Original Article

MiR-193b as an effective biomarker in human cancer prognosis for Asian patients: a meta-analysis

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Background: MiR-193b has been widely investigated in the last few years and an aberrant association has been observed between its expression levels and the prognosis of several human malignancies. We performed a meta-analysis to evaluate the prognostic effect of miR-193b on human cancers.

Methods: PMC, PubMed, Web of Science (WOS), Embase in English and VIP, Wanfang, SinoMed and the China National Knowledge Infrastructure (CNKI) in Chinese were searched up to May 16, 2020. The pooled hazard ratio (HR) with a 95% confidence interval (CI) was calculated to evaluate its prognosis in human cancers. Also, the pooled odd ratios and the relevant 95% CIs were computed to assess the association of miR-193b levels and clinicopathological characteristics of cancer patients.

Results: In overall analysis, a significant association was identified between miR-193b levels and overall survival (HR =0.77, 95% CI: 0.64–0.92), but this association was not significant in the random pooling model. Then, two outliers were identified through sensitivity analysis. After removing outliers, the significant association was identified with random pooling model (HR =0.45, 95% CI: 0.30–0.69). In addition, the significance exited among Asian (HR =0.45, 95% CI: 0.28–0.74), studies with the sample size (≥100) (HR =0.39, 95% CI: 0.27–0.56) and sample size (<100) (HR =0.51, 95% CI: 0.28–0.92), Newcastle-Ottawa scale (NOS) scores (≥8) (HR =0.44, 95% CI: 0.30–0.67) and NOS scores (<8) (HR =0.45, 95% CI: 0.25–0.80) and patients of non-digestive carcinoma (HR =0.35, 95% CI: 0.24–0.52), digestive carcinoma (HR =0.54, 95% CI: 0.31–0.92), non-urogenital carcinoma (HR =0.52, 95% CI: 0.33–0.82) or urogenital carcinoma (HR =0.28, 95% CI: 0.16–0.50). Lower expression of miR-193b was found to be related to larger tumor size and the potential of lymph node metastasis and distance metastasis.

Discussion: We have demonstrated that miR-193b serves as an ideal biomarker in the cancer prognosis for Asian patients, and the low expression levels of miR-193b is significantly associated with poor overall survival rates in various human malignancies. Moreover, the patients with lower miR-193b tend to develop the cancers with higher potential of metastasis.

Keywords: MiR-193b; cancer; prognosis; meta-analysis

Submitted Nov 16, 2021. Accepted for publication May 10, 2022.
doi: 10.21037/tcr-21-2557
View this article at: https://dx.doi.org/10.21037/tcr-21-2557

Introduction

Cancer is one of the leading causes of mortality in countries and regions worldwide (1). Early diagnosis and treatment are vital approaches to improve the prognosis of cancers. Thus, identifying reliable molecular markers associated with early diagnosis and prognosis of cancers is urgently needed (2). MicroRNAs are small non-coding RNAs which are remarkably stable and are protected from degradation because of their small length (about 18–22 nucleotides) (3). These small molecules regulate the expression of specific target genes and exert important functions in several biological processes and have become a source of clinically potential biomarkers for the diagnosis or prognosis of various human carcinomas and also the key therapeutic targets (4). A rising evidence indicates that tumor tissues show specific miRNA signatures (i.e., miRNome, or miRNA fingerprints), composed of both up-regulated and down-regulated miRNAs (5). In terms of their remarkable stability and unique expression profiles in human cancers, miRNAs have a great promise as distinctive biomarkers for clinical cancer diagnosis and prognosis (6,7).

Functioning on specific gene targets, miR-193b is greatly involved in cancer cell proliferation, metastasis, invasion and migration in the development of various cancers (8). Many cohort studies have investigated miR-193b role in predicting cancer prognosis and observed an aberrant association between its expression level and the prognosis of several human malignancies. More than half of current clinical cohort studies (9-11) observed the anti-oncogenic functions of miR-193b in certain types of cancers (acute myeloid leukemia, colorectal cancer, etc.), suggesting the potential linkage of up-regulated miR-193b and superior prognosis. However, other studies found opposing evidences, indicating that miR-193b served as an oncogene (12,13). Although miR-19b is related to the prognosis of some tumors, Jamali *et al.* elaborated that the expression of mir-19b in Head and Neck Squamous Cell Carcinoma (HNSCC) has no significant correlation with the survival rate of patients (14,15). Another study showed no significant association between miR-193b and the prognosis of pancreatic cancer (16). Therefore, the role of miR-193b as a biomarker for human malignancies prognosis needs a further investigation, but no meta-analysis has been performed to clarify its precise role ever. Thus, we conducted this meta-analysis to evaluate data from studies of miR-193b in various cancer types comprehensively and verified the value of miR-193b expression levels as a prognostic biomarker. We present the following article in accordance with the PRISMA reporting checklist (available at https://tcr.amegroups.com/article/view/10.21037/tcr-21-2557/rc).

Methods

Literature collection

Relevant literatures were comprehensively searched by two independent authors on the online databases PubMed Central (PMC), PubMed, Web of Science (WOS), Embase in English and VIP, Wanfang, SinoMed and the China National Knowledge Infrastructure (CNKI) in Chinese up to May 16, 2020. The following combination of keywords was used for the article search: "microRNA-193b" or "microrna-193b" or "miRNA-193b" or "miR-193b" and "tumor" or "cancer" or "carcinoma" or "neoplasm" or "malignancies" or "prognosis" or "survival". In order to increase the sensitivity of the searching strategy, both Medical Subject Headings (MeSH) terms and free words were applied. We also retrieved literatures from other sources, such as the reference lists of relevant review articles.

Inclusion and exclusion criteria

Prognostic miRNA studies are eligible if they satisfy all of the following initial inclusion criteria: (I) human carcinoma was involved; (II) the miRNA-193b expression was measured in tissues or blood samples; (III) miRNA measurement approaches were clearly described; and (IV) the association between miRNA-193b expression and survival data was examined. Studies were excluded if (I) they are letters, case reports, laboratory studies, reviews, conference reports, letters or expert opinions; (II) they are unpublished data from meeting abstracts; (III) they are neither English nor Chinese language articles; (IV) lack of data on survival outcomes; (V) the data is not primary but extracted from secondary databases [such as The Cancer Genome Atlas (TCGA), etc.].

Data extraction

The following information was extracted from each study: author, year of publication, country of the population enrolled, tumor type, clinical stage of tumor, sample size (high/low), specimen, detection method of quantifying

miRNA expression, cut-off values used to classify subjects into high and low groups, survival analysis methodology, miR-193b expression levels, source of hazard ratio (HR) and HRs for overall survival (OS), their 95% confidence interval (CI) and quality of study. HR and CI were extracted according to the following two approaches. Firstly, the reported HRs and their 95% CIs were obtained directly from tables, text and figures. Secondly, for those articles in which HRs and 95% CIs were not directly illustrated, Engauge Digitizer version 9.8 was used to get necessary data from Kaplan-Meier Curves and then calculated survival rates was input into the spreadsheet designed by Tierney *et al.* (17) to calculate HRs and their 95% CIs.

