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Prognostic Value of MicroRNAs in Esophageal Carcinoma: A Meta-Analysis

Song Gao, PhD¹, Zhi-Ying Zhao, PhD², Zhen-Yong Zhang, PhD¹, Yue Zhang, PhD³ and Rong Wu, PhD¹

Abstract

Background: Numerous articles have reported that abnormal expression levels of microRNAs (miRNAs) are related to the survival times of esophageal carcinoma (EC) patients, which contains esophageal adenocarcinoma (EAC) and esophageal squamous cell carcinoma (ESCC). Nevertheless, there has not been a comprehensive meta-analysis to assess the accurate prognostic value of miRNAs in EC.

Methods: Studies published in English up to April 12, 2018 that evaluated the correlation of the expression levels of miRNAs with overall survival (OS) in EC were identified by online searches in PubMed, EMBASE, Web of Science, and the Cochrane Database of Systematic Reviews performed by two independent authors. The pooled hazard ratios (HRs) with 95% confidence intervals (CIs) were used to estimate the correlation between OS and miRNA expression. $HR \geq 2$ was considered cutoff for considering the miRNA as prognostic candidate.

Results: Forty-four pertinent articles with 22 miRNAs and 4310 EC patients were ultimately included. EC patients with tissue expression levels of high miR-21 or low miR-133a ($HR = 2.48$, 95% CI = 1.50–4.12), miR-133b ($HR = 2.15$, 95% CI = 1.27–3.62), miR-138 ($HR = 2.27$, 95% CI = 1.68–3.08), miR-203 ($HR = 2.83$, 95% CI = 1.35–5.95), miR-375 and miR-655 ($HR = 2.66$, 95% CI = 1.16–6.12) had significantly poorer OS ($P < 0.05$). In addition, EC patients with blood expression levels of high miR-21 ($HR = 2.19$, 95% CI = 1.31–3.68) and miR-223 had significantly shorter OS ($P < 0.05$).

Conclusions: In conclusion, tissue expression levels of miR-21, miR-133a, miR-133b, miR-138, miR-203, miR-375, and miR-655 and blood expression levels of miR-21 and miR-223 demonstrate significant prognostic value. Among them, the expression levels of miR-133a, miR-133b, miR-138, miR-203, and miR-655 in tissue and the expression level of miR-21 in blood are potential prognostic candidates for predicting OS in EC.

Introduction

During the past 10 years, a substantial number of articles have reported the survival of esophageal carcinoma (EC) patients with dysregulated microRNA (miRNA) expression^{1–96}. As the twelfth origin of incident cases and the seventh major cause of cancer-related death all over the

world⁹⁷, it contains two main types: esophageal adenocarcinoma (EAC) and esophageal squamous cell carcinoma (ESCC). In the United States, EAC nowadays occupies about 7% of all EC cases. ESCC is the main subtype of EC among Asian patients. Although the treatment and prognosis of EC have been improved by multimodal therapies, the rate of 5-year overall survival (OS) remains poor⁹⁸.

It is well known that EC is a complex inherited disease that is characterized by altered expression levels of certain coding or non-coding genes. As the high-throughput analysis develops, an increasing number of cancer-related non-coding RNAs have been recognized⁹⁹. miRNAs, a class of small non-coding RNAs <25 nucleotides in length,

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act as negative regulatory factors of gene expression by depressing translation or causing deadenylation-dependent degradation of target messenger RNAs (mRNAs)¹⁰⁰. They have been shown to be involved in various processes of tumor progression, including proliferation and metastasis of cancer cells¹⁰¹. In particular, EC-related miRNAs have been proved to exert functional diversity via multiple biological processes.

Despite comprehensive research aimed at illuminating the molecular mechanisms in EC, there are still challenges facing the identification of prognostic biomarkers that are minimally invasive and sensitive. Therefore, it is crucial to develop prognostic cancer biomarkers that can be expediently and reliably applied in the clinical setting, improving the survival of EC patients.

Recently, an increasing amount of evidence indicates that miRNAs can act as possible biomarkers for cancer prognosis in clinical practice that is fairly encouraging and exciting^{1–96}. However, there has not been a systematic review and meta-analysis to estimate the associations between miRNA expression and the survival of EC patients. Therefore, the current study aimed to identify that correlation by searching the recently published evidence regarding miRNAs as prognostic tools for EC in cancer tissues and in blood.

Materials and methods

Search strategy

The comprehensive online search about articles from four databases, PubMed, Web of Science, Embase, and Cochrane Database of Systematic Reviews, was performed by two independent authors (S.G. and Z.-Y.Z.). Subsequently, Y.Z. re-evaluated uncertain data. A comprehensive search was conducted employing the subject terms: “microRNA,” “miRNA,” “miR,” and “esophageal carcinoma,” “esophagus carcinoma,” “oesophageal carcinoma.” Of the four databases, there were 461 records after duplicates were removed. Subsequently, we excluded 335 records by titles and abstracts. For the remaining 126 records, 30 full-text articles were excluded. The details are shown in Fig. 1. The search deadline was April 12, 2018.

Inclusion criteria

We came up with inclusion criteria for qualified articles that were analyzed by our full-text estimation: (1) articles concerning the pertinence between miRNA level and prognosis of EC patients; (2) the survival results that were estimated by OS; (3) full-text articles published in English.

Exclusion criteria

Articles that were not satisfied with the aforementioned inclusion criteria, reviews, letters, or laboratory studies without raw data (Kaplan–Meier survival curves or HR with 95% CI) were excluded. Articles of non-dichotomous miRNA expression levels and frequency of studies

assessing prognostic value of miRNAs equal to 1 were also excluded. If more than one paper had been published on the identical study cohort, only the most well-rounded investigation was selected for the current study. Besides, if both of the univariate and multivariate outcomes were reported, only the latter were chosen, since they were adjusted for confounding factors.

Quality assessment

S.G. and Z.-Y.Z. confirmed all eligible investigations that analyzed the prognostic value of miRNAs in EC, and Y.Z. reassessed uncertain data. Quality assessment for each study was done using modified Newcastle–Ottawa Scale (NOS)¹⁰². NOS scores were calculated on the basis of selection, comparability, and outcome. Papers with NOS scores ≥ 6 were considered high-quality articles¹⁰³.

Study selection

A flow diagram with details of the study selection process was presented in Fig. 1.

Study frequency

The frequency of studies estimating the prognostic value of miRNAs in EC was shown in Supplementary Tables 1 (tissue) and 2 (blood), including the miRNA names, the frequency of studied miRNAs, and the references. In addition, frequency of strong miRNAs is shown in Table 1.

Study characteristics

The basic information of the included articles is comprehensively detailed in Supplementary Table 3. If the data were not provided in the text but only as Kaplan–Meier survival curves, the data were extracted from the graphical survival plots, and estimations of the HR with 95% CI were then performed using a previously described method¹⁰⁴ with the software Engauge Digitizer version 4.1.

