MiR-24-3p and various cancers: From a meta-analysis view

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Research article

Keywords: MiR-24-3p, Human carcinoma, Prognosis, Clinical characteristics, Meta-analysis

DOI: https://doi.org/10.21203/rs.3.rs-42539/v1

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Abstract

Background: A growing number of researches suggests that microRNAs (miRNAs) as oncogene or tumor suppressor genes play a fundamental role in various kinds of cancers. Among them, miR-24-3p, as a star molecule, is widely studied. However, the prognostic value of miR-24-3p is unclear and controversial. We conducted this meta-analysis to evaluate the prognostic value of miR-24-3p in a variety of cancers by integrated existing articles from four databases.

Methods: PubMed, Embase, Web of Science, and Cochrane Library (last update in March 2020) were searched for approach literature. Hazard ratios (HRs) and odds ratios (ORs) were used to evaluate the association between miR-24-3p expression levels and prognostic value or clinicopathological characteristics, respectively.

Results: A total of 15 studies from 14 literature were finally qualified and concluded in the present meta-analysis. A significantly worse overall survival was observed in higher expression of miR-24-3p cancer group for OS (Overall survival) of log rank tests and cox multivariate regression by fixed effects model. Also, we found a significant correlation between elevated miR-24-3p levels to RFS (Recurrence-free survival) and DFS (Disease free survival). In addition, the pooled odds ratios (ORs) showed that evaluated miR-24-3p was also associated with the larger tumor size (≥5cm) and advanced TNM stage (≥3).

Conclusion: Based on the above findings, elevated expression levels of miR-24-3p may serve as a promising biomarker used to predict the worse prognosis of cancer patients.

1. Background

MicroRNAs (miRNAs), a kind of endogenous non-coding RNAs of 18–22 nucleotides in length, negatively regulate target genes expression at post-transcriptional level [1–3]. As either oncogenes or anti-oncogenes, they are found to play vital roles in a wide range of fundamental biological processes, such as proliferation[4, 5], differentiation[6, 7], apoptosis[8, 9], cell cycle[10–13], metastasis[14–16], stress response[17–19], metabolic[20–22] and etc. Owing to its detectability and stability in tissues, marrow or blood, a growing number of studies suggests that miRNAs can serve as promising biomarkers for the prognosis of carcinomas[23].

MiR-24-3p (used name was miR-24), a master regulator from the gene cluster of miR-23a–24-27a, has been identified as an onco or oncosuppressor-miR and its expression is closely associated with cancer occurrence and development by recent studies[24, 25]. Previous studies showed that miR-24-3p was highly expressed in many carcinomas[26, 27]. In addition, the evaluated expression of miR-24-3p was also found to be associated with cancer prognosis and tumor clinicopathological features but there were some opposite consequences[28, 29]. Up to now, a number of studies have been investigate this molecule in many kinds of cancer, but most individual study have their own limits, for example, small sample size or obtaining controversial results, and so on.

Accordingly, to explore the clinical prognostic value of miR-24-3p in various cancers, we performed this systematic review and meta-analysis to give a better understanding.

2. Methods

2.1. Literature search strategy

In this meta-analysis, the statement was used to as a guideline[30]. We performed a literature search using the online databases including PubMed, Embase, Web of science (WOS) and Cochrane library from inception to March 2020. The terms "miR-24 OR microRNA-24 OR miRNA-24 OR miR24" and "cancer OR tumor OR neoplasm OR carcinoma OR malignancy" were used to determine the correlative literature.

2.2. Inclusion and exclusion criteria

The inclusion criteria were: (1) studies were published in English; (2) miR-24-3p was investigated in carcinomas; (3) studies were identified the correlation between miR-24-3p expression levels and the prognosis of cancer patients; and (4) studies were provided hazard ratio (HR) and its corresponding 95% confidence intervals (CIs) or sufficient data which can further to assess its HR. The exclusion criteria: (1) studies were published in non-English; (2) studies were case report, abstracts, reviews, letters or meta-analysis; (3) studies were not relevant to the prognostic of cancer patients or the prognosis data originated from TCGA; or (4) studies did not offer sufficient data to calculate the HRs and 95% CI.

2.3. Data extraction

Built on the above criteria, all included studies were managed separately by two investigators (H Wang and CY Chen) and any disagreement were further to examined by a third author (KK Ding). The following characteristics were collected: the first author's name, year of publication, nationality, cancer type, specimen, method of detection, sample size, type of miRNA, outcome, tumor stage, lymph node metastasis, cut-off value, follow-up time, HR and its corresponding 95% CI. Moreover, the clinicopathological parameter data were also collected from qualified articles. For studies which not provide HR and 95% CI, the data were extracted from the Kaplan-Meier curves via Engauge Digitizer version 4.1[31]. The Newcastle-Ottawa Scale (NOS) was used to assess the quality of the pooled studies. High quality required an NOS score ≥ 5.

2.4. Statistical analysis

The present meta-analysis was assessed by Stata SE12.0 software, RevMan5.2 software and Engauge Digitizer 4.1 software. Pooled HRs with their CIs were applied to describe the correlation between the expression of miR-24-3p and relevant survival outcome (OS, DFS, RFS), and the relation between miR-24-3p and relevant clinicopathologic features were also described by pooled odds ratios (ORs) and their CIs. The heterogeneity was evaluated by $I^2$ statistics and Q

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tests. \( P < 0.05 \) and / or \( I^2 > 50\% \) were defined as significant heterogeneity and random effects model was further to used. In addition, sensitivity analysis was used to evaluate the contribution of each study to the pooled HR and we could further to estimate the stability of the consequence. Finally, we evaluate the potential publication bias by funnel HR, Begg's test and Egger's test. \( P < 0.05 \) was known as obvious publication bias[32].