Quality assessment

Ten articles were reviewed independently by the two researchers (Hao Yu and Yizhong Peng). In the situation of a disagreement, a consensus was reached by a senior researcher (Minjie Wang). Quality of non-randomized studies was scored using the Newcastle-Ottawa scale (NOS) (18). This is recommended by the Cochrane Non-Randomized Studies Methods Working Group and has been widely applied in biomarker meta-analyses for cohort studies (19). The score has a maximum of nine stars and those studies marked with more than four stars are judged to be of higher quality. Only studies getting more than four stars were included in the present systematic review and subsequent pooled analysis.

Statistical analysis

(I) Pooled HRs for survival analysis, and the corresponding 95% CIs were merged using a fixed-effect model (Mantel-Haenszel) firstly. If the heterogeneity was observed, a random-effect model (Mantel-Haenszel-heterogeneity) was implemented alternatively. The HR >1 suggests that the subjects with higher miRNA-193b expression are linked to a poorer survival outcome and those with lower miRNA-193b expression have a better prognosis. And the source of heterogeneity was explored by subgroup, sensitivity analysis and meta-regression based on factors related to heterogeneity. (II) For the studies from which clinicopathological features were available, the odd ratios (ORs) for the clinicopathological features and the corresponding 95% CIs were merged to assess the relation of miR-193b expression levels to various characteristics including gender, ages, tumor sizes, lymph node metastasis and distant metastasis potential for different malignancies. (III) The test for heterogeneity of pooled HRs was evaluated by a χ^2 based Cochran Q test and Higgins I^2 statistic. $P<0.05$ or $I^2>50\%$ was considered to be statistically significant. Publication bias was carried out by using funnel plots, Begg's test and Egger's test. A two-tailed $P<0.05$ was considered statistically significant. Statistical analyses and graphical representations were conducted by Stata software version 14.0 (Stata Corporation, College Station, TX, USA).

Results

Characteristics of the enrolled studies

By searching databases, bibliographies from articles, reviews and other sources, we recognized 1,804 records in total (PMC =1,430, PubMed =68, WOS =90, Embase =10 in English and VIP =39, SinoMed =31, Wanfang =82 and CNKI =12, other sources =42) (*Figure 1*). Through titles and abstracts screening, we eliminated 325 duplicates, 1,364 articles of no relevance, 20 reports not retrieved due to unavailabillity of full text, obtaining the remaining studies in which 95 studies' full-text were available. The articles were carefully inspected according to the exclusion and inclusion criteria. In the end, ten cohort studies, of which one is in Chinese and the others are in English, were enrolled into the meta-analysis.

Among these ten studies, a total of 1,015 participants were recruited with the mean sample size of 101.5 (range from 47 to 234). Four studies enrolled more than 100 subjects. The accrual period of these studies ranged from 2014 to 2018. The regions represented in the studies include the German, Austria and China. Nine different types of cancer were evaluated which could be divided into digestive system carcinoma (6 studies) or non-digestive system carcinoma (4 studies) and urogenital system carcinoma (3 studies) or non-urogenital system carcinoma (7 studies) (20,21). Ten studies analyzed the miR-193b expression level by real-time quantitative polymerase chain reaction (RT-qPCR), while two studies applied the methods of miRNA array or miRNA cards (22). OS, event-free survival (EFS), disease-free survival (DFS) and progression-free survival (PFS) were estimated as survival outcome measures in 100% (10/10), 12.5% (1/10), 20% (2/10) and 20% (2/10) of the studies, respectively. The main characteristics of each study were listed in *Table 1*.

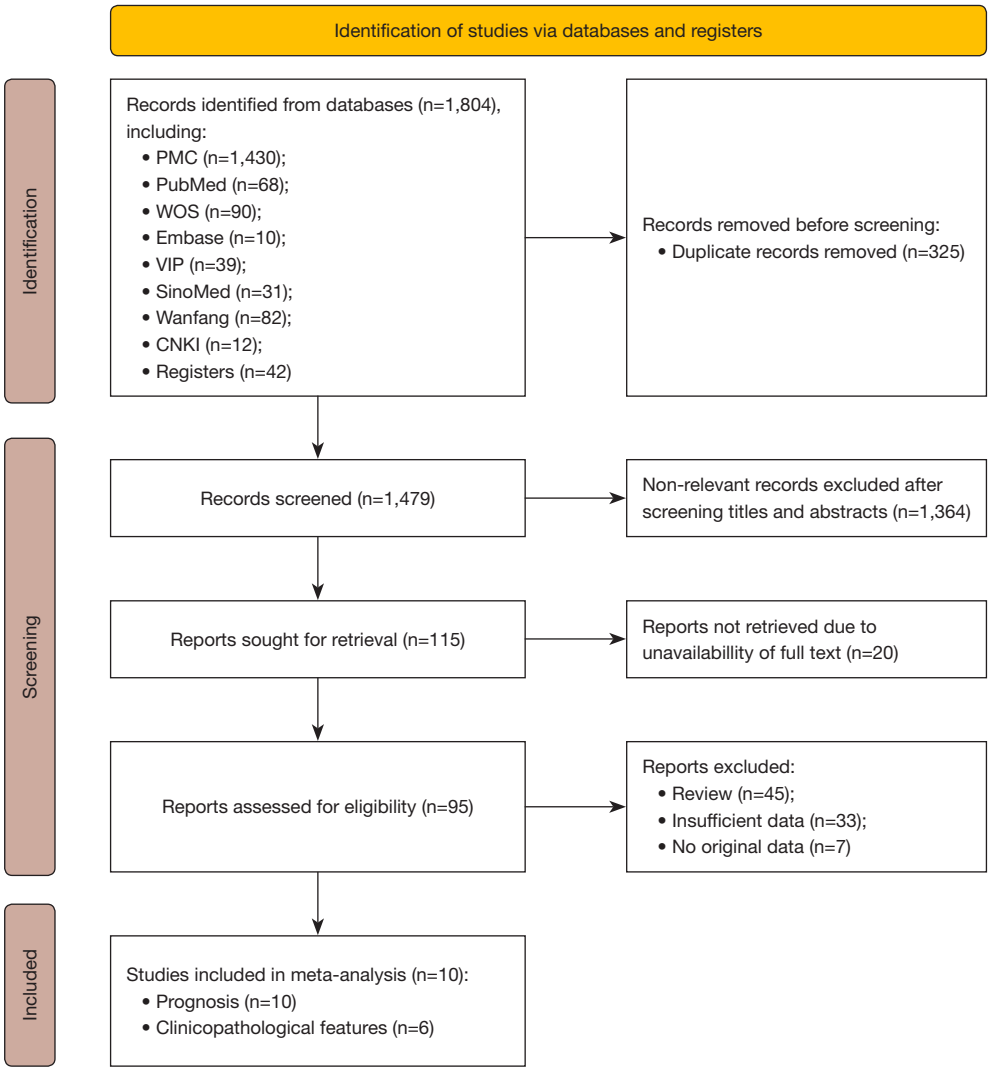

Figure 1 The flow diagram of the meta-analysis. From: Page MJ, McKenzie JE, Bossuyt PM, *et al.* The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ* 2021;372:n71. doi: 10.1136/bmj.n71. For more information, visit: http://www.prisma-statement.org/.

