83**	**1.23-2.73**	**0.003**	**0.11 (45%)**
≥4 scores	**2**	**REM**	**2.17**	**1.28-3.67**	**0.004**	**0.83(0%)**
Positive cells	**4**	**REM**	**2.40**	**1.73-3.32**	**< 0.00001**	**0.56(0%)**
Others	**3**	**REM**	**1.08**	**0.50-2.37**	**0.84**	**0.008(79%)**
Ethnicity						
Asia	**9**	**REM**	**2.25**	**1.80-2.82**	**< 0.00001**	**0.97 (0%)**
Non-Asia	**6**	**REM**	**1.19**	**0.68-2.09**	**0.54**	**0.002 (73%)**
Treatment						
Surgery	**11**	**REM**	**2.00**	**1.65-2.41**	**< 0.00001**	**0.52 (0%)**
Surgery + Chemotherapy	**4**	**REM**	**0.99**	**0.37-2.63**	**0.98**	**0.002 (80%)**

REM: random-effects model; FEM: fixed-effects model; HR: hazard ratio; CI: confidence interva.

Table 4
Meta-analysis of Galectin-3 expression and clinicopathological features of colorectal cancer.

Clinicopathological features	Studies	Cases	Analytical model	OR	95% CI	P value for OR	P value/I^2 (%) For heterogeneity
Cancer tissues vs. Normal tissues	**4**	**410**	**FEM**	**12.22**	**7.11-21.01**	**< 0.00001**	**0.87 (0%)**
Gender	**8**	**733**	**FEM**	**1.00**	**0.73-1.37**	**1.00**	**0.90 (0%)**
Age	**3**	**185**	**FEM**	**0.95**	**0.50-1.80**	**0.87**	**0.84 (0%)**
Grade	**9**	**738**	**REM**	**1.85**	**0.80-4.30**	**0.15**	**0.01 (58%)**
Tumor sites	**5**	**315**	**FEM**	**0.65**	**0.38-1.12**	**0.12**	**0.99 (0%)**
Tumor size	**5**	**371**	**REM**	**1.41**	**0.57-3.50**	**0.45**	**0.01 (69%)**
TNM stages	**4**	**258**	**FEM**	**5.30**	**2.42-11.61**	**< 0.0001**	**0.59 (0%)**
Duke's stages	**4**	**314**	**FEM**	**4.00**	**2.22-7.22**	**< 0.00001**	**0.90 (0%)**
CEA level	**2**	**174**	**FEM**	**2.09**	**1.09-4.03**	**0.03**	**0.78 (0%)**
Distant metastases	**3**	**310**	**REM**	**3.42**	**0.56-20.68**	**0.18**	**0.06 (65%)**
Lymph node metastases	**6**	**527**	**REM**	**2.08**	**0.75-5.77**	**0.16**	**0.0002 (79%)**
Venous invasion	**3**	**338**	**FEM**	**3.02**	**1.75-5.22**	**< 0.0001**	**0.64 (0%)**

REM: random-effects model; FEM: fixed-effects model; OR: odds ratio; CI: confidence interva.

meta-analysis aims to clarify this issue.

Our meta-analysis systematically evaluated the mortality risk in a larger population, which showed high galectin-3 expression was associated with worse OS in colorectal cancer. To explain the heterogeneity in CRC, we performed a subgroup analysis that indicated a significant relationship between higher galectin-3 expression of CRC also shown by tissue, cut-off value ≥2scores, Asia, surgery treatment. About subgroup analysis for samples, we observed that only tissue was statistically significant, the reason for this may be that researches on serum samples were too limited and indicating the role of galectin-3 in the tissue is more stable. Another subgroup analysis of dominant ethnicity, we observed that were statistically significant only in Asian ethnicity, suggesting that the detection of high galectin-3 expression in these patients might be useful for prognosis prediction. Our results also suggested that surgery treatment had a significant relationship with galectin-3 expression, indicating that it could provide a certain guiding significance for clinical decision-making, especially for chemotherapy.

