

DOI: 10.14744/ejmo.2023.24253 EJMO 2023;7(4):298–305

Systematic Meta Analysis



# The Prognostic Significance of miR-613 in Malignant Tumors and Association with Clinical Characteristics: A Systematic Review and Meta-Analysis

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#The authors contributed equally to the study.

#### Abstract

**Objectives:** Previous studies have shown that microRNA-613 (miR-613) functions as a tumor suppressor gene in various organ tissues. Our meta-analysis aimed to systematically evaluate the prognostic role of miR-613 and its association with clinical characteristics of malignant tumors.

**Methods:** We searched the PubMed/MEDLINE, Web of Science, Cochrane Library, and Google Scholar databases for relevant studies until July 25, 2023. Then, We pooled individual data and estimated the overall Hazard ratio (HR) and Odds ratio (OR) of miR-613 for prognosis and patient characteristic linking evaluations, respectively.

**Results:** After selection, 14 eligible studies with 1510 patients enrolled in final analyses. The lower level of miR-613 expression is associated with advanced stages (OR=3.08, 95% confidence interval [Cl]: 2.27-4.18), larger tumor size (OR=2.05, 95%Cl: 1.11-3.78), and lymph-node metastasis (OR=3.62, 95%Cl: 2.55-5.14). Notably, downregulated miR-613 is associated with inferior progression-free survival (adjusted HR=1.65, 95%Cl: 1.31-2.10) and overall survival (adjusted HR=1.83, 95%Cl: 1.59-2.11). No significant heterogeneity was found in the analyses (I2=0%, P-values were 0.473 and 0.685, respectively).

**Conclusion:** The results of this study indicate that low miR-613 expression is associated with advanced stages, larger tumor size, and lymph node metastasis in malignant tumors. Besides, low miR-613 is a poor prognosis indicator for PFS and OS. **Keywords:** Cancers, miR-613, meta-analysis, prognostics

**Cite This Article:** Tran VT, Phan TT, Huynh KQ, Ho TT, Pho SP, Nguyen HT, et al. The Prognostic Significance of miR-613 in Malignant Tumors and Association with Clinical Characteristics: A Systematic Review and Meta-Analysis. EJMO 2023;7(4):298–305.

Recent advances in diagnosis and treatment, especially the appearance of targeted therapies, have improved the 5-year survival of cancers.<sup>[1]</sup> Despite that, survival rates of common cancers such as liver, lung, stomach, esophagus, pancreas, and brain are still low (5-40%).<sup>[1]</sup> Consequently, studying and seeking new biomarkers (tumor DNA and cells, DNA methylation, long non-coding RNAs, microRNAs...) that serve as novel therapeutic targets and assist current tests in the early diagnosis and prognosis of cancers is necessary. Among the molecular biomarkers, microRNAs (miR-21, miR-155, miR-222, Etc.) are highly attracted and studied as promising candidates.<sup>[2]</sup> After production, the mature microRNA binds to targeted mRNA genes, then inhibits the translation and initiation of gene cleavage.<sup>[2]</sup> In

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Submitted Date: July 25, 2023 Accepted Date: November 19, 2023 Available Online Date: December 29, 2023 <sup>®</sup>Copyright 2023 by Eurasian Journal of Medicine and Oncology - Available online at www.ejmo.org

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malignant cells, this physiological process is dysregulated by increasing oncogenic microRNA activity while restricting tumor suppressor microRNA, leading to tumorigenesis, invasion, migration, and metastasis.<sup>[2]</sup> One of the interested microRNAs, miR-613, has been shown to target multiple genes and pathways (cMET, CXCR4, KRAS, SPHK1/2, MMP9, CDK4/9/14, PDK1, E2F5, SOX9, ID4/PI3K/AKT, AXL/AKT, Jagged-1/Notch/CXCR4, DNMT3B/TIMP3/STAT1/FOXO1), and function as a tumor suppressor but downregulated in various cancers.<sup>[3-7]</sup> Thus, its expression suggests that miR-613 might be the clinically reliable biomarker. This meta-analysis aimed to evaluate the prognostic role of miR-613 and its association with cancer characteristics.

## Methods

This meta-analysis was conducted following the guideline of Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).<sup>[8]</sup>

## **Database Searching and Study Selection**

We searched the databases of PubMed/MEDLINE, Web of Science, Cochrane Library, and Google Scholar for eligible studies from inception to 25 July 2023. The keywords used in searching include "miR-613", "miR613", "miRNA-613", "miRNA-613", "miRNA-613", "miRONA-613", "miRONA-613", "miRONA-613". In addition, We reviewed citation reports of potential studies to find more articles. After searching, relevant studies (n=3257) were managed by the EndNote software and filtered, removed duplicates (997 records, Fig. 1). By screening titles and abstracts, We excluded 2178, including retracted articles. Of the detailed assessment, 66 without required data, one with public data, and one with previously treated patients did not progress further. Ultimately, 14 studies with miR-613 expression and prognostic data enrolled in the meta-analysis.

# Quality Assessment and Data Extraction

The quality of included studies was assessed by two investigators using the Newcastle-Ottawa Scale (NOS), which comprises selection (4 points), comparability (2 points), and outcome categories (3 points).<sup>[9]</sup> A study was awarded 2 points in the comparability aspect if similar in (1) demographic feature (age, gender) and (2) treatment method between the study (low miR-613) and control (high miR-613) arms. A greater than or equal to six points was classified as high quality. In case of no consensus on assessments, evaluators discussed with each other and determined the final decision.

Data extracted from articles include author names, year of publication, country, cancer type, disease stage, treatment method, sample type, sample size, techniques used in miR-613 detecting, reference gene, cut-off, HR values,

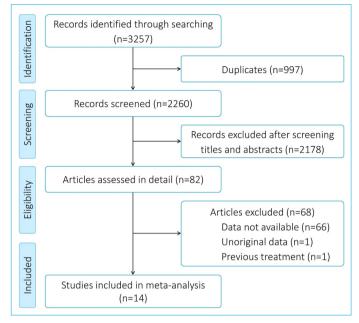


Figure 1. Database searching and study selection.

HR extraction method, and analysis model (multivariable or univariable that HR values have been adjusted for clinical confounders or not). Besides, We extracted the truepositive, false-positive, true-negative, and false-negative numbers corresponding to the clinical characteristics (age, gender, clinical stage, tumor size, lymph node metastasis, and tumor differentiation) to support association analyses. In case of not directly extractable, We used the Engauge Digitizer 12.1 software to extrapolate data from the Kaplan-Meier curves, then calculated HR values according to suggestions of Tierney.<sup>[10]</sup>

#### **Statistical Analysis**

All statistical analyses were performed with the guidance of Harrer and Shim,<sup>[11,12]</sup> using R v.4.3 software (R foundation, 1020 Vienna, Austria) and package meta. We used the random-effects model to estimate the overall HR value to support prognosis assessments. HR>1 indicates a poor prognosis of low miR-613 expression and vice versa for elevated gene expression. HR=1 is an indicator of no significant difference in survival time between groups. The heterogeneity of estimates between studies was measured by Higgins & Thompson's I2-statistic, which is substantial if I2>50%. We adopted the funnel plot asymmetry based on the linear regression test to detect potential publication bias. Once bias exists, We used the Trim-and-Fill statistics to impute missing studies, then calculated the adjusted HR values. For the association analyses between miR-613 expression and clinical features, We summarized OR values to give evaluations. The statistical analyses were significant if p<0.05.

