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REVIEW ARTICLE

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Long non-coding RNA MIR31HG as a prognostic predictor for malignant cancers: A meta- and bioinformatics analysis

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Abstract

Background: The possible regulatory mechanism of MIR31HG in human cancers remains unclear, and reported results of the prognostic significance of MIR31HG expression are inconsistent.

Methods: The meta-analysis and related bioinformatics analysis were conducted to evaluate the role of MIR31HG in tumor progression.

Results: The result showed that high MIR31HG expression was not related to prognosis. However, in the stratified analysis, we found that the overexpression of MIR31HG resulted in worse OS, advanced TNM stage, and tumor differentiation in respiratory system cancers. Moreover, our results also found that MIR31HG overexpression was related to shorter OS in cervical cancer patients and head and neck tumors. In contrast, the MIR31HG was lower in digestive system tumors which contributed to shorter overall survival, advanced TNM stage, and distant metastasis. Furthermore, the bioinformatics analysis showed that MIR31HG was highly expressed in normal urinary bladder, small intestine, esophagus, stomach, and duodenum and low in colon, lung, and ovary. The results obtained from FireBrowse indicated that MIR31HG was highly expressed in LUSC, CESC, HNSC, and LUAD and low in STAD and BLCA. Gene Ontology analysis showed that the co-expressed genes of MIR31HG were most enriched in the biological processes of peptide metabolism and KEGG pathways were most enriched in Ras, Rap1, and PI3K-Akt signaling pathway.

Conclusion: MIR31HG may serve as a potential biomarker in human cancers.

KEYWORDS
bioinformatics analysis, cancer, meta-analysis, MIR31HG, prognostic biomarker

Yuanfeng Wei, Yingjie Zhai and Xiaoang Liu are co-first authors.

1 | INTRODUCTION

Cancer has become one of the main public health problems, which served as the leading cause of morbidity and mortality in globally.[1] According to Global Cancer Statistics 2018, it was predicted that there were 18.1 million new cancer cases and 9.6 million cancer deaths.[2] Although radiotherapy, surgery, chemotherapy, immune therapy, and the application of molecular-targeted drugs provide various means for treatment of cancer.[3] However, the overall survival (OS) rate is still not optimistic for most types of cancer, and the majority of patients with cancer have a poor prognosis.[4] Therefore, it is urgent and critically important to find novel prognostic biomarkers to provide useful therapeutic strategies for cancers.

Long non-coding RNAs, without protein coding ability and the length >200 nucleotides, play crucial roles in various biological processes, including protein function, post-transcriptional mRNA processing, chromatin modification, modulating gene expression, and controlling gene transcription.[5,6] MIR31HG, which was previously known as LncHIFCAR or LOC554202, acts as a host gene for miR-31. Recently, MIR31HG attracted increasing interest because of its aberrant expression in a series of human cancers. Chen et al discovered that Loc554202 was up-regulated in cervical cancer (CC) tissues and the overexpression of Loc554202 predicted a shorter OS.[7] In addition, up-regulated MIR31HG expression was observed in NSCLC,[8] oral squamous cell carcinoma (OSCC),[9] laryngeal squamous cell cancer (LSCC),[10] breast cancer (BC),[11] pancreatic ductal adenocarcinoma (PDAC),[12] and esophageal squamous cell carcinoma (ESCC),[13] leading to short survival time and poor clinicopathologic features. In contrast, some articles demonstrated that low MIR31HG expression was associated with reduced survival rates in gastric cancer (GC),[14] ESCC,[15] hepatocellular carcinoma (HCC),[16] and colorectal cancer (CRC).[17]

Accumulating evidence indicated that MIR31HG might be a potential biomarker to predict the prognosis of tumors. However, the reported results of prognostic significance of MIR31HG in cancers are controversial. Therefore, this meta-analysis was performed to explore the prognostic value of lncRNA MIR31HG expression in tumors. Moreover, the related bioinformatics analysis was applied to further explore the possible regulatory mechanisms of MIR31HG in tumor progression.

2 | MATERIALS AND METHODS

2.1 | Search strategy

A literature search was conducted on four electronic databases, including PubMed, EMBASE, Web of Science, and Cochrane Library (up to July 25, 2019). The searched terms were ("MIR31HG" or "LOC554202" or "the host gene of miR-31" or "the MIR31 host gene" or "microRNA-31 host gene" or "LncRNA HIFCAR") and ("Tumor" or "cancer").

2.2 | Inclusion and exclusion criteria

The inclusion criteria were as follows: (1) articles explored the association between MIR31HG and cancer prognosis, (2) the hazard ratios (HRs) for the OS could be extracted and calculated through the K-M curves or directly provided in the article, (3) reported the correlation of MIR31HG expression and clinicopathological features, (4) high and low MIR31HG expression in patients, and (5) full-text was available.

Exclusion criteria were as follows: (1) comments, reviews, and case reports; (2) cell or animal experiments; (3) sample <20 cases; (4) the data were obtained from TCGA database or other database without qRT-PCR validation; and (5) insufficient data.

2.3 | Quality assessment

The quality of included studies was assessed by The Newcastle–Ottawa Scale (NOS) criteria. This important process was independently operated by two authors. A consensus was reached by a third author when they had any disagreements. The high-quality article is one with NOS ≥6 scores.

2.4 | Data extraction

Two authors independently screened each included article and extracted the essential information, which are summarized in Table 1. When univariate and multivariate analyses were provided in the study, the data were extracted from multivariate analysis. Engauge Digitizer 4.1 (http://digitizer.sourceforge.net/) was used to extracted HR and 95% CI from survival curves.[18]

2.5 | Statistical analysis

MIR31HG expression and cancer prognosis were estimated by HRs and 95% CIs. Moreover, the correlation between MIR31HG expression and clinical features was conducted by ORs and 95% CIs. The heterogeneity among articles was determined by I^2 value and a p-value. If $I^2 \leq 50\%$ or $p \geq 0.05$, the fixed-effects model was applied; otherwise, a random-effects model was used. Publication bias was evaluated by funnel plot. The sensitivity analysis was conducted to evaluate the stability of results. Moreover, $p < 0.05$ was regarded statistically significant.

2.6 | Bioinformatics analysis

The National Center for Biotechnology Information (NCBI) Gene integrates information from a wide range of species (https://www.ncbi.nlm.nih.gov/gene/). In our study, we used it to clarify the

TABLE 1 Main characteristics of the selected studies

Author	Year	Country	Tumor type	Cases/Controls	Detection methods	Internal control	Cutoff value	Outcome	HR (95% CI) High/Low	NOS
Chen J	2017	China	CC	120/120	qRT-PCR	GAPDH	Median	OS	2.875 (1.539–3.536)	7
Ding J	2015	China	CRC	48/48	qRT-PCR	GAPDH	Median	NA	NA	6
Dandan W	2019	China	NSCLC	50/50	qRT-PCR	GAPDH	Median	OS	2.398 (1.292–3.205)	7
He A	2016	China	BC	55/55	qRT-PCR	GAPDH	Median	NA	NA	6
Nie FQ	2015	China	GC	42/42	qRT-PCR	GAPDH	Median	OS	0.411 (0.236–0.716)	7
Qin J	2018	China	LUAD	132/20	qRT-PCR	GAPDH	Median	OS	1.734(1.043–2.882)	6
Ren ZP	2017	China	ESCC	185/185	qRT-PCR	GAPDH	Median	OS	0.448 (0.256–0.894)	7
Shih JW	2017	Taiwan, China	OSCC	42/42	qRT-PCR	GAPDH	Fold changes	OS	2.239 (0.719–6.966)	6
Sui J	2018	China	LUAD	43/43	qRT-PCR	GAPDH	Fold changes	OS	1.665 (1.129–2.454)	6
Wang R	2018	China	LSCC	60/60	qRT-PCR	18s rRNA	Median	OS	4.170 (1.069–16.268)	7
Yan S	2018	China	HCC	42/42	qRT-PCR	GAPDH	Median	NA	0.396 (0.228–0.688)	7
Yang L	2016	China	CRC	178/178	qRT-PCR	β-actin	Median	OS	0.408 (0.129–0.747)	8
Zheng S	2019	China	NSCLC	88/88	qRT-PCR	GAPDH	Median	OS	2.147 (1.235–3.733)	7

Abbreviations: BC, bladder cancer; CC, cervical cancer; CI, confidence interval; CRC, colorectal cancer; ESCC, esophageal squamous cell carcinoma; GC, gastric cancer; HCC, hepatocellular carcinoma; HR, hazard ratio; LSCC, laryngeal squamous cell cancer; LUAD, lung adenocarcinoma; NA, not available; NSCLC, non-small-cell lung cancer; OS, overall survival; OSCC, oral squamous cell carcinoma.

MIR31HG expression in different normal tissues. MIR31HG expression in carcinoma and adjacent tissues from FireBrowse (http://firebrowse.org/), an interactive web-based TCGA database. In this study, it was applied to analyze the tumor/normal differential MIR31HG expression. GEPIA (http://gepia.cancer-pku.cn/) database as a tool to analyze the relevance MIR31HG with OS in TCGA dataset.

2.7 | Functional analysis of lncRNA MIR31HG

Co-expressed genes of MIR31HG were identified by the MEM web (http://biit.cs.ut.ee/mem/) in Human Genome U133 Plus 2.0.[19] These co-expressed genes were ranked according to a score of significance by the MEM tool. The top 100 co-expressed genes of MIR31HG were selected for the advanced analysis. Subsequently, Gene Ontology (GO) analysis was conducted using the Functional Enrichment Analysis tool (FunRich 3.1.3).[20] Results from KEGG were obtained through KOBAS 3.0 (kobas.cbi.pku.edu.cn/),[21] which is a web used to annotate input genes and identify pathways involved.

