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SNF2 histone linker PHD RING helicase related Has_circ_0001649 as a diagnostic and prognostic biomarker in solid cancer

A PRISMA-compliant meta-analysis based on the Chinese population

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Abstract

Background Dysregulated circular RNAs have been implicated in the pathogenesis of cancer. Recent studies indicate that has_circ_0001649 lowly expressed in multiple types of cancer. The purpose of this study is to investigate the roles of has_circ_0001649 as a diagnostic and prognostic marker for Chinese patients with cancer.

Methods Adhering to preferred reporting items for systematic reviews and meta-analyses guidelines, systematic literature searches were performed using Pubmed, Embase, and the web of Science to retrieve articles fulfilled all inclusion criteria. The significance of has_circ_0001649 in diagnosis and prognosis of cancer patients were evaluated. Meta-Disc 1. 4 and STATA 12. 0 were used to analyze the data from collected studies.

Results Eleven articles with 761 patients were included in present meta-analysis, of which 4 were about diagnosis, 5 were about prognosis, and 6 were about tumor differentiation grade. For the diagnostic value of has_circ_0001649, the pooled results for sensitivity, specificity, positive likelihood ratio, negative likelihood ratio, and diagnostic odds ratio with their 95% confidential intervals were 0. 78 (0. 73–0. 83), 0. 75 (0. 70–0. 80), 3. 17 (2. 56–3. 93), 0. 29 (0. 23–0. 36), and 11. 41 (7. 80–16. 7), respectively. The area under the curve of summary receiver operator characteristic was 0.8408 ($Q = 0.7725$). Meanwhile, the result showed no obvious publication bias in this analysis for the *P*-value of Deeks' test was .489. For the prognostic value, the pooled hazard ratio for overall survival was 0.45 (0.324–0.626). Lower expression of has_circ_0001649 was also prone to lower tumor differentiation grade (odds ratio = 2.58, $P < .0001$).

Conclusions Has_circ_0001649 could be used as a potential biomarker for diagnosis and prognosis in solid cancer. Further prospective studies are required to validate its clinical application.

Abbreviations: AUC = area under the curve, CI = confidence interval, circRNAs = circular RNAs, DOR = diagnostic odds Ratio, HR = hazard ratio, NLR = negative likelihood ratio, OS = overall survival, PLR = positive likelihood ratio, SHPRH = SNF2 histone linker PHD RING helicase, SROC = summary receiver operating characteristic.

Keywords: biomarker, cancer, has_circ_0001649, meta-analysis

1. Introduction

In recent years, circular RNAs (circRNAs), initially considered as transcriptional noise, have been widely studied, due to the remarkable progress of genome sequencing technology. CircRNAs are characterized by circular loops, which covalently link the 5′ and 3′ ends together. With this special structure, circRNAs are difficult to be degraded by RNA enzyme. The initial detection of circRNAs in eukaryotes was performed in 1979.[1] Subsequently, numerous studies have revealed that circRNAs had a close relationship with a wide range of cancers and played a crucial role in the progression of tumors.[2] Studies found circRNAs worked as competitive endogenous RNAs to compete for micro RNA (miRNA) then affect miRNA's function.[3,4] For example, circular RNA-7 (ciRS-7) acts as a sponge for micro RNA-7 (miR-7) and inhibit miRNA-7 activity. In gastric cancer, upregulation of ciRS-7 inhibited the effect of miR-7 through PTEN/PI3K/AKT signaling.[5]

Among cancer-related circRNAs, has_circ_0001649 is a novel circRNA in cancer research.[6–16] It is the transcription of *SHPRH* which is a gene with an official full name SNF2 histone

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linker PHD RING helicase and was identified in 2003 by Sood.[17] Based on current studies, SHPRH is considered to be a tumor suppressor gene and plays a negative role in regulating tumor cell development.[17,18] At present, several researches have demonstrated that has_circ_0001649 is under-expression in multiple types of cancer, such as pancreatic ductal adenocarcinoma and colorectal cancer.[9,14] Furthermore, previous studies have found its role in tumor diagnosis and prognosis aspects, suggesting that it may be a good tumor marker.[6,7,9–15]

At present, several meta articles have analyzed the diagnostic value of circRNAs in cancer,[19,20] but mainly focused on the researches about all circRNAs rather than a single one specifically. Therefore, our research is the first study to elaborate on the relationship between a specific circRNA has_circ_0001649 and cancer systematically. The main purpose is to verify the diagnostic and prognostic roles of has_circ_0001649 and the relationship between its expression and tumor differentiation grade.

2. Material and methods

The present meta-analysis was conducted according to the preferred reporting items for a systematic review and meta-analysis.[21] Ethical approval was not necessary for this study was based on existing literature not including human participants and animals.