Author Ve																	
	Year (	Country	Cancer C type	Clinical stage	Clinical Treatment stage	Sample type	Sample size	Method	Ref. Gene	Cut-off	HR (95%Cl)	Survival	HR extraction	Analysis model	CCA	NOS score	Ref.
Guan S 20	2016	China	ESCC	Ē	Surg	Tissue	109	RT-qPCR	U6	Mean (0.0016)	1.524 (1.095-2.123) 1.692	PFS	Direct	Multi	Yes	6	[13]
Hu J 20	2016	China	CRC	A-D	Surg	Tissue	100	RT-qPCR	GAPDH	Mean (0.1805)	(1.004-2.851) 2.486 (1.169-5.286) 3.256	DFS DFS	Indirect	Uni	Yes	6	[14]
Li D 20	2016	China	NSCLC	≥	Surg	Tissue	56	RT-qPCR	U6	Mean	(1.403-7.556) 3.829 41.464.10.015	S S	Indirect	Uni	No No	œ	[15]
Zhang X 20	2016	China	00	≥-	Surg	Tissue	236	RT-qPCR	U6	(0.540) Median (3.25)	(610.01-404-11) 2.417 (1.771-10.871)	PFS	Direct	Multi	Yes	6	[16]
Cai H 20	2017	China	ЫС	≥-	Surg	Tissue	59	RT-qPCR	U6	Median	C12.2 (1.671-8.882) 2.398 (1.181-4.868)	SO SO	Indirect	Uni	Yes	6	[17]
Wang Y 20	2017	China	GBM	≥-	Surg	Tissue	64	RT-qPCR	U6	Median	2.216 2.216 (1.194-4.112) 2.834	DFS	Indirect	Uni	Yes	6	[18]
Zhang Y 20	2017	China	RB	≥ -	Surg, Chem, Dod	Tissue	45	RT-qPCR	U6	Median	(1.273-6.309) 3.262 (1.168.0.100)	os os	Indirect	Uni	Yes	6	[19]
Jiang X 20	2018	China	НСС	≥l-	Surg	Tissue	64	RT-qPCR G	RT-qPCR GAPDH, U6		(1.106-2.103) 1.945 (1.105 2.165)	SO	Indirect	Uni	Yes	6	[20]
Sang Q 20	2018	China	Glioma	<b>⊳</b>  -	Surg	Tissue	30	RT-qPCR	U6	Median (0.25)	(201-2-2010) 3.488 (1 419-8 574)	os	Indirect	Uni	٩ N	œ	[21]
Yang G 20	2018	China	RB	≥_	Surg, Chem, Rad	Tissue	276	RT-qPCR	U6	Mean	2.69 (1 44-5 04)	SO	Direct	Multi	Yes	6	[22]
Zhu Y 20	2018	China Os	China Osteosarcoma	≥-	Surg	Tissue	211	RT-qPCR	U6	Median (0.364)	1.669	SO	Indirect	Uni	N	8	[23]
Liu H 20	2019	China	СG	≥-	Surg	Tissue	176	RT-qPCR	U6	Mean	1.195-2.924)	SO	Direct	Multi	Yes	6	[24]
Zhou N 20	2019	China	HCC	N-I	Surg	Tissue	52	RT-qPCR	U6	Median (0.052)	2.378 (1.107-5.15)	os	Direct	Uni	Yes	6	[25]
LuoJ 20	2021	China	NSCLC	Ē	Surg	Tissue	32	RT-qPCR	U6	Median (0.675)	3.383 (0.672-10.033)	SO	Direct	Uni	Yes	6	[26]

# Results

## **Characteristics of Included Studies**

Among 14 studies,<sup>[13-26]</sup> three studies demonstrated the role of miR-613 in predicting progression-free survival (PFS) and overall survival (OS),<sup>[13,16,18]</sup> one presented data of disease-free survival and OS,<sup>[14]</sup> while ten others exhibited data of OS<sup>[15,17,19-26]</sup> (Table 1). All studies detected miR-613 in tissue samples derived from surgery, using the polymerase chain reaction method, and obtained a NOS score above six. Eleven out of 14 studies showed correlations of miR-613 levels with clinical traits (details in Table S1). The total numbers included in the meta-analysis were 1510 patients.

#### The Prognostic Significance of miR-613

The pooled results indicated that the low miR-613 level is associated with shorter PFS/DFS (HR=1.86, 95%Cl: 1.37-2.52, Fig. 2A) and OS time (HR=2.13, 95%Cl: 1.79-2.53, Fig. 2B). Also, We found that overall estimates are highly consistent between studies (I2=0%, p were 0.473 and 0.685 for PFS and OS, respectively). By the data extraction and analysis methods, the heterogeneity within groups and the HR differences between groups are not statistically significant (Fig. 2C and 2D). However, a publication bias might be present in analyses (Fig. 3A and 3B). We used the Trim-and-Fill statistics to impute assumed studies (Fig. 3C and 3D) and noted an adjusted HR value of 1.65 (95%Cl: 1.31-2.10, p<0.001) for PFS/DFS and 1.83 (95%Cl: 1.59-2.11, p<0.001) for OS.

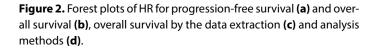
#### Association of miR-613 with Clinical Characteristics

As shown in Figure 4, the miR-613 expression did not correlate with patient age and gender. Significantly, low miR-613 levels are linked to the advanced disease stages (OR=3.08, 95%CI: 2.27-4.118, Fig. 4C), lymph-node metastasis (OR=3.62, 95%CI: 2.55-5.14, Figure 4D), and larger tumor size (OR=2.05, 95%CI: 1.11-3.78, Fig. 4E). Downregulation of miR-613 was observed more frequently in poorly differentiated tumors but not with significance (Fig. 4F).

### Discussion

Increasing evidence expressed that miR-613 regulates multiple genes and functions as a tumor suppressor to inhibit cell proliferation, carcinogenesis, migration, invasion, and metastasis.<sup>[3]</sup> Nevertheless, miR-613 was targeted directly by the long noncoding or circular RNAs as HOTAIR, RMRP, MALAT1, UCA1, LINC00152, LINC00460, CircRIMS..., thus downregulated in numerous malignant tumors like hepatocellular carcinoma, gastric, lung, breast, thyroid, bladder, cervical cancers, glioma, retinoblastoma, and osteosarcoma. <sup>[3,4,27-30]</sup> Accordingly, the miR-613 expression might contrib-