3 | RESULTS

3.1 | Study characteristics

The details about the screening process of MIR31HG are shown in Figure 1. Finally, 13 studies were included in this article. The included studies were involved in nine types of cancer, including NSCLC (n = 2),[8,22] lung adenocarcinoma (LUAD, n = 2),[23,24] ESCC (n = 1),[15] GC (n = 1),[14] HCC (n = 1),[16] CRC (n = 2),[17,25] OSCC (n = 1),[9] LSCC (n = 1),[10] BC (n = 1),[26] CC (n = 1).[7] The detail of the included articles is summarized in Table 1. The studies were of good quality that confirmed by the NOS scoring system.

3.2 | MIR31HG expression and survival

Eleven studies were included for OS. The result showed that the expression of MIR31HG was not associated with prognosis (HR = 1.21, 95% CI: 0.73–2.01, p = 0.45; Figure 2A). However, there is significant heterogeneity among studies (I^2 = 86%); then, a random-effects model was used. The funnel plot showed no significant evidence of publication bias (Figure 2B).

Considering the heterogeneity, subgroup meta-analysis was performed to explore whether type of cancers was the reason. There were four studies that provided an OS for digestive system cancers, four studies for respiratory system cancers, two articles for head and neck tumors, and one for cervical cancer. In the stratified analysis, we found that overexpression MIR31HG had worse OS of the patients with respiratory system cancers (HR = 1.87, 95% CI: 1.46–2.40, p < 0.00001; Figure 3). Moreover, MIR31HG overexpression was also associated with shorter OS in head and neck tumors (HR = 2.89, 95% CI: 1.21–6.91, p = 0.02; Figure 3) and cervical cancer

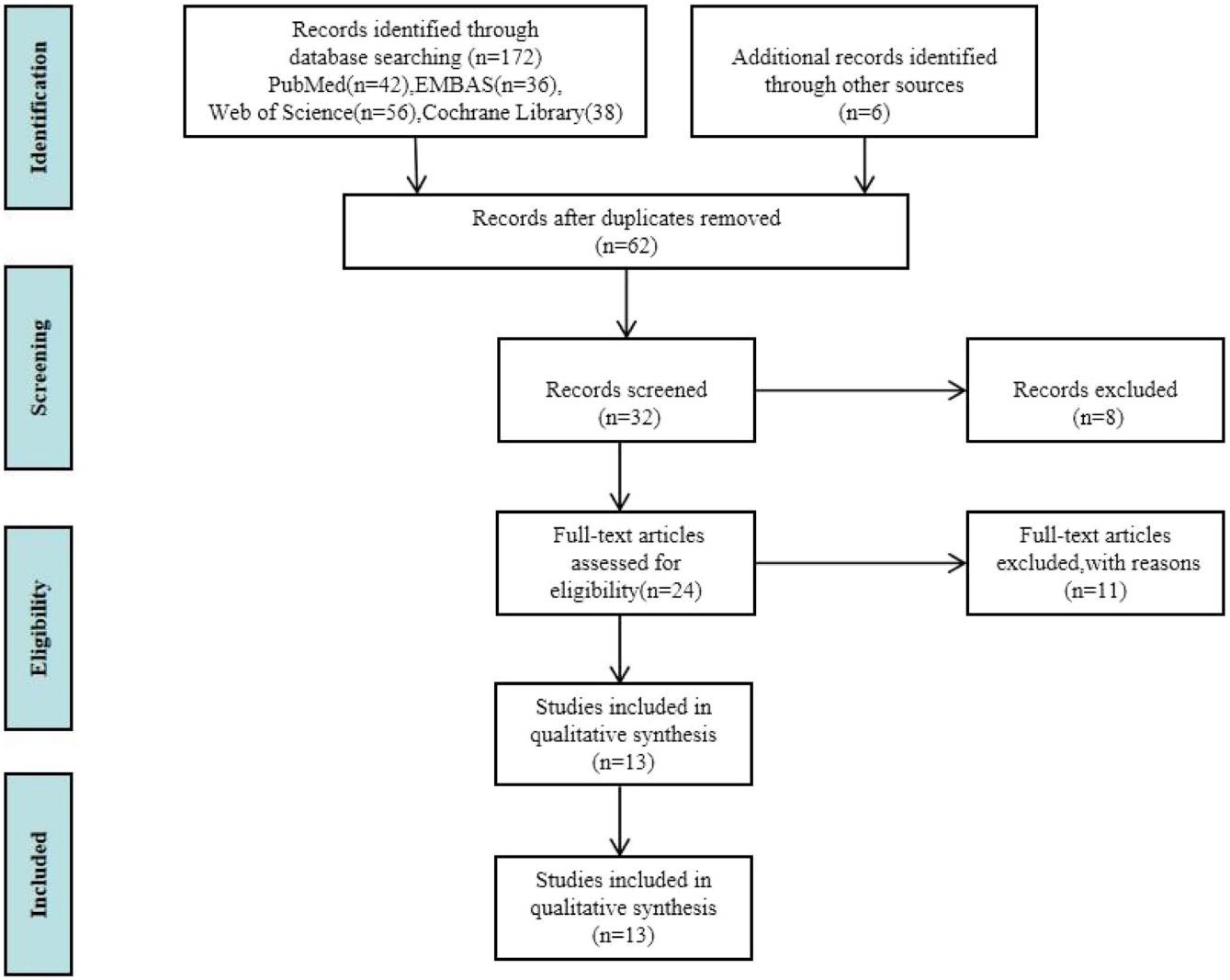


FIGURE 1 Flow diagram of the study search and selection process in the meta-analysis

patients (HR = 2.88, 95% CI: 1.54–5.37; $p = 0.0009$; Figure 3). In contrast, the pooled results revealed that the low MIR31HG expression was significantly related to shorter OS in digestive system tumors (HR = 0.42, 95% CI: 0.31–0.57, $p < 0.00001$; Figure 3). There was no significant publication bias in different systems of cancers, performed by funnel plot (Figure 4).

3.3 | MIR31HG expression and clinicopathological characteristics of cancer

In respiratory system cancers, high MIR31HG1 expression was related to tumor differentiation (OR = 4.12, 95% CI: 2.39–7.10, $p < 0.00001$; Figure 5B) and advanced TNM stage (OR = 6.28, 95% CI: 3.55–11.10, $p < 0.00001$; Figure 5A). There was no significant association between MIR31HG expression and lymph node metastasis, age, tumor size, or gender, which are summarized in Table 2. In contrast, Table 3 and Figure 6 presents that patient with low expression of MIR31HG was related to advanced TNM stage (OR = 0.32, 95% CI: 0.22–0.47, $p < 0.00001$; Figure 6A), and distant recurrence (OR = 0.39, 95% CI: 0.21–0.73, $p = 0.003$; Figure 6B) in digestive system tumors. Subsequently, the publication bias is presented in Figures 7 and 8.

3.4 | Sensitivity analysis

The sensitivity analysis is important for the reliability of the results. Because of the significant heterogeneity in over survival ($p < 0.00001$, $I^2 = 86\%$), we excluded the article one by one for sensitivity analysis. As presented in Table 4, after removing any single study, the pooled HR was not significantly affected.

3.5 | Validation of the results by Bioinformatics analysis

To exploring the potential functional impact of MIR31HG expression on cancers, we evaluated its level in different normal tissues

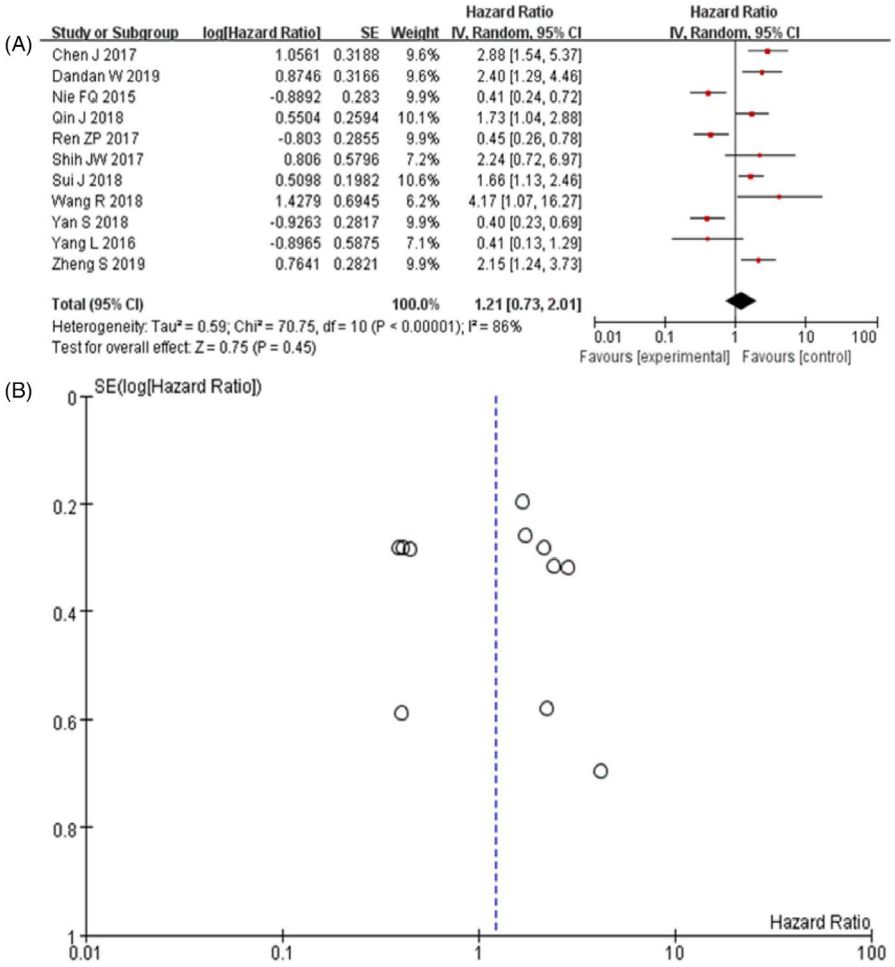


FIGURE 2 FIGURE Forest plots for the association between MIR31HG and OS (A) of tumors. Funnel plot (B) for publication bias of MIR31HG and OS. Funnel plot showing the relation hazard ratio (HR) and standard error (log HR). Abbreviations: CI, confidence interval; OS, overall survival; SE, standard error

