Meta-Analysis of Observational Studies in Epidemiology

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The prognostic and diagnostic values of MicroRNA-10b in gastric cancer

A comprehensive study based on meta-analysis and TCGA database

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Abstract

We conducted a study to evaluate the prognostic and diagnostic values of microRNA-10b (miR-10b) in gastric cancer (GC) based on meta-analysis and TCGA database. Relevant studies were searched in English and Chinese database and meta-analysis was conducted on Stata 12.0. The expression value of miR-10b and clinical parameters of GC patients were downloaded from TCGA database, and relevant analyses were conducted on SPSS. High expression of miR-10b was linked with unfavorable overall survival (OS) in GC (HR = 1.572, 95% CI: 1.240–1.992, $P < .001$). However, the meta-analysis was significant for patients in early stage, but not for patients in advanced stage. The expression of miR-10b-3p was significantly lower in cancer tissue compared with adjacent tissue ($P < .001$). Meanwhile, the area under the ROC curve (AUC) value was 0.652 (0.562–0.742), $P = .001$. Disease-free survival analysis showed increasing miR-10b-5p was correlated with worse survival outcome (HR = 2.366, 95% CI: 1.414–3.959, $P = .001$). In conclusion, miR-10b acts as a tumor suppressor with prognostic and diagnostic values for GC.

Abbreviations: CBM = China Biology Medicine disc, CNKI = China National Knowledge Infrastructure, DFS = disease free survival, GC = gastric cancer, ISH = in situ hybridization, miRNAs, microRNAs, OS = overall survival, TCGA = The Cancer Genome Atlas.

Keywords: gastric cancer, meta-analysis, MicroRNA-10b, TCGA

1. Introduction

Gastric cancer (GC) is the fifth most common cancer worldwide, and the third most common cause of all cancer deaths.[1] About 1 million people are diagnosed with GC worldwide each year,[2] which cause a high disease burden worldwide.[3] Both genetic and environmental factors are important to the development of GC. Even if improvements in chemotherapy and radiotherapy have been achieved, the average 5-year survival rate for GC patients is less than 40% because of late diagnosis.[4,5] Identifying a reliable marker is important for GC diagnose and prognosis.

MicroRNAs (miRNAs) are small non-coding RNAs, which play a vital role in the pathogenesis of GC.[6–8] Several miRNAs, including miR-1246,[9] miR-421,[10] and miR-515-3p,[11] have been identified as diagnostic markers for GC. miR-10b is located in the homeobox gene cluster which belongs to the transcriptional regulator family.[12] The impact of miR-10b has been explored in several cancers, including colorectal cancer,[13] hepatitis B-related liver cancer,[14] and breast cancer.[15] Recently, several studies[16,17] have explored the relationship between miR-10b and GC. However, the sample size is not enough.

Meta-analysis is a well methodology for pooling the results of different research.[18] Thus, a meta-analysis on the impact of miR-10b on GC was conducted in this study, and data from The Cancer Genome Atlas (TCGA) was used to verify the results. This study is aimed at clarifying the diagnostic and prognostic values of miR-10b in GC.

2. Methods

This study was conducted following the Meta-Analysis of Observational Studies in Epidemiology (MOOSE) guidelines. The ethical approval is not required, because this meta-analysis was conducted through reviewing issued papers.

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LM and ZL contributed equally to this work and should be considered as co-first authors.

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All authors declare that there was no conflict of interest.

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2.1. Search strategy

Relevant studies were searched in PubMed, Web of Science, Science Direct, Cochrane Central Register of Controlled Trials, Wiley Online Library and Chinese Databases, including China National Knowledge Infrastructure (CNKI), China Biology Medicine disc (CBM), Chongqing VIP and Wan Fang Data (updated on November 5, 2019) using the following keywords (miR-10b OR miRNA-10b OR microRNA-10b OR miR10b OR miRNA10b OR microRNA10b OR "miR 10b" OR "miRNA 10b" OR "microRNA 10b") and (malignan* OR cancer OR tumor OR tumor OR carcinoma OR adenocarcinoma) and (digestive OR gastric OR stomach). Similar meta-analyses, reviews and references cited in these studies were also evaluated for eligible studies. The searches were performed by 2 authors independently, and any disagreement was resolved through discussion.

2.2. Inclusion and exclusion criteria

Included studies met the following inclusion criteria:

1. study of GC patients, and the expression value of miR-10b was detected;
2. survival analysis or clinicopathological parameters were assessed based on miR-133a expression, and
3. sufficient data was provided to conduct meta-analysis.

