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The prognostic value of microRNA-183 in human cancers

A meta-analysis

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Abstract

Background: Several studies have been conducted to explore the prognostic value of miR-183 in different types of cancer; however, their results were controversial. Therefore, the present meta-analysis was conducted to comprehensively evaluate the prognostic value of miR-183 expression level in cancer.

Methods: A comprehensive literature search was carried out by searching PubMed and EMBASE database between January 1966 and April 2017. Fixed effect and random effect models were used to evaluate the pooled hazard risk (HR) and the relevant 95% confidence intervals (CIs). Subgroup analyses and sensitivity analysis were also carried out.

Results: A total of 12 studies published between 2011 and 2017 were included in the present meta-analysis. The meta-analysis result indicated that there was a significant association between miR-183 expression level and overall survival (HR = 2.642; 95%CI: 2.152–3.245), and there was a significant association between miR-183 expression level and tumor progression (HR = 2.403; 95% CI: 1.267–4.559). In subgroup analysis, we found that high expression level was significantly associated with poor prognosis in most cancers (HR = 2.824, 95%CI: 2.092–3.813); however, low miR-183 level was significantly associated with poor prognosis in melanoma and pancreatic ductal adenocarcinoma (HR = 2.322, 95%CI: 1.337–4.031).

Conclusions: The results of our meta-analysis indicated that the highly expressed miR-183 might predict poor survival of patients with most cancer types, whereas the downregulated miR-183 level might be associated with poor prognosis in patients with melanoma and pancreatic ductal adenocarcinoma.

Abbreviations: CI = confidence intervals, CRC = colorectal cancer, DFS = disease-free survival, HR = hazard risk, miR-183 = miRNA-183, miRNA = microRNA, mRNA = messenger RNA, OS = overall survival, PFS = progression-free survival, RFS = recurrence-free survival, UTR = untranslated region.

Keywords: cancer, meta-analysis, microRNA-183, prognosis

1. Introduction

MicroRNAs (miRNAs), a family of endogenous noncoding, small RNAs with ~19 to 22 nucleotides, are able to regulate gene expression at posttranscriptional level by binding to the 3late gene expression at post-transcriptionmessenger RNA(mRNA), leading to the degradation or inhibition of the target mRNA. miRNAs play important roles in many fundamental and biological processes, such as cellular growth, proliferation, development, differentiation, angiogenesis, metabolism, and apoptosis. Previous studies have demonstrated that some miRNAs function as oncogenes, which are frequently upregulated in cancer, whereas some miRNAs function as tumor-suppressor, which are frequently downregulated in cancer.[1,2] Due to their good stability and unique expression profles in human cancers, the success of utilizing miRNAs as diagnostic or prognostic biomarkers has received substantial attention in cancer research.[3,4]

miRNA-183 (miR-183) belongs to the miR-183 family, which is located on chromosome 7q32, and consists of miR-96, miR-182, and miR-183.[5] Previous investigations revealed that miR-183 might function as an oncogene in most cancer types, such as colorectal cancer(CRC), pancreatic cancer, lung cancer, gastric cancer, and breast cancer.[6–9] However, it might also function as a tumor suppressor in few cancer types, such as cervical cancer.[10] Therefore, the role of miR-183 might be depending on different cancer types. Recently, several studies have been conducted to explore the prognostic value of miR-183 in different types of cancer, however, their results were controversial. Therefore, the present meta-analysis was conducted to comprehensively evaluate the prognostic value of miR-183 expression level in cancer.

2. Materials and methods

Ethical approval was obtained from the Ethics Committee of the Shaoxing People's Hospital, Shaoxing Hospital of Zhejiang University.

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XLZ and SHP contributed equally to this study.

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The authors have no conflicts of interest to disclose.

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2.1. Data sources and searches

The present meta-analysis was carried out in the light of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines,[11] as well as Meta-analysis of Observational Studies in Epidemiology group (MOOSE) guidelines.[12] A comprehensive literature search was undertaken by searching PubMed, and EMBASE database between January 1966 and April 2017. There were no restriction of origin and languages. Search terms included: "miR-183" or "microRNA-183" and "cancer" or "neoplasm" or "tumor" or "carcinoma" or "malignancy" or "malignant" and "survival" or "prognosis" or "prognostic." Moreover, the references of the initially identified studies and previous reviews were manually assessed to find out additional relevant studies.

