Pathology - Research and Practice 215 (2019) 152726

Contents lists available at ScienceDirect

Pathology - Research and Practice

journal homepage: www.elsevier.com/locate/prp

Review

Prognostic value of microRNA-451 in various cancers: A meta-analysis

Weihao Kong[a,1], Linfei Feng[b,1], Mingwei Yang[c,1], Qihang Chen[b], Hengyi Wang[a,*,2], Xingyu Wang[a,*,2], Jun Hou[b,**,2]

[a] Department of Emergency Surgery, Department of Emergency Medicine, The First affiliated hospital of Anhui Medical University, Heifei, China
[b] Department of Oral and Maxillofacial Surgery, The First Affiliated Hospital of Anhui Medical University, Hefei, China
[c] Department of Radiation Oncology, The First affiliated hospital of Anhui Medical University, Heifei, China

ARTICLE INFO

Keywords:
MicroRNA-451
Cancer
Prognosis
Meta-analysis

ABSTRACT

Background: Increasing evidence shows microRNA-451 plays a crucial role in various tumors, but there is inconsistency. The aim of this study was to explore the prognostic role of miR-451 in various tumors.
Methods: Online PubMed, EMBASE, Web of Science, and the Cochrane library database were searched through February 2019. Hazard ratios (HRs) were extracted and used to describe the association between expression of microRNA-451 and survival outcome, and the correlation between microRNA-451 and clinicopathologic features were described by pooled odds ratios (ORs).
Results: Sixteen retrospective studies containing 2122 patients were incorporated in this meta-analysis. High expression of miR-451 was considered statistically associated with prolonged overall survival (OS) (HR = 0.62, 95% CI 0.49-0.80, p < 0.001) as well as RFS/DFS (HR = 0.55, 95% CI 0.42-0.71, p < 0.001) compared with low expression of miR-451. Besides, the pooled ORs revealed significant association between high expression of miR-451 with lymph node invasion (yes vs. no) (OR = 0.64, 95% CI 0.46-0.90, P = 0.01), tumor diameter (big vs. small) (OR = 0.77, 95% CI 0.60-0.97, P = 0.028) and tumor stage (III + IV vs. I + II) (OR = 0.62, 95% CI 0.42-0.93, P = 0.019).
Conclusion: MicroRNA-451 may serve as a promising clinical prognostic biomarker in various carcinomas.

1. Introduction

Cancer is expected to be the leading cause of death throughout the world in the 21 st century. According to the Global Cancer Statistics 2018, there would be an estimated 18.1 million new cancer cases and 9.6 million cancer deaths last year [1]. Tremendous work needs to be done including early diagnosis and suitable therapeutic strategies to alleviate this situation. It is crucial to make a precise prognosis at moment of diagnosis by imaging examinations as well as chemical biomarkers.

Microribonucleic acids (miRNAs) are single-stranded, highly conserved, noncoding RNAs with 18–25 nucleotides in length. By binding to the 3′ untranslational region (3′UTR) of target messenger RNA (mRNA), miRNAs play a negative role in gene expression resulting in translation inhibition or mRNA degradation. Mounting studies collectively revealed that miRNAs play a vital role in various biological processes and is tightly involved in the development of cancers [2,3]. Therefore, miRNA could serve as prognostic biomarker in cancers, which has already validated in several studies [4–6].

Recently, low level microRNA-451 was revealed to bear significant correlation with unfavorable outcome in various cancers, including prostate cancer, gastric cancer, non-small cell lung cancer (NSCLC), and hepatocellular cancer [4,7–9]. However, Guo et al. suggested over expression of miR-451 was close linked with metastasis and poor prognosis [10]. The magnitude and consistency of the prognostic effect of miR-451 remains unclear. Therefore, it is necessary to integrate existing evidences and carry out a meta-analysis to clarify the prognostic role of miR-451 in diverse cancers.

* Corresponding authors at: Department of Emergency Surgery, Department of Emergency Medicine, The First affiliated hospital of Anhui Medical University, 218 Jixi Avenue, Heifei, 230032, China.
** Corresponding author at: Department of Oral and Maxillofacial Surgery, The First Affiliated Hospital of Anhui Medical University, 218 Jixi Avenue, Heifei, 230032, China.
E-mail addresses: wanghengyi123456@163.com (H. Wang), wangxingyu@ahmu.edu.cn (X. Wang), houjun1234567@126.com (J. Hou).
[1] These authors contributed equally to this work.
[2] These authors contributed equally to this work.

https://doi.org/10.1016/j.prp.2019.152726
Received 30 August 2019; Received in revised form 13 October 2019; Accepted 26 October 2019

2. Materials and methods

2.1. Search strategy

This meta-analysis was carried out according to the reporting items preferred by the PRISMA guidelines [11]. Online PubMed, EMBASE, Web of Science, and the Cochrane library database were searched through August 2019 to identify studies reporting the association between microRNA-451 and prognosis in various cancers. Key words employed in the search were "prognosis OR prognostic OR survival" [Title/Abstract] AND "cancer OR carcinoma OR neoplasm OR tumor" [Title/Abstract] AND "microRNA-451 OR microna-451 OR miR-451 OR miRNA-451" [Title/Abstract]. The references of identified literatures were screened to further explore relevant studies. The literature search and review were conducted independently by two authors, and disagreements were resolved by panel discussion.