The exclusion criteria:

1. miR-10b was combined with other biomarkers to be investigated, and
2. no sufficient data for meta-analysis.

2.3. Data extraction

All data was acquired independently by 2 authors. The following information was collected from included studies: first author, year of publication, country, sample source, stage, detection method, case, follow-up time, survival index, statistical method, HR as well as 95% CI, and the survival outcome of the high miR-10b expression group. When both univariate and multivariate HR were available, the multivariate were chosen. If only Kaplan–Meier curve was available, HR and 95% CI were calculated by the previous method.[19] The Newcastle-Ottawa quality assessment scale was used to evaluate the quality of the included studies.[20] Meanwhile, relevant data of miR-10b (including miR-10b-5p and miR-10b-3p) in GC patients was collected from TCGA database (https://cancergenome.nih.gov/).

3. Statistical analysis

The prognostic value of miR-10b for GC was investigated by pooled HRs with 95% CI. High expression group was set as the case group, and HR > 1 with 95%CI not overlapping 1 predicted worse survival outcome for the case group. Considering there were many heterogeneities among included studies which led to heterogeneity among individual HRs, pooled HRs were calculated under random-effect model.[21] Meta-analysis was performed by the Stata 12.0 software (Stata Corporation, TX, USA). Based on TCGA data, the relationship between clinicopathological parameters and miR-10b expression value was evaluated by the independent T test. The diagnostic value of miR-10b was assessed by the ROC curve. Survival analysis was investigated by Cox regression. Patients were divided into high or low expression group according to the mean expression level of miR-10b. All statistical analyses were conducted by SPSS statistical software package, version 21.0 (IBM Corporation, Armonk, NY, USA), and $P < .05$ indicated statistically significant.

4. Results

4.1. Increasing miR-10b was associated with unfavorable survival outcome

Literature search totally identified 103 relevant articles. After reviewing titles and abstracts, 37 studies were found to be duplicated publications and 25 studies did not investigate miR-10b or GC. Thus, 41 unique publications were remained for full text review, 19 articles were removed as review or meta-analysis, and 16 studies were excluded for not investigating survival outcome or clinicopathological parameters. After further analyses of the remaining 6 potential studies, 2 studies without sufficient data were excluded. Finally, 4 studies with 768 GC patients were included in this meta-analysis.[12,16,17,22]Figure 1 showed the flow chart of literature search. Among the included articles, all studies analyzed overall survival (OS) and only 2 studies assessed disease-free survival (DFS).[16,17] Of 4 studies, 3 were from China, 1 was from Czech. Three studies assessed tissue samples, 1 assessed serum samples. Two studies tested samples by in situ hybridization (ISH), others used qRT-PCR. The characteristics of included studies were summarized in Table 1.

We evaluated 4 studies which assessed OS based meta-analyses, the result showed that high expression of miR-10b was significantly associated with unfavorable OS (HR = 1.572, 95% CI: 1.240–1.992, $P < .001$, $I^2 = 47.1\%$) (Fig. 2A, Table 2). Besides DFS which had been investigated in 2 studies was also analyzed, but no statistical significance was detected (HR = 1.497, 95% CI: 0.795–2.819, $P = .212$, $I^2 = 40.7\%$) (Fig. 2B, Table 2). According to different test methods, we conducted further analysis on qRT-PCR and ISH studies, and HR was 1.272 (95% CI: 0.569–2.841, $P = .558$, $I^2 = 73.4\%$) and 1.664 (95% CI: 1.320–2.098, $P < .001$, $I^2 = 32.0\%$), respectively (Fig. 2C-D, Table 2). In addition, subgroup meta-analyses were conducted on specific cancer stage I-IV, and pooled HRs in these 3 subgroups were found to be 2.023 (95% CI: 1.493–2.74, $P < .001$, $I^2 = 0\%$), 2.632 (95% CI: 1.557–4.446, $P = .001$, $I^2 = 0\%$), 1.363 (95% CI: 0.959–1.937, $P = .084$, $I^2 = 0\%$) and 1.175 (95% CI: 0.799–1.727, $P = .412$, $I^2 = 83.9\%$), respectively (Fig. 3, Table 2). Meanwhile, survival data of GC patients from TCGA was also analyzed based on miR-10b expression, and high expression of miR-10b-5p was significantly linked with worse DFS (HR = 2.366, 95% CI: 1.414–3.959, $P = .001$) (Fig. 4A, Table 3). However, no statistical significance was observed in other survival outcomes, and the HRs were 1.296 (95% CI: 0.933–1.801, $P = .122$), 1.254 (95% CI: 0.905–1.736, $P = .173$) and 0.848 (95% CI: 0.53–1.356, $P = .49$) for miR-10b-5p in OS, miR-10b-3p in OS, and miR-10b-3p in DFS, respectively (Fig. 4B-D, Table 3).

