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REVIEW

Survival advantage and clinicopathological significance of microRNA-22 in cancers: a meta-analysis

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Abstract: An increasing number of studies revealed that microRNA-22 as a biomarker may play a significant role in the cancer patients' prognosis, but the accurate prognosis value of microRNA-22 remains somewhat controversial. Thus, we comprehensively searched the database and performed this study to explicate the accurate value of microRNA-22 in the cancer patients' prognosis. This meta-analysis revealed that elevated expression of microRNA-22 correlated with good overall survival (OS) and disease-free survival (DFS)/progression-free survival (PFS)/recurrence-free survival (RFS) in cancers, while no significant association was found in metastasis-free survival (MFS)/distant metastasis-free survival (DMFS). Through the subgroup analysis for OS and DFS/PFS/RFS, we found that elevated expression of miR-22 significantly correlated with good prognosis in most subgroups, while it predicted a worse prognosis in nasopharyngeal carcinoma subgroup. And besides that, elevated expression of miR-22 was negatively correlated with TNM stage, lymph node metastasis, distant metastasis and recurrence, while no significant association was found between microRNA-22 expression and T stage, tumor differentiation, and lymphatic invasion. Our meta-analysis demonstrated that elevated expression of microRNA-22 predicted a good OS and DFS/PFS/RFS in cancer patients; meanwhile, its high expression also means earlier TNM stage, and lower likelihoods of lymph node metastasis, of distant metastasis and of recurrence. If we regularly monitor miR-22 expression in cancer patients, it might be useful for us to predict cancer prognosis in future clinical applications.

Keywords: hsa-miR-22, cancer, prognosis, clinicopathological, biomarker, meta-analysis

Introduction

Due to the growth of population, the deterioration of the environment and unhealthy lifestyle, cancer has become the leading cause of death worldwide for a long time, and the incidence of cancer has increased substantially in recent years.[1] Despite the extensive use of surgical operations, radiotherapy, chemotherapy, hormone treatment and biological treatment, the prognosis in most cancers remains unsatisfactory.[2,3] Thus, it is of great clinical value for researchers to find valuable prognosis indicators, which may help doctors promote early prognostic classification and find novel therapy strategy for cancer patients. Among them, microRNAs have been an attractive direction of research in recent years.

MicroRNAs, approximately 22–25 nucleotides in length and abundant among plants, animals and even viruses,[4,5] belong to a single-stranded noncoding RNA. The sequence of most microRNAs is highly conserved, but not all. In fact, a substantial portion of microRNAs in many species is species specific.[6–9] The microRNAs of animals and most plants exert their regulatory effect by base-pairing with the 3′-untranslated region of

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target mRNA and inhibiting target gene translation to protein,[10] leading to mRNA degradation or translational inhibition.[5,11] Unlike animal miRNAs, some plant miRNAs can pair with genic regions that are not in 3′UTRs and direct cleavage of the target gene.[12] In various kinds of tumor, the aberrantly expressed miRNAs have been observed,[13] and they contribute significantly to many biological processes of the tumor, such as cellular growth, proliferation, apoptosis, development, differentiation, angiogenesis, and metastasis.[14,15] Therefore, researchers hold great expectations toward microRNAs as conceivable biomarkers for cancer prognosis.

As a cancer-related microRNA located in chromosome 17 (17p13.3),[16] microRNA-22 (miR-22, miRNA-22, hsa-miR-22) was one of the most frequently studied microRNAs, which has been revealed to participate in many biological processes such as cardiac remodeling, cell cycle control,[17–19] proliferation, differentiation and apoptosis, and their deregulation is also a forewarning of human cancer.[20] Many previous studies have demonstrated a significant association between high miR-22 expression and good prognosis in cancer patients, such as epithelial ovarian cancer (EOC),[21–23] hepatocellular carcinoma (HCC),[24,25] and breast cancer (BC);[26–28] but some studies did not reveal significant association,[29] and still others showed a negative correlation.[30–32] Thus, we conducted this meta-analysis to clarify the accurate correlation between miR-22 expression and the prognosis, as well as the clinicopathological significance of cancer patients.

Method

We carried out this meta-analysis as per the guidelines of PRISMA criteria.[33]

Search strategy, inclusion and exclusion criteria

We carefully searched Web of Science, PubMed and Embase to identify relevant literature published until 20 June 2017; gray literature was not found during our meta-analysis. Keywords used in the search strategy were "miR-22 OR miRNA-22 OR microRNA-22 OR hsa-miR-22" (all fields) AND "cancer OR neoplasm OR carcinoma OR tumor" (all fields). We did not employ any advanced limitations during the searching period. The inclusion criteria of this study are as follows: i) the correlation between miR-22 expression levels and cancer patients' prognosis or clinicopathological significance was studied; (ii the expression level of miR-22 was measured in tumor tissue, serum or urine; iii) the HR for prognostic outcome indicator according to miR-22 expression level either had to be reported or could be calculated from the information presented, and we described the method of analysis in the data extraction in detail;[34,35] iv) when several studies used the same sample source, the most accurate and most representative one was chosen, only in this way can we avoid the overlap between cohorts. Finally, articles that fulfilled the aforementioned eligibility criteria were further excluded on the basis of following criteria: i) non-English articles, meeting letters or review articles; ii) not dichotomous variable or human studies and iii) lack of essential information.

Quality assessment

We evaluated the quality of all the articles on the basis of a critical review checklist of the Dutch Cochrane Centre, which was previously described by MOOSE.[36,37] The key points of the quality assessment were as follows: i) the country and ethnic composition; ii) clear definition of cutoff value; iii) clear definition of outcome assessment; iv) the measurement method of miR-22; v) the type of cancer and vi) sufficient period of follow-up. Studies were excluded if they did not mention all the key points aforementioned.

Data extraction

The following data were carefully extracted by two investigators independently: i) publications details, including first author and publication year; ii) main characteristic of this study population, including nationality, cancer type, sample number and clinicopathological features; iii) the cutoff value and measurement method of miR-22; iv) HRs of elevated expression levels of miR-22 for overall survival (OS), recurrence-free survival (RFS), disease-free survival (DFS), progression-free survival (PFS), metastasis-free survival (MFS) and distant metastasis-free survival (DMFS) and v) if a study reported the results by both univariate and multivariate analysis, the multivariate analysis was our first choice. Because the multivariate analysis weakens the effects of confounding factors. Additionally, if only Kaplan–Meier curves are available, the methods described by Parmar et al[34] and Tierney et al[35] were used to calculate HR and 95% CI. The Engauge Digitizer version 9.8 was used to read Kaplan–Meier survival curves and get the data we need, and we repeated this process three times to reduce variability. To reduce reading

variability, three researchers read the curves independently and disagreements were discussed among themselves.