Statistical analysis

All analyses were conducted using Stata version 13.0 (StataCorp, College Station, TX, USA). OS was the main and only reference standard for prognostic value of miRNAs. The HR was considered significant at the $P < 0.05$ level if the 95% CI did not include the value 1. In addition, a single miRNA was regarded as the strong candidate if its HR was ≥ 2 . Owing to different types of samples (formalin-fixed, paraffin-embedded, frozen tissue, plasma, and serum) from EC patients at different stages, cutoff values, and miRNA methods in individual studies, random-effects models were more appropriate than fixed-effects models for most of the analyses. Accordingly, the former were employed in the current meta-analysis. Publication bias was estimated using Begg’s funnel plot. A

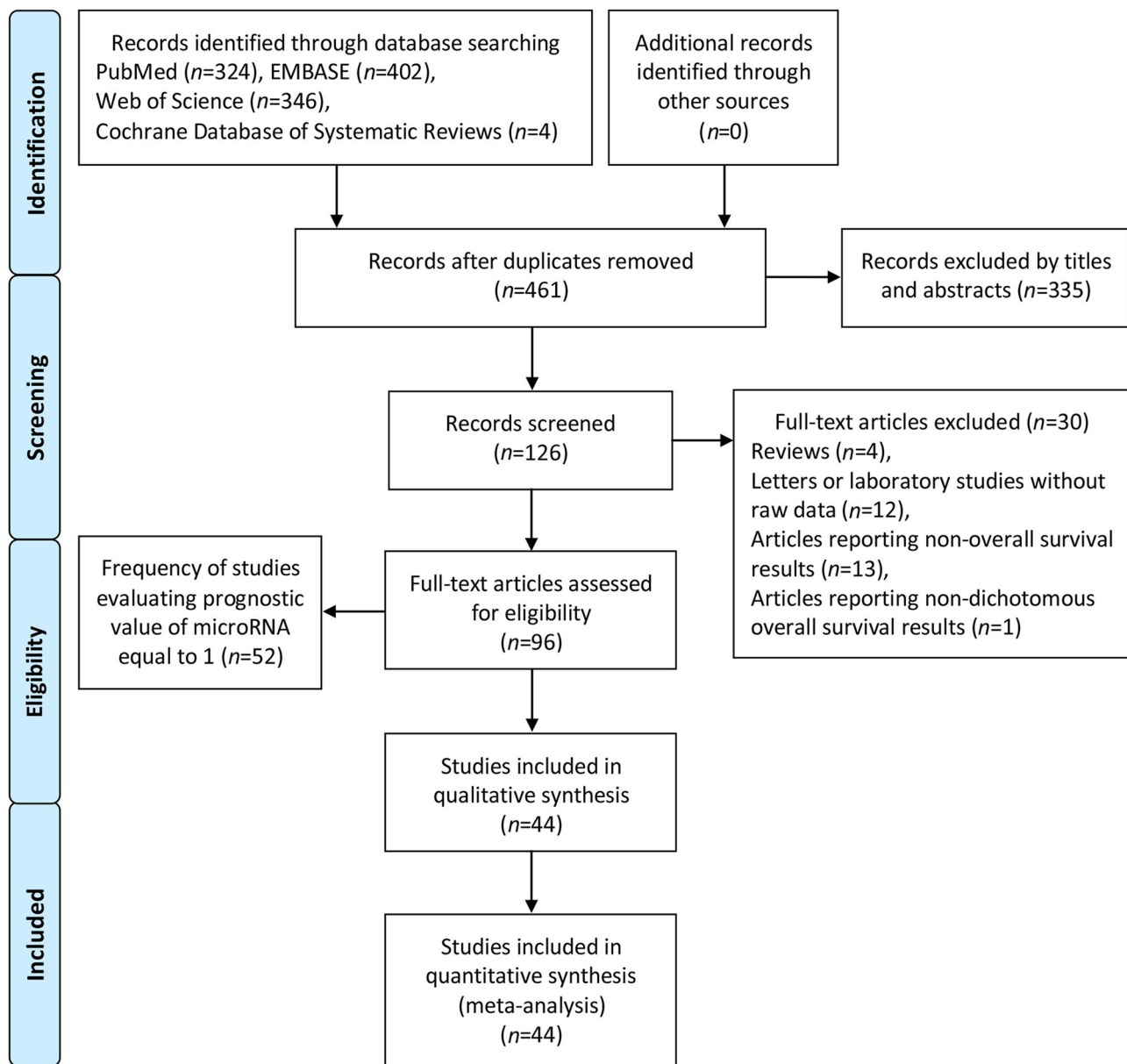


Fig. 1 Flow diagram of the literature search and selection

Table 1 Frequency of strong microRNAs studied in esophageal carcinoma

Tissue	Blood				
	miR	F	R		
miR	F	R	miR	F	R
133a	2	32.33	21	2	87.89
133b	2	13.34			
138	2	35.36			
203	2	49.50			
655	2	75.76			

F frequency of the studied microRNAs, R reference

two-tailed P value <0.05 was considered significant. A sensitivity analysis (influence analysis) was carried out to test how sensitive the combined effect size was to the removal of individual investigations. If the point assessment was outside of the 95% CI of the pooled effect size after it was removed from the analysis, an individual study was considered to have excessive influence.

Results

Meta-analysis

A summary of the HR with 95% CI evaluated from the whole combined analysis for all the miRNAs is shown in Table 2. The forest plots, Begg's funnel plots, and sensitivity