4.2. MiR-10b with diagnostic value for GC

Three hundred eighty six GC patients were enrolled from TCGA. As shown in Table 4, the expression of miR-10b-3p was

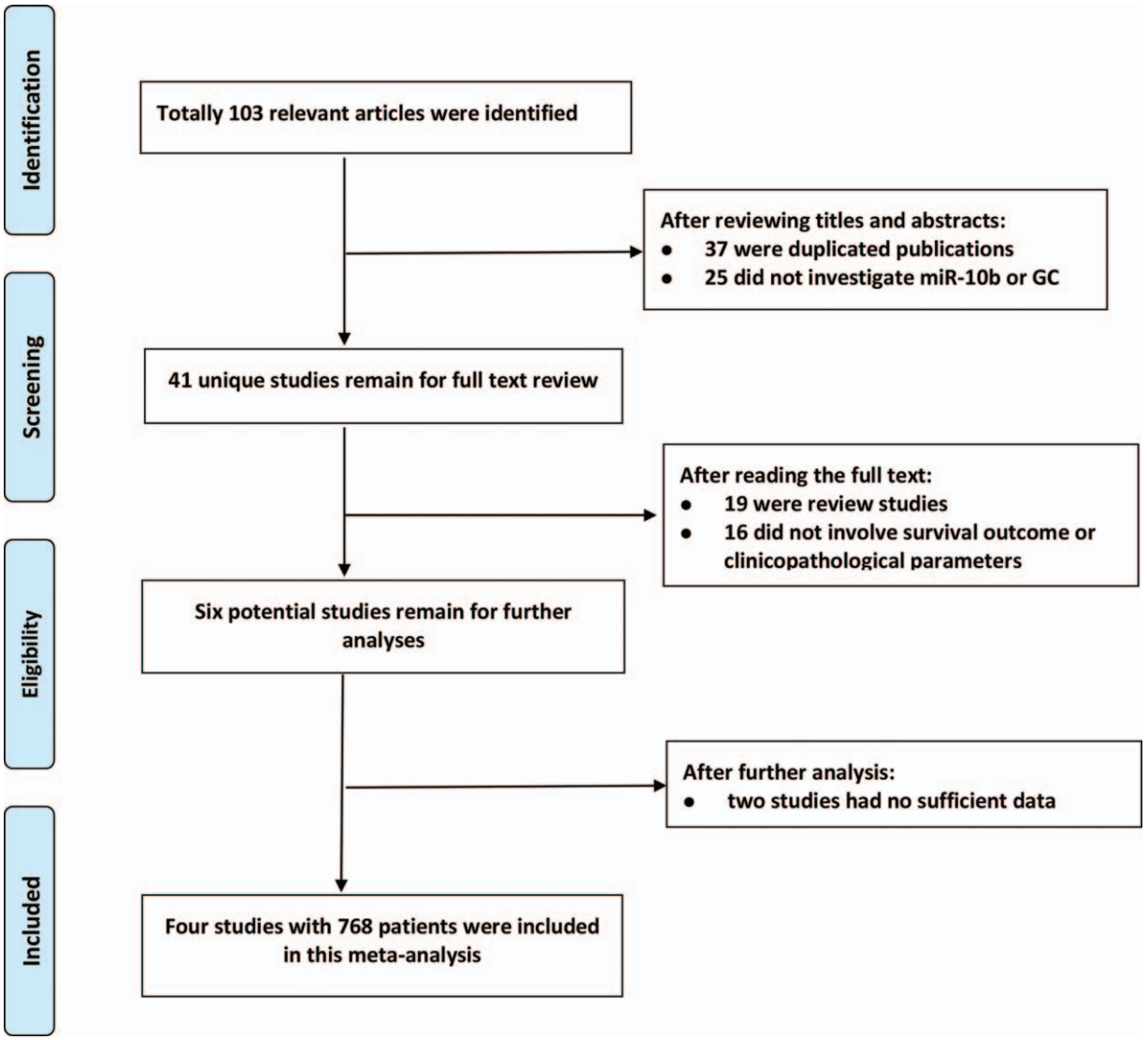

Figure 1. Flow chart showing the selection process for the including studies.

significantly lower in cancer tissue compared with adjacent tissue ($P < .001$). The ROC curve showed a diagnostic value of miR-10b-3p for GC ($P = .001$), and the optimum diagnostic point with sensitivity and specificity were also showed in Table 3. Corresponding information of miR-10b-5p for GC was summarized in Table 3, and the relationships between miR-10b and clinicopathological parameters were also showed in Table 4.

