Original Article

Diagnostic and prognostic role of microRNA-525 in different cancers: a systematic review and meta-analysis

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Background: New prospect of cancer therapeutical management seems to be early diagnosis and prognosis prediction by microRNAs. The aim of our study is to explore the role of miR-525 in cancer diagnosis and prognosis through a systematic review and meta-analysis.

Methods: We conducted systematic search on PubMed, Embase, Web of Science, Scopus, Medline, Chinese National Knowledge Infrastructure (CNKI) and Wanfang databases as at November 25, 2023, regardless of languages. Sensitivity, specificity, and diagnostic odds ratio (DOR) were extracted for diagnostic meta-analysis, while hazard ratio (HR) with 95% confidence interval (CI) for prognostic meta-analysis. Subgroup analysis and publication bias analysis were performed appropriately to investigate possible sources of heterogeneity.

Results: A total of 8 studies were included in the meta-analysis, of which 7 were used for diagnostic meta-analysis, covering 559 patients, and 3 were used for prognostic meta-analysis, covering 324 patients. The pooled sensitivity was 0.75 (95% CI: 0.70–0.79), specificity was 0.73 (95% CI: 0.68–0.78), DOR was 13.08 (95% CI: 4.18–40.91), and the area under the curve (AUC) was 0.86 (95% CI: 0.83–0.89). Subgroup analysis showed that miR-525 may have good diagnostic ability in the early tumor node metastasis (TNM) stage of cancer. Prognostic meta-analysis showed that low miR-525 expression in patients was associated with preferable survival (HR =0.17, 95% CI: 0.07–0.41).

Conclusions: Our findings suggest that miR-525 could be used as a potential biomarker for cancer patients. Low expression of miR-525 in cancers predicted a good prognosis.

Keywords: MiR-525; diagnosis; prognosis; cancer; meta-analysis

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Introduction

As a major cause of human death, cancer is still a leading threat to human health, while improving early detection and precision treatment of cancer are effective ways to improve cancer prognosis and reduce the economic burden on patients and health systems (1,2). For developing more precise prognostic and diagnostic prediction strategies, we amplified the understanding on the tumor biomarkers involved in key biological processes of human disease progression (3). Harnessing this new knowledge will enable us to provide stratified and personalized treatment options for the diagnosis and clinical management of human tumors (4). In tissue or blood samples of patients with different types and subtypes of tumors, there are differentially expressed cancer biomarkers which can be detected, such as overexpression of proto-oncogenes (5), fusion genes caused by chromosomal translocations (6), and

the selection of appropriate biomarkers can be used to assist in the diagnosis of tumors and indicate potential therapies to guide the clinical use of targeted drugs (7), or facilitate the development of a new class of drugs, so that patients whose tumors cannot benefit from conventional therapies can obtain precise clinical treatment and help. And the microRNA-based biomarkers can greatly improve the early detection of cancer and the progress of targeted therapy of patients (8).

MicroRNAs (miRNAs) have emerged as an interesting area of translational medicine research, with miRNAs influencing messenger RNA (mRNA) primarily through recognition sites in the 3' untranslated region (UTR), thereby regulating its stability and influencing mRNA relative levels (9). MiRNAs are involved in a variety of biological activities of neoplastic and non-neoplastic diseases related pathways and immune escape processes, and they have complex roles in cancers. Based on evidence from miRNA-related studies and pre-clinical trials, miRNAs have been proposed as potential biomarkers relevant to cancer diagnosis and treatment, and many miRNA mimics and inhibitors are involved in drug resistance mechanisms of conventional cancer chemotherapy to support therapeutic targeting oncogenic pathways using miRNAs (10). Several studies have shown that miR-525 exerts different effects in different tumors. Genetic information of hsa-miR-525 is located on chromosome 19, and it is abnormally expressed in diffuse large B-cell lymphoma (11), osteoarthritis (12), and prostate cancer (13), and is involved in tumor development process. MiR-525 can play a critical role in formatting, developing, and epithelial-to-mesenchymal transition (14) of cancers, for example, miR-525-3p is reported to be overexpressed in liver cancer tissues, targeted to inhibit ZNF395 gene and promote liver cancer cells to migrate and invade (15). MiR-525 can also inhibit tumor cell proliferation, migration and invasion. Overexpression of miR-525 can inhibit the migration and invasion of chondrosarcoma cells and induce cell apoptosis, and down-regulated miR-525 activates the FAK/Src/PI3K/Akt signaling pathway by targeting F-spondin1 gene to promote the malignant progression of chondrosarcoma (16). However, miR-525-5p and miR-525-3p play different roles in different cancers respectively, and the ratio of the two mature strands of miRNA duplex can vary depending on developmental stage and in various diseases (17).

Although there are still unresolved problems with miRNAs as diagnostic markers for cancers, they can show good potential in clinical application according to different cancer types and sample sources (18). In study related to esophageal squamous cell carcinoma, miRNAs can be potential therapeutic targets as well as potential prognostic indicators (19). The use of miR-525 in cancer diagnosis and treatment has rarely been investigated in studies. Therefore, we systematically reviewed the literatures and conducted a meta-analysis of the data extracted from the study to explore whether miR-525 can be used as a novel tumor biomarker and its prognostic ability in cancer patients. We present this article in accordance with the PRISMA-DTA reporting checklist (available at https://tcr.amegroups.com/article/view/10.21037/tcr-24-383/rc) (20).

Highlight box

Key findings

- MiR-525 can be used as a novel tumor biomarker and has certain predictive ability for the prognosis of cancer patients, which is of significance for the early clinical diagnosis and prognosis prediction of cancer patients.

What is known and what is new?

- Many miRNAs have been proposed as potential biomarkers relevant to cancers, and are involved in drug resistance mechanisms of cancer chemotherapy.
- MiR-525 can be used as a potential biomarker for cancer diagnosis, and lower expression of miR-525 predicts a preferable prognosis for some types of cancer.

What is the implication, and what should change now?

