Meta-Analysis of Observational Studies in Epidemiology

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Prognostic and clinicopathologic significance of MicroRNA-125a-5p in cancers

A meta-analysis

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Abstract

The aim of the study was to estimate the prognostic and clinicopathologic significance of miR-125a-5p in human cancers. Eligible studies were obtained from PubMed, Embase, and the Cochrane Library. Combined hazard ratios (HRs) and odds ratios (ORs) were used to evaluate the prognostic and clinicopathologic value of miR-125a-5p. In pan-cancer, high miR-125a-5p expression was associated with better overall survival (OS) (HR = 0.459, 95% confidence interval [CI]: 0.369–0.57, $P < .001$), and disease-free survival (HR = 0.343, 95% CI: 0.237–0.496, $P < .001$). Furthermore, favorable OS was also found in lung cancer (HR = 0.343, 95% CI: 0.228–0.517, $P < .001$) and gastric cancer (HR = 0.341, 95% CI: 0.160–0.725, $P = .005$) patients with high miR-125a-5p expression. Besides, high miR-125a-5p expression was correlated with early stage (OR = 0.413, 95% CI: 0.228–0.749, $P = .004$) and negative lymph node metastasis (OR = 0.262, 95% CI: 0.073–0.941, $P = .04$) in gastric cancer, and was linked with better tumor differentiation in pan-cancer (OR = 1.623, 95% CI: 1.064–2.476, $P = .025$) and lung cancer (OR = 2.371, 95% CI: 1.358–4.141, $P = .002$). In conclusion, miR-125a-5p is a tumor suppressor with prognostic and clinicopathologic values for human cancer, and miR-125a-5p overexpression predicted favorable prognosis, early stage, negative lymph node metastasis, and better tumor differentiation. More research should be conducted to test these results.

Abbreviations: 95% CIs = 95% confidence intervals, DFS = disease-free survival, ESCC = esophageal squamous cell carcinoma, GIST = gastrointestinal stromal tumor, HCC = hepatocellular cancer, HRs = hazard ratios, miR-125a-5p = MicroRNA-125a-5p, OR = odds ratio, OS = overall survival, qRT-PCR = quantitative real-time PCR, SACC = salivary adenoid cystic carcinoma.

Keywords: cancer, clinicopathologic parameter, meta-analysis, MicroRNA-125a-5p, prognosis

1. Introduction

MicroRNAs (miRNAs) are small noncoding RNA molecules containing 19 to 25 nucleotides and regulate posttranscriptional gene expression by binding to their target mRNAs, usually in the 3′-untranslated region.[1] Numerous miRNAs are abnormally expressed in tumors and can function as tumor suppressors or oncogenes. They often have prognostic value regarding tumor development and clinicopathologic parameters.[2,3] miRNAs serve a vital role in various cellular processes, including cellular growth, differentiation, proliferation, metastasis, migration, and apoptosis.[4] The aberrant expression of MicroRNA-125a-5p (miR-125a-5p) located on 19q13.41, may function as tumor suppressors in various cancers, including gastric,[5,6] lung,[7] breast,[8] and gliomas.[9] The prognostic value and clinicopathologic significance of miR-125a-5p were inconsistent among previous studies. In the present study, we conducted a meta-analysis to estimate the prognostic and clinicopathologic significance of miR-125a-5p.

2. Methods

Our study was conducted following the Meta-Analysis of Observational Studies in Epidemiology (MOOSE) guidelines. In addition, our meta-analysis was conducted by reviewing issued papers, thus, the ethical approval is not required.

2.1. Literature search

We performed a literature search in PubMed, Embase, and the Cochrane Library (last update by February 12, 2019), using the following keywords (miR-125a-5p OR miRNA-125a-5p OR microRNA-125a-5p OR miR125a-5p OR miRNA125a-5p OR microRNA125a-5p OR "miR 125a-5p" OR "miRNA 125a-5p" OR "microRNA 125a-5p"OR miR-125a-5p OR miRNA-125a-5p OR microRNA-125a-5p OR miR-125a-5p OR miRNA-125a-5p OR microRNA-125a-5p) AND (malignan* OR cancer OR tumor OR tumour OR neoplas* OR carcinoma OR adenocarcinoma OR sarcoma). A manual review of the reference lists in relevant articles was also conducted.