Table 2 HR with 95% CI of microRNA expression in esophageal carcinoma

Sample	MicroRNA	N	Included articles	HR	95% CI	Figure	P value	Heterogeneity (I ² statistic)	Total patients
Tissue	Low let-7g	2	1, 2	1.27	0.66–2.45	Supplementary Figure 1	0.47	I ² = 58.6%, P = 0.12	197
Tissue	High miR-9	2	2, 5	1.07	0.45–2.57	Supplementary Figure 1	0.88	I ² = 72.8%, P = 0.06	342
Tissue	High miR-21	10	1, 2, 7–14	1.63	1.26–2.11	Supplementary Figure 1	<0.01	I ² = 23.8%, P = 0.22	1071
Tissue	High miR-26a	2	15, 17	1.09	0.19–6.39	Supplementary Figure 2	0.92	I ² = 47.5%, P = 0.17	116
Tissue	Low miR-34a	2	2, 24	1.87	0.88–3.99	Supplementary Figure 2	0.11	I ² = 45.4%, P = 0.18	210
Tissue	High miR-92a	2	6, 25	1.47	0.64–3.34	Supplementary Figure 2	0.36	I ² = 54.4%, P = 0.14	170
Tissue	Low miR-100	4	13, 27–29	2.12	0.86–5.21	Supplementary Figure 2	0.10	I ² = 73.2%, P = 0.01	410
Tissue	Low miR-133a	2	32, 33	2.48	1.50–4.12	Fig. 2	<0.01	I ² = 0.0%, P = 0.76	210
Tissue	Low miR-133b	2	13, 34	2.15	1.27–3.62	Fig. 2	<0.01	I ² = 0.0%, P = 0.97	265
Tissue	Low miR-138	2	35, 36	2.27	1.68–3.08	Fig. 2	<0.01	I ² = 0.0%, P = 0.33	333
Tissue	High miR-143–3p	2	37, 38	1.12	0.13–9.33	Supplementary Figure 2	0.92	I ² = 95.4%, P < 0.01	199
Tissue	High miR-145	2	1, 29	0.85	0.27–2.66	Supplementary Figure 2	0.79	I ² = 73.1%, P = 0.05	143
Tissue	High miR-155	2	1, 13	1.17	0.64–2.14	Supplementary Figure 3	0.61	I ² = 47.6%, P = 0.17	283
Tissue	High miR-200a	2	2, 47	0.71	0.19–2.60	Supplementary Figure 3	0.60	I ² = 78.6%, P = 0.03	187
Tissue	Low miR-203	2	49, 50	2.83	1.35–5.95	Fig. 2	<0.01	I ² = 0.0%, P = 0.40	70
Tissue	High miR-205	2	51, 52	0.75	0.09–6.45	Supplementary Figure 3	0.79	I ² = 72.4%, P = 0.06	57
Tissue	High miR-223	2	13, 55	1.13	0.25–5.03	Supplementary Figure 3	0.87	I ² = 89.5%, P < 0.01	294
Tissue	Low miR-375	6	7, 10, 11, 57–59	1.64	1.05–2.58	Supplementary Figure 3	0.03	I ² = 64.8%, P < 0.01	729
Tissue	High miR-455–3p	2	62, 63	0.67	0.10–4.48	Supplementary Figure 3	0.68	I ² = 93.6%, P < 0.01	326
Tissue	Low miR-655	2	75, 76	2.66	1.16–6.12	Fig. 2	0.02	I ² = 0.0%, P = 0.97	63
Blood	Low miR-16	2	87, 88	1.23	0.14–10.86	Supplementary Figure 4	0.86	I ² = 90.3%, P < 0.01	62
Blood	High miR-21	2	87, 89	2.19	1.31–3.68	Fig. 2	<0.01	I ² = 0.0%, P = 0.79	164
Blood	High miR-25	2	90, 91	1.75	0.56–5.54	Supplementary Figure 4	0.34	I ² = 67.2%, P = 0.08	257
Blood	High miR-223	2	90, 91	1.62	1.12–2.34	Supplementary Figure 4	0.01	I ² = 0.0%, P = 0.50	257
Blood	Low miR-375	3	87, 89, 91	1.44	0.93–2.22	Supplementary Figure 4	0.10	I ² = 29.1%, P = 0.24	358

N number of the included articles, HR hazard ratio, CI confidence interval

analyses are shown in Supplementary Figures 1–8 according to the logic sequencing of miRNA names. For the included 96 studies, 52 were excluded because the frequency of them evaluating prognostic value of miRNA was equal to 1^{3,4,16,18–23,26,30,31,39–46,48,53,54,56,60,61,64–74,77–86,92–96}. In addition, although one article reported OS results about miR-193a-5p, it was excluded because it had non-dichotomous miRNA expression value¹⁰⁵. The mean NOS score of the included researches was 6.5 (4.0–8.0), indicating that the quality of them was adequate (Supplementary Table 4).

Tissue-based high miR-21 and low miR-133a, miR-133b, miR-138, miR-203, miR-375, and miR-655 levels predict poor OS

Ten studies^{1,2,7–14} analyzed the connections between high tissue miR-21 levels and OS, suggesting that EC patients with high tissue miR-21 levels had significantly worse OS than those with low levels (HR = 1.63, 95% CI = 1.26–2.11, $P < 0.01$, Supplementary Figure 1).

Two studies^{32,33} reported the associations between low tissue miR-133a levels and OS, indicating that EC patients with low tissue miR-133a levels had significantly shorter OS than those with high levels (HR = 2.48, 95% CI = 1.50–4.12, $P < 0.01$, Fig. 2).

Two studies^{13,34} covered the relationship between low tissue miR-133b levels and OS, showing that EC patients with low tissue miR-133b levels had significantly poorer OS than those with high levels (HR = 2.15, 95% CI = 1.27–3.62, $P < 0.01$, Fig. 2).

Two studies^{35,36} focused on the pertinence between low tissue miR-138 levels and OS, suggesting that EC patients with low tissue miR-138 levels had significantly worse OS than those with high levels (HR = 2.27, 95% CI = 1.68–3.08, $P < 0.01$, Fig. 2).

Two studies^{49,50} stressed the correlations between low tissue miR-203 levels and OS, indicating that EC patients with high tissue miR-203 levels had significantly shorter OS than those with low levels (HR = 2.83, 95% CI = 1.35–5.95, $P < 0.01$, Fig. 2).

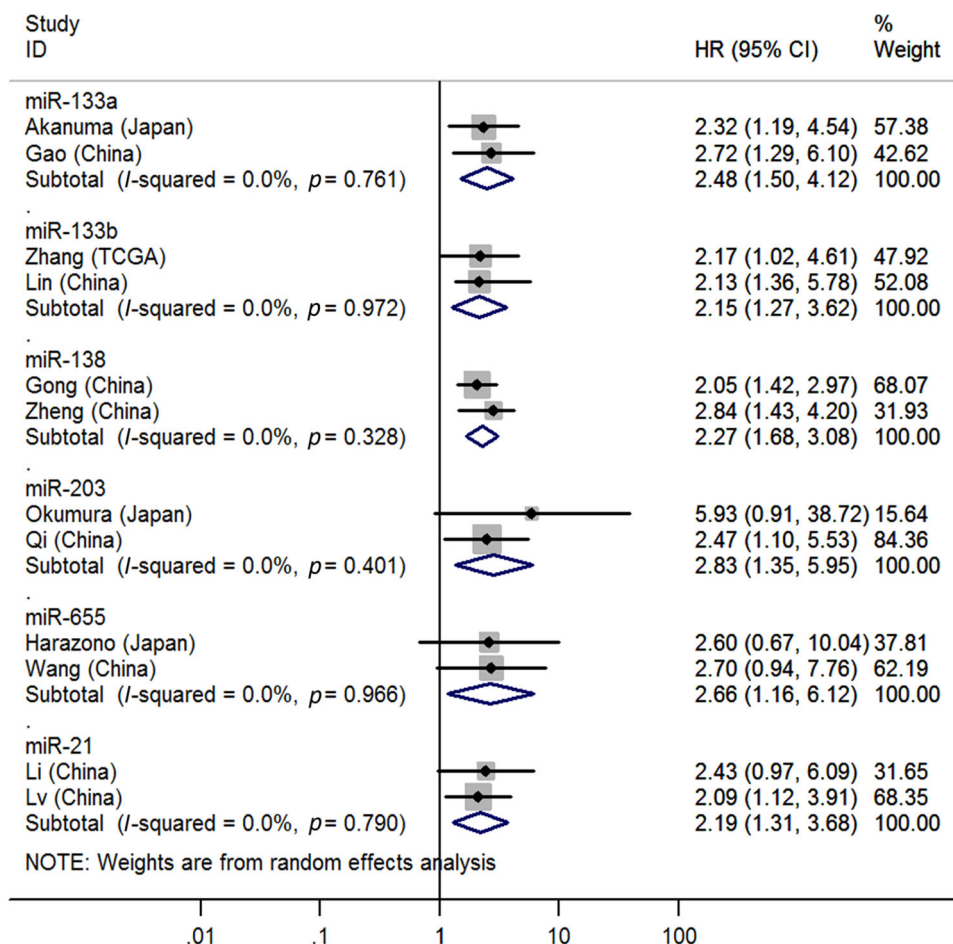


Fig. 2 Forest plot of pooled analyses of OS in association with tissue expression levels of low miR-133a, miR-133b, miR-138, miR-203, and miR-605 and blood expression levels of high miR-21