2.2. Inclusion and exclusion criteria

Titles and abstracts of the identified literature were evaluated and then those considered irrelevant were screened out. Further evaluation was performed by viewing the full text carefully. Eligible literature meets the inclusion criteria were incorporated in this meta-analysis. The inclusion criteria is as follows: 1) human research predicting the association between microRNA-451 and the prognosis including overall survival (OS), progression-free survival (PFS), disease-free survival (DFS), cancer-specific survival (CSS), or relapse-free survival (RFS); 2) microRNA-451 were detected from tumor tissue; 3) sufficient data enables hazard ratios (HRs) and 95% confidence intervals (CIs) to be extracted; 4) the study was written in English and its full text was available.

Articles were excluded if: 1) they were letters, editorials, expert opinions, systematic reviews, case reports or non-human researches; 2) the study was not written in English; 4) the study lacked significant data for further analysis; and 5) the study was a repeated study.

2.3. Data extraction

Three researchers (Kong WH, Feng LF, Yang MW) independently extracted the required data and information from the enrolled articles and disagreements were resolved by consensus. Extracted data included: the first author's surname, publication year, region of patients, age, gender, tumor type, sample size, specimen source, method of detection, time of recruitment, tumor stage, tumor invasion depth, lymph node metastasis, distant metastasis, tumor diameter, follow-up time, definition of high microRNA-451 expression, outcome, HRs with corresponding 95% CIs of the high microRNA-451 expression group versus the low one for OS, DFS, PFS, RFS or CSS, and analysis method. For studies whose HRs were not provided, survival data were extracted from the original study data (Kaplan-Meier curves or the required data) using the software Engauge Digitizer 4.1 and the estimated survival data were calculated by Tierney's method [12].

2.4. Quality assessment

The quality of the identified studies was assessed according to the Newcastle-Ottawa scale (NOS) in this meta-analysis [13]. A score of 0 and 9 was considered as the lowest and highest quality, respectively. A NOS score of six or higher would be deemed as high-quality study.

2.5. Statistical analysis

Pooled HRs with their corresponding CIs were used to describe the association between

expression of microRNA-451 and survival outcome, and the correlation between microRNA-451 and clinicopathologic features were described by pooled odds ratios (ORs) and their CIs. Statistical analyses of the HRs and ORs were computed using STATA software. Q tests and I^2 statistics were applied to evaluate heterogeneity. $P < 0.05$ and/or $I^2 > 50\%$ were considered to be statistically significant heterogeneity which would adopt random effects model for statistical analysis, otherwise, a fixed effects model was used. Egger's test, Begg's test, and funnel plots were implemented to detect publication bias. We use sensitive analysis to evaluate the stabilization of the results. A P-value below 0.05 was deemed to be statistically significant.

3. Results

3.1. Literature search and study characteristics

A total of 306 articles were initially retrieved by adopting the search strategy mentioned in the materials and methods. Afterwards, all the articles were evaluated by viewing the titles and abstracts and 266 were excluded according to the inclusion and exclusion criteria. Sixteen articles were eventually included in this meta-analysis after full text view (Fig. 1). The NOS score of enrolled studies ranged from 6 to 7, details of the evaluation contents are shown in Supplementary file1.

This meta-analysis incorporated 16 retrospective studies containing 2122 patients who were diagnosed with various cancers ranging from nasopharyngeal carcinoma (NPC), non-small lung cancer (NSCLC), hepatocellular carcinoma (HCC), pancreatic cancer (PC), gastric cancer (GC), renal cell carcinoma (RCC), epithelial ovarian cancer (EOC), osteosarcoma (OS), liposarcoma (LPS) to acute lymphoblastic leukemia (ALL) [4,5,7–10,14–23]. The studies were published from 2009 to 2018, and the recruitment time is from 1984 to 2014 except two studies did not report [10,23]. Most of the patients are from China except four studies where patients come from Japan, Greece, Spain and Israel, respectively [4,15,17,23]. The major features of the selected studies are presented in Table 1. Across the 16 studies, microRNA-451 expression was detected in tissue except bone marrow aspirates in Avigad's study, and the detection methods included in situ hybridization (ISH) adopted in Ren's and Bandrs' studies, while polymerase chain reaction (PCR) used in other studies. The tumor stage was evaluated by specific methods including TNM, FIGO and Enneking's staging. Definition of high microRNA-451 expression differed among studies. Thirteen studies reported OS, while 6 studies presented DFS or RFS. HRs or RRs with their 95% CIs were provided directly in 11 studies and for other studies data were extracted from the survival curve. DFS and RFS in six studies were combined to calculate HR with 95% CI.

3.2. MicroRNA-451 expression and OS

For 13 studies reporting the correlation between micrRNA-451 and OS, heterogeneity is significant, ($I^2 = 76.7\%$, $p < 0.001$). Thus, random effect model was employed to calculate the HRs and 95% CIs. As shown in Fig. 2, compared with low expression of miR-451, high expression of miR-451 is statistically associated with prolonged OS (HR = 0.62, 95% CI 0.49-0.80, $p < 0.001$).