from NCBI Gene. The project title is HPA RNA-seq normal tissues (BioProject: PRJEB4337). As shown in Figure 9, MIR31HG was highly expressed in urinary bladder, small intestine, esophagus, stomach, and duodenum and was low in colon, lung, and ovary. The results obtained from FireBrowse indicated that MIR31HG was highly expressed in some tumor tissues, such as LUSC, CESC, HNSC, and LUAD, and expressed lower in STAD and BLCA (Figure 10). Then, we accessed the relationship of MIR31HG expression with OS in cancers included in TCGA dataset. As shown in Figure 11, based on median expression of MIR31HG, 9,411 patients in all were separated into high or low expression group, patient with the high expression MIR31HG was not associated with prognosis compared to the low expression group, which was consistent with the results of our meta- analysis.

3.6 | Analysis of co-expressed genes of lncRNA MIR31HG in human tumors

To questing the potential biological functions of MIR31HG, the top 100 co-expressed genes of MIR31HG were selected, which was shown in Figure 12. Next, we performed the Gene Ontology (GO) and KEGG pathways enrichment analysis based on the top 100 co-expressed target genes. Gene Ontology terms enrichment analysis showed that the most significantly enriched on biological processes (BP) were peptide metabolism, glycosaminoglycan metabolism, immune cell migration, signal transduction, and cell communication. In addition, cellular components (CC) and molecular functions (MF) are also presented in Figure 13. The results of KEGG analysis revealed that the target genes were enriched in PI3K-Akt signaling pathway, Rap1 signaling pathway, Ras signaling pathway, and so on (Figure 14). The most significant pathways are summarized in Table 5.

4 | DISCUSSION

Emerging evidences have demonstrated that abnormal lncRNA expression was related to human diseases, especially cancer.[27,28] Moreover, lncRNAs play crucial roles in gene regulation and thus act as an oncogene or tumor suppressor via both oncogenic and tumor-suppressive pathways.[29] Some studies reported that lncRNAs were promising to be the new tumor biomarker for prognosis and diagnostic of tumors.[28,30-33] Recently, dysregulation of MIR31HG has been reported in cervical cancer,[7] GC,[14] LSCC,[10] and other types of cancer. The expression levels and prognostic value of MIR31HG

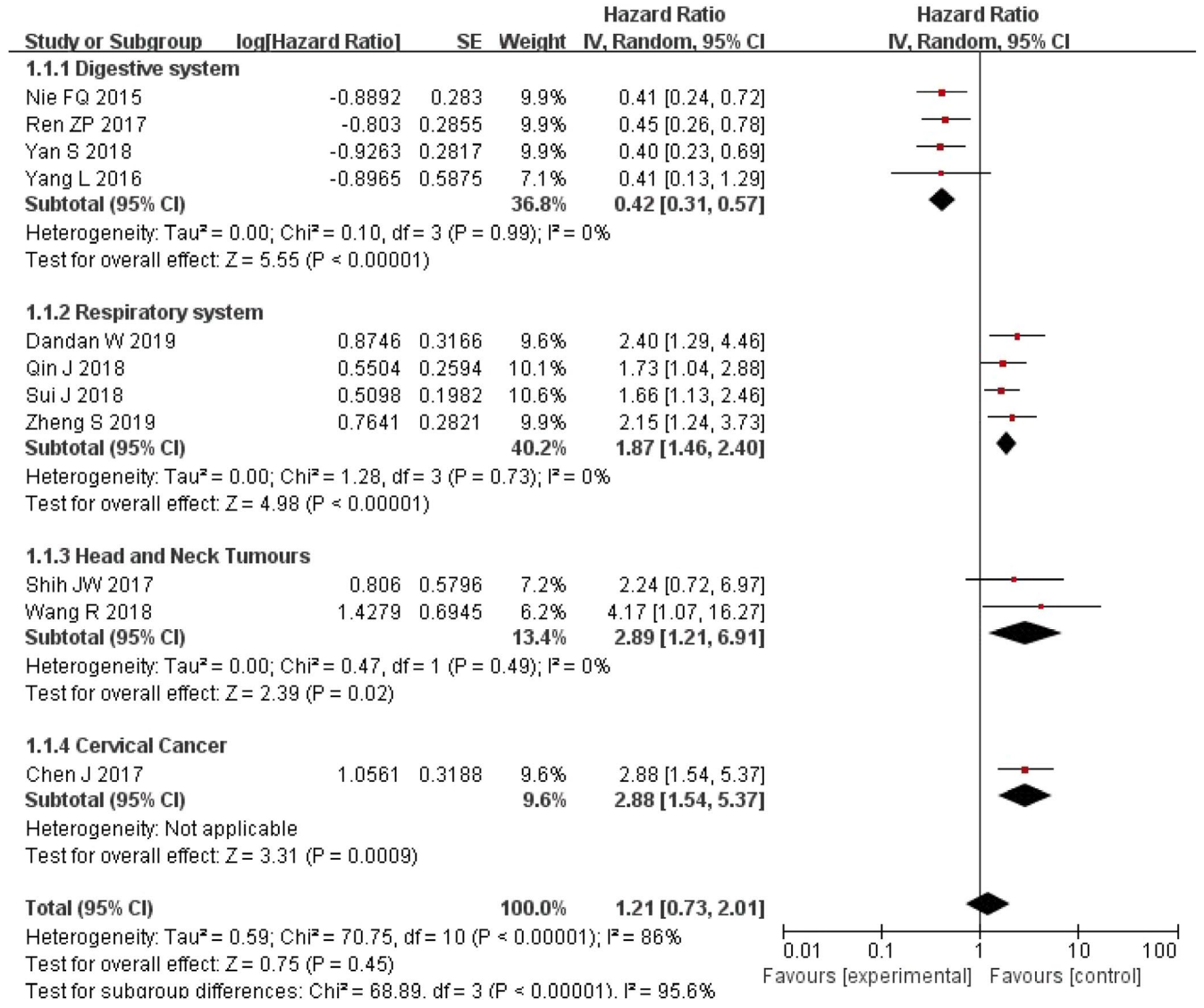


FIGURE 3 Forrest plot of the hazard ratio for the association of MIR31HG expression with OS by subgroup analysis

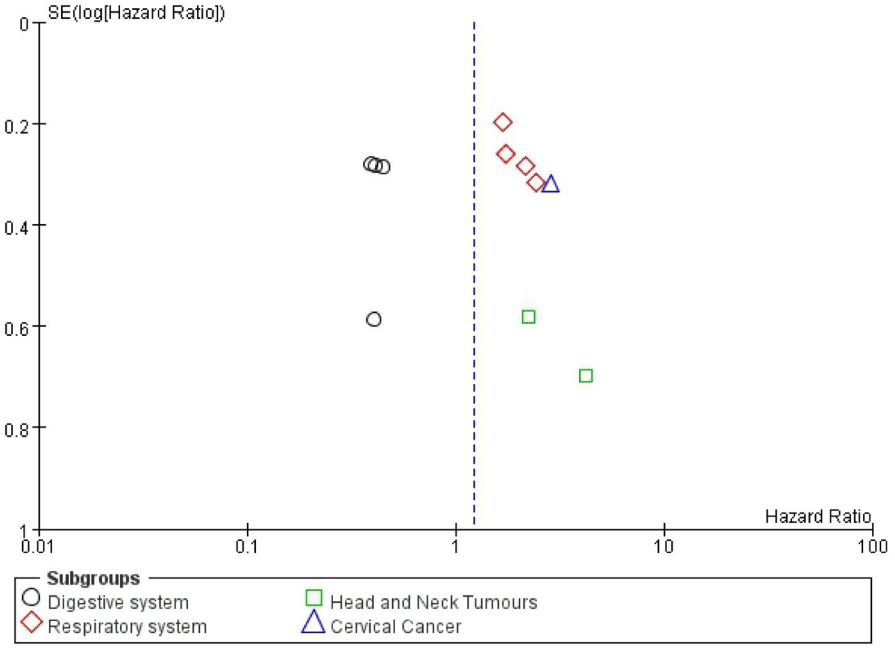


FIGURE 4 Funnel plot for publication bias of MIR31HG and OS. Funnel plot showing the relation hazard ratio (HR) and standard error (log HR) by subgroup analysis