Six studies^{7,10,11,57–59} emphasized the relevance between low tissue miR-375 levels and OS, showing that EC patients with low tissue miR-375 levels had significantly poorer OS than those with high levels (HR = 1.64, 95% CI = 1.05–2.58, $P = 0.03$, Supplementary Figure 3).

Two studies^{75,76} paid attention to the relation between low tissue miR-655 levels and OS, suggesting that EC patients with low tissue miR-655 levels had significantly worse OS than those with high levels (HR = 2.66, 95% CI = 1.16–6.12, $P = 0.02$, Fig. 2).

Blood-based high miR-21 and miR-223 levels predict poor OS

Two studies^{87,89} analyzed the connections between high blood miR-21 levels and OS, suggesting that EC patients with high blood miR-21 levels had significantly worse OS than those with low levels (HR = 2.19, 95% CI = 1.31–3.68, $P < 0.01$, Fig. 2).

Two studies^{90,91} reported the associations between low blood miR-223 levels and OS, indicating that EC patients with low blood miR-223 levels had significantly shorter OS than those with high levels (HR = 1.62, 95% CI = 1.12–2.34, $P = 0.01$, Supplementary Figure 4).

Publication bias

Begg's funnel plot was used to evaluate publication bias in the OS of EC patients with high tissue miR-21 levels (Supplementary Figure 5). The results showed that the P value was 0.33, indicating the absence of a publication bias.

Begg's funnel plot was used to evaluate publication bias in the OS of EC patients with low tissue miR-375 levels (Supplementary Figure 6). The results showed that the P value was 0.73, indicating the absence of a publication bias.

Sensitivity analysis

The sensitivity analysis was applied to evaluate whether any individual study had excessive influence in the OS of EC patients with high tissue miR-21 levels (Supplementary Figure 7). The outcomes showed that no single investigation significantly influenced the merged HR and 95% CI.

The sensitivity analysis was applied to evaluate whether any individual study had excessive influence in the OS of EC patients with low tissue miR-375 levels (Supplementary Figure 8). The outcomes showed that no single investigation significantly influenced the merged HR and 95% CI.

Discussion

Primary discoveries

The present meta-analysis included 44 articles published in English that included 22 miRNAs and 4310

patients. miR-21 is the most studied miRNA, and EC patients with high tissue miR-21 levels have significantly shorter OS times than those with low levels. Similarly, high blood miR-21 levels have a significantly prognostic value for OS. In addition, some other miRNAs have significantly prognostic value for EC, including tissue miR-133a, miR-133b, miR-138, miR-203, miR-375, and miR-655 and blood miR-223. Among them, the tissue miR-133a, miR-133b, miR-138, miR-203, and miR-655 levels and the blood miR-21 level are strong biomarkers of prognosis in EC.

Molecular mechanisms of the studied miRNAs

Furthermore, a summary of the 22 miRNAs with altered levels, including their potential targets and pathways, is presented in Fig. 3. Several miRNAs were not marked with up or down arrows since either they were not reported in the original articles or inconsistent expression levels of them were shown in the papers about the single miRNA. In general, Fig. 3 can help us better understand the functions of miRNAs in EC. As the strong candidate biomarkers of EC, tissue miR-133a, miR-138, and miR-203 were with down-regulated expression and blood miR-21 was with upregulated expression. In addition, metadherin was the target of miR-21. miR-138 downregulation caused lipid raft formation by upregulating flotillin 1, flotillin 2, and caveolin-1 and promoted invasion of ESCC cells as well as sustained nuclear factor- κ B activity. Furthermore, pituitary tumor-transforming 1, zinc finger E-box binding homeobox 1, and transforming growth factor beta receptor 2 were identified as direct targets of miR-655, overexpression of which could suppress migration and invasion of EC9706 and KYSE150 cells.

Strengths of the meta-analysis

This work had certain strengths: (1) we searched for and identified almost all articles with survival outcomes in EC patients with altered miRNA levels. In addition, the current expression profiles of miRNAs were distinctly listed in Supplementary Tables 1 and 2 by distinguishing miRNA names and the kinds of detected samples; (2) most of our included articles had large sample sizes (≥ 30 , except 4 studies [refs. 49,51,75,88]), strengthening and broadening the applicability of the prognostic results to EC patients; (3) combined analyses for most of miRNAs with significantly prognostic value indicated low heterogeneity ($I^2 \leq 50$, except tissue miR-375).

Limitations

The following limitations of our meta-analysis should be noted: (1) there were multiple variables in