MiR-193b as a prognosis indicator for various types of carcinomas for Asian patients

All of the ten studies including 1,015 patients illustrated OS data with corresponding miR-193b expression level. Pooling HRs of OS in fixed model revealed a significant association between miR-193b levels and OS (HR =0.77, 95% CI: 0.64–0.92, *Table 2*), and there was an obvious and significant heterogeneity existing among the data (I^2=86.90%, P<0.05, *Table 2*). Then the random pooling model was implemented and the significance of miR-193b levels being an indicator for OS was not significant (HR =0.62, 95% CI: 0.36–1.07, *Table 2*). To identify the source of the heterogeneity, we applied subgroup analyses by factors as population (Asian and Caucasian), sample size (≥100 and <100), NOS scores (≥8 and <8), tumor origins (non-digestive system and digestive system) or (non-urogenital system and urogenital system) (*Table 2*). Heterogeneity among all the subgroups was still significant, and the results remained unstable. Furthermore, meta regression of covariates analysis was applied, but no significant relationship was observed between the OS and covariates (*Table 2*). To further identify the heterogeneity source, the sensitivity analysis was further performed, and Madhavan *et al.* (12) and Mu *et al.* (13) were

Table 1 Characteristics of studies included in the meta-analysis

No.	Study	Year	Country	Tumor type	Clinical stage of tumor	Sample size (high/low) for OS	Specimen	Detection method	Cut-off value	Survival analysis for OS	Outcome	Source of HR	Largest follow-up time	NOS
1	Bhayadia *et al.*	2018	German, Austria	AML	FAB: M0–M7 and none	161 (98/63)	BM	RT-qPCR	N/D	Univariate	OS, EFS	Reported	5 years	8
2	Chan *et al.*	2018	China	ESCC	ypTNM: ypCR and y-stage I–IV	47 (24/23)	Serum	MiRNA array and RT-qPCR	Median	Univariate	OS	K-M curve	About 175 months*	7
3	Guo *et al.*	2016	China	CRC	TNM stage: I–IV	106 (53/53)	Tumor	RT-qPCR	N/D	Univariate, multivariate	OS	Reported	60 months	8
4	Li *et al.*	2015	China	OC	FIGO Stage: I–IV	116 (48/68)	Tumor	RT-qPCR	Median	Univariate, multivariate	OS	Reported	5 years	7
5	Madhavan *et al.*	2016	German	BC	according to the RECIST guidelines[#]	234 (175/59)	Blood	MicroRNA cards and RT-qPCR	Lower quartile	Univariate	OS, PFS, DFS	Reported	More than 30 months*	8
6	Mu *et al.*	2014	China	GC	UICC stage: I–IV	48 (19/29)	Tumor	RT-qPCR	Median	Univariate	OS	K-M curve	More than 54 months*	6
7	Zhou *et al.*	2018	China	PC	TNM stage: I–IV	64 (N/D)	Plasma	RT-qPCR	Median	Univariate	OS	Reported	About 75 months*	7
8	Tan *et al.*	2017	China	ccRCC	Fuhrman grade: II–IV	99 (N/D)	Tumor	MiRNA array and RT-qPCR	Median	Univariate, multivariate	OS, PFS	Reported	62 months	7
9	Xu *et al.*	2017	China	CRC	TNM stage: I–IV	90 (47/43)	Serum	RT-qPCR	N/D	Univariate, multivariate	OS, DFS	Reported	More than 60 months*	7
10	Yin *et al.*	2018	China	LC	TNM stage: I–IV	50 (N/D)	Tumor	RT-qPCR	N/D	Univariate	OS	K-M curve	More than 60 months*	6

[#], more detailed information about the tumor stage is in its supplementary materials which we failed to download from the electronic databases; *, we extract the largest follow-up time from the Kaplan-Meier curves. AML, acute myeloid leukemia; BC, breast cancer; BM, bone marrow; ccRCC, clear cell renal cell carcinoma; CRC, colorectal cancer; DFS, disease-free survival; EFS, event-free survival; ESCC, esophageal squamous cell carcinoma; FAB, the French-American-British classification; FIGO, the International Federation of Gynecology and Obstetrics; GC, gastric cancer; HR, hazard ratio; LC, liver cancer; N/D, not described; NOS, Newcastle-Ottawa scale scores; OC, ovarian cancer; OS, overall survival; PC, pancreatic cancer; PFS, progression-free survival; RECIST, response evaluation criteria in solid tumors; RT-qPCR, Real-time quantitative Polymerase Chain Reaction; UICC, the Union for International Cancer Control classification criteria (Sobin and Fleming, 1997).

Table 2 Meta-analysis of miR-193b as a prognostic indicator for patients of various carcinoma

Variables	No. of studies	No. of patients	Pooled HR (95% CI)		Meta regression	Heterogeneity	
			Fixed	Random	P value	I^2	P value
Overall	10	1,015	0.77 (0.64, 0.92)	0.62 (0.36, 1.07)		86.90%	0.001
Population					0.187		
Asian	8	620	0.62 (0.50, 0.78)	0.53 (0.32, 0.88)		77.20%	0.001
Caucasian	2	395	1.25 (0.89, 1.76)	1.06 (0.18, 6.30)		96.20%	0.001
Sample size					0.999		
≥100	4	617	0.83 (0.63, 1.10)	0.61 (0.20, 1.86)		93.50%	0.001
<100	6	398	0.72 (0.56, 0.92)	0.62 (0.34, 1.14)		77.80%	0.001
NOS scores					0.705		
≥8	3	501	1.00 (0.75, 1.35)	0.82 (0.23, 2.86)		94.10%	0.001
<8	7	514	0.65 (0.51, 0.82)	0.54 (0.30, 0.98)		79.90%	0.001
Tumor category 1					0.182		
Non-digestive system carcinoma	4	610	0.84 (0.63, 1.13)	0.57 (0.17, 1.89)		93.60%	0.001
Digestive system carcinoma	6	405	0.72 (0.56, 0.91)	0.65 (0.37, 1.13)		76.60%	0.001
Tumor category 2					0.231		
Non-urogenital system carcinoma	7	566	0.66 (0.53, 0.82)	0.60 (0.37, 0.98)		75.50%	0.001
Urogenital system carcinoma	3	449	1.12 (0.80, 1.59)	0.62 (0.12, 3.28)		94.70%	0.001

95% CI, 95% confidence interval; Fixed, fixed model; HR, hazard ratio; NOS, Newcastle-Ottawa scale scores; Random, random model.

found to contribute to heterogeneity (*Figure 2*). After the article retrieving research, we spotted a potential bias within Madhavan *et al.* from samples enrollment, cut-off value selection. Also, the miR-193b detection was performed on the blood samples in Madhavan *et al.*, while tissue samples were collected for the detection in most of the other studies. As for Mu *et al.*, HR and its CI extracted by the Kaplan-Meier Curves with Engauge Digitizer 9.8 and the spreadsheet calculator designed by Tierney *et al.* (17) were contradictory to the significance claimed in the articles. Besides, the sample size [48] is limited, with relatively low NOS score [6], indicating poor quality. These factors may contribute to the generation of heterogeneity.

