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ORIGINAL ARTICLE

Exosomal miRNAs as Biomarkers of Cancer: a Meta-Analysis

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SUMMARY

Background: **Tumor-derived exosomal miRNAs secreted by cancer cells play significant roles in the pathological processes of cancer, but no systematic meta-analysis has focused on the diagnostic efficiency of exosomal miRNAs. This meta-analysis assessed the diagnostic value of circulating exosomal miRNA in cancer.**
Methods: **Studies evaluating the diagnostic value of exosomal miRNA were identified in EMBASE, PubMed, Cochrane Library, and Web of Science up to August 1, 2018. The quality of each study was assessed according to the Quality Assessment of Diagnostic Accuracy Studies 2, and STATA 14.0 was used for the analyses. The true positive (TP), false positive (FP), true negative (TN), and false negative (FN) rates were extracted from each study to obtain the pooled sensitivity, specificity, positive likelihood ratio (PLR), negative likelihood ratio (NLR), diagnostic odds ratio (DOR), and their 95% confidence intervals (CIs).**
Results: **The meta-analysis included 16 studies with 1,591 patients. Five studies reported sensitivity values, and the pooled sensitivity was 0.86 (95% CI = 0.80 - 0.90, while 29 studies reported specificity values, and the pooled specificity was 0.89 (95% CI = 0.83 - 0.93). The pooled PLR was 7.8 (95% CI = 4.9 - 12.4), the pooled NLR was 0.16 (95% CI = 0.11 - 0.24), the pooled DOR was 48 (95% CI = 23 - 101), and the AUC was 0.94 (0.91 - 0.96).**
Conclusions: **Our meta-analysis indicated that body fluid exosomal miRNAs are highly accurate for distinguishing patients from healthy individuals, and exosomal miRNAs have superior diagnostic value in plasma, prostate cancer patients, and non-Asian individuals.**
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KEY WORDS

exosome, microRNA, biomarker, cancer, meta-analysis

INTRODUCTION

Cancer is one of the major diseases affecting human health, and the cost of treatment is very high. Lung carcinoma is the malignant tumor with the highest mortality rate worldwide. The overall survival rate of lung cancer is 15% in China [1], 20% in Japan, and between 15% and 18% in the United States [2]. The incidence of liver cancer increased by 75% between 1990 and 2015. In 2015, of the 854,000 cases of liver cancer worldwide, 810,000 died [3]. Diagnosis of cancer in the early stage

significantly improves treatment efficiency, increases the survival rates of cancer patients, and further reduces the cost of treatment.

Existing body fluid biomarkers, such as serum carbohydrate antigen 15-3 (CA15-3) and carcinoembryonic antigen (CEA) levels [4,5], are commonly used in the clinical laboratories of hospitals, but they do not have high sensitivity and specificity for the diagnosis of tumors because they lack accuracy in the early stages and are not correlated with disease stage in body fluid test methods. Currently, increasing numbers of biomarkers of free nucleic acids have been developed, such as free cellular DNA and circulating tumor cell lncRNA, miRNA, and circRNA. Among these biomarkers, miRNA has attracted increasing attention. The relationships between cancer and exosomal microRNAs have also been extensively researched in recent years [6]. MiRNAs, which are 19 - 24 nucleotides in length, are the most widely studied noncoding RNAs, and they are vital factors affecting posttranscriptional levels in cancer. These small RNAs act as oncogenes or tumor suppressor genes, regulating downstream effectors [7]. However, the presence of miRNAs in body fluids is not stable; they are easily decomposed by RNA enzymes, and miRNA is often degraded during the processes involved in its extraction, preservation, and determination [8,9], further affecting the accuracy of diagnosis.

Exosomes, which are widely distributed in body fluids, including blood, urine, and saliva, are membrane vesicles with a size of 40 - 100 nm that contain a large number of miRNAs [10]. Increasing evidence has reported that tumor-derived exosome miRNAs secreted by cancer cells play a significant role in the pathological processes of cancer. In lung cancer, exosome-derived miR-21 promotes angiogenesis via the production of vascular endothelial growth factor (VEGF), which promotes the metastasis of tumor cells [11]. Tumor-derived exosomal miR-21 and miR-29a significantly enhance tumor growth and metastasis by activating the TLR-mediated NF-κB pathway [12]. Breast cancer-derived exosomal miR-122 significantly enhances tumor metastasis via glucose metabolism [13]. Exosomes have been reported to isolate miRNAs from circulating RNases in body fluids, which can increase the stability of endogenous miRNAs [8], and higher miRNA concentrations were observed in exosomes compared to miRNA concentrations in urine [14]. Therefore, miRNAs derived from serum exosomes may be more suitable for use as tumor biomarkers.