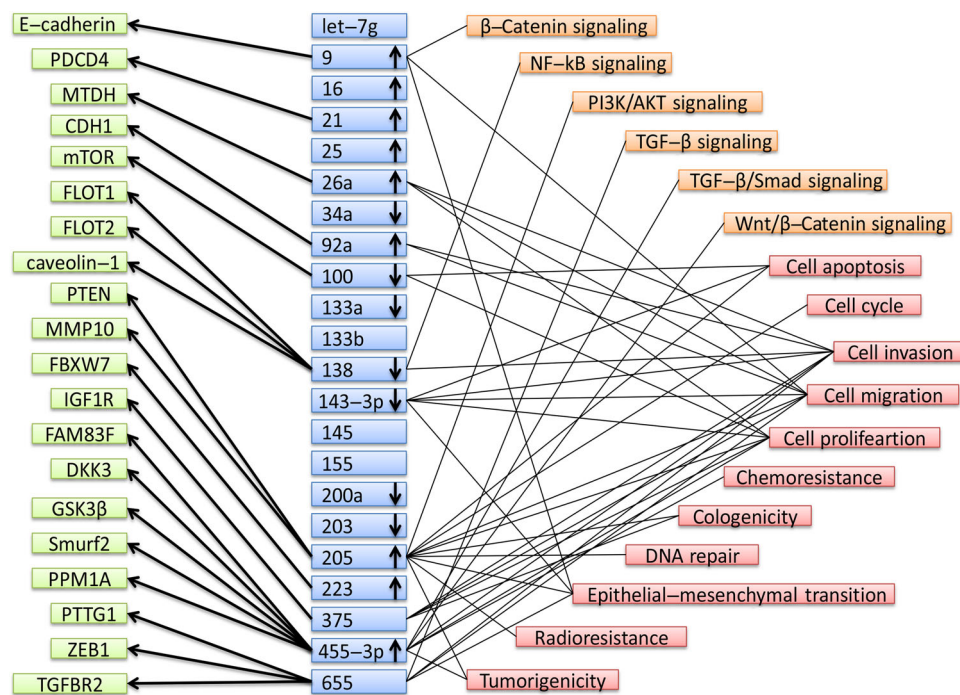


Fig. 3 Summary of microRNAs with altered expression, potential targets, and pathways entered in this study. E-cadherin cadherin 1, type 1, E-cadherin (epithelial), PDCD4 programmed cell death 4, MTDH metadherin, CDH1 cadherin 1, mTOR mechanistic target of rapamycin kinase, FLOT1 flotillin 1, FLOT2 flotillin 2, PTEN phosphatase and tensin homolog, MMP10 matrix metalloproteinase 10, FBXW7 F-box and WD repeat domain containing 7, IGF1R insulin like growth factor 1 receptor, FAM83F family with sequence similarity 83 member F, DKK3 dickkopf WNT signaling pathway inhibitor 3, GSK3 β glycogen synthase kinase 3 beta, Smurf2 SMAD specific E3 ubiquitin protein ligase 2, PPM1A protein phosphatase, Mg²⁺/Mn²⁺ dependent 1A, PTTG1 pituitary tumor-transforming 1, ZEB1 zinc finger E-box binding homeobox 1, TGFBR2 transforming growth factor beta receptor 2, NF- κ B nuclear factor-kappaB, PI3K phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit beta, AKT AKT serine/threonine kinase 1, TGF- β transforming growth factor- β

the present study, including different types of samples (formalin-fixed, paraffin-embedded, frozen tissue, plasma, and serum) from EC patients at different stages, cutoff values, and miRNA methods, among which the sample type and cutoffs were major limitations; (2) we only included articles published in English, probably excluding potential studies published in other languages about miRNA expression and prognosis in EC patients; (3) we only included studies estimating OS, possibly excluding potential researches with prognosis with other survival outcomes, such as cause-specific survival, disease-free survival, recurrence-free survival, progression-free survival, and metastasis-free survival; (4) although the mean NOS score of the included researches was 6.5, which indicated that the quality of them was adequate, we still could not ignore the low scores among them (the NOS scores were 4–5).

Implications for future clinical and basic research

It was worth noting that this meta-analysis was the first systematic estimation of the associations between dysregulated miRNA levels and the prognosis of EC patients.

There were implications for future clinical and basic investigations: (1) combined detection of multiple miRNA levels could be used by clinical workers and other healthcare providers, which might greatly augment the ability to estimate survival time of EC patients so that timely treatment could be provided; (2) the present research advances and trends regarding miRNA levels and the prognosis of EC patients could be clearly obtained by basic researchers in Tables 1 and 2. Meanwhile, the molecular mechanisms of miRNAs could be seen in Fig. 3, which could be referred to at the same time as Tables 1 and 2; (3) some conflicting results regarding the prognostic value of miRNAs might be resolved based on this work.

Conclusions

In conclusion, the tissue expression levels of miR-21, miR-133a, miR-133b, miR-138, miR-203, miR-375, and miR-655 and the blood expression levels of miR-21 and miR-223 demonstrate significant prognostic value. Among them, the expression levels of miR-133a, miR-133b, miR-138, miR-203, and miR-655 in tissue, and the expression level of miR-21 in blood are

potential prognostic candidates for predicting OS in EC.

Study Highlights

What is current knowledge

- Increasing evidence indicates that microRNAs can act as possible biomarkers for cancer prognosis in clinical practice.
- However, there has not been a systematic review and meta-analysis to estimate the associations between microRNA expression and the survival of esophageal carcinoma patients.

What is new here

- This work is the first systematic review and meta-analysis about prognostic value of microRNAs in esophageal carcinoma.
- Several microRNAs suggest significantly prognostic value and are potential prognostic candidates for predicting overall survival for esophageal carcinoma.

Translational impact

- Combined detection of multiple microRNA levels could be used by clinical workers and other healthcare providers, which might greatly augment the ability to estimate survival time of esophageal carcinoma patients so that timely treatment could be provided.

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Competing interests

Guarantor of article: Yue Zhang

Specific author contributions: Study concept and design: Y.Z. Acquisition of data: S.G. and Z.-Y. Zhao. Analysis and interpretation of data: S.G., Z.-Y. Zhao and Z.-Y. Zhang. Drafting of the manuscript: Y.Z. Revision of manuscript: S.G., Z.-Y. Zhao, Z.-Y. Zhang, Y.Z. and R.W. Supervision of work: Y.Z. and R.W. All authors read and approved the final manuscript.