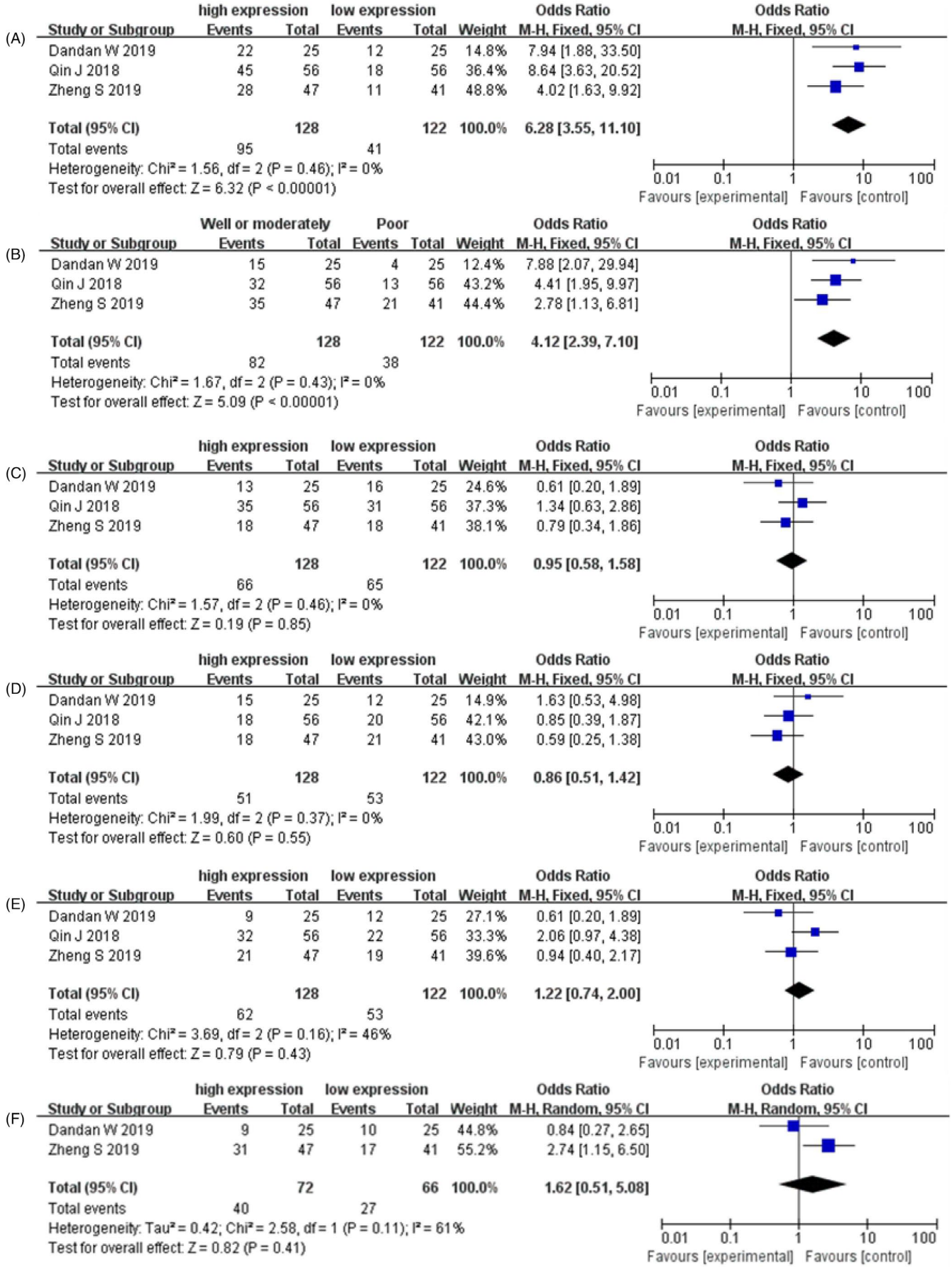


FIGURE 5 Forrest plot of odds ratios for the association of MIR31HG expression with clinicopathological features in lung cancer. (A) TNM stage, (B) tumor differentiation, (C) age, (D) gender, (E) tumor size, (F) lymph node metastases

TABLE 2 Meta-analysis for the association between lncRNA MIR31HG expression and clinicopathological parameters in respiratory system tumors

Clinicopathological parameters	Studies (*n*)	Total cases	OR (95% CI)	*p*-Value	Heterogeneity		
					I^2(%)	Ph	Model
Age (old vs. young)	3	250	0.95 (0.58–1.58)	0.85	0	0.46	FEM
Gender (man vs. female)	3	250	0.86 (0.51–1.42)	0.55	0	0.37	FEM
Tumor size (larger size vs. small size)	3	250	1.22 (0.74–2.00)	0.43	46	0.16	FEM
TNM stage (III-IV vs. I-II)	3	250	6.28 (3.55–11.10)	<0.00001	0	0.46	FEM
Lymph node metastasis (positive vs. negative)	2	138	1.62 (0.51–5.08)	0.41	61	0.11	REM
Differentiation (well or moderately vs. poor)	3	250	4.12 (2.39–7.10)	<0.00001	0	0.43	FEM

Abbreviations: CI, confidence interval; FEM, fixed-effects model; OR, odds ratio; REM, random-effects model.

TABLE 3 Meta-analysis for the association between lncRNA MIR31HG expression and clinicopathological parameters in digestive system tumors

Clinicopathological parameters	Studies (*n*)	Total cases	OR (95% CI)	*p*-Value	Heterogeneity		
					I^2 (%)	Ph	Model
Age (old vs. young)	5	495	1.02 (0.72–1.45)	0.91	0	0.78	FEM
Gender (man vs. female)	5	495	0.92 (0.63–1.33)	0.65	0	0.83	FEM
Tumor size (larger size vs. small size)	4	310	0.44 (0.14–1.41)	0.17	79	0.002	REM
TNM stage (III-IV vs. I-II)	5	495	0.32 (0.22–0.47)	<0.00001	21	0.28	FEM
Lymph node metastasis (positive vs. negative)	4	453	0.61 (0.32–1.15)	0.13	52	0.1	REM
Distant metastasis (positive vs. negative)	2	227	0.39 (0.21–0.73)	0.003	0	0.62	FEM
Differentiation (well or moderately vs. poor)	4	447	0.61 (0.22–1.67)	0.33	80	0.002	REM

Abbreviations: CI, confidence interval; FEM, fixed-effects model; OR, odds ratio; REM, random-effects model.

in cancers are still controversial and the underlying mechanism remains unclear.

In this study, our results found that MIR31HG expression was not associated with prognosis (HR = 1.21, 95% CI: 0.73–2.01, $p = 0.45$), which was consistent with the results of the TCGA survival data. However, there was significant heterogeneity among studies. Considering the heterogeneity, we choose a random effect model. Sequentially, we conducted subgroup analyses of OS based on the system of cancer. The results indicated that MIR31HG could be a potential prognostic biomarker for respiratory system cancers, head and neck tumors, and digestive system cancers.

In respiratory system tumors, MIR31HG overexpression was associated with worse OS of the patients. Additionally, high MIR31HG expression was significantly related to advanced TNM stage and tumor differentiation. On the contrary, the lower MIR31HG expression was significantly associated with shorter OS in digestive system cancers. Moreover, low expression of MIR31HG was associated with advanced TNM stage and distant metastasis. Both results indicated that MIR31HG played an important role in tumor progression and metastasis.

To gain insight into the potential functional impact of the MIR31HG expression on cancers, we evaluated the expression of MIR31HG in different normal tissues and some tumor tissues; MIR31HG was highly expressed in normal urinary bladder, small intestine, esophagus, stomach, and duodenum and was low in colon, lung, and ovary normal tissues. In cancer tissues, MIR31HG was highly expressed in LUSC, HNSC, and LUAD and low in BLCA, STAD, and so on. These results were consistent with the results in the literature.[7,8,24,26] For example, Wu et al. revealed that MIR31HG in the NSCLC cell lines and tissues was up-regulated compared with normal cell line and adjacent normal tissues.[8] Qin et al.[24] also found that MIR31HG was highly expressed in lung adenocarcinoma cell lines and tissues. Chen et al.[7] showed that MIR31HG was lower in adjacent non-tumor tissues compared with cervical cancer tissues. He et al.[26] discovered that MIR31HG expression was decreased in bladder cancer tissues compared with noncancerous tissues. Nie et al.[14] found that MIR31HG was decreased in GC tissues and related to malignantly pathological stage. Ren et al.[15] revealed that MIR31HG was downregulated in ESCC tissues compared with controls. The above results may explain the reason of the opposite results obtained in digestive and respiratory tumors.