### 3. Results

As is shown in Fig. 1, 1099 literatures were obtained from online databases PubMed, Embase, Web of science (WOS) and Cochrane library. After removing the duplicates, abstract, review, case report, meta-analysis, studies which were not written in English and unrelated researches, 86 articles were subsequently full-text review. Among these, 71 articles were further to removed according to these criteria: studies not on patient (n = 2), studies without survival data (n = 45), survival data from TCGA (n = 5), multiple miRNAs (n = 1), or insufficient data (n = 19). Eventually, a total of 15 studies from 14 articles were included (Liu et al., 2014; Meng et al., 2017; Gao et al., 2015; Organista-NAVA et al., 2015; Zhao et al., 2015; Wang et al., 2016; Mori et al., 2016; Kerimis et al., 2017; Dong et al., 2018; Su et al., 2018; Pan et al., 2018; Zhou et al., 2018; Liu et al., 2018; Yan et al., 2019) (Table 1). The overall sample size is 1518 patients coming from 25 to 247 which from 4 countries. Among these studies, several types of cancer include lung cancer (n = 3)[33–35], hepatocellular carcinoma (n = 2)[36, 37], colorectal cancer (n = 2)[29, 38], nasopharyngeal carcinoma (n = 2)[39, 40], osteosarcoma (n = 1)[41], ALL (n = 1)[42], AML (n = 1)[42], advanced gastric cancer (n = 1)[28], esophageal cancer (n = 1)[43], head and neck squamous cell carcinoma (n = 1)[44]. As for OS, RFS and DFS, there were seven studies directly provide HRs and its 95% CI [28, 29, 35–39]. In addition, the remaining eight studies only provided Kaplan-Meier curves[28, 33, 34, 40–44]. All studies measured the miR-24-3p expression level by qRT-PCR (quantitative real-time polymerase chain reaction).

### 3.1. The association between miR-24-3p expression levels and the overall survival (OS)

Ten enrolled articles including eleven studies and 1212 patients were used to investigate the correlation between miR-24-3p expression levels and the OS by using log rank tests and presented the data of univariate. Generally, a significant correlation between miR-24-3p expression levels and OS (HR = 1.609, CI: 1.291–2.004, Figure 2a). However, an obvious heterogeneity was also observed (\( I^2 = 85.20\% \), \( P = 0.000 \), Table 2). Hence, the random effects model was followed in the study. After that, the significance was disappeared (HR = 1.507, CI: 0.810–2.803, Table 2), indicating that the heterogeneity significantly influence the consequence.

In order to explore the source of the heterogeneity, subgroup analyses were applied by factors including population (Asian/Chinese and Non-Asian), sample size (≥ 100 and <100), NOS scores (≥ 8 and <8), specimen (tissue and non-tissue) tumor category 1 (solid tumor and non-solid tumor), tumor category 2 (digestive system and non-digestive system) and tumor (esophageal cancer, osteosarcoma, lung cancer, gastric cancer, colorectal cancer, ALL, AML and hepatocellular carcinoma). As a consequence, the heterogeneity was controlled successfully in six subgroups and all them have significant correlations: 1). The subgroup of non-Asian (HR = 2.615, CI: 1.668–4.099; \( I^2 = 0.000\% \), \( P = 0.693 \)). 2). The specimen derived from non-tissue (HR = 2.399, CI: 1.659–3.470; \( I^2 = 0.000\% \), \( P = 0.949 \)). 3) The sample size greater than or equal to 100 (HR = 2.779, CI:2.051–3.766; \( I^2 = 0.000\% \), \( P = 0.873 \)). 4) The patients of hematologic tumor (HR = 2.425, CI: 1.491–3.944; \( I^2 = 0.000\% \), \( P = 0.751 \)). 5). The patients of hepatocellular carcinoma (HR = 2.607, CI: 1.756–3.871; \( I^2 = 0.000\% \), \( P = 0.637 \)) and 6). The patients of lung cancer (HR = 3.274, CI: 1.422–7.539; \( I^2 = 0.000\% \), \( P = 0.698 \)). In addition, significant correlations are also observed in the study of NOS score less than 8 by random effects model, which were consistent with the significance of the results by fixed effects model (Table 2). Moreover, significant correlations were observed between miR-24-3p expression levels and OS in the studies with the population derived from Asian/Chinese (HR = 1.381, CI: 1.219–2.004), solid tumor (HR = 1.448, CI: 1.131–1.852), digestive system (HR = 1.705, CI: 1.291–2.253) and non-digestive system (HR = 1.461, CI: 1.021–2.090) by fixed effects model, while there were no significances identified in these groups when the random effects model was applied (Table 2). For patients of Colorectal cancer, the prognostic value of miR-24-3p expression levels to the OS was completely different (Kerimis D et al.[38] HR = 2.607, CI: 1.756–3.871). As for OS, RFS and DFS, there were seven studies directly provide HRs and its 95% CI [28, 29, 35–39]. In addition, the remaining eight studies only provided Kaplan-Meier curves[28, 33, 34, 40–44]. All studies measured the miR-24-3p expression level by qRT-PCR (quantitative real-time polymerase chain reaction).