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References

1. Hamano, R. et al. Overexpression of miR-200c induces chemoresistance in esophageal cancers mediated through activation of the Akt signaling pathway. *Clin. Cancer Res.* **17**, 3029–3038 (2011).
2. Hu, Y. et al. Prognostic significance of differentially expressed miRNAs in esophageal cancer. *Int. J. Cancer* **128**, 132–143 (2011).
3. Matsui, D. et al. Primary tumor microRNA signature predicts recurrence and survival in patients with locally advanced esophageal adenocarcinoma. *Oncotarget* **7**, 81281–81291 (2016).
4. Hara, K. et al. Significance and function of microRNA-7 in oesophageal squamous cell carcinoma. *Anticancer Res.* **37**, 1043–1048 (2017).
5. Song, Y. et al. MicroRNA-9 promotes tumor metastasis via repressing E-cadherin in esophageal squamous cell carcinoma. *Oncotarget* **5**, 11669–11680 (2014).
6. Xu, X. L. et al. MicroRNA-17, microRNA-18a, and microRNA-19a are prognostic indicators in esophageal squamous cell carcinoma. *Ann. Thorac. Surg.* **97**, 1037–1045 (2014).
7. Mathé, E. A. et al. MicroRNA expression in squamous cell carcinoma and adenocarcinoma of the esophagus: associations with survival. *Clin. Cancer Res.* **15**, 6192–6200 (2009).
8. Zhao, Y. et al. microRNA and inflammatory gene expression as prognostic marker for overall survival in esophageal squamous cell carcinoma. *Int. J. Cancer* **132**, 2901–2909 (2013).
9. Liu, T. et al. MicroRNA-21 promotes cell growth and migration by targeting programmed cell death 4 gene in Kazakh's esophageal squamous cell carcinoma. *Dis. Markers* **2014**, 232837 (2014).
10. Meng, X. R., Lu, P., Mei, J. Z., Liu, G. J. & Fan, Q. X. Expression analysis of miRNA and target mRNAs in esophageal cancer. *Braz. J. Med. Biol. Res.* **47**, 811–817 (2014).
11. Winther, M. et al. Evaluation of miR-21 and miR-375 as prognostic biomarkers in esophageal cancer. *Acta Oncol.* **54**, 1582–1591 (2015).
12. Klimczak-Bitner, A. A., Kordek, R., Bitner, J., Musiał, J. & Szemraj, J. Expression of MMP9, SERPINE1 and miR-134 as prognostic factors in esophageal cancer. *Oncol. Lett.* **12**, 4133–4138 (2016).
13. Zhang, H. C. & Tang, K. F. Clinical value of integrated-signature miRNAs in esophageal cancer. *Cancer Med.* **6**, 1893–1903 (2017).
14. Zhang, J. et al. Prognostic significance of miR-21 and PDCC4 in patients with stage II esophageal carcinoma after surgical resection. *J. Cell. Biochem.* **119**, 4783–4791 (2018).
15. Ogawa, R. et al. Expression profiling of micro-RNAs in human esophageal squamous cell carcinoma using RT-PCR. *Med. Mol. Morphol.* **42**, 102–109 (2009).
16. Hua, Y., Zhao, K., Tao, G., Dai, C. & Su, Y. miR-25 promotes metastasis via targeting FBXW7 in esophageal squamous cell carcinoma. *Oncol. Rep.* **38**, 3030–3038 (2017).
17. Yang, C. et al. Down-regulated miR-26a promotes proliferation, migration, and invasion via negative regulation of MTDH in esophageal squamous cell carcinoma. *FASEB J.* **31**, 2114–2122 (2017).
18. Yang, S. et al. Construction of differential mRNA-lncRNA crosstalk networks based on ceRNA hypothesis uncover key roles of lncRNAs implicated in esophageal squamous cell carcinoma. *Oncotarget* **7**, 85728–85740 (2016).
19. Qi, B. et al. Down-regulation of miR-30a-3p/5p promotes esophageal squamous cell carcinoma cell proliferation by activating the Wnt signaling pathway. *World J. Gastroenterol.* **23**, 7965–7977 (2017).
20. Li, Q., Zhang, X., Li, N., Liu, Q. & Chen, D. miR-30b inhibits cancer cell growth, migration, and invasion by targeting homeobox A1 in esophageal cancer. *Biochem. Biophys. Res. Commun.* **485**, 506–512 (2017).
21. Ma, T. et al. MicroRNA-30c functions as a tumor suppressor via targeting SNAIL in esophageal squamous cell carcinoma. *Biomed. Pharmacother.* **98**, 680–686 (2018).
22. Lin, R. J. et al. MiR-142-3p as a potential prognostic biomarker for esophageal squamous cell carcinoma. *J. Surg. Oncol.* **105**, 175–182 (2012).
23. Cui, X. B. et al. MicroRNA-34a functions as a tumor suppressor by directly targeting oncogenic PLCE1 in Kazakh esophageal squamous cell carcinoma. *Oncotarget* **8**, 92454–92469 (2017).
24. Lin, X., Xu, X. Y., Chen, Q. S. & Huang, C. Clinical significance of microRNA-34a in esophageal squamous cell carcinoma. *Genet. Mol. Res.* **14**, 17684–17691 (2015).
25. Chen, Z. L. et al. microRNA-92a promotes lymph node metastasis of human esophageal squamous cell carcinoma via E-cadherin. *J. Biol. Chem.* **286**, 10725–10734 (2011).