- The meta-analysis results showed that miR-525 may be suitable as a potential biomarker for the clinical diagnosis of cancer. This marker can improve the early detection of cancer, guide the clinical use of targeted drugs, so that patients can obtain accurate clinical treatment and help.

Methods

Registration and protocol

The protocol of this study was registered on International Prospective Register of Systematic Reviews (PROSPERO) on September 27, 2023, with the registration ID: CRD42023458283.

Literature search strategy

We conducted a comprehensive literature search on PubMed, Embase, Web of Science, Scopus, Medline, and Chinese databases, China National Knowledge

Infrastructure (CNKI) and Wan Fang databases, as at November 25, 2023, without language restrictions. The included literature was searched using Medical Subject Headings (MeSH), entry terms, and free-text keywords. We used different combinations of terms related to miR-525 and cancer, such as "neoplasm" or "tumor" or "cancer" and "hsa-miR-525" or "microRNA-525, human" or "miR-525, human", screened the literature containing the data needed for extraction. The comprehensive database search was performed by two researchers (M.Z. and Y.P.), and the detailed search strategies are provided in Appendix 1.

Inclusion and exclusion criteria

For studies evaluating the diagnostic value of miR-525 in cancer, the inclusion criteria were as follows: (I) any types of cancers associated with miR-525, (II) human-based cancer studies providing diagnostic research samples, including tissue, serum, (III) detection of low/high levels of miR-525 expression in different cancers, and (IV) providing sufficient sample data [true positive (TP), false positive (FP), true negative (TN), false negative (FN)] to calculate diagnostic indicators, including sensitivity and specificity. Meanwhile, the inclusion criteria for studies on the prognostic value of miR-525 were as follows: (I) any type of cancers concerning miR-525, (II) human-related cancer studies providing research samples with prognostic value, (III) determination of low/high level expression of miR-525 in various cancers, and (IV) providing sufficient data to calculate or extract prognostic indicators related to miR-525, including survival curve, hazard ratio (HR), and their corresponding 95% confidence intervals (95% CIs).

Exclusion criteria were as follows: (I) other types of articles, such as reviews, letters, conference abstracts, meta-analyses, case reports, animal or laboratory studies, (II) insufficient data for calculating or extracting indicators of diagnostic or prognostic value of miR-525 in cancers, and (III) miR-525-related studies that were not based on human cancers.

Data extraction and quality assessment

Data extraction

We extracted the first author's name, publication year, nationality, cancer type, specimen type, and the type and detection method of miR-525 from all literatures. For the articles included in the diagnostic evaluation, we extracted the exact case number of TP, FP, FN and TN from the literature retrieved in diagnostic meta-analysis, and calculated the corresponding sensitivity and specificity and other diagnostic indicators. For the studies included in the prognostic meta-analysis, follow-up time, prognostic outcome, HR with 95% CI were extracted from all included articles. If HR was not reported in research or there was only Kaplan-Meier curve reported in literature, we would use the EngaugeDigitizer12.1 (https://engauge-digitizer.software.informer.com) extracted HR from Kaplan-Meier curve. Some of the data included in our study were obtained by contacting the first author and the corresponding author by email.

Quality assessment

We used the Quality Assessment Diagnostic Accuracy Studies 2 (QUADAS-2) tool to access the quality of studies included in the diagnostic meta-analysis, which consists of 14 assessment items for systematic review of diagnostic accuracy studies, and each of the 14 items was rated as yes (score 1), no (score –1) or unclear (score 0) (21). And the Newcastle-Ottawa Scale (NOS) was applied to evaluate the quality of studies used for prognostic meta-analysis (22). NOS scores <4 were classified as low quality, scores 4–6 as medium quality, and scores greater than 6 as high quality. Full text searching, screening and evaluation, data extraction and quality assessment were all conducted by two researchers (M.Z. and Y.P.) respectively, and the differences between the two researchers are resolved through the assistance of the third researcher (B.G.).

Statistical analysis

We calculated the pooled diagnostic indicators of miR-525 in various cancers: pooled sensitivity, specificity, diagnostic odds ratio (DOR), positive likelihood ratio (PLR), negative likelihood ratio (NLR) and their corresponding 95% CI of the included studies of diagnostic meta-analysis through the random-effects Model (Der Simonian-Laird method), and the corresponding forest maps and subgroup analysis were drawn and processed though Meta-DiSc® software (Version 1.4, Madrid, Spain) and Stata SE 17.0 software (Stata Corp, College Station, TX, USA). We drew the summary receiver operating characteristic (SROC) curve based on original data extracted from included studies, the area under the curve (AUC), ranging from 0.5 to 1.0, was calculated to assess the overall diagnostic value of miR-525 in cancers. If the AUC value is closer to 0.5, it means that the cancer diagnostic ability of miR-525 is poor, and

if it is close to 1.0, the diagnostic performance of miR-525 is good. Review Manager 5.4 (Nordic Cochrane Centre, Cochrane Collaboration, UK) and Stata SE 17.0 (Stata Corp, College Station, TX, USA) were used to calculate the pooled HR with 95% CI and perform the subgroup analysis of all included literatures in prognostic meta-analysis. For studies which did not report HR, we applied Engauge Digitizer 12.1 to digitize the Kaplan-Meier curve to extract HR and corresponding 95% CI from included study, with P value <0.05 defined as significant. If there were only cancer patients with high miR-525 expression included in the meta-analysis, HR >1 could indicate that cancer patients with high expression of miR-525 had poor prognosis, and HR <1 would indicate high expression of miR-525 had a protective effect on the prognosis of cancer patients.

Heterogeneity between included studies was evaluated using Cochran's Q test, defined as low heterogeneity, and we could apply fixed-effects mode to pool the extracted data, and the random-effects model could be used in other cases, but the random-effects model can also be used for meta-analysis with any situation of heterogeneity. When I^2>50%, it indicated a large heterogeneity among the combined study, a subgroup analysis should be performed to determine the source of heterogeneity in the diagnostic and prognostic meta-analyses. Deeks' funnel plot was used to evaluate publication bias of diagnostic meta-analysis, and publication bias of prognostic meta-analysis was detected through Funnel Plot, Begg's test and Egger's test.