Among previous researches, mostly suggesting that the increased expression of galectin-3 in serum or tissue was related to invasion of depth, vessel invasion, lymph node metastasis, distant metastasis, and TNM stages of colorectal cancer and increased expression of galectin-3 often predicted poor prognosis [10,13,14,20–23]. Lu W et al. suggest that miR-128 can enhance the chemosensitivity of CRC cells, and inhibited the potential invasiveness, whereas galectin-3 impaired the cancer suppressive effects of miR-128 [15]. Wu KL et al. demonstrated that extracellular CEA interacted with galectin-3 and promoted the migration of colorectal cancer cells and distal metastasis [16]. Contrary to the above results, Gopalan V and Dawson H et al. considered that CRC patients with high levels of galectin-3 mRNA or protein expression showed better prognosis [17,18]. To explore the correlation of galectin-3 expression with clinicopathological parameters, we further conducted a subgroup analysis. Our results showed that cancer tissues exhibited higher positive galectin-3 expression as compared to normal tissues. Moreover, patients with higher TNM stages, Duke's stages, CEA level, and Venous invasion were higher than those in CRC patients without these clinicopathological parameters. However, galectin-3 expression was not significant associated with gender, age, grade of pathological differentiation, tumor sites, tumor size, distant metastases, lymph node metastases. These results were basically consistent with the previous studies, but still purely heterogeneous. We conducted the subgroup analysis to explain the heterogeneity. There was no significant inter-study heterogeneity in differentiation grade, tumor size, distant metastases, and lymph node metastases did not show evident inter-study heterogeneity, while other histological features showed heterogeneity.

Galectin-3 was increased in patients with colorectal cancer and markedly increased in advanced diseases [13,14,30,31]. Furthermore, galectin-3 is a stable biomarker, which is not associated with the circadian variation, body mass index, or sex [32–34]. Therefore, galectin-3 may have a promising application prospect as a biological marker for colorectal cancer compared with current biomarkers. However, research increasingly suggests that galectin-3 expression level was also closely related to heart, renal, and liver disease and infections. When considering galectin-3 as a biological marker for colorectal cancer, it is essential to find whether the patient has other diseases which may increase the galectin-3 expression level.

Our studies showed galectin-3 is a promising area for biomarkers and a novel therapeutic target of colorectal cancer, which is consistent with the results of a study by Wang et al. [8]. However, the study of Wang et al. is lack of subgroup analysis of clinicopathological parameters. Furthermore, more studies were included in our meta-analysis.

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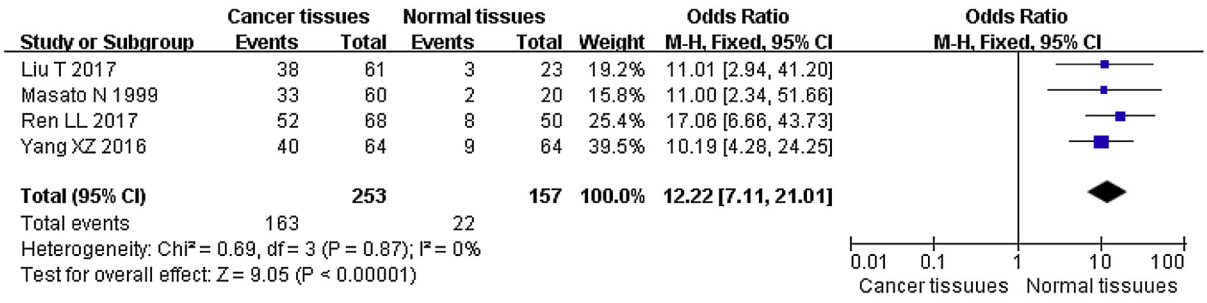