26. Ma, G. et al. MicroRNA-92b represses invasion-metastasis cascade of esophageal squamous cell carcinoma. *Oncotarget* **7**, 20209–20222 (2016).
27. Sun, J. et al. MicroRNA-99a/100 promotes apoptosis by targeting mTOR in human esophageal squamous cell carcinoma. *Med. Oncol.* **30**, 411 (2013).
28. Zhou, S. et al. Prognostic value of microRNA-100 in esophageal squamous cell carcinoma. *J. Surg. Res.* **192**, 515–520 (2014).
29. Feber, A. et al. MicroRNA prognostic signature for nodal metastases and survival in esophageal adenocarcinoma. *Ann. Thorac. Surg.* **91**, 1523–1530 (2011).
30. Okumura, T. et al. The expression of microRNA 574-3p as a predictor of postoperative outcome in patients with esophageal squamous cell carcinoma. *World J. Surg. Oncol.* **14**, 228 (2016).
31. Zhao, L. et al. Tumor suppressor miR-128-3p inhibits metastasis and epithelial-mesenchymal transition by targeting ZEB1 in esophageal squamous-cell cancer. *Acta Biochim. Biophys. Sin. (Shanghai)*. **50**, 171–180 (2018).
32. Akanuma, N. et al. MicroRNA-133a regulates the mRNAs of two invadopodia-related proteins, FSCN1 and MMP14, in esophageal cancer. *Br. J. Cancer* **110**, 189–198 (2014).
33. Gao, S. H., Liu, J., Zhang, H. J., Zhao, N. & Zhang, J. Low miR-133a expression is a predictor of outcome in patients with esophageal squamous cell cancer. *Eur. Rev. Med. Pharmacol. Sci.* **20**, 3788–3792 (2016).
34. Lin, C. et al. Functional role of a novel long noncoding RNA TTN-AS1 in esophageal squamous cell carcinoma progression and metastasis. *Clin. Cancer Res.* **24**, 486–498 (2018).
35. Gong, H. et al. Downregulation of miR-138 sustains NF-κB activation and promotes lipid raft formation in esophageal squamous cell carcinoma. *Clin. Cancer Res.* **19**, 1083–1093 (2013).
36. Zheng, S., Zhang, X., Wang, X. & Li, J. Downregulation of miR-138 predicts poor prognosis in patients with esophageal squamous cell carcinoma. *Cancer Biomark.* **20**, 49–54 (2017).
37. He, Z. et al. MiR-143-3p functions as a tumor suppressor by regulating cell proliferation, invasion and epithelial-mesenchymal transition by targeting QKI-5 in esophageal squamous cell carcinoma. *Mol. Cancer* **15**, 51 (2016).
38. Wang, Y. et al. MicroRNA expression in esophageal squamous cell carcinoma: Novel diagnostic and prognostic biomarkers. *Mol. Med. Rep.* **15**, 3833–3839 (2017).
39. Wang, C. et al. Prognostic and diagnostic potential of miR-146a in oesophageal squamous cell carcinoma. *Br. J. Cancer* **114**, 290–297 (2016).
40. Hezova, R. et al. Diagnostic and prognostic potential of miR-21, miR-29c, miR-148 and miR-203 in adenocarcinoma and squamous cell carcinoma of esophagus. *Diagn. Pathol.* **10**, 42 (2015).
41. Yokobori, T. et al. MiR-150 is associated with poor prognosis in esophageal squamous cell carcinoma via targeting the EMT inducer ZEB1. *Cancer Sci.* **104**, 48–54 (2013).
42. Xiang, Z., Dong, X., Sun, Q., Li, X. & Yan, B. Clinical significance of up-regulated miR-181a in prognosis and progression of esophageal cancer. *Acta Biochim. Biophys. Sin. (Shanghai)*. **46**, 1007–1010 (2014).
43. Gao, X. et al. Overexpression of miR-191 predicts poor prognosis and promotes proliferation and invasion in esophageal squamous cell carcinoma. *Yonsei Med. J.* **58**, 1101–1110 (2017).
44. Sun, N., Ye, L., Chang, T., Li, X. & Li, X. microRNA-195-Cdc42 axis acts as a prognostic factor of esophageal squamous cell carcinoma. *Int. J. Clin. Exp. Pathol.* **7**, 6871–6879 (2014).
45. Wang, T. Y. et al. Implications of microRNA-197 downregulated expression in esophageal cancer with poor prognosis. *Genet. Mol. Res.* **13**, 5574–5581 (2014).
46. Qi, B. et al. Involvement of microRNA-198 overexpression in the poor prognosis of esophageal cancer. *Asian Pac. J. Cancer Prev.* **14**, 5073–5076 (2013).
47. Zhang, H. F. et al. miR-200b suppresses invasiveness and modulates the cytoskeletal and adhesive machinery in esophageal squamous cell carcinoma cells via targeting Kindlin-2. *Carcinogenesis* **35**, 292–301 (2014).
48. Liu, Y. et al. Methylation-mediated repression of potential tumor suppressor miR-203a and miR-203b contributes to esophageal squamous cell carcinoma development. *Tumour Biol.* **37**, 5621–5632 (2016).
49. Okumura, T. et al. MicroRNA-203 inhibits the progression of esophageal squamous cell carcinoma with restored epithelial tissue architecture in vivo. *Int. J. Oncol.* **44**, 1923–1932 (2014).
50. Qi, Q. et al. Hypermethylation and low expression of miR-203 in patients with esophageal cancer in Chinese population. *Int. J. Clin. Exp. Pathol.* **9**, 6245–6251 (2016).
51. Hezova, R. et al. MiR-205 functions as a tumor suppressor in adenocarcinoma and an oncogene in squamous cell carcinoma of esophagus. *Tumour Biol.* **37**, 8007–8018 (2016).
52. Pan, F. et al. Sp1-mediated transcriptional activation of miR-205 promotes radioresistance in esophageal squamous cell carcinoma. *Oncotarget* **8**, 5735–5752 (2017).
53. Qi, B. et al. Overregulation of microRNA-212 in the poor prognosis of esophageal cancer patients. *Genet. Mol. Res.* **13**, 7800–7807 (2014).
54. Zhou, Y. & Hong, L. Prediction value of miR-483 and miR-214 in prognosis and multidrug resistance of esophageal squamous cell carcinoma. *Genet. Test. Mol. Biomark.* **17**, 470–474 (2013).
55. Kurashige, J. et al. Overexpression of microRNA-223 regulates the ubiquitin ligase FBXW7 in oesophageal squamous cell carcinoma. *Br. J. Cancer* **106**, 182–188 (2012).
56. Zhang, B. J., Gong, H. Y., Zheng, F., Liu, D. J. & Liu, H. X. Up-regulation of miR-335 predicts a favorable prognosis in esophageal squamous cell carcinoma. *Int. J. Clin. Exp. Pathol.* **7**, 6213–6218 (2014).
57. Kong, K. L. et al. MicroRNA-375 inhibits tumour growth and metastasis in oesophageal squamous cell carcinoma through repressing insulin-like growth factor 1 receptor. *Gut* **61**, 33–42 (2012).
58. Li, J. et al. Cell-specific detection of miR-375 downregulation for predicting the prognosis of esophageal squamous cell carcinoma by miRNA in situ hybridization. *PLoS ONE* **8**, e53582 (2013).
59. Isozaki, Y. et al. Usefulness of microRNA-375 as a prognostic and therapeutic tool in esophageal squamous cell carcinoma. *Int. J. Oncol.* **46**, 1059–1066 (2015).
60. Li, B. et al. MicroRNA-377 suppresses initiation and progression of esophageal cancer by inhibiting CD133 and VEGF. *Oncogene* **36**, 3986–4000 (2017).
61. Qi, B. et al. Downregulation of microRNA-382 is associated with poor outcome of esophageal squamous cell carcinoma. *World J. Gastroenterol.* **21**, 6884–6891 (2015).
62. Liu, A. et al. Antagonizing miR-455-3p inhibits chemoresistance and aggressiveness in esophageal squamous cell carcinoma. *Mol. Cancer* **16**, 106 (2017).
63. Yang, H., Wei, Y. N., Zhou, J., Hao, T. T. & Liu, X. L. MiR-455-3p acts as a prognostic marker and inhibits the proliferation and invasion of esophageal squamous cell carcinoma by targeting FAM83F. *Eur. Rev. Med. Pharmacol. Sci.* **21**, 3200–3206 (2017).
64. Xue, L. et al. Upregulated miR-483-5p expression as a prognostic biomarker for esophageal squamous cell carcinoma. *Cancer Biomark.* **19**, 193–197 (2017).
65. Ren, C. et al. miR-486-5p expression pattern in esophageal squamous cell carcinoma, gastric cancer and its prognostic value. *Oncotarget* **7**, 15840–15853 (2016).
66. Mao, Y., Li, L., Liu, J., Wang, L. & Zhou, Y. MiR-495 inhibits esophageal squamous cell carcinoma progression by targeting Akt1. *Oncotarget* **7**, 51223–51236 (2016).
67. Islam, F. et al. MiR-498 in esophageal squamous cell carcinoma: clinicopathological impacts and functional interactions. *Hum. Pathol.* **62**, 141–151 (2017).
68. Lin, C. et al. miR-508 sustains phosphoinositide signalling and promotes aggressive phenotype of oesophageal squamous cell carcinoma. *Nat. Commun.* **5**, 4620 (2014).
69. Chen, Z. et al. Up-regulated miR-548k promotes esophageal squamous cell carcinoma progression via targeting long noncoding RNA-LET. *Exp. Cell Res.* **362**, 90–101 (2018).
70. Guan, S. et al. MiR-613: a novel diagnostic and prognostic biomarker for patients with esophageal squamous cell carcinoma. *Tumour Biol.* **37**, 4383–4391 (2016).
71. Song, C. et al. MiR-622 functions as a tumor suppressor and directly targets E2F1 in human esophageal squamous cell carcinoma. *Biomed. Pharmacother.* **83**, 843–849 (2016).
72. Li, C. et al. The decreased expression of miR-625 predicts poor prognosis of esophageal squamous cell carcinoma. *Int. J. Clin. Exp. Med.* **8**, 9560–9564 (2015).
73. Jin, L. et al. MiR-630 inhibits invasion and metastasis in esophageal squamous cell carcinoma. *Acta Biochim. Biophys. Sin. (Shanghai)*. **48**, 810–819 (2016).