### 3.2. The independent role of miR-24-3p expression levels as a prognostic indicator

Five studies containing 775 patients implemented the cox multivariate regression to assess the prognostic value of miR-24-3p expression levels in carcinoma patients by adjusting other factors. The significant correlation of miR-24-3p expression levels in the OS (HR = 2.384, CI: 1.813–3.134) was observed by fixed effects model. However, the heterogeneity was relatively obvious (\( I^2 = 82.30\% \), \( P = 0.000 \), Table 3) and the significance was vanished by random effects model (HR = 1.994, CI: 0.991–4.015). Homoplasmatically, Subgroup analyses were applied to reduce the heterogeneity. As a result, the homogeneity was reached within the studies of sample size greater than or equal to 100 (\( I^2 = 0.000\% \), \( P = 0.861 \)), NOS less than 8 (\( I^2 = 45.50\% \), \( P = 0.176 \)) and the patients of hepatocellular carcinoma (\( I^2 = 45.50\% \), \( P = 0.176 \)). And the significant association was identified between miR-24-3p expression levels and OS with the sample size greater than 100 (HR = 3.369, CI: 2.414–4.701), NOS less than 8 (HR = 3.041, CI: 2.150–4.300) and the patients of hepatocellular carcinoma (HR = 3.041, CI: 2.150–4.300). In addition, the significant correlations were identified between miR-24-3p expression levels to the OS in the population from Asian/Chinese (HR = 2.373, CI: 1.813–3.134), the specimen derived from tissue (HR = 2.448, CI: 1.804–3.323) and NOS larger than or equal 8 by fixed effects model, which become to no significances within those subgroups by random effects model (Table 3). For patients of Colorectal cancer (HR = 0.752, CI: 0.212–0.978), the prognostic value of miR-24-3p expression levels to the OS was also opposite (Kerimis D et al.[38] HR = 2.60, CI: 0.780–8.660; Gao Y et al.[29] HR = 0.456, CI: 0.394–1.434). Thus, more pertinent studies are required to perform the analysis. Similarly, there was no noteworthy contribution identified to greatly influence the
variation of HR by meta regression (Table 3). But the sensitivity analysis suggested that Gao et al.[29] has significant impact on the result (Figure. 4c). The heterogeneity was vanishing ($I^2 = 0.000\%$, $P = 0.591$, Figure. 4b) by removing this outlier and the correlation of miR-24-3p expression levels to the OS was also significant (HR = 3.039, CI: 2.268–4.074, Figure. 4b). Finally, funnel plots, Beggs’s test ($P = 0.734$) and Egger’s test ($P = 0.460$) indicated that there was no bias. But, the number of enrolled studies was few, more data are needed to reinforce this result.

3.3. The correlation of miR-24-3p expression levels to the RFS /DFS

Except OS as a prognostic indicator, RFS and DFS are also be accepted as an evaluation criterion. Here, four studies reported RFS including 393 patients applied log rank tests, while only one also utilized cox multivariate regression. After pooling the HR, we observed a significant association between miR-24-3p expression levels to the RFS of log rank tests (HR = 2.315, CI: 1.491–3.594, figure. 5a) by fixed effects model. However, the heterogeneities were quite obvious ($I^2 = 66.70\%$, $P = 0.290$, Table 4). The random effects model was further implemented but the significance was disappeared (HR = 1.814; CI: 0.741–4.440), indicating that the heterogeneity influenced the consequences significantly. Furthermore, owing to limited number of statistics from cox multivariate regression, the sensitivity analysis and publication bias were only applied to analysis with data extracted from log rank tests. The sensitivity analysis result indicated that no studies had significant influence on the consequent (Figure. 5c). However, the investigation of potential publication bias identified an outlier (Figure. 5d, Wang S et al.[40]). After deleting this study, the heterogeneity was obvious declined ($I^2 = 45.30\%$, $P = 0.161$) and the significance of correlation between miR-24-3p expression levels and the RFS was not altered (HR = 2.575, CI: 1.642–4.029, Figure. 5b). Due to the limit included studies, more data are needed in order to enhance the result. In addition, there were only two studies containing 226 patients revealed the DFS statistics and almost no heterogeneity in both log rank tests and cox multivariate regression ($I^2 = 3.600\%$, $P = 0.309$, $I^2 = 0.000\%$, $P = 0.330$, respectively, Table 4) by used a fixed effects model. We also observed significant strong correlation between miR-24-3p expression levels to the DFS of both log rank tests (HR = 2.361, CI: 1.390–4.012) and cox regression tests (HR = 2.313, CI: 1.315–4.067) by fixed effects model.

3.4. Correlations between miR-24-3p levels and clinicopathological features among various carcinomas

Six studies containing 536 patients investigated the correlation of miR-24-3p expression levels to different clinical characteristics. As showed in Table 5, miR-24-3p expression levels were significant correlation with tumor size (OR = 1.655, CI: 1.124–2.437) by the fixed effects model with lesser heterogeneity ($I^2 = 37.50\%$, $P = 0.184$). In addition, there were no significance identified in the correlation between age (OR = 0.684, CI: 0.357–1.310), gender (OR = 1.286, CI: 0.758–2.107), lymph node metastasis (OR = 1.591, CI: 0.758–3.339) or TNM stage (OR = 1.437, CI: 0.959–2.154) with the expression levels of miR-24-3p. There were no heterogeneity in the analysis of age ($I^2 = 0.000\%$, $P = 0.525$) and gender ($I^2 = 0.000\%$, $P = 0.842$), but the heterogeneity of lymph node metastasis and TNM stage were obviously ($I^2 = 70.90\%$, $P = 0.064$; $I^2 = 85.50\%$, $P = 0.000$, respectively). In order to decrease the heterogeneity, sensitivity analysis and publication bias were further investigated to each of them. As a result, an outlier was found (Liu et al.[36]) in the TNM stage. After removing the outlier, the heterogeneity was dramatically decreased from 85.50–0.000% and the associations between high miR-24-3p expression levels to advanced TNM stage were significant (OR = 2.328, CI: 1.490–3.637). (Figure. 6). Moreover, there was no potential publication bias about TNM stage by funnel plot, Beggs’s test ($P = 0.086$) and Egger’s test ($P = 0.734$). For the analyze of lymph node metastasis, there were only two studies and have obvious opposite result (Pan et al.[33], OR = 2.974, CI: 1.101–8.037, Zhou et al.[35], OR = 0.725, CI: 0.238–2.208). Due to insufficient data, the consequence would be lack of efficiency and the reasons of heterogeneity were unacceptable. Thus, more pertinent studies are required to perform the analysis.