Study	logHR	SE(logHR)	Hazar	d Ratio	HR	95%-CI	Weight (common)	Weig (rando
Guan S 2016	0 4213	0.1689		-	1.52	[1.09; 2.12]	62.0%	53.8
duan 3 2016	0.9107	0.3849			2.49	[1.17; 5.29]	11.9%	14.7
Zhang X 2016	0.8825	0.4629			- 2.42	[1.77; 10.87]	8.3%	10.5
Vang Y 2017	0.7957	0.3155			2.22	[1.19; 4.11]	17.8%	20.9
valig 1 2017	0.7557	0.0100			6.66	[1.13, 4.11]	17.076	20.0
Common effect model					1.79	[1.38; 2.33]	100.0%	
andom effects model				I	1.86		100.0%	100.0
random effects model				-	1.86	[1.37; 2.52]		100.0
			0.1 0.5	1 2 1	0			
Heterogeneity: $I^2 = 0.0\%$ , $\tau^2$	<sup>2</sup> = 0.0166,	p = 0.473	0.1 0.5		0			
3							Weight	Weig
Study	logHR	SE(logHR)	Hazar	d Ratio	HR	95%-CI	(common)	(rando
auan S 2016	0.5259	0.2662			1.69	[1.00; 2.85]	8.9%	9.5
łu J 2016 i D 2016	1.1805	0.4295			- 3.83	[1.40; 7.56]	3.4% 2.6%	4.0
				1		[1.46; 10.01]		3.1
hang X 2016	0.7953	0.4262		T	2.21	[1.67; 8.88]	3.5%	
ai H 2017	0.8746	0.3613			2.40	[1.18; 4.87]	4.8%	5.5
/ang Y 2017	1.0417	0.4083			2.83	[1.27; 6.31]	3.8%	4.4
hang Y 2017	1.1823	0.5240			3.26	[1.17; 9.11]	2.3%	2.7
iang X 2018	0.6653	0.2485			1.95	[1.20; 3.16]	10.2%	10.8
ang Q 2018	1.2493	0.4589		+	3.49	[1.42; 8.57]	3.0%	3.5
ang G 2018	0.9895	0.3196			2.69	[1.44; 5.04]	6.2%	6.9
hu Y 2018	0.5122	0.1373			1.67	[1.27; 2.18]	33.6%	27.0
iu H 2019	0.6254	0.2283			1.87	[1.20; 2.92]	12.1%	12.4
hou N 2019	0.8663	0.3922			2.38	[1.11; 5.15]	4.1%	4.7
uo J 2021	1.2188	0.6896	_		- 3.38	[0.67; 10.03]	1.3%	1.6
common effect model				+	2.07	[1.77; 2.42]	100.0%	,
andom effects model			· · · · ·	+	2.13	[1.79; 2.53]		100.0
			0.1 0.5	1 2	10			
eterogeneity: $I^2 = 0.0\%$ , $\tau^2$	<sup>2</sup> = 0.0096,	<i>p</i> = 0.685						
; itudy	logHR	SE(logHR)	Hazar	d Ratio	HR	95%-CI	Weight (common)	Weig (rando
R.extraction = Direct		,		1 :				
iuan S 2016	0.5259	0.2662			1.69	[1.00; 2.85]	8.9%	9.5
hang X 2016	0.7953	0.4262			2.21	[1.67; 8.88]	3.5%	4.0
	0.9895	0.4262		1	2.69		6.2%	4.0
ang G 2018						[1.44; 5.04]		
iu H 2019	0.6254	0.2283			1.87	[1.20; 2.92]	12.1%	12.4
hou N 2019	0.8663	0.3922			2.38	[1.11; 5.15]	4.1%	4.7
uo J 2021	1.2188	0.6896	_	+ • • •	- 3.38	[0.67; 10.03]	1.3%	1.6
common effect model				+	2.07	[1.60; 2.69]	36.2%	
andom effects model				4	2.07	[1.60; 2.69]		39.2
leterogeneity: $l^2 = 0\%$ , $\tau^2 =$	= 0, <i>p</i> = 0.8	35						
R.extraction = Indirect								
łu J 2016	1.1805	0.4295			3.26	[1.40; 7.56]	3.4%	4.0
i D 2016	1.3426	0.4905			- 3.83	[1.46; 10.01]	2.6%	3.1
ai H 2017	0.8746	0.3613			2.40	[1.18; 4.87]	4.8%	5.5
Vang Y 2017	1.0417	0.4083			2.40	[1.16; 4.67]	4.8%	4.4
		0.4083						
hang Y 2017	1.1823				3.26	[1.17; 9.11]	2.3%	2.7
iang X 2018	0.6653	0.2485			1.95	[1.20; 3.16]	10.2%	10.8
ang Q 2018	1.2493	0.4589			3.49	[1.42; 8.57]	3.0%	3.5
hu Y 2018	0.5122	0.1373			1.67	[1.27; 2.18]	33.6%	27.0
				•	2.06	[1.70; 2.51]	63.8%	
andom effects model	2-0.0416	0 - 0 222		-		[1.70; 2.51] [1.77; 3.04]	63.8%	60.4
andom effects model leterogeneity: $l^2 = 12.6\%$ ,	τ <sup>2</sup> = 0.0416	, <i>p</i> = 0.332		•	2.06 2.32	[1.77; 3.04]		60.8
tandom effects model leterogeneity: $l^2 = 12.6\%$ , s common effect model	τ <sup>2</sup> = 0.0416	, <i>p</i> = 0.332		• •	2.06 2.32 2.07		63.8%  100.0% 	
andom effects model leterogeneity: $l^2 = 12.6\%$ , sommon effect model	τ <sup>2</sup> = 0.0416	, <i>p</i> = 0.332	01 05	1 2	2.06 2.32 2.07 2.13	[1.77; 3.04]		
andom effects model leterogeneity: $l^2 = 12.6\%$ , common effect model andom effects model leterogeneity: $l^2 = 0.0\%$ , $t^2$	<sup>2</sup> = 0.0096,	p = 0.685	0.1 0.5		2.06 2.32 2.07	[1.77; 3.04]		
andom effects model leterogeneity: $l^2 = 12.6\%$ , s common effect model andom effects model leterogeneity: $l^2 = 0.0\%$ , $\tau^2$ est for subgroup difference	<sup>2</sup> = 0.0096, es (commor	p = 0.685 effect): $\chi_1^2 = 0.$	0.1 0.5	.981)	2.06 2.32 2.07 2.13	[1.77; 3.04]		
andom effects model leterogeneity: $l^2 = 12.6\%$ , $t^2$ common effect model andom effects model leterogeneity: $l^2 = 0.0\%$ , $t^2$ est for subgroup difference est for subgroup difference	<sup>2</sup> = 0.0096, es (commor	p = 0.685 effect): $\chi_1^2 = 0.$	0.1 0.5	.981)	2.06 2.32 2.07 2.13	[1.77; 3.04]		100.0
andom effects model elerogeneity: $l^2 = 12.6\%$ , 1: common effect model andom effects model elerogeneity: $l^2 = 0.0\%$ , $t^2$ est for subgroup difference est for subgroup difference	<sup>2</sup> = 0.0096, es (commor	p = 0.685 effect): $\chi_1^2 = 0.$	0.1 0.5 00, df = 1 (p = 0 34, df = 1 (p = 0	.981)	2.06 2.32 2.07 2.13	[1.77; 3.04]	 100.0% 	100.0 Weig
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iandom effects model leterogeneity: i <sup>2</sup> = 12.6%, isommon effect model andom effects model leterogeneity: i <sup>2</sup> = 0.0%, r <sup>2</sup> andom effects model leterogeneity: i <sup>2</sup> = 0.0%, r <sup>2</sup> leterogeneity: i <sup>2</sup> =	<sup>2</sup> = 0.0096, is (commor is (random <b>logHR</b> 0.5259 0.7953 0.9895	p = 0.685 effect): $\chi_1^2 = 0$ effects): $\chi_1^2 = 0$ <b>SE(logHR)</b> 0.2662 0.4262 0.3196	0.1 0.5 00, df = 1 (p = 0 34, df = 1 (p = 0	.981) .558)	2.06 2.32 2.07 2.13 10 HR 1.69 2.21 2.69	[1.77; 3.04] [1.77; 2.42] [1.79; 2.53] 95%-Cl [1.00; 2.85] [1.67; 8.88] [1.44; 5.04] [1.20; 2.92] [1.50; 2.64]	 100.0%  Weight (common) 8.9% 3.5% 6.2%	100.0 Weig (rando 9.5 4.0 6.5 12.4