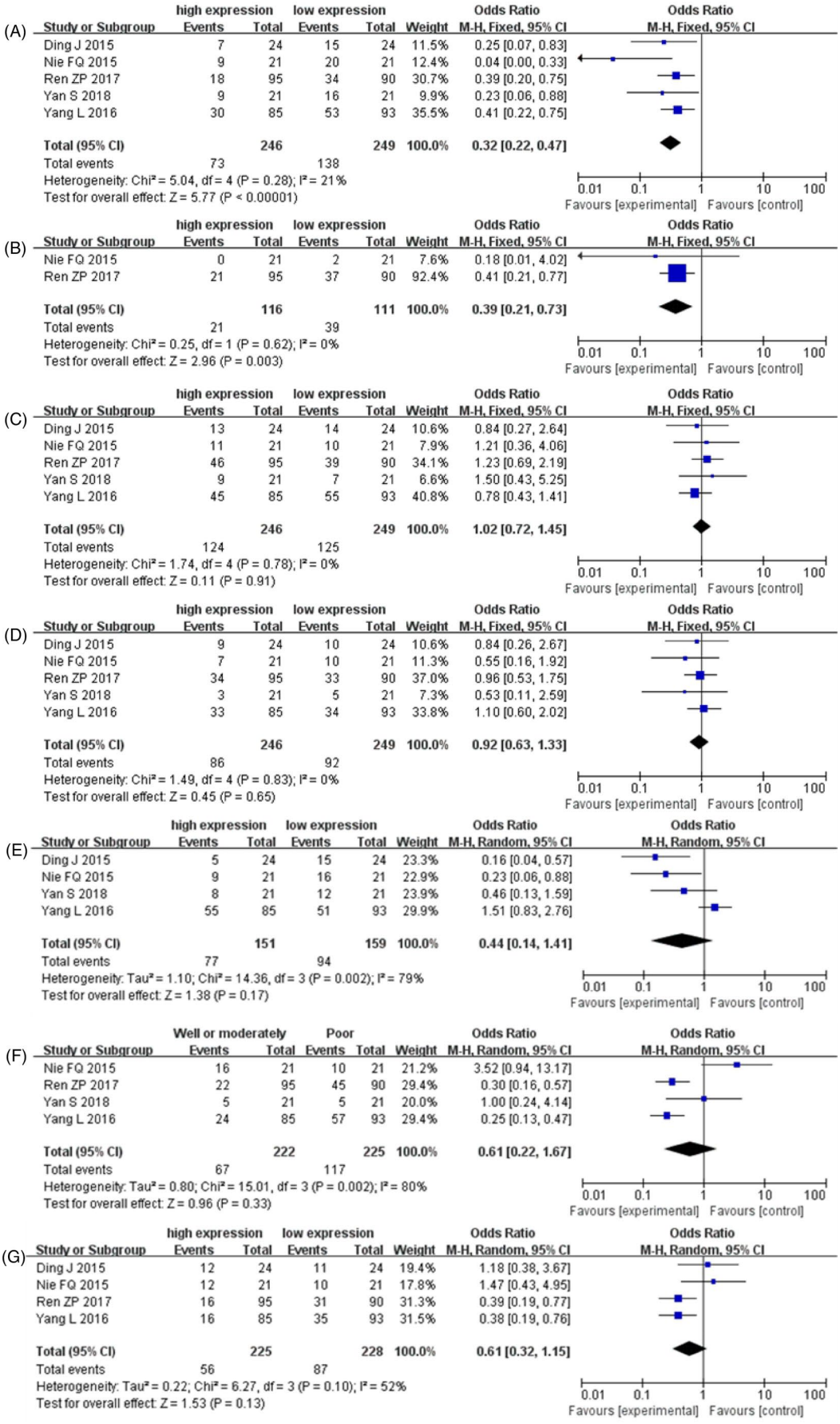


FIGURE 6 Forrest plot of odds ratios for the association of MIR31HG expression with clinicopathological features in digestive system tumors. (A) TNM stage, (B) distant metastasis, (C) age, (D) gender, (E) tumor size, (F) tumor differentiation, (G) lymph node metastases

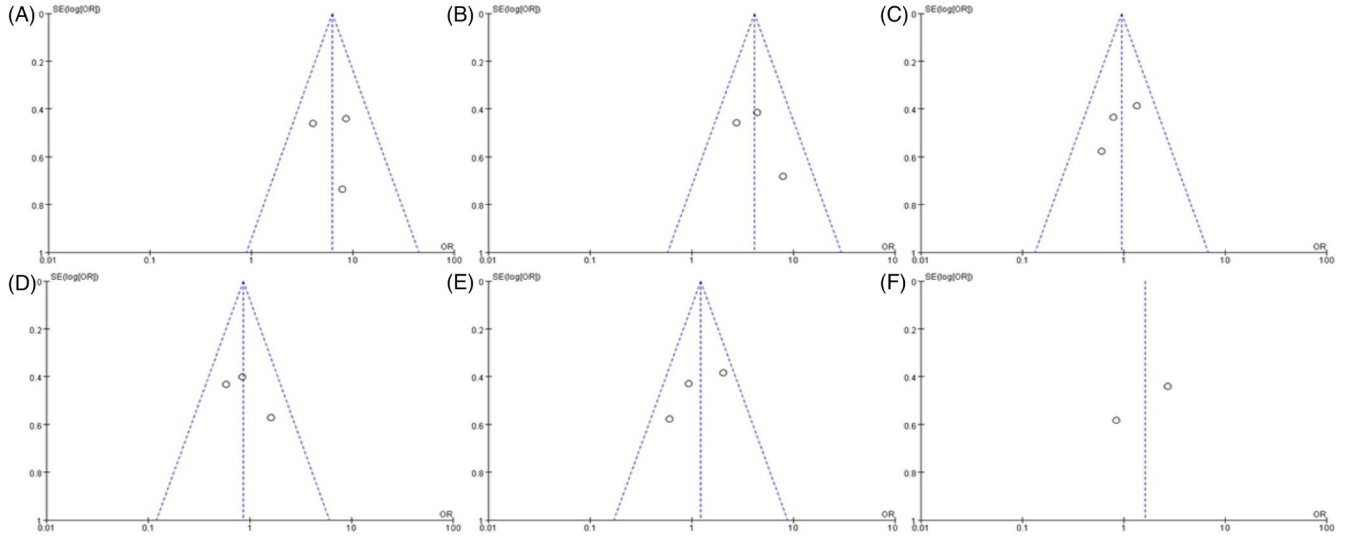


FIGURE 7 Funnel plot for publication bias of MIR31HG and clinicopathological features in lung cancer. (A) TNM stage, (B) tumor differentiation, (C) age, (D) gender, (E) tumor size, and (F) lymph node metastases

Gene ontology and KEGG pathway enrichment analysis found that target genes were mostly enriched in p53, Rap1 signaling pathway, focal adhesion, PI3K-Akt, MAPK signaling pathway, microRNAs in cancer, and HIF-1 signaling pathway. Shih et al.[9] found that MIR31HG was a HIF-1α co-activator promoting oral cancer progression. Wang et al.[34] observed that MIR31HG may contribute to gefitinib resistance via the EGFR/PI3K/AKT pathway. Dandan et al.[8] revealed that MIR31HG could reverse miR-214-induced inhibition of NSCLC progression. Zheng et al.[22] discovered that MIR31HG by activating the Wnt/β-catenin signaling pathway to promote cell invasion and proliferation in NSCLC. Wang et al.[10] found that MIR31HG could improve the proliferation of head and neck cancer by targets HIF1A and P21. Yan et al.[16] revealed that MIR31HG might reduce the proliferation and metastasis of HCC. Yang et al.[12] found that MIR31HG was negatively regulated by miR-193b and could promote tumor progression in PDAC. Lin et al.[35] shown that MIR31HG could promote migratory abilities of GC cells through downregulating E-cadherin and p21. Ma et al.[36] suggested that MIR31HG could modulate chordoma cell invasion by up-regulation of EZH2 and RNF144B by miR-31. Our results were in agreement with the previous reports that MIR31HG was involved in tumor progression by regulating various pathways, and further research is necessary to verify the possible mechanisms.

Moreover, there were some limitations in our article which should be considered. Firstly, included articles all came from China, which made the results could only represent Chinese patients. Next, we extracted HR and relevant data from the survival curve, which might bring about subtle bias of HR values. Moreover, the cutoff values of our included articles were not all the same. There were 11 articles with cutoff values of median and two articles with fold changes to define the high and low expression of MIR31HG. Finally, the potential regulatory mechanism of MIR31HG and its target genes needed to be validated via further experiments in future studies. Therefore, in future, well-designed studies with more sample size, and further research studies are needed to verify our analysis results.

5 | CONCLUSIONS

In digestive system cancers, low MIR31HG expression was significantly related to shorter OS. The high MIR31HG expression was associated with worse OS of the patients with respiratory system cancers, head and neck tumors, and cervical cancer patients. MIR31HG might act as a potential prognostic biomarker. Moreover, in future, the well-designed studies and further research studies are needed to verify our analysis results.