4. Discussion

It is of great importance to explore prognostic biomarkers with the patients of carcinoma as specific biomarkers can further help to directly stratify patients and effectively guide clinical decision-making. MiR-24-3p, as an oncogene or tumor suppressor, plays a key role in the occurrence, progression and metastasis of human carcinoma was realized by more and more researchers gradually[24, 25]. Quan et al.[45] had made a meta-analysis to research the correlation between miR-23a/24 – 2/27a cluster with human cancers, but they only had limited data to draw a conclusion that high expression levels of miR-23a/24 – 2/27a indicated a worse prognosis and no further analyzing the correlation between miR-24-3p expression levels to the clinicopathological characteristics.

Subsequently, more and more studies which focusing on the miR-24-3p expression levels with cancer progression, metastasis and prognosis of patients were carried on[4–7, 14–16]. Thus, the exact role of miR-24-3p on the clinical prognosis of patients in various human carcinomas still need to further investigate. In this meta-analysis, total 15 studies including 1518 people were recruited. Among them, ten studies containing 1212 patients provided the statistics of the OS by log rank tests. By the pooling strategy, we know that the elevated miR-24-3p expression levels were linked to worse prognosis of cancer patients. But, the number of enrolled studies was few, more data are needed to reinforce this result. By removing those two outliers, greatly declined of the heterogeneity was observed. Built on the mentioned above, these two studies could be the major sources of heterogeneity. However more relevant data are needed to further investigate because of the limit number of studies. There were five studies including 775 patients obtained the data of HRs by cox multivariate regression. Cox multivariate regression has been known as an effective approach because it can evaluate the contribution of each factor independently by adjusting other factors[46]. Thus, the consequences by cox multivariate regression are always considered as independent effects of each factor on the clinical outcome. As a result, we found that the significance was inconsistent among different effects model. This phenomenon suggested that the heterogeneity was relatively obvious and the consequences were instable. Through the subgroup analyses, we found that the heterogeneity was declined in hepatocellular carcinoma and achieved in
the studies of sample size larger than or equal 100. In addition, the sensitivity analysis identified one outlier, Gao et al. [29] who has an opposite conclusion with Kerimis et al. [38]. After removing this study, the heterogeneity had been significantly vanished. High miR-24-3p expression had a significantly worse survival and there was no publication bias. Thus, the power of miR-24-3p expression levels might serve as an independent prognostic indicator and we need more data to reinforce this conclusion. Also, we detected additional indexes such as RFS and DFS. MiR-24-3p expression levels were deemed to be significantly associated with DFS of statistics extracted from both log rank tests and cox regression analysis. For the RFS of cancer patients, only the fixed effects model revealed a significant correlation between miR-24-3p expression with this prognostic index and the heterogeneity was palpable. We identified an outlier (Wang et al. [40]) through publication bias evaluation. After removing this study, the heterogeneity was declined and the significance of association between miR-24-3p expression levels and the RFS was not altered.

As for the clinicopathological parameters, six studies including 536 patients had evaluated the association of miR-24-3p expression levels to the distinctive clinical parameters. The over-expression of miR-24-3p was found to be significantly related to larger tumor size by fixed effects model. Moreover, we found a significant heterogeneity between miR-24-3p expression levels to TNM stage. Applying sensitivity analyses, we identified one study (Liu et al. [36]) which had greatly impact on the result for the TNM stage. After removing this study, the heterogeneity completely disappeared, the association between miR-24-3p expression levels to the TNM stage was also significant. In addition, there were only two studies about the lymph node metastasis are enrolled and the conclusion might be not reliable. The analyzes of clinical features of a definite carcinoma should be normalized for the cut-off values, the feature categories and so on, to enrich the enrolled cases and characteristics for the meta-analysis.

As far as we know, this meta-analysis was the most comprehensive and systematic one to explore the correlation between the miR-24-3p expression levels with the prognosis of cancer patients in depth. Subgroup analysis, meta regression, sensitivity analysis and publication bias had been used to investigate the possible source of the heterogeneity to the greatest extent [47]. In spite of this, several flaws were hard to avoid in this meta-analysis. First, inevitable limitation from insufficient data in this analysis (only 15 studies with 1518 patients). Second, the cut-off values of the miR-24-3p expression levels were not exactly among those studies, thus, the accuracy of prognostic results may be influenced. Third, part of HRs was calculated from the survival curves which may cause some bias. Four, the number of recruited studies for DFS, RFS and clinicopathological features analyses were relatively insufficient. Taking above reasons into account, we need better designed and large sample size studies for further research before applying miR-24-3p as a prognostic biomarker of tumor in clinical applications.

5. Conclusions

The over expression of miR-24-3p was an underlying risk of poor prognosis in various human carcinomas, especially in hepatocellular carcinoma and lung cancer. As for other types of carcinomas, the results are not yet stable and more studies including normalized research conditions are required to further identify miR-24-3p prognostic values. In addition, high miR-24-3p expression levels were linked to the progression of cancers, developing more malignant behavior, such as larger tumor sizes and the advanced TNM stages. miR-24-3p expression levels could serve as a potential prognostic marker of human carcinoma.