Results

Study selection and characteristics of included studies

There were 335 records retrieved with the search strategy, including 20 articles from PubMed, 40 from Embase, 41 from Web of science, 1 from Scopus, 18 from Medline in English database, 19 from CNKI and 196 from Wanfang database records in Chinese database. After removing duplicates records, reviews, and letters, there were 179 articles remained. And we browsed and screened the titles and abstracts of the remained articles, then excluded 139 irrelevant studies. After evaluating the full text of the remaining 40 articles, 30 articles related to cell or animal studies which did not contain the diagnostic or prognostic data, as well as 2 studies with incomplete clinical data, were excluded, and only 8 studies were included in the systematic review and meta-analysis, including 629 cancer patients, and 7 of the studies were included in the diagnostic meta-analysis and 3 were included in the prognostic meta-analysis (*Figure 1*).

We analyzed in 559 patients from 7 studies to evaluate the pooled diagnostic indicators and diagnostic value of miR-525 in different cancers and the association between high/low expression level of miR-525 and different clinical characteristics of cancer patients (23-29). And the pooled prognostic analysis of the predictive value of low expression levels of miR-525 in survival outcomes in cancer patients was conducted in 324 patients from 3 studies (28-30). The characteristics of the literatures included in the diagnostic meta-analysis are summarized in *Table 1*, while detailed information about the literatures included in the prognostic meta-analysis is shown in *Table 2*. These studies were conducted from 2013 to 2023, with one in the Czech Republic, one in Turkey and six in China (23-30). These selected studies have included various types of cancer: hepatocellular carcinoma (HCC, n=1), colorectal cancer (COAD, n=1), breast cancer (BC, n=1), gestational trophoblastic tumor (GTT, n=1), Burkitt lymphoma (BL, n=1), Hodgkin's lymphoma (HL, n=1), diffuse large B-cell lymphoma (DLBCL, n=1), and thymoma and thymic carcinoma (THYM, n=1) (23–30). Different assay methods (TaqMan or SYBR) were used to detect miR-525 expression in tissues (n=7) and serum (n=1) by quantitative real-time polymerase chain reaction (RT-qPCR) (23-30). Two studies in the diagnostic meta-analysis involved miR-525-3p and five involved miR-525-5p, while three studies in the prognostic meta-analysis were all related to miR-525-5p (23-30). The included studies were classified according to the miR-525 expression, three studies in the diagnostic meta-analysis involved high miR-525 expression in cancer patients and four involved low expression of miR-525, while all studies included in the prognostic meta-analysis had low expression of miR-525 (23-30).

Quality assessment

We assessed the quality of the studies included in the diagnostic meta-analysis using the QUADAS-2 tool (21). All the studies were scored between 7 and 11, indicating that the studies included in the meta-analysis were of medium or high quality, as shown in *Table 1*, and Figures S1,S2. For the prognostic meta-analysis, we used the NOS tool (22), and all the studies scored 7 to 8 points, indicating that the included studies were of high quality, as shown in Table S1.

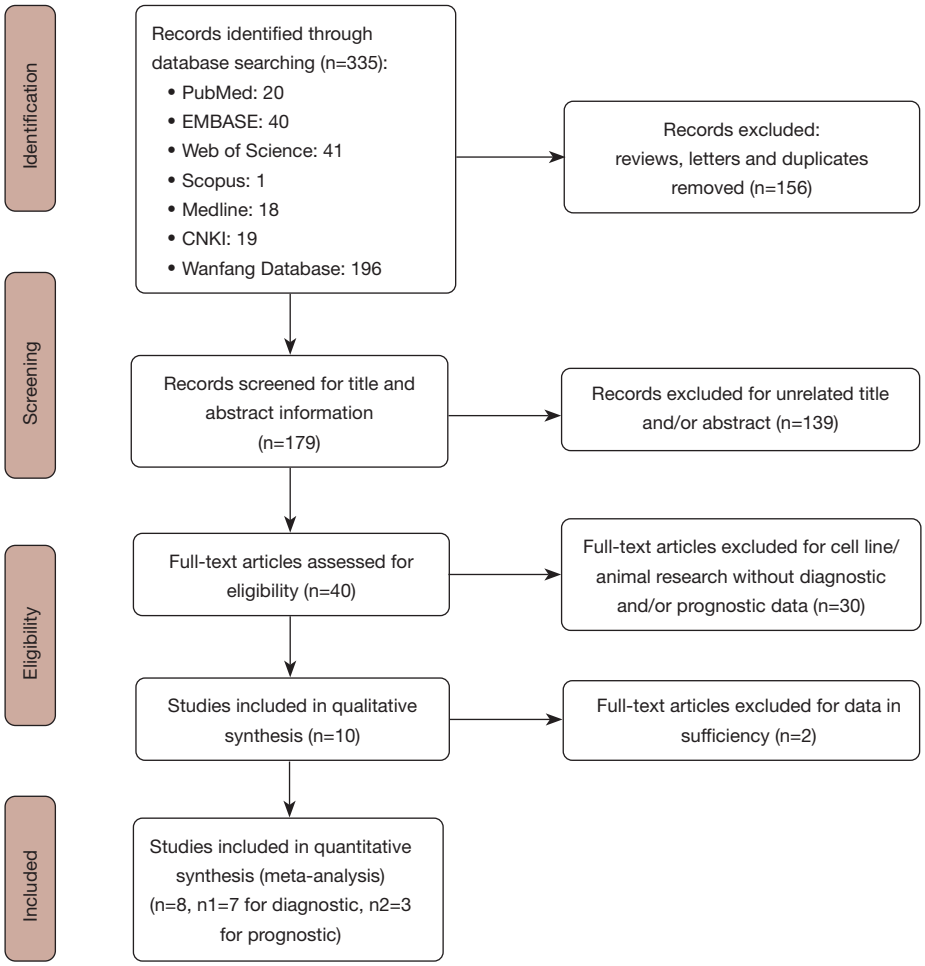

Figure 1 Flow diagram of the literature search and study selection, and the number of remaining literatures after screening by inclusion and exclusion criteria. n1=7: 7 out of 8 studies were included in the diagnostic meta-analysis; n2=3: 3 out of 8 studies were included in the prognostic meta-analysis.