2.2. Study selection

Two reviewers (XLZ and SHP) independently screened out trials which were conforming to inclusion criteria. Inconsistencies between them were solved by discussing with other reviewers (JJY and GX). Inclusion criteria were: the study subjects were patients with any type of cancer, the expression level of miR-183 was measured in tumor tissue or plasma, the relationship between miR-183 expression and clinical outcomes, such as overall survival (OS), progression-free survival (PFS), recurrence-free survival (RFS), or disease-free survival (DFS) were reported. Studies were excluded based on the following criteria: reviews, case report, or letters to editor, lacked key information regarding survival outcomes, such as HRs or 95% CIs or unable to calculate such parameters, when there were multiple publications from the same population, only data from the most recent report were included in the meta-analysis and remaining papers were excluded.

2.3. Data extraction

The following data were collected by 2 reviewers independently using a purpose-designed form: name of first author, publishing time, country of the population studied, study period, cancer type, follow up duration, tumor stage, miR-183 assay method, miR-183 cut-off value, sample type, and HRs for OS and/or DFS, PFS, RFS, and the corresponding 95% CIs. If HRs were not directly reported in the studies, then the data were extracted from Kaplan–Meier survival plots using Engauge Digitizer v.5.1 to calculate HRs with 95% CIs using methods that are previously described.[13] Furthermore, if both the univariate and multivariate results were reported, then only the latter was selected, since these results were adjusted for confounding factors.

2.4. Statistical analysis

All of the HRs and corresponding 95% CIs were used to calculate the pooled HR. Cochran Q and I^2 test were applied to assess the heterogeneity among the included studies. When significant heterogeneity was detected (P value $< .05$ for Q test, or $I^2 > 50\%$ for I^2 test), random effect model was applied to calculate the

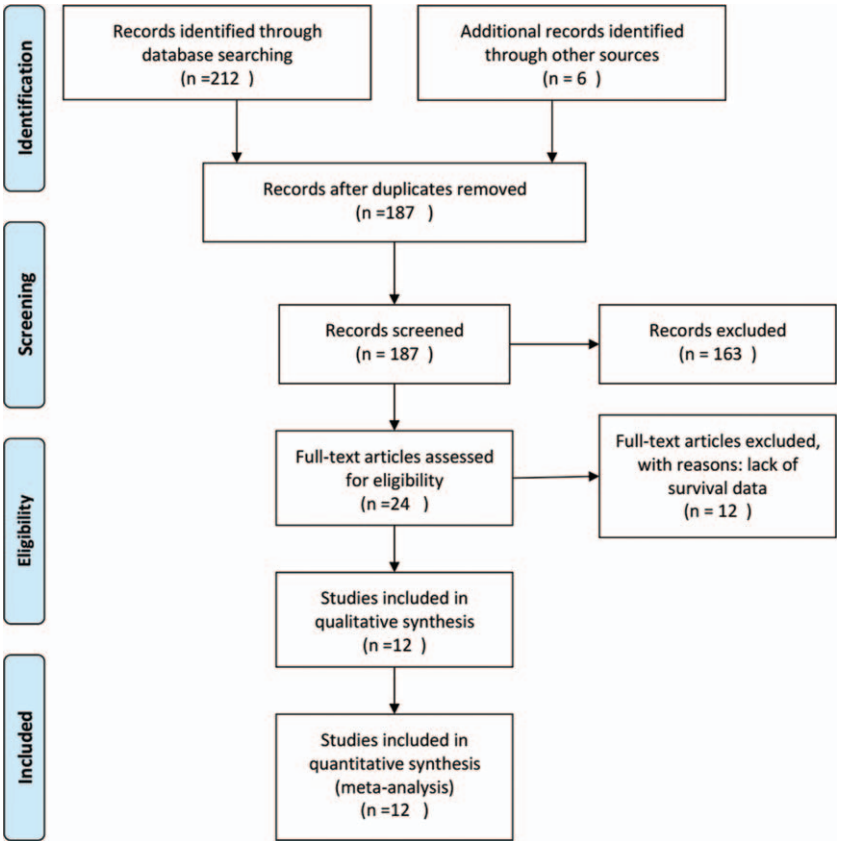

Figure 1. Flow chart of study selection process.

pooled effect, otherwise, fixed effect model was used.[14] We performed the leave-one-out sensitivity analysis to assess the robustness of the results. Egger's test and Begg's test were performed to assess the Publication bias.[15,16] Stata (version 11.0, StataCorp, College Station, TX) was used for all the statistical analysis.