After removing Madhavan *et al.* and Mu *et al.*, the heterogeneity was significantly reduced in subgroup analyses of sample size (≥100) (I^2=4.00%, P=0.353), NOS scores (≥8) (I^2=0.00%, P=0.811), non-digestive carcinoma (I^2=0.00%, P=0.467), urogenital carcinoma (I^2=0.00%, P=0.491) (Table S1). Also, the significant association between miR-193b and pooled OS was identified after withdrawing the studies and utilizing pooling strategy with random pooling model (HR =0.45, 95% CI: 0.30–0.69, *Figure 3A*). The significance was consistent to the results of fixed pooling mode (HR =0.56, 95% CI: 0.46–0.69, Table S1), suggesting that the over expression of miR-193b could be an indicator of better prognosis. As for the updated subgroup analysis, the expression levels of miR-193b was recognized to be significantly related to the OS among Asian (HR =0.45, 95% CI: 0.28–0.74) and Caucasian (HR =0.43, 95% CI: 0.25–0.72) (*Figure 3B*), studies with the sample size (≥100) (HR =0.39, 95% CI: 0.27–0.56) and sample size (<100) (HR =0.51, 95% CI: 0.28–0.92) (*Figure 3C*), NOS scores (≥8) (HR =0.44, 95% CI: 0.30–0.67) and NOS scores (<8) (HR =0.45, 95% CI: 0.25–0.80) (*Figure 3D*) and patients of non-digestive carcinoma (HR =0.35, 95% CI: 0.24–0.52), digestive carcinoma (HR =0.54, 95% CI: 0.31–0.92) (*Figure 3E*), non-urogenital carcinoma (HR =0.52, 95% CI: 0.33–0.82) or urogenital carcinoma (HR =0.28, 95% CI: 0.16–0.50) (*Figure 3F*). Therefore, higher miR-193b expression level is related to better prognostic outcomes, since the remaining eight studies contained seven cohort studies of Asian patients and only one of Caucasian

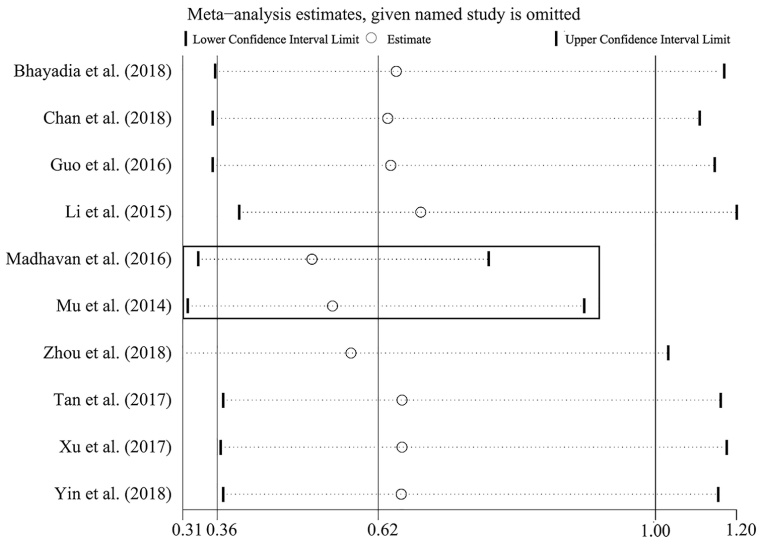

Figure 2 Sensitivity analyses for HRs of overall survivals. HR, hazard ratio.

patients, the conclusion is more robust for Asian patients. We also applied meta regression (Table S1), and sensitivity analyses (Figure S1A), but no potential interference was spotted, which indicated the stableness and reliability of the results after removing Madhavan *et al.* and Mu *et al.*

Funnel plots, Begg's rank correlation and Egger's weighted regression method were utilized to identify the publication bias. The funnel plot of all eight studies reported symmetric and the Begg's, Egger's tests revealed no significant publication bias (P=1.000, P=0.199, respectively, Table S2). After we removed the study from Madhavan *et al.* and Mu *et al.*, the funnel plots was still symmetric, and no obvious publication bias was observed by Begg's and Egger's tests (P=0.902, P=0.116, respectively, Table S2).

Furthermore, four studies from China, including 411 patients, detected the prognosis significance of miR-193b expression levels in patients of carcinoma with cox multivariate regression. After pooling the results, we identified the significant relation of miR-193b expression to the OS (HR =0.36, 95% CI: 0.23–0.54, *Figure 4*) and the heterogeneity was not significant (I^2=0.00%, P=0.395, *Figure 4*), which suggested that the expression level of miR-193b could serve as an independent prognosis factor for the clinical outcome of Asian carcinoma patients. Sensitivity analyses revealed no studies had significant impacts on the results (Figure S1B) and no obvious publication bias was observed (P=0.734 for Begg's test and P=0.380 for Egger's test, respectively, Table S2).

Correlations between miR-193b levels and clinicopathological features among various carcinomas

There are six articles containing 652 cancer patients reported the expression level of miR-193b as dichotomous and investigated the association between miR-193b levels and multiple clinic characteristics. Though there was no significant relation observed between gender and miR-193b levels (OR =0.98, 95% CI: 0.69–1.40, *Figure 5A*), the associated significance was obvious between miR-193b levels and tumor size (OR =2.36, 95% CI: 1.48–3.76, *Figure 5B*), lymph node metastasis (OR =3.16, 95% CI: 2.02–4.93, *Figure 5C*), distant metastasis (OR =3.59, 95% CI: 2.12–6.09, *Figure 5D*), and the homogeneity was achieved (I^2=0.00%, P=0.965; I^2=0.00%, P=0.987, I^2=0.00%, P=0.965; I^2=0.00%, P=0.932, respectively) (*Table 3*). Therefore, higher miR-193b expression level is related to smaller tumor size and less potential of lymph node metastasis and distant metastasis (*Table 3*). Ages were not significantly associated to different miR-193b expression levels in fixed pooling model (OR =0.92, 95% CI: 0.49–1.75) with no significant heterogeneity observed (I^2=11.30%, P=0.288) (*Table 3*). Sensitivity analyses were performed, and no studies in any of the pooling processes of characteristics related to miR-193b had a significant impact on the results (Figure S1C-S1F). However, there was significant publication bias observed by Begg's or Egger's tests in gender groups and distant metastasis, and the bias came from Chan *et al.* (23) (Figure S2A,S2B). But