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2.2. Literature selection

Studies met the following inclusion criteria were included: study with any type of cancer; detection of miR-125a-5p expression in blood-based samples or primary tissue samples; survival and/or clinicopathologic parameters were investigated and miR-125a-5p expression were grouped into high expression or low expression; and raw data of clinicopathologic parameter was available, or the survival curve or sufficient relevant data were available to calculate hazard ratio (HR). The exclusion criteria were: miR-125a-5p was combined with other biomarker; no sufficient data; and duplicated publication.

2.3. Data extraction and quality assessment

The following details were collected from each included study: 1st author, publication year, country, cancer type, stage, sample source, test method, sample size, clinicopathologic parameters, follow-up time, survival index, statistical method, HR as well as 95% confidence interval (CI; extracted using the described method in previous studies[10,11]), the survival outcome of the high miR-125a-5p expression group and quality score of study. The quality of the study was evaluated by the Newcastle–Ottawa scale.[12]

2.4. Statistical analysis

Combined HRs and odds ratios (ORs) with corresponding 95% CIs were used to evaluate the prognostic and clinicopathologic value. HR < 1 with 95% CI not overlapping 1 was indicated a better survival for the case group (high expression of miR-125a-5p). Given that the various heterogeneities among individual HR, we calculated pooled HR by random-effect model as proposed in previous studies.[13] Heterogeneity among studies involved clinicopathologic parameters was estimated by the Q-statistic and I^2-statistic. If significant heterogeneity ($I^2 > 50\%$), the random-effect model was applied; if not, the fixed-effects mode. Publication bias was detected by Begg test. Analyses were carried out by the STATA 15.0 software (Stata Corporation, College Station, TX), and $P < .05$ indicates statistically significant.

3. Results

3.1. Literature research and characteristics

Totally 194 articles were retrieved from the initial search. As shown in Figure 1, 16 studies[2,3,5–9,14–22] with 2088 patients were included, from which 12 studies with 1803 patients involved prognosis and 12 studies with 1467 patients involved