andom effects model eterogeneity: I <sup>2</sup> = 12.6%, iommon effect model andom effects model eterogeneity: I <sup>2</sup> = 0.0%, r <sup>2</sup> etor subgroup difference est for subgroup difference ist for subgroup difference ist subgroup dist subgroup difference ist sub	<sup>2</sup> = 0.0096, is (commor is (random <b>logHR</b> 0.5259 0.7953 0.9895 0.6254	p = 0.685 effect): $\chi_1^2$ = 0 effect): $\chi_1^2$ = 0 <b>SE(logHR)</b> 0.2662 0.4262 0.3196 0.2283	0.1 0.5 00, df = 1 (p = 0 34, df = 1 (p = 0	.981) .558)	2.06 2.32 2.07 2.13 10 HR 1.69 2.21 2.69 1.87 1.99	[1.77; 3.04] [1.77; 2.42] [1.79; 2.53] 95%-Cl [1.00; 2.85] [1.67; 8.88] [1.44; 5.04] [1.20; 2.92]	 100.0%  Weight (common) 8.9% 3.5% 6.2% 6.2% 12.1%	100.0 Weig (rando 9.5 4.0 6.5 12.4
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landom effects model leterogeneity: $l^2 = 12.6\%$ , sommon effect model landom effects model leterogeneity: $l^2 = 0.0\%$ , $\tau^2$ and/or effects model leterogeneity: $l^2 = 0.0\%$ , $\tau^2$ witudy unalysis.model = Multi suan S 2016 hang X 2016 hang X 2016 hang C 2018 lui H 2019 common effect model leterogeneity: $l^2 = 0\%$ , $\tau^2$ = malysis.model = Uni lui J 2016	<ul> <li><sup>2</sup> = 0.0096, is (commorise (random)</li> <li>logHR</li> <li>0.5259</li> <li>0.7953</li> <li>0.9895</li> <li>0.6254</li> <li>= 0, p = 0.71</li> <li>1.1805</li> </ul>	p = 0.685 effect); $\chi_1^2$ = 0 effect); $\chi_1^2$ = 0 <b>SE(logHR)</b> 0.2662 0.4262 0.3196 0.2283 26	0.1 0.5 00, df = 1 (p = 0 34, df = 1 (p = 0	.981) .558)	2.06 2.32 2.07 2.13 10 HR 1.69 2.21 2.69 1.87 1.99 1.99	[1.77; 3.04] [1.77; 2.42] [1.79; 2.53] 95%Cl [1.00; 2.85] [1.67; 8.88] [1.44; 5.04] [1.44; 5.04] [1.50; 2.64] [1.50; 2.64]	 100.0%  Weight (common) 8.9% 3.5% 6.2% 6.2% 9.7%  3.4%	100.0 Weig (randoi 9.5 4.0 6.9 12.4 32.9
landom effects model leterogeneity: $l^2 = 12.6\%$ , sommon effect model landom effects model leterogeneity: $l^2 = 0.0\%$ , $\tau^2$ and/or effects model leterogeneity: $l^2 = 0.0\%$ , $\tau^2$ witudy unalysis.model = Multi suan S 2016 hang X 2016 hang X 2016 hang C 2018 lui H 2019 common effect model leterogeneity: $l^2 = 0\%$ , $\tau^2$ = malysis.model = Uni lui J 2016	<ul> <li><sup>2</sup> = 0.0096, ss (commores (random)</li> <li>logHR</li> <li>0.5259</li> <li>0.7953</li> <li>0.9895</li> <li>0.6254</li> <li>= 0, p = 0.71</li> </ul>	p = 0.685 effect); χ <sup>2</sup> <sub>1</sub> = 0 effects): χ <sup>2</sup> <sub>1</sub> = 0 <b>SE(logHR)</b> 0.2662 0.4262 0.3196 0.2283 26	0.1 0.5 00, df = 1 (p = 0 34, df = 1 (p = 0	.981) .558)	2.06 2.32 2.07 2.13 10 HR 1.69 2.21 2.69 1.87 1.99 1.99	[1.77; 3.04] [1.77; 2.42] [1.79; 2.53] 95%-Cl [1.00; 2.85] [1.47; 8.88] [1.44; 5.04] [1.50; 2.84] [1.50; 2.64]	 100.0%  Weight (common) 3.5% 6.2% 12.1% 30.7% 	100.0 Weig (randoi 9.5 4.0 6.9 12.4 32.9
landom effects model leterogeneity: $l^2 = 12.6\%$ , common effect model landom effects model landom effects model leterogeneity: $l^2 = 0.0\%$ , $\tau^2$ study ualysis.model = Multi uan S 2016 hang X 2016 hang X 2016 leterogeneity: $l^2 = 0\%$ , $\tau^2$ = unalysis.model = Uni lu J 2016 lo D 2016 la H 2017	<ul> <li><sup>2</sup> = 0.0096, is (commorise (random)</li> <li>logHR</li> <li>0.5259</li> <li>0.7953</li> <li>0.9895</li> <li>0.6254</li> <li>= 0, p = 0.71</li> <li>1.1805</li> </ul>	p = 0.685 effect); $\chi_1^2$ = 0 effect); $\chi_1^2$ = 0 <b>SE(logHR)</b> 0.2662 0.4262 0.3196 0.2283 26	0.1 0.5 00, df = 1 (p = 0 34, df = 1 (p = 0	.981) .558)	2.06 2.32 2.07 2.13 10 HR 1.69 2.21 2.69 1.87 1.99 1.99	[1.77; 3.04] [1.77; 2.42] [1.79; 2.53] 95%Cl [1.00; 2.85] [1.67; 8.88] [1.44; 5.04] [1.44; 5.04] [1.50; 2.64] [1.50; 2.64]	 100.0%  Weight (common) 8.9% 3.5% 6.2% 6.2% 9.2% 12.1% 30.7%  3.4%	100.0 Weig (randou 9.5 4.0 6.9 12.4 32.9 4.0 3.1
andom effects model eterogeneity: $l^2 = 12.6\%$ , isommon effect model andom effects model eterogeneity: $l^2 = 0.0\%$ , $\tau^2$ stor subgroup difference est for subgroup difference budy nalysis.model = Multi uian S 2016 hang X 2016 ang G 2018 lu H 2019 ommon effect model andom effects model eterogeneity: $l^2 = 0\%$ , $\tau^2$ = nalysis.model = Uni u 2016 in H 2017	<ul> <li><sup>2</sup> = 0.0096, is (commores (random</li> <li>logHR</li> <li>0.5259</li> <li>0.7953</li> <li>0.9895</li> <li>0.6254</li> <li>= 0, p = 0.7i</li> <li>1.1805</li> <li>1.3426</li> </ul>	p = 0.685 effect); χ <sup>2</sup> <sub>1</sub> = 0 effects): χ <sup>2</sup> <sub>1</sub> = 0 <b>SE(logHR)</b> 0.2662 0.4262 0.3196 0.2283 26	0.1 0.5 00, df = 1 (p = 0 34, df = 1 (p = 0	.981) .558)	2.06 2.32 2.07 2.13 10 HR 1.69 2.21 2.69 1.87 1.99 1.99	[1.77; 3.04] [1.77; 2.42] [1.79; 2.53] 95%Cl [1.00; 2.85] [1.67; 8.88] [1.44; 5.04] [1.50; 2.64] [1.50; 2.64] [1.40; 7.56] [1.40; 7.56]	 100.0%  Weight (common) 8.9% 6.2% 6.2% 6.2% 30.7%  3.4% 2.6%	100.0 Weig (rando 9.: 4.( 6.: 5. 32.: 4.( 3: 5.5