Results of the diagnostic meta-analysis

The results of the diagnostic meta-analysis of the 7 included studies are illustrated in the forest plots as shown in *Table 1* and *Figure 2* and by using the random-effects model (23-29). The pooled sensitivity, specificity, and DOR were shown in *Figure 2* as follows: 0.75 (95% CI: 0.7–0.79), 0.73 (95% CI: 0.68–0.78), and 13.08 (95% CI: 4.18–40.91), and the pooled PLR and NLR were 3.74 (95% CI: 1.53–9.13) and 0.33 (95% CI: 0.20–0.55), respectively (*Figure 2A-2E*). And the ROC and SROC curve were shown as an untypical 'shoulder-arm' pattern which means no significant threshold effect existed in the current -meta-analysis, with the AUC under SROC was 0.86 (95% CI: 0.83–0.89) (*Figure 2F,2G*). The pooled meta-analysis results suggested that miR-525 had high diagnostic accuracy, in which the pooled sensitivity was 0.75, the specificity was 0.73, and AUC was 0.86 close to 1, and the Youden index was 0.48. We used Fagan's nomogram to assess the clinical utility of the index test (*Figure 3A*). In the Fagan plot, the prior probability was 20%, the posterior-positive probability (PPP) was 47%, the posterior-negative probability (PPN) was 6%, and LR+ was 4, and LR- was 0.24. And the larger the LR+ was, the stronger the detection capability of miR-525 as a diagnostic marker, while the smaller the LR- was, the stronger the ability of the test biomarker to exclude the disease. While the likelihood ratio in the Likelihood Ratio Scattergram is greater than 0.1 and less than 10 (*Figure 3B*). Taken together, miR-525 had a preferable accuracy as a diagnostic identification marker for cancer patients.

Table 1 Main characteristics of the eligible studies for diagnostic meta-analysis

Author	Country/year	MiR-525 type	Cancer type	Specimen	Test method	Expression status	Patients [control]	TP	FP	FN	TN	SEN (%)	SPE (%)	PLR	NLR	DOR	QUADAS-2
Fei Pang	China/2013	miR-525-3p	HCC	Tissue	RT-qPCR	Up-regulated	136	80	2	47	7	63	78	2.83	0.48	5.96	7
Guo-Zhen Wang	China/2023	miR-525-5p	COAD	Tissue	RT-qPCR	Up-regulated	68 [50]	24	26	8	61	75	70	2.51	0.36	7.04	11
Hui-Hua Tang	China/2023	miR-525-5p	BC	–	RT-qPCR	Down-regulated	180	38	14	10	118	79	89	7.46	0.23	32.03	10
Ilona Hromadnikova	Czech Republic/2017	miR-525-5p	GTT	Plasma	RT-qPCR	Up-regulated	60 [38]	39	3	0	35	100	92	11.00	0.01	801.29	11
Qing-Qing Wang	China/2021	miR-525-5p	BL	Tissue	RT-qPCR	Down-regulated	9 [25]	8	5	1	20	89	80	4.44	0.14	32.00	10
Semra Paydas	Turkey/2016	miR-525-3p	HL	Tissue	RT-qPCR	Down-regulated	32 [60]	26	47	6	13	81	22	1.04	0.87	1.20	10
Ting Zhao	China/2020	miR-525-5p	DLBCL	Tissue	RT-qPCR	Down-regulated	74 [30]	55	5	19	25	74	83	4.46	0.31	14.47	11

TP, true positive; FP, false positive; FN, false negative; TN, true negative; SEN, sensitivity; SPE, specificity; PLR, positive likelihood ratio; NLR, negative likelihood ratio; DOR, diagnostic odds ratio; QUADAS-2, quality assessment of diagnostic accuracy studies-2; HCC, hepatocellular carcinoma; RT-qPCR, quantitative real-time polymerase chain reaction; COAD, colorectal cancer; BC, breast cancer; GTT, gestational trophoblastic tumor; BL, Burkitt lymphoma; HL, Hodgkin's lymphoma; DLBCL, diffuse large B-cell lymphoma.

Table 2 Main characteristics of the eligible studies for prognostic meta-analysis

Author	Country/year	MiR-525 type	Expression status	Cancer type	Specimen	Test method	Patients	Follow-up period (months)	Survival result	HR (95% CI)
Hui-Hua Tang	China/2023	miR-525-5p	Down-regulated	BC	Tissue	RT-qPCR	180	60	RFS, OS	0.13 (0.02–0.78)
Jin Wang	China/2021	miR-525-5p	Down-regulated	THYM	Tissue	RT-qPCR	70	60	OS	0.31 (0.05–2.09)
Ting Zhao	China/2020	miR-525-5p	Down-regulated	DLBCL	Tissue	RT-qPCR	74	180	OS	0.14 (0.04–0.49)

HR, hazard ratio; CI, confidence interval; BC, breast cancer; RT-qPCR, quantitative real-time polymerase chain reaction; RFS, recurrence free survival; OS, overall survival; THYM, thymoma and thymic carcinoma; DLBCL, diffuse large B-cell lymphoma.