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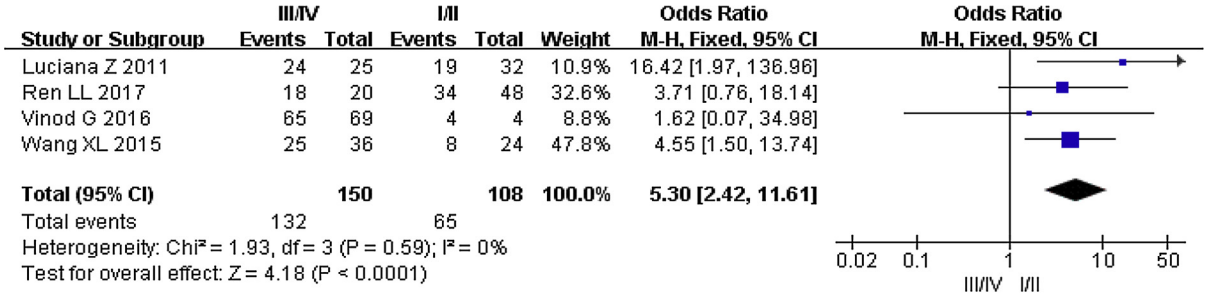

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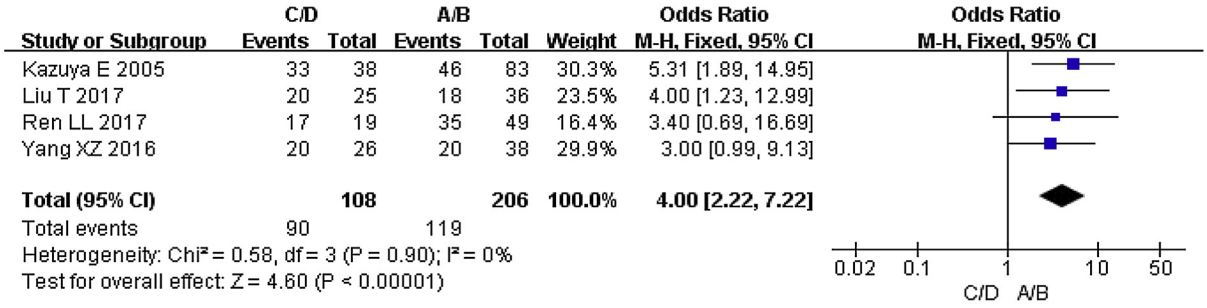
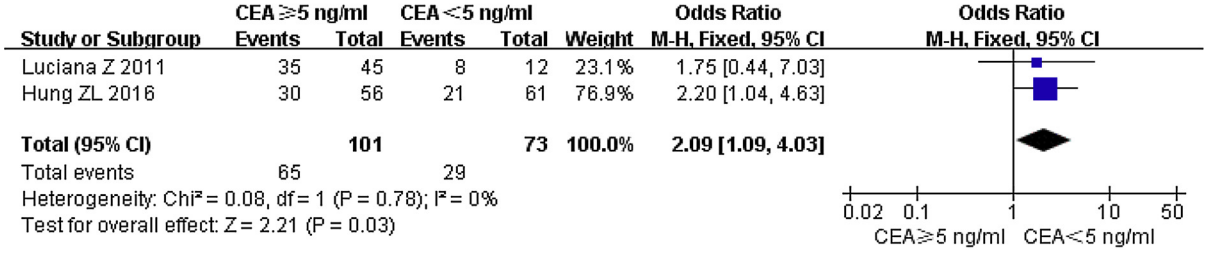


D



E

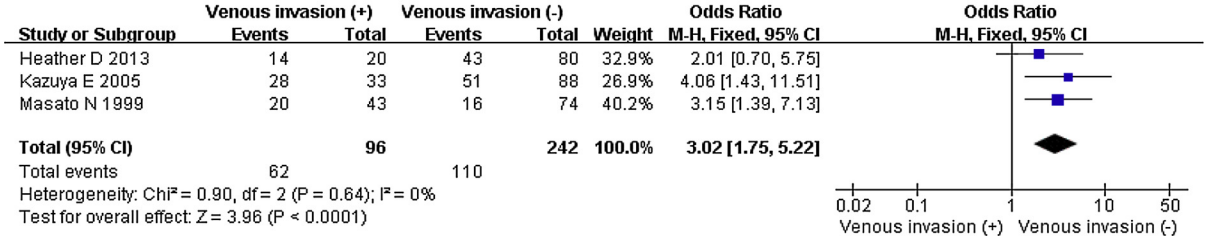


Fig. 4. Forrest plot of odds ratios for the association of Galectin-3 expression with clinicopathological features. ORs with corresponding 95% CIs of the Galectin-3 expression between Cancer tissues and Normal tissues (A), TMN stages (B), Duke's stages (C), CEA level (D), Venous invasion (E).
Note: Weights are from random or fixed effects analysis.