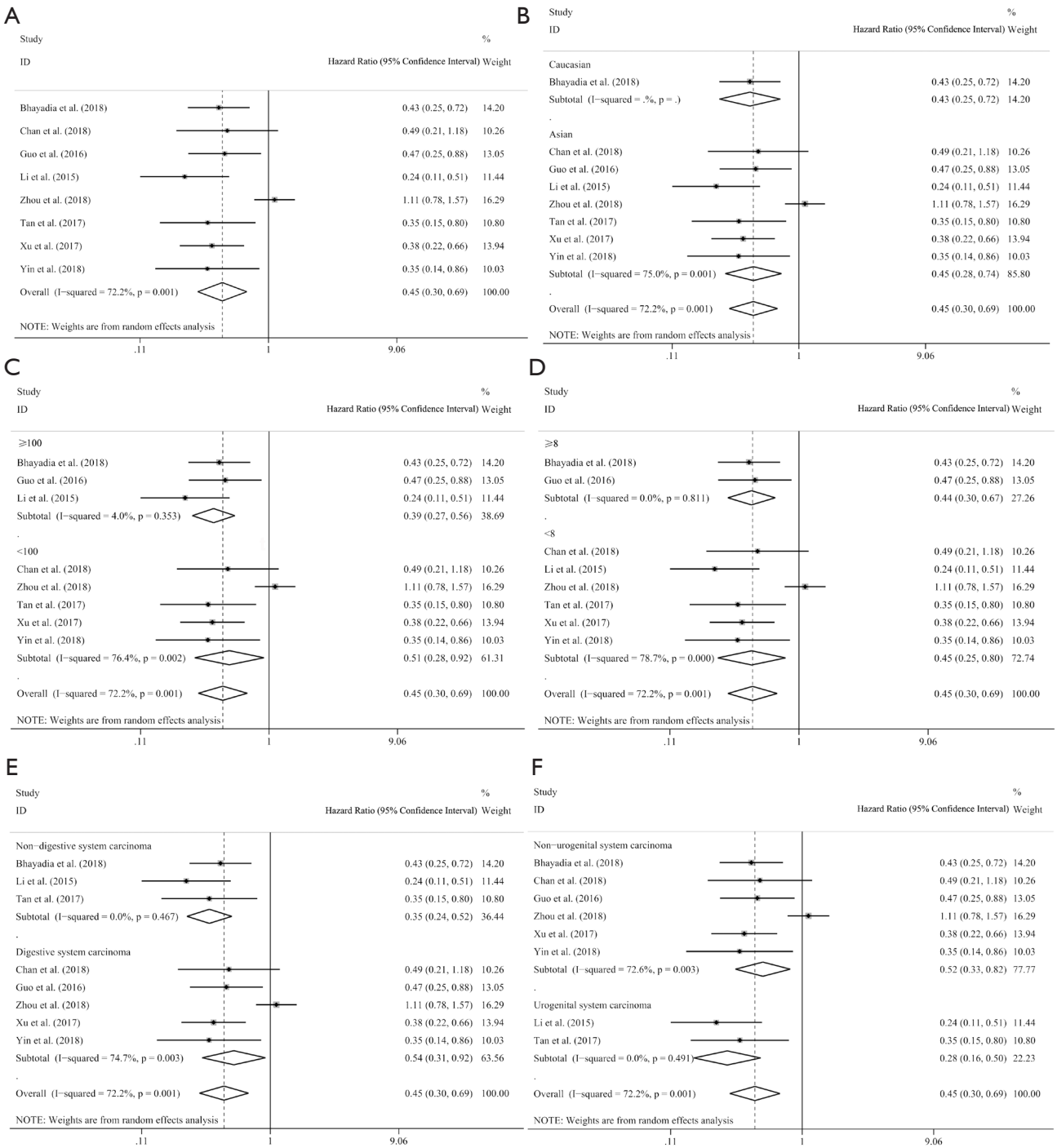

Figure 3 The association between miR-193b expression levels and overall survivals (A), and subgroup analyses of population (Asian and Caucasian) (B), sample sizes (≥100 and <100) (C), NOS scores (≥8 and <8) (D), tumor category (non-digestive system and digestive system) (E) and tumor category (non-urogenital system and urogenital system) (F) without outlier. NOS, Newcastle-Ottawa scale.

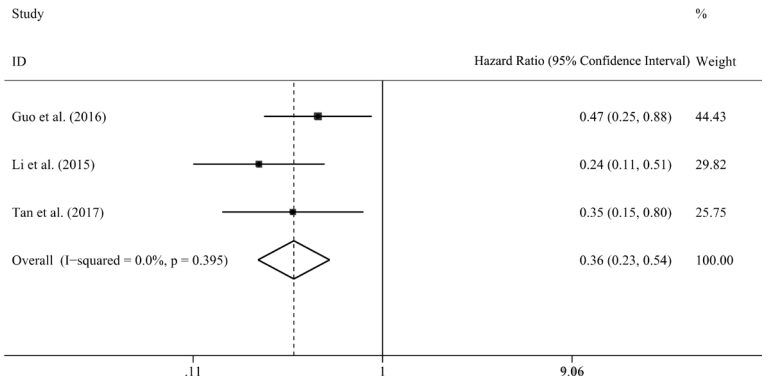

Figure 4 The independent role of miR-193b as a prognosis detector for the overall survivals of carcinomas in Asian patients.