Subgroup analysis on the basis of sample size, region, statistical mode, statistics and cancer types was further conducted in order to explore heterogeneity across these studies. The details are presented in Table 2. Our study demonstrated that there was significant relation between upregulated microRNA-451 and a better OS in the subgroups of sample size < 100 (HR = 0.49, 95% CI 0.34-0.69, $P < 0.001$), Asian (HR = 0.61, 95% CI 0.47-0.79, $P < 0.001$), univariate (HR = 0.77, 95% CI 0.65-0.91, P = 0.003), multivariate (HR = 0.55, 95% CI 0.37-0.83, P = 0.004), data from RR (HR = 0.39, 95% CI 0.28-0.54, $P < 0.001$), data extracted from SC (HR = 0.77, 95% CI 0.65-0.91, P = 0.003), cancer of urogenital system (HR = 0.68, 95% CI 0.48-0.97, P = 0.033), cancer of respiratory system (HR = 0.45, 95% CI 0.24-0.84, P = 0.012), other cancers (HR = 0.53, 95% CI 0.31-0.88, P = 0.015). Nevertheless, statistical association between high level of microRNA-451 and OS was not detected in other groups, including sample size ≥ 100 (HR = 0.83, 95% CI 0.55–1.24, P = 0.354), Caucasian (HR = 0.99, 95% CI 0.36–2.71, P = 0.984), data from HR

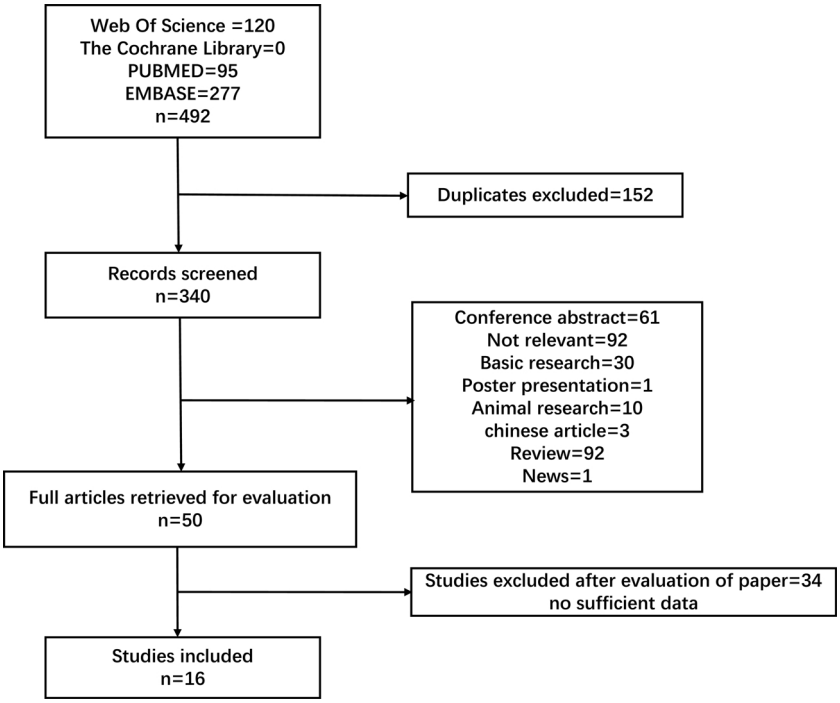

Fig. 1. Flow diagram for screening literature.

(HR = 0.71, 95% CI 0.39–1.27, P = 0.249), cancer from digestive system (HR = 0.72, 95% CI 0.45–1.13, P = 0.147). Furthermore, we conducted a meta-regression and did not find a potential source of heterogeneity (Supplementary file2).

3.3. MicroRNA-451 expression and RFS/DFS

RFS and DFS were combined to analyze due to likeness between them and limited studies (6 in this meta-analysis) describing the correlation between high level microRNA-451 and RFS/DFS. Fixed effect model was performed because of non-significant heterogeneity (I^2 = 29.9%, P = 0.211). We observed that elevated microRNA-451 was significantly associated with better RFS/DFS (HR = 0.55, 95% CI 0.42-0.71, p < 0.001) (Fig. 3).

3.4. MicroRNA-451 expression and clinicopathological characteristics

The relationship between microRNA-451 and clinicopathological characteristics was described by pooled OR and 95% CI (Table 3). High expression of miR-451 showed significant association with lymph node invasion (yes vs. no) (OR = 0.64, 95% CI 0.46-0.90, P = 0.01), tumor diameter (big vs. small) (OR = 0.77, 95% CI 0.60-0.97, P = 0.028) and tumor stage (III + IV vs. I + II) (OR = 0.62, 95% CI 0.42-0.93, P = 0.019). Nevertheless, the upregulated microRN-451 was revealed to have no significant correlation with Age (old vs. < young) (OR = 0.92, 95% CI 0.81–1.04, P = 0.171), gender (male vs. female) (OR = 1.08, 95% CI 0.92–1.28, P = 0.345), invasion depth (T3 + T4 vs. T1 + T2) (OR = 0.84, 95% CI 0.61–1.16, P = 0.277) and distant metastasis (yes vs. no) (OR = 0.68, 95% CI 0.43–1.19, P = 0.191).