5. Discussion

Studies have identified that aberrant expression of miRNAs can be used for diagnose and prediction of prognosis in many cancers, including GC. miR-10b is imbedded in HOX gene clusters on chromosomes 2q.[23] Until now, several meta-analyses concluded that expression of miR-10b can predict outcomes in some types of cancer.[24–26] However, these meta-analyses did not include GC study. In 2017, Huang et al[27] included 1 GC study[22] and conducted a meta-analysis to show expression of miR-10b strongly predicts poor prognosis for patients with cancers. To the best of our knowledge, this is the first meta-analysis to explore prognostic value of miR-10b in GC. Moreover, data from TCGA was used for validation. We also analyzed diagnostic value of miR-10b in GC by TCGA data analysis. In this study, our meta-analysis demonstrated that high expression of miR-10b was associated with poor OS, but not with DFS. Further TCGA data analysis showed that high expression of miR-10b-5p was related with poor DFS and miR-10b-3p can be a diagnostic marker for GC.

Overall, we observed an association between expression of miR-10b and OS in GC patients. Further subgroup analyses showed high expression of miR-10b related with poor OS in GC patients with stage I or stage II. These results suggested that expression of miR-10b in GC should be noted in stage I or stage II patients, which can be a prognostic marker for those patients. In addition, we found that there was no difference between the expression of miR-10b and DFS in GC patients. This might be caused by the small sample size. Thus, more studies about the relationship between miR-10b and DFS are needed in the future. Further subgroup analysis was conducted based on test methods.

Table 1

The characteristics and quality score of included studies.

Author	Year	Country	Sample source	Stage	Test method	Case	Follow-up (month)	Survival	Statistic method	HR	LL	UL	Outcome	NOS
Wang Y	2013	China	Tissue	I	ISH	393	60–132	OS	Survival curve	1.868	1.245	2.532	Worse	6
				II	ISH					2.178	1.231	5.287	Worse	
				III	ISH					1.254	1.106	3.521	Worse	
				IV	ISH					1.147	0.893	2.385	NS	
Huang Z	2017	China	Serum	I-IV	qRT-PCR	188	50–65	OS	Survival curve	0.877	0.531	1.352	NS	7
								DFS		1.124	0.857	2.964	NS	
Gao Y	2018	China	Tissue	I	ISH	120	60	OS	Survival curve	2.512	1.352	4.364	Worse	6
				II	ISH					3.225	1.278	5.792	Worse	
				III	ISH					1.431	1.025	2.481	Worse	
				IV	ISH					1.221	0.705	2.437	NS	
Obermannova R	2018	Czech	Tissue	I-IV	qRT-PCR	67	100	OS	Univariate analysis	2.000	1.003	3.984	Worse	6
								DFS		2.155	1.053	4.831	Worse	

ISH = in situ hybridization, OS = overall survival, DFS = disease-free survival, HR, hazard ratio, LL = lower limit, UL = upper limit, * = outcome was for patient with high miR-10b expression, NS = not significant; NOS, the scores of Newcastle-Ottawa quality assessment scale.

Result showed expression of miR-10b related with OS in ISH group, but not in qRT-PCR group. One possible reason is that ISH group has more patients than qRT-PCR group, which can bring more statistical power.

In fact, there are 2 kinds of miR-10b, one is miR-10b-3p, and the other is miR-10b-5p. The 3p strand exists in the reverse position (3′→5′) and the 5p strand is located in the forward position (5′→3′). The role of miR-10b-3p has been investigated in