Although there are many meta-analyses on miRNAs that can be used as biomarkers for various cancer diagnoses, no systematic meta-analysis has focused on the diagnostic efficiency of exosomal miRNAs in cancer. In the current meta-analysis, we explored the diagnostic value of circulating exosomal miRNAs in different sample types and cancer types and provided sufficient evidence to guide the clinical laboratory application of different exosomal miRNAs for the diagnosis of cancer.

MATERIALS AND METHODS

This meta-analysis was conducted based on the guidelines for diagnostic meta-analyses. EMBASE, PubMed, Cochrane Library, and Web of Science were searched by two authors (BY and WXY) up to August 1, 2018, using the following keywords: cancer, tumor, miRNA, exosomes, sensitivity, specificity, and accuracy. In addition, the reference lists of related reviews were manually scanned to identify additional relevant articles.

Inclusion and exclusion criteria

In this meta-analysis, the inclusion standards for studies were as follows: (1) studies with gold standard tests for the diagnosis of various cancers vs. healthy controls; (2) studies related to the diagnostic effect of exosomal miRNAs on cancer; (3) studies providing relevant data regarding true positive (TP), false positive (FP), false negative (FN), and true negative (TN) rates. The exclusion criteria were as follows: (1) the subject of the study was not human; (2) the studies focused on exosomal miRNAs in cell lines or cancer tissue; and (3) studies for which the data and full text were not available.

Data extraction and quality assessment

All the studies were carefully independently selected by two investigators (BY and HJH), and disagreements were resolved by discussion. Data extracted from each study in this meta-analysis included the following characteristics: (1) basic characteristics of studies, including the first author's name, year of publication, country, sample type, assay methods, numbers of cases and controls, and microRNA type and (2) diagnostic outcomes, including TPs, FPs, FNs, and TNs. The quality of each study was assessed according to the Quality Assessment of Diagnostic Accuracy Studies 2 (QUADAS-2). QUADAS-2 is a tool that comprises four key domains and uses seven questions to appraise the quality of diagnostic accuracy studies.

Statistical analysis

STATA 14.0 (Stata Corporation, College Station, TX, USA) was used for the analyses. The TPs, FPs, TNs, and FNs were extracted from each study to obtain the pooled sensitivity, specificity, positive likelihood ratio (PLR), negative likelihood ratio (NLR), diagnostic odds ratio (DOR), and their 95% CIs. The sensitivities and specificities in individual studies were extracted to generate the summary receiver operator characteristic (SROC) curve and calculate the area under the curve (AUC). Forest plots were used to present the sensitivity, specificity, PLR, NLR, and DOR of 16 studies. The Q test and I^2 statistics were used to assess heterogeneity among the studies. When the p-value of the Q test was less than 0.10 and the I^2 value was greater than 50%, the existence of substantial heterogeneity was indicated, and the random effects model was used. We performed Deek's funnel plot asymmetry test to investigate publiccation bias, p-values less than 0.05 indicated statistical

Table 1. Characteristics of the included trials.

First author	Year	Country	No. of Cases/ Controls	Cancer type	Specimen	Assay methods	microRNA type	TP	FP	FN	TN
Goto [15]	2018	Japan	32/22	pancreatic cancer	serum	qRT-PCR (TaqMan)	miR-21	26	4	6	18
							miR-191	23	3	9	19
							miR-451a	21	3	11	19
Wang [16]	2017	China	20/20	gastric cancer	serum	qRT-PCR (TaqMan)	miR-106a-5p, miR-19b-3p	19	2	1	18
Zhou [17]	2017	China	141/124	lung cancer	plasma	qRT-PCR (SYBR)	miR-19b3p, miR-21-5p, miR-221-3p, miR-409-3p, miR-425-5p, miR-584-5p	98	34	43	90
Lai [18]	2017	USA	29/11	pancreatic cancer	plasma	qRT-PCR (TaqMan)	miR-let-7a	29	0	0	11
							miR-10b	29	0	0	11
							miR-21	29	0	0	11
							miR-30c	29	0	0	11
							miR-181a	29	0	0	11
Jin [19]	2017	China	47/13	lung cancer	plasma	qRT-PCR (TaqMan)	miR-let-7b-5p, miR-let-7e-5p, miR-23a-3p, miR-486-5p	43	1	4	12
Rodríguez [20]	2017	Norway	20/9	prostate cancer	urine	next-generation sequencing	miR-196a	18	0	2	9
Bryzgunova [21]	2016	Russia	35/35	prostate cancer	urine	qRT-PCR (TaqMan)	miR-19b	33	7	2	28
							miR-25	25	11	10	24
							miR-125b	30	12	5	23
							miR-205	20	9	15	26
Meng [22]	2016	Germany	163/20	ovarian cancer	serum	qRT-PCR (TaqMan)	miR-200a	137	2	26	18
							miR-200b	86	0	77	20
							miR-200c	50	0	113	20
							miR-200a, miR-200b, miR200c	144	2	19	18
Sansonov [23]	2016	Russia	35/35	prostate cancer	urine	qRT-PCR (SYBR)	miR-21-5p	23	2	12	33
							miR-141-5p	23	2	12	33
							miR-574-3p	30	0	5	35