74. Zhang, J. X. et al. Downregulation of MicroRNA-644a promotes esophageal squamous cell carcinoma aggressiveness and stem cell-like phenotype via dysregulation of PITX2. *Clin. Cancer Res.* **23**, 298–310 (2017).
75. Harazono, Y. et al. miR-655 is an EMT-suppressive microRNA targeting ZEB1 and TGFBR2. *PLoS ONE* **8**, e62757 (2013).
76. Wang, Y. et al. Mir-655 up-regulation suppresses cell invasion by targeting pituitary tumor-transforming gene-1 in esophageal squamous cell carcinoma. *J. Transl. Med.* **11**, 301 (2013).
77. Zhou, Y. W. et al. miR-675-5p enhances tumorigenesis and metastasis of esophageal squamous cell carcinoma by targeting REPS2. *Oncotarget* **7**, 30730–30747 (2016).
78. Ge, C. et al. miR-942 promotes cancer stem cell-like traits in esophageal squamous cell carcinoma through activation of Wnt/ β -catenin signalling pathway. *Oncotarget* **6**, 10964–10977 (2015).
79. Gopalan, V. et al. Overexpression of microRNA-1288 in oesophageal squamous cell carcinoma. *Exp. Cell Res.* **348**, 146–154 (2016).
80. Xie, R. et al. Prognostic value of combined and individual expression of microRNA-1290 and its target gene nuclear factor I χ in human esophageal squamous cell carcinoma. *Cancer Biomark.* **20**, 325–331 (2017).
81. Liu, K, Li, L, Rusidanmu, A, Wang, Y, & Lv, X. Down-regulation of miR-1294 is related to dismal prognosis of patients with esophageal squamous cell carcinoma through elevating C-MYC expression. *Cell. Physiol. Biochem.* **36**, 100–110 (2015).
82. Liu, J. et al. Low expression of miR-1469 predicts disease progression and unfavorable post-surgical clinical outcomes in patients with esophageal squamous cell cancer. *Oncol. Lett.* **13**, 4469–4474 (2017).
83. Wang, C. et al. Clinical potential of miR-3651 as a novel prognostic biomarker for esophageal squamous cell cancer. *Biochem. Biophys. Res. Commun.* **465**, 30–34 (2015).
84. Qin, H. D. et al. Genomic characterization of esophageal squamous cell carcinoma reveals critical genes underlying tumorigenesis and poor prognosis. *Am. J. Hum. Genet.* **98**, 709–727 (2016).
85. Cui, Y, Xue, Y, Dong, S, & Zhang, P. Plasma microRNA-9 as a diagnostic and prognostic biomarker in patients with esophageal squamous cell carcinoma. *J. Int. Med. Res.* **45**, 1310–1317 (2017).
86. Li, J, Li, M, Gao, F, & Ge, X. Serum microRNA-15a level acts as a potential diagnostic and prognostic biomarker for human esophageal squamous cell carcinoma. *Cancer Biomark.* **18**, 11–17 (2017).
87. Li, B. X., Yu, Q., Shi, Z. L., Li, P. & Fu, S. Circulating microRNAs in esophageal squamous cell carcinoma: association with locoregional staging and survival. *Int. J. Clin. Exp. Med.* **8**, 7241–7250 (2015).
88. Yu, Q. et al. Plasma microRNAs to predict the response of radiotherapy in esophageal squamous cell carcinoma patients. *Am. J. Transl. Res.* **7**, 2060–2071 (2015).
89. Lv, H, He, Z, Wang, H, Du, T, & Pang, Z. Differential expression of miR-21 and miR-75 in esophageal carcinoma patients and its clinical implication. *Am. J. Transl. Res.* **8**, 3288–3298 (2016).
90. Wu, C. et al. Diagnostic and prognostic implications of a serum miRNA panel in oesophageal squamous cell carcinoma. *PLoS ONE* **9**, e92292 (2014).
91. Wu, C., Li, M., Hu, C. & Duan, H. Clinical significance of serum miR-223, miR-25 and miR-375 in patients with esophageal squamous cell carcinoma. *Mol. Biol. Rep.* **41**, 1257–1266 (2014).
92. Zhang, B. et al. Pemetrexed plus dendritic cells as third-line therapy for metastatic esophageal squamous cell carcinoma. *Oncol. Targets Ther.* **9**, 3901–3906 (2016).
93. Chan, C. M. et al. Serum microRNA-193b as a promising biomarker for prediction of chemoradiation sensitivity in esophageal squamous cell carcinoma patients. *Oncol. Lett.* **15**, 3273–3280 (2018).
94. Yu, H. et al. Serum miR-200c and clinical outcome of patients with advanced esophageal squamous cancer receiving platinum-based chemotherapy. *Am. J. Transl. Res.* **6**, 71–77 (2013).
95. Sun, J., Song, K., Feng, X. & Gao, S. MicroRNA-367 is a potential diagnostic biomarker for patients with esophageal squamous cell carcinoma. *Biochem. Biophys. Res. Commun.* **473**, 363–369 (2016).
96. Takeshita, N. et al. Serum microRNA expression profile: miR-1246 as a novel diagnostic and prognostic biomarker for oesophageal squamous cell carcinoma. *Br. J. Cancer* **108**, 644–652 (2013).
97. Global Burden of Disease Cancer Collaboration et al. Global, regional, and national cancer incidence, mortality, years of life lost, years lived with disability, and disability-adjusted life-years for 29 cancer groups, 1990 to 2016: a systematic analysis for the Global Burden of Disease Study. *JAMA Oncol.* <https://doi.org/10.1001/jamaoncol.2018.2706> 2018.
98. Pohl, H. & Welch, H. G. The role of overdiagnosis and reclassification in the marked increase of esophageal adenocarcinoma incidence. *J. Natl. Cancer Inst.* **97**, 142–146 (2005).
99. Djebali, S. et al. Landscape of transcription in human cells. *Nature* **489**, 101–108 (2012).
100. Lopez-Camarillo, C. et al. MetastamiRs: non-coding microRNAs driving cancer invasion and metastasis. *Int. J. Mol. Sci.* **13**, 1347–1379 (2012).
101. Ventura, A. & Jacks, T. MicroRNAs and cancer: short RNAs go a long way. *Cell* **136**, 586–591 (2009).
102. Stang, A. Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. *Eur. J. Epidemiol.* **25**, 603–605 (2010).
103. Wong, W. C., Cheung, C. S. & Hart, G. J. Development of a quality assessment tool for systematic reviews of observational studies (QATSO) of HIV prevalence in men having sex with men and associated risk behaviours. *Emerg. Themes Epidemiol.* **5**, 23 (2008).
104. Tierney, J. F., Stewart, L. A., Ghersi, D., Burdett, S. & Sydes, M. R. Practical methods for incorporating summary time-to-event data into meta-analysis. *Trials* **8**, 16 (2007).
105. Lin, C. H. et al. MiR-193a-5p/ERBB2 act as concurrent chemoradiation therapy response indicator of esophageal squamous cell carcinoma. *Oncotarget* **7**, 39680–39693 (2016).