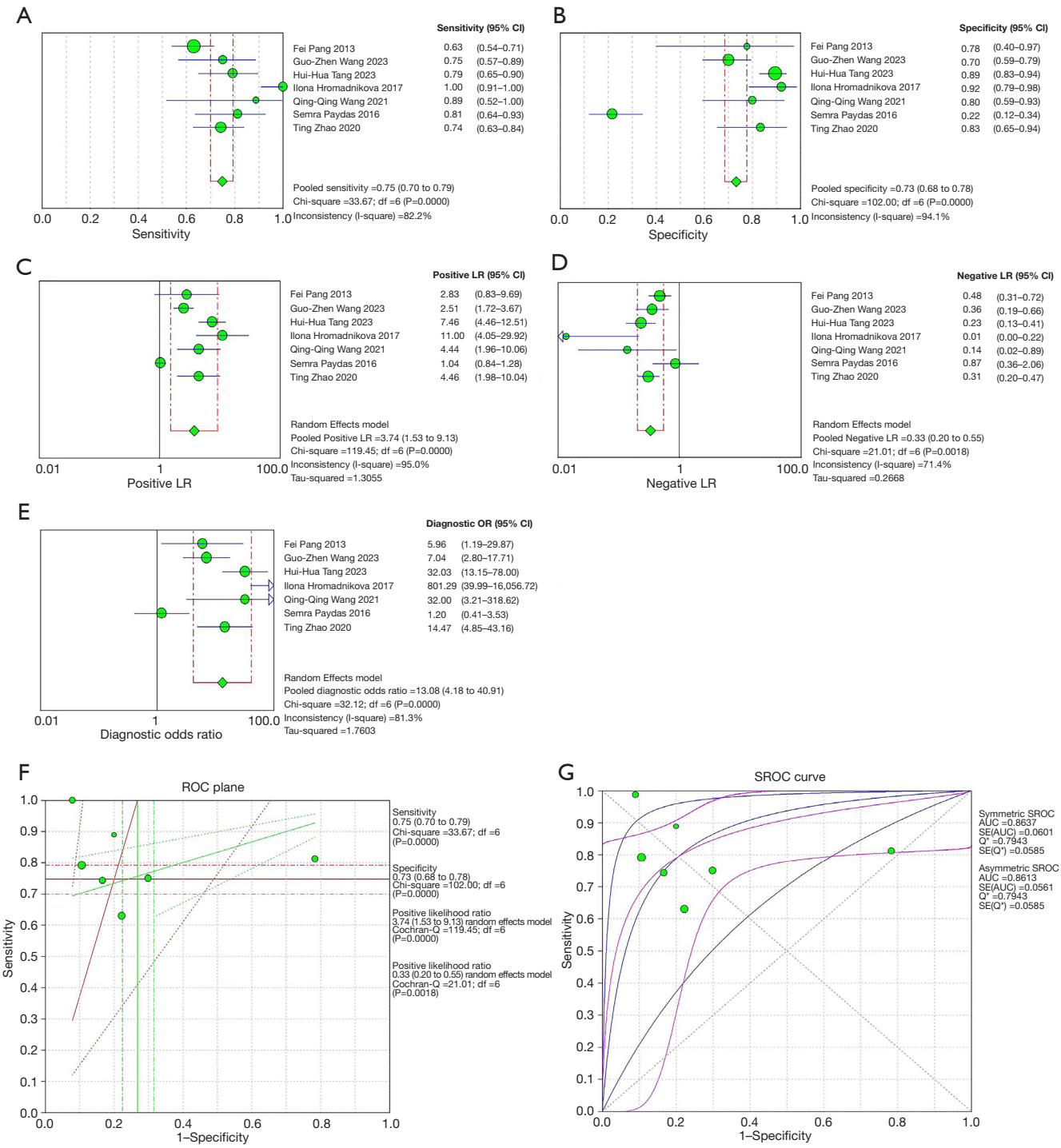

Figure 2 Diagnostic accuracy of miR-525 in patients of carcinoma: forest plot of (A) sensitivity, (B) specificity, (C) PLR, (D) NLR, (E) DOR, (F) ROC curve, and (G) SROC curve. PLR, positive likelihood ratio; NLR, negative likelihood ratio; DOR, diagnostic odds ratio; ROC, receiver operator characteristic curve; SROC, summary receiver operating characteristic curve; AUC, area under curve; SE, standard error.