3.5. Sensitivity analysis

Sensitivity analysis was performed to evaluate the influence of each study on the overall results by removing each study. The results showed that the removal of any study will not affect the overall results (Fig. 4). Thus, we could interpret our conclusion is reliable.

3.6. Publication bias

Begg's funnel plot and Egger's test were employed to evaluate the publication bias of included studies in the OS and RFS/DFS analysis. It revealed symmetry for both OS and RFS/DFS in the funnel plot figures (Fig. 5). P value of Begg's tests and Egger's tests were not statistical (OS, Begg's test: P = 0.134, Egger's test: P = 0.360; RFS/DFS, Begg's test: P = 0.452, Egger's test: P = 0.411). Therefore, no publication bias was detected in our study.

4. Discussion

MiR-451 is located on chromosome at 17q11.2. Since the first introduction of miR-451, it has accumulated increasing attention due to its intimate association with progression of various tumors [10,14,22]. Recent study reported that the diagnostic ability of miRNA-451 was moderately high for various cancers [24], but the prognostic role of miRNA-451 in various cancers has not been explored. Hence, this meta-analysis is the first to quantitatively analyze the correlation between the level of miR-451 and the prognosis of patients in various tumors.

The PRISMA guidelines were adopted to perform this meta-analysis and NOS was applied to evaluate the quality of the identified studies. This study revealed that high expression of miR-451 bore a positive correlation with OS (HR = 0.62, 95% CI 0.49-0.80, p < 0.001) and RFS/DFS (HR = 0.55, 95% CI 0.42-0.71, p < 0.001). Since heterogeneity is significant, a random effect model was employed to calculate. Then, we performed subgroup analysis, sensitivity analysis, and meta-regression, respectively. The results of the subgroup analysis showed no factors that caused the subgroup heterogeneity to disappear. The results of the sensitivity analysis showed that eliminating any of the studies did not have a significant impact on the overall effect size. Meta-regression did not explore variables that explain the source of heterogeneity. Therefore, due to the limited sample size or other possible confounding factors, we did not examine the source of heterogeneity. Besides, the results of the sensitivity analysis and subgroup analysis showed that our outcome did not change significantly. No potential publication bias was found in Begg's funnel plot and Egger's test, so our results are stable and reliable.

Table 1
Main features of the included studies.

First author	Publication year	Region	Cancer type	Number of patients	Detected sample	Detected method	Time of recruitment	Follow-up (months)	Stage range	Definition of high miR-451 expression	Outcome	HR type	analysis method	NOS
Ling	2015	china	EOC	115	tissue	qRT-PCR	2005-2007	from surgery to 2012	FIGO(I-IV)	median	OS	RR	M	7
Chen	2018	china	PC	59	tissue	qRT-PCR	2009.1-2013.6	maximum (40)	TNM (IV)	ROC(0.895)	OS	HR	M	6
Ren	2016	china	GC	180	tissue	ISH	2006-2008	79.2–97.2	TNM (I-IV)	expression ratios of tumor/normal > 1	OS	HR	M	7
Wang	2011	china	NSCLC	23	tissue	qRT-PCR	2006-2008	maximum (20)	TNM (I-III)	median ratio (83.4)	OS	SC	U	6
Huang	2015	china	HCC	87	tissue	qRT-PCR	2005-2007	maximum (100)	TNM (I-III)	ROC(0.972)	OS	RR	M	6
Shen	2017	china	GC	268	tissue	qRT-PCR	2009.5-2014.12	48 (3-60)	TNM (I-IV)	0.01	OS	HR	M	7
Zhu	2016	china	RCC	51	tissue	qRT-PCR	2011	1571 (342-2500) day	TNM (I-IV)	median	OS	SC	U	7
Su	2015	china	GC	107	tissue	qRT-PCR	2010-2012	maximum (80)	TNM (I-IV)	expression ratios of tumor/normal > 1	OS	SC	U	7
Goto	2017	Japan	NSCLC	370	tissue	qRT-PCR	2005-2014	maximum (180)	TNM (I-IV)	0.761	DFS	HR	M	7
Guo	2017	china	PC	20	tissue	qRT-PCR	NR	maximum (60)	NR	median	OS	HR	M	6
Wang	2011	china	NSCLC	200	tissue	qRT-PCR	2001-2007	maximum (100)	TNM (I-IV)	NR	OS	RR	M	6
Liu	2013	china	NPC	280	tissue	qRT-PCR	2003.1-2006.2	63.9 (3.7-91.87)	TNM (I-IV)	median	OS/DFS	HR	M	7
Yuan	2015	china	OS	118	tissue	qRT-PCR	2002.1-2008.3	76 (10-112)	Enneking's staging (II-III)	median	OS/DFS	RR	M	6
Bandres	2009	Spain	GC	45	tissue	ISH	NR	65 (5.7-172)	TNM (I-IV)	median	DFS	HR	M	7
Kapodistrias	2016	Greece	LPS	61	tissue	qRT-PCR	1990-2012	73 (2-215)	TNM (I-IV)	median	OS/RFS	SC	U	7
Avigad	2015	Israel	ALL	138	bone marrow aspirates	qRT-PCR	1984-2005	maximum (400)	NR	first quartile	RFS	SC	U	6