Abbreviations

WOS
Web of science, OS:Overall survival, DFS:Disease-free survival, RFS:Recurrence-free survival, DMFS:Distant metastasis-free survival, NOS:Newcastle-Ottawa scale scores, U:univariate, M:multivariate, qRT-PCR:Quantitative Real-time PCR, 95%CI:95% confidence interval, Fixed:Fixed effects model, HR:hazard ratio, Random:Random pooling model, HCC:Hepatocellular carcinoma, CRC:Colorectal cancer, Advanced GC:Advanced Gastric cancer, ALL:Acute Lymphocytic Leukemia, AML:Acute Myelocytic Leukemia, NPC:Nasopharyngeal carcinoma, HNSCC:Head and neck squamous cell carcinoma, NSCLC:Non-small cell lung carcinoma.

Declarations

-Ethics approval and consent to participate:
All analyses were based on previous published studies, thus no ethical approval and patient consent are required.

-Consent for publication
All subjects participating in the image acquisition signed the consent form

-Availability of data and material
The authors declare that all data supporting the findings of this study are available within the article and the enrolled articles for meta-analysis.

The datasets generated and/or analysed during the current study are available in the PubMed, Embase, Web of science (WOS) and Cochrane library repository.

PubMed: https://pubmed.ncbi.nlm.nih.gov/
Embase: https://www.embase.com/login
Competing interests

The authors declare that they have no competing interests.

Funding

Not applicable

Authors' contributions

He Wang and Chunyang Chen contributed equally to this work and shall share first authorship. Study design and basic data extraction: He Wang, Chunyang Chen, Weijie Zhang, Jianquan Hou. Data extraction from the Kaplan–Meier curves: He Wang, Chunyang Chen and Weijie Zhang. Third party evaluation: Keke Ding. Manuscript composition: He Wang and Chunyang Chen. All authors read and approved the final manuscript.

Acknowledgements

We would like to thank all the people who helped us in the current study.

References

1. Felekkis K, Touvana E, Stefanou C, Deltas C. microRNAs: a newly described class of encoded molecules that play a role in health and disease. Hippokratia. 2010;14(4):236–40.
2. Ling H, Fabbri M, Calin GA. MicroRNAs and other non-coding RNAs as targets for anticancer drug development. Nat Rev Drug Discov. 2013;12(11):847–65.
3. Liu H, Lei C, He Q, Pan Z, Xiao D, Tao Y. Nuclear functions of mammalian MicroRNAs in gene regulation, immunity and cancer. Mol Cancer. 2018;17(1):64.
4. Liu M, Zhang Y, Zhang J, Cai H, Zhang C, Yang Z, Niu Y, Wang H, Wei X, Wang W, et al. MicroRNA-1253 suppresses cell proliferation and invasion of non-small-cell lung carcinoma by targeting WNT5A. Cell Death Dis. 2018;9(2):189.
5. Zhuang M, Qiu X, Cheng D, Zhu C, Chen L. MicroRNA-524 promotes cell proliferation by down-regulating PTEN expression in osteosarcoma. Cancer Cell Int. 2018;18:114.
6. Li N, Long B, Han W, Yuan S, Wang K. microRNAs: important regulators of stem cells. Stem Cell Res Ther. 2017;8(1):110.
7. Song L, Tuan RS. MicroRNAs and cell differentiation in mammalian development. Birth Defects Res C Embryo Today. 2006;78(2):140–9.
8. Pilecki Z, Cojocneanu-Petric R, Maralani M, Neagoe IB, Sandulescu R. MicroRNAs as regulators of apoptosis mechanisms in cancer. Clujul Med. 2016;89(1):50–5.
9. Slattery ML, Mullany LE, Sakoda LC, Wolff RK, Samowitz WS, Herrick JS. Dysregulated genes and miRNAs in the apoptosis pathway in colorectal cancer patients. Apoptosis. 2018;23(3–4):237–50.
10. Bueno MJ, Malumbres M. MicroRNAs and the cell cycle. Biochim Biophys Acta. 2011;1812(5):592–601.
11. Mens MMJ, Ghanbari M. Cell Cycle Regulation of Stem Cells by MicroRNAs. Stem Cell Rev Rep. 2018;14(3):309–22.
12. Shirjang S, Mansoori B, Asghari S, Duijf PHG, Mohammadi A, Gjerstorff M, Baradaran B. MicroRNAs in cancer cell death pathways: Apoptosis and necroptosis. Free Radic Biol Med. 2019;139:1–15.
13. Abdelalim EM. Molecular mechanisms controlling the cell cycle in embryonic stem cells. Stem Cell Rev Rep. 2013;9(6):764–73.
14. Baranwal S, Alahari SK. miRNA control of tumor cell invasion and metastasis. Int J Cancer. 2010;126(6):1283–90.
15. Kim J, Yao F, Xiao Z, Sun Y, Ma L. MicroRNAs and metastasis: small RNAs play big roles. Cancer Metastasis Rev. 2018;37(1):5–15.
16. Lou W, Liu J, Gao Y, Zhong G, Chen D, Shen J, Bao C, Xu L, Pan J, Cheng J, et al. MicroRNAs in cancer metastasis and angiogenesis. Oncotarget. 2017;8(70):115787–802.
17. Du J, Li M, Huang Q, Liu W, Li WQ, Li YJ, Gong ZC. The critical role of microRNAs in stress response: Therapeutic prospect and limitation. Pharmacol Res. 2019;142:294–302.
18. Olejniczak M, Kotowska-Zimmer A, Krzyzosiak W. Stress-induced changes in miRNA biogenesis and functioning. Cell Mol Life Sci. 2018;75(2):177–91.
19. Wiegand C, Savelserbergh A, Heusser P. MicroRNAs in Psychological Stress Reactions and Their Use as Stress-Associated Biomarkers, Especially in Human Saliva. Biomed Hub. 2017;2(3):1–15.
20. Dupont C, Kappeler L, Saget S, Grandjean V, Levy R. Role of miRNA in the Transmission of Metabolic Diseases Associated With Paternal Diet-Induced Obesity. Front Genet. 2019;10:337.
21. Huang Y, Yan Y, Xv W, Qian G, Li C, Zou H, Li Y. A New Insight into the Roles of MiRNAs in Metabolic Syndrome. Biomed Res Int. 2018;2018:7372636.
22. Rottiers V, Naar AM. MicroRNAs in metabolism and metabolic disorders. Nat Rev Mol Cell Biol. 2012;13(4):239–50.