2.1. Search strategy

Retrieval of PubMed, Web of Science and EmBase databases by computer is scheduled for August 1st, 2019. Because of the variety of cancer, this study scoured the literatures on all types of tumors and screened out all those related. The retrieval strategies were "has_circ_0001649," "circ_0001649," and "tumor," "cancer," "carcinoma." To prevent omission, we also retrieved the studies of SHPRH in cancer. The following search terms were used: "SHPRH," "SNF2 histone linker PHD RING helicase," "tumor," "cancer," "carcinoma."

2.2. Literature inclusion and exclusion criteria

Inclusion criteria:

the subjects of the study were has_circ_0001649 and solid cancer;

all malignancies were confirmed by pathology;

patients did not receive radiotherapy or chemotherapy before collecting specimens;

health control group; and

similar studies published by the same research center or author selected the most influential factors.

Exclusive criteria:

summary;

conference papers, abstracts, and lectures;

animal or cell experiments;

sample size <10.

2.3. Extracted data and quality assessment

Two investigators (GT and NL) extracted the following information from each publication: author, year of publication, area, expression, specimens, test method, cut-off value, number of cases, survival analysis, sensitivity, specificity, and hazard ratio (HR). The quality of all diagnostic studies was assessed by the quality assessment of diagnostic accuracy studies-2 criteria,[22] and the quality of selected prognostic studies was assessed using the Newcastle–Ottawa scale.[23]

2.4. Statistical analysis

Analytical software Meta-Disc (version 1.4)[24] and STATA (version 12.0) were used to analyze the diagnostic and prognostic value of has_circ_0001649. First, pooled sensitivity, specificity, positive likelihood ratio (PLR), negative likelihood ratio (NLR), and diagnostic odds ratio (DOR) with their 95% confidential intervals (95% CIs) were calculated. Pooled sensitivity and specificity of each study were plotted as summary receiver operator characteristic (SROC) curves to evaluate diagnostic effects.[25] Then area under the curves (AUCs) of SROC curves and the maximum point of intersection between sensitivity and specificity (Q-value) were auto-generated. Heterogeneity was examined using an I-squared test ($P < .1$ or I-squared $> 50\%$ indicated significant heterogeneity).[26] We used a fixed-effect model in the minimal heterogeneity (I-squared $< 50\%$) and a random-effects model in the significant heterogeneity (I-squared $> 50\%$). The threshold effect was quantified by the Spearman correlation analysis. Deeks' funnel plot was used to check the potential publication bias ($P < .05$ showed statistically significant publication bias).[27]

For prognostic analysis, multivariate analysis was employed to avoid the confounding of exposure effects. Heterogeneity of combined HRs was performed using the Cochran's Q test and Higgins I-squared statistic. A fixed model was needed in the significant heterogeneity when $P > .10$ or I-squared $< 50\%$.[28] Otherwise, a random-effects model was used.[29] Furthermore, the Begg funnel plots were used to evaluate the publication bias.[30] Sensitivity analysis was used to examine the stability of the pooled results.