Table 1. Characteristics of the included trials (continued).

First author	Year	Country	No. of Cases/ Controls	Cancer type	Specimen	Assay methods	microRNA type	TP	FP	FN	TN
Zhang [24]	2016	China	82/80	renal Cell Carcinoma	serum	qRT-PCR (SYBR)	miR-210	57	30	25	50
							miR-1233	67	19	15	61
Chiam [25]	2015	Australia	18/29	esophageal carcinoma	serum	miRNA microarray	miR-16-5p	14	6	4	23
							miR-16-5p, miR-25-3p/miR-320a, let-7e-5p/miR15b-5p, miR-30a-5p/miR-324-5p, miR-17-5p/miR-194-5p	17	0	1	29
Butz [26]	2015	Canada	109/51	renal cell carcinoma	urine	qRT-PCR (TaqMan)	miR-126-3p, miR-449a	86	15	23	36
							miR-126-3p, miR-34b-5p	92	17	17	34
Wang [27]	2014	China	52/49	laryngeal carcinoma	serum	qRT-PCR (SYBR)	miR-21	36	12	16	40
Kawata [28]	2014	Japan	88/11	colon cancer	serum	miRNA microarray	miR-23a	81	0	7	11
							miR-1246	84	1	4	10
Madhavan [29]	2014	Germany	12/75	pancreatic cancer	serum	qRT-PCR (SYBR)	miR-1246, miR-4644, miR-3976, miR-4306	60	0	15	12
Cazzoli [30]	2013	Italy	50/30	lung cancer	plasma	qRT-PCR (SYBR)	miR-151a-5p, miR-30a-3p, miR-200b-5p, miR-629, miR-100, miR-154-3p	48	12	2	18

significance.

RESULTS

Selection of studies

The results of the literature search are presented in Figure 1. A preliminary literature search identified 1,314 publications related to the topic of diagnosing cancer with exosomal miRNA. After reviewing the titles and abstracts of each article, 426 were excluded. The retrieved 287 studies received full text reviews, and 6 studies were finally discarded because of the lack of sufficient data. Finally, 16 articles were included based on the inclusion criteria; the detailed process is presented in Figure 1.

Study characteristics and quality assessment

The basic information for the included literature is shown in Table 1. In the present meta-analysis, 16 studies were included. All eligible studies included a total of 1,000 patients and 591 healthy controls. Eight studies presented the results for serum samples, 4 trials used plasma samples, and urine samples were reported in 4 trials; 8 studies used a single exosomal miRNA, 6 studies used a panel of exosomal miRNAs, and 2 studies reported both single and combination exosomal miRNAs. We used the QUADAS-2 quality assessment to assess the quality of the included studies, and the results are shown in Figure 2. The overall quality of the included studies was generally high.

Table 2. Subgroup analysis of the diagnostic efficiency of exosomal miRNAs.