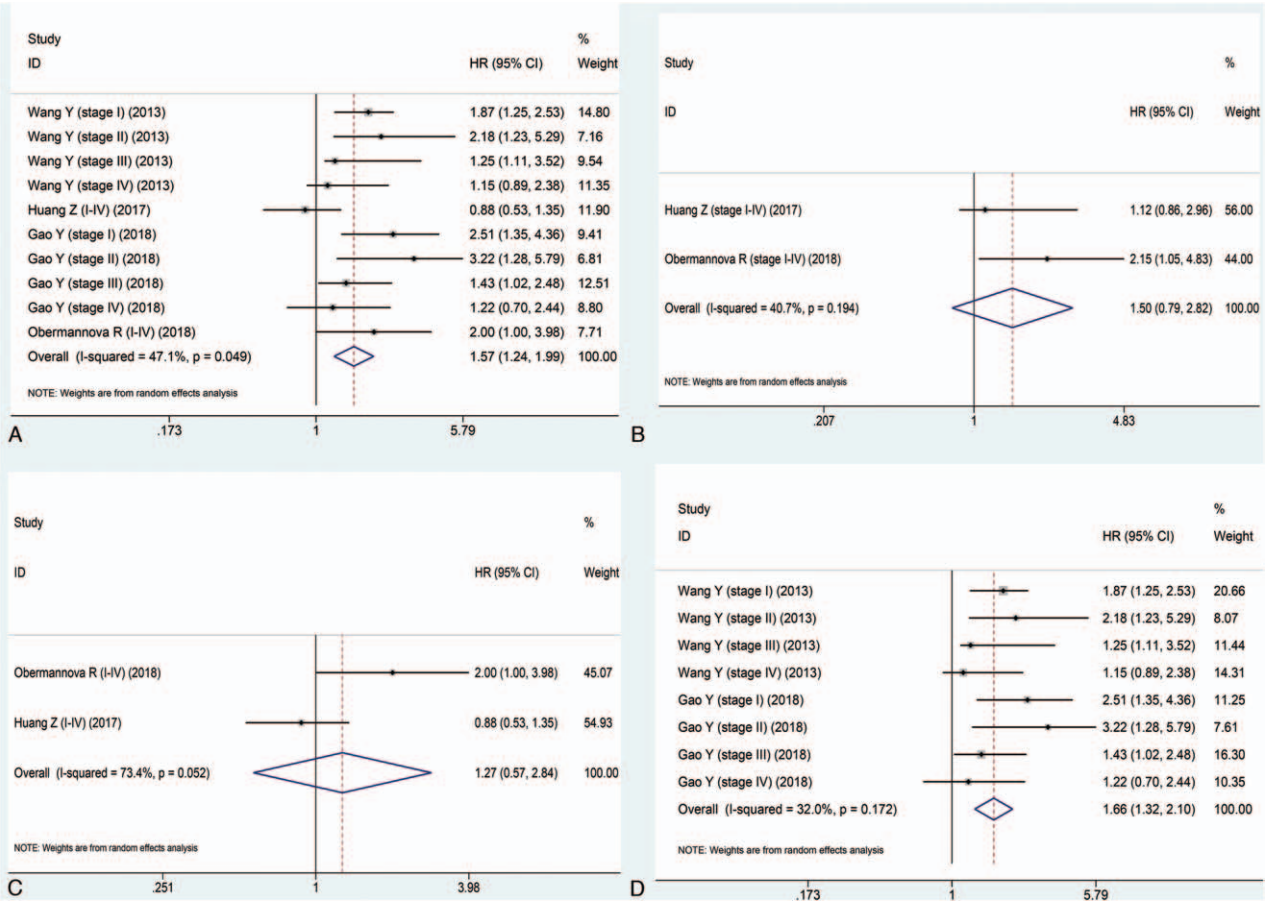

Figure 2. (A) Forest plot for the association between miR-10b expression and OS of GC; (B) Forest plot for the association between miR-10b expression and DFS of GC; (C) Forest plot for the association between miR-10b expression and OS of GC in qRT-PCR group; (D) Forest plot for the association between miR-10b expression and OS of GC in ISH group.

Table 2

Summarized HRs in this meta-analysis.

Survival (stage and method)	Number of patients	HR (95% CI)	*P* value	Heterogeneity test		Model
				I^2 (%)	*P* value	
OS (pooled stages and methods)	768	1.572 (1.240-1.992)	<.001	47.10%	.049	Random effect model
OS (pooled stages and qRT-PCR)	255	1.272 (0.569–2.841)	.5580	73.40%	.052	Random effect model
OS (pooled stages and ISH)	513	1.664 (1.320–2.098)	<.001	32.00%	.172	Random effect model
OS (stage I and ISH)	115	2.023 (1.493–2.74)	<.001	0.00%	.397	Random effect model
OS (stage II and ISH)	133	2.632 (1.557–4.446)	<.001	0.00%	.464	Random effect model
OS (stage III and ISH)	221	1.363 (0.959–1.937)	.0840	0.00%	.722	Random effect model
OS (stage IV and ISH)	44	1.175 (0.799–1.727)	.4120	0.00%	.877	Random effect model
DFS (pooled stages and qRT-PCR)	255	1.497 (0.795–2.819)	.2120	40.70%	.194	Random effect model

OS = overall survival, DFS = disease-free survival, ISH = in situ hybridization, HR = hazard ratio.