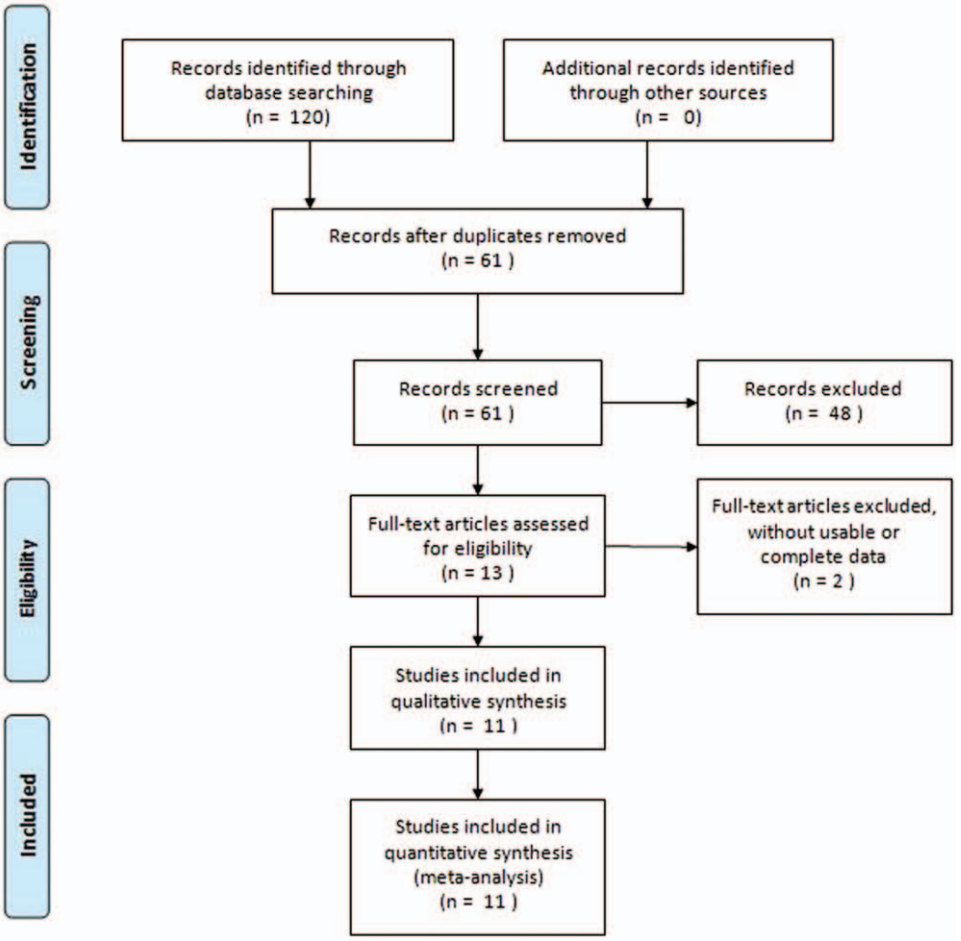
3. Results

3.1. Eleven eligible published studies were enrolled after information retrieving

The flow diagram for the literature search is presented in Figure 1A. Based on the inclusion criteria, 11 eligible published studies were enrolled in this meta-analysis.[6–16] Among the included studies, 4 were about has_circ_0001649 in tumor diagnosis aspect.[6,7,9,10] With respect to prognosis, 5 were related to overall survival (OS).[11–15] Six studies were included for evaluating the relationship between the expression of has_circ_0001649 and tumor differentiation grade.[8,11–14,16]

3.2. Potential diagnostic value of has_circ_0001649 in solid tumor

A total of 4 publications involving 279 cases were analyzed. The main characteristics of all included studies are shown in Table 1. The quality assessment results of the diagnostic studies are shown in Figure 1B. The expression of has_circ_0001649 was detected using quantitative real-time reverse transcription PCR (qRT-PCR) in these studies. A meta-analysis of the sensitivity, specificity, PLR, NLR, DOR, and SROC for has_circ_0001649 was conducted. We analyzed pooled sensitivity and specificity by using fixed effect model due to the low heterogeneity (I-squared =



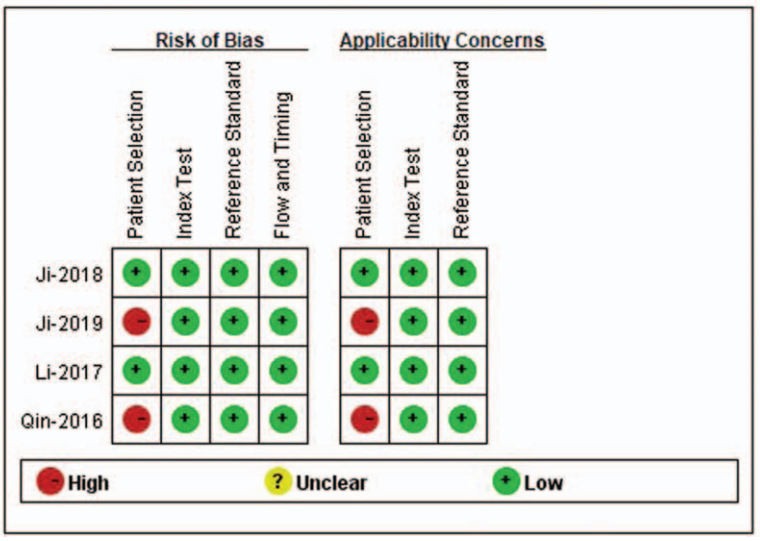


Figure 1. (A) A flowchart of literature search and study selection. (B) QUADAS-2 of included diagnostic studies. QUADAS-2 = quality assessment of diagnostic accuracy studies 2.

12.9% and 27.1%, separately). Pooled sensitivity and specificity were 0.78 (0.73–0.83) and 0.75 (0.70–0.80), respectively. Pooled PLR and NLR were also calculated, which were considered to be more valuable than the sensitivity or specificity in clinical application, the results for which were 3.17 (2.56–3.93) and 0.29 (0.23–0.36) (Fig. 2). DOR value was 11.41 (7.80–16.7) (Fig. 3A). Corresponding area under SROC curve (AUC) was calculated to be 0. 8408 ($Q = 0.7725$), revealing a moderate diagnostic

Table 1

Main characteristics of the diagnostic studies included in the meta-analysis.