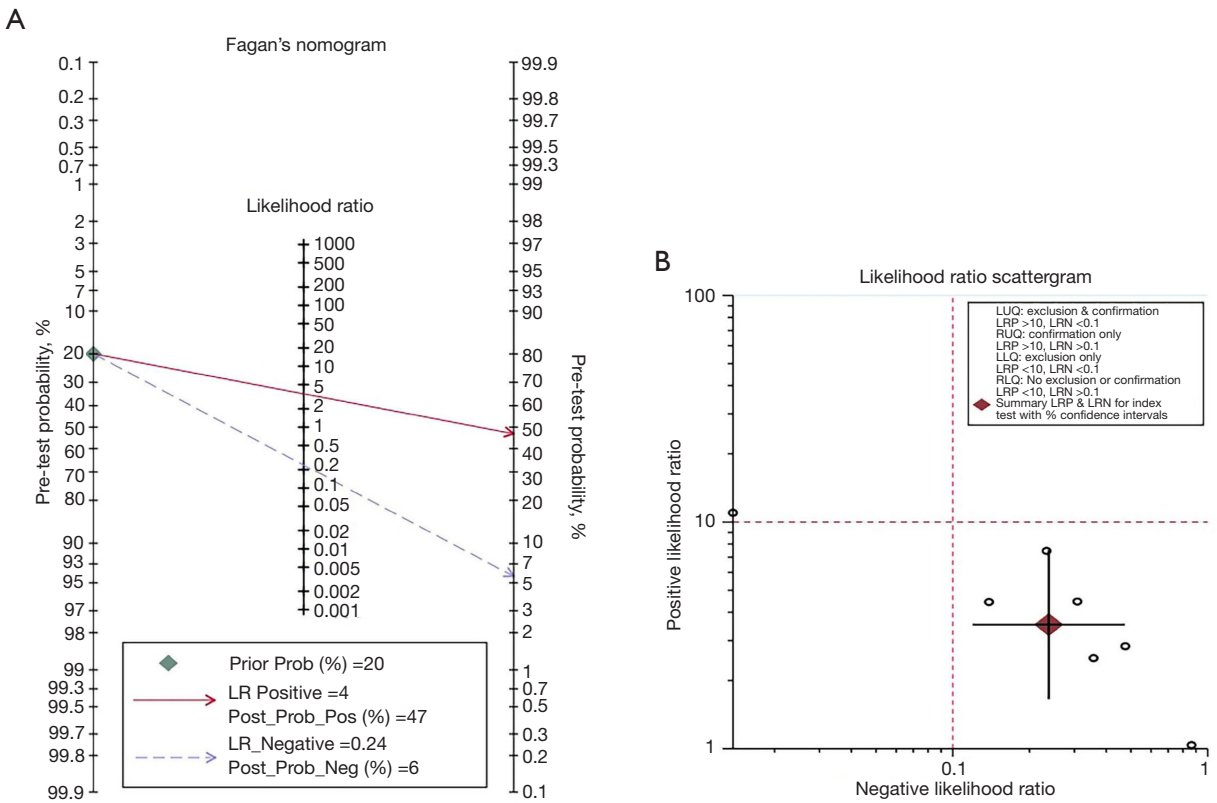

Figure 3 Clinical diagnostic value of miR-525 in cancer patients: (A) Fagan's nomogram plot, and (B) likelihood ratio scattergram. LR, likelihood ratio; LUQ, left upper quadrant; LRP, likelihood ratio positive; LRN, likelihood ratio negative; RUQ, right upper quadrant; LLQ, left lower quadrant; RLQ, right lower quadrant.

The significant heterogeneity was found among the included studies of diagnostic meta-analysis, shown as follows: sensitivity (I^2=82.2, P<0.001), specificity (I^2=94.1, P<0.001), PLR (I^2=95, P<0.001), NLR (I^2=71.4, P<0.001), and DOR (I^2=81.3, P<0.01) (*Figure 2A-2E*). This result suggests that the diagnostic efficacy of miR-525 needs further analysis to explain the source of heterogeneity. To account for potential sources of heterogeneity, we also performed sensitivity analyses and subgroup analyses, and explored the relationship between miR-525 and patient clinical characteristics.

Subgroup analysis of diagnostic value of miR-525 in various cancers

Since the meta-analysis of diagnosis and prognosis in our study included less than ten articles, multivariate-meta-regression could not be performed, and only subgroup analysis could be used to explore the source of heterogeneity in meta-analysis. The results of a subgroup analysis of the diagnostic performance of miR-525 are summarized in Figure S3 and Table S2. MiR-525 showed good diagnostic accuracy when the tumor node metastasis (TNM) stage of cancer was early, such as stage I-II with sensitivity =0.89 (0.80–0.94), and specificity =0.90 (0.84–0.94). For ethnicity, it showed high diagnostic efficacy in Asian populations with sensitivity =0.74 (0.68–0.79), specificity =0.58 (0.50–0.67), and AUC =0.84 (0.83–0.85), but the higher sensitivity to cancer diagnosis in Caucasian populations with sensitivity =0.92 (0.83–0.97), and specificity =0.49 (0.39–0.59). For different subtypes of miR-525, compared with miR-525-3p [sensitivity =0.67 (0.59–0.74), specificity =0.29 (0.19–0.41)], the accuracy of miR-525-5p for cancer diagnosis was higher [sensitivity =0.81 (0.75–0.86), specificity =0.83 (0.78–0.87), AUC =0.90 (0.83–0.97)]. Compared studies publication in the year of pre-2020 [sensitivity =0.74 (0.68–0.79), specificity =0.58 (0.50–0.67), AUC =0.85 (0.83–0.87)], in the literature published after 2020, miR-525 has a better

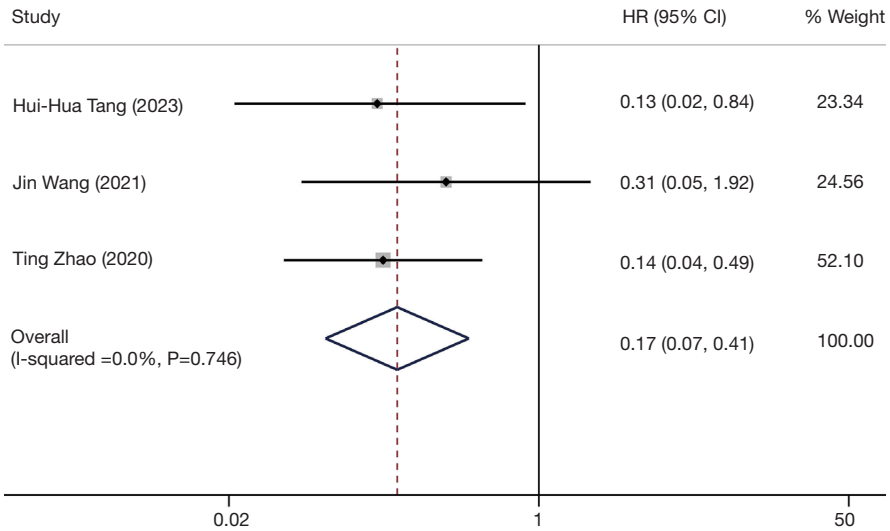

Figure 4 Forest plot for prognostic meta-analysis of low expression of miR-525 in cancers. HR, hazard ratio; CI, confidence interval.

diagnostic value in cancers [sensitivity =0.79 (0.69–0.87), specificity =0.82 (0.76–0.86), AUC =0.87 (0.84–0.90)]. And miR-525 was found to have high to moderate diagnostic accuracy in cancer of the female reproductive system [sensitivity =0.89 (0.80–0.94), specificity =0.90 (0.84–0.94)], lymphoma [sensitivity =0.77 (0.69–0.85), specificity =0.50 (0.41–0.60), AUC =0.84 (0.80–0.88)], and gastrointestinal cancers [sensitivity =0.65 (0.57–0.73), specificity =0.71 (0.61–0.80)]. Subgroup analysis of specimen type showed that miR-525 had high diagnostic accuracy for histological specimens [sensitivity =0.72 (0.66–0.77), specificity =0.71 (0.66–0.76), AUC =0.83 (0.78–0.88)], but among the included studies, there was only one study in which miR-525 was extracted from plasma for diagnostic analysis, which could not fully explain its diagnostic ability in different specimen types.