various cancers, and 1 study showed that miR-10b-3p expression levels were significantly unregulated in the esophageal squamous cell carcinoma tumor tissues.[28] Moreover, Yoon et al[29] identified that expression of serum miR-10b-3p may prove valuable in the diagnosis of hepatocellular carcinoma. Our TCGA data analysis found that miR-10b-3p is down-regulated in GC tissues compared with normal tissues. Further survival analysis showed that miR-10b-3p is not associated with OS and DFS in GC patients. These findings suggested that miR-10b-3p may not suitable as GC prognostic marker. Notably, we also analyzed the role of miR-10b-5p in GC. Wang et al indicated that miR-10b-5p is down-regulated in breast cancer.[30] Moreover, some studies suggested that miR-10b-5p is an independent prognostic biomarkers for non-small-cell lung cancer[31] and lower grade glioma.[32] Based on TCGA data, our survival analysis found that high expression of miR-10b-5p is related with poor DFS. Thus, miR-10b-5p can be a prognostic biomarker for GC. However, the mechanism by which miR-10b-5p affects the pathogenesis of GC needs to be further illustrated.

The diagnostic value of miR-10b in cancer has been reported in some studies. Lai et al[33] showed that the expression of plasma miR-10b distinguished normal controls from pancreatic ductal adenocarcinoma patients, with a sensitivity and specificity of 100% and 100%, respectively. miR-10b also showed diagnostic

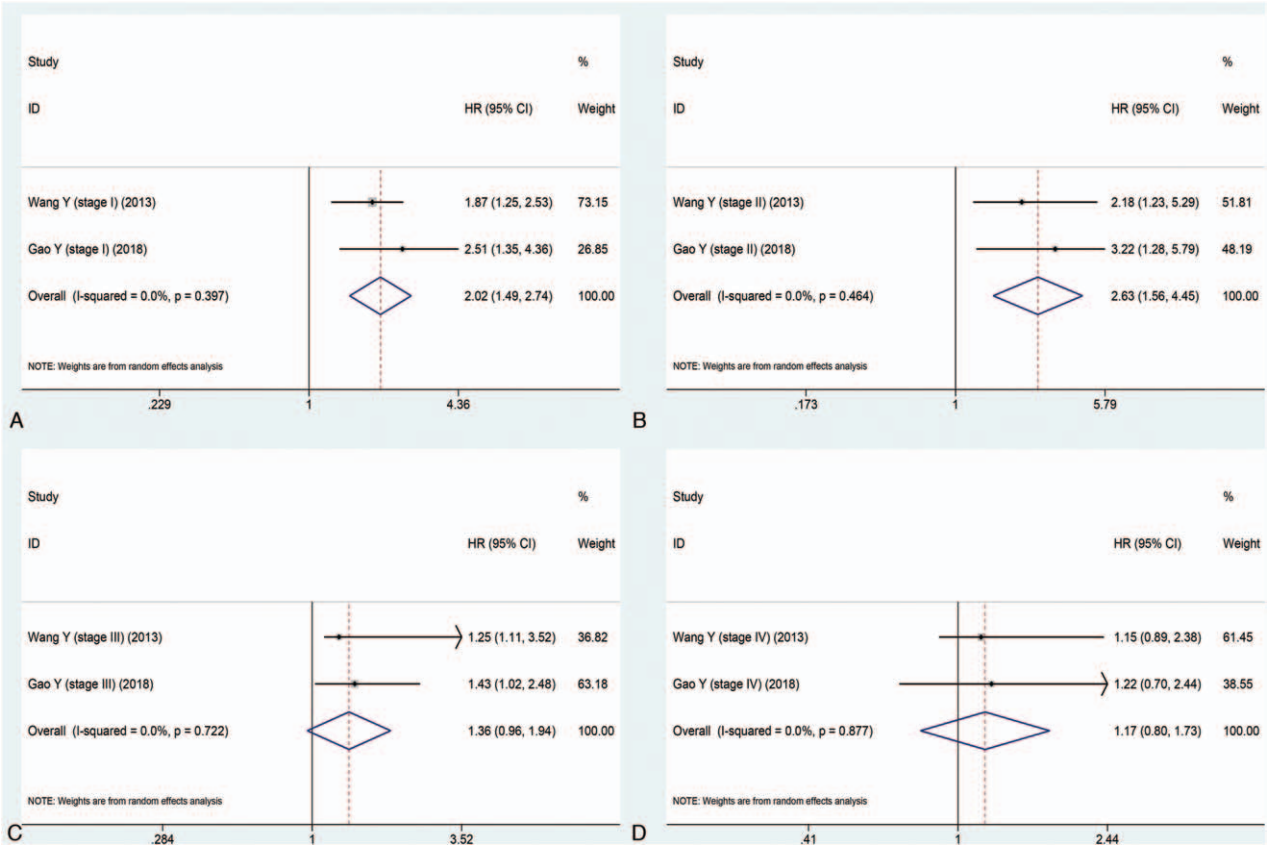

Figure 3. Forest plot for the association between miR-10b expression and OS of GC in different stages. (A) stage I; (B) stage II; (C) stage III; (D) stage IV.