Author	Year	Country	Cancer type	Sample size		Specimens	Method	Cutoff value	Sen	Spe	AUC	TP	FP	FN	TN
				Case	Control										
Qin	2016	China	Hepatocellular cancer	89	89	Tissue	qRT-PCR	0. 0007855	0. 81	0. 69	0. 63	72	28	17	61
Li	2017	China	Gastric cancer	76	76	Tissue	qRT-PCR	0. 2269225	0. 711	0. 816	0. 834	54	14	22	62
Ji	2018	China	Colorectal cancer	64	64	Tissue	qRT-PCR	0. 2784690288	0. 828	0. 781	0. 857	53	14	11	50
Ji	2019	China	Colorectal cancer	50	50	Tissue	qRT-PCR	0. 328	0. 80	0. 74	0. 828	40	13	10	37

AUC = area under the curve, FN = false negative, FP = false positive, Sen = sensitivity, Spe = specificity, TP = true positive, TN = true negative.

accuracy (Fig. 3B). The threshold effect was also considered in this study. Spearman correlation coefficient was 0.400, and the *P*-value was .600, suggesting that there was no heterogeneity from the threshold effect. Deeks' funnel plot was conducted to evaluate the publication bias. The shape of funnel plots showed symmetry for all included studies and the *P*-value of Deeks' test was .489 (Fig. 3C). The result suggested no evidence of publication bias in this analysis.

3.3. High expression of has_circ_0001649 predicted better OS in solid tumors

There were 5 studies included for evaluating OS, main features of which were presented in Table 2. Has_circ_0001649 was investigated by qRT-PCR. Due to the low heterogeneity (*I*-squared = 0.0%), a fixed model was selected for evaluating OS. High expression of has_circ_0001649 predicted better OS in solid tumor (HR: 0.45; 95% CI, 0.324–0.626, $P < .01$) (Fig. 4A). Sensitivity analysis was also conducted which showed the result was stable after removing each single study (Fig. 4B). Finally, the Begg funnel plot was applied to assess the publication bias. The *P*-value of the Begg test for OS was .086, indicating no obvious publication bias for evaluating OS (Fig. 4C).

3.4. Lower expression of has_circ_0001649 is associated with lower tumor differentiation grade

Six studies included in this research for evaluating the relationship between the expression of has_circ_0001649 and tumor differentiation grade. The characteristics of the included studies were presented in Table 3. To unify classification and facilitate statistics, we equated grade I and II with well-differentiated and moderately-differentiated. Grade III and IV were equivalent to poorly differentiated and undifferentiated. Given that there was no severe heterogeneity across these studies (*I*-squared = 42.9%, $P = .119$), a fixed model was used. The result demonstrated that lower expression of has_circ_0001649 predicted lower differentiation grade in solid tumors (OR: 2.58; 95% CI, 1.71–3.91, $P < .01$) (Fig. 5A). Sensitivity analysis was performed to assess whether the individual study affected the overall results. The results showed that individual study had little influence on our final results (Fig. 5B). We used the Begg test to evaluate the publication bias. The *P*-values of Begg test was .707, indicating no obvious publication bias for evaluating the relationship between the expression of has_circ_0001649 and tumor differentiation grade (Fig. 5C).

4. Discussion

Recent studies have found that has_circ_0001649 acts as a biomarker for detection and prognosis.[6–16] Consistently, our findings support this point of view. According to our knowledge, the present article is the first meta-analysis of a specific circRNA has_circ_0001649 directing at its diagnostic/prognostic value and the relationship between its expression and differentiation grade in tumors.

Through statistical analysis, the pooled sensitivity and specificity and DOR were calculated. We got a high value of DOR which indicates a better diagnostic accuracy and shows the diagnostic significance of has_circ_0001649 in solid tumor. Another