Analysis	Sensitivity (95% CI)	Specificity (95% CI)	PLR (95% CI)	NLR (95% CI)	DOR (95% CI)	AUC (95% CI)
Study location						
Asia	0.81 (0.74 - 0.86)	0.81 (0.73 - 0.87)	4.30 (2.50 - 6.50)	0.24 (0.17 - 0.34)	18.00 (9.00 - 38.00)	0.88 (0.85 - 0.90)
Not Asia	0.88 (0.80 - 0.93)	0.92 (0.84 - 0.96)	11.40 (5.40 - 24.20)	0.13 (0.07 - 0.23)	89.00 (29.00 - 271.00)	0.96 (0.94 - 0.97)
Sample types						
Serum	0.77 (0.69 - 0.84)	0.88 (0.81 - 0.93)	6.40 (3.90 - 10.60)	0.26 (0.19 - 0.36)	25.00 (13.00 - 48.00)	0.90 (0.87 - 0.92)
Plasma	1.00 (0.81 - 1.00)	0.98 (0.65 - 1.00)	62.00 (2.60 - 1,943.00)	0.00 (0.00 - 0.24)	12,541.00 (28.00 - 5715,151.00)	1.00 (0.99 - 1.00)
Urine	0.81 (0.74 - 0.87)	0.83 (0.71 - 0.91)	4.80 (2.70 - 8.60)	0.23 (0.16 - 0.33)	21.00 (9.00 - 49.00)	0.88 (0.85 - 0.91)
Cancer type						
Lung cancer	0.89 (0.69 - 0.96)	0.70 (0.60 - 0.78)	3.00 (2.20 - 4.00)	0.16 (0.06 - 0.48)	18.00 (6.00 - 59.00)	0.85 (0.71 - 0.79)
Prostate cancer	0.81 (0.71 - 0.88)	0.87 (0.73 - 0.94)	6.20 (2.80 - 13.80)	0.22 (0.13 - 0.35)	29.00 (9.00 - 88.00)	0.90 (0.87 - 0.92)
Renal carcinoma	0.79 (0.73 - 0.84)	0.69 (0.63 - 0.75)	2.60 (2.00 - 3.30)	0.30 (0.22 - 0.41)	9.00 (5.00 - 15.00)	0.80 (0.76 - 0.83)
Pancreatic cancer	0.89 (0.79 - 0.94)	0.89 (0.83 - 0.93)	8.30 (5.10 - 13.50)	0.12 (0.06 - 0.24)	65.00 (25.00 - 182.00)	0.93 (0.90 - 0.95)
Biomarker type						
Single	0.79 (0.69 - 0.83)	0.86 (0.76 - 0.91)	5.40 (3.60 - 8.30)	0.27 (0.20 - 0.36)	20.00 (11.00 - 36.00)	0.90 (0.87 - 0.93)
Multiple	0.87 (0.80 - 0.91)	0.85 (0.72 - 0.93)	5.90 (2.90 - 11.80)	0.16 (0.10 - 0.25)	37 (13 - 104.00)	0.92 (0.89 - 0.94)

Meta-analysis findings

These 16 studies included 9 types of cancer and 1,591 subjects, and significant heterogeneity was observed in the results for sensitivity and specificity (I^2 = 94.98% and I^2 = 83.76%, respectively). Spearman's correlation coefficient was 0.31 (p = 0.943), and no "shoulder" shape was observed; therefore, non-threshold heterogeneity was present. The random effects model was used to analyze the diagnostic accuracy of exosomal miRNA for cancers, and the summary results are shown in Table 1. The pooled sensitivity and specificity were 0.86 (95% CI = 0.80 - 0.90) and 0.89 (95% CI = 0.83 - 0.93), respectively. The pooled PLR was 7.8 (95% CI = 4.9 - 12.4), the pooled NLR was 0.16 (95% CI = 0.11 - 0.24), and the pooled DOR was 48 (95% CI = 23 - 101); the results are shown in Figure 3. Finally, the AUC was 0.94 (0.91 - 0.96), and the overall SROC curve is presented in Figure 3. To clarify the source of heterogeneity, we further used meta-regression and subgroup analyses.

Meta-regression

The study factors of study location (Asia or not), sample type (serum or not), cancer type (lung cancer, prostate cancer, or renal carcinoma), marker type (single or not) were analyzed by the meta-regression method. The results indicated that all the above factors might be the source of heterogeneity in the pooled sensitivity and that study location, sample type, and cancer type might be the sources of heterogeneity in the pooled specificity. The results of the meta-regression are shown in Figure 4.

Subgroup analyses

The subgroup analyses were based on the results of the meta-regression, and we conducted research on diagnostic accuracy according to study location (Asia or not), sample type (serum, plasma and urine), cancer type (lung cancer, prostate cancer and renal carcinoma), and biomarker type (single miRNA, multiple miRNAs). The results are shown in Table 2. The results show higher accuracy in non-Asian populations than in Asian populations, with sensitivities of 0.88 vs. 0.81, specificities of 0.92 vs. 0.81, and AUCs of 0.96 vs. 0.88. In terms of sample type, exosomal miRNAs showed higher diagnostic accuracy for cancer detection in plasma than in serum and urine. For cancer type, miRNAs showed the highest diagnostic accuracy in pancreatic cancer, with an AUC of 0.93, and multiple exosomal miRNAs had similar results, with sensitivities of 0.87