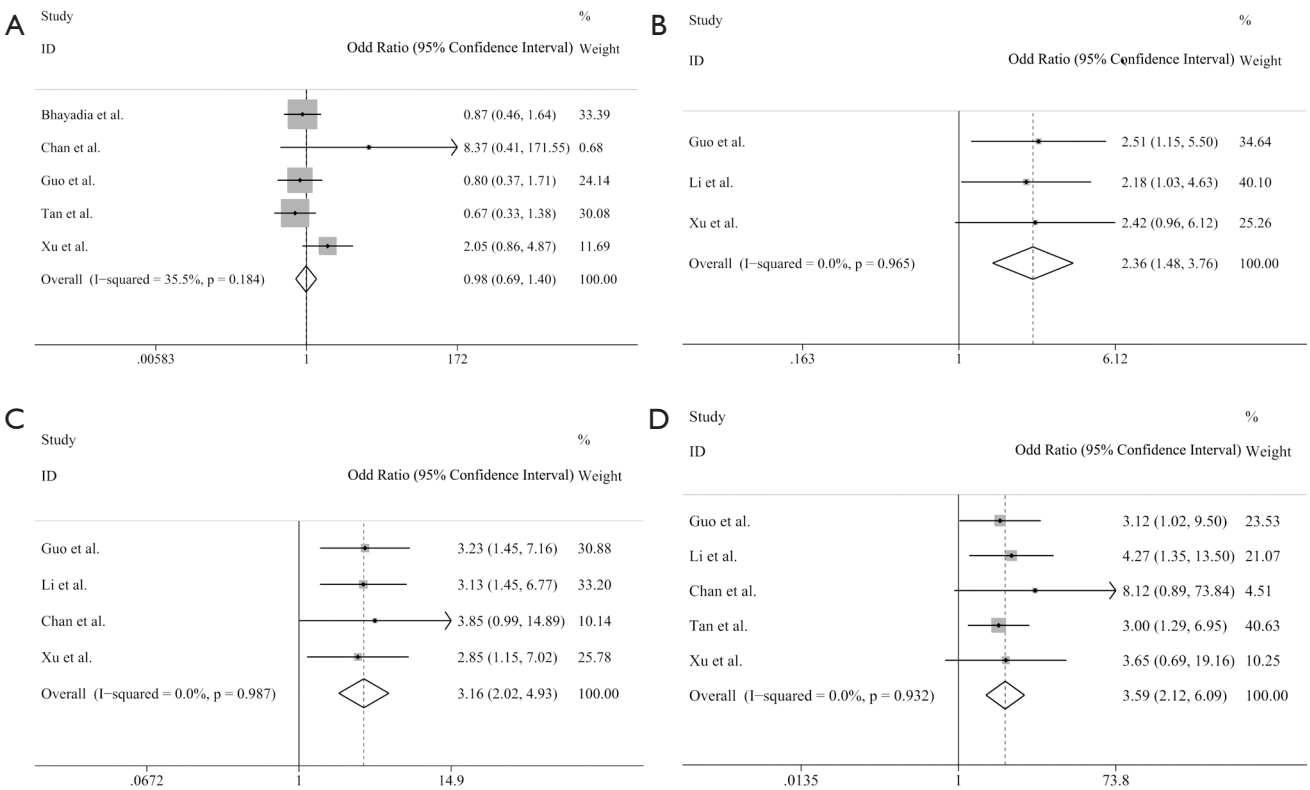

Figure 5 Clinicopathology characteristics for association between miR-193b expression levels and gender (A), tumor size (B), lymph node metastasis (C), distant metastasis (D).

the significance was not altered after removal of Chan *et al.* (Figure S2C,S2D).

Discussion

MiRNA regulates the physiological function of cells, while its abnormal expression might contribute to development of tumors (24). It has been confirmed that miRNAs have effects on the expression of their target genes, thus regulating various cellular processes (25). The expression of miRNA-193b is closely associated with the proliferation, differentiation and apoptosis of the cancer cells, though many studies have explored the profiles of miR-193b in the development of various types of carcinomas (26) and

Table 3 Overall analysis of miR-193b expression associated with clinicopathological characteristics

Clinicopathological parameters	No. of studies	No. of patients	Pooled OR (95% CI)		Heterogeneity	
			Fixed	Random	I^2	P value
Gender (male *vs.* female)	5	536	0.98 (0.69, 1.40)	1.00 (0.62, 1.61)	35.50%	0.184
Age (≤64.5 *vs.* >64.5 years)	2	153	0.92 (0.49, 1.75)	0.91 (0.46, 1.82)	11.30%	0.288
Tumor size (≤5 *vs.* >5 cm)	3	312	2.36 (1.48, 3.76)	2.36 (1.48, 3.76)	0.00%	0.965
Lymph node metastasis (absent *vs.* present)	4	359	3.16 (2.02, 4.93)	3.16 (2.02, 4.93)	0.00%	0.987
Distant metastasis (absent *vs.* present)	5	491	3.59 (2.12, 6.09)	3.52 (2.07, 6.00)	0.00%	0.932

95% CI, 95% confidence interval; Fixed, fixed model; OR, odds ratio; Random, random model.

the underlying mechanism of the tumor metastasis (27,28). However, the potential effects of miR-193b in tumors of distinguished origins are still controversial. Many studies revealed its suppression impacts on the progression of cancer growth. For example, Li *et al.* (28) reported the role of miR-193b as a tumor suppressor and significantly decreased proliferative and invasive capacity of the pancreatic cancer cell lines. Also it has been demonstrated that transcription of estrogen receptor-α could be greatly reduced by the over expression of miR-193b, resulting in the inhibition of estrogen-induce proliferation of breast cancer (29). In addition, miR-193b was reported to enhance urokinase-type plasminogen activator and inhibited breast cancer cell invasion (30). However, there were also some studies identifying the oncogene motivating role of miR-193b. The increased expression level of miR-193b inhibited the expression of SMAD3 and TGF-β, and suppressed apoptosis of colon cancer cells (31). Jamali *et al.* elaborated that the expression of mir-19b in HNSCC has no significant correlation with the survival rate of patients (14,15). Since the cellular function of miR-193b is of great diversity, to clarify the clinical role of miR-193b in carcinoma, we carried out the meta-analysis to summarize related cohort studies and comprehensively investigate the association between miR-193b expression levels and the clinic outcomes of various cancers.

In our findings, a significant relation of miR-193b expression levels to the OS was identified: lower expression of miR-193b was significantly related to the poor OS in different types of carcinoma patients including acute myeloid leukemia, esophageal squamous cell carcinoma, gastric cancer, breast cancer, colorectal cancer, pancreatic cancer, liver cancer, clear cell renal cell carcinoma and ovarian cancer, indicating that high expression of miR-193b is a potential indicator as a better clinic outcomes. Since the enrolled studies were mostly Chinese cohort studies, the conclusion is more robust for Asian patients, which is also supported by subgroup analysis in *Figure 3B*. The investigation of the relationship between miR-193b and clinical characteristics indicated that in the patients of lower miR-193b expression, the tumor size was tended to be larger, and the possibility of lymph node metastasis and distant metastasis was relatively higher. This result was consistent to the majority of the published articles reporting miR-193b as a suppressor of cancer cells proliferation (32), migration (33), vasculogenesis (34), invasive activity (35). For example, Roth *et al.* observed the inhibiting function of miRNA-193b on neuroblastoma cell growth through downregulation of Cyclin D1, MCL-1 and MYCN (36). Yin *et al.* (37) reported that deregulation of miRNA-193b affected liver cancer proliferation via myeloid cell leukemia-1. Mets *et al.* found that miRNA-193b suppressed T-cell acute lymphoblastic leukemia via targeting the *MYB* oncogene (38). Wang *et al.* explored the inhibitory function of the proliferation, migration and invasion for miRNA-193b in gastric cancer cells (35).