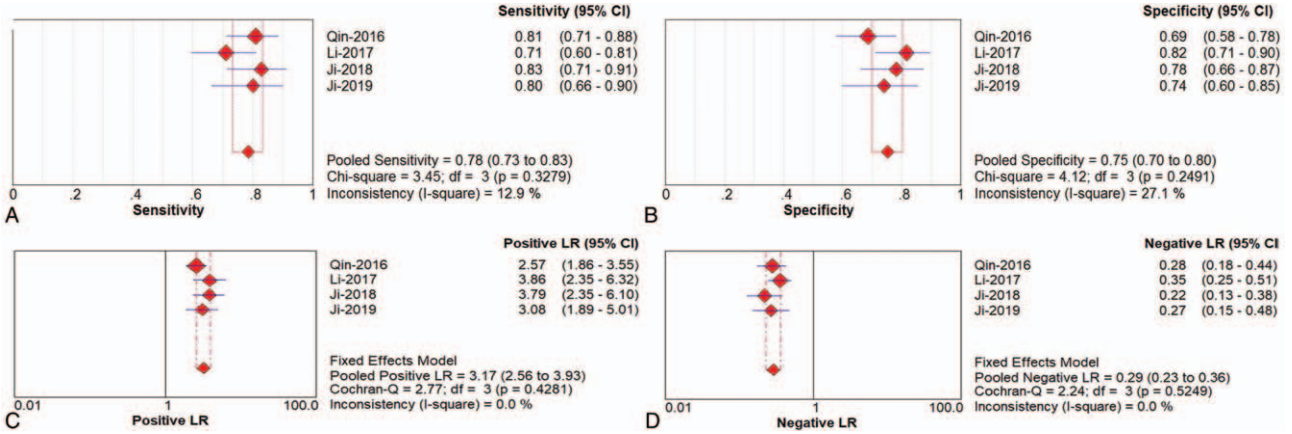


Figure 2. Forest plots of diagnostic accuracy index for has_circ_0001649 in solid cancer. Notes: (A) Sensitivity. (B) Specificity. (C) PLR. (D) NLR. NLR = negative likelihood ratio, PLR = positive likelihood ratio.

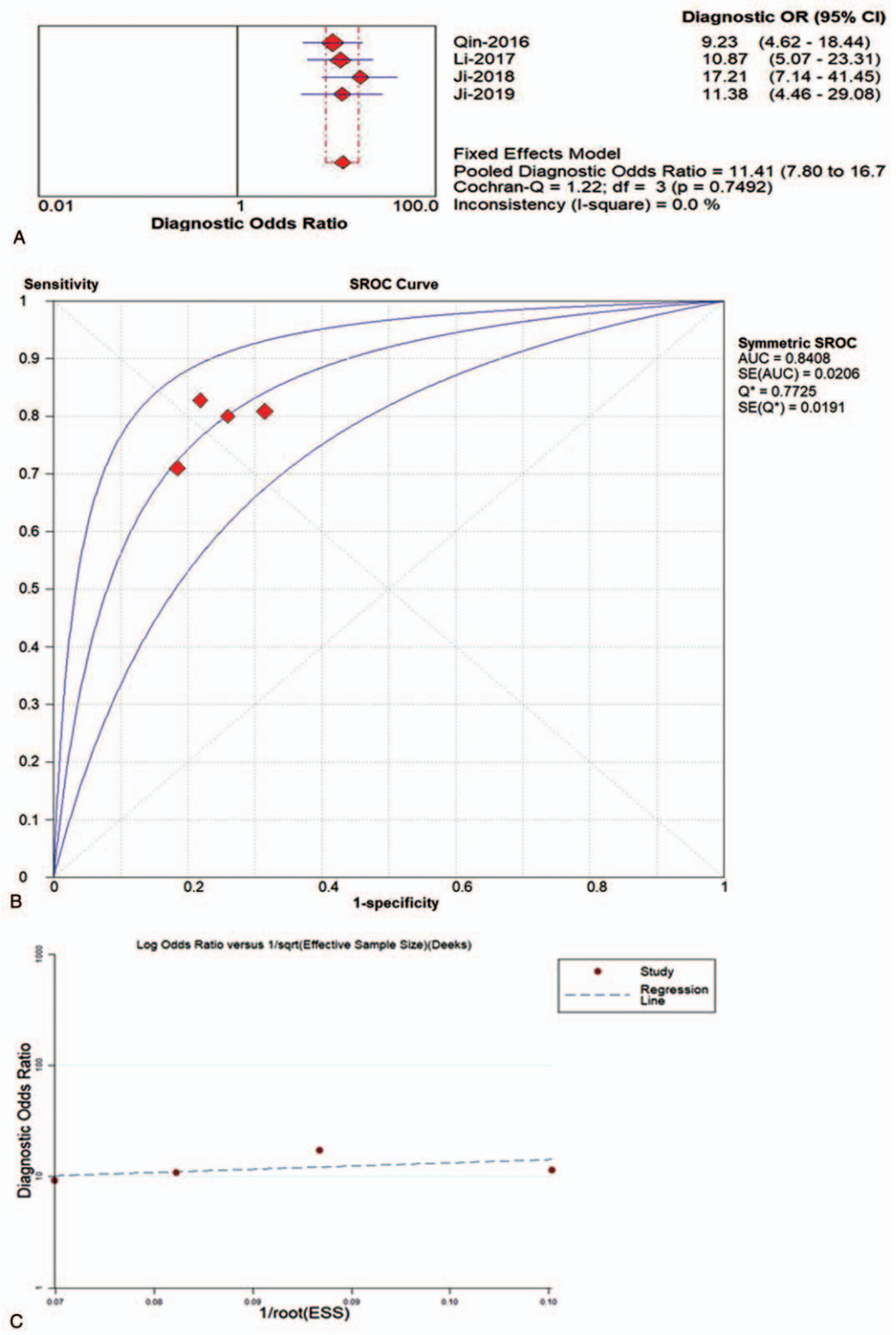


Figure 3. (A) DOR of has_circ_0001649 in solid cancer. (B) SROC curve of has_circ_0001649 in solid cancer. (C) Deeks' funnel plot evaluating the potential publication bias of the included studies. DOR = diagnostic odds ratio, SROC = summary receiver operator characteristic curve.

diagnostic parameter AUC was also calculated to assess the overall test performance. Our AUC was 0.8408, which indicated a moderate diagnostic accuracy overall. Additionally, there was no publication bias and threshold effect. In another important aspect, we summarized and analyzed has_circ_0001649's prognostic role in cancer. The pooled HR was 0.45 (0.324–0.626), which indicated that elevated expression of has_circ_0001649 was associated with better survivals for cancer patients. Sensitivity

Table 2

Main characteristics of the prognostic studies included in the meta-analysis.