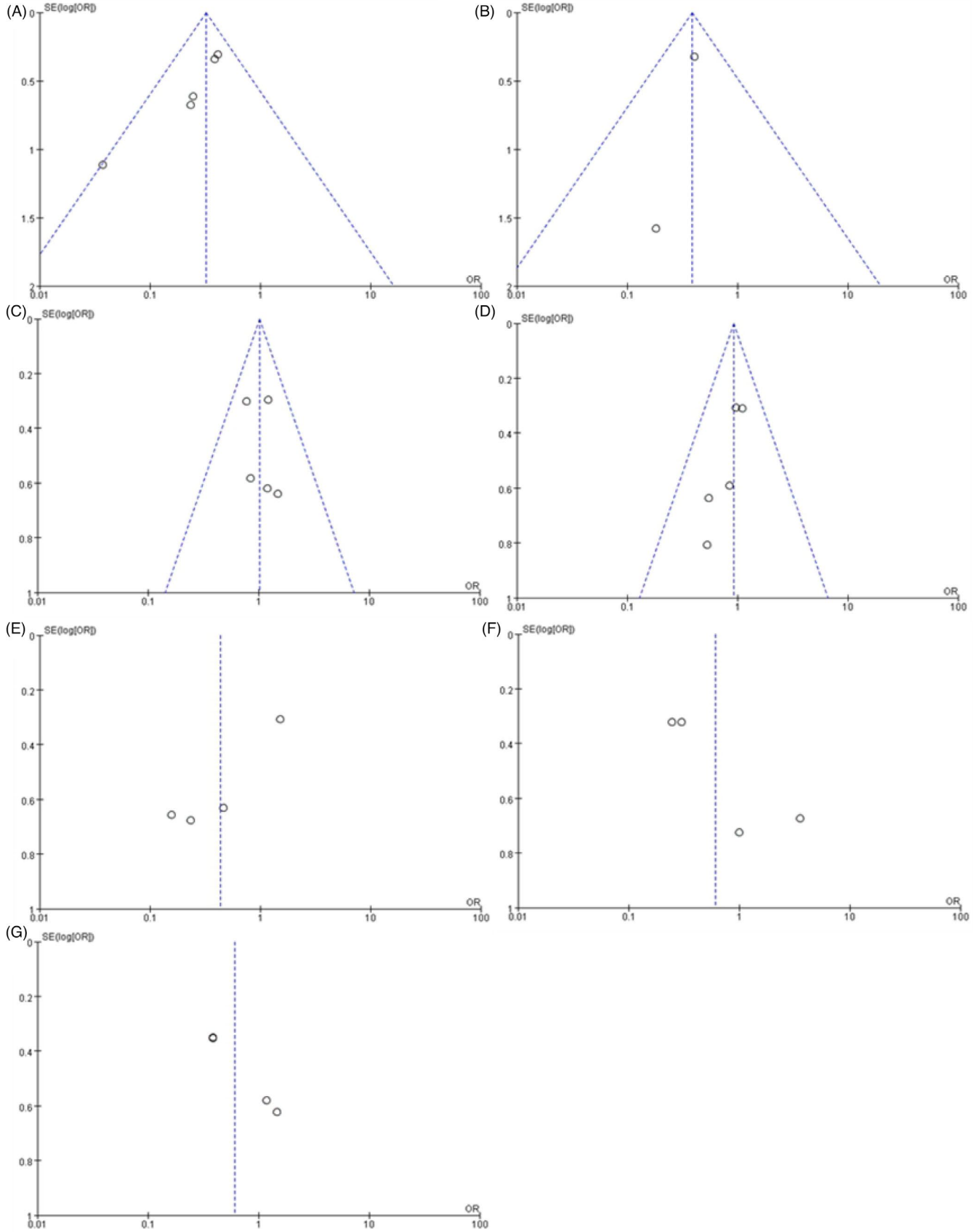


FIGURE 8 Funnel plot for publication bias of MIR31HG and clinicopathological features in digestive system tumors. (A), TNM stage (B), distant metastasis (C), age (D), gender (E), tumor size (F), tumor differentiation, (G) lymph node metastases

TABLE 4 Sensitivity analysis for overall survival

Study omitted (year)	OS HR (95% CI)	I^2 (%)	Statistical method	*p*-Value
Chen J 2017	1.11 (0.66–1.87)	86	Random	0.7
Dandan W 2019	1.13 (0.66–1.93)	86	Random	0.66
Nie FQ 2015	1.36 (0.83–2.25)	84	Random	0.22
Qin J 2018	1.17 (0.67–2.05)	87	Random	0.58
Ren ZP 2017	1.35 (0.81–2.26)	84	Random	0.25
Shih JW 2017	1.16 (0.68–1.97)	87	Random	0.59
Sui J 2018	1.17 (0.66–2.10)	87	Random	0.58
Wang R 2018	1.12 (0.67–1.88)	87	Random	0.67
Yan S 2018	1.37 (0.84–2.25)	83	Random	0.21
Yang L 2016	1.32 (0.78–2.22)	87	Random	0.3
Zheng S 2019	1.14 (0.66–1.97)	86	Random	0.63

Abbreviations: CI, confidence interval; Fixed, fixed-effects model; HR, hazard ratio; OS, overall survival; Random, random-effects model.

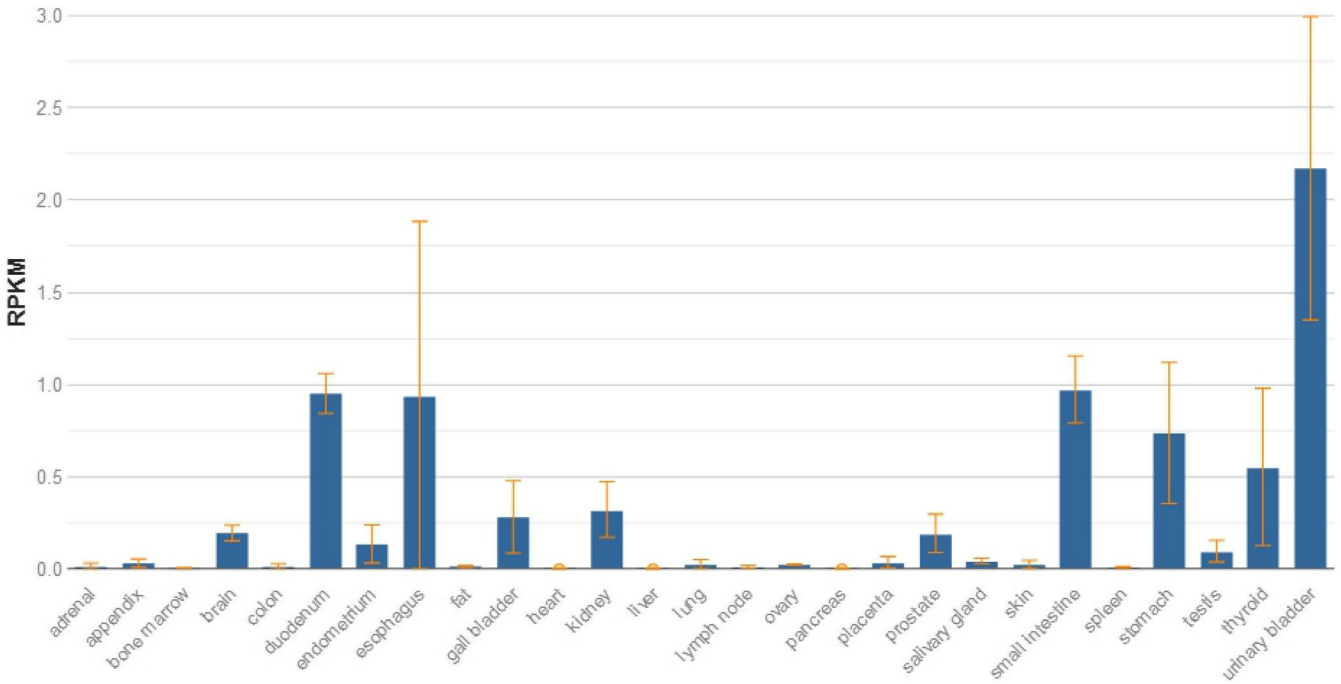


FIGURE 9 MIR31HG is widely expressed in human normal tissues

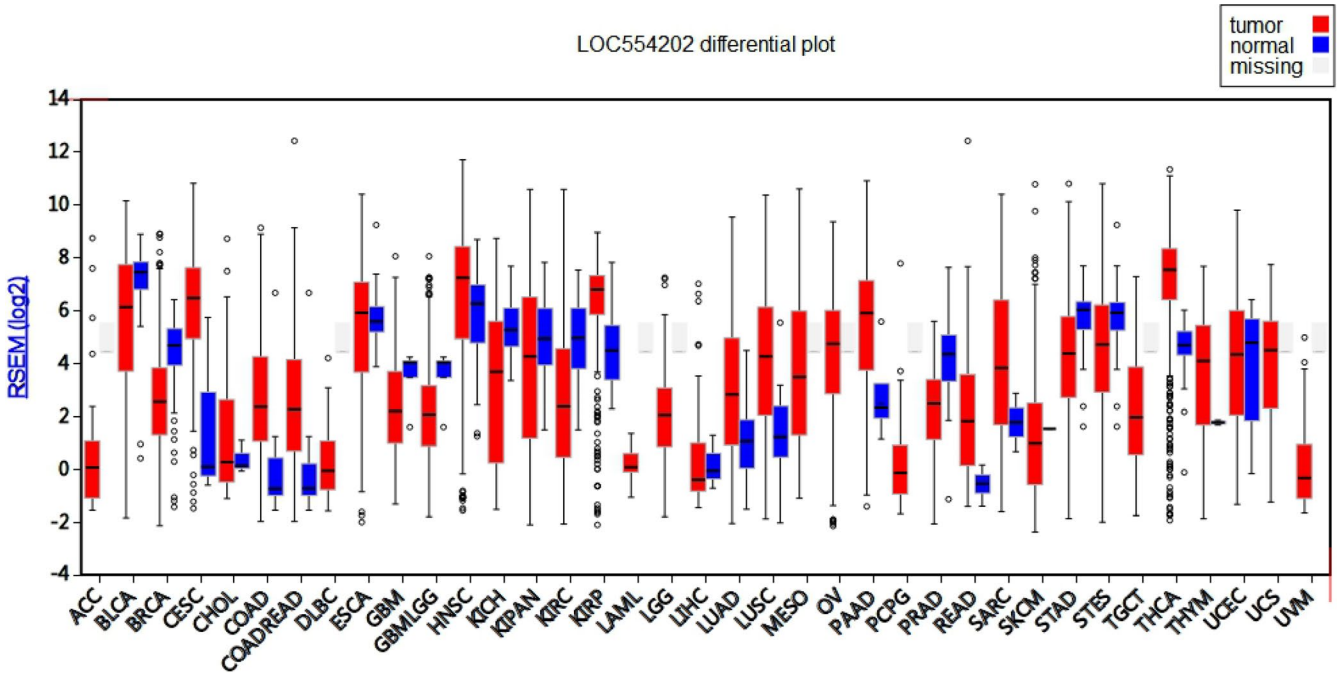


FIGURE 10 MIR31HG expression profile across tumor samples and adjacent normal tissues from FireBrowse (box plot)