However, basic studies are not always consistent with cohort studies. miR-193b has been identified to arrest cell cycle and acts as a suppressor in breast cancer cells (39), and lower expression level of miR-193b was observed in triple negative breast cancer cell lines, which represented poor clinical outcomes. But cohort study, Madhavan *et al.* (12), showed that higher miR-193b was an indicator for poor prognosis of metastatic breast cancer. In pancreatic cancer cells line, miR-193b was found to suppress the malignant transformation by targeting the downstream genes (40,41). But the cohort study, Zhou *et al.*, showed no significance in miR-193b expression and the prognosis of pancreatic cancer patients (16). Therefore, the performance of cancer cell lines and animals with regulation of miR-193b may

not actually reflect the association of miR-193b expression levels and clinic outcomes. Clinic studies directly report the human pathology and molecular expression profile and provide the most reliable statistics, while animals' experiments still need to be verified on human subjects. Thus, when this inconsistency occurs, we suggest that rigorous cohort studies better reflect actual effects of miR-193b. Considering that existing clinical studies focusing on mir-193b only performed on certain human cancers, more studies including the survival analysis of cancer patients with different miR-193b expression levels are needed to draw a more comprehensive and reliable conclusion.

There exist a few flaws that shall be clarified in our research. First of all, the languages of enrolled studies were restricted to English and Chinese and may cause the bias due to lack of other populations. Second, the HRs and its CIs extracted from Chan *et al.* (23) and Mu *et al.* (13) by the Kaplan-Meier curves with Engauge Digitizer 9.8 and the spreadsheet calculator designed by Tierney *et al.* (17) were contradictory to the significance claimed in the articles. Two independent co-authors (Hao Yu and Yizhong Peng) had extracted the data from Chan *et al.* (23) and Mu *et al.* (13) for several times using the methods described above whose accuracy had been proved by many researches (42-44). The extracted data was always consistent but significantly different from the original articles. The bias needed to be avoided by more precise data extracting methods or improving the quality of the enrolled studies. Third, the cut-off values of the expression levels of miR-193b were not identical among the studies, though most of them were presupposed as median. Fourth, the amount of research included was not enough. When this inconsistency occurs, we suggest that strict cohort studies better reflect the actual effect of mir-193b. Therefore, after strict screening, the number of samples included is greatly reduced. More relevant studies and patients should be identified for this analysis to enhance the reliability and confidence of our findings.

Conclusions

In conclusion, miR-193b is an ideal biomarker in the human cancer prognosis, and the low expression level of miR-193b is significantly associated with poor OS in many human malignancies. Moreover, the patients with lower miR-193b tend to facilitate tumor metastasis and develop solid tumor of larger size. Owing to the complex functions of miR-193b in cancer progression and metastasis, further studies at a larger scale are needed to establish the specific utility of miR-193b as a prognostic biomarker for more types of cancers.

Acknowledgments

We would like to thank all the people who helped us in the current study.
Funding: This study was funded by the National Natural Science Foundation of China (No. 81974390).

Footnote

Reporting Checklist: The authors have completed the PRISMA reporting checklist. Available at https://tcr.amegroups.com/article/view/10.21037/tcr-21-2557/rc

Peer Review File: Available at https://tcr.amegroups.com/article/view/10.21037/tcr-21-2557/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tcr.amegroups.com/article/view/10.21037/tcr-21-2557/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Cite this article as: Yu H, Peng Y, Wu Z, Wang M, Jiang X. MiR-193b as an effective biomarker in human cancer prognosis for Asian patients: a meta-analysis. Transl Cancer Res 2022;11(7):2249-2261. doi: 10.21037/tcr-21-2557

Supplementary

Table S1 Meta-analysis of miR-193b as a prognostic indicator for patients of various carcinoma without outliers

Variables	No. of studies	No. of patients	Pooled HR (95% CI)		Meta regression	Heterogeneity	
			Fixed	Random	P value	I^2	P value
Overall	8	733	0.56 (0.46, 0.69)	0.45 (0.30, 0.69)	–	72.20%	0.001
Population					0.503		
Asian	7	572	0.59 (0.47, 0.74)	0.45 (0.28, 0.74)		75.00%	0.001
Caucasian	1	161	0.43 (0.25, 0.72)	0.43 (0.25, 0.72)		–	–
Sample size					0.212		
≥100	3	383	0.39 (0.27, 0.55)	0.39 (0.27, 0.56)		4.00%	0.353
<100	5	350	0.67 (0.52, 0.87)	0.51 (0.28, 0.92)		76.40%	0.002
NOS scores					0.339		
≥8	2	267	0.44 (0.30, 0.67)	0.44 (0.30, 0.67)		0.00%	0.811
<8	6	466	0.61 (0.48, 0.77)	0.45 (0.25, 0.80)		78.70%	0.001
Tumor category 1					0.206		
Non-digestive system carcinoma	3	376	0.35 (0.24, 0.52)	0.35 (0.24, 0.52)		0.00%	0.467
Digestive system carcinoma	5	357	0.68 (0.53, 0.86)	0.54 (0.31, 0.92)		74.70%	0.003
Tumor category 2					0.351		
Non-urogenital system carcinoma	6	518	0.62 (0.50, 0.78)	0.52 (0.33, 0.82)		76.70%	0.003
Urogenital system carcinoma	2	215	0.28 (0.16, 0.50)	0.28 (0.16, 0.50)		0.00%	0.491

95% CI, 95% confidence interval; Fixed, fixed model; HR, hazard ratio; NOS, Newcastle-Ottawa scale scores; Random, random model.

Table S2 Summary of publication bias in various analyses

Variables	No. of studies	No. of patients	Begg's test (P value)	Egger's test (P value)
Pooling HR with outliers	10	1,015	1.000	0.199
Pooling HR without outliers	8	733	0.902	0.116
Pooling HR for multivariate regression analysis	4	411	0.734	0.380
Pooling OR for gender	5	536	0.086	0.017
Pooling OR for ages	2	153	1.000	–
Pooling OR for tumor sizes	3	312	1.000	0.742
Pooling OR for lymph node metastasis	4	359	0.734	0.322

HR, hazard ratio; OR, odds ratio.