We conducted the sensitivity analysis by ignoring each of the included studies, and heterogeneity was found to be due to the perfect sensitivity (sensitivity =1), high specificity (specificity =0.9), high DOR (DOR =801.29), high PLR (PLR =11) and very low NLR (NLR =0.01) of one included individual study (Ilona Hromadnikova *et al.*, 2017), with a significant decrease in heterogeneity after removing this study (data not shown) (25).

Results of prognostic meta-analysis

We extracted relevant OS and RFS data from the 3 included studies, and miR-525 was low expressed in cancer specimen of all the included studies (28-30). The prognostic meta-analysis was conducted by random-effects model, with the pooled HR 0.17 (95% CI: 0.07–0.41), and this result indicated that the low expression of miR-525 may be a protective factor for the prognosis of cancer patients, that is, cancer patients with high expression of miR-525 might have a poor prognosis (*Figure 4*). The total I^2 of the included studies was 0, with no significant heterogeneity. However, subgroup analysis results showed that there were no statistically significant differences (P>0.05) among subgroups of cancers in different ethnic groups (Asian or Caucasian), year of publication (before 2020 or after 2020), different detection methods (TaqMan or SYBR), different TNM stages and different types of cancer (digestive system tumors, female reproductive system tumors, lymphoma, and female reproductive system tumors) (Figure S4 and Table S3). Sensitivity analysis indicated that there was no significant heterogeneity among the included studies (*Figure 5*).

Publication bias

Deeks' funnel plot showed that no publication bias was found among the seven studies included in the diagnostic meta-analysis (P=0.90, *Figure 6A*) (23-29). We conducted Begg's test and Egger's test and used the Funnel Plot for evaluating publication bias of the included 3 studies through the random-effects model, and the result shown in the Funnel Plot (included studies were evenly distributed on both sides of the central axis of the funnel plot), Begg's test (P>0.99) and Egger's test (P=0.68) suggested that

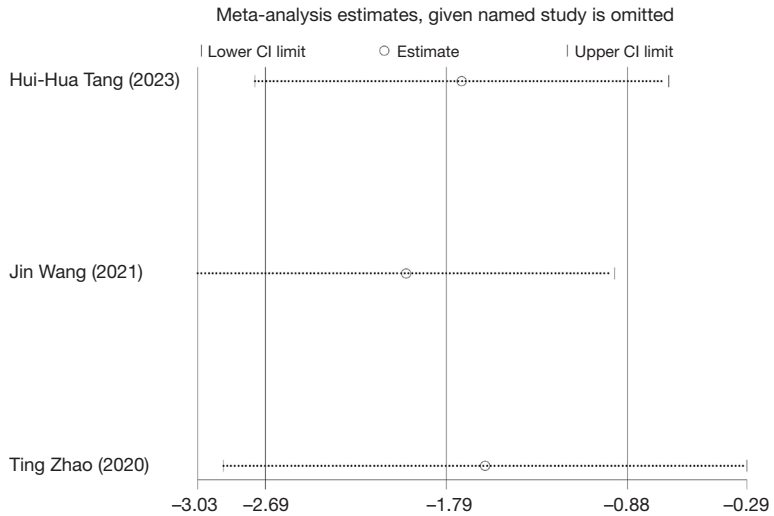

Figure 5 Sensitivity analysis of three included studies in prognostic meta-analysis. CI, confidence interval.

publication bias was not found in the 3 studies included for prognosis meta-analysis (*Figure 6B-6D*) (28-30).

Discussion

Once cancer is discovered by conventional clinical detective methods, most of them have already entered into the advanced stage, which brings difficulties to clinical treatment, resulting in only a small number of patients being able to obtain a better prognosis through conventional radiotherapy and chemotherapy, so it is urgent to conduct some analyses on biomarkers for early screening of clinical tumors. An ideal cancer biomarker should be able to identify the potential aggressiveness of the tumor in the early stage when the cancer can still be cured, and miRNA has been used as a prospective predictive cancer biomarker in breast cancer and prostate cancer (28,31).

MiRNAs have long been shown to regulate or play epigenetic modifying roles in the relative signaling pathway of most cancer development, such as cell proliferation, differentiation, and epithelial-mesenchymal transition (EMT), and promote or inhibit the occurrence or development of cancer by regulating the expression of multiple downstream mRNAs (32-34). Based on differences of specimen type, detection methods of miRNAs as biomarkers are also highly diverse. For formalin-fixed paraffin-embedded (FFPE) samples of tumor tissues or blood or plasma of patients, one or a group of miRNAs can be detected by RT-qPCR, Droplet Digital PCR (ddPCR), or even Next Generation Sequencing (NGS) (35). And more advanced technologies have been applied to the detection of miRNAs, for example, electrochemical sensors can directly detect miRNAs on human samples without pre-processing such as extraction and amplification of total mRNA, which has high sensitivity and significant amplification effect (36), and the researchers can also use NanoString technology to quantitatively identify exosome miRNAs in serums (former miRNAs) without digital amplification, providing a new idea for future miRNA detection (37).

The role of miR-525 in different cancers still needs a further discussion, and some studies suggest that it can promote cancer development. LINC01234 accelerates the decreasing expression of miR-525-5p in breast cancer through the miR-525-5p/CSDE1 axis, and it predicts the poor prognosis and recurrence of breast cancer (38). Regulated by hsa-circ-0001361, miR-525-5p can promote the progression of lung adenocarcinoma cells through the miR-525-5p/VMA21 axis (39). And exosome miR-525-5p inhibits anoikis in highly metastatic triple-negative breast cancer (TNBC) and promotes metastasis of low-metastatic TNBC cancer cells by down-regulating Bax gene (40). And there are still accumulating evidence describes that miR-525 also has effect of inhibiting carcinogenesis process. High expression of miR-525 can significantly improve the overall survival of patients with lung squamous cell carcinoma (41). Overexpression of miR-525-5p in brain gliomas negatively regulates Stat-1, inhibiting cell proliferation, migration, invasion and epithelial-mesenchymal transition (14). And miR-525-5p inhibits cervical cancer metastasis and anoikis resistance by blocking UBE2C/ZEB1/2 signaling axis.