Notes: EOC: epithelial ovarian cancer; PC: pancreatic cancer; GC: gastric cancer; NSCLC: non-small lung cancer; HCC: hepatocellular carcinoma; RCC: renal cell carcinoma; NPC: nasopharyngeal carcinoma; OS: osteosarcoma; LPS: liposarcoma; ALL: acute lymphoblastic leukemia; qRT-PCR: quantitative Real-time polymerase chain reaction; ISH: In Situ Hybridization; NR: Not reported; FIGO: Federation Internationale Of Gynecologie And Obstetrigue; TNM: tumor node metastasis; ROC: receiver operating characteristic curve; OS: Overall survival; RFS: Recurrence-free survival; DFS: Disease-free survival; RR: relative risk; HR: hazard ratio; SC: survival curve; M: multivariate; U:univariate; NOS: Newcastle-Ottawa scale.

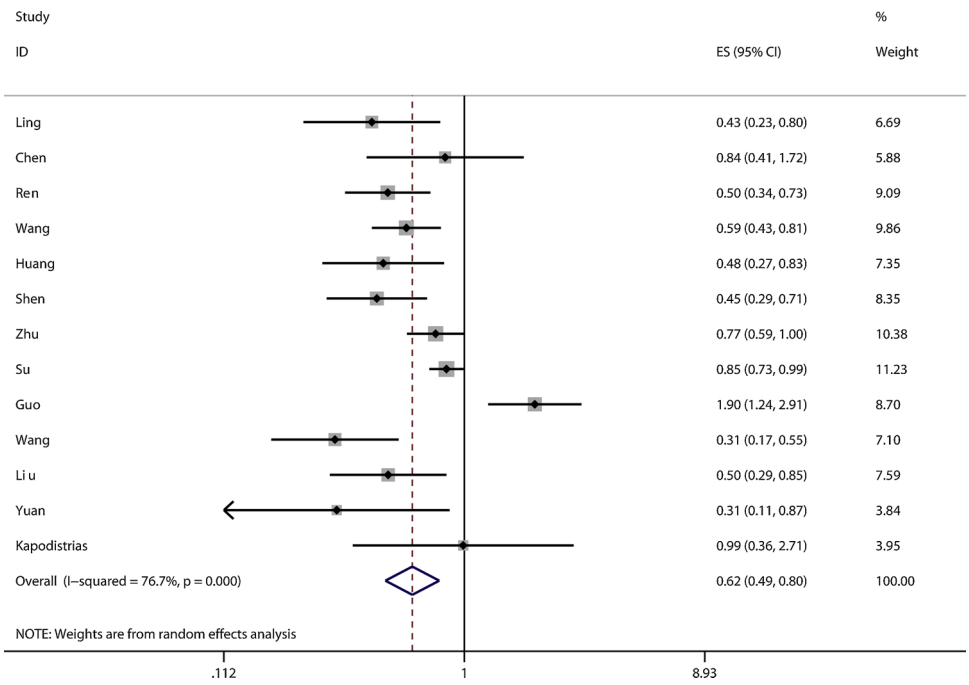

Fig. 2. Forest plot of the combined HRs for OS in cancer patients.
Notes: HRs: Hazard ratios; OS: Overall survival.

Subgroup analysis also revealed elevated miR-451 is significantly related with Asian (HR = 0.61, 95% CI 0.47-0.79, P < 0.001) rather than Caucasian (HR = 0.99 95% CI 0.36–2.71, P = 0.984), which may be interpreted by different genetic backgrounds, climates and geographic factor etc. As a result, we drew the conclusion that miR-451 might predict better in Asian populations. To elucidate the impact of cancer type, we divided all the cancers into urogenital system, digestive system, respiratory system and other cancers. It showed high level miR-451 correlated prominently with cancer of urogenital system (HR = 0.68, 95% CI 0.48-0.97, P = 0.033), cancer of respiratory system (HR = 0.45, 95% CI 0.24-0.84, P = 0.012), and other cancers (HR = 0.53, 95% CI 0.31-0.88, P = 0.015). Therefore, we concluded miR-451 as a positive prognostic biomarker for cancers, especially of urogenital, respiratory origin.

In the meta-analysis, we further explored the association between miR-451 and clinicopathological characteristics. It suggested that lymph node invasion (OR = 0.64, 95% CI 0.46-0.90, P = 0.01), big tumor diameter (OR = 0.77, 95% CI 0.60-0.97, P = 0.028) and advanced tumor stage (OR = 0.62, 95% CI 0.42-0.93, P = 0.019) tended to have low level of miR-451. Therefore, we hypothesized that miR-451 might be involved in the process of lymphatic metastasis and local invasion in cancer.

Mechanisms by which miR-451 interfere with cancer may be targeting numbers of oncogenic genes. For example, Chen et al revealed that miR-451 increased chemosensitivity by targeting neural-precursor-cell-expressed developmentally downregulated protein 9 (NEDD9) in prostate cancer cells thus improving the prognosis [7]. Tian et al. discovered miR-451 downregulated the PI3K/AKT pathway through

Table 2
Subgroup analysis for OS in cancer patients.