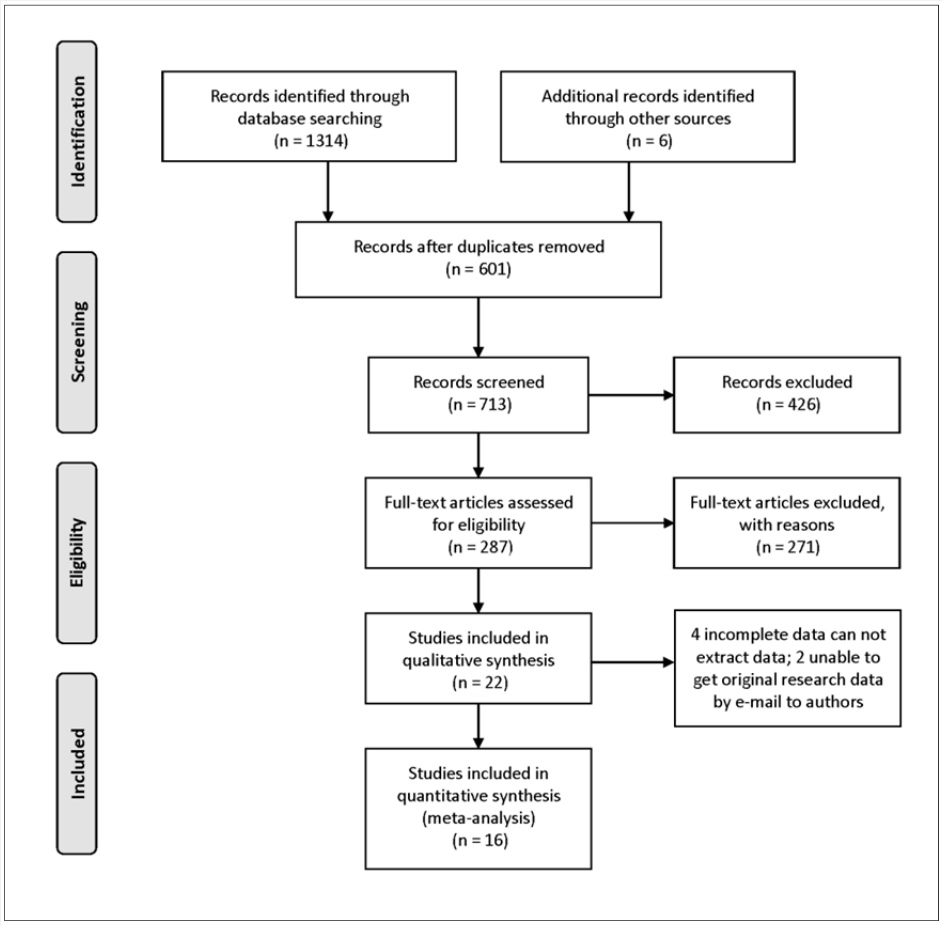

Figure 1. The flowchart shows the algorithm to identify inclusion articles.

This study found 16 eligible articles that used exosomal miRNA as biomarkers for tumor diagnosis.

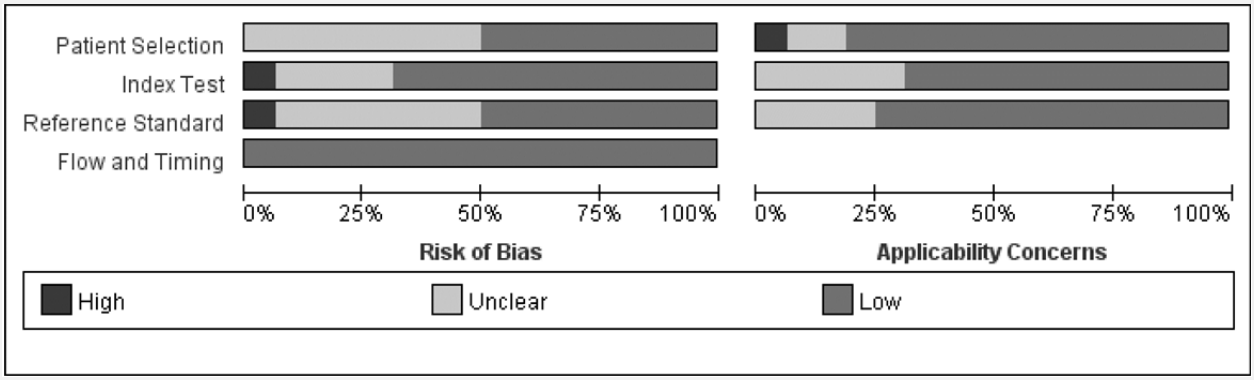

Figure 2. QUADAS-2 quality evaluation result of 16 eligible articles.