Statistical analysis

HR and their 95% CI were used to evaluate the correlation between miR-22 high expression and cancer patients' prognosis. Generally, a 95% CI of HR completely >1 in the forest plot suggested that elevated expression of miR-22 correlated with poor prognosis of cancer patients. If the 95% CI of HR contains one, it indicates that no significant association exists between miR-22 expression and the cancer patients' prognosis. In addition, if the pooled HR <1 and 95% CI completely lower than one, the high expression of miR-22 predicted a good OS. We employed the Cochran Q test (significant at $P<0.10$) and Higgins I^2 statistic (ranging from 0% to 100%)[38] to test heterogeneity of this meta-analysis, which was considered statistically significant at $P_{heterogeneity}$ <0.1 or $I^2>50\%$. If $P_{heterogeneity}$ >0.1 and $I^2<50\%$, we ignored the influence of heterogeneity, and a fixed-effects model[39] was employed to pool the overall result; otherwise, the random-effects model was employed.[40] Funnel plot, Begg's test, and Egger's test were used to estimate the publication bias (publication bias was statistically significant for $P<0.05$).[41] Sensitivity analysis was performed to evaluate the stability of the results and further seek out the sources of heterogeneity. A two–tailed $P<0.05$ was considered statistically significant.

Result

Summary of enrolled studies

Using the searching strategy aforementioned, we found 213 articles in PubMed, 500 articles in Embase and 349 articles in Web of Science. Seven hundred and sixty articles remained after duplicates were removed. We excluded 724 articles after glancing over the title, abstract, and main figures; then 10 articles were further removed as per the evaluation of full text (Figure 1). Finally, 26 articles spanning 28 studies, which revealed the correlation between miR-22 expression and cancer patients' prognosis or clinicopathological significance, were considered qualified for current meta-analysis. In the course of searching, no gray literature was found in these articles. The main characteristics of eligible articles were systematically summarized in Table 1. The 26 included articles covered participants from China, USA and Japan, among whom 5467 participants had OS data, 3534 had DFS/PFS/RFS/DMFS/MFS data and 846 had clinicopathological features data. Studied cancers include HCC, BC, esophageal squamous cell carcinoma, colorectal cancer (CRC), EOC, gastric cancer (GC), osteosarcoma (OST), myelodysplastic syndrome (MDS), nasopharyngeal carcinoma (NPC), renal cell carcinoma, primary plasma cell leukemia, bladder cancer and glioma. Notably, either the mean value or the median value was selected as the cutoff value in most articles.

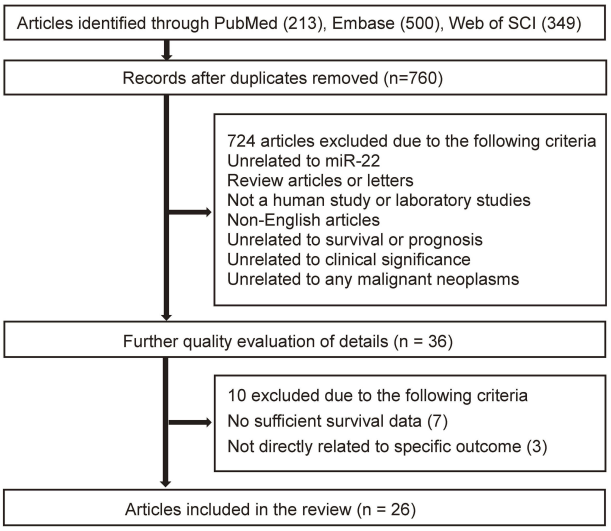

Figure 1 Flowchart of the study selection process.

Relationship between miR-22 expression and OS

Due to obvious heterogeneity among the studies (I^2=78.4%), which included 19 studies about OS, a random-effects model was employed to pool all HRs of OS and their 95% CIs. As revealed in Figure 2, high expression of miR-22 represents a good OS of cancer patients (HR =0.76, 95% CI: 0.62–0.92), indicating that patients with high miR-22 expression may have longer survival time.

Afterward, subgroup analyses were performed on the basis of cancer type, the anatomical system of cancer (digestive system and reproductive system), the ethnic background of participants (Asian and Caucasian), the sample type (tissue or serum), the main pathological type (squamous cell carcinoma and adenocarcinoma), tissue preservation method (formalin-fixed paraffin-embedded, frozen tumor tissue, Fresh tissue) and the miR-22 assay method (q-PCR and ISH). As no significant heterogeneity was found among HCC (I^2=0.0%), CRC (I^2=49.6%) and NPC (I^2=0.0%) (Figure S1B, Table 2), a fixed-effects model was employed to pool the HRs of OS. We also pooled the HRs of EOC, GC and BC via random-effects model as a result of significant heterogeneity (Figure S1A, Table 2).

Table 1 Main characteristics of 26 studies after screening

Study ID	Origin of population	Tissue type	Disease	Specimen	Number	Stage	miR-22 assay	Cutoff	Survival analysis	HR (95% CI)	*p*-value	Follow-up time (months)
Wan 2014[21]	China	Fresh	EOC	Tissue	109	I-IV	qRT-PCR	Median value	OS/PFS	Reported	0.007/0.005	60
Delfino 2013[23]	TCGA	–	EOC	Tissue	418/249	I-IV	qRT-PCR	NR	OS/RFS	Reported	<0.0001	160
Li 2013[42]	China	FTT	EOC	Tissue	45	I-IV	qRT-PCR	Mean values	OS/PFS	SC	0.550/0.175	80/160
Zhou 2013[25]	China	FTT	HCC	Tissue	192	I-IV	qRT-PCR	Median value	OS	SC	0.046	80
Zhang 2010[43]	China	–	HCC	Tissue	160	I-IV	qRT-PCR	Median value	DFS	SC	0.025	48
Chen 2016[24]	TCGA	FTT	HCC	Tissue	372	I-IV	qRT-PCR	Mean value	OS	Reported	0.0109	120
Zhang 2012[44]	China	FFPE	CRC	Tissue	86	I-IV	qRT-PCR	Median value	OS	Reported	0.042	68
Slattery 2015[29]	American	FTT	CRC	Tissue	1141	I-IV	qRT-PCR	Mean value	OS (Co/Re)	Reported	>0.05	120
Xia 2017[45]	China	–	CRC	Tissue	110	I-IV	qRT-PCR	log2 (miR-22)>0	RFS	Reported	0.0018	82
Zuo 2015[31]	China	Fresh	GC	Tissue	61	I-IV	qRT-PCR	Mean value	OS	SC	0.038	40
Tang 2015[46]	China	FFPE	GC	Tissue	89	I-IV	ISH	Expression score	–	–	–	–
Wang.2013[47]	China	FTT	GC	Tissue	98	I-IV	qRT-PCR	Median value	OS	Reported	0.04	60
Patel 2011[27]	GEO	Fresh	BC	Tissue	1809	NR	qRT-PCR	Mean value	OS/RFS/MFS	Reported	0.82/0.0047/0.06	170
Chen 2015[26]	China	FTT	BC	Tissue	122	I-IV	qRT-PCR	Median value	OS/DFS	Reported/SC	0.006/0.003	120
Yoshimoto 2011[28]	Japan	–	BC	Tissue	171	I-IV	qRT-PCR	Mean value	OS	Reported	0.67	150
Song 2013[30]	American	FTT	BC	Tissue	108	I-IV	qRT-PCR	NR	RFS	Reported	0.022	84
Fan 2016[48]	China	FTT	RCC	Tissue	68	I-IV	qRT-PCR	Mean value	–	–	–	–
Zhang 2016[49]	China	FTT	RCC	Tissue	50	I-IV	qRT-PCR	Median value	–	–	–	–
Wang 2015[50]	China	-	OST	Tissue	52	I-IV	qRT-PCR	Median value	OS/DFS	Reported	0.004/0.002	60
Song 2013[51]	American	FTT	MDS	Tissue	107	I-IV	ISH	Expression score	OS	SC	<0.0005	75
Wang X C 2013[52]	China	–	ESCC	Tissue	100	I-IV	qRT-PCR	Mean value	OS	SC	0.237	80
Liu 2014[32]	China	–	NPC	Serum	512	I-IV	qRT-PCR	Median risk score	OS/DMFS (T,V)	Reported	<0.01	132
Li 2014[53]	China	FTT	glioma	Tissue	72	I-IV	qRT-PCR	Mean value	OS	SC	<0.05	42
Lionetti 2013[54]	American	–	pPCL	Tissue	18	I-IV	qRT-PCR	NR	PFS	SC	0.001	32
Du 2017[55]	China	FTT	Bla Ca	Urine	240	I-IV	qRT-PCR	Median value	RFS	Reported	0.024	80
Zou 2017[56]	China	FTT	BC	Tissue	72	I-IV	qRT-PCR	Mean	–	–	–	–