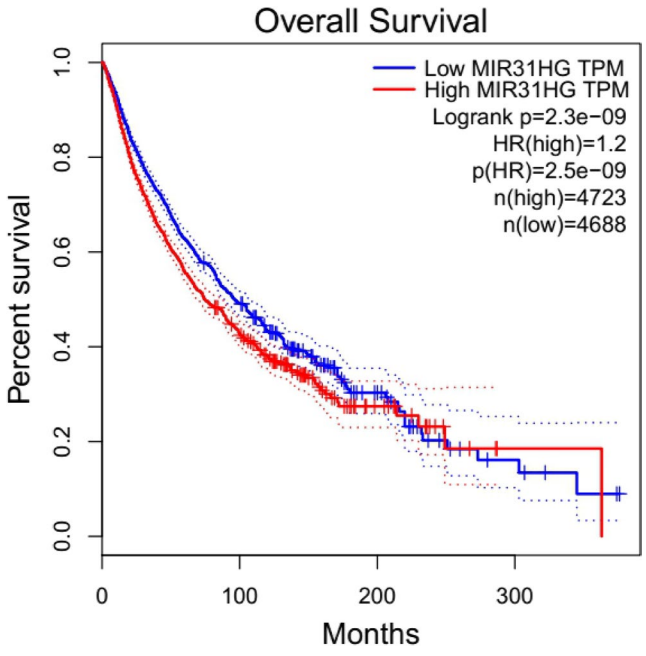
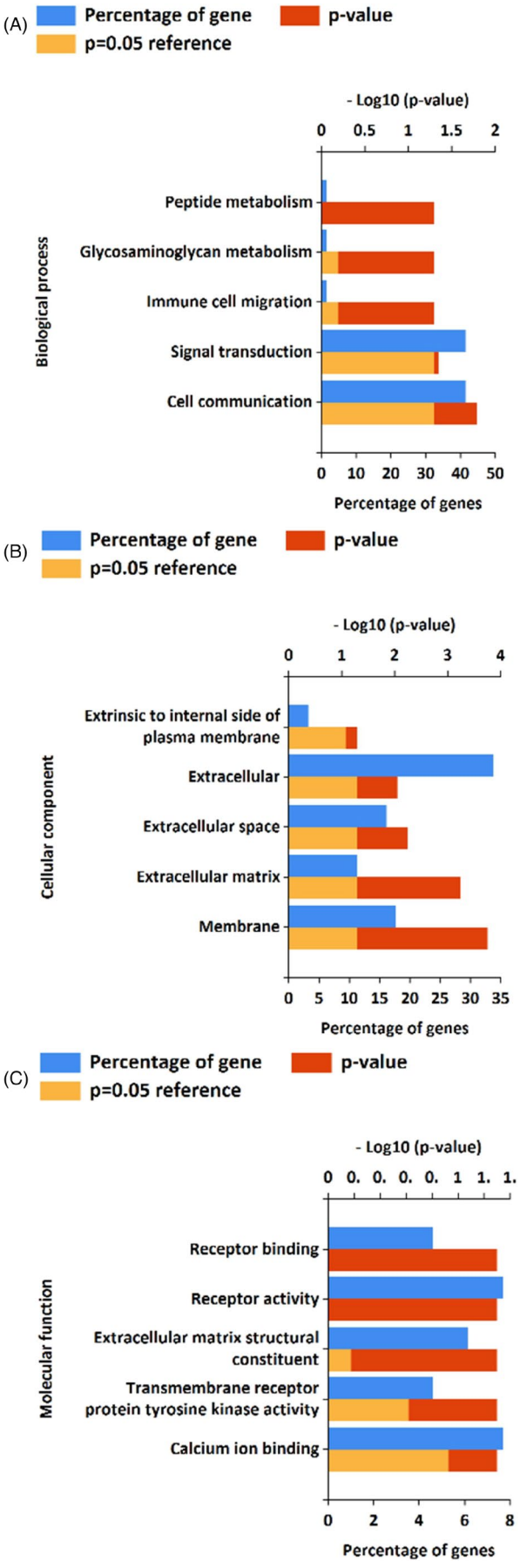


FIGURE 11 Survival curves of MIR31HG are plotted for all kinds of cancers from TCGA dataset ($n = 9411$)

FIGURE 12 The heatmap of top 100 MIR31HG co-expressed genes in tumor expression chips

FIGURE 13 Gene ontology enrichment analysis for the top 100 co-expressed genes of MIR31HG. This figure presents a representative, partial list of the significantly enriched GO terms associated with the top 100 co-expressed genes of MIR31HG in the biological process (A), cellular component (B), and molecular function (C)


(A)
Percentage of gene
p-value
p=0.05 reference
- Log10 (p-value)
0 0.5 1 1.5 2
Biological process
Peptide metabolism
Glycosaminoglycan metabolism
Immune cell migration
Signal transduction
Cell communication
0 10 20 30 40 50
Percentage of genes
(B)
Percentage of gene
p-value
p=0.05 reference
- Log10 (p-value)
0 1 2 3 4
Cellular component
Extrinsic to internal side of plasma membrane
Extracellular
Extracellular space
Extracellular matrix
Membrane
0 5 10 15 20 25 30 35
Percentage of genes
(C)
Percentage of gene
p-value
p=0.05 reference
- Log10 (p-value)
0 0. 0. 0. 0. 1 1. 1.
Molecular function
Receptor binding
Receptor activity
Extracellular matrix structural constituent
Transmembrane receptor protein tyrosine kinase activity
Calcium ion binding
0 2 4 6 8
Percentage of genes

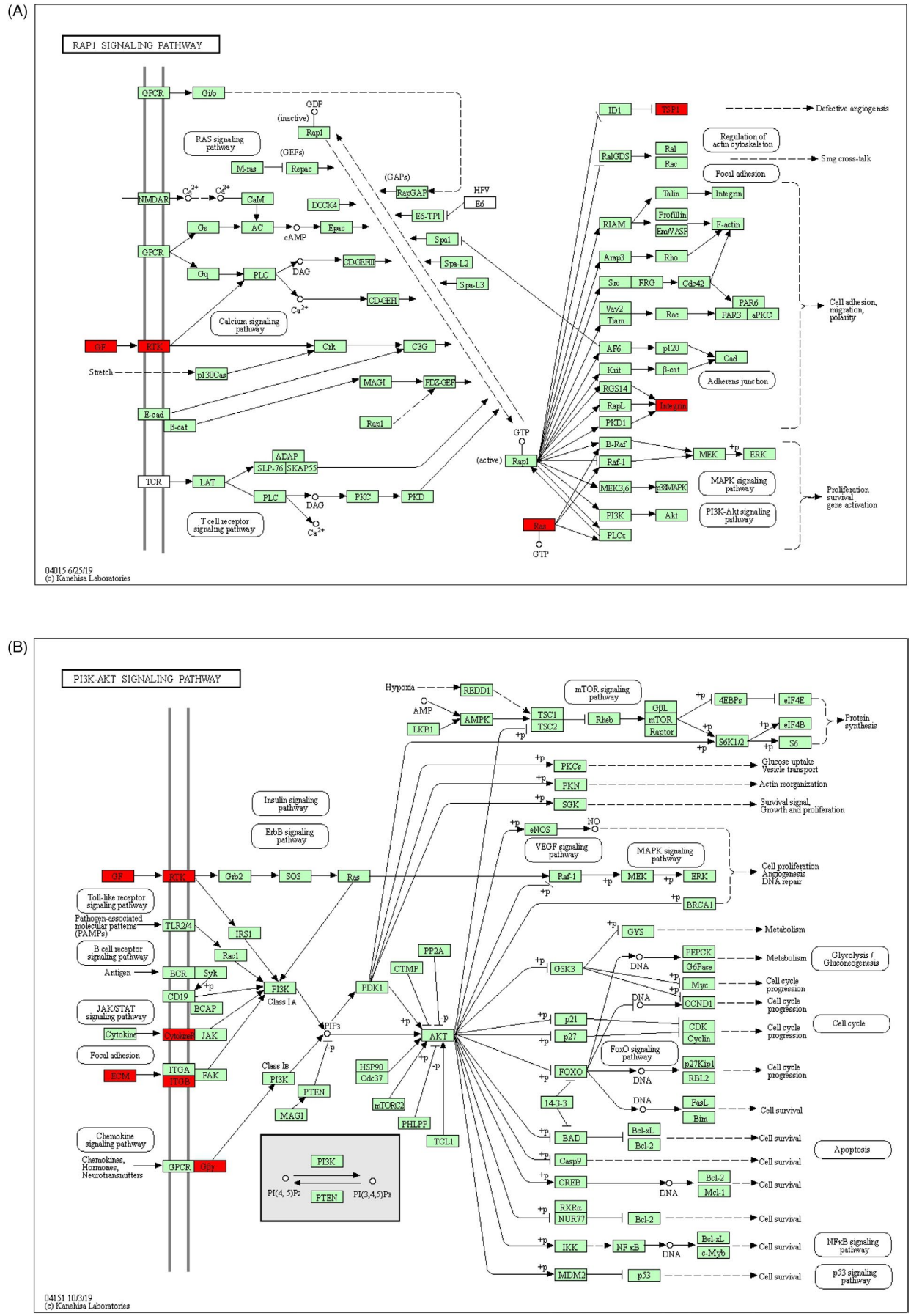


FIGURE 14 KEGG analysis for the main signaling pathway. This figure presents a representative, the significantly signaling pathway associated with co-expressed genes of MIR31HG: Rap1 signaling pathway (A) and PI3K-Akt signaling pathway (B)