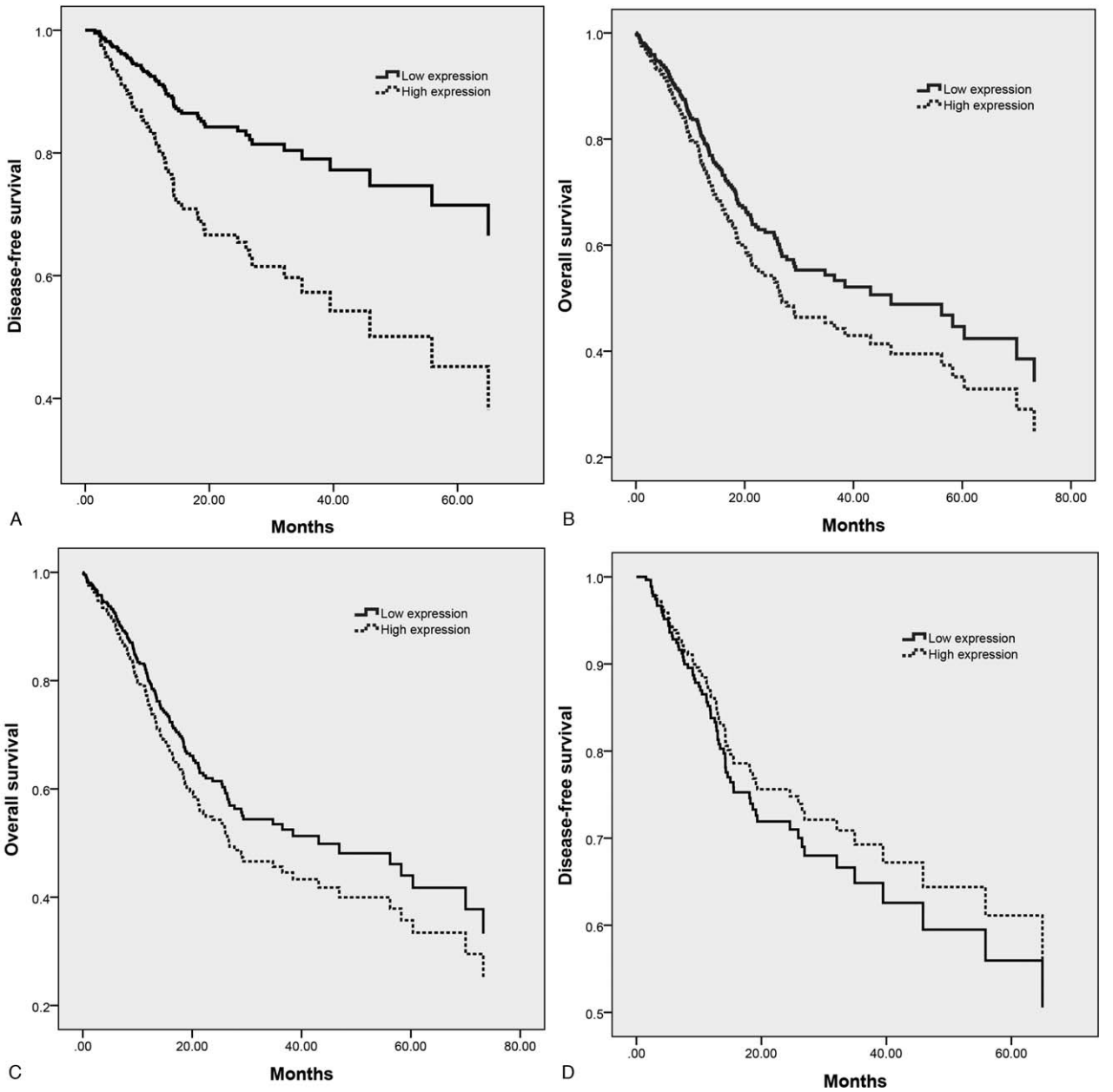

Figure 4. (A) DFS of miR-10b-5p for GC; (B) OS of miR-10b-5p for GC; (C) OS of miR-10b-3p for GC; (D) DFS of miR-10b-3p for GC.