Abbreviations: miR-22, microRNA-22; T, training set; V, validation set; NR, not reported; Co, colon set; Re, rectal set; "-", not mentioned; q-RCR, quantitative real-time polymerase chain reaction; ISH, in situ hybridization; SC, survival curve; OS, overall survival; PFS, progression-free survival; DFS, disease-free survival; RFS, recurrence free survival; MFS, metastasis-free survival; DMFS, distant metastasis-free survival; TCGA, The Cancer Genome Atlas; GEO, gene expression omnibus; BC, breast cancer; EOC, epithelial ovarian cancer; CRC colorectal carcinoma; HCC, hepatocellular carcinoma; NPC, nasopharyngeal carcinoma; GC, gastric cancer; OST, osteosarcoma; MDS, myelodysplastic syndrome; ESCC, esophageal squamous cell carcinoma; pPCL, primary plasma cell leukemia; Bla Ca, bladder cancer; RCC, renal cell carcinoma.

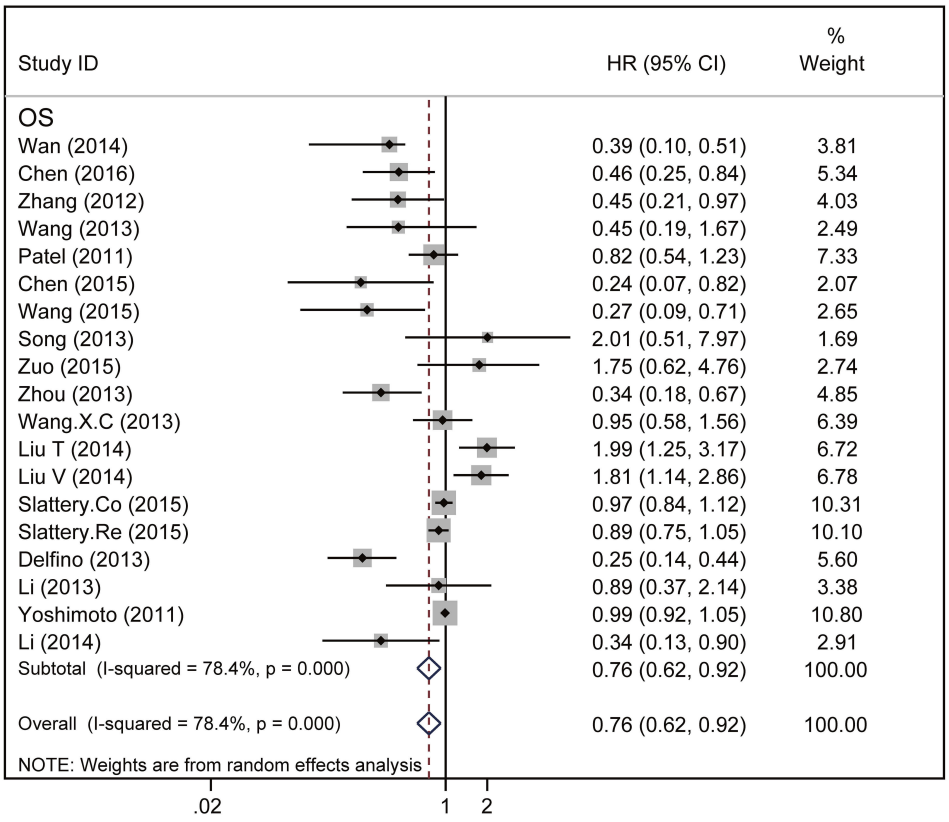

Figure 2 Forest plot of miR-22 expression and overall survival in various cancers.

According to the subgroup analysis for cancer type, elevated expression of miR-22 predicted a good OS in HCC (HR =0.40, 95% CI: 0.26–0.62) and EOC (HR =0.42, 95% CI: 0.20–0.86) (Table 2); meanwhile, it predicted a worse OS in NPC (HR =1.90, 95% CI: 1.37–2.63). But the prognostic value of miR-22 for GC (HR =0.90, 95% CI: 0.24–3.39), CRC (HR =0.92, 95% CI: 0.83–1.03) and BC (HR =0.81, 95% CI: 0.54–1.22) remains unclear. In addition, we test the conclusion using TCGA data (Figure S5–S9). When grouped as per the anatomical system of cancer, as Figure 3A shows, the combined HRs of the digestive system and of the reproductive system were 0.74 (95% CI: 0.58–0.95) and 0.55 (95% CI: 0.33–0.93), respectively, indicating that miR-22 was indicator of good prognosis in the digestive system and reproductive system. In the subgroup analysis by the ethnic background of participants, there was no obvious association between elevated expression of microRNA-22 and good prognosis in the Asian group (Figure S1D, Table 2) and the Caucasian group (Figure S1C, Table 2). Among the 19 studies, 14 articles recruited patients with adenocarcinoma and three articles recruited patients with squamous cell carcinoma. Therefore, subgroup analysis was performed in adenocarcinoma and squamous cell carcinoma. The results revealed that elevated expression of miR-22 was related with good survival outcome in adenocarcinoma (HR =0.75, 95% CI: 0.61–0.92), while no significant correlation was found in squamous cell carcinoma (HR =1.52, 95% CI: 0.97–2.37) (Figure 3B, Table 2). Subgroup analysis was also carried out on the basis of sample type, namely, tissue and serum. The results suggested that increased expression of miR–22 indicated a good prognosis in tissue, while it predicted a worse OS in serum (Figure 3C, Table 2). Subgroup analysis was further performed according to the preservation method of tumor tissue, while no significant association was found in these subgroups other than FFPE (Figure S4), which indicated that miR-22 predicted a good OS in FFPE subgroup (Table 2). Additionally, we also found a significant correlation between miR–22 expression and OS in q-PCR assay subgroup, while no significant association was found in the ISH assay subgroup (Figure 3D, Table 2).