3. Results

3.1. Literature selection and study characteristics

The study search and selection for the present meta-analysis were shown in Figure 1. A total of 212 citations were identified during the initial search from PubMed and Embase database. Moreover, 6 additional records identified through other sources. On the basis of the title and abstract, we identified 24 papers. After reading the full manuscripts, 12 studies were excluded for lack of survival data. At last, 12 studies published between 2011 and 2017 were included in the meta-analysis.[17–28]Table 1 shows the characteristics of the 12 included studies. All of the 12 studies were from China, and a total of 1260 participants were enrolled. The types of cancers in these studies included lung cancer, gastric cancer, breast cancer, glioma, hepatocellular carcinoma, pancreatic ductal adenocarcinoma, lung cancer, colorectal cancer, ovarian cancer, and melanoma. The expression of miR-183 was increased in these cancer types, except pancreatic ductal adenocarcinoma and melanoma. The expression levels of miR-183 were measured in plasma or tissue. The method of miR-183 detection was all qRT-PCR. The paper by Zhu et al[28] reported both tissue and serum miR-183 expression level and cancer prognosis, therefore, we regarded this paper as 2 studies.

3.2. miR-183 expression level and overall survival, tumor progression

For studies evaluating overall survival analysis, a fix-effects model was performed due to low heterogeneity ($P = .123$, $I^2 = 32.4\%$). The meta-analysis result indicated that there was a significant association between miR-183 expression level and overall survival (HR = 2.642; 95%CI: 2.152–3.245, shown in Fig. 2). In general, tumor progression was assessed by combining disease recurrence and metastasis. A total of 4 studies reported DFS/PFS analysis. For studies evaluating DFS/ PFS analysis, a random-effects model was performed due to significant heterogeneity ($P = .018$, $I^2 = 70.1\%$). The meta-analysis result indicated that there was a significant association between miR-183 expression level and tumor progression (HR = 2.403; 95%CI: 1.267– 4.559, shown in Fig. 3).

3.3. Subgroup analysis

In the present study, we did subgroup analysis according to sample source, expression level, and analysis model (shown in Table 2). We found that both tissue and serum miR-183 level were significantly associated with cancer prognosis. The expression level of miR-183 is upregulated in most cancer types, and they play the oncogene role. We found that high expression level was significantly associated with poor prognosis in these cancers (HR = 2.824, 95%CI: 2.092–3.813). However, the expression level of miR-183 is downregulated in melanoma and pancreatic ductal adenocarcinoma, suggesting it might play tumor suppressor role in these 2 cancer types. And we found that low miR-183 level was significantly associated with poor

Table 1

The characteristics of the included studies.

First author	Publication year	Region	Type of cancer	Cases	Stage	Sample	MiR-183 assay	Cut-off value	Regulated features	Survival analysis	HR and 95% CI
Zhu W	2011	China	Lung cancer	70	I–IV	Tissue, serum	qRT- PCR	Median: 4.44	Up	OS	Tissue: 8.616 (1.918-38.705); serum: 5.972 (1.289-27.658)
Zheng WW	2012	China	Gastric cancer	72	II	Tissue	qRT- PCR	Median: 6.76	Up	OS	2.172(1.028-4.293)
Liang Z	2013	China	Hepatocellular carcinoma	92	I–IV	Tissue	qRT- PCR	Median: 9.015	Up	OS, DFS	OS: 1.382(0.733-2.663); DFS: 1.178(0.683-1.972)
Zhou L	2014	China	Pancreatic ductal Adenocarcinoma	91	I–IV	Tissue	qRT- PCR	NR	Down	OS	3.283(1.283-8.926)
Xu F	2014	China	lung cancer	100	I–IV	Tissue	qRT-PCR	NR	Up	OS, PFS	OS: 2.54 (1.19–5.44); PFS: 2.30 (1.22–4.35)
Zhou T	2014	China	Colorectal cancer	94	I–IV	Tissue	qRT-PCR	Mean: 3.1	Up	OS	2.754(1.198–6.330)
Yuan D	2015	China	Colorectal cancer	118	I–IV	Plasma	qRT-PCR	Mean: 1.727	Up	OS	1.831 (1.098–3.054)
Ye Z	2016	China	Glioma	105	I–IV	Tissue	qRT-PCR	Median: 2.731	Up	OS, PFS	OS: 7.34 (2.11–12.70); PFS: 7.28 (1.10–9.73)
Chen H	2016	China	Epithelial ovarian cancer	75	I–IV	Serum	qRT-PCR	Mean: 1.128	Up	OS	3.862 (2.774-7.963)
Song C	2016	China	Breast cancer	41	I–IV	Tissue	qRT-PCR	NR	Up	OS, DFS	OS: 2.563(1.283-6.229); DFS: 2.638(1.829-7.285)
Li CY	2017	China	Gastric cancer	361	NR	Tissue	qRT-PCR	NR	Up	OS	3.173(1.836-8.293)
Sun Y	2017	China	Melanoma	41	I–IV	Tissue	qRT-PCR	NR	Down	OS	1.967(1.382-5.287)