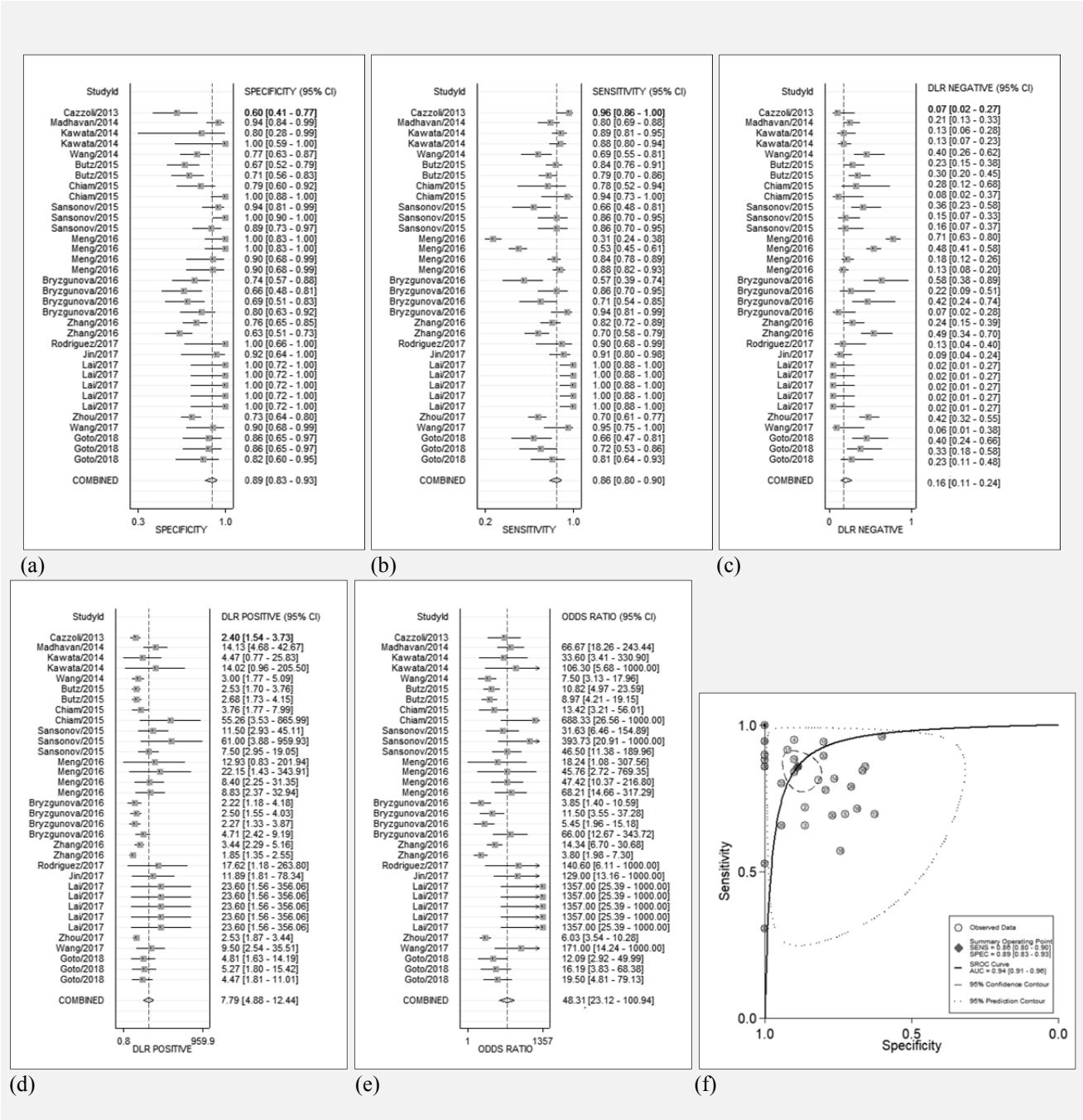

Figure 3. Forest plots of sensitivity, specificity, PLR, NLR, DOR, and AUC for diagnosis of circRNA in tumors among 16 studies.