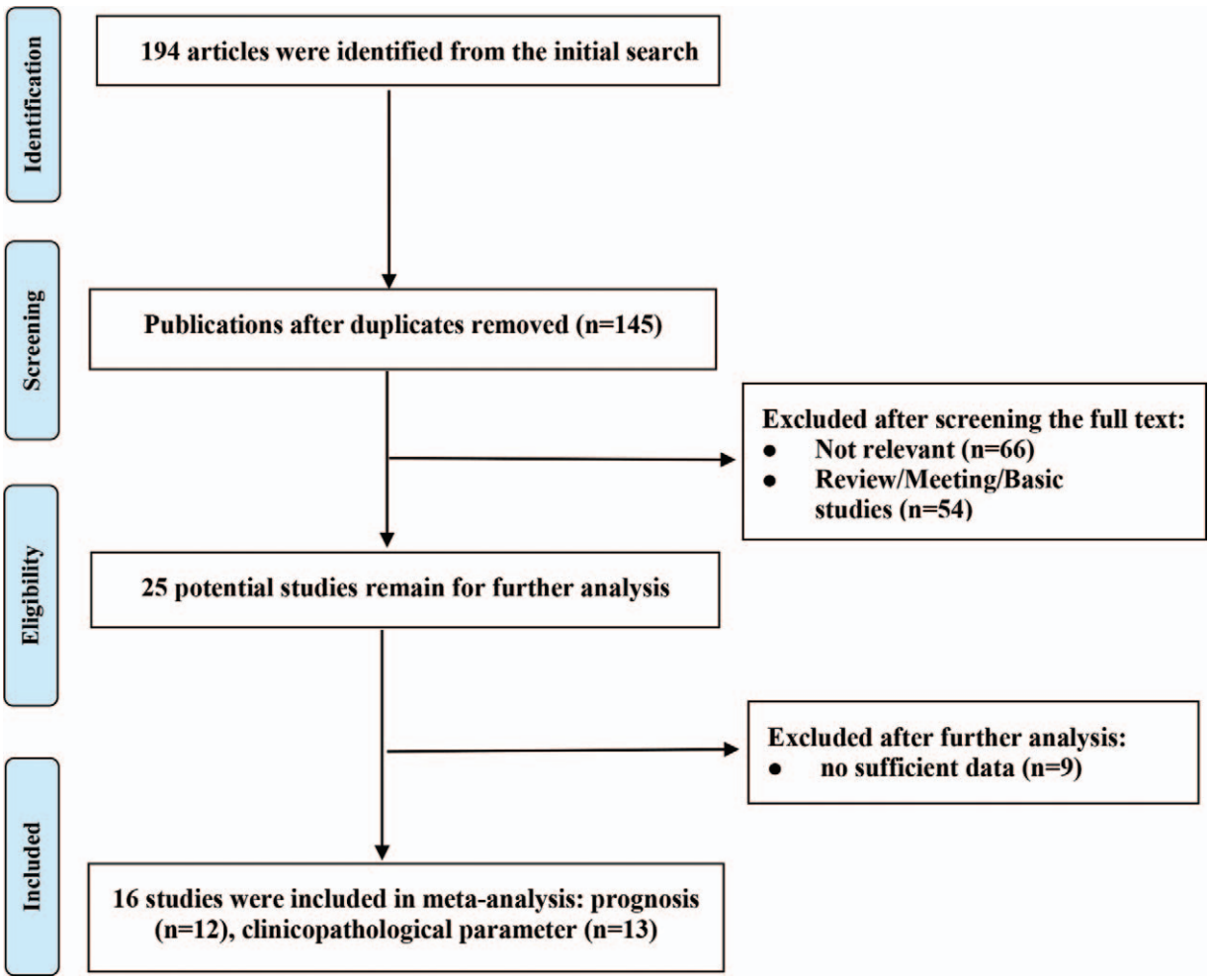

Figure 1. The flow chart of literature research.

Table 1

The main characteristics and quality of the included studies.

First author	Year	Country	Cancer Type	Stage	Sample source	test method	Sample size	Survival	Statistic method	HR	LL	UL	Outcome*	NOS
Nishida et al	2011	Japan	Gastric cancer	I–IV	Tissue	qRT-PCR	87	OS	Multivariate	0.410	0.149	0.966	Better	6
Zhang et al	2012	China	Lung cancer	I–IV	Tissue	qRT-PCR	105	OS	Multivariate	0.310	0.090	1.090	NS	7
Zhu et al	2014	China	Lung cancer	I–IV	Tissue/Serum	qRT-PCR	70	OS	Multivariate	0.134/1.291	0.028/0.444	0.64/3.758	Better/NS	7
Hsieh et al	2015	China	Breast cancer	I–III	Serum	qRT-PCR	300	OS	Multivariate	0.421	0.184	0.961	Better	6
Zheng et al	2015	China	HCC	NR	Serum	qRT-PCR	120	OS	Survival Curve	0.476	0.250	0.903	Better	7
Sun et al	2016	China	Glioma	I–IV	Tissue	qRT-PCR	167	OS	Survival Curve	0.560	0.390	0.810	Better	7
Liang et al	2017	China	SACC	I–IV	Tissue	qRT-PCR	106	OS	Survival Curve	0.561	0.270	0.937	Better	7
Yang et al	2018	China	Colorectal cancer	I–IV	Tissue	qRT-PCR	40	OS	Multivariate	0.563	0.350	0.906	Better	6
Zhao et al	2018	China	ESCC	I–IV	Tissue	qRT-PCR	56	OS	Survival Curve	0.460	0.230	0.950	Better	6
Cao et al	2018	China	Gastric cancer	I–IV	Tissue	qRT-PCR	82	OS	Survival Curve	0.52	0.27	0.99	Better	7
Cai et al	2018	China	Gastric cancer	I–IV	Tissue	qRT-PCR	286	OS/DFS	Multivariate	0.125/0.227	0.037/0.069	0.416/0.770	Better	7
Liu et al	2018	China	Lung cancer	I–IV	Tissue	qRT-PCR	384	OS/DFS	Multivariate	0.376/0.358	0.237/0.240	0.584/0.521	Better	7

DFS = disease-free survival, ESCC = esophageal squamous cell carcinoma, HCC = hepatocellular cancer, HR = hazard ratio, LL = lower limit, NOS = the scores of Newcastle–Ottawa quality assessment scale, NR = not report, OS = overall survival, qRT-PCR = quantitative real-time polymerase chain reaction, SACC = salivary adenoid cystic carcinoma, UL = upper limit.