Subgroups	Number of studies	Number of patients	Pooled HR (95%CI)	P-value	Heterogeneity		
					I^2 (%)	P-value	Model
Sample size							
< 100	6	301	0.49 (0.34-0.69)	**0.000**	77.00	0.000	random
≥100	7	1268	0.83 (0.55-1.24)	0.354	78.40	0.000	random
Region							
Asian	12	1508	0.61 (0.47-0.79)	**0.000**	78.50	0.000	random
Caucasian	1	61	0.99 (0.36-2.71)	0.984	–	–	random
Statistical mode							
Univariate	4	242	0.77 (0.65-0.91)	**0.003**	31.60	0.223	random
Multivarite	9	1327	0.55 (0.37-0.83)	**0.004**	80.20	0.000	random
Statistics							
HR	5	807	0.71 (0.39-1.27)	0.249	86.40	0.000	random
RR	4	520	0.39 (0.28-0.54)	**0.000**	0.00	0.699	random
SC	4	242	0.77 (0.65-0.91)	**0.003**	31.60	0.223	random
Cancer type							
Urogenital system	3	225	0.68 (0.48-0.97)	**0.033**	34.20	0.219	random
Digestive system	5	662	0.72 (0.45-1.13)	0.147	87.30	0.000	random
Respiratory system	2	223	0.45 (0.24-0.84)	**0.012**	73.20	0.053	random
others	3	459	0.53 (0.31-0.88)	**0.015**	21.00	0.282	random

Notes: RR: relative risk; HR: hazard ratio; SC: survival curve.
Bold represents P value less than 0.05.

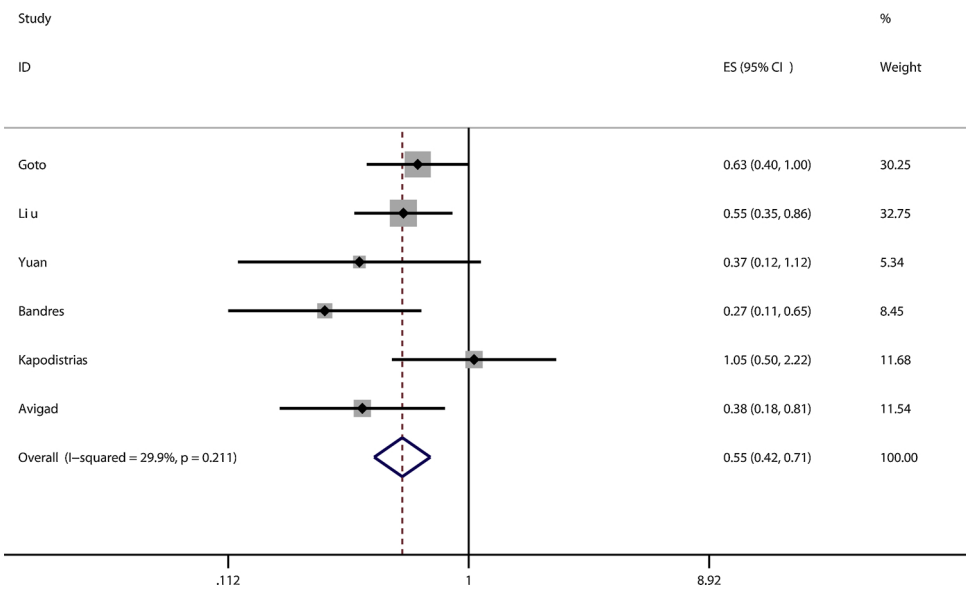

Fig. 3. Forest plot of the combined HRs for RFS/DFS in cancer patients.
Notes: HRs: Hazard ratios; RFS: Recurrence-free survival; DFS: Disease-free survival.

Table 3
Correlation between miR-451 and clinicopathologic features.

Stratified analysis	No. of studies	No. of patients	Pooled OR (95% CI)	p-value	Heterogeneity		
					I^2 (%)	P-value	Model
Age (old vs. < young)	7	1088	0.92 (0.81-1.04)	0.171	0	0.580	Fixed
Gender (male vs. female)	5	773	1.08 (0.92-1.28)	0.345	36	0.181	Fixed
invasion depth (T3 + T4 vs. T1 + T2)	4	777	0.84 (0.61-1.16)	0.277	74.3	0.009	random
lymph node invasion (yes vs. no)	6	970	0.64 (0.46-0.90)	**0.010**	79.3	0.000	random
Distant metastasis (yes vs. no)	2	298	0.68 (0.43-1.19)	0.191	53.5	0.142	random
Tumor diameter (big vs. small)	4	493	0.77 (0.60-0.97)	**0.028**	37.5	0.187	fixed
Tumor stage (III + IV vs. I + II)	6	954	0.62 (0.42-0.93)	**0.019**	85.6	0.000	random

Notes: OR: odds ratio.

calcium binding protein 39 gene (CAB39) in human glioma [25]. Huang et al. demonstrated miR-451 inhibited tumor metastasis in hepatocelluar carcinoma through activation of the Erk1/2 signaling, at least partially by targeting c-Myc [9]. Eva Bandres et al. suggested miR-451 acted as a tumoral suppressor in gastrointestinal cancer, at least in part through direct suppression of macrophage migration inhibitory factor (MIF) [23]. MIF was also validated as a target of miR-451 in NSCLC in Goto's study [4]. Other researchers provided evidence that elevated miR-451 promoted cell viability and invasion by suppressing the expression of calcium-binding protein 39 (CAB39) [10]. Considering the complexity and diversity of connection between microRNA and target mRNAs, specific mechanism demands further exploration.