(a) Sensitivity; (b) Specificity; (c) PLR; (d) NLR; (e) DOR; (f) AUC.

vs. 0.79, specificities of 0.85 vs. 0.86 and AUCs of 0.92 vs. 0.90.

Publication bias

The Deek's funnel plot asymmetry test evaluated potential publication bias in the enrolled studies. The result indicated that no publication bias existed, with a p-value of 0.05, as shown in Figure 5.

DISCUSSION

Cancer is the leading cause of mortality in developed countries. It is also the second leading cause of mortality in developing countries. Exosomal miRNA has potential value for the early stage diagnosis of most cancers; for example, the level of exosomal miR-21 is clearly increased in the early stage of prostate cancer

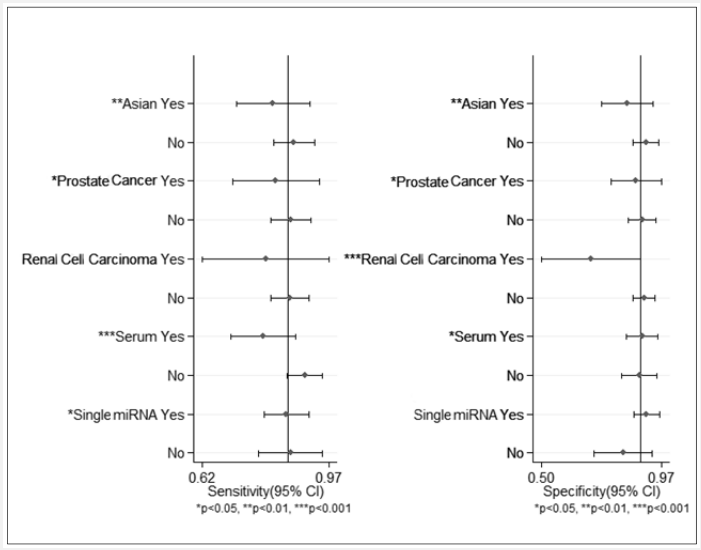

Figure 4. Univariate meta-regression and subgroup analysis on ethnicity for sensitivity and specificity.

Factors with asterisk are potential sources of heterogeneity.

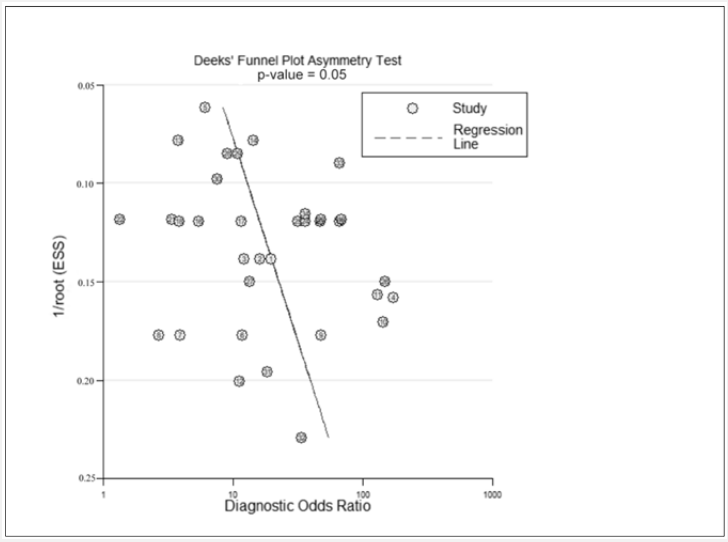

Figure 5. Graph of Deeks' funnel plot asymmetry test.

[31] and not in advanced cancer. Lodes et al. indicated that prostate cancer-derived exosomal miRNA can be used to distinguish healthy patients from those with stage 3 and 4 cancer [32], and miR-16 is upregulated in the plasma of metastatic prostate cancer patients [33]. Furthermore, in urine samples, miRNAs are also potential biomarkers to discriminate bladder cancer patients from the normal population [34]. However, Meng et al. showed that exosomal miR-125b had low sensitivity in the diagnosis of ovarian cancer [22], and Cazzoli et al.