* Outcome was for patient with high miR-125a-5p expression.

clinicopathologic features. The characteristics of enrolled studies were summarized in Tables 1 and 2. The included studies published from 2010 to 2018, and the sample sizes ranged from 30 to 384. Except the study of Akcakaya et al was conducted in Sweden,[16] other studies were all carried out in Asia (China and Japan). Totally 10 kinds of cancers were included: lung cancer, gastric cancer, hepatocellular cancer, esophageal squamous cell carcinoma, gastrointestinal stromal tumor, breast cancer, glioma, retinoblastoma, salivary adenoid cystic carcinoma, and colorectal cancer, and only 3 OS studies based on serum sample, others based on tissue sample to investigate prognosis and clinicopathologic features. The expression level of miR-125a-5p was measured by quantitative real-time polymerase chain reaction (qRT-PCR) in all included studies. The survival index of overall survival (OS) was applied in all studies, but disease-free survival (DFS) was only enrolled in 2 studies. Multivariate analysis was used to estimate survival outcome in 7 studies, others applied Kaplan–Meier survival curve.

3.2. High miR-125a-5p expression predicted better prognosis

For OS, totally 1383 tissue samples and 490 serum samples were collected to detect the expression level of miR-125a-5p. Based on tissue samples, significant link was found between high miR-125a-5p expression and better OS (HR = 0.459, 95% CI: 0.369–0.57, $P < .001$), but publication bias was also detected ($P < .001$)

Table 2

The clinicopathologic parameters and quality of the included studies.

First author	Year	Country	Cancer type	Sample source	Test method	Sample size	Clinicopathologic parameters	NOS
Jiang et al	2010	China	Lung cancer	Tissue	qRT-PCR	52	Gender, age, tumor differentiation, stage, and lymph node metastasis	6
Nishida et al	2011	Japan	Gastric cancer	Tissue	qRT-PCR	87	Gender, tumor differentiation, stage, and lymph node metastasis	6
Zhu et al	2014	China	Lung cancer	Tissue	qRT-PCR	70	Gender, age, tumor differentiation, stage, and lymph node metastasis	7
Xu et al	2014	China	Gastric cancer	Tissue	qRT-PCR	51	Gender, age, tumor differentiation, stage, lymph node metastasis, and distant metastasis	7
Akcakaya et al	2014	Sweden	GIST	Tissue	qRT-PCR	30	Distant metastasis	6
Sun et al	2016	China	Glioma	Tissue	qRT-PCR	167	Gender, age, and tumor differentiation	7
Zhang et al	2016	China	Retinoblastoma	Tissue	qRT-PCR	112	Gender, age, tumor differentiation, and stage	7
Liang et al	2017	China	SACC	Tissue	qRT-PCR	106	Gender, age, tumor differentiation, stage, lymph node metastasis, and distant metastasis	7
Cao et al	2018	China	Gastric cancer	Tissue	qRT-PCR	82	Gender, age, tumor differentiation, stage, and lymph node metastasis	7
Cai et al	2018	China	Gastric cancer	Tissue	qRT-PCR	286	Gender, age, tumor differentiation, and lymph node metastasis	7
Liu et al	2018	China	Lung cancer	Tissue	qRT-PCR	384	Gender, age, tumor differentiation, stage, lymph node metastasis, and distant metastasis	7
Yang et al	2018	China	Colorectal cancer	Tissue	qRT-PCR	40	Gender, age, tumor differentiation, stage, and lymph node metastasis	6

GIST = gastrointestinal stromal tumor, NOS = the scores of Newcastle–Ottawa quality assessment scale, qRT-PCR = quantitative real-time polymerase chain reaction, SACC = salivary adenoid cystic carcinoma.