23. Lan H, Lu H, Wang X, Jin H. MicroRNAs as potential biomarkers in cancer: opportunities and challenges. Biomed Res Int. 2015;2015:125094.

24. Kang H, Rho JG, Kim C, Tak H, Lee H, Ji E, Ahn S, Shin AR, Cho HI, Huh YH, et al. The miR-24-3p/p130Cas: a novel axis regulating the migration and invasion of cancer cells. Sci Rep. 2017;7:44847.

25. Yan L, Ma J, Zhu Y, Zan J, Wang Z, Ling L, Li Q, Lv J, Qi S, Cao Y, et al. miR-24-3p promotes cell migration and proliferation in lung cancer by targeting SOX7. J Cell Biochem. 2018;119(9):3989–98.

26. Du WW, Fang L, Li M, Yang X, Liang Y, Peng C, Qian W, O'Malley YQ, Askeland RW, Sugg SL, et al. MicroRNA miR-24 enhances tumor invasion and metastasis by targeting PTPN9 and PTPRF to promote EGF signaling. J Cell Sci. 2013;126(Pt 6):1440–53.

27. Khodadadi-Jamayran A, Akgol-Oksuz B, Afanasieva Y, Heguy A, Thompson M, Ray K, Giro-Perafita A, Sanchez I, Wu X, Tripathy D, et al. Prognostic role of elevated mir-24-3p in breast cancer and its association with the metastatic process. Oncotarget. 2018;9(16):12686–78.

28. Dong X, Liu Y. Expression and significance of miR-24 and miR-101 in patients with advanced gastric cancer. Oncol Lett. 2018;16(5):5769–74.

29. Gao Y, Liu Y, Du L, Li J, Qu A, Zhang X, Wang L, Wang C. Down-regulation of miR-24-3p in colorectal cancer is associated with malignant behavior. Med Oncol. 2015;32(1):362.

30. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gotzsche PC, Clarke M, Devereaux PJ, Kleijnen J, Moher D. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. BMJ. 2009;339:b2700.

31. Parmar MK, Torri V, Stewart L. Extracting summary statistics to perform meta-analyses of the published literature for survival endpoints. Stat Med. 1998;17(24):2815–34.

32. Irwig L, Macaskill P, Berry G, Glasziou P: Bias in meta-analysis detected by a simple, graphical test. Graphical test is itself biased. BMJ 1998, 316(7129):470; author reply 470–471.

33. Pan Y, Wang H, Ma D, Ji Z, Luo L, Cao F, Huang F, Liu Y, Dong Y, Chen Y. miR24 may be a negative regulator of menin in lung cancer. Oncol Rep. 2018;39(5):2342–50.

34. Zhao G, Liu L, Zhao T, Jin S, Jiang S, Cao S, Han J, Xin Y, Dong Q, Liu X, et al. Upregulation of miR-24 promotes cell proliferation by targeting NAIF1 in non-small cell lung cancer. Tumour Biol. 2015;36(5):3693–701.

35. Zhou N, Yan HL. MiR-24 promotes the proliferation and apoptosis of lung carcinoma via targeting MAPK7. Eur Rev Med Pharmacol Sci. 2018;22(20):6845–52.

36. Liu YX, Long XD, Xi ZF, Ma Y, Huang XY, Yao JG, Wang C, Xing TY, Xia Q. MicroRNA-24 modulates aflatoxin B1-related hepatocellular carcinoma prognosis and tumorigenesis. Biomed Res Int. 2014;2014:482926.

37. Meng FL, Wang W, Jia WD. Diagnostic and prognostic significance of serum miR-24-3p in HBV-related hepatocellular carcinoma. Med Oncol. 2014;31(9):177.

38. Kerims D, Kontos CK, Christodoulou S, Papadopoulos IN, Scorilas A. Elevated expression of miR-24-3p is a potentially adverse prognostic factor in colorectal adenocarcinoma. Clin Biochem. 2017;50(6):285–92.

39. Su B, Xu T, Bruce JP, Yip KW, Zhang N, Huang Z, Zhang G, Liu FF, Liang J, Yang H, et al. Elevated mir-24-3p in breast cancer and its association with the metastatic process. Oncotarget. 2015;6(19):27665–77.

40. Wang S, Pan Y, Zhang R, Xu T, Wu W, Zhang R, Wang C, Huang H, Calin CA, Yang H, et al: Hsa-miR-24-3p increases nasopharyngeal carcinoma radiosensitivity by targeting both the 3’UTR and 5’UTR of Jab1/CSN5. Oncogene 2016, 35(47):6096–6108.

41. Liu L, Pan J, Wang H, Ma Z, Yin J, Yuan F, Yuan Q, Zhou L, Liu X, Zhang Y, et al: von Willebrand factor rescued by miR-24 inhibition facilitates the proliferation and migration of osteosarcoma cells in vitro. Biosci Rep 2018, 38(6).