landom effects model leterogeneity: $l^2 = 12.6\%$ , kommon effect model landom effects model leterogeneity: $l^2 = 0.0\%$ , $\tau^2$ est for subgroup difference est for subgroup difference by tudy unal ysis.model = Multi uan S 2016 hang X 2016 ang G 2018 lu H 2019 formmon effect model landom effects model leterogeneity: $l^2 = 0\%$ , $\tau^2$ = unalysis.model = Uni lu J 2016 lo J 2016 la J 2017 Xang Y 2017	<ul> <li><sup>2</sup> = 0.0096, is (commoris) (random</li> <li>logHR</li> <li>0.5259</li> <li>0.7953</li> <li>0.9895</li> <li>0.6254</li> <li>a, p = 0.71</li> <li>1.1805</li> <li>1.3426</li> <li>0.8746</li> </ul>	p = 0.685 effect); $\chi_1^2 = 0$ effect); $\chi_1^2 = 0$ <b>SE(logHR)</b> 0.2662 0.4262 0.3196 0.2283 06 0.4295 0.4305 0.3613	0.1 0.5 00, df = 1 (p = 0 .34, df = 1 (p = 0	.981) .558)	2.06 2.32 2.07 2.13 10 HR 1.69 2.21 2.69 1.87 1.99 1.99 1.99	[1.77; 3.04] [1.77; 2.42] [1.79; 2.53] 95%-Cl [1.00; 2.85] [1.67; 8.88] [1.44; 5.04] [1.44; 5.04] [1.59; 2.64] [1.40; 7.56] [1.46; 7.56] [1.46; 7.56] [1.46; 7.56]	 100.0%  Weight (common) 8.9% 3.5% 6.2% 12.1% 30.7% 2.6% 4.8% 3.8% 3.8%	100.0 9.5 4.0 6.5 12.4 3.5 5.5 5.5 4.4
iandom effects model leterogeneity: $l^2 = 12.6\%$ , sommon effect model andom effects model leterogeneity: $l^2 = 0.0\%$ , $\tau^2$ andom effects model stor subgroup difference est for subgroup difference b) <b>tudy</b> <b>unalysis.model = Multi</b> Juan S 2016 hang X 2016 ang G 2018 leterogeneity: $l^2 = 0\%$ , $\tau^2 =$ <b>unalysis.model = Uni</b> ku J 2016 ID 2016 ID 2017 Vang Y 2017 Vang Y 2017	<ul> <li><sup>2</sup> = 0.0096, is (commor logHR</li> <li>0.5259</li> <li>0.7953</li> <li>0.9895</li> <li>0.6254</li> <li>= 0, p = 0.71</li> <li>1.1805</li> <li>1.3426</li> <li>0.8746</li> <li>0.8746</li> <li>1.0417</li> </ul>	p = 0.685 effect); χ <sup>2</sup> <sub>1</sub> = 0 effects): χ <sup>2</sup> <sub>1</sub> = 0 <b>SE(logHR)</b> 0.2662 0.4262 0.3196 0.2283 0.6 0.4295 0.4905 0.3613 0.4095	0.1 0.5 00, df = 1 (p = 0 .34, df = 1 (p = 0	.981) .558)	2.06 2.32 2.07 2.13 10 HR 1.69 2.21 2.69 2.21 2.69 1.99 1.99 1.99	[1.77; 3.04] [1.77; 2.42] [1.79; 2.53] 95%-Cl [1.00; 2.85] [1.67; 8.88] [1.44; 5.04] [1.50; 2.64] [1.50; 2.64] [1.40; 7.56] [1.46; 10.01] [1.18; 4.63] [1.77; 9.1]	 100.0% (common) 8.9% 3.5% 6.2% 12.1% 30.7%  3.4% 2.6% 4.8% 3.8%	100.0 Weig (randor 9.5 4.0 6.5 5.1 2.4 32.6 4.4 3.2 5.5 5.5 4.4 4.2 7.
landom effects model leterogeneity: $l^2 = 12.6\%$ , kommon effect model landom effects model leterogeneity: $l^2 = 0.0\%$ , $\tau^2$ est for subgroup difference est for subgroup difference by tudy unalysis.model = Multi Juan S 2016 hang X 2016 hang X 2018 iu H 2019 formmon effect model landom effects model leterogeneity: $l^2 = 0\%$ , $\tau^2$ = unalysis.model = Uni lu J 2016 iai H 2017 Yang Y 2017 hang Y 2017 hang X 2018	<sup>2</sup> = 0.0096, is (commor is (random logHR 0.5259 0.7953 0.6254 = 0, <i>p</i> = 0.71 1.1805 1.3426 0.8746 1.0417 1.1823 0.6653	<i>p</i> = 0.685 effect); <i>x</i> <sup>2</sup> <sub>1</sub> = 0 effect); <i>x</i> <sup>2</sup> <sub>1</sub> = 0 <b>SE(logHR)</b> 0.2662 0.4262 0.3196 0.2283 0.2283 0.6 0.4295 0.4905 0.3613 0.4095 0.3613 0.4005 0.3613 0.4005 0.2405 0.2405 0.2405 0.2405 0.2405 0.2405 0.2405 0.2405 0.2405 0.2405 0.2405 0.2405 0.2405 0.2405 0.2405 0.2405 0.2405 0.2405 0.2405 0.2524 0.2524 0.4255 0.45555 0.45555 0.45555 0.45555 0.455555 0.45555555 0.4555555555	0.1 0.5 00, df = 1 (p = 0 .34, df = 1 (p = 0	.981) .558)	2.06 2.32 2.07 2.13 10 HR 1.69 1.89 1.99 1.99 1.99 1.99	[1.77; 3.04] [1.77; 2.42] [1.79; 2.53] 95%Cl [1.00; 2.85] [1.67; 8.88] [1.44; 5.04] [1.44; 5.04] [1.44; 5.04] [1.44; 5.04] [1.44; 5.04] [1.46; 7.56] [1.46; 7.56] [1.46] [1.46; 7.56] [1.46; 7.56]\\[1.46; 7.56]\\[1.46; 7.56]\\[1.46; 7.56]\\[1.46; 7.56]\\[1.46] [1.46; 7.56]\\[1.46; 7.	 100.0% (common) 8.9% 3.5% 6.2% 12.1% 30.7%  3.4% 2.6% 4.8% 3.3% 2.3%	100.0 Weig (rando 9.5 6.5 6.5 12.4 32.6 4.0 3.1 2.4 4.0 3.1 2.7 12.4 12.4 12.4 12.4 12.4 12.4 12.4 12.4
iandom effects model leterogeneity: $l^2 = 12.6\%$ , isommon effect model andom effects model leterogeneity: $l^2 = 0.0\%$ , $\tau^2$ andom effects model set for subgroup difference est for subgroup difference b) tudy unalysis.model = Multi auan S 2016 hang C 2018 iu H 2019 formmon effect model tandom effect model leterogeneity: $l^2 = 0\%$ , $\tau^2 =$ analysis.model = Uni lu J 2016 iai H 2017 Yang Y 2017 Yang Y 2017 Jang C 2018	<ul> <li><sup>2</sup> = 0.0096, is (commor is (random) is (random) is (random) 0.5259</li> <li>0.7953</li> <li>0.9835</li> <li>0.6254</li> <li>= 0, p = 0.7</li> <li>1.1805</li> <li>1.3426</li> <li>0.8746</li> <li>1.0417</li> <li>1.1823</li> <li>0.6653</li> <li>1.2493</li> </ul>	<i>p</i> = 0.685 ieffect); <i>χ</i> <sup>2</sup> <sub>1</sub> = 0 effect); <i>χ</i> <sup>2</sup> <sub>1</sub> = 0 <b>SE(logHR)</b> 0.2662 0.4295 0.4295 0.4295 0.4295 0.316 0.4295 0.3613 0.5240 0.2485 0.4285	0.1 0.5 00, df = 1 (p = 0 .34, df = 1 (p = 0	.981) .558)	2.06 2.32 2.07 2.13 10 HR 1.69 2.21 2.69 2.21 2.69 1.99 1.99 1.99 1.99 1.99	[1.77; 3.04] [1.77; 2.42] [1.79; 2.53] 95%Cl [1.07; 8.88] [1.44; 5.04] [1.67; 8.88] [1.44; 5.04] [1.50; 2.64] [1.50; 2.64] [1.50; 2.64] [1.46; 10.01] [1.17; 9.11] [1.17; 6.31] [1.17; 9.316] [1.42; 8.57]	 Weight (common) 8.9% 3.5% 6.2% 30.7%  3.4% 2.6% 4.8% 3.8% 5.23% 5.23%	100.0 Weig (randof 9.5 4.0 3.1 2.4 4.0 3.1 2.4 4.4 2.7 5.5 5.5 5.5 5.5 5.5 5.5 5.5 5.5 5.5 5