found that exosome-derived plasma miRNAs (miR-1246, miR-4644, miR-3976 and miR-4306) had low specificity in the diagnosis of lung cancer [30]. Therefore, we conducted a meta-analysis to estimate the potential diagnostic value of exosomal miRNAs in cancer. In our meta-analysis of the 16 included studies, which included different types of cancer, the pooled sensitivity and specificity were 0.86 and 0.89, respectively, which are statistical measures of the diagnostic value of the miRNAs. The AUC, which is an index of diagnostic accuracy, was 0.94 in our meta-analysis, and it represents relatively good accuracy for cancer diagnosis. Moreover, the values of PLR and NLR were 7.8 and 0.16, respectively, which demonstrate that the probability of a TP diagnosis is 7.8 times higher than the probability of a FP diagnosis and that there is a 16% error rate in the negative individuals. The DOR, which is a combined index of sensitivity and specificity, reflects the test capacity to discriminate cancer, and our DOR indicated high diagnostic accuracy, with a value of 48. Exosomes can provide a protective, enriched source of miRNA and increase the stability of endogenous miRNAs. Goto et al. demonstrated that exosomal miRNA (miRNA-191, -21, and -451a) is superior to serum circulating miRNA in establishing a diagnosis of pancreatic neoplasms [15]. This demonstrates that the stability of exosome miRNA can further increase its diagnostic value. In comparing different cancer types, exosomal miRNA had a better accuracy than circulating miRNA, with AUCs of 0.85 vs. 0.83 in lung cancer [35], AUCs of 0.90 vs. 0.79 in prostate cancer [36], AUCs of 0.81 vs. 0.93 in renal carcinoma [37], and AUCs of 0.93 vs. 0.91 in pancreatic cancer [38]; therefore, we believe that exosomal miRNA has a higher diagnostic value than circulating miRNA, and it is worth more research.

With the existence of significant heterogeneity, a meta-regression analysis and subgroup analyses were performed based on factors including the research population, sample types, and cancer type, which may cause heterogeneity. The meta-regression analysis indicated heterogeneity resulting from all the factors, especially the research population and sample types. With regard to the type of biomarker, it is generally believed that the use of multiple biomarkers can compensate for the shortcomings of a single biomarker. Yin et al. found that the specificity of a single miRNA is not greater than that of miRNA panels in serum or plasma [39]. Meng et al. and Chiam et al. indicated consistent diagnostic results of multiple exosomal miRNAs [22,30]. In our meta-analysis, multiple exosomal miRNAs show superior sensitivity and specificity compared to single miRNAs, but single exosomal miRNAs had better specificity. It is worth noting that multiple exosomal miRNAs show better diagnostic accuracy than single exosomal miRNAs, with AUCs of 0.92 vs. 0.90, respectively; therefore, choosing the appropriate panel of exosomal miRNAs is the future direction for laboratory diagnosis. However, compared with single exosomal miRNAs, which were in 26 studies, multiple exosomal miRNAs were only in 9 studies; therefore, more research on multiple exosomal miRNAs is needed in the future. The sample type subgroup analysis indicated higher diagnostic efficiency in plasma samples than in urine and serum samples. There is currently no research related to this finding, and Cheng et al. indicated that the amounts of exosomal RNA (small RNAs and miRNAs) and exosomal markers (flotillin, CD-63) were higher in exosomes than in serum [8], which supports our finding and may be related to RNase inhibition of EDTA in plasma samples [40]. Exosomal miRNA showed a higher accuracy in pancreatic cancer patients and non-Asian populations, which has certain implications for the selection of cancer markers in specific populations. Future researchers should focus on these aspects.

This study had many advantages. First, there has been no previous study on the diagnostic value of exosomal miRNAs in cancer. Second, this paper reports the results of a meta-regression analysis of the heterogeneity of the results and explores the sources of heterogeneity. It also includes the results of subgroup analyses based on the results of the meta-regression, and the analysis was very detailed. Third, the paper draws conclusions regarding the clinical significance of the findings. For example, the diagnostic value of exosomal miRNA is higher in plasma than in other sample types, and the diagnostic value for cancer is better when multiple miRNAs are used. At the same time, this study had some limitations. First, the sample size was insufficient to stratify the analysis by individual cancer or exosomal miRNA types. In addition, the populations in the studies were not comprehensively representative, and there was a lack of research with African populations.

CONCLUSION

Our meta-analysis indicated that body fluid exosomal miRNAs are accurate when used to distinguish patients from healthy individuals and that exosomal miRNAs have better diagnostic efficiency than circulating miRNAs. In the subgroup analysis, exosomal miRNA had a better diagnostic value in plasma, prostate cancer patients, and non-Asian individuals. However, more studies on the diagnostic value of exosomal miRNAs are urgently needed to highlight the practical value of exosomal miRNAs and to focus on specific cancer types and specific miRNAs or miRNA panels.

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Declaration of Interest:
The authors have no conflicts of interest to declare.

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