42. Organista-Nava J, Gomez-Gomez Y, Illades-Aguiar B, Alarcon-Romero, Saavedra-Herrera L, Rivera-Ramirez MV, Garzon-Barrientos AB, Leyva-Vazquez VH, MA: High miR-24 expression is associated with risk of relapse and poor survival in acute leukemia. Oncol Rep. 2015;33(4):1639–49.

43. Yan Q, Chen T, Yang H, Yu H, Zheng Y, He T, Wang J. The Effect of FERMT1 Regulated by miR-24 on the Growth and Radiation Resistance of Esophageal Cancer. J Biomed Nanotechnol. 2019;15(3):621–31.

44. Mori F, Ferraiuolo M, Santoro R, Sacconi A, Goeman F, Pallocca M, Pulito C, Korita E, Fanciulli M, Muti P, et al. Multitargeting activity of miR-24 inhibits long-term melatonin anticancer effects. Oncotarget. 2016;7(15):20532–48.

45. Quan J, Liu S, Dai K, Jin L, He T, Pan X, Lai Y. MicroRNA-23a/24-2/27a as a potential diagnostic biomarker for cancer: A systematic review and meta-analysis. Mol Clin Oncol. 2018;8(1):159–69.

46. Royston P, Altman DG. External validation of a Cox prognostic model: principles and methods. BMC Med Res Methodol. 2013;13:33.

47. Evangelou E, Ioannidis JP. Meta-analysis methods for genome-wide association studies and beyond. Nat Rev Genet. 2013;14(6):379–89.

Tables

Table 1:

Note: The dashes mean no data

HCC: Hepatocellular carcinoma, CRC: Colorectal cancer, Advanced GC: Advanced Gastric cancer, ALL: Acute Lymphocytic Leukemia, AML: Acute Myelocytic Leukemia, NPC: Nasopharyngeal carcinoma, HNSCC: Head and neck squamous cell carcinoma, NSCLC: Non-small cell lung carcinoma, OS: Overall survival,
DFS: Disease-free survival, RFS: Recurrence-free survival, DMFS: Distant metastasis-free survival, NOS: Newcastle-Ottawa scale scores, U: univariate, M: multivariate, qRT-PCR: Quantitative Real-time PCR
| Study(year)         | Country | Malignancy       | Sample type | Sample size(high/low) | Assay   | Survival | miRNA    | HR (95%CI)                  | Follow-up | Cut-off value |
|-------------------|---------|------------------|-------------|-----------------------|---------|----------|----------|-----------------------------|-----------|----------------|
| (2015)       | PCR  | 24-3p   | 7.200) U(K-M Curve) |
|--------------|------|---------|----------------------|
| Liu et al. (2018) |  China Osteosarcoma Tissue 84(42/42) qRT-PCR OS miR-24 | OS: 0.310(0.160-0.630) U(K-M Curve) | 50 Median |
| Pan et al. (2018) |  China Lung cancer Tissue 70(41/29) qRT-PCR OS miR-24 | OS: 3.570(1.390-9.150) U(K-M Curve) | 60 - |

Table 2:

Note: 95% CI: 95% confidence interval, Fixed: Fixed effects model, HR: hazard ratio, Random: Random pooling model
| Subgroups       | No. of studies | No. of patients | Pooled HR (95% CI) | Meta regression | Heterogeneity |
|-----------------|----------------|-----------------|--------------------|-----------------|---------------|
|                 | Fixed          | Random          |                    |                 |               |
| Overall         |                |                 |                    |                 |               |
| OS              | 1.609 (1.291-2.004) | 1.507 (0.810-2.803) | 85.20%     | 0               |
| Population      |                |                 |                    |                 |               |
| Asian (Chinese) | 1.381 (1.073-1.777) | 1.271 (0.585-2.762) | 0.341     | 88.50%          |
| Non-Asian       | 2.615 (1.668-4.099) | 2.615 (1.668-4.099) | 0.00%     | 0.693           |
| Specimen        |                |                 |                    |                 |               |
| Tissue          | 1.291 (0.982-1.698) | 1.336 (0.574-3.108) | 0.505     | 88.40%          |
| Non-Tissue      | 2.399 (1.659-3.470) | 2.399 (1.659-3.470) | 0.00%     | 0.949           |
| Sample size     |                |                 |                    |                 |               |
| ≥100            | 2.779 (2.051-3.766) | 2.779 (2.051-3.766) | 0.069     | 0.00%           |
| <100            | 0.882 (0.641-1.212) | 0.951 (0.376-2.404) | 85.30%   | 0               |
| NOS             |                |                 |                    |                 |               |
| ≥8              | 1.078 (0.771-1.507) | 1.336 (0.456-4.094) | 0.688     | 89.60%          |
| <8              | 2.177 (1.627-2.913) | 1.932 (1.152-3.241) | 59.80%   | 0.041           |
| Tumor Category 1|                |                 |                    |                 |               |
| Solid tumor     | 1.448 (1.131-1.852) | 1.427 (0.687-2.960) | 0.675     | 87.50%          |
| Hematologic     | 2.425 (1.491-3.944) | 2.425 (1.491-3.944) | 0.00%     | 0.751           |
| Tumor Category 2|                |                 |                    |                 |               |
| Digestive system| 1.705 (1.291-2.253) | 1.520 (0.676-3.420) | 0.982     | 87.40%          |
| Non-Digestive system | 1.461 (1.021-2.090) | 1.505 (0.466-4.863) | 85.50%   | 0.891           |
| Tumor           |                |                 |                    |                 |               |
| Esophageal Cancer| 0.540 (0.210-1.350) | 0.540 (0.210-1.350) | -        | -               |
| Osteosarcoma    | 0.310 (0.160-0.630) | 0.310 (0.160-0.630) | -        | -               |
| Gastric cancer  | 2.945 (1.344-4.575) | 2.945 (1.344-4.575) | -        | -               |
| ALL             | 2.450 (1.500-4.000) | 2.450 (1.500-4.000) | -        | -               |
| AML             | 1.320 (0.030-58.25) | 1.320 (0.030-58.25) | -        | -               |
| Hepatocellular carcinoma | 2.607 (1.756-3.871) | 2.607 (1.756-3.871) | 0.00%   | 0.637           |
| Lung cancer     | 3.274 (1.422-7.539) | 3.274 (1.422-7.539) | 0.00%   | 0.698           |
| Colorectal cancer| 0.585 (0.317-1.080) | 1.032 (0.076-13.954) | 93.00%   | 0               |