accuracy for esophageal squamous cell carcinoma, with a sensitivity and specificity of 76% and 84%, respectively.[34] Regarding GC, the diagnostic accuracy of miR-10b has not been explored. In this study, we analyzed the diagnostic value of miR-10b-3p and miR-10b-5p in GC based on TCGA data. ROC curve analyses revealed that the AUC value for miR-10b-3p and miR-10b-5p were 0.652 (95% CI: 0.562–0.742; $P = .001$) and 0.565 (95% CI: 0.471–0.660; $P = .165$), respectively. This suggested

Table 3

Summarized results in the analysis of TCGA data.

	ROC curve					Overall survival		Disease-free survival	
miR-10b	AUC	*P*	The optimum diagnostic point	Sensitivity	Specificity	HR (95% CI)	*P*	HR (95% CI)	*P*
5p	0.565 (0.471–0.660)	.165	13.7816	0.524	0.663	1.296 (0.933–1.801)	.122	2.366 (1.414–3.959)	.001
3p	0.652 (0.562–0.742)	.001	1.8821	0.849	0.429	1.254 (0.905–1.736)	.173	0.848 (0.53–1.356)	.49

AUC = the area under the ROC curve.

Table 4

Association between miR-10b expression and clinicopathological parameters of gastric cancers (TCGA data).

		miR-10b-5p Expression				miR-10b-3p Expression		
Variables	**Case**	**Mean**	**SD**	***P***	**Case**	**Mean**	**SD**	***P***
Tissue								
Tumor	386	13.44	0.9	.276	385	2.15	0.72	<.001
Non-tumor	42	13.6	0.92		42	2.59	0.74	
Age								
<60 years	117	13.42	0.93	.747	120	2.55	0.80	.562
≥60 years	256	13.46	0.92		261	2.60	0.72	
Gender								
Male	246	13.44	0.89	.878	253	2.62	0.76	.272
Female	130	13.45	0.94		132	2.53	0.7	
T								
T1-T2	94	13.64	1.02	.017	97	2.58	0.8	.916
T3-T4	282	13.38	0.88		288	2.59	0.72	
N								
N0	116	13.42	0.94	.739	119	2.62	0.78	.624
N1	235	13.46	0.91		259	2.58	0.73	
M								
M0	339	13.45	0.91	.132	346	2.59	0.75	.34
M1	22	13.75	0.78		22	2.74	0.71	
Stage								
Stage I-II	167	13.5	0.93	.231	119	2.57	0.77	.844
Stage III-IV	201	13.39	0.9		258	2.58	0.72	
Anatomic								
Antrum/Distal	140	13.38	0.86	.303	143	2.49	0.76	.062
Other	228	13.48	0.94		233	2.64	0.74	
Barretts esophagus								
No	223	13.52	0.90	.319	225	2.65	0.71	.055
Yes	16	13.29	1.05		17	2.3	0.91	
Family history								
No	308	13.47	0.92	.594	315	2.58	0.76	.803
Yes	17	13.35	0.97		18	2.62	0.70	
HP infection								
No	159	13.47	0.92	.917	161	2.70	0.76	.733
Yes	19	13.45	1.12		19	2.64	0.68	

HP = *Helicobacter pylori*.

that miR-10b-3p has potential to be noninvasive screening tools for GC detection.

There are several limitations in this study. First, only 4 studies were included in this meta-analysis, the number of patients was limited. Second, sensitive analysis and meta-regression were not conducted due to limited studies. Third, we only included studies published in English, the language bias is inevitable. Last but not least, this study lack of experiments to confirm our finding based on our own patient samples. We plan to perform experimental validation in the future study in subsequent years.

In conclusion, this is first meta-analysis indicated that expression of miR-10b is associated with OS in GC patients. Moreover, miR-10b-3p is promising to be a new biomarker for diagnosis of GC and high expression of miR-10b-5p is associated with poor DFS in GC patients. Considering above limitations, more larger sample size studies can help to verify the diagnostic and prognostic value of miR-10b in GC.

Author contributions

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Formal analysis: Zhouxiang Lu.
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Methodology: Zhouxiang Lu, Zhangguo Shen.
Software: Zhouxiang Lu, Zhangguo Shen.
Validation: Zhangguo Shen.
Writing – original draft: Lina Mei, Zhouxiang Lu, Sumei Xu.
Writing – review & editing: Zhangguo Shen, Sumei Xu.

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