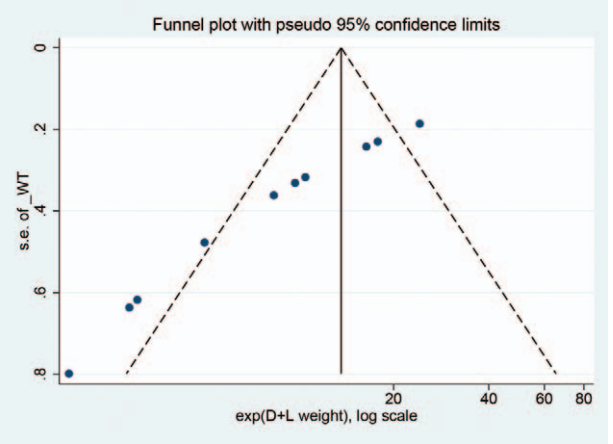

Figure 2. Funnel plot for tissue miR-125a-5p in overall survival.

(Fig. 2). Subsequently, for tissue samples associated studies, subgroup analysis of OS was conducted by different statistic method, and better OS for patients with high miR-125a-5p expression remained statistically significant irrespective if the study used multivariate analysis (HR = 0.359, 95% CI: 0.240–0.539, $P < .001$) or survival curve (HR = 0.539, 95% CI: 0.414–0.701, $P < .001$). However, as for serum sample, the association between higher miR-125a-5p expression and better OS was not significant (HR = 0.574, 95% CI: 0.320–1.03, $P = .063$). Additionally, statistical significance between high miR-125a-5p expression and favorable DFS was achieved based on tissue samples (HR = 0.343, 95% CI: 0.237–0.496, $P < .001$). Furthermore, we conducted subgroup meta-analysis based on lung cancer and gastric cancer, and favorable OS was also found in lung cancer (HR = 0.343, 95% CI: 0.228–0.517, $P < .001$) and gastric cancer (HR = 0.341, 95% CI: 0.160–0.725, $P = .005$) patients with high miR-125a-5p expression (Table 3, Fig. 3).

3.3. High miR-125a-5p expression indicated favorable clinicopathologic parameters

The correlations between miR-125a-5p and clinicopathologic features including gender, age, tumor differentiation, stage, lymph node metastasis, and distant metastasis were analyzed based on pan-cancer/lung cancer/gastric cancer. High miR-125a-5p expression was only correlated with early stage (OR = 0.413, 95% CI: 0.228–0.749, $P = .004$) and negative lymph node metastasis (OR = 0.262, 95% CI: 0.073–0.941, $P = .04$) in gastric cancer, and was linked with better tumor differentiation in pan-cancer (OR = 1.623, 95% CI: 1.064–2.476, $P = .025$) and lung cancer (OR = 2.371, 95% CI: 1.358–4.141, $P = .002$). However, no significant association was detected in other clinicopathologic features (Table 3, Fig. 4).

4. Discussion

This was the 1st meta-analysis estimating the prognostic and clinicopathologic value of miR-125a-5p in human cancers. We found that high miR-125a-5p expression was related to significantly better prognosis and clinicopathologic parameters. The overexpression of miR-125a-5p in cancer tissue predicted better OS and DFS for patient, and also associated with less aggressive tumor biology, including better tumor differentiation and early stage and negative lymph node metastasis. However, based on the serum samples from cancer patients, the association between overexpression of miR-125a-5p and better OS was not statistically significant.

The expression of miRNA can be measured using various sources, including tissue, blood, and other bodily fluids, and the sampling and extraction methods had a significant effect on the results obtained.[23] Although miRNAs are very stable in blood because they bind with Argonaute proteins,[24] the miRNA levels in blood samples are minuscule and do not contain pure tumor cells.[25] Our study did not reveal a prognostic value for serum-based miR-125a-5p sampling, and current studies also did not support blood-based sampling to investigate circulating miRNAs.[26] Evidence suggested different miRNA concentrations in serum and plasma, mainly influenced by miRNAs generated from platelets, indicating that the coagulation process affects the detection of miRNAs in the blood.[27] However, only 490 serum samples from 3 studies were included in our meta-analysis; thus, larger sample sizes are needed to verify our result.