Table 3:

Note: 95% CI: 95% confidence interval, Fixed: Fixed effects model, HR: hazard ratio, Random: Random pooling model.
### Table 4:

| Subgroups                      | No. of studies | No. of patients | Pooled HR/95%CI) | Meta regression | Heterogeneity |
|--------------------------------|----------------|-----------------|------------------|-----------------|---------------|
|                                |                |                 | Fixed           | Random          |               |
| Overall OS                     | 5              | 775             | 2.384(1.813-3.134) | 1.994(0.991-4.015) | 82.30%        |
|                               |                |                 | 0.801           |                 |               |
| Population Asian (Chinese)     | 4              | 621             | 2.373(1.792-3.142) | 1.897(0.848-4.242) | 86.70%        |
| Non-Asian                      | 1              | 154             | 2.600(0.780-8.660) | 2.600(0.780-8.660) | –             |
| Specimen Tissue                | 4              | 703             | 2.448(1.804-3.323) | 1.940(0.765-4.922) | 86.60%        |
| Blood                          | 1              | 72              | 2.141(1.158-3.960) | 2.141(1.158-3.960) | –             |
| Sample size ≥100               | 3              | 608             | 3.369(2.414-4.701) | 3.369(2.414-4.701) | 0.157         |
| Sample size ≤100               | 2              | 167             | 1.166(0.722-1.883) | 1.005(0.221-4.575) | 89.50%        |
| NOS ≥8                         | 3              | 496             | 1.593(1.020-2.488) | 1.530(0.402-5.818) | 0.00%         |
| NOS ≤8                         | 2              | 279             | 3.041(2.150-4.300) | 2.914(1.778-4.774) | 45.50%        |
| Tumor Colorectal cancer        | 2              | 249             | 0.752(0.394-1.434) | 1.021(0.186-5.904) | 82.50%        |
| Tumor Hepatocellular carcinoma | 2              | 279             | 3.041(2.150-4.300) | 2.914(1.778-4.774) | 45.50%        |

Table 4:

Note: 95% CI: 95% confidence interval, Fixed: Fixed effects model, HR: hazard ratio, Random: Random pooling model

### Table 5:

| Clinicopathological parameters | No. of studies | No. of patients | Pooled OR (95%CI) | Heterogeneity |
|--------------------------------|----------------|-----------------|-------------------|---------------|
|                                |                |                 | Fixed           | Random          |               |
| RFS Univariate                 | 4              | 393             | 2.315(1.491-3.594) | 1.814(0.741-4.440) | 66.70%        |
| DFS Univariate                 | 2              | 226             | 2.361(1.390-4.012) | 2.386(1.362-4.180) | 3.60%         |
| DFS Multivariate              | 2              | 226             | 2.313(1.315-4.067) | 2.313(1.315-4.067) | 0.00%         |

Table 5:

Note: 95% CI: 95% confidence interval, Fixed: Fixed effects model, HR: hazard ratio, Random: Random pooling model
Figure 1

The flow chart of the meta-analysis

Figure 2

Association between miR-24-3p expression levels and (A) overall survival and (B) overall survival without the outliers as well as corresponding (C) sensitivity analysis and (D) publication bias evaluation
Figure 3

Subgroup analyses of (A) population (Asian and Non-Asian), (B) sample sizes (<100 and ≥100), (C) NOS scores (<8 and ≥8), (D) specimen (Tissues and Non-Tissue), (E) tumor category1 (Solid tumor and Hematologic tumor), (F) tumor category2 (Digestive system and Non-Digestive system) for overall survival.

| Study    | RR (95% CI) | Weight |
|----------|-------------|--------|
| Ming et al. (2014) | 2.14 (1.36, 3.39) | 10.09  |
| Lin et al. (2014)  | 3.58 (2.33, 5.47) | 42.55  |
| Cai et al. (2015)  | 0.46 (0.21, 0.99) | 21.81  |
| Kwon et al. (2017) | 2.50 (0.78, 8.64) | 9.17   |
| Dong et al. (2018) | 5.98 (3.67, 9.60) | 11.06  |
| Overall (I² = 82.3%, p < 0.001) | 2.28 (1.31, 3.92) | 100.00 |

Figure 4

The independent role of miR-24-3p as a prognostic indicator for (A) overall survival, (B) overall survival without outliers, and (C) sensitivity analysis, (D) publication bias evaluation.
Figure 5

Association between miR-24-3p expression levels and (A) recurrence-free survival and (B) recurrence-free survival without the outliers as well as corresponding (C) sensitivity analysis and (D) publication bias evaluation.

Figure 6

Association between miR-24-3p expression level and TNM stages of cancer patients, (A) overall pooling result, (B) pooling result without the outliers, and (C) sensitivity analysis, (D) publication bias evaluation.
Supplementary Files

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