Several limitations exist in this meta-analysis. First, only 16 studies with 2122 patients were enrolled in this study, which inevitably leads to insufficient data for analyzing. Second, different definitions of high miR-451 expression were applied among diverse studies, thus, the prognostic accuracy of miR-451 may be influenced. Third, a number of HRs were extracted and calculated from the survival curves which may bring about some error. Finally, this study has significant heterogeneity, which may be introduced by region, publication time, sample source, definition method, statistical mode, cancer type across various studies. However, subgroup analysis, sensitivity analysis, and meta-regression did not explore potential sources of heterogeneity due to the limited sample size and other confounding factors. Take all these

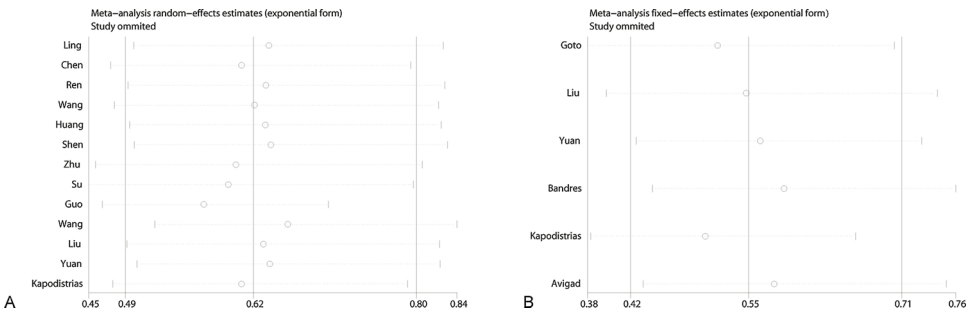

Fig. 4. Sensitivity analysis for (A) OS and (B) RFS/DFS.
Notes: OS: Overall survival; RFS: Recurrence-free survival; DFS: Disease-free survival.

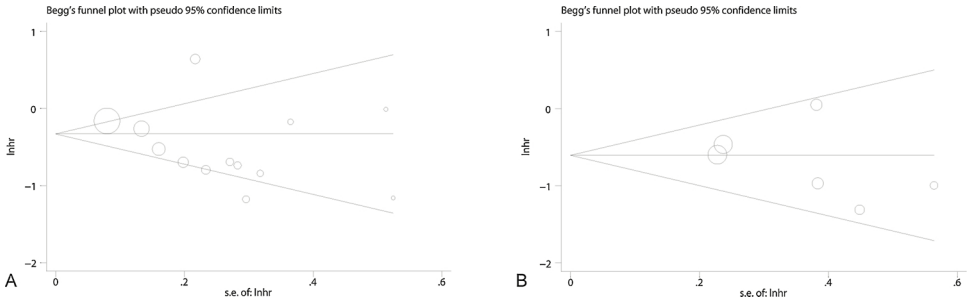

Fig. 5. Publication bias for (A) OS and (B) RFS/DFS.
Notes: OS: Overall survival; RFS: Recurrence-free survival; DFS: Disease-free survival.

factors into consideration, well-designed and large sample size researches are required before applying miR-451 as a prognostic biomarker into clinical use.

5. Conclusion

Our study revealed miR-451 may serve as a prognostic biomarker in various cancers, especially for urogenital system cancers and respiratory system cancers. In consideration of the limitations, further researches concerning miR-451 are warranted.

Data availability

Data used to support the results of this study can be obtained from the corresponding author.

CRediT authorship contribution statement

Weihao Kong: Data curation, Software, Writing - original draft. **Linfei Feng:** Data curation, Writing - original draft. **Mingwei Yang:** Data curation, Writing - original draft. **Qihang Chen:** Data curation, Software. **Hengyi Wang:** Supervision, Writing - review & editing. **Xingyu Wang:** Supervision, Writing - review & editing. **Jun Hou:** Supervision, Writing - review & editing.

Declaration of Competing Interest

The author states that there is no conflict of interest

Acknowledgements

This work was supported by the 2015 Clinical Science Research Project of Anhui Medical University (Project Number: 2015xkj089) and Anhui Natural Science Foundation (Project Number: 1608085QH182).

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.prp.2019.152726.