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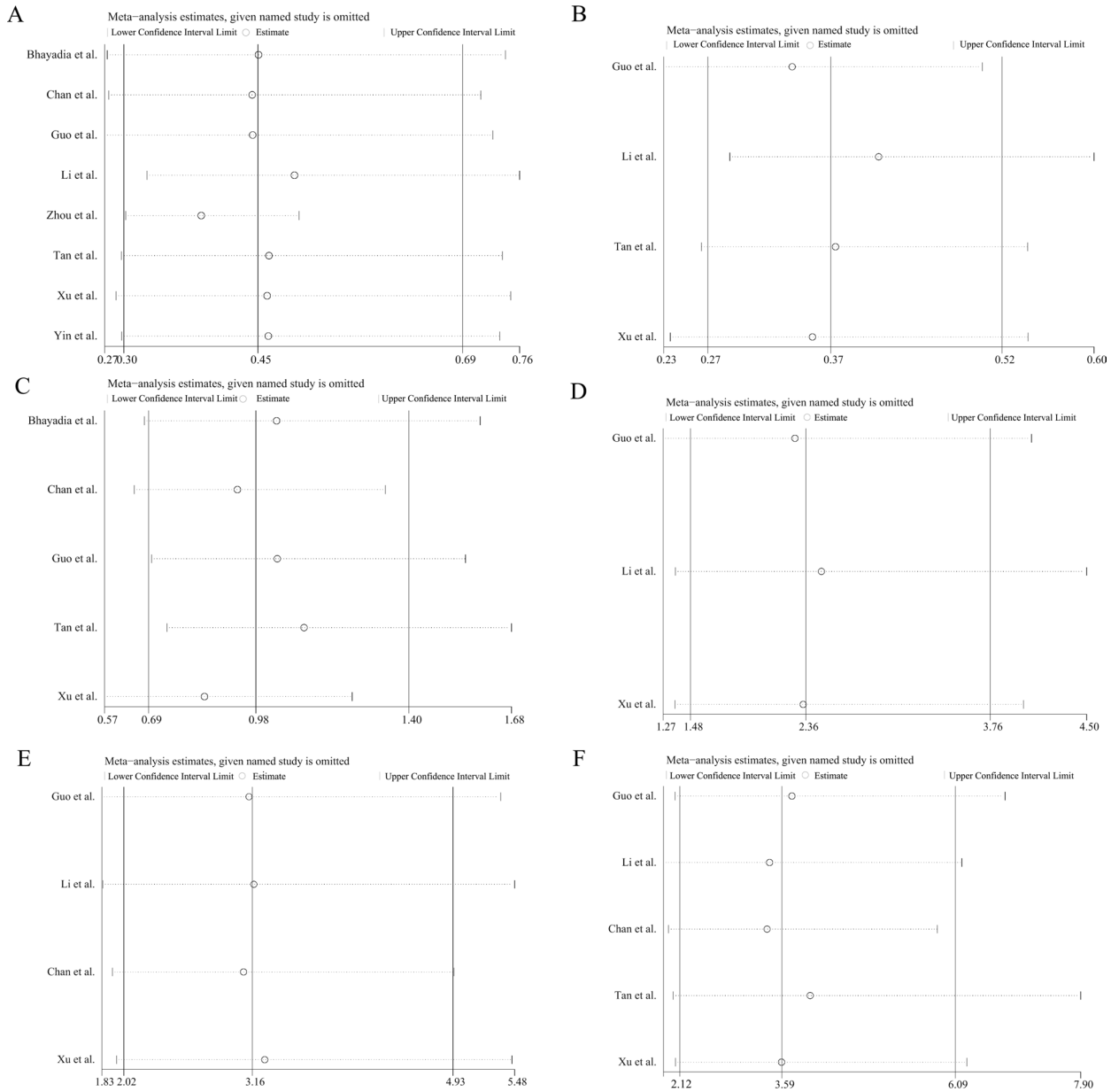

Figure S1 Sensitivity analyses for HRs of (A) overall survivals without outliers, (B) multivariate regression analysis, and the association between miR-193b levels and (C) gender, (D)tumor size, (E) lymph node metastasis, (F) distant metastasis.

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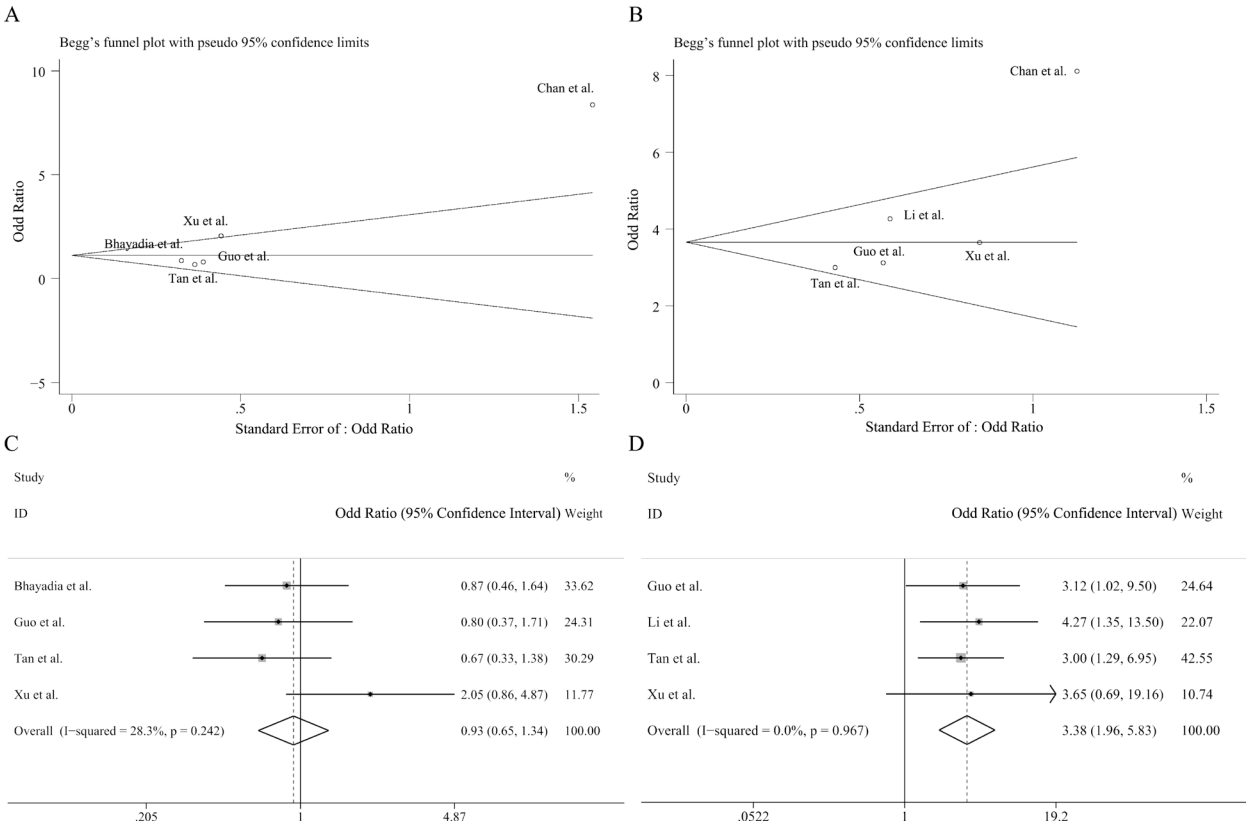

Figure S2 Clinicopathology characteristics analyses including publication bias for association analysis of miR-193b expression levels and (A) gender, (B) distant metastasis; forest plots for association between miR-193b expression levels and (C) gender without the outlier, (D) distant metastasis without the outlier.

https://dx.doi.org/10.21037/tcr-21-2557