CI = confidence intervals, DFS = disease-free survival, NR = not reported, OS = overall survival, PFS = progression-free survival.

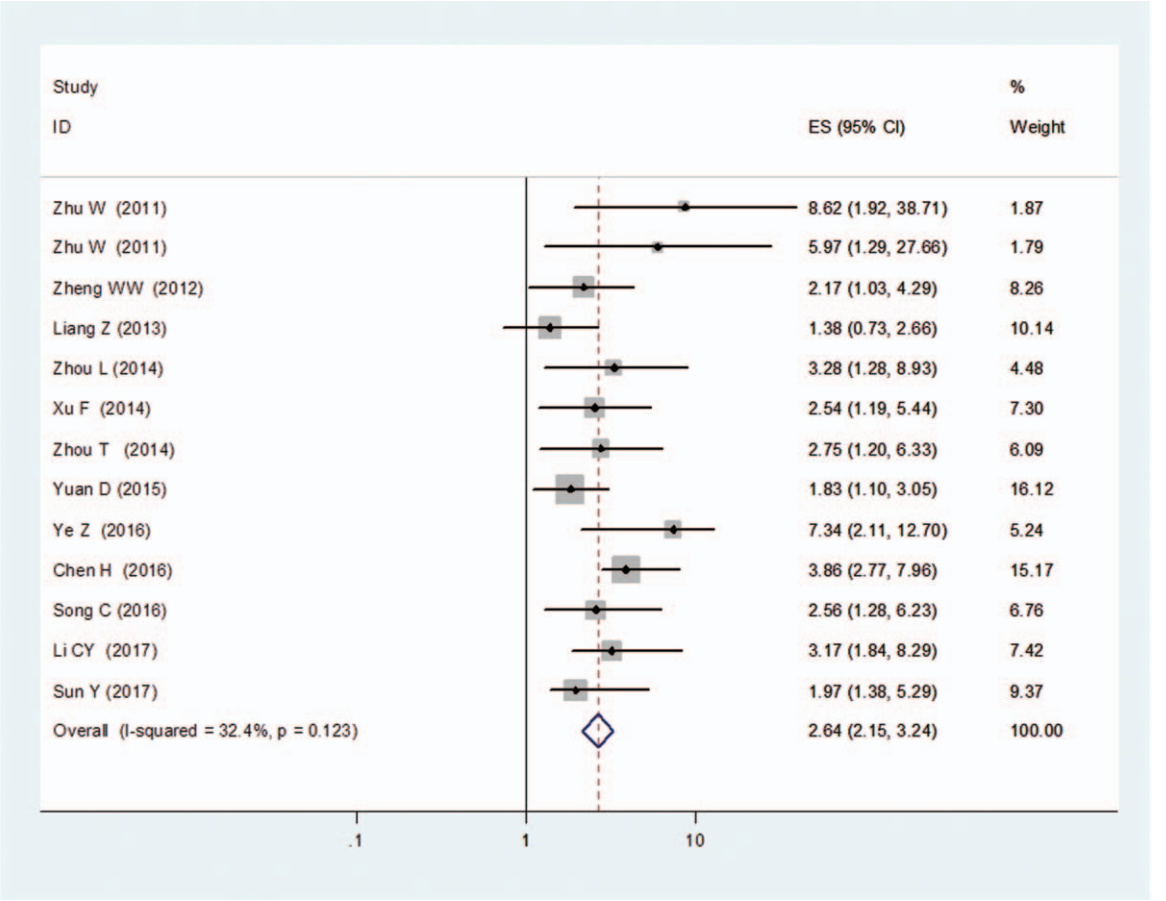

Figure 2. Meta-analysis of miR-183 expression and overall survival in various cancers.

prognosis in these cancers (HR = 2.322, 95%CI: 1.337–4.031). Furthermore, miR-183 level was significantly associated with cancer prognosis in both univariate group and multivariate group.