The relationship between miR-22 expression and disease progression

Among the 26 articles, 12 articles, which include 14 studies and 3534 participants, investigated the correlation between miR-22 expression and PFS/RFS/DFS/DMFS/

Table 2 Meta-analysis of overall and subgroup analysis for miR-22 expression and OS in cancers

Categories	Studies	HR (95% CI)	Model	Heterogeneity	
				I^2%	$P_{heterogeneity}$
OS (overall)	19	0.76 (0.62–0.92)	Random	78.4	0.000
OS (Subgroup analysis)					
Cancer type					
HCC	2	0.40 (0.26–0.62)	Fixed	0	0.511
CRC	3	0.92 (0.83–1.03)	Fixed	49.6	0.137
NPC	2	1.90 (1.37–2.63)	Fixed	0	0.776
EOC	3	0.42 (0.20–0.86)	Random	64.7	0.059
GC	2	0.90 (0.24–3.39)	Random	68.5	0.075
BC	3	0.81 (0.54–1.22)	Random	66	0.053
Sample type					
Tissue	17	0.67 (0.55–0.81)	Random	75.5	0.000
Serum	2	1.90 (1.37–2.63)	Random	0	0.776
The system of cancer					
Digestive system	8	0.74 (0.58–0.95)	Random	65.9	0.005
Reproduction system	6	0.55 (0.33–0.93)	Random	84.5	0.000
The main pathological type					
Adenocarcinoma	11	0.75 (0.61–0.92)	Random	74.9	0.000
Squamous cell carcinoma	3	1.52 (0.97–2.37)	Random	62.3	0.022
Tumor of mesenchymal tissue	2	0.70 (0.10–4.99)	Random	80.8	0.071
Ethnic background					
Asian	13	0.73 (0.52–1.01)	Random	77.6	0.000
Caucasian	3	0.94 (0.84–1.05)	Fixed	0	0.414
Assay method					
q-PCR	18	0.74 (0.61–0.91)	Random	79.3	0.000
ISH	1	2.01 (0.51–7.95)	Random	–	–
Preservation method					
Fresh tissue	4	1.31 (0.68–2.52)	Random	76.7	0.005
Unclear method (-)	4	0.58 (0.28–1.16)	Random	79.5	0.002
FTT	9	0.88 (0.76–1.01)	Random	53.7	0.027
FFPE	2	0.32 (0.18–0.56)	Fixed	0	0.634

Abbreviations: miR-22, microRNA-22; "-", not mentioned; ISH, in situ hybridization; OS, overall survival; BC, breast cancer; EOC, epithelial ovarian cancer; CRC colorectal carcinoma; HCC, hepatocellular carcinoma; NPC, nasopharyngeal carcinoma; GC, gastric cancer.

MFS; hence we performed a meta-analysis among them. Because PFS, RFS, and DFS were similar as outcome indicators, we regard the PFS, RFS, and DFS as the same outcome indicators, so that we can pool more HRs of PFS/RFS/DFS in this meta-analysis to get a more accurate result about the miR-22 expression and disease progress. We pooled the HR of PFS, DFS, and RFS by random-effects model given the significant heterogeneity (I^2=79.1%). The results revealed that high expression of miR-22 indicated a longer PFS/DFS/RFS of cancer patients (HR =0.57, 95% CI: 0.37–0.87), indicating that high miR-22 expression prevented the progress and recurrence of cancer (Figure 4A, Table 3). Due to significant heterogeneity, we pooled the MFS/DMFS via random-effects model. As shown in Figure 4A, no significant correlation was found between miR-22 expression and DMFS/MFS with a pooled HR of 1.57 (0.67–3.68) (Figure 4A, Table 3).

According to subgroup analysis, on the basis of cancer type (EOC, NPC and BC), main ethnic background (Asian or Caucasian) and outcome indicator type (PFS, DFS and RFS), elevated expression of miR-22 prevented progress and recurrence in EOC patients (HR =0.28, 95% CI: 0.17–0.44) (Figure 4C,