Author	Year	Country	Cancer type	Regulation	Sample size	Specimens	Method	Cutoff value	Survival Analysis	survival	HR(95% CI)	Quality (NOS)
Wang	2018	China	Glioma	Down	64	Tissue	qRT-PCR	Median	Multivariate	OS	0. 497(0. 250–0. 988)	7
Xing	2018	China	Retinoblastoma	Down	60	Tissue	qRT-PCR	Median	Multivariate	OS	0. 442(0. 218–0. 893)	7
Liu	2018	China	NSCLC	Down	53	Tissue	qRT-PCR	Mean	Multivariate	OS	0. 471(0. 238–0. 945)	7
Jiang	2018	China	PDAC	Down	58	Tissue	qRT-PCR	Mean	Multivariate	OS	0. 502(0. 261–0. 966)	7
Zhang	2018	China	Hepatocellular cancer	Down	77	Tissue	qRT-PCR	NR	Multivariate	OS	0. 191(0. 053–0. 682)	6

NR = not reported, NSCLC = non-small cell lung cancer, OS = overall survival, PDAC = pancreatic ductal adenocarcinoma.

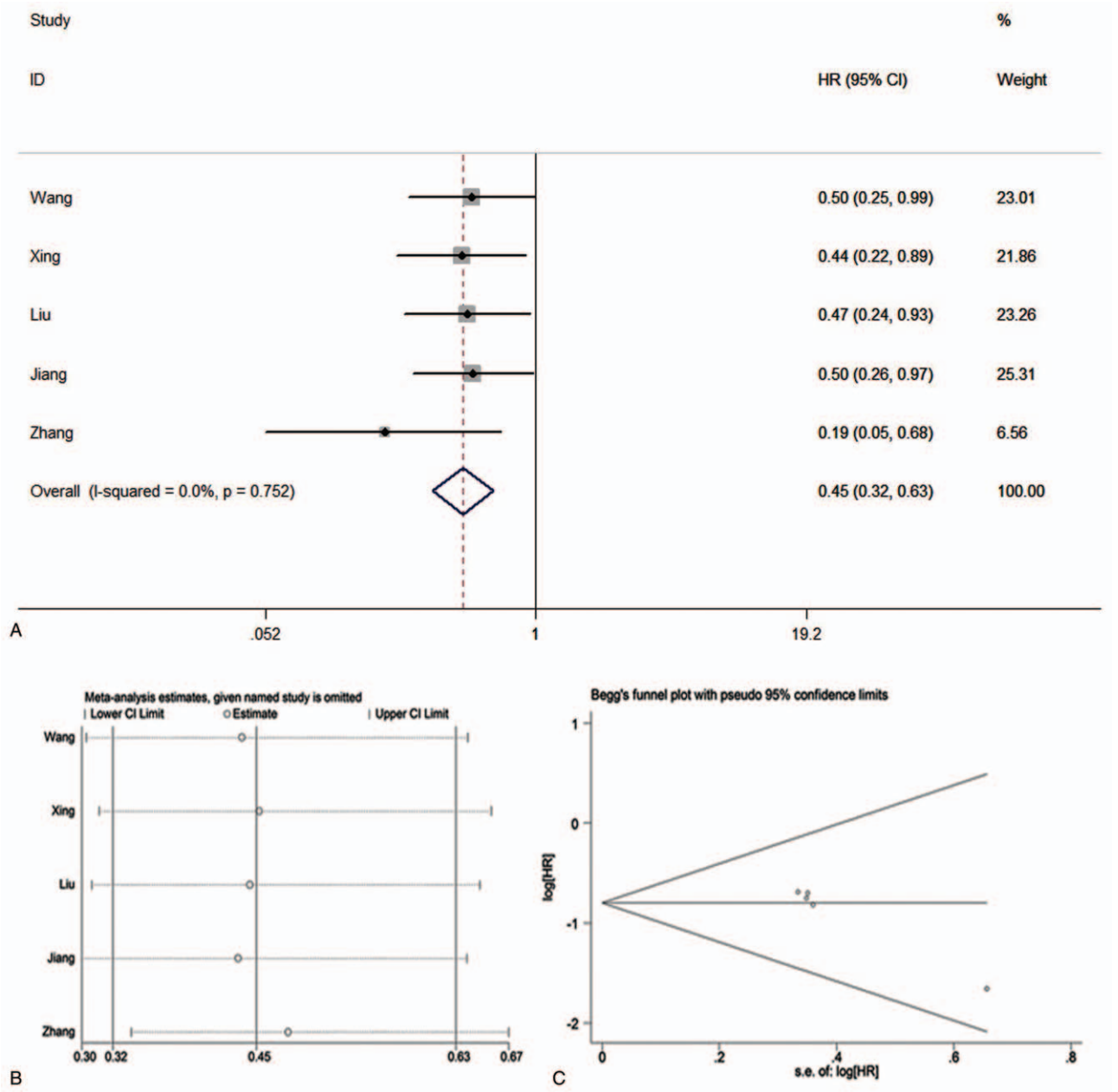


Figure 4. (A) Forest plot for the association between has_circ_0001649 expression with OS in solid cancer. Sensitivity (B) and publication bias (C) for OS. OS = overall survival.

analysis confirmed the results. Furthermore, we found that lower expression of has_circ_0001649 predicted lower tumor differentiation grade. Given the above findings, we speculate that has_circ_0001649 may be an outstanding tumor diagnostic and prognostic factor.

According to recent studies, circRNAs served as good candidates for tumor biomarkers with high specificity and sensitivity. More and more circRNAs have been studied in cancer diagnosis and prognosis analysis, and good outcomes have been obtained,[31–33] which may be associated with remarkable characteristics of circRNAs. CircRNAs are stable due to the RNase R resistance. The half-life of circRNAs is quite long, even up to 48 hours.[34] So the expression of circRNAs is in a relatively high level. In some cases, the abundance of circular molecules even exceeds the relative linear mRNA >10 folds.[35] Most importantly, circRNAs could influence the pathogenesis of tumor through miRNA or corresponding gene. Take has_circ_0001649 for example, it could inhibit tumor progression via sponging miR-331-3p and miR-338-5p in non-small cell lung cancer,[13] and it was also revealed to function as a tumor-suppressor gene in gastric cancer, pancreatic ductal adenocarcinoma, and HCC.[5,14,15] Moreover, as the gene that coding Has_circ_0001649, SHPRH was found to be truncated or contain missense mutations in tumor cell lines, which is consistent with a tumor-suppressor function.[36] Surprisingly, researchers found that has_circ_0001649