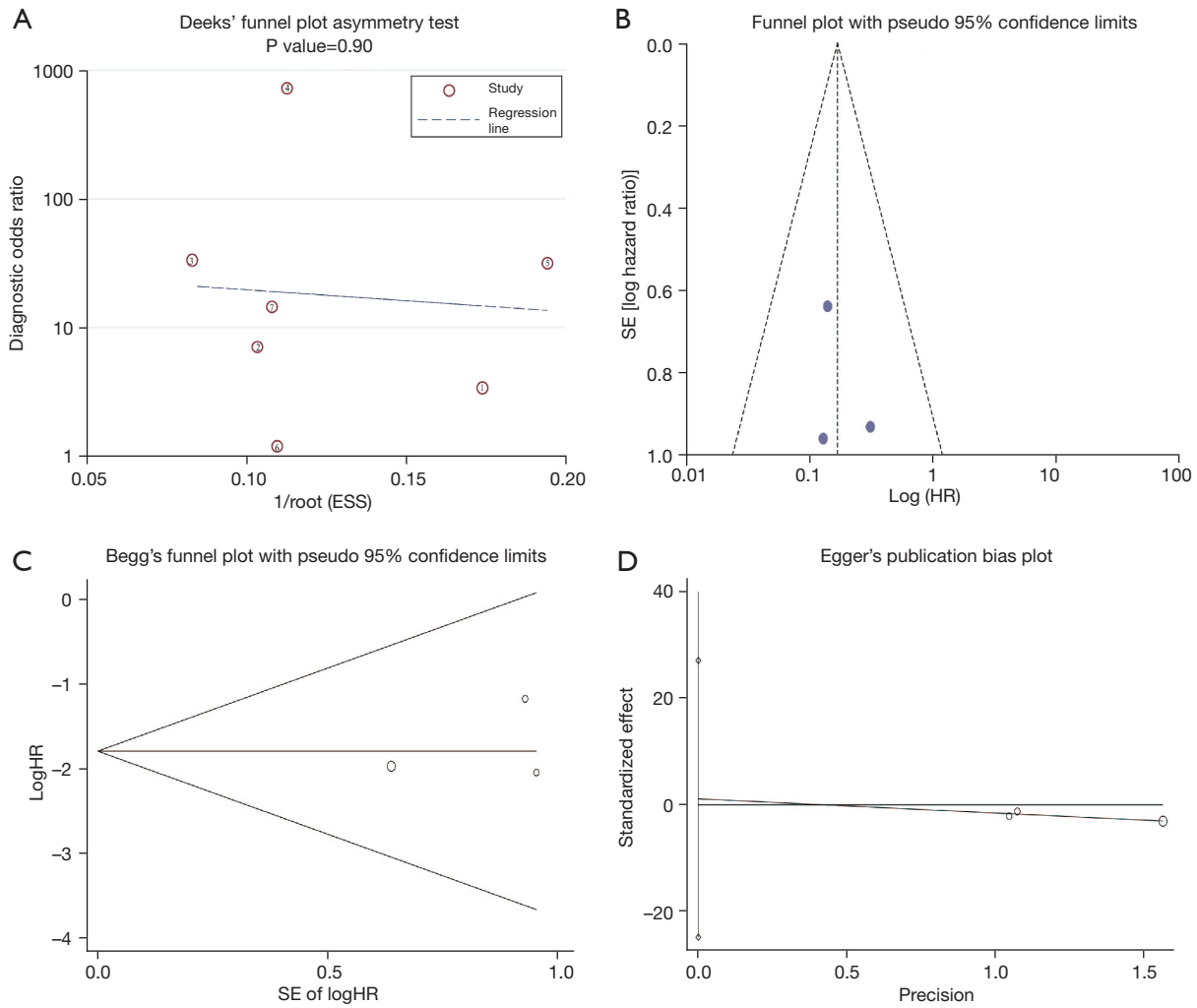

Figure 6 Publication bias of meta-analysis. (A) Deeks' funnel plot for diagnostic meta-analysis; (B) Funnel plot, (C) Begg's funnel plot, and (D) Egger's publication plot for prognostic meta-analysis. SE, standard error; HR, hazard ratio; ESS, effect-size estimate.

However, the conclusions of these studies are inconsistent, and the ability of miR-525 as a biomarker for cancer diagnosis and prognosis needs to be further discussed after summary. In the diagnostic meta-analysis, the pooled sensitivity of the selected data was 0.75 (95% CI: 0.7–0.79), specificity was 0.73 (95% CI: 0.68–0.78), AUC was 0.86 (95% CI: 0.83–0.89), and the Youden index was 0.48. These results indicated that miR-525 had high diagnostic efficiency and accuracy. Subgroup analysis showed that miR-525 performed a good diagnostic sensitivity in early TNM stage of cancer, and the diagnostic sensitivity in Caucasian population was higher than that in Asian population, and it showed a good diagnostic ability in different tumors. We believe that miR-525 may be suitable as a potential biomarker for clinical diagnosis of cancer. However, the prognosis meta-analysis showed that the pooled HR and 95% CI were 0.17 (0.07–0.41), indicating that the low expression of miR-525 is a protective factor for the prognosis of patients in some cancers, in other words, the high expression of miR-525 in some cancer patients can serve as a signal of poor prognosis.

The limitation of this study is that there was only one study using plasma specimen to detect the expression of miR-525 included in the diagnostic meta-analysis, so it cannot be accurately determined whether miR-525 is more suitable in tissue or plasma samples for cancer diagnosis. There are only few studies included in some subgroup analyses and only 3 studies can be used to extract prognosis

data related to miR-525 and cancers among the published papers, which were also limitations of our study. In the further research, it is still necessary to include larger number of original researches to explore the clinical value of miR-525.

Conclusions

In conclusion, our research demonstrates that miR-525 can be used as a potential biomarker for cancer diagnosis, and lower expression of miR-525 predicts a preferable prognosis for some types of cancer.

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Footnote

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tcr.amegroups.com/article/view/10.21037/tcr-24-383/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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