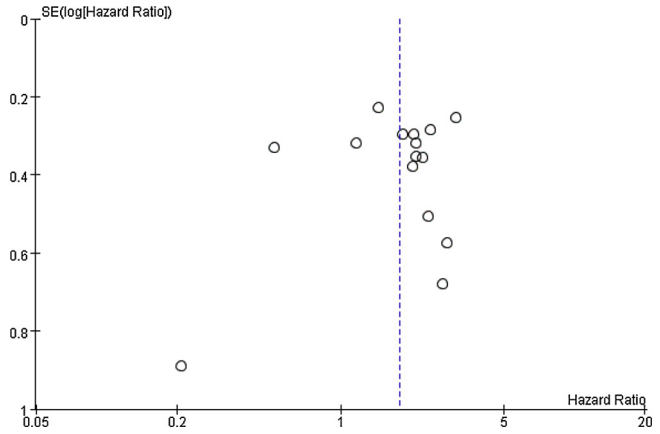


Fig. 5. Funnel plot (B) for publication bias of Galectin-3 and OS. Funnel plot showing the relation hazard ratio (HR) and standard error (log HR).
Note: Weights are from random or fixed effects analysis.
Abbreviations: OS: overall survival; CRC: colorectal cancer; SE: standard error; CI: confidence interva.

Therefore, the results from our meta-analysis are more instructive.

Although galectin-3 has been investigated in the last few decades, the mechanism involve galectin-3 influences the progression of CRC patients' remains unknown. Numerous reports have shown that the biologic activity of galectin-3 was dependent on cellular location. In the nucleus, galectin-3 showed an antitumor effect whereas cytoplasmic galectin-3 promoted tumor progression in cancer [23,35,36,37,38]. Other potential mechanisms involve galectin-3 influences the progression of colorectal cancer including the following aspects. One possible mechanism is galectin-3 mediated the localization of β-catenin to the cell membrane by protocadherin-24 in CRC which associated with tumor growth and inhibition of cell proliferation [39]. Another possible mechanism is galectin-3 binding protein down-regulated expression of galectin-3 at the cell surface to stimulate the shedding of protein tyrosine phosphatase kappa by proprotein convertase 5, thereby stimulating cancer cell proliferation via autocrine signaling [40]. Moreover, galectin-3 interacts with heterogeneous nuclear ribonucleoprotein Q (hnRNP Q), and forming a complex with galectin-3 can maintain the stability of hnRNP Q. When suppressing galectin-3 can weaken this interaction and significantly inhibit proliferation of human colon cancer cells and reduce susceptibility to 5-FU [41]. More studies of the functional mechanism of galectin-3 expression in CRC are needed.

In our study, some limitations still existed. Firstly, the galectin-3 antibodies used was different and the detection method for immunohistochemical staining under the microscope is subjectivity and contingency. Secondly, various cut-off values are utilized because of missing a consensus to date. Thirdly, there may be a moderate potential risk of bias because of the quality assessment results of all were retrospective studies.

5. Conclusion & future perspective

Despite some limitations, the meta-analysis is still significant. High expression of galectin-3 was associated with a worse prognosis for CRC patients and indicates galectin-3 may provide a new available drug target of CRC. Moreover, larger sample size and more excellently-designed researches are needed to confirm these results.

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Research involving human participants and/or animals

Our study followed all applicable international, national and/or institutional guidelines for animal care and use.

Declaration of Competing Interest

The authors declare they have no conflict of interest.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.prp.2019.152612.

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