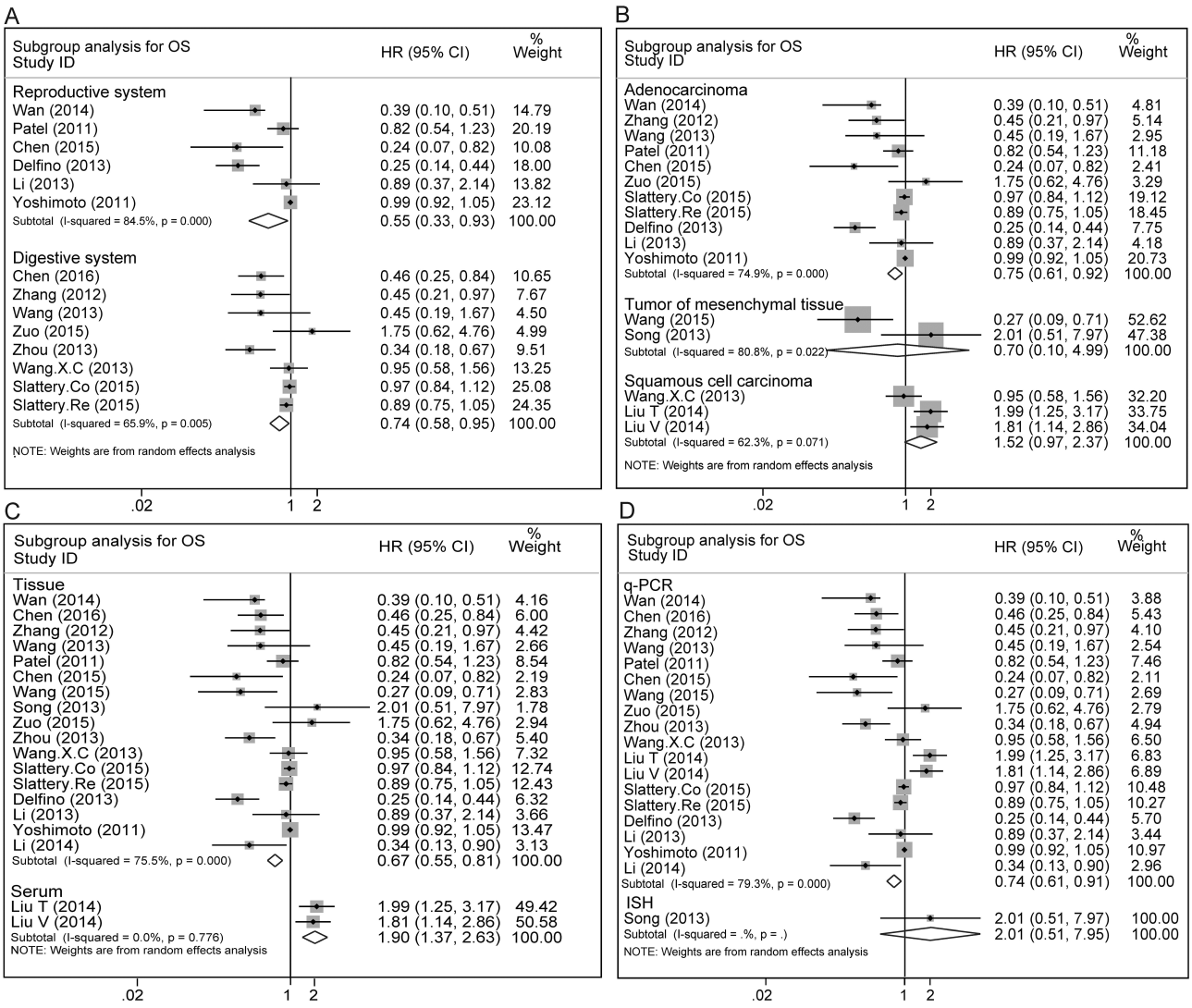

Figure 3 Forest plot of subgroup analysis for OS: (**A**) subgroup analysis for the anatomy system of cancer (digestive system and reproduction system); (**B**) subgroup analysis for the main pathological type of cancer; (**C**) subgroup analysis for different sample type (tissue or serum); (**D**) subgroup analysis for different assay method for miR-22 expression (q-PCR and ISH).

Table 3), while in BC patients (Figure S2A), Asiatic cancer patients (HR =0.69, 95% CI: 0.36–1.31) and Caucasian cancer patients (HR =2.09, 95% CI: 0.46–9.48) (Figure S2B, Table 3), the prognostic value of miR-22 remains unclear. Besides that, the results showed in Figure 4B potently indicated that elevated expression of miR-22 prolonged the cancer patients' DFS time, but no significant association was found in PFS and RFS subgroup (Figure 4B, Table 3). In addition, we got the opposite outcome in NPC, which indicates that elevated expression of miR-22 promotes the distant metastasis of NPC patients (Figure S2C, Table 3).

Sensitivity analysis

The sensitivity analysis was performed among the OS and PFS/RFS/DFS, which was used to test the stability of our results. The result remained similar when any single article in the current study was removed each time, which reflects the limited influence of any single study on the overall pooled result. The pooled HRs for OS ranged from 0.70 (95% CI: 0.55–0.91) after removing the study of Yoshimoto[28] to 0.83 (95% CI: 0.69–0.99) after removing the study Delfino[23] (Figure 5A, Table S1), and the pooled HRs of PRS/RFS/DFS ranged from 0.48 (95% CI: 0.32–0.74) to 0.63 (95% CI: 0.41–0.96) (Figure 5B, Table S2), both of which indicate that

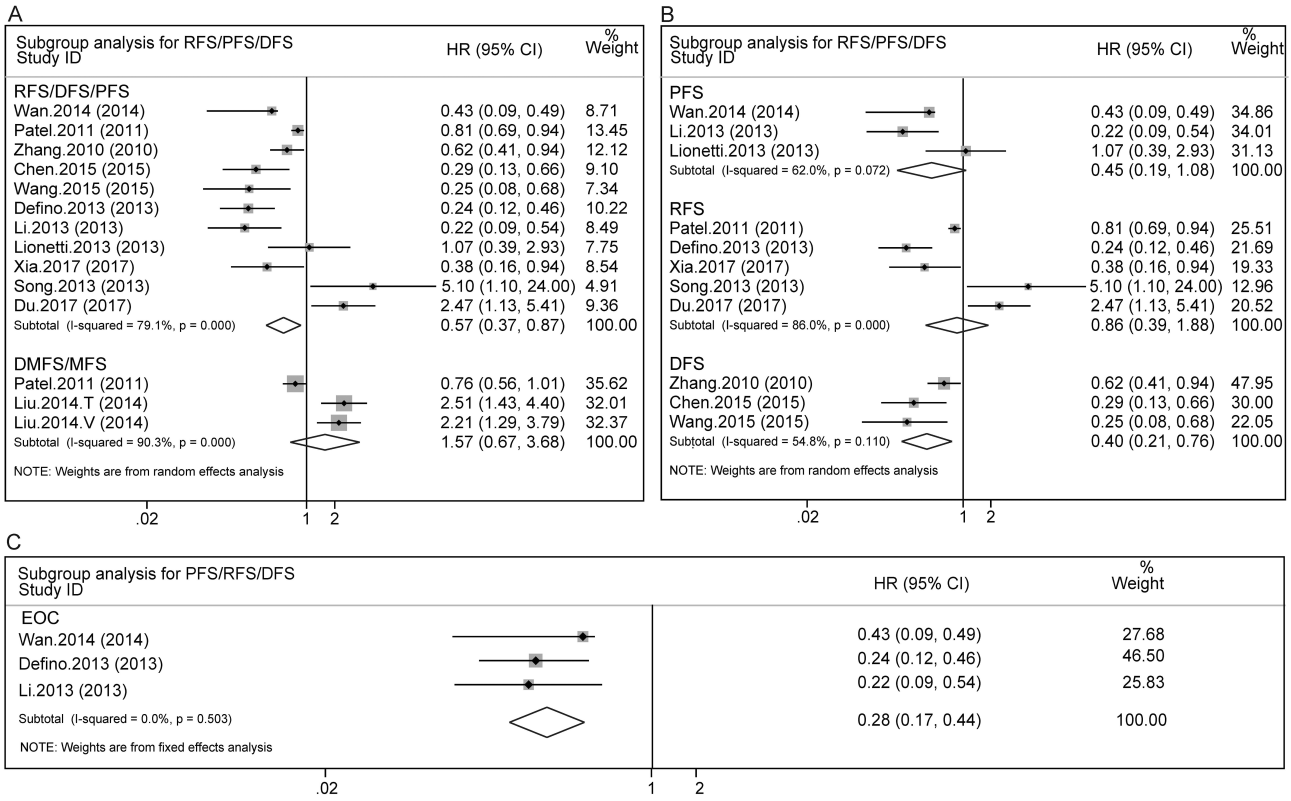

Figure 4 Forest plot of miR-22 expression and disease progress: (**A**) subgroup analysis for PFS/DFS/RFS and MFS/DMFS; (**B**) subgroup analysis for different indicator type (PFS, DFS, RFS); (**C**) subgroup analysis for PFS/DFS/RFS in EOC subgroup.

Table 3 Meta-analysis of overall and subgroup analysis for miR-22 expression and disease progress in cancers

Categories	Studies	HR (95% CI)	Model	Heterogeneity	
				I^2%	P_{heter}
PFS/DFS/RFS (overall)	11	0.57 (0.37–0.87)	Random	79.1	0
MFS/DMFS (overall)	3	1.57 (0.67–3.68)	Random	90.3	0
PFS/DFS/RFS (subgroup)					
Indicator type					
PFS	3	0.45 (0.19–1.08)	Random	62	0.072
RFS	5	0.86 (0.39–1.88)	Random	86	0.000
DFS	3	0.40 (0.21–0.76)	Random	54.8	0.11
Cancer type (all)					
NPC	2	2.35 (1.59–3.47)	Fixed	0	0.749
BC	3	0.86 (0.30–2.47)	Random	82.6	0.003
EOC	3	0.28 (0.17–0.44)	Fixed	0	0.016
Ethnic background					
Asian	9	0.69 (0.36–1.31)	Random	87.0	0.000
Caucasian	2	2.09 (0.46–9.48)	Random	63.8	0.097

Abbreviations: miR-22, microRNA-22; OS, overall survival; PFS, progression-free survival; DFS, disease-free survival; RFS, recurrence-free survival; MFS, metastasis-free survival; EOC, epithelial ovarian cancer; NPC, nasopharyngeal carcinoma; DMFS, distant metastasis-free survival.

the pooled results for OS and PFS/DFS/RFS are stable. We also employ the sensitivity analysis to seek out the source of heterogeneity further. The result revealed that the heterogeneity for OS or PFS/RFS/DFS did not change significantly, no matter which article was removed (Table S1, Table S2).