landom effects model leterogeneity: $l^2 = 12.6\%$ , icommon effect model landom effects model leterogeneity: $l^2 = 0.0\%$ , $\tau^2$ and/or effects model leterogeneity: $l^2 = 0.0\%$ , $\tau^2$ itudy analysis.model = Multi uan S 2016 hang X 2016 hang X 2018 lui H 2019 leterogeneity: $l^2 = 0\%$ , $\tau^2$ = analysis.model = Uni lui J 2016 i D 2016 i D 2017 hang Y 2017 hang Y 2017 hang Y 2018 ang Q 2018 hu Y 2018	<ul> <li><sup>2</sup> = 0.0096, is (commores (random))</li> <li>logHR</li> <li>0.5259</li> <li>0.7953</li> <li>0.9895</li> <li>0.6254</li> <li>a.9895</li> <li>a.6254</li> <li>a.8746</li> <li>a.8746</li> <li>a.8746</li> <li>a.8746</li> <li>a.8746</li> <li>a.8746</li> <li>a.8748</li> <li>b.8748</li> <li>b.87</li></ul>	<i>p</i> = 0.685 effect); <i>x</i> <sup>2</sup> <sub>1</sub> = 0 effects); <i>x</i> <sup>2</sup> <sub>1</sub> = 0 <b>SE(logHR)</b> 0.2662 0.4262 0.3196 0.2283 0.2283 0.4295 0.4905 0.4693 0.5406 0.42455 0.4659 0.4559 0.4559	0.1 0.5 00, df = 1 (p = 0 .34, df = 1 (p = 0	.981) .558)	2.06 2.32 2.07 2.13 10 HR 1.69 2.21 2.69 2.21 2.69 1.99 1.99 1.99 1.99 1.99 1.99 1.99 1	[1.77; 3.04] [1.77; 2.42] [1.79; 2.53] [1.79; 2.53] [1.67; 8.88] [1.44; 5.04] [1.44; 5.04] [1.44; 5.04] [1.46; 7.56] [1.46; 7.56] [1.46; 7.56] [1.46; 7.56] [1.46; 7.56] [1.47; 7.56] [1.47	 100.0% (common) 8.9% 3.5% 6.2% 12.1% 30.7%  3.4% 2.6% 4.8% 3.8% 2.3% 3.0% 3.3.6%	100.0 Weig (randor 9.9. 5.5 12.4 32.9 32.9 32.9 32.9 10.8 3.5 5.5 5.5 5.5 5.5 5.5 5.5 5.5 5.5 10.8 10.8 10.8 10.8 10.8 10.8 10.8 10.8
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tandom effects model leterogeneity: $l^2 = 12.6\%$ , isommon effect model indication effect model leterogeneity: $l^2 = 0.0\%$ , $t^2$ andom effects model leterogeneity: $d^2$ enormality tudy unalysis.model = Multi isun S 2016 hang X 2016 ang G 2018 Lu H 2019 lu H 2019 lu H 2019 lu H 2019 lu H 2019 lu J 2016 al H 2017 hang Y 2017 hang Y 2017 hang X 2018 ang Q 2018 hu Y 2017 hang X 2018 hu Y 2017 hang X 2018 hu Y 2017 hang X 2018 hu Y 2017 hang X 2018 hu Y	<sup>2</sup> = 0.0096, is (commo- logHR 0.5259 0.6254 0.6254 0.6254 1.1805 1.3426 0.8746 0.8746 0.8746 0.8746 0.8653 0.5122	<ul> <li><i>p</i> = 0.685</li> <li>effect); <i>x</i><sub>1</sub><sup>2</sup> = 0</li> <li>effect); <i>x</i><sub>1</sub><sup>2</sup> = 0</li> <li>effects); <i>x</i><sub>1</sub><sup>2</sup> = 0</li> <li>0.2262</li> <li>0.4262</li> <li>0.4295</li> <li>0.4905</li> <li>0.3613</li> <li>0.4905</li> <li>0.5240</li> <li>0.2485</li> <li>0.4599</li> <li>0.1373</li> <li>0.3922</li> </ul>	0.1 0.5 00, df = 1 (p = 0 .34, df = 1 (p = 0	.981) .558)	2.06 2.32 2.07 2.13 10 10 10 10 1.69 2.21 2.69 1.87 1.99 1.87 1.99 1.99 1.99 1.99 1.99 3.26 3.83 3.26 3.49 3.49 3.49 3.49 2.38	[1.77; 3.04] [1.77; 2.42] [1.79; 2.53] 95%Cl [1.00; 2.85] [1.47; 8.86] [1.44; 5.04] [1.50; 2.64] [1.50; 2.64] [1.46; 10.01] [1.46; 10.01]\\[1.46; 10.01]\\[1.46; 10.01]\\[1.46; 10.01]\\[1.46; 10.01]\\[1.46; 10.01]\\[1.46; 10.01]\\[1.46; 10.01]\\[1.46; 10.01]\\[1.46; 10.01]\\[1.46; 10.01]\\[1.46; 10.01]\\[1.46; 10.01]\\[1.46; 10.01]\\[1.46; 10.01]\\[1.46; 10.01]\\[1.46; 10.01]\\[1	 Weight (common) 8.9% 3.5% 6.2% 6.2% 6.2% 6.2% 3.4% 2.6% 2.6% 3.8% 3.8% 3.3% 3.3%	100.0 Weig (rando 9.9.4.( 6.8. 12.4 3.2.5 4.4 4.2.5 5.5 4.4 4.2.7 10.0 3.3.7 27.7 4.7 1.6
common effect model landom effects model landom effects model andom effects model andom effects model landom effects model landom effects model landom effects model set for subgroup difference est for subgroup difference est for subgroup difference est for subgroup difference est for subgroup difference land set for subgroup difference est for subgroup difference	<sup>2</sup> = 0.0096, is (commor is (random 0.5259 0.7953 0.6254 0.9995 0.6254 1.1805 1.3426 0.8746 1.1423 0.6653 0.8746 1.1423 0.5122 0.8663 1.2188	<i>ρ</i> = 0.685 effect); χ <sup>2</sup> <sub>1</sub> = 0 effects); χ <sup>2</sup> <sub>1</sub> = 0 <b>SE(logHR)</b> 0.2662 0.4262 0.3196 0.2283 0.6896 0.4295 0.4905 0.4905 0.4905 0.4905 0.4905 0.4693 0.5240 0.2485 0.4595 0.4595 0.4595 0.4595 0.4595 0.4595 0.4595 0.4595 0.4595 0.4595 0.4595 0.4595 0.4595 0.4595 0.4595 0.5245 0.5255 0.5555 0.5555 0.5555 0.5555 0.5555 0.5555 0.5555 0.5555 0.55555 0.55555 0.55555 0.55555 0.55555 0.555555 0.5555555555	0.1 0.5 00, df = 1 (p = 0 .34, df = 1 (p = 0	.981) .558)	2.06 2.32 2.07 2.13 10 10 10 10 1.69 2.21 1.69 2.21 1.99 1.99 1.99 1.99 1.99 1.99 1.9	[1.77; 3.04] [1.77; 2.42] [1.79; 2.53] 95%Cl [1.00; 2.85] [1.47; 8.88] [1.44; 5.04] [1.59; 2.64] [1.46; 10.01] [1.46; 10.01] [1.46; 10.01] [1.46; 10.01] [1.46; 10.01] [1.46; 10.01] [1.46; 10.01] [1.46; 10.01] [1.47; 8.18] [1.42; 8.16] [1.42; 8.16] [1.44; 8.17] [1.44; 8.17] [1	 100.0% (common) 8.9% 3.5% 6.2% 12.1% 30.7%  3.4% 2.6% 4.8% 3.3% 3.3% 3.3%	60.8 100.0 (randor (randor 6.5 4.0 4.0 3.1 2.4 3.2 5 5 4.4 4.7 3.2 5 5 4.4 4.7 3.2 5 5 5 4.4 4.7 3.2 5 5 5 4.6 4.7 10 6 5 5 5 5 4.6 10 6 5 5 5 5 10 6 5 5 10 10 10 10 10 10 10 10 10 10 10 10 10
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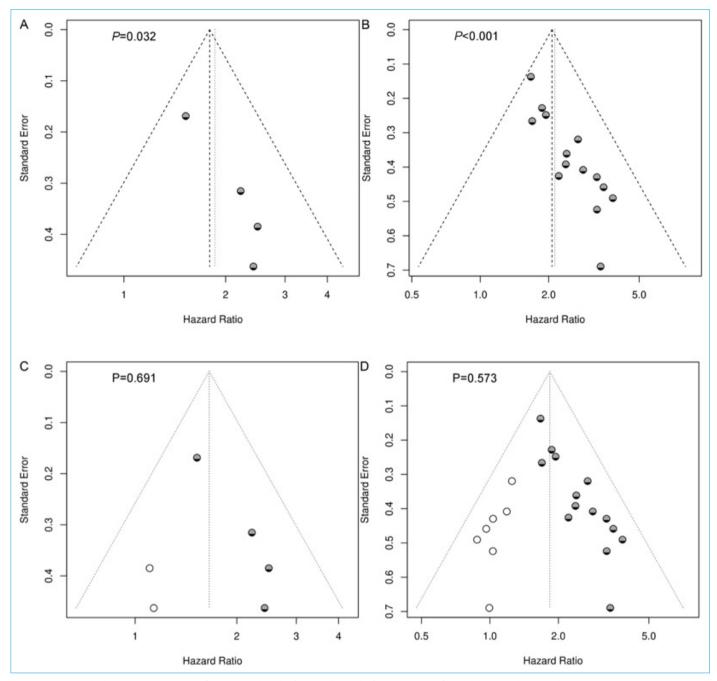