A recent study[21] found that miR-125a-5p inhibits the proliferation, migration, and invasion of colorectal cancer cell lines, and suppresses growth and metastasis in vivo. Additionally, miR-125a-5p suppresses the tube formation ability of human umbilical vein endothelial cells and VEGFA, a target of miR-125a-5p, may reverse this suppression caused by miR-125a-5p upregulation. In bladder cancer, high expression of miR-125a-5p was a cell cycle inhibitor; miR-125a-5p inhibited proliferation, migration, and invasion of cancer cells while inducing apoptosis. The upregulation of miR-125a-5p reversed the epithelial-mesenchymal transition, and FUT4, which targets the mRNA of miR-125a-5p, reversed the effects of miR-125a-5p on bladder cancer progression.[28] Furthermore, miR-125a-5p inhibited cell proliferation and migration through NAIF1 in prostate cancer[29] and suppressed cervical cancer cell proliferation and migration by targeting ABL2.[30]

Although our study revealed that miR-125a-5p overexpression predicted better prognosis and tumor differentiation for cancer patients, there were also several limitations in our study. Firstly, we could only analyze data from literature rather than original data, this impeded us to estimate all the data by consistent method and inevitably led to significant heterogeneity.[31]

Table 3

Summarized HRs and ORs in this meta-analysis.

Group	Studies	Sample size	HR/OR (95% CI)	*P*-value	Heterogeneity test		Model
					I^2 (%)	*P*-value	
OS (pan-cancer, tissue)	10	1383	0.459 (0.369–0.57)	<.001	13.20%	.322	Random effect model
OS (pan-cancer, tissue, multivariate)	6	972	0.359 (0.240–0.539)	<.001	34.50%	.177	Random effect model
OS (pan-cancer, tissue, survival curve)	4	411	0.539 (0.414–0.701)	<.001	0.00%	.967	Random effect model
OS (pan-cancer, serum)	3	490	0.574 (0.320–1.03)	.063	34.40%	.218	Random effect model
DFS (pan-cancer, tissue)	2	670	0.343 (0.237–0.496)	<.001	0.00%	.481	Random effect model
OS (lung cancer, tissue)	3	559	0.343 (0.228–0.517)	<.001	0.00%	.456	Random effect model
OS (gastric cancer, tissue)	3	455	0.341 (0.160–0.725)	.005	51.90%	.125	Random effect model
Gender (pan-cancer/lung cancer/gastric cancer)	11/3/4	1437/506/506	1.116 (0.884–1.409)/0.770 (0.302–1.967)/1.295 (0.868–1.932)	.354/.585/.206	3%/65.1%/0%	.413/.057/.6	Fixed effect model/ random effect model/ fixed effect model
Age (pan-cancer/lung cancer/gastric cancer)	10/3/3	1360/506/419	0.782 (0.608–1.005)/0.758 (0.510–1.128)/0.807 (0.501–1.301)	.055/.172/.379	0%0%/0%	.987/.419/.955	Fixed effect model/fixed effect model/fixed effect model
Stage (pan-cancer/lung cancer/gastric cancer)	9/3/3	984/506/220	0.647 (0.352–1.19)/0.866 (0.224–3.347)/0.413 (0.228–0.749)	.162/.835/.004	71.3%/85.1%/0%	<.001/.001/.396	Random effect model/ random effect model/ ixed effect model
Tumor differentiation (pan-cancer/lung cancer/gastric cancer)	11/3/4	1437/506/506	1.623 (1.064–2.476)/2.371 (1.358–4.141)/0.904 (0.438–1.865)	.025/.002/.785	56.2%/0%/59.1%	.011/.759/.062	Random effect model/ fixed effect model/ random effect model
Lymph node metastasis (pan-cancer/lung cancer/gastric cancer)	10/3/4	1158/506/506	0.473 (0.219–1.019)/0.979 (0.242–3.955)/0.262 (0.073–0.941)	.056/.976/.04	81.4%/87%/82.9%	<.001/<.001/<.001	Random effect model/ random effect model/ random effect model
Distant metastasis (pan-cancer)	4	571	0.770 (0.183–3.233)	0.721	84.00%	<.001	Random effect model

DFS = disease-free survival, HR = hazard ratio, OR = odds ratio, OS = overall survival.