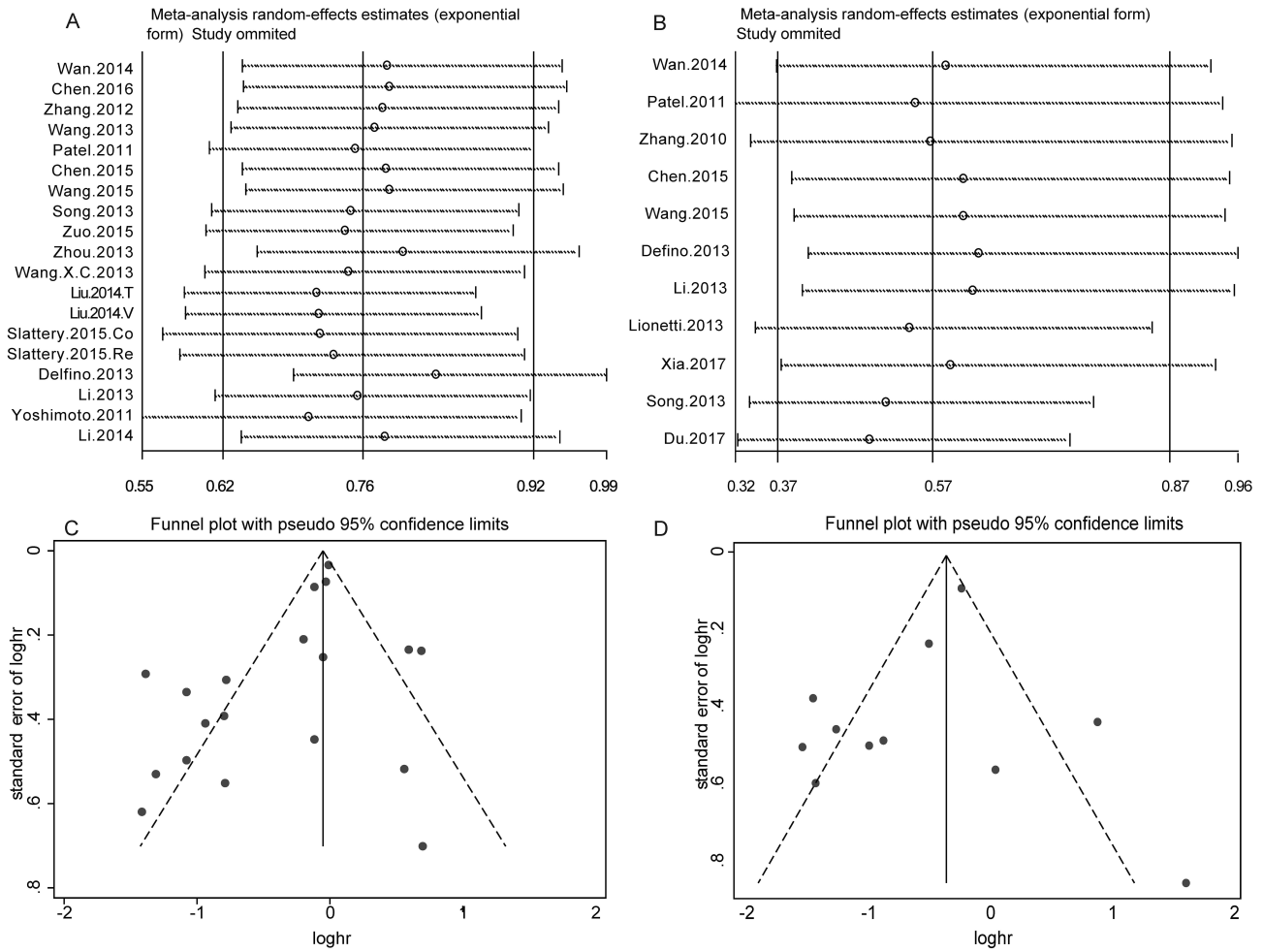

Figure 5 Forest plot of miR-22 expression and clinicopathological features. (**A**) subgroup analysis for miR-22 expression and TNM stage; (**B**) subgroup analysis for miR-22 high expression and lymph node metastasis; (**C**) subgroup analysis for miR-22 high expression and distant metastasis; (**D**) subgroup analysis for miR-22 high expression and recurrence.

miR-22 expression and clinicopathological characteristics

Ten articles were considered eligible in this analysis, among which nine studies were used to evaluate the correlation between the high expression of miR-22 and TNM stage. Nine out of 10 studies investigated the relationship between the expression of miR-22 and lymph node metastasis, and the combined RRs were 0.48 (95% CI: 0.34–0.67, I^2=72.9%) and 0.55 (95% CI: 0.40–0.77, I^2=72.1%), respectively, which indicates that the elevated expression of miR-22 was negatively related to TNM stage (Figure 6A, Table 4), as well as lymph node metastasis (Figure 6B, Table 4). We also revealed that increased expression of miR-22 was negatively related to distant metastasis (Figure 6C, Table 4) and recurrence (Figure 6D, Table 4), while no significant association was found between elevated expression of miR-22 and tumor tissue differentiation (Figure S3, Table 4), T stage (Figure S3, Table 4) and lymphatic invasion (Figure S3, Table 4).

Assessment of publication bias

We assessed the publication bias of the enrolled studies via Funnel plot, Begg's test and Egger's test. The Funnel plot of OS and PFS/DFS/RFS was revealed in Figure 5C and D. The *p*-values of Begg 's test and Egger's test for OS were 0.294 and 0.053; meanwhile, for PFS/RFS/DFS, they are 0.876 and 0.320. Collectively, no significant publication bias exists in this meta-analysis.