Figure 3. Funnel plot asymmetry tests for PFS and OS before (a, b) and after adjusting for publication bias (c, d).

ute as a promising biomarker for diagnosis and prognosis, but no comprehensive evaluations have been made to date. We conducted a systematic review and meta-analysis on 14 studies and noted that lower tissue miR-613 expression levels are related to advanced diseases, larger tumor size, and lymph node metastasis in cancers (Fig. 4). Impressively, We found highly consistent evidence across studies that low miR-613 is an unfavorable prognostic marker for PFS and OS regardless of data extraction methods (Fig. 2). Despite of publication bias existence, the adjusted HR values remain significant. Meanwhile, some reviewed studies but not eligible for this meta-analysis, where their results strengthen the hypothesis that low miR-613 is related to therapy resistance and poor prognosis.<sup>[5,31,32]</sup> Hence, these findings will lead the way for future studies before miR-613 becomes a prognostic biomarker clinically.

Regarding the limitations of meta-analysis, We suggest that subsequent studies should deal with liquid biopsy samples such as plasma, serum, body fluids, and urine, leading to practical and easy miR-613 testing in the real

A								в								
A	Experimental	C	ontrol						Experim	nental	С	ontrol				
Study	Events Total			Odds Ratio	OR	95%-CI	Weight	Study	Events	Total	Events	Total	Odds Ratio	OR	95%-CI	Weight
Guan S 2016	22 43	6	17		- 1.92	[0.60; 6.13]	4.4%	Guan S 2016	25	43	10	17		0.97	[0.31; 3.04]	8.0%
Hu J 2016	25 50	26	50		0.92	[0.42; 2.02]	9.6%	Cai H 2017	15	28	12	31		1.83	[0.65; 5.15]	9.4%
Zhang X 2016	54 114	64	122		0.82	[0.49; 1.36]	22.5%									
Cai H 2017	16 28	14	31		1.62	[0.58; 4.53]	5.6%	Wang Y 2017	17	32	18	32		0.88	[0.33; 2.36]	10.3%
Wang Y 2017	20 32	18	32		1.30	[0.48; 3.52]	5.9%	Zhang Y 2017	13	31	7	14		0.72	[0.20; 2.57]	6.6%
Zhang Y 2017	5 31	2	14		- 1.15	[0.20: 6.82]	1.9%	Jiang X 2018	23	34	23	30		0.64	[0.21; 1.93]	8.4%
Jiang X 2018	14 34	11	30		1.21	[0.44; 3.32]	5.8%	Yang G 2018	103	186	40	90		1.55	[0.93; 2.57]	28.6%
Yang G 2018	90 186	46	90		0.90	[0.54: 1.48]	23.2%	Liu H 2019	77	112	48	64		0.73	[0.37; 1.47]	18.4%
Liu H 2019	67 112	46	64		0.58	[0.30; 1.13]	13.4%	Zhou N 2019	24	32	17	20		0.53	[0.12; 2.29]	5.0%
Zhou N 2019	17 32	11	20		0.93	[0.30; 2.85]	4.7%	Luo J 2021	9	16	10	16		0.77	[0.12; 2.23]	5.4%
Luo J 2021	9 16	8	16	· · · · · · · · · · · · · · · · · · ·	1.29	[0.32; 5.17]	3.0%	LU0 J 2021	9	10	10	10		0.77	[0.19, 3.17]	5.4%
	• ••					[0:02, 0:17]	01070	_								
Random effects mod	el 678		486	+	0.94	[0.74; 1.20]	100.0%	Random effects m		514		314		1.00	[0.72; 1.41]	100.0%
Heterogeneity: $l^2 = 0.0\%$	$t_{0}, \tau^{2} = 0, p = 0.837$							Heterogeneity: $I^2 = 0$	$.0\%, \tau^2 = 0.0383,$	p = 0.5	571					
				0.2 0.5 1 2 5									0.2 0.5 1 2 5			
с								D								
C	Experimental	Co	ontrol					b	Experim	ental	C	ontrol				
Study	Events Total	Events		Odds Ratio	OR	95%-CI	Weight	Study				Total	Odds Ratio	OR	95%-CI	Weight
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Guan S 2016	23 43	4	17		3.74	[1.05; 13.32]	5.0%	Guan S 2016	38	43	10	17	1	5.32	[1.39; 20.37]	6.0%
Hu J 2016	26 50	14	50		2.79	[1.21: 6.39]	10.0%									
Zhang X 2016	79 114	40	122		4.63	[2.67; 8.01]	17.3%	Hu J 2016	28	50	12	50			[1.71; 9.49]	12.4%
Cai H 2017	21 28	14	31		3.64	[1.20; 11.05]	6.3%	Zhang X 2016	50	114	34	122			[1.18; 3.48]	22.2%
Wang Y 2017	26 32	16	32		4.33	[1.41; 13.36]	6.2%	Cai H 2017	21	28	12	31		4.75	[1.55; 14.56]	8.1%
Zhang Y 2017	22 31	7	14		2.44	[0.66; 9.00]	4.8%	Zhang Y 2017	19	31	6	14		2.11	[0.59; 7.61]	6.5%
Jiang X 2018	10 34	12	30		0.62	[0.22; 1.76]	7.1%	Yang G 2018	101	186	17	90		5.10	[2.80; 9.31]	19.8%
Yang G 2018	110 225	34	125	-	2.56	[1.60; 4.11]	20.2%	Liu H 2019	94	112	41	64		2.93	[1.43; 6.00]	15.9%
Liu H 2019	82 112	28	64		3.51	[1.84; 6.71]	14.2%	Zhou N 2019	18	32	3	20			[1.77; 29.91]	5.5%
Zhou N 2019	20 32	6	20		3.89	[1.18; 12.84]	5.6%	Luo J 2021	14	16	7	16			[1.52; 53.40]	3.6%
Luo J 2021	13 16	6	16			[1.44; 36.22]	3.3%	LUU J 2021	14	10	/	10		9.00	[1.52, 55.40]	3.0%
Random effects mode	el 717		521	+	3.08	[2.27; 4.18]	100.0%	Random effects m		612		424	<b>_</b>	3.62	[2.55; 5.14]	100.0%
Heterogeneity: I2 = 27.8	%, $\tau^2 = 0.0619$ , $p = 0$	180						Heterogeneity: $I^2 = 1$	$2.6\%, \tau^2 = 0.0685$	, p = 0.3	329		1 111 1			
				0.1 0.51 2 10									0.1 0.51 2 10			
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-	Experimental	Co	ontrol						Experim	ental	C	ontrol				
Study	Events Total	Events	Total	Odds Ratio	OR	95%-CI	Weight	Study	Events	Total	Events	Total	Odds Ratio	OR	95%-CI	Weight
Guan S 2016	23 43	10	17		0.80	[0.26; 2.51]	8.6%								· · · · · · · · · · · · · · · · · · ·	
Hu J 2016	39 50	19	50			[2.40; 13.94]	9.8%	Guan S 2016	13	43	6	17		0.79	[0.24; 2.61]	12.8%
Zhang X 2016	49 114	39	122		1.60	[0.94; 2.73]	11.2%	Zhang X 2016	53	104	12	122		9.53	[4.69; 19.36]	15.8%
Cai H 2017	18 28	13	31		2.49	[0.87; 7.14]	9.0%	Cai H 2017	19	28	11	31		3.84	[1.30; 11.32]	13.5%
Wang Y 2017	21 32	10	32			[1.48; 11.94]	9.0%	Zhang Y 2017	16	31	3	14			[0.91; 16.81]	11.2%
Zhang Y 2017	18 31	2	14	1.		[1.58; 43.62]	6.5%	Jiang X 2018	7	34	12	30		0.39	[0.13; 1.18]	13.3%
Jiang X 2018	9 34	18	30	_	0.24	[0.08; 0.69]	9.0%	Yang G 2018	88	225	33	125		1.79	[1.11; 2.89]	17.0%
Yang G 2018	83 225	29	125		1.93	[1.18; 3.18]	11.4%		64	112	27	64				
Liu H 2019	102 112	47	64	-		[1.57; 8.67]	9.9%	Liu H 2019	64	112	27	64		1.83	[0.98; 3.40]	16.3%
Zhou N 2019	12 32	10	20	_	0.60	[0.19; 1.86]	8.7%									
Luo J 2021	12 16	5	16			[1.40; 31.05]	6.9%	Random effects m		577		403		2.08	[0.95; 4.55]	100.0%
200 0 2021	12 10	5	10		0.00	[1.40, 31.00]	0.376	Heterogeneity: $I^2 = 8$	$0.8\%, \tau^2 = 0.8760$	, p < 0.	001		1 1 1 1 1			
Random effects mod	el 717		521	-	2.05	[1.11; 3.78]	100.0%						0.1 0.5 1 2 10			
Heterogeneity: $l^2 = 73.5^{\circ}$		.001			2.00											
				0.1 0.51 2 10												