TABLE 5 KEGG pathway enrichment analysis of MIR31HG target genes

Pathway description	KEGG ID	Input number	Background number	*p*-Value	Corrected *p*-value
Proteoglycans in cancer	hsa05205	9	205	7.77E-11	7.23E-09
Focal adhesion	hsa04510	7	203	5.51E-08	2.56E-06
Rap1 signaling pathway	hsa04015	6	211	1.54E-06	3.91E-05
PI3K-Akt signaling pathway	hsa04151	7	342	1.68E-06	3.91E-05
Bacterial invasion of epithelial cells	hsa05100	4	78	1.03E-05	0.000191027
Ras signaling pathway	hsa04014	5	228	4.08E-05	0.000631626
Endocytosis	hsa04144	5	260	7.49E-05	0.000950683
Cytokine-cytokine receptor interaction	hsa04060	5	265	8.18E-05	0.000950683
Complement and coagulation cascades	hsa04610	3	79	0.000335152	0.003345781
EGFR tyrosine kinase inhibitor resistance	hsa01521	3	81	0.000359761	0.003345781
Regulation of actin cytoskeleton	hsa04810	4	215	0.00046319	0.003916061
Pathways in cancer	hsa05200	5	397	0.00051363	0.003980636
Nicotinate and nicotinamide metabolism	hsa00760	2	30	0.001260517	0.009017544
Phagosome	hsa04145	3	155	0.002234798	0.014064537
Bladder cancer	hsa05219	2	41	0.002268474	0.014064537
Malaria	hsa05144	2	49	0.003176205	0.017389501
Axon guidance	hsa04360	3	176	0.003178726	0.017389501
Central carbon metabolism in cancer	hsa05230	2	67	0.005734976	0.028188599
Epithelial cell signaling in Helicobacter pylori infection	hsa05120	2	68	0.005897473	0.028188599
p53 signaling pathway	hsa04115	2	69	0.006062064	0.028188599
Melanoma	hsa05218	2	71	0.006397499	0.028331783
Adherens junction	hsa04520	2	74	0.00691618	0.029236577
ECM-receptor interaction	hsa04512	2	82	0.008389096	0.033846184
MAPK signaling pathway	hsa04010	3	255	0.008734499	0.033846184
AGE-RAGE signaling pathway in diabetic complications	hsa04933	2	101	0.012393072	0.04595296
HIF-1 signaling pathway	hsa04066	2	103	0.012854595	0.04595296
MicroRNAs in cancer	hsa05206	3	299	0.013341182	0.04595296

CONFLICT OF INTEREST

The authors declare that they have no competing interests.

AUTHOR CONTRIBUTIONS

LJP designed the study. YFW and YJZ wrote the original draft. YFW, YJZ, and LJP revised the manuscript. YFW, YJZ, XAL, and SJ analyzed data. YFW, YJZ, JFJ, and XAL organized the figure data. LJP, LZ, CYW, HZ, JMH, LHW, and XHS reviewed and edited the manuscript. All authors read and approved the final manuscript.

DATA AVAILABILITY STATEMENT

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

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REFERENCES

1. Torre LA, Siegel RL, Ward EM, Jemal A. Global cancer incidence and mortality rates and trends – an update. *Cancer Epidemiol Biomark Prev*. 2016;25(1):16-27.
2. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global Cancer Statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin*. 2018;68(6):394-424.
3. Lee AW, Ma BB, Ng WT, Chan AT. Management of nasopharyngeal carcinoma: current practice and future perspective. *J Clin Oncol*. 2015;33(29):3356-3364.
4. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2017. *CA Cancer J Clin*. 2017;67(1):7-30.
5. Li J, Li Z, Zheng W, et al. LncRNA-ATB: an indispensable cancer-related long noncoding RNA. *Cell Prolif*. 2017;50(6).
6. Kumar MM, Goyal R. LncRNA as a therapeutic target for angiogenesis. *Curr Top Med Chem*. 2017;17(15):1750-1757.
7. Chen J, Zhu J. Elevated expression levels of long non-coding RNA, Loc554202, are predictive of poor prognosis in cervical cancer. *Tohoku J Exp Med*. 2017;243(3):165-172.

8. Dandan W, Jianliang C, Haiyan H, Hang M, Xuedong L. Long noncoding RNA MIR31HG is activated by SP1 and promotes cell migration and invasion by sponging miR-214 in NSCLC. *Gene*. 2019;692:223-230.
9. Shih JW, Chiang WF, Wu ATH, et al. Long noncoding RNA LncHIFCAR/MIR31HG is a HIF-1α co-activator driving oral cancer progression. *Nat Commun*. 2017;8:15874.
10. Wang R, Ma Z, Feng L, et al. LncRNA MIR31HG targets HIF1A and P21 to facilitate head and neck cancer cell proliferation and tumorigenesis by promoting cell-cycle progression. *Mol Cancer*. 2018;17(1):162.
11. Shi Y, Lu J, Zhou J, et al. Long non-coding RNA Loc554202 regulates proliferation and migration in breast cancer cells. *Biochem Biophys Res Comm*. 2014;446(2):448-453.
12. Yang H, Liu P, Zhang J, et al. Long noncoding RNA MIR31HG exhibits oncogenic property in pancreatic ductal adenocarcinoma and is negatively regulated by miR-193b. *Oncogene*. 2016;35(28):3647-3657.
13. Sun K, Zhao X, Wan J, et al. The diagnostic value of long non-coding RNA MIR31HG and its role in esophageal squamous cell carcinoma. *Life Sci*. 2018;202:124-130.
14. Nie FQ, Ma S, Xie M, Liu YW, De W, Liu XH. Decreased long noncoding RNA MIR31HG is correlated with poor prognosis and contributes to cell proliferation in gastric cancer. *Tumour Biol*. 2016;37(6):7693-7701.
15. Ren ZP, Chu XY, Xue ZQ, et al. Down-regulation of lncRNA MIR31HG correlated with aggressive clinicopathological features and unfavorable prognosis in esophageal squamous cell carcinoma. *Eur Rev Med Pharmacol Sci*. 2017;21(17):3866-3870.
16. Yan S, Tang Z, Chen K, et al. Long noncoding RNA MIR31HG inhibits hepatocellular carcinoma proliferation and metastasis by sponging microRNA-575 to modulate ST7L expression. *J Exp Clin Cancer Res*. 2018;37(1):214.
17. Yang L, Wei H, Xiao HJ. Long non-coding RNA Loc554202 expression as a prognostic factor in patients with colorectal cancer. *Eur Rev Med Pharmacol Sci*. 2016;20(20):4243-4247.
18. Tierney JF, Stewart LA, Ghersi D, Burdett S, Sydes MR. Practical methods for incorporating summary time-to-event data into meta-analysis. *Trials*. 2007;8:16.
19. Ge H, Yan Y, Wu D, Huang Y, Tian F. Potential role of LINC00996 in colorectal cancer: a study based on data mining and bioinformatics. *Onco Targets Ther*. 2018;11:4845-4855.
20. Ma Q, Xu Y, Liao H, et al. Identification and validation of key genes associated with non-small-cell lung cancer. *J Cell Physiol*. 2019;234(12):22742-22752.
21. Liu L, He C, Zhou Q, Wang G, Lv Z, Liu J. Identification of key genes and pathways of thyroid cancer by integrated bioinformatics analysis. *J Cell Physiol*. 2019;234(12):23647-23657.
22. Zheng S, Zhang X, Wang X, Li J. MIR31HG promotes cell proliferation and invasion by activating the Wnt/β-catenin signaling pathway in non-small cell lung cancer. *Oncol Lett*. 2019;17(1):221-229.
23. Sui J, Yang S, Liu T, et al. Molecular characterization of lung adenocarcinoma: a potential four-long noncoding RNA prognostic signature. *J Cell Biochem*. 2019;120(1):705-714.
24. Qin J, Ning H, Zhou Y, Hu Y, Yang L, Huang R. LncRNA MIR31HG overexpression serves as poor prognostic biomarker and promotes cells proliferation in lung adenocarcinoma. *Biomed Pharmacother*. 2018;99:363-368.
25. Ding J, Lu B, Wang J, et al. Long non-coding RNA Loc554202 induces apoptosis in colorectal cancer cells via the caspase cleavage cascades. *J Exp Clin Cancer Res*. 2015;34(1):100.
26. He A, Chen Z, Mei H, Liu Y. Decreased expression of LncRNA MIR31HG in human bladder cancer. *Cancer Biomark*. 2016;17(2):231-236.
27. Kwok ZH, Tay Y. Long noncoding RNAs: lincs between human health and disease. *Biochem Soc Trans*. 2017;45(3):805-812.
28. Song X, Yao H, Liu J, Wang Q. The prognostic value of long noncoding RNA Sox2ot expression in various cancers: a systematic review and meta-analysis. *Clin Chim Acta*. 2018;484:52-59.
29. Li J, Meng H, Bai Y, Wang K. Regulation of lncRNA and its role in cancer metastasis. *Oncol Res*. 2016;23(5):205-217.
30. Liu JL, Zhang WQ, Zhao M, Huang MY. Upregulation of long noncoding RNA XIST is associated with poor prognosis in human cancers. *J Cell Physiol*. 2019;234(5):6594-6600.
31. Mehrad-Majd H, Akhtari J, Haerian MS, Ravanshad Y. Clinicopathological and prognostic value of lncRNA PANDAR expression in solid tumors: evidence from a systematic review and meta-analysis. *J Cell Physiol*. 2019;234(4):4206-4216.
32. Zhuang C, Zheng L, Wang P. Prognostic role of long non-coding RNA HNF1A-AS1 in Chinese cancer patients: a meta-analysis. *Onco Targets Ther*. 2018;11:5325-5332.
33. Liu C, Jin J, Liang D, et al. Long noncoding RNA PVT1 as a novel predictor of metastasis, clinicopathological characteristics and prognosis in human cancers: a meta-analysis. *Pathol Oncol Res*. 2019;25(3):837-847.
34. Wang B, Jiang H, Wang L, et al. Increased MIR31HG lncRNA expression increases gefitinib resistance in non-small cell lung cancer cell lines through the EGFR/PI3K/AKT signaling pathway. *Oncol Lett*. 2017;13(5):3494-3500.
35. Lin Y, Zhang CS, Li SJ, Li Z, Sun FB. LncRNA LOC554202 promotes proliferation and migration of gastric cancer cells through regulating p21 and E-cadherin. *Eur Rev Med Pharmacol Sci*. 2018;22(24):8690-8697.
36. Ma X, Qi S, Duan Z, et al. Long non-coding RNA LOC554202 modulates chordoma cell proliferation and invasion by recruiting EZH2 and regulating miR-31 expression. *Cell Prolif*. 2017;50(6):e12388.

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