Discussion

Alteration of biological markers in serum or tissues plays an important role in predicting the cancer patients' prognosis, and so great efforts have been made to establish reliable and convincing prognosis biomarkers for cancer patients,

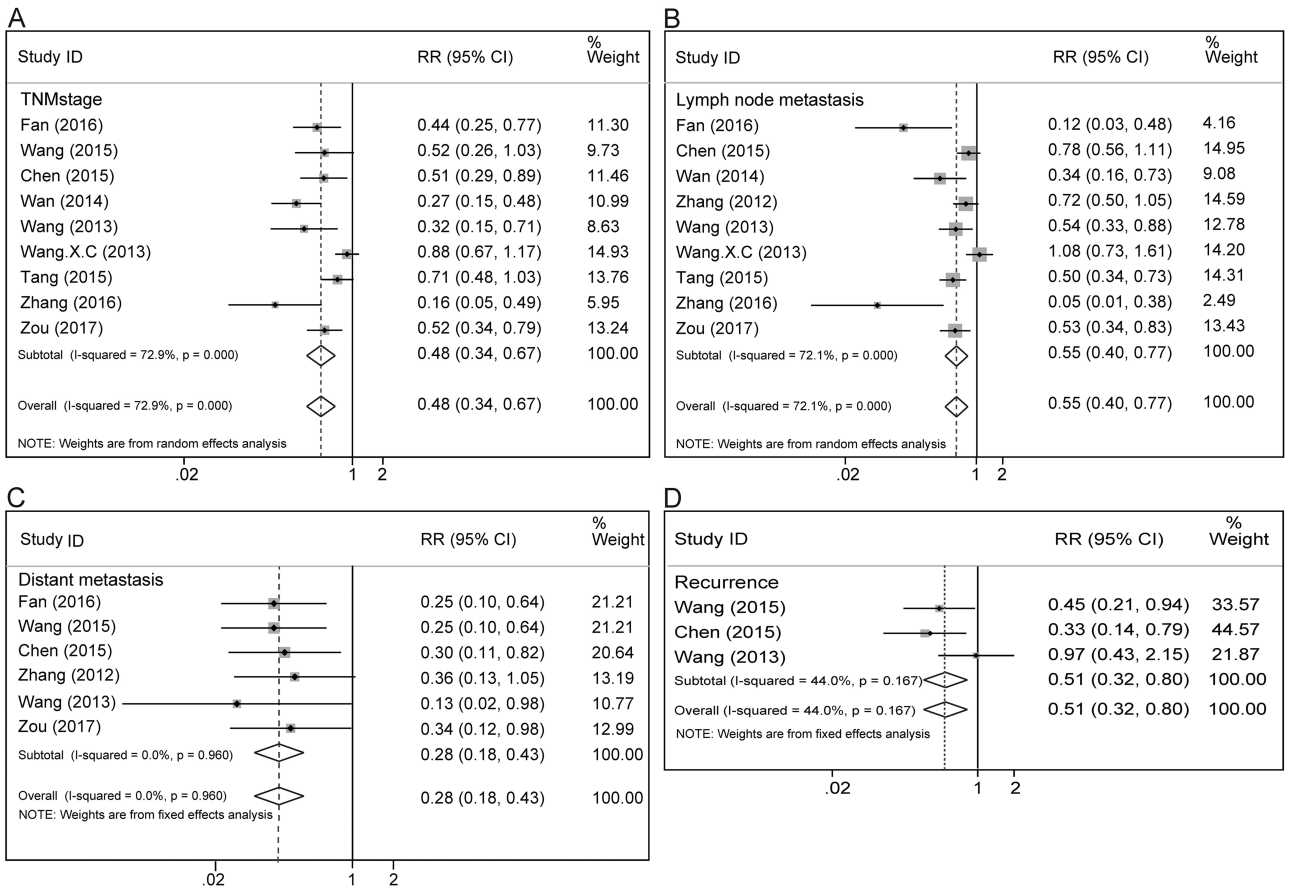

Figure 6 Sensitivity analysis and publication bias analysis under a specific model. (**A**), sensitivity analysis for overall survival; (**B**) sensitivity analysis for disease progress (PFS/RFS/DFS); (**C**) funnel plot of publication bias for OS; (**D**) funnel plot of publication bias for disease progress (PFS/RFS/DFS).

Table 4 Meta-analysis of miR-22 high expression and clinicopathological features

Categories	Studies	RR (95% CI)	Model	Heterogeneity	
				I^2%	P_{heter}
TNM stage	9	0.48 (0.34–0.67)	Random	72.9	0.000
Lymph node metastasis	9	0.55 (0.40–0.77)	Random	72.1	0.000
T stage	5	0.87 (0.70–1.07)	Fixed	37.2	0.173
Distant metastasis	6	0.28 (0.18–0.43)	Fixed	0	0.960
Tumor differentiation	5	0.99 (0.85–1.15)	Fixed	49.0	0.0970
Recurrence	3	0.51 (0.32–0.80)	Fixed	44	0.167
Lymphatic invasion	3	0.86 (0.70–1.05)	Fixed	33.5	0.222

through which we can provide doctors useful information and guide clinical precision medicine. During the last decade, accumulating studies have revealed that miRNAs are novel biomarkers involved in cancer patients' tumorigenesis and progression, acting as an oncogene or tumor-suppressive gene.[57,58] Moreover, some studies have shown that miRNAs bear a special expression profile in cancerous tissues, and they can be precisely detected by qRT-PCR in paraffin-embedded, frozen, formalin-fixed tissues and serum samples.[59] Compared with mRNA, microRNAs are more stable and easily detected by qRT-PCR. Among them, miR-22 is one of the most frequently studied microRNAs in cancer patients, which was revealed to be aberrantly expressed in various tumors including BC,[28] GC,[47] CRC,[29] HCC,[25] ovarian carcinoma[42] and others. Therefore, we conduct this meta-analysis to evaluate the association between

high expression of miR-22 and the OS as well as clinicopathological significance of cancer patients.

The current meta-analysis, for the first time, evaluated the correlation between elevated expression of miR-22 and cancer patients' prognosis, progress and clinicopathological significance in various tumors. In our study, high expression of miR-22 predicted a good OS (HR =0.76, 95% CI: 0.62–0.92) (Figure 2, Table 2) and PFS/RFS/DFS (HR =0.57, 95% CI: 0.37–0.87) (Figure 4A, Table 3) for cancer patients, while no significant correlation was found between the expression of miR-22 and MFS/DMFS (Figure 4A, Table 3). Afterward, we performed the subgroup analysis of OS to attempt to explain the sources of heterogeneity and find out the specific relationship between miR-22 expression and the OS of cancer type, sample type, the anatomical system of cancer, main pathologic type, main ethnic background and assay method (q-PCR and ISH). Cancer type's subgroup analysis showed that increased expression of miR-22 predicts a good OS in HCC (Figure S1B, Table 2) patients and EOC patients (Figure S1A, Table 2); meanwhile, no obvious association was found between miR-22 high expression and prognosis in GC patients (Figure S1A, Table 2), CRC patients (Figure S1B, Table 2) and BC patients (Figure S1A, Table 2). However, 512 participants in NPC (namely serum subgroup) showed an opposite outcome (Figure S1B, Table 2), which indicates that miR-22 high expression might shorten the OS time and promote the distant metastasis of NPC patients. Perhaps that overexpression of miR-22 might downregulate a tumor-suppressor gene or other genes involved in cell differentiation, hence promoting tumorigenesis by stimulating tumor proliferation, angiogenesis and invasion.[60] As was shown in Figure S5–S9, we test the conclusion of cancer type's subgroup analysis in TCGA data. However, we found some inconsistent even opposite conclusions. We found most patients in TCGA are Caucasians, while most patients in our research are Asians, so it is reasonable for us to get these conclusions. Through the subgroup analysis of OS, we could find that elevated expression of miR-22 predicted a good OS in the digestive system subgroup, reproduction system subgroup, adenocarcinoma subgroup, q-PCR subgroup, FFPE subgroup and tissue subgroup, and no significant association was found in other subgroups of OS (Table 2). In the subgroup analysis of PRS/RFS/DFS, high expression of miR-22 might predict a good DFS (Figure 4B), which suggested that the miR-22 high expression prolongs the DFS time of cancer patients, while no significant association was found in RFS and PFS subgroup (Figure 4B). Additionally, in subgroup analysis based on the characteristics of the individual studies, we observed statistically significant outcomes in the PFS/DFS/RFS of EOC subgroup (Figure 4C), with pooled HRs of 0.28 (95% CI: 0.17–0.44); no significant association was found between miR-22 high expression and PFS/RFS/DFS in BC patients (Figure S2A), Asiatic cancer patients (Figure S2B) subgroup and Caucasian cancer patients subgroup (Figure S2B).