3.4. Sensitivity analysis and publication bias

To test the robustness of association and characterize possible sources of statistical heterogeneity, sensitivity analyses were carried out by excluding studies one-by-one and analyzing the homogeneity and effect size for all of the remaining studies. Sensitivity analysis indicated that no significant variation in combined HR by excluding any of the study, confirming the stability of present results. In the present meta-analysis, no publication bias was observed among studies using Begg's *P* value (*P* = .094); Egger's (*P* = .183) test, which suggested there was no evidence of publication bias (shown in Fig. 4).

4. Discussion

miRNA, a class of small noncoding RNAs, play important roles in gene expression and diverse biological processes. Recently, miRNAs are demonstrated to have potential to predict the prognosis of cancer patients; therefore, they can be used as prognostic biomarkers. For example, the meta-analysis by Dong et al[29] indicated that a high level of miR-126 played a favorable role in the overall survival, especially for patients with digestive or respiratory system cancers. In the meta-analysis conducted by Liu et al[30], their results demonstrated that higher expression level of miR-9 significantly predicted worse overall survival in various carcinomas and that miR-9 might act as a novel biomarker in the prognosis of malignant neoplasms.

miR-183 belongs to the miR-183 family, which is located on chromosome 7q32, and consists of miR-96, miR-182, and miR-183.[5] Previous investigations revealed that miR-183 might function as an oncogene in most cancer types, such as colorectal cancer(CRC), pancreatic cancer, lung cancer, gastric cancer, and breast cancer.[6–9] However, it might also function as a tumor suppressor in few cancer types, such as cervical cancer.[10] Therefore, the role of miR-183 might be depending on different cancer types. Recently, several studies have investigated the prognostic value of miR-183 in different types of cancer; however, their results were inconsistent. Therefore, our meta-analysis was designed to pool the currently available data to determine the association between miR-183 expression level and cancer prognosis. In the present meta-analysis, 12 studies published between 2011 and 2017 were involved, including 1260 participants diagnosed with different cancer types. Overall, the meta-analysis result indicated that there was a significant association between miR-183 expression level and overall survival; furthermore, miR-183 expression level was significantly associated with tumor progression. The expression level of miR-