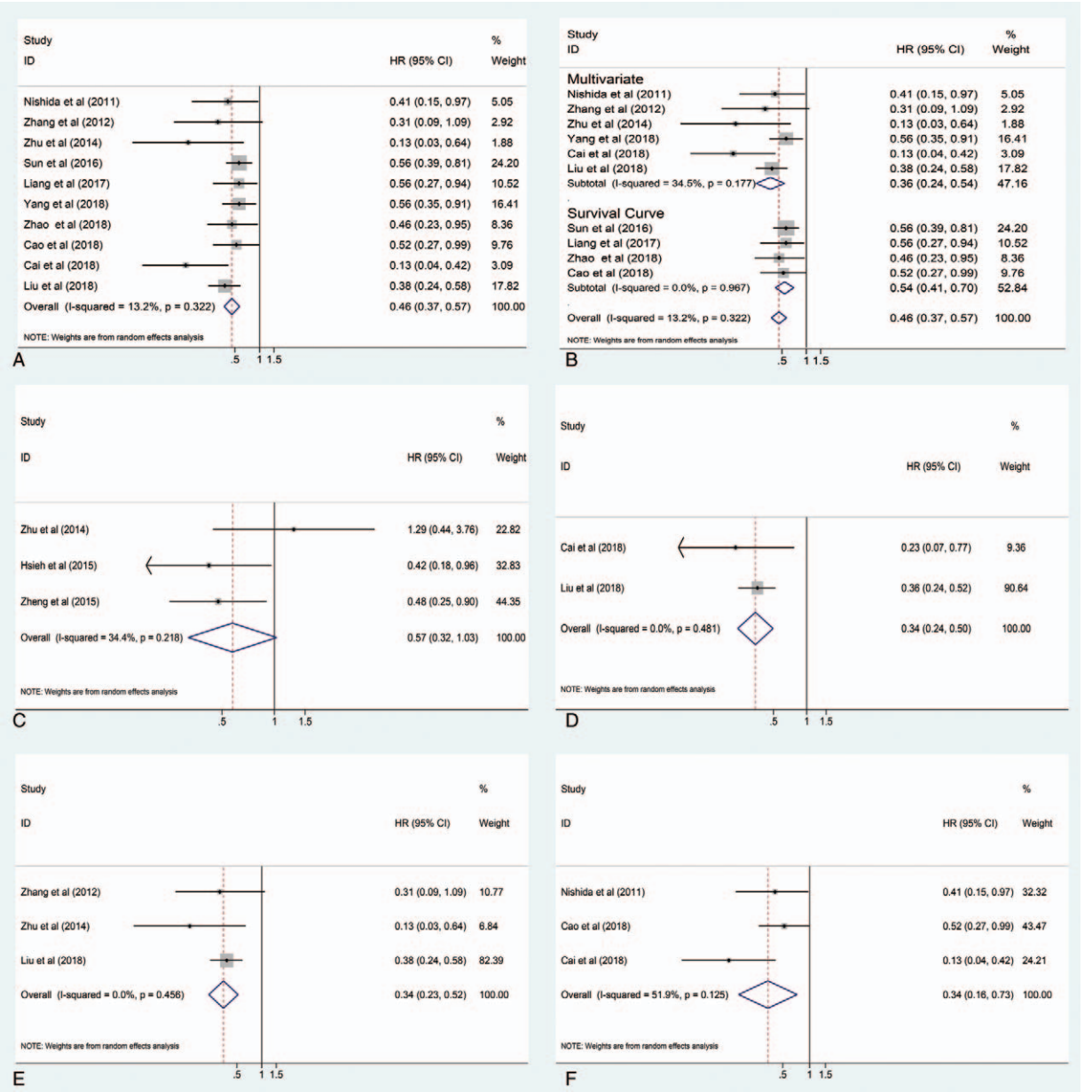

Figure 3. The forest plots for pan-cancer: the impact of tissue miR-125a-5p in OS (A) by multivariate analysis and survival curve (B), serum miR-125a-5p in OS (C), and tissue miR-125a-5p in DFS (D). The forest plots for the prognostic value of tissue miR-125a-5p in lung cancer (E), and gastric cancer (F).

Secondly, due to no available original data, the confounding factors such as treatment, race, and age cannot be evaluated and might also contribute to heterogeneity. Additionally, all studies were carried out in Asia with the exception of one study was conducted in Sweden; more studies should be carried out in other regions. Finally, significant publication bias was detected in the studies for OS which based on tissue sample.

In conclusion, miR-125a-5p is a tumor suppressor with prognostic and clinicopathologic values for human cancer, and miR-125a-5p overexpression predicted favorable prognosis, early stage, negative lymph node metastasis, and better tumor differentiation. More research should be conducted to test these results.

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Author contributions

Conceptualization: Haidong Ye, Lina Mei, Zhouxiang Lu.
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Validation: Wei Zhu, Lina Mei.
Writing – original draft: Haidong Ye, Zhouxiang Lu.
Writing – review & editing: Wei Zhu, Lina Mei, Zhouxiang Lu.

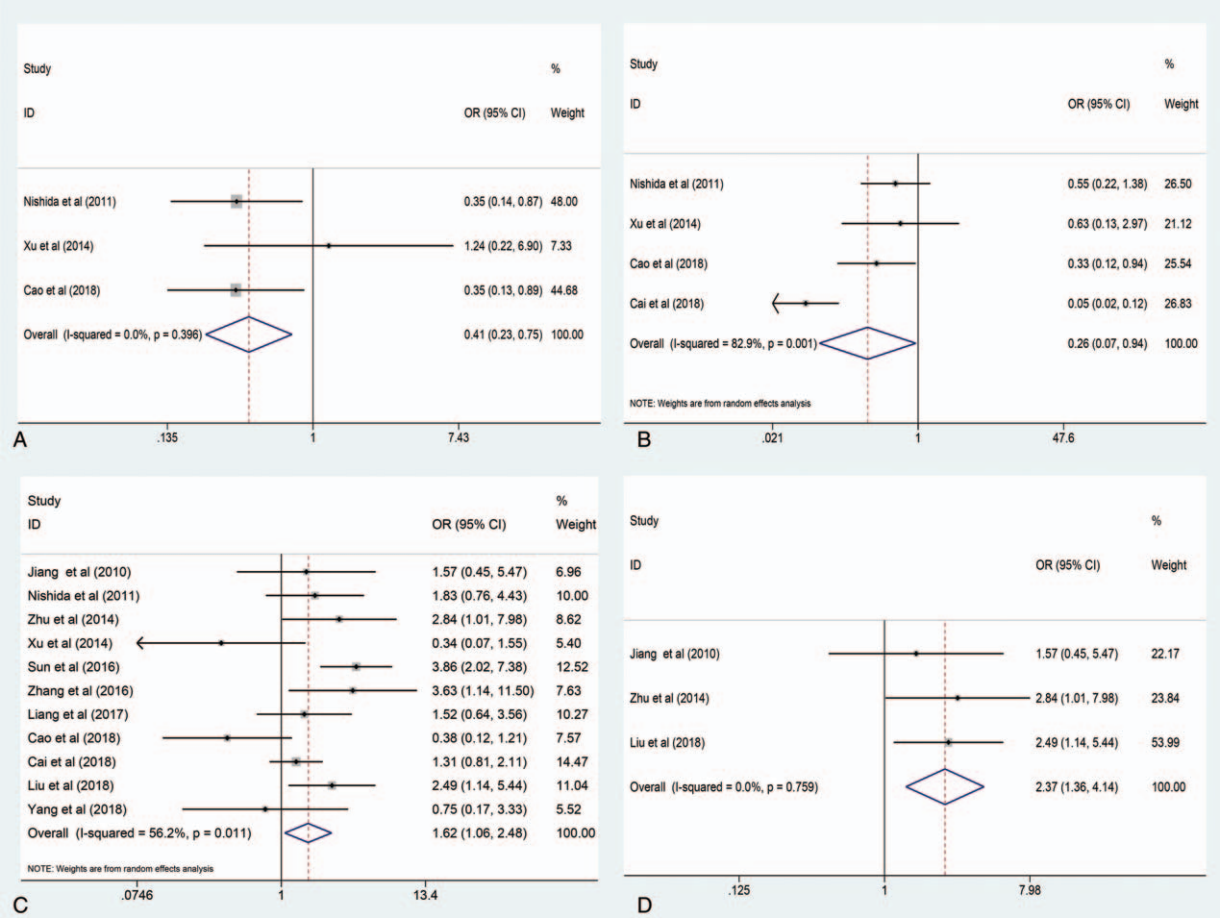

Figure 4. The forest plots for the associations between miR-125a-5p and stage (A), lymph node metastasis (B) in gastric cancer, tumor differentiation in pan-cancer (C), and lung cancer (D).

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