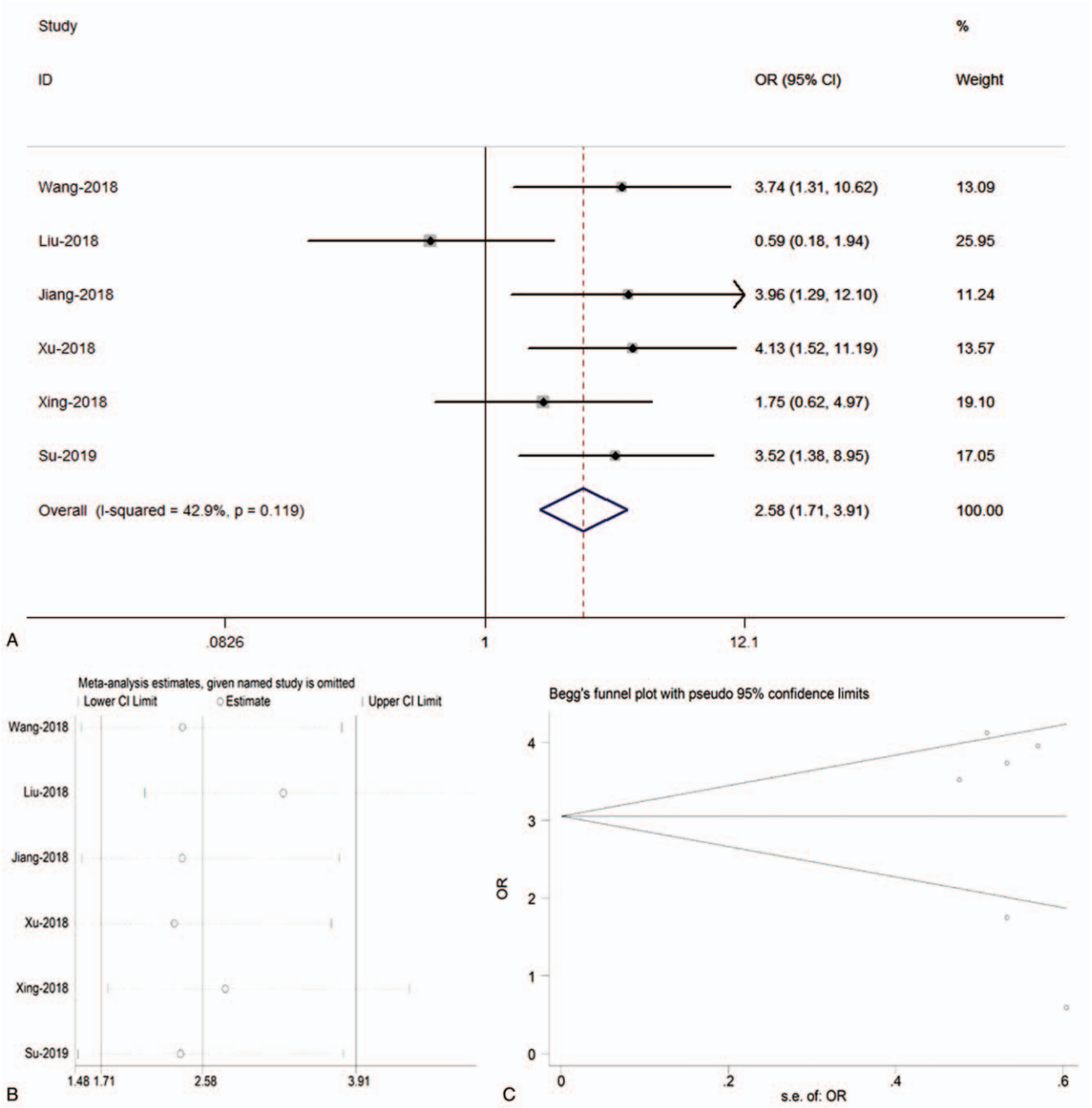


Figure 5. (A) Forest plot for the association between has_circ_0001649 expression with tumor differentiation grade. Sensitivity (B) and publication bias (C) for tumor differentiation grade.

Table 3

Main characteristics of the studies showed the relationship between has_circ_0001649 and differentiation grade included in the meta-analysis.

Author	Year	Country	Cancer type	Differentiation grade	No	Has_circ_0001649 expression		*P*-value
						High	Low	
Wang	2018	China	Glioma	I II	28	19	9	. 023
				III IV	36	13	23	
Xing	2018	China	Retinoblastoma	Well/moderately	24	14	10	. 430
				Poorly/undifferentiated	36	16	20	
Liu	2018	China	NSCLC	Well/moderately	18	6	12	. 557
				Poorly/undifferentiated	35	16	19	
Jiang	2018	China	PDAC	Well/moderately	27	18	13	. 018
				Poorly/undifferentiated	31	7	20	
Xu	2018	China	Cholangiocarcinoma	Well/moderately	27	18	9	. 008
				Poorly/undifferentiated	49	16	33	
Su	2019	China	Hepatocellular carcinoma	Well/moderately	52	32	20	. 013
				Poorly/undifferentiated	32	10	22	

could be translated into a 17 KD protein (SHPRH-146aa) in glioma, due to it containing an open reading frame. SHPRH-146aa is also downregulated and acts as a tumor suppressor and prognostic markers in human glioblastoma as well as SHPRH.[37] Perhaps, with the further studies of this protein, more clinical significance may be excavated and has_circ_0001649's clinical application of has_circ_0001649 will be promoted.

However, there are some limits in its clinical application. In the studies included in our research, as a biomarker, has_circ_0001649 expression level in tissues samples was used to determine its relationship with tumor diagnosis and prognosis, and it will be better applied in clinic if has_circ_0001649 level could be directly detected by a noninvasive method, such as in plasma or serum. As yet no consensus about defining the expression degree of has_circ_0001649 has been reached. Therefore, more problems need to be solved for clinical application of has_circ_0001649.