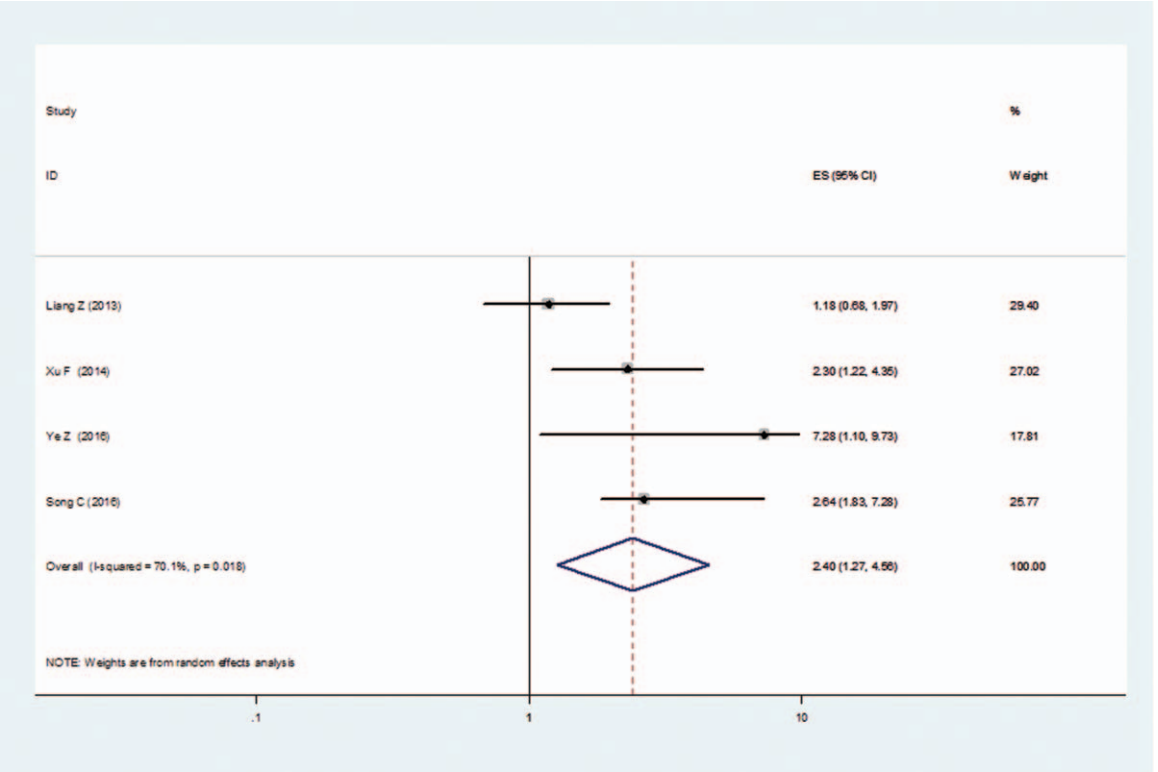

Figure 3. Meta-analysis of miR-183 expression and tumor progression in various cancers.

183 is upregulated in most cancer types, and they might play the oncogene role. We found that high expression level was significantly associated with poor prognosis in these cancers. However, the expression level of miR-183 is downregulated in melanoma and pancreatic ductal adenocarcinoma, suggesting it might play tumor suppressor role in these 2 cancer types. Also we found that low miR-183 level was significantly associated with poor prognosis in these cancers.

Our meta-analysis has several limitations. Firstly, all 12 articles are from China, so the statistical results are geographically limited. Because of the genetic differences between different races, the present meta-analysis results may not be applicable to other races. Moreover more articles from different races are needed. Secondly, the number of included studies, in particular for DFS/RFS/PFS, was relatively small; therefore, more studies are needed in the future. Thirdly, as there were only a limited number of included studies for each cancer type, we have not done subgroup analysis according to different cancer types.

5. Conclusions

These results of our meta-analysis indicated that the highly expressed miR-183 might predict poor survival of patients with most cancer types, whereas the downregulated miR-183 level might be associated with poor prognosis in patients with melanoma and pancreatic ductal adenocarcinoma.

Table 2

Subgroup analysis for miR-183 expression and overall survival in cancers.

Subgroup	Number of studies	Model	HR (95% CI)
Sample source			
Tissue	10	Fix-effects model	2.683(1.982–3.631)
Serum	3	Random-effects model	2.963(1.553–5.652)
Expression level			
Up	11	Fix-effects model	2.824(2.092–3.813)
Down	2	Fix-effects model	2.322(1.337–4.031)
Analysis model			
Univariate	8	Fix-effects model	2.444(1.770–3.374)
Multivariate	5	Random-effects model	3.080(1.981–4.791)

CI = confidence intervals, HR = hazard risk.

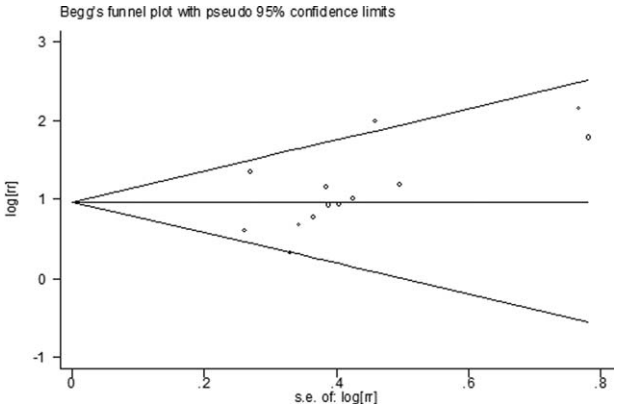

Figure 4. Funnel plot for publication bias in the studies investigating miR-183 expression level and cancer prognosis.

Author contributions

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Formal analysis: Xiao-long Zhang, Shou-hua Pan.
Funding acquisition: Xiao-long Zhang, Shou-hua Pan.
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Project administration: Shou-hua Pan.
Resources: Jia-jun Yan, Gang Xu.
Writing – original draft: Xiao-long Zhang.
Writing – review & editing: Jia-jun Yan.

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