Through the subgroup analysis, the heterogeneity of some subgroup remains large still, so the subgroup analysis could not account for the sources of heterogeneity completely. According to the subgroup analysis, the heterogeneity of OS might derive from the different characteristics of the studies, such as cancer type, sample type, the anatomical system of cancer, main pathological type, main ethnic background, as well as the cutoff value of the miR-22 expression. For example, when we stratified them according to cancer type and sample type, heterogeneity became insignificant in CRC,and disappeared in serum samples, in HCC subgroup, as well as in NPC subgroup (Table 2). The heterogeneity was also reduced when the DFS/RFS/PFS studies were classified by the indicator type and main ethnic subgroup, through which we can partly explain the source of heterogeneity for PFS/RFS/DFS (Table 3). According to the sensitivity analysis of OS (Figure 5A, Table S1) and PFS/RFS/DFS (Figure 5B, Table S2), no single study significantly influenced the pooled results, which indicates that the outcome for prognosis and disease progress are stable. Additionally, the sensitivity analysis also suggested that no single study significantly influences the heterogeneity of OS and PFS/RFS/DFS (Table S1, Table S2).

Furthermore, we analyzed the correlation between miR-22 expression and clinicopathological characteristics of cancer patients. As shown in Table 4, elevated expression of miR-22 was negatively correlated with TNM stage (Figure 6A), lymph node metastasis (Figure 6B), distant metastasis (Figure 6C) and recurrence (Figure 6D). The results indicate that cancer patients with higher expression level of microRNA-22 means lower likelihoods of lymph node metastasis, of distant metastasis and of recurrence. miR-22 is also negatively correlated with TNM stage (Figure 6A), which indicates that miR-22 high expression means earlier TNM stage. In addition, there was no significant association between high expression of microRNA-22 and T stage (RR =0.87, 95% CI: 0.71–1.07), tumor

differentiation (HR =0.99, 95% CI: 0.85–1.15) and lymphatic invasion (RR =0.86, 95% CI: 0.70–1.05) (Figure S3).

In our meta-analysis, elevated expression of miR-22 suggested a good prognosis of cancer patients in most subgroup, but we can also find inconsistent even opposite outcome in some subgroups (NPC subgroup, serum subgroup, squamous cell carcinoma subgroup and so on). As is known to all, miR-22 acts as oncogene or antioncogene which largely depends on their corresponding target gene. If the target gene of miR-22 involved in the process of tumor suppressor, through binding to the mRNA of target gene at the 3′-untranslated region, miR-22 may lead to the mRNA of target gene degradation or translational repression[11,61] and act as oncogenes.[62] Otherwise, miR-22 act as antioncogene[62] In this meta-analysis, most articles suggested that miR-22 act as antioncogene and their elevated expression predicted a good OS.[21,23–26,50,53] Whereas a few studies reported inconsistent results,[31,32] indicating miR-22 maybe an oncogene in some specific type of cancer. This is mainly because miR-22 regulates different target genes in different types of cancer (Table S3), thus resulting in the different prognostic value in different cancer types. In these subgroups, in which miR-22 acts as an oncogene, the result affected most by NPC. Perhaps that miR-22 target some specific oncogene, although further research needs to be performed. In addition, because of the limit of language, the result of Asian and Caucasian becomes less persuasive (lose non-English study in Asian). So it is reasonable for us to get these conclusions, but we should treat these results cautiously in some specific types of cancer; only in this way can we get more accurate result.

Although meta-analysis is robust, several limits still persist in this meta-analysis. First, the miR-22 expression data in global populations are not available for us, making it impossible for us to set a standard cutoff value, which leads to the inconsistent cutoff value of miR-22 and makes our conclusion less persuasive. Second, miR-22 expression was detected most in tumor tissue (23 studies) but little in serum (two studies) and urine (one study), which was more easily accepted and monitored by patients than tissue. Third, this meta-analysis exists relatively large heterogeneity, which was likely because of the different characteristics of studies (cancer type, sample type, the anatomical system of cancer, the main ethnic background and main pathological type), measurement method and the cutoff value of miRNA-22 expression. Fourth, some data were extracted from survival curves, which might be less accurate than calculated via raw data. Finally, a panel of miRNAs may have stronger predictive value for prognosis than a single miRNA, which should be cheaper and have higher sensitivity and specificity.

In our meta-analysis, neither Begg's test nor Egger's test showed significant evidence of publication bias (0.294 and 0.053 for OS; meanwhile, it is 0.876 and 0.320 for PFS/RFS/DFS); publication bias might still exist because the tendency for journals to publish positive results could also make certain bias. Language bias might exist because the studies retrieved in our study were limited in English.

Despite the limits described above, our study clearly demonstrated that elevated expression of miR-22 predicted a good OS, clinicopathological features and PFS/RFS/DFS in cancer patients. To better understand and apply the effect of miR-22 in cancer, more multicenter clinical investigations should be conducted before the application of miR-22 in predicting prognosis of some specific type of cancers.

Abbreviations

miR-22, microRNA-22; T, training set; V, validation set; NR, not reported; Co, colon set; Re, rectal set; "-", not mention; ISH, in situ hybridization; SC, survival curve; OS, overall survival; PFS, progress free survival; DFS, disease-free survival; RFS, recurrence-free survival; MFS, metastasis-free survival; DMFS, distant metastasis-free survival; mth, month; TCGA, The Cancer Genome Atlas; GEO, Gene Expression Omnibus; BC, breast cancer; EOC, Epithelial ovarian cancer; CRC colorectal carcinoma; HCC, hepatocellular carcinoma; NPC, nasopharyngeal carcinoma; GC, gastric cancer; OST, osteosarcoma; MDS, myelodysplastic syndrome; ESCC, esophageal squamous cell carcinoma; pPCL, primary plasma cell leukemia; RCC, renal cell carcinoma; Bla Ca, bladder cancer; FFPE, formalin-fixed paraffin-embedded; FTT, frozen tumor tissue; "-", not mentioned.

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Author contributions

All authors contributed to data analysis, drafting or revising the article, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflict of interest in this work.

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