References

[1] F. Bray, J. Ferlay, I. Soerjomataram, et al., Global cancer statistics 2018: globocan estimates of incidence and mortality worldwide for 36 cancers in 185 countries, CA Cancer J. Clin. 68 (6) (2018) 394–424.
[2] G.A. Calin, C.M. Croce, Microrna signatures in human cancers, Nat. Rev. Cancer 6 (11) (2006) 857–866.
[3] D.P. Bartel, Micrornas: genomics, biogenesis, mechanism, and function, Cell 116 (2) (2004) 281–297.
[4] A. Goto, M. Tanaka, M. Yoshida, et al., The low expression of mir-451 predicts a worse prognosis in non-small cell lung cancer cases, PLoS One 12 (7) (2017) e0181270.
[5] J. Yuan, J. Lang, C. Liu, et al., The expression and function of mirna-451 in osteosarcoma, Med. Oncol. (Northwood, London, England) 32 (1) (2015) 324.
[6] G. Di Leva, C.M. Croce, Mirna profiling of cancer, Curr. Opin. Genet. Dev. 23 (1) (2013) 3–11.
[7] D.Q. Chen, C. Yu, X.F. Zhang, et al., Hdac3-mediated silencing of mir-451 decreases chemosensitivity of patients with metastatic castration-resistant prostate cancer by targeting nedd9, Ther. Adv. Med. Oncol. 10 (2018) 1758835918783132.
[8] C. Ren, H. Chen, C. Han, et al., High expression of mir-16 and mir-451 predicating better prognosis in patients with gastric cancer, J. Cancer Res. Clin. Oncol. 142 (12) (2016) 2489–2496.
[9] J.Y. Huang, K. Zhang, D.Q. Chen, et al., Microrna-451: epithelial-mesenchymal transition inhibitor and prognostic biomarker of hepatocelluar carcinoma, Oncotarget 6 (21) (2015) 18613–18630.
[10] R. Guo, J. Gu, Z. Zhang, et al., Mir-451 promotes cell proliferation and metastasis in pancreatic cancer through targeting cab39, Biomed. Res. Int. 2017 (2017) 2381482.
[11] K. Knobloch, U. Yoon, P.M. Vogt, Preferred reporting items for systematic reviews and meta-analyses (prisma) statement and publication bias, J. Craniomaxillofac. Surg. 39 (2) (2011) 91–92.
[12] J.F. Tierney, L.A. Stewart, D. Ghersi, et al., Practical methods for incorporating summary time-to-event data into meta-analysis, Trials 8 (2007) 16.
[13] A. Stang, Critical evaluation of the newcastle-ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses, Eur. J. Epidemiol. 25 (9) (2010) 603–605.
[14] Y. Shen, J.M. Gong, L.L. Zhou, et al., Mir-451 as a new tumor marker for gastric cancer, Oncotarget 8 (34) (2017) 56542–56545.
[15] N. Kapodistrias, K. Mavridis, A. Batistatou, et al., Assessing the clinical value of micrornas in formalin-fixed paraffin-embedded liposarcoma tissues: overexpressed mir-155 is an indicator of poor prognosis, Oncotarget 8 (4) (2017) 6896–6913.
[16] S. Zhu, Y. Huang, X. Su, Mir-451 correlates with prognosis of renal cell carcinoma patients and inhibits cellular proliferation of renal cell carcinoma, Med. Sci. Monit. 22 (2016) 183–190.
[17] S. Avigad, I.R. Verly, A. Lebel, et al., Mir expression profiling at diagnosis predicts relapse in pediatric precursor b-cell acute lymphoblastic leukemia, Genes Chromosomes Cancer 55 (4) (2016) 328–339.
[18] Z. Su, J. Zhao, Z. Rong, et al., Mir-451, a potential prognostic biomarker and tumor suppressor for gastric cancer, Int. J. Clin. Exp. Pathol. 8 (8) (2015) 9154–9160.
[19] S. Ling, M. Ruiqin, Z. Guohong, et al., Expression and prognostic significance of microrna-451 in human epithelial ovarian cancer, Eur. J. Gynaecol. Oncol. 36 (4) (2015) 463–468.
[20] N. Liu, N. Jiang, R. Guo, et al., Mir-451 inhibits cell growth and invasion by targeting mif and is associated with survival in nasopharyngeal carcinoma, Mol. Cancer 12 (1) (2013) 123.
[21] X.C. Wang, L.L. Tian, X.Y. Jiang, et al., The expression and function of mirna-451 in non-small cell lung cancer, Cancer Lett. 311 (2) (2011) 203–209.
[22] R. Wang, Z.X. Wang, J.S. Yang, et al., Microrna-451 functions as a tumor suppressor in human non-small cell lung cancer by targeting ras-related protein 14 (rab14), Oncogene 30 (23) (2011) 2644–2658.
[23] E. Bandres, N. Bitarte, F. Arias, et al., Microrna-451 regulates macrophage migration inhibitory factor production and proliferation of gastrointestinal cancer cells, Clin. Cancer Res. 15 (7) (2009) 2281–2290.
[24] Z. Li, Y. Li, J. Fu, et al., Clinical utility of microrna-451 as diagnostic biomarker for human cancers, Biosci. Rep. 39 (1) (2019).
[25] Y. Tian, Y. Nan, L. Han, et al., Microrna mir-451 downregulates the pi3k/akt pathway through cab39 in human glioma, Int. J. Oncol. 40 (4) (2012) 1105–1112.