Although we had made great efforts to complete the analysis, it still has several limitations. First, the number and the sample size of included studies are relatively small, and more large-scale clinical researches are still needed to enrich and verify our outcome. Second, all the enrolled studies are Chinese population, thus the results can only be representative Chinese cancer patients. Third, we could not carry out subgroup analysis to excavate for more meaningful conclusions due to the small sample size. Finally, although significant publication bias was not detected, considering most of the 11 articles included were all positive data, there may be potential publication bias in our study.

5. Conclusion

In summary, the role of this new circRNA, has_circ_0001649, in the diagnosis and prognosis of tumors is comprehensively evaluated by meta-analysis. Has_circ_0001649 could be a potential and promising diagnostic and prognostic biomarker for tumor. To make it genuinely translate into clinical practice, more related basic researches and multiracial studies are needed.

Author contributions

Conceptualization: Guang Li, Nan Li.
Data curation: Guangwei Tian, Lin Guan.
Formal analysis: Guangwei Tian, Lin Guan.
Funding acquisition: Nan Li.
Investigation: Guangwei Tian, Nan Li.
Methodology: Guangwei Tian, Lin Guan.
Project administration: Nan Li.
Software: Zihui Wang.
Writing – original draft: Guangwei Tian, Nan Li.
Writing – review and editing: Guang Li, Zihui Wang.

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