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Contents

Semimonthly Volume 7 Number 2 January 26, 2019

ORIGINAL ARTICLE

Case Control Study

Retrospective Cohort Study

Retrospective Study

SYSTEMATIC REVIEW

CASE REPORT

Contents

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Volume 7 Number 2 January 26, 2019

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SYSTEMATIC REVIEW

Clinical significance of exosomes as potential biomarkers in cancer

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Abstract

BACKGROUND

Exosomes are microvesicles, measuring 30-100 nm in diameter. They are widely distributed in body fluids, including blood, bile, urine and saliva. Cancer-derived exosomes carry a wide variety of DNA, RNA, proteins and lipids, and may serve as novel biomarkers in cancer.

AIM

To summarize the performance of exosomal biomarkers in cancer diagnosis and prognosis.

METHODS

Relevant publications in the literature were identified by search of the "PubMed" database up to September 11, 2018. The quality of the included studies was assessed by QUADAS-2 and REMARK. For assessment of diagnostic biomarkers, 47 biomarkers and 2240 patients from 30 studies were included.

RESULTS

Our results suggested that these exosomal biomarkers had excellent diagnostic ability in various types of cancer, with good sensitivity and specificity. For assessment of prognostic markers, 50 biomarkers and 4797 patients from 42 studies were included. We observed that exosomal biomarkers had prognostic values in overall survival, disease-free survival and recurrence-free survival.

CONCLUSION

Exosomes can function as potential biomarkers in cancer diagnosis and prognosis.

Key words: Exosome; Biomarker; Cancer; Diagnosis; Prognosis

Core tip: Cancer-derived exosomes carry a wide variety of DNA, RNA, proteins and lipids, which may serve as novel biomarkers in cancer. The current systematic review and meta-analysis summarized the performance of exosomal biomarkers in cancer diagnosis and prognosis. We analyzed 47 diagnostic markers and 50 prognostic markers from 56 studies with various type of cancer. We found that exosomal biomarkers had both diagnostic and prognostic power in many cancers.

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INTRODUCTION

Cancer is the uncontrolled growth of cells and eventually leads to death. Cancer is the second cause of death, contributing to more than 8.8 million deaths every year[1,2]. Among various types of cancer, lung cancer, gastrointestinal cancers (GI cancer), including liver cancer, pancreatic cancer and colorectal cancer, and breast cancer are the most common cause of cancer-related death[2-4]. Although chemotherapy, targeted therapy, surgical recession and radiotherapy