Figure 4. Association of low miR-613 levels with old age (a), male gender (b), advanced disease staging (c), lymph-node metastasis (d), larger tumor size (e), and poor tumor differentiation (f).

world. The non-invasive approach also allows us to evaluate the prognostic role of miR-613 adequately because it is not certain that miR-613 expression levels in the blood are matched directly to tissue samples. Moreover, We still do not know whether using a single or both types of samples will be best. Secondly, future studies should be done globally other than Asian ethnicities due to the certain genetic variations between populations.[33] Thirdly, prognostic assessments on other specific regimens such as chemotherapy, radiotherapy, and targeted therapies are encouraged. In that trials, a multivariate analysis model combined miR-613 with other diagnostic tests and clinical features should be applied, which were less observed in this meta-analysis. <sup>[13,16,22,24]</sup> Finally, standardization of the RT-gPCR technique used in detecting miR-613 is requested to increase reproducibility between centers. Such variables may include time and conditions of sample storage, processing, extraction method, normalization gene, and cut-off value.[34] For example, experts recommended using miR-16 and miR-103a as endogenous normalization control alternatives to U6 in the RT-qPCR reactions.[35,36]

## Conclusion

In conclusion, this meta-analysis indicates that low expression of miR-613 in tissue samples is associated with advanced disease staging, larger tumor size, and lymph node metastasis in cancers. Importantly, low miR-613 is a poor prognosis factor for PFS and OS, enabling its clinical usage near future.

#### Disclosures

Peer-review: Externally peer-reviewed.

Conflict of Interest: None declared.

Authorship Contributions: Concept – T.T.P., S.T.N.; Design – T.T.P., S.T.N., T.T.N.; Supervision – T.T.P., S.T.N., T.T.N.; Materials – S.T.N., T.T.N.; Data collection &/or processing – V.T.T., T.T.P., K.Q.H., T.T.H., S.P.P., H.T.N., H.D.T., L.T.N., T.H.P., B.T.L.; Analysis and/or interpretation – V.T.T., T.T.P., K.Q.H.; Literature search – T.T.P., S.T.N.; Writing – V.T.T., T.T.P., K.Q.H.; Critical review – S.T.N., T.T.N.

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