

RESEARCH ARTICLE

MicroRNA-155 Expression has Prognostic Value in Patients with Non-small Cell Lung Cancer and Digestive System Carcinomas

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Abstract

Objective: Published data have shown that microRNAs (miRNAs) could play a potential role as diagnostic and prognostic indicators in cancers. Data for the predictive value of microRNA-155 are inconclusive. The aim of the present analysis was therefore to evaluate the role of miR-155 in prognosis for patients with a variety of carcinomas. **Methods:** Relevant studies were identified by searching PubMed and EMBASE. Data were extracted from studies comparing overall survival (OS), recurrence-free survival (RFS) or cancer-specific survival (CSS) in patients with carcinoma with higher miR-155 expression and those with lower levels. The pooled hazard ratios (HRs) and 95% confidence intervals (CIs) of miR-155 for clinical outcome were calculated. **Results:** A total of 15 studies were included. The pooled hazard ratio (HR) for OS of higher miR-155 expression in cancerous tissue was 1.89 (95% CI: 1.20-2.99, $P = 0.006$), which could markedly predict poorer survival in general cancer. For RFS/CSS, elevated miR-155 was also associated with poor prognosis of cancer (HR= 1.50, 95% CI: 1.10-2.05, $P = 0.01$). On subgroup analysis, the pooled HR for OS in non-small cell lung cancer (NSCLC) was 2.09 (95% CI: 0.68-6.41, $P > 0.05$), but for RFS/CSS was 1.28 (95% CI: 1.05-1.55, $P = 0.015$), with statistical significance; the pooled HRs for OS and RFS/CSS in digestive system neoplasms were 3.04 (95% CI: 1.48-6.24, $P = 0.003$) and 2.61 (95% CI: 1.98-3.42, $P < 0.05$), respectively. **Conclusions:** The results indicated that the miR-155 expression level plays a prognostic role in patients with cancer, especially NSCLCs and digestive system carcinomas.

Keywords: Cancer - MiR-155 - prognosis - biomarker - meta-analysis

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Introduction

MicroRNAs are highly conserved, small, single-stranded non-coding RNAs of 19-24 nucleotides in length that were first identified in 1993 (Lee et al., 1993). They can regulate gene expression at a post-transcriptional level and play a significant role in regulation of cell development, metabolism, immunity, proliferation, differentiation, and apoptosis. Published data found that miRNA are involved in carcinogenesis as either oncogenes or tumor suppressors (Ambros et al., 2003; Chen, 2005), and many cancer-related microRNAs have been identified functionally (Calin et al., 2006). Evidences from clinical data indicated that many miRNAs were upregulated or downregulated in diverse carcinomas, and their expression levels associated with the stage of diseases (Ferracin et al., 2010; Nana-Sinkam et al., 2010). Hence, these miRNAs hold great promise as potential biomarkers for cancer prognosis. Evidences from laboratory studies have found that miR-155 is over expressed in a variety of malignant

diseases and that it plays a significant role in the process of carcinogenesis (Esquela-Kerscher et al., 2006).

Recent studies have showed that miR-155 gene is one of the miRNAs most consistently over-expressed in both hematopoietic malignancies and solid tumors, such as leukemia (O'Connell et al., 2008; Raponi et al., 2009), thyroid carcinoma (Nikiforova et al., 2008), breast cancer (Iorio et al., 2005; Greither et al., 2010), cervical cancer (Wang et al., 2008), colorectal cancer (Chen et al., 2012), pancreatic ductal adenocarcinoma (PDAC) (Lee et al., 2007; Szafranska et al., 2007), hepatocellular carcinoma (Han et al., 2012; Huang et al., 2012), and lung cancer (Yanaihara et al., 2006; Donnem et al., 2011). Therefore, overexpression miR-155 may be a general characteristic of cancer and be detected as a biomarker for cancer diagnosis and prognosis. However, prognostic role of miR-155 expression in cancers remained inconclusive. In this study, we conducted a systematic review and meta-analysis to pool the overall hazard ratios (HRs) of elevated miR-155 for survival in patients with carcinomas.

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Table 1. Methodological Quality of Studies Included in the Final Analysis Based on the Newcastle-Ottawa Scale for Assessing the Quality of Cohort Studies

Studies	Selection (score)			Comparability (score)		Exposure (score)		Total score	
	Representativeness of the exposed cohort	Selection of the non-exposed cohort	Ascertainment of exposure	Outcome of interest was not present at start of study	Based on the design or analysis	Assessment of outcome	Follow-up long enough for outcomes to occur		Adequacy of follow-up of cohorts
Huang et al. (2012)	1	1	1	1	2	1	1	1	9
Han et al. (2012)	1	1	0	1	1	1	1	1	7
Yanaiharu et al. (2006)	1	1	0	0	1	1	1	1	6
Ishihara et al. (2012)	1	1	1	1	1	1	1	1	8
Papaconstantinou et al. (2012)	0	1	1	1	2	1	1	1	8
Shibuya et al. (2010)	1	1	1	1	1	1	1	1	8
Raponi et al. (2009)	0	1	1	0	2	1	1	1	7
Chen J et al. (2012)	1	1	1	1	2	1	1	1	9
Greither et al. (2010)	1	1	1	1	1	1	1	1	8
Shinmei et al. (2012)	1	1	1	1	2	1	1	1	9
Monsalvez et al. (2012)	1	1	0	0	1	1	1	1	6
Saito et al. (2011)	1	1	1	1	1	1	1	1	8
Voortman et al. (2010)	1	1	1	1	2	1	1	1	9
Donnem et al. (2011)	1	1	0	1	1	1	1	1	7
Jung et al. (2009)	1	1	0	1	1	1	1	1	7

Materials and Methods

Literature search strategy

Original articles studying the prognostic value of microRNA-155 in carcinomas were searched with PubMed, EMBASE. Studies were selected by using the following search terms: 'cancer or carcinoma or neoplasm or tumor', 'microRNA-155 or miR-155', 'prognosis or prognostic or outcome'. Original and review articles published until February 2013 were sought, considering the latter as an additional source of original works otherwise overlooked. References of the retrieved articles were further screened for earlier original studies. The eligible reports were identified by three reviewers (Xu, Han and Xia), and controversial studies were adjudicated by a fourth reviewer (Shu).

Selection criteria

The inclusion criteria were the following: (1) studied the patients with any types of carcinomas, (2) detected the expression of miR-155 in tissue or serum, (3) analyzed the association between miR-155 expression levels and clinical prognosis, and (4) published in English. Articles were excluded from the analysis if met the following criteria: (1) non-English reports, (2) analysis of a set of miRNAs but not miR-155 alone, (3) no dichotomous miR-155 expression groups and (4) absence of key information such as hazard ratio (HR), 95% CI and *P* value.

Date extraction

We followed the guidelines of a critical checklist of the Dutch Cochrane Centre proposed by Meta-analysis of Observational Studies in Epidemiology (MOOSE) to guarantee the quality of the meta-analysis (Stroup et al., 2000). The extracted data information included the following: (1) first author's last name, publication year; (2) characteristics of the studied population: sample size, sample source, disease, stage of disease and histological type; (3) miR-155 assessment and cut-off values; (4) follow-up time; (5) HR of elevated miR-155 for overall survival (OS), recurrence-free survival (RFS) or cancer-

specific survival (CSS), as well as their 95% confidence interval (CI) and *P* value. If the HRs and their 95% confidence interval were not available directly, the total numbers of observed deaths/cancer recurrences and the numbers of samples in each group were extracted to calculate HR (Tierney et al., 2007). If only Kaplan-Meier curves are available, data were extracted from the graphical survival plots and estimation of the HR was then performed using the described method (Tierney et al., 2007).

Quality assessment

We assessed the methodological quality of included studies based on Newcastle-Ottawa scale (NOS) for quality of case-control and cohort studies (Stang et al., 2010). The NOS contains eight items, categorized into three dimensions including selection, comparability, and depending on the study type-outcome (cohort studies) or exposure (case-control studies). A star system of the NOS (range, 0-9 stars) has been developed for the assessment. The highest quality studies are awarded a maximum of one star for each item with the exception of the item related to comparability that allows the assignment of two stars. The highest value for quality assessment was 9 stars (Table 1).

Statistical methods

To identify the prognostic effect of microRNA-155, we evaluated the overall hazard ratios (HRs) and 95% confidence intervals (CIs) of eligible data for elevated miR-155. A HR equal to 1 indicates a lack of association between miR-155 and clinical outcome. A HR greater than 1 corresponds to worse outcome for increased miR-155, while HR less than 1 represents better prognosis. A test of heterogeneity of combined HRs was carried out using Cochran's Q test and Higgins I-squared statistic. A *P* value of <0.05 was considered statistically significant. A random effect model was applied if heterogeneity was observed ($P < 0.05$ or $I^2 > 50\%$), while the fixed effect model was used in the absence of between-study heterogeneity ($P > 0.05$). Sensitivity analyses were performed to check the stability of meta-analysis by comparing the results of

Table 2. Main Characteristics of All Studies Included in the Analysis

Studies population	Origin of	Disease	N	Stage	microRNA assay	Cut-off	Source of samples	Survival analysis	Hazard ratio	Follow up (months)
Huang et al. (2012)	Taiwan	HCC	216	I-IV	qRT-PCR	NR	Tissue	RFS	R	High:110 Low:140
Han et al. (2012)	China	HCC	100	I-IV	qRT-PCR	median	FFPE	OS,RFS	R	High:94 Low:100
Yanaiharu et al. (2006)	USA	NSCLC-ADC	64	I-IV	qRT-PCR	mean	tissue	OS	R	High:68 Low:74
Ishihara et al. (2012)	Japan	ATL	35	NR	qRT-PCR	median	plasma	OS	DE	High:29.6 Low:18.6
Papaconstantinou et al. (2012)	Greece	PC	88	I-IV	qRT-PCR	mean	FFPE	OS	DE	High:40 Low:80
Shibuya et al. (2010)	Japan	CRC	156	I-IV	qRT-PCR	mean	FT	OS	R	60
Raponi et al. (2009)	USA	SCLC	54	I-IV	qRT-PCR	median	SFT	OS	R	60
Chen et al. (2012)	China	BC	92	I-IV	qRT-PCR	mean	FT	OS,RFS	R,DE	66
Greither (2010)	Germany	PDAC	55	I-IV	qRT-PCR	median	SFT	CSS	DE	61
Shinmei et al. (2012)	Japan	RC	137	I-IV	qRT-PCR	median	FFPE	CSS	R	High:188 Low:164
Monsalvez et al. (2012)	Spain	B-cell lymphomas	43	I-IV	qRT-PCR	median	FFPE	RFS	R	1-196
Saito et al. (2011)	USA	NSCLC-ADC	89	I-III	qRT-PCR	median	FT	CSS	R	80
	Norway		37					CSS		
	Japan		191					RFS		
Voortman et al. (2010)	Multicentre	NSCLC	639	I-III	qRT-PCR	median	FFPE	OS	R	96
Donnem et al. (2011)	Norway	NSCLC-SCC, NSCLC-ADC	187 94	I-III	ISH	median	FFPE	CSS	DE	86 (48-216)
Jung et al. (2009)	USA	DLBCL ABC-DLBCL	129 24	I-IV	NR	median	NR	OS	DE	High:146 Low:140 High:101 Low:85

Abbreviations: OS, overall survival; RFS, recurrence-free survival; CSS, cancer-specific survival; HCC, hepatocellular carcinomas; ATL, adult T-cell leukemia; PC, pancreatic cancer; CRC, colorectal cancer; SCLC, small cell lung cancer; BC, breast cancer; PDAC, pancreatic ductal adenocarcinomas; RC, renal cancer; ADC, adenocarcinoma; SCC, squamous cell carcinoma; NSCLC, non-small cell lung cancer; DLBCL, diffuse large B cell lymphoma; ABC, activated B-cell-like; ISH, in situ hybridization; qRT-PCR, quantitative real-time polymerase chain reaction; FFPE, formalin-fixed, paraffin embedded; R, reported; NR, not reported; DE, data-extrapolated

the fixed-effect model with the random-effect. Publication bias was evaluated using the funnel plot with the Egger's and Begg's test bias indicator test. All P values were two sided. All CIs had two-sided probability coverage of 95%. All analyses were performed using the Stata software (Stata Corporation, College Station, Texas).

Results

Identification of relevant studies

A total of 82 records for miR-155 and cancer prognosis were identified from a primary literature search in PubMed and EMBASE. After manually screening the titles, abstracts and key words, 55 studies were out of our scope because they were review articles, letters, non-English articles, laboratory studies or studies irrelevant to the current analysis. Of the 27 candidate studies, three studies investigated a set of miRNAs but not miR-155 alone; and nine others lacked the key survival data. A total of 15 studies remained met the inclusion criteria.

Characteristics of studies included in the main analysis

A total of 15 studies were used in the pooled analysis. The main features of identified studies were listed in Table 2. Sample sizes in each ranged from 35 to 639 patients. We collected data from 15 reports including a total of 2463 subjects from the United States, Spain, Greece, Norway, German, China, Taiwan and Japan. The patients were of a variety of carcinomas, including lung cancer, renal cancer, breast cancer, pancreatic cancer, hepatocellular cancer, colorectal cancer, leukemia and lymphoma. Of all the reports, five studies including a total of 1355 patients assessed lung cancer; and seven studies with a total of 616 subjects evaluated digestion system cancers, including pancreatic ductal adenocarcinoma, colorectal

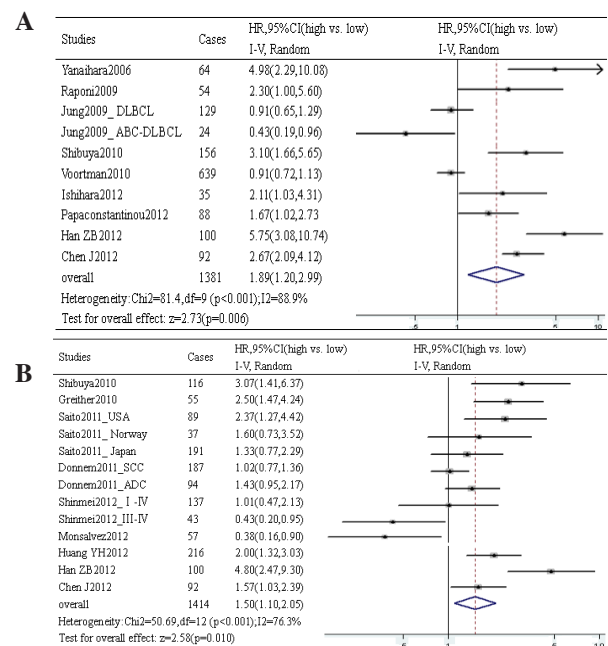


Figure 1. Forrest Plots of Studies Evaluating Hazard Ratios of High miR-155 Expression vs. Low Expression. Survival data are reported as overall survival (A) and recurrence-free survival or cancer-specific survival (B) in variety of carcinomas

cancer and hepatocellular cancer. The quantitative real-time polymerase chain reaction (qRT-PCR) assay was used in 14 studies, whereas in situ hybridizations (ISH) assay was used in only one study. Frozen or formalin-fixed, paraffin-embedded (FFPE) tumor tissues were used in 14 studies, while one study used plasma as samples. Notably, the cut-off values of miR-155 were different in each study, with median applied in eleven studies and mean used in other studies. All hazard ratios (HRs) were extracted from univariate analysis in each report.

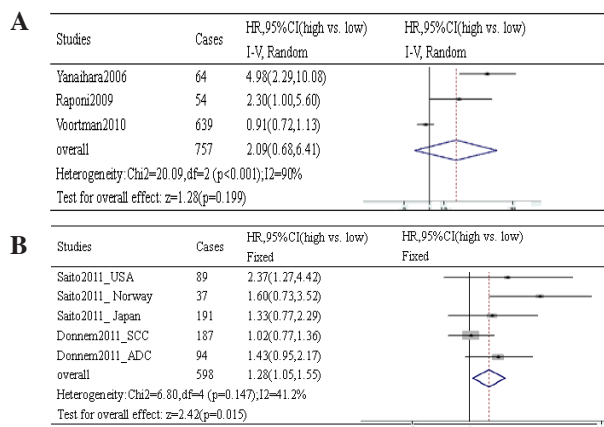


Figure 2. Forrest Plots of Overall Survival (A) and Recurrence-free Survival or Cancer-specific Survival (B) in Lung Cancer

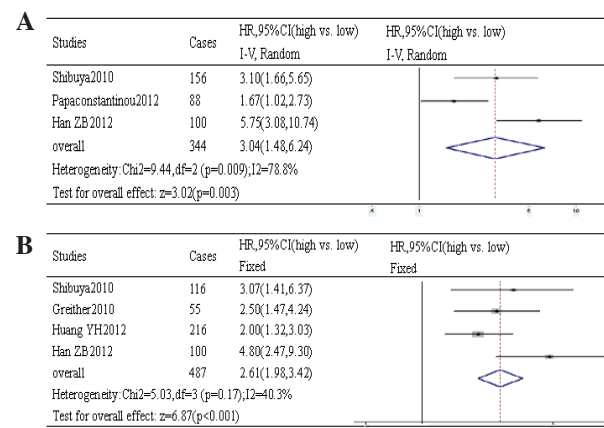


Figure 3. Forrest Plots of Overall Survival (A) and Recurrence-free Survival or Cancer-specific Survival (B) in Digestive System Carcinomas

Overall association of MiR-155 conditions with the risk of OS and RFS/CSS

For studies evaluating OS, there appeared to have heterogeneity between studies for miR-155 ($P < 0.05$). Hence, a random model was applied to calculate a pooled HR and its 95% CI. We found that higher expression levels of miR-155 significantly predicted poorer OS, with the pooled HR being 1.89 (95% CI: 1.20-2.99, $P=0.006$) (Figure 1A). For studies evaluating RFS/CSS, a random model was also applied because of the heterogeneity between studies. MiR-155 over-expression was also significantly correlated to RFS/CSS, with the combined HR being 1.50 (95% CI: 1.10-2.05, $P = 0.01$) (Figure 1B). Then subgroup analysis was conducted in two types of common cancer, lung cancer and carcinomas of digestive system. In subgroup of lung cancer, we pooled HR for OS using random effect model, showed statistically insignificant (HR, 2.09; 95% CI, 0.68-6.41, $p=0.199$; $P<0.05$ for heterogeneity, $I^2 = 90%$) (Figure 2A). While, the combined HR for RFS/CSS indicated that higher expression of miR-155 was correlated to poor survival with the estimated HR being 1.28 (95% CI: 1.05-1.55, $p=0.015$; $P=0.15$ for heterogeneity, $I^2 = 41%$) (Figure 2B). In subgroup of patients with digestion system cancer, the pooled HRs for OS and RFS/CSS were 3.04 (95% CI: 1.48-6.24, $p=0.003$; $P=0.009$ for heterogeneity,

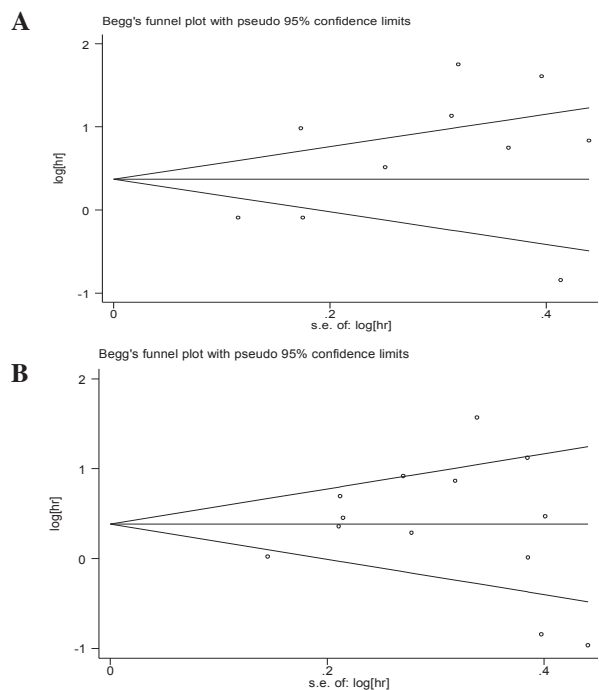


Figure 4. The Begg's Funnel Plot for Overall Survival (A) and Recurrence-free Survival or Cancer-specific Survival (B), and Both of Them Did Not Show There Were Publication Biases

$I^2=79%$) and 2.61 (95% CI: 1.98-3.42, $p=0.05$; $P=0.17$ for heterogeneity, $I^2=40%$), respectively (Figure 3A, Figure 3B). The result indicated that overexpression of miR-155 was significantly associated with worse clinical outcome in patients with digestion system cancer.

Sensitivity Analysis

In order to compare the differences and to evaluate the sensitivity of the meta-analyses, we also performed the results of the fixed-effect model and are almost consistent with the random-effect model, suggesting stability of the meta-analysis (data not shown).

Publication bias

Publication bias of all included studies for was evaluated by funnel plots and Egger's tests. The funnel plots were almost symmetric and the P values in OS and RFS/CSS meta-analysis of Egger's regression intercepts were 0.123 and 0.760, respectively. Hence, there was no evidence for significant publication bias in the meta-analysis, because their P values were > 0.05 (Figure 4A, Figure 4B).

Discussion

Emerging studies have indicated that aberrant expression of microRNAs played a significant role in diagnosis and prognosis for malignant diseases. Most of the protective microRNAs such as let-7 family are down-regulated, while the risky microRNAs including miR-155 are up-regulated in carcinoma (Esquela-Kerscher et al., 2006; Wang et al., 2009). Moreover, overexpression microRNAs such as miR-21 and miR-155 were more common than others in malignant diseases. Recent

world literatures have found that among the presently known miRNAs, miR-155 is one of the miRNAs most consistently involved in neoplastic diseases. Clinical data showed that miR-155 was a potent prognostic value in carcinomas, but remained inconsistent. In this study, to derive a more accurate evaluation of the impact of miR-155 expression on patient prognosis, we conducted a meta-analysis of 15 published articles including 2463 subjects. Our analysis indicated that elevated miR-155 expression was significantly associated with poor overall survival and recurrence in diverse carcinomas.

Oncogenic properties of miR-155 are attributed to its anti-apoptotic function through a blockade of caspase-3 activity or suppressing proapoptotic genes such as TP53BP1 (Gironella et al., 2007; Ovcharenko et al., 2007), and promote cell proliferation by downregulating the SOCS1 gene (Jiang et al., 2010), or activate AKT signaling via down-regulation of tumor suppressors including PTEN, PDCD4 and SHIP1 (Yamanaka et al., 2009). Besides, miR-155 is regulated by the transforming growth factor-beta (TGF- β)/Smad4 pathway and plays a role in cell invasion by targeting RhoA (Kong et al., 2008). MiR-155 has been identified to down-regulate gene of JMJD1A, which is associated with N stage and poor prognosis of nasopharyngeal carcinoma patients (Du et al., 2011). Thompson et al found that increased miR-155 down-regulated PU.1 and resulted in reduced CD10 mRNA and protein expression, which is a prognostic marker for diffuse large B-cell lymphoma (DLBCL) (Thompson et al., 2011). In addition, the expression level of miR-155 in patients with renal carcinoma tended to be associated with a tumor size (Shinmei et al., 2012), and high expression of miR-155 was correlated to higher tumor grade, advanced tumor stage and lymph node metastasis in patients with breast cancer (Chen et al., 2012). These evidence indicated that significant correlation between miR-155 expression and clinical outcome of cancer is biologically plausible.

Yanaiharu et al first identified that high miR-155 expression could serve as a poor prognostic marker in lung cancer (Yanaiharu et al., 2006). Several studies have corroborated this finding in lung cancer and other malignant diseases including colorectal cancer, breast cancer, hepatocellular carcinomas, pancreatic ductal adenocarcinomas and adult T-cell leukemia (Raponi et al., 2009; Greither et al., 2010; Shibuya et al., 2010; Chen et al., 2012; Han et al., 2012; Huang et al., 2012; Ishihara et al., 2012; Papaconstantinou et al., 2012); however, other reports provided insignificant or opposite evidences (Jung et al., 2009; Voortman et al., 2010; Donnem et al., 2011; Saito et al., 2011; Monsálvez et al., 2012; Shinmei et al., 2012). In order to investigate the precise association between miR-155 expression and the prognosis of patients, we combined the HRs extracted from the eligible data, and found that patients with high miR-155 expression were likely to have an unfavorable outcome. Stratified analysis indicated that overexpression of miR-155 was no statistically correlated to OS in lung cancer; however, when combined HR for RFS/CSS, the result manifested increased expression of miR-155 was significantly associated with RFS/CSS. These evidences

manifested miR-155 may serve as a prognostic predictor in lung cancer recurrence. In subgroup of patients with digestion system cancer, data showed that over-expression miR-155 was markedly related to both OS and RFS/CSS, respectively. Empirically, HR of more than 1.5 is considered to be a strong prognostic factor (Hayes et al., 2001). So miR-155 could be considered as a potent prognostic biomarker for digestive system cancer.

Despite our efforts to conduct a comprehensive analysis, a few limitations should be noted. First, the samples and studies were limited, with a presence of heterogeneity between the studies. Statistical heterogeneity among the studies may be due to the differences in the baseline characteristics of patients, technical platforms, disease type, source of samples, normalization controls, cut-off values, the duration of follow-up and other technical issues. For example, for RFS/CSS studies, when we stratified them according to tumor types, heterogeneity markedly decreased both in lung cancer and digestion system subgroups. Because such differences might have a residual confounding effect within these studies, we attempted to minimize the effect by using a random effect model. Second, the result of stratified analysis for lung cancer and digestion system carcinoma was less powerful because studies were so limited with a relatively small sample size. Third, the result for OS was inconsistent with that for RFS/CSS in lung cancer. Elevated miR-155 expression was associated with poor RFS/CSS but not worse OS. This result may be due to the insufficient reports concerning the relation between miR-155 and prognosis in lung cancer. Fourth, among the eligible studied, extracted HR values for renal cancer and lymphoma had opposite clinical implication, in which low expression miR-155 represented worse clinical outcome. But we failed to conduct the stratified analysis due to inadequate data provided this information. Future prospective studies on those two cancers with large sample sizes and better study designs are required to perform. Fifth, the conclusion was somewhat faint because of the difference in miR-155 cut-off definition, source of samples and the duration of follow-up. Last but not least, although miR-155 has been revealed by the present meta-analysis to be a predictor, the current statistical analysis could not elicit it independently because of the methodological limits. Lack of individual HR data of other factors makes it difficult to exclude the influences by confounding factors in a meta-analysis.

In conclusion, the analysis revealed that aberrant overexpression of miR-155 is associated with unfavorable survival and recurrence in various types of carcinomas. Furthermore, elevated miR-155 is markedly related to poor outcome in digestive system cancer and worse RFS/CSS in lung cancer. So the remarkable potential of miR-155 as prognostic biomarkers cannot be underestimated. Further large-scale clinical investigations will give more insight into the role of miR-155 in cancer prognosis and clinical implementation.

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The author (s) declare that they have no competing interests.

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