European Archives of Oto-Rhino-Laryngology (2019) 276:957–968
https://doi.org/10.1007/s00405-019-05325-8

REVIEW ARTICLE

The microRNA-375 as a potentially promising biomarker to predict the prognosis of patients with head and neck or esophageal squamous cell carcinoma: a meta-analysis

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Received: 30 September 2018 / Accepted: 31 January 2019 / Published online: 12 February 2019

Abstract

Background The prognostic value of microRNA-375 (miR-375) expression in squamous cell carcinoma (SCC) had been reported in the previous studies; however, the results remain inconsistent. This study was performed to investigate the prognostic significance of miR-375 expression in SCC based on all eligible evidences.

Methods Relevant studies were identified by searching PubMed, Embace, Medline, Cochrane Library, and China Biology Medicine disk. Survival outcome including overall survival (OS) and other survival outcomes were used as the primary endpoint to evaluate the prognostic outcome of patients with SCC. All statistical analyses were performed in RevMan software version 5.3 and STATA software version 14.1. Furthermore, the quality of included studies was assessed by The Newcastle–Ottawa Scale.

Results In total, 13 studies, including 1340 patients, met the inclusion criteria for our meta-analysis. The pooled analysis results indicated that downregulation of miR-375 significantly predicted poor OS (HR 1.58, 95% CI 1.34–1.88, $P < 0.001$). Downregulated miR-375 was also correlated with the other survival outcomes. Subgroup analysis based on tumor type found that lower expression of miR-375 was significantly related with poor OS in patients with esophageal squamous cell carcinoma (ESCC) (HR 1.58, 95% CI 1.29–1.94, $P < 0.001$) and head and neck squamous cell carcinoma (HNSCC) (HR 1.59, 95% CI 1.16–2.18, $P = 0.004$).

Conclusions This meta-analysis demonstrated that the downexpression of miR-375 was significantly correlated with poor OS in patients with SCCs and indicated the potential clinical use of miR-375 as a molecular biomarker, particularly in assessing prognosis for patients with ESCC and HNSCC.

Keywords MicroRNA-375 · Squamous cell carcinoma · Prognosis

Introduction

Cancer is one of the most common causes of death worldwide and has become a major public health issue [1]. As a major type of cancer, squamous cell carcinoma (SCC), also called epidermoid carcinoma, is a number of different types of cancer that result from squamous cells, which are thin, flat cells that look like fish scales, and are found in the tissue that forms the surface of the skin, the lining of the hollow organs of the body, and the lining of the respiratory and digestive tracts. Most cancers of the anus, cervix, head and neck, esophagus, and vagina are SCCs [2]. For northern and central China, esophageal squamous cell carcinoma (ESCC), as the eighth most common cancer and the sixth leading cause of cancer-related mortality in 2008, dominates 90% of esophageal cancer cases and has become a worldwide health concern, with 455,800 new cases and 400,200 deaths estimated in 2012 [1, 3–5]. ESCC is characterized by an insidious onset without major signs or symptoms, leading to late diagnoses of advanced ESCC, which partially accounts for the extremely poor prognosis, high mortality, and high

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recurrence observed in this disease [6]. Head and neck squamous cell carcinomas (HNSCC), another major type of SCC, are malignancies of epithelial origin that are consistently among the most common cancers worldwide, with one of the highest mortality rates. They include cancers of the oral cavity, oropharynx, and larynx [7]. The peak incidence occurs at the ages of 50–70 years [8]. Worldwide, estimated 650,000 new cases occur per year [3] and approximately half of all patients with the disease die after exhausting multiple treatment efforts including surgery, radiation, and chemotherapy [9, 10].

Noncoding RNAs play important roles in cancer biology, providing potential targets for cancer intervention. During the last decade, one of the noncoding RNAs, so-called microRNAs (miRNAs), a class of short noncoding RNA molecules that range in size from 19 to 25 nucleotides, have also been demonstrated to regulate gene expression by targeting mRNAs for translational repression or cleavage. Consequently, some miRNAs have recently become known as new factors related to oncogenesis and the progression of various cancer tumors [11] and proposed as promising biomarkers of early cancer detection and accurate prognosis as well as targets for more efficient treatment [12, 13]. Wei et al. found miR-145-5p served as a negative regulator of fascin actin-bundling protein 1 (FSCN1) expression which was significantly lower in laryngeal squamous cell carcinoma (LSCC) with poor prognosis [14]. In addition, lower expression of miR-6775-3p was related to poor prognosis of ESCC patients [15]. Meanwhile, some miRNAs, such as miR-19a, miR-21, and miR-205, were upregulated in HNSCC patients' tumor compared with healthy tissue [16, 17]. Zhao et al. reported that miR-543 in ESCC tissues was conspicuously higher than in the adjacent normal tissues and proved that miR-543 enhanced the cell mobility and the invasiveness cascade in ESCC cells via the downregulation of PLA2G4A expression [18]. Substantial evidence has supported that miR-375 is one of the most downregulated miRNAs in HNSCC [19–21] summarized by Kinoshita et al. [22]. MicroRNA-375 (miR-375) was originally identified from murine pancreatic β-cell line MIN 6 [23]. However, genome-wide miRNA expression profiling studies revealed that miR-375 is widely present in various tissues. It is becoming increasingly clear that miR-375 is an important cancer-related miRNA, or organs and is significantly reduced in malignant cell [19, 24–27]. Kong et al. elucidated a tumor suppressive role of miR-375 via inhibiting cell proliferation of ESCC, colony formation ability, and metastasis in vitro and in vivo [28].

Nowadays, a meta-analysis suggests that miR-375 expression is associated with overall survival (OS) of cancer patients and could be a useful clinical prognostic biomarker [29]. To our knowledge, no published meta-analysis has investigated miR-375 and SCC prognosis. The aim of the current study was to quantitatively and comprehensively summarize the available evidence on the prognostic value of miR-375 and different survival outcomes (overall survival, OS; disease-specific survival, DSS; progression-free survival, PFS) in patients with ESCC or HNSCC.

Materials and methods

This meta-analysis was carried out in accordance with the guidelines of meta-analysis of observational studies in epidemiology (MOOSE) [30].

Literature retrieval strategy

To obtain the potentially eligible studies, Studies were performed by searching PubMed, Embace, and Cochrane Library (updated by October 15 2017). The search strategy was (microRNA-375 OR miRNA-375 OR miR-375) AND (cancer OR tumor OR neoplasm OR tumor OR malignant OR metastasis OR carcinoma OR squamous cell carcinoma OR SCC). The reference lists of relative reviews and meta-analysis were also manually screened to further identify more studies.

Inclusion and exclusion criteria

Eligible studies included in this meta-analysis met the following criteria: (1) reporting specific methods for the detection of miR-375 expression in tumor tissue collected by surgical resection or biopsy or blood obtained before treatment; (2) patients received therapies including surgical resection (R0 or R1) or radiochemotherapy; (3) investigating the association between miR-375 expression and survival outcome like OS, DSS, and PFS; (4) patients were stratified according to the expression level of miR-375; (5) reporting sufficient data to estimate the hazard ratio (HR) and 95% confidence intervals (CI) according to miR-375 expression. The exclusion criteria for the articles were as follows: (1) patients without SCC; (2) duplicate study publications; (3) studies without valuable data or data acquired through animal experiments; (4) studies only using cell lines; (5) reviews, letters, case reports, and expert opinions;

Date extraction and quality assessment

The data and information from all eligible studies were independently extracted by two investigators (Peng Wang and Lian Li) through cross-check. The following data and information were collected from each study: author, publication year, country, race, cancer type, total number of patients, detected sample type, miR-375 assessment methods and the cut-off definition, and HR of miR-375 expression for OS as

well as 95% confidence interval (CI) and *P* value, and so on. To reduce reading variability, the data from Kaplan–Meier survival curves were evaluated by three independent persons as described by Engauge Digitizer version 4.1. The additional information and original data needed for the meta-analysis were acquired by contacting with the corresponding authors of eligible articles. The Newcastle–Ottawa Scale (NOS) was applied to assess the quality of all included studies. The NOS scores ranged from 0 (lowest) to 9 (highest), including selection, comparability, and outcome, the study with an NOS score ≥ 6 was considered to be of high quality [31].

Statistical analysis

The high expression or low expression of miR-375 was defined according to the cut-off values provided by the authors. The pooled HRs and corresponding 95% CIs were used to evaluate the association between miR-375 expression and prognosis. All statistical analyses of present meta-analysis were conducted using the RevMan5.3 software and Stata 15.0 software. The heterogeneity among the enrolled studies was determined by the Chi-square-based *Q* test and I^2 statistics; a *P* value for the *Q* test < 0.05; a I^2 value $> 50\%$ were considered as indicators of severe heterogeneity. The random-effects model was applied to the studies with a significant heterogeneity ($P_Q \leq 0.05$, $I^2 \geq 50\%$). Otherwise, the fixed-effects model was adopted ($P_Q > 0.05$, $I^2 < 50\%$). To decrease the heterogeneity among studies and recognize the prognostic value of miR-375 in depth, the subgroup analyses were conducted based on multiple criteria such as tumor type, sample type, treatment, and patient ethnicity. To test the reliability of the main outcomes in our analysis, sensitivity analysis was performed by removing one single study in turn. Publication bias was estimated by visually assessing the asymmetry of an inverted funnel plot. Furthermore, Begg's test and Egger's test were performed to provide quantitative evidence of publication bias. The *P* value < 0.05 was considered statistically significant.

Results

Studies' characteristics

A flow diagram presented the process of literature selection (Fig. 1). According to the criteria mentioned in "Materials and methods", a total of 329 studies were initially identified with the keywords used to search the databases. By screening the titles and abstracts, 44 potential studies were retrieved and 31 studies were then excluded, because they were insufficient of data (18 studies) or irrelevant to SCCs (13 studies). Finally, 13 studies [11, 21, 32–42] met the inclusion criteria for our meta-analysis, which were published between 2011 and 2017. The total number of patients in all studies was 1340, ranging from 38 to 249 patients. The category of cancers was ESCC or HNSCC. Quantitative RT-PCR was used to detect miR-375 expression in 11 studies. The expression of miR-375 was detected in tumor tissues (9 studies) or blood samples (4 studies). The cut-off values of miR-375 expression varied in different studies, including lower quartile level, mean level, and median level. HRs were reported in the text of five studies and were estimated according to "Materials and methods", of eight studies. Summary characteristics of these studies are shown in Table 1.

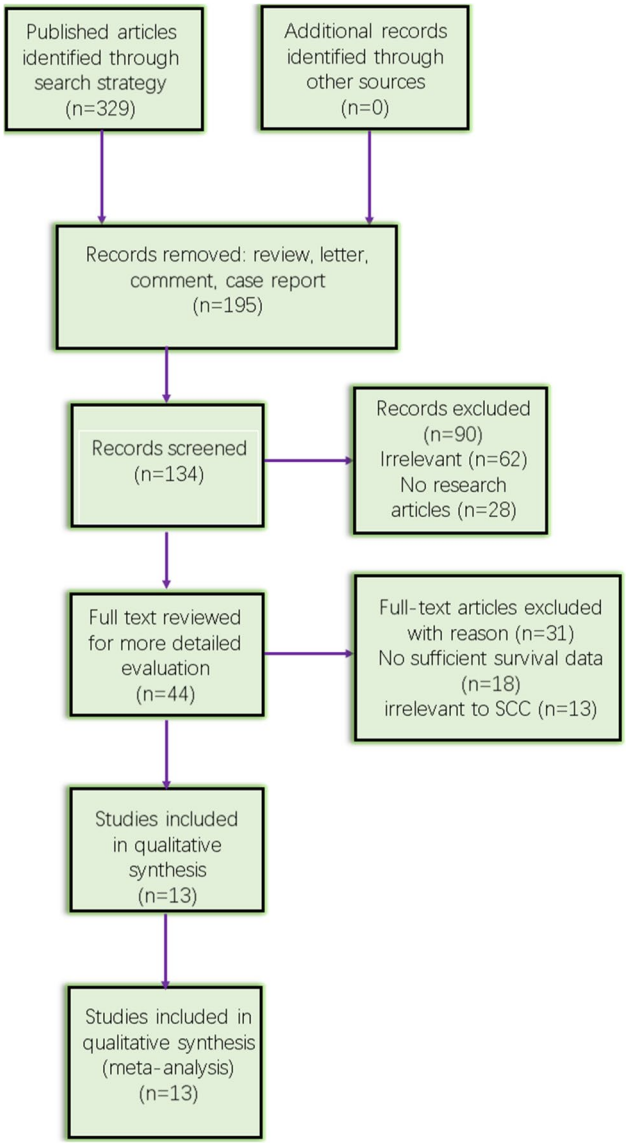

Fig. 1 Flowchart depicting the selection of eligible studies

Table 1 The main characteristics of all included studies in this meta-analysis

No.	Study	Year	Country	Tumor type	Detected sample	Assay method	Expression in tumor	Cut-off value	Sample number (high /low)	Follow-up (month)	Survival end-points	HR source	Independent risk factor
1	Kong et al.	2011	China	ESCC	Frozen	qRT-PCR	Down	Normal	60 (13/47)	93	OS,PFS	DE	NR
2	Harris et al.	2012	USA	HNSCC	Frozen	qRT-PCR	Down	Lower quartile	123 (95/28)	71	OS	Reported (m)	Yes
3	He et al.	2016	China	ESCC	Frozen	qRT-PCR	Down	Mean	88 (43/45)	90	OS	Reported (m)	No
4	Hu et al.	2014	China	HNSCC	Frozen	qRT-PCR	Down	Median	92 (46/46)	60	OS	DE	No
5	Hudcova et al.	2016	Czech Republic	HNSCC	RNAlater	qRT-PCR	Down	Median	42 (39/42)	48	OS, DSS	Reported	No
6	Jia et al.	2014	China	HNSCC	Frozen	qRT-PCR	Down	Mean	105 (36/69)	48	OS	DE	Yes
7	Komatsu et al.	2012	Japan	ESCC	Plasma	qRT-PCR	Down	Median	50 (22/28)	36	OS	DE	Yes
8	Li et al.	2012	USA	ESCC	FFPE	microarray	Down	Median	249 (135/114)	66	OS	DE	NR
9	Li et al.	2015	China	ESCC	Plasma	qRT-PCR	Up	Median	38 (19/19)	40	OS PFS	DE	No
10	Lv et al.	2016	China	ESCC	Serum	qRT-PCR	Down	Median	126 (63/63)	66	OS	DE	Yes
11	Winther et al.	2015	Denmark	ESCC	FFPE	Microarray	Down	Median	129 (64/65)	36	OS, DSS	Reported (u)	No
12	Wu et al.	2014	China	ESCC	Serum	qRT-PCR	Down	Not defined	194 (131/63)	60	OS	Reported (m)	Yes
13	Zhang et al.	2017	China	HNSCC	Frozen	qRT-PCR	Down	Median	44 (25/19)	67	OS	DE	NR

DSS disease-specific survival, *DE* data extrapolated, *ESCC* esophageal squamous cell carcinomas, *FFPE* formalin fixed and parafiin-embedded tissues, *HNSCC* head and neck squamous cell carcinomas, *HR* hazard ratio, *PFS* progression-free survival, *qRT-PCR* quantitative real-time polymerase chain reaction, *(u)* univariate analysis, *(m)* multivariate analysis, *OS* overall survival

Qualitative assessment

While there was a small variation in the methodological quality of included studies, all of the included studies were judged relatively high quality according to the NOS assessment tool, with scores from 6 to 8. A higher value indicated a better methodology. Therefore, all studies were included in the subsequent analysis.

The expression of miR-375 and survival in patients with SCCs

As the studies evaluating OS were of no statistical heterogeneity ($I^2 = 0\%$, $P = 0.75$), we use a fixed model to pool the HRs. The results showed that downregulated miR-375 was significantly associated with poor OS outcome in SCCs with the pooled HR of 1.58 (95% CI 1.34–1.88, $P < 0.001$) (Table 2; Fig. 2a). In addition, the low expression of miR-375 was also significantly correlated with poor PFS (pooled HR 1.91, 95%CI: 0.51–7.10, Fig. 2b). Decreased miR-375 was significantly associated with poor DSS (pooled HR 1.30, 95%CI: 0.86–1.96, Fig. 2c).

Subgroup analysis

Although there was no obvious heterogeneity (Fig. 2a), we still conducted subgroup analysis to seek more information. The subgroups were stratified based on following criteria: tumor type, patient origin, patient treatment, miR-375 identification methods, type of method used to obtain the HR, independent risk factor or not, and cut-off value. In the subgroup of patient origin, we found that the downregulation of miR-375 was significantly associated with worse OS in Asian patients (HR 1.69, 95% CI 1.38–2.07; $P < 0.001$; fixed-effects model) and Western patients (HR 1.34, 95% CI 0.97–1.85; fixed-effects model), without any heterogeneity in the data ($I^2 = 0\%$, $P = 0.80$; $I^2 = 0\%$, $P = 0.49$, resp.) (Table 2; Fig. 3). In the group of therapeutic method,

Table 2 Summary of the subgroup analysis results

Subgroup	Number of studies	Number of patients	Pooled HR (95% CI)	*P* value	Heterogeneity	
					I^2	*P*
Overall effect	13	1400	1.58 (1.34, 1.88)[F]	< 0.0001*	0	0.75
Tumor type						
ESCC	8	934	1.58 (1.29, 1.94)[F]	< 0.0001*	6	0.39
HNSCC	5	466	1.59 (1.16, 2.18)[F]	0.004	0	0.90
Patient treatment						
Surgical resection	12	1335	1.58 (1.32, 1.89)[F]	< 0.0001*	0	0.67
Radiochemotherapy	1	38	1.10 (0.69, 1.77)[F]	0.69	/	/
HR resource						
Reported	5	615	1.49 (1.16, 1.92)[F]	0.002*	0	0.52
Data extrapolated	8	785	1.67 (1.32, 2.11)[F]	0.002*	0	0.68
Region						
Asia	9	818	1.69 (1.38, 2.07)[F]	< 0.0001*	0	0.80
Europe and America	4	582	1.34 (0.97, 1.85)[F]	0.07	0	0.49
Identification method						
qRT-PCR	11	2246	1.64 (1.36, 1.98)[F]	< 0.0001*	0	0.87
Microarray	2	378	1.54 (0.73, 3.27)[R]	0.26	59	0.12
Cut-off value						
Median	8	830	1.43 (1.16, 1.77)[F]	0.0009*	0	0.59
Others	5	570	1.91 (1.43, 2.55)[F]	< 0.0001*	0	0.98
Independent risk factor						
Yes	5	598	1.85 (1.37, 2.48)[F]	0.03*	0	0.46
No	5	428	1.32 (1.03, 1.70)[F]	0.001*	0	0.67
NR	3	374	1.86 (1.28, 2.71)[F]	0.02*	0	0.75

ESCC esophageal squamous cell carcinomas,; *CI* confidence intervals, *HNSCC* head and neck squamous cell carcinomas, *HR* hazard ratio, *NR* not reported, *qRT-PCR* quantitative real-time PCR

*The difference was statistically significant

[F]Fixed-effects model

[R]Random-effects model

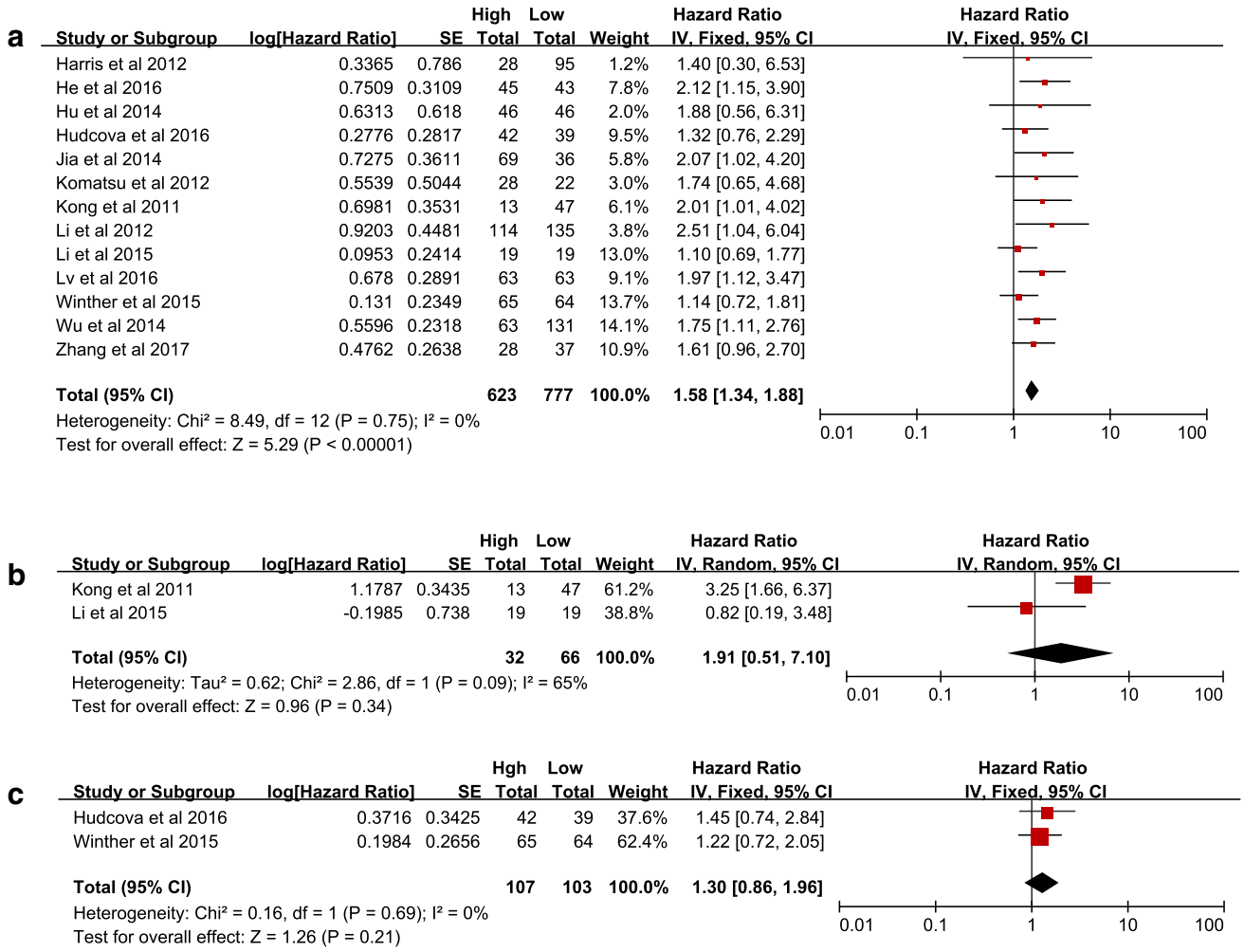

Fig. 2 Forest plot of pooled HR of miR-375 in predicting survival outcomes in SCCs. **a** miR-375 and OS. **b** miR-375 and PFS. **c** miR-375 and DSS

patients received surgical resection. The association between lower miR-375 expression and worse OS outcome was statistically significant in flowing subgroups, including miR-375 assay by microarray (HR 1.35, 95% CI 0.90–2.03, random-effects model; $P = 0.12$ for heterogeneity test, $I^2 = 59\%$) and tumor type in ESCC (HR 1.58, 95% CI 1.29–1.94, fixed-effects model; $P = 0.39$ for heterogeneity test, $I^2 = 6\%$). The pooled HR values and their 95%CI in each subgroup analysis are demonstrated in Table 2. Taken together, the pooled HRs indicated that low miR-375 expression was significantly associated with poor OS in each subgroup.

Sensitivity analysis

To gage the stability of the results, sensitivity analysis was performed by sequential omission of individual studies using the fixed-effects model to see if a single study could have significant impact on the pooled HRs for survival. The results were not significantly altered by removing anyone of the included studies (Fig. 4a: OS, Fig. 4b: DSS, Fig. 4c: PFS).

Publication bias

Begg's funnel plot and Egger's test were used to evaluate the publication bias (Fig. 5). The *P* values of Egger's and Begg's tests were all over 0.05 ($P = 0.36$ for Begg's test; $P = 0.152$ for Egger's test). Hence, there was no evidence for significant publication bias in the meta-analysis.

The funnel plots of Egger's test are displayed in Fig. 5. Both Begg's test and Egger's revealed no significant publication bias in this meta-analysis about miR-375 and OS (Fig. 5a: Begg's test: *Z* value = 0.92, < 1.96; *P* value = 0.360, > 0.05; Fig. 5b: Egger's *P* value = 0.152, > 0.05).

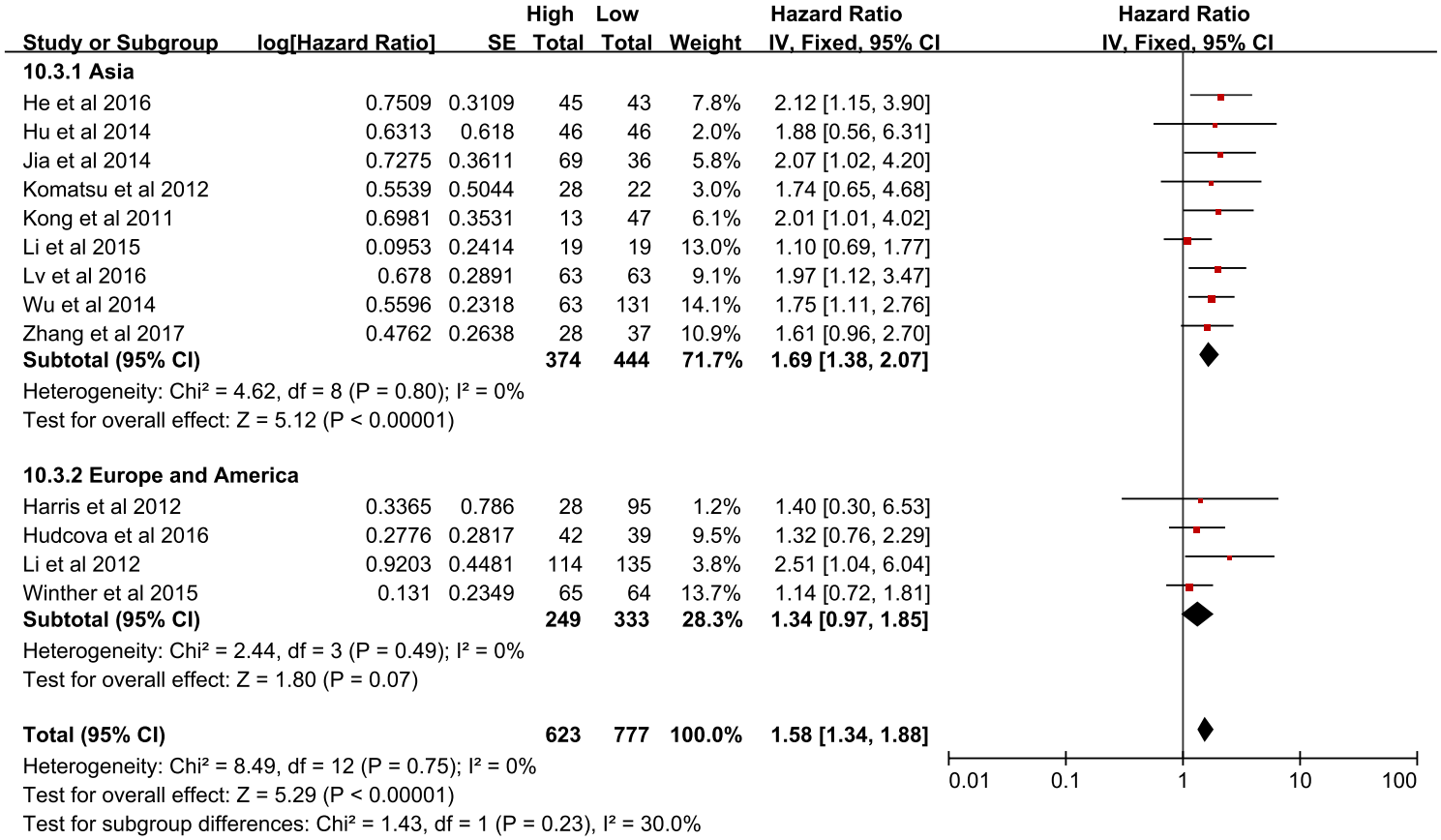

Fig. 3 Forest plots of pooled HR of miR-375 in predicting OS in different regions of patients

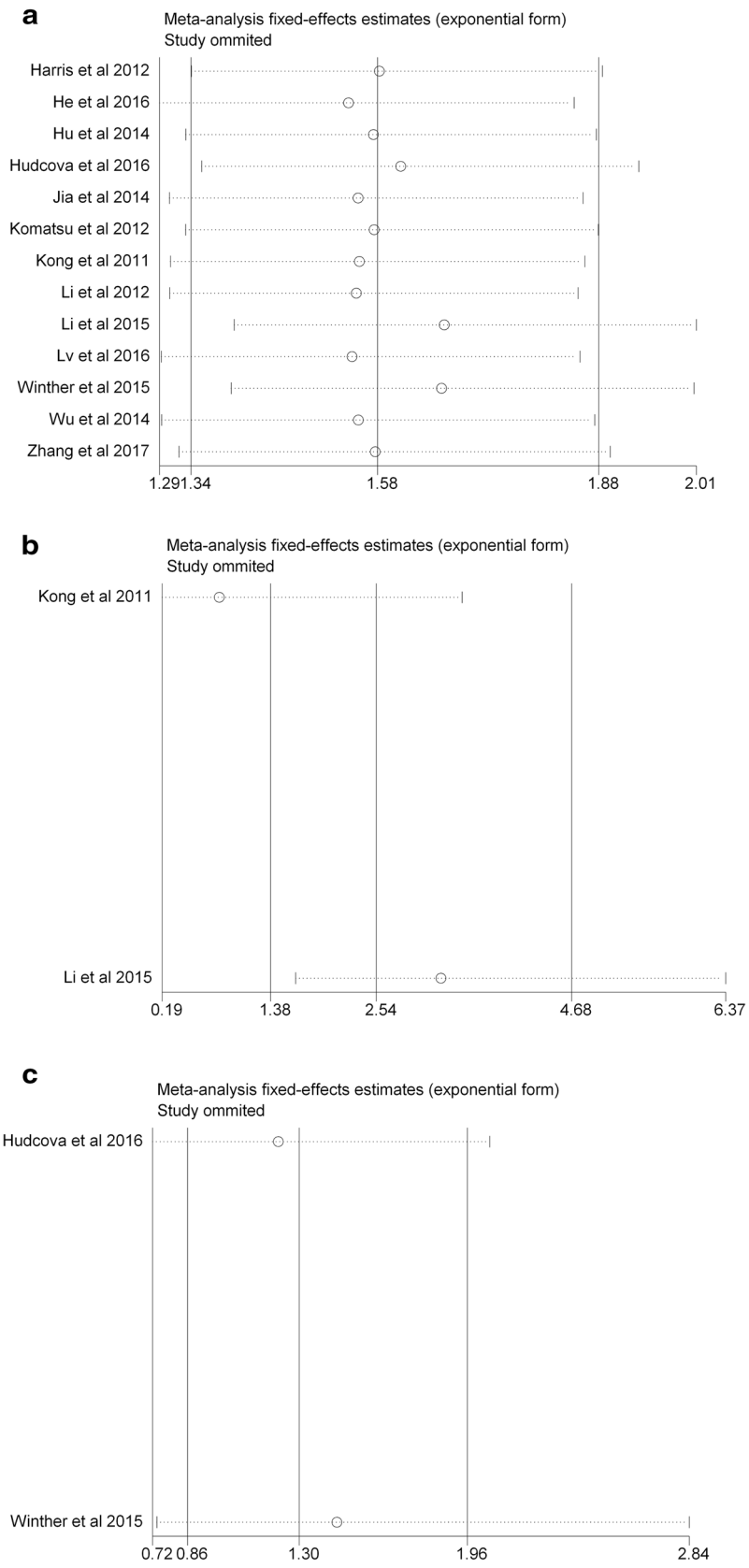

Fig. 4 Sensitivity analysis of included studies. **a** miR-375 and OS. **b** miR-375 and PFS. **c** miR-375 and DSS

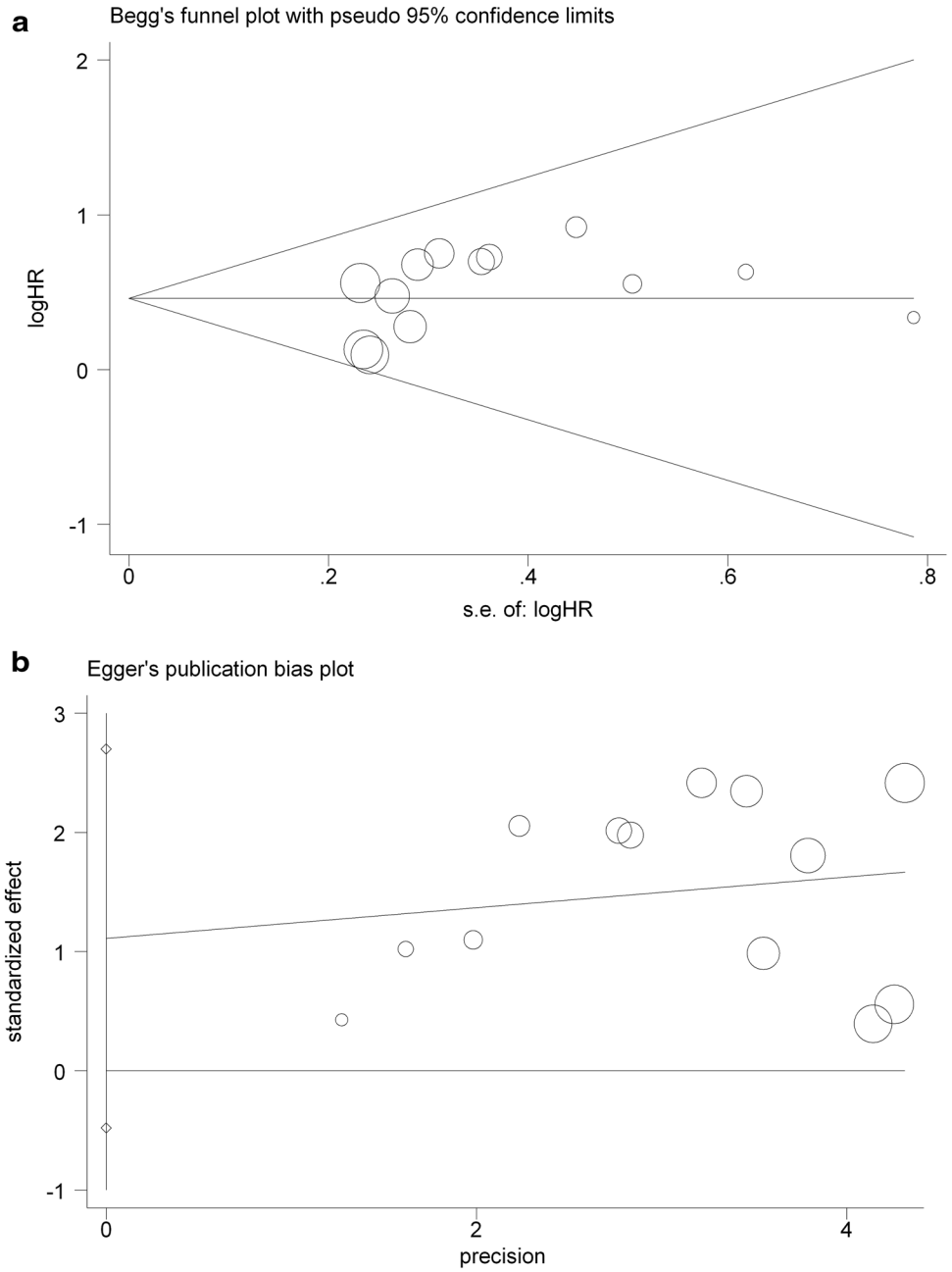

Fig. 5 Plots of **a** Egger's test and **b** Bgger's test

Discussion

Recently, miR-375 has been shown to function as a tumor suppressor in various human cancers. For example, Lian et al. reported that miR-375 functions as a tumor-suppressor gene in gastric cancer by targeting recepteur d'Origine Nantais [43]. In another report, miR-375 is also found to inhibit the invasion and metastasis of colorectal cancer via targeting SP1 and regulating EMT-associated genes [44]. Osako et al. also showed that miR-375 markedly inhibits cancer cell migration and invasion by regulation of MMP13 by in ESCC [45]. Jung and his colleagues showed that four anti-cancer drugs (doxorubicin, 5-fluorouracil, trichostatin A, and etoposide) could induce the expression of tumor-suppressor miR-375 in tongue cancer [46]. This research group also testified that downexpression of tumor-suppressor miR-375 contributes to promoting cancerous phenotypes by inducing uncontrolled CIP2A expression and extended stability of MYC [47]. Besides, the downregulation of miR-375 was frequently detected in primary ESCC, which was significantly correlated with advanced stage, distant metastasis. MiR-375 could interact with the three-untranslated region of IGF1R and downregulate its expression. The dysregulation of miR-375/IGF-1R axis might play important roles in SCCs

development. This finding is consistent with Mathe et al.'s [26] finding that reduced levels of miR-375 are associated with worse prognosis. Pooled HR of upregulated miR-375 for OS in ESCC patients were 0.55, indicating that low level of miR-375 has a negative impact on OS.

In response to the need for independently prognostic molecular marker for SCC that are readily assayable on routinely acquired clinical specimens, we conducted this meta-analysis of the global published literatures on SCCs to identify miR-375 for which the data support validation as prognostic biomarker of SCC outcomes. We searched all the documents about SCC, but found only the original studies of miR-375 and HNSCC or SCC. To the best of our knowledge, this is the first extensive report describing the role of miR-375 in SCCs prognosis, in which 13 studies involving 1400 subjects were analyzed and the relationship between miR-375 and prognosis of SCCs was assessed. Our results demonstrated that lower miR-375 expression was associated with poor survival in patients with various SCCs (HR 1.58 95% CI 1.34–1.88, $P < 0.001$, fixed-effects model), indicating that miR-375 may serve as a positive prognostic marker for SCCs. In the subgroup analyses, the association between lower miR-375 expression and worse OS was statistically significant in most subgroups, especially in ESCC (HR 1.58, 95% CI 1.29–1.94; $P < 0.001$; fixed-effects model) and HNSCC (HR 1.49, 95% CI 1.05–2.12; fixed-effects model).

Our findings suggest that the abnormal expression of miR-375 in SCCs is significantly associated with tumor prognosis. Downregulated miR-375 is related to worse prognosis. The previous studies show that miR-375 is downregulated in multiple types of cancer and acts as a tumor suppressor [48, 49]. Downexpression of miR375 indicates that patients are at high risk of recurrence and have poor OS, and these patients, maybe, improve outcome from post-operative comprehensive treatment. This means that miR-375 could be used not only an indicator of prognosis but also as a guide to treatment. Some of patients with HNSCC or ESCC need to undergo radiotherapy. Zhang et al. reported that upregulated miR-375 significantly enhances radiosensitivity in oral squamous cell carcinoma (OSCC) cells by targeting IGF-1R in vitro [32]. Therefore, miR-375, maybe, serves as an indicator of efficacy of reactive radiotherapy. At present, molecular-targeted therapy is attracting more attention in oncological research, either as a primary approach or, more likely, in combination with the conventional therapy. MiR-375 participates in tumor progression through a variety of pathways. This means that miR-375, as a crucial molecule, maybe act as a new therapeutic target.

Although the predictive value of miR-375 was statistically proved by the meta-analysis in this study, it should be carefully comprehended for the following reasons. First, we reported two major types of SCCs, and HNSCC also include multiple types (the oral cavity, oropharynx, and larynx), leading to bias in patients' homogeneity. Second, due to the lack of uniform cut-off value in miR-375 expression, the cut-off values applied by different researchers deviated from the actual value, which may affect the validity of miR-375 as a predictive factor in cancer prognosis. Third, several HRs were calculated based on the data extracted from the survival curve, bringing minor deviations. Meanwhile, the statistical heterogeneity was not obvious in this meta-analysis, but the clinical and methodological heterogeneity existed in the baseline demographic characteristics, including population, tumor types and stages, treatment therapy, the cut-off value of miR-375 expression, and duration of follow-up. Finally, although no significant publication bias was detected in this meta-analysis, the results still need to be verified by many publications.

In conclusion, this meta-analysis summarized the global researches on the relationship of aberrant miR-375 expression and the prognosis of patients with SCCs, and clarified that downregulation of miR-375 is significantly associated with poor survival in patients with various types of SCCs, including ESCC and HNSCC. In view of the limitation of the current analysis, it should be cautious to appreciate the conclusion, and further prospective multicenter studies designed adequately with larger sample size are needed to verify the association between miR-375 expression and SCCs prognosis as well as the efficiency of therapies.

Acknowledgements All sources of funding of the study should be disclosed. Please clearly indicate grants that you have received in support of your research work. Clearly state if you received funds for covering the costs to publish in open access.

Author contributions PW and LX designed the study under the supervision of MX and MZ. PW and LX performed the literature search and evaluated their eligibility independently. PW, LX, LL, and SR extracted and analyzed the data. JT prepared the initial report. PW wrote the paper, and MZ edited the manuscript.

Funding This study was supported by the grants of National Natural Science Foundation of China (no. 71673193), the Key Technology Research and Development Program of the Sichuan Province (2015SZ0131 and 2017FZ0082), and the Natural Science Foundation for Young Scientists of Gansu Province and the Science and Technology Planning Project of Gansu Province (Grant no. 18JR3RA058).

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. This article does not contain any studies with animals performed by any of the authors.

Informed consent Informed consent was obtained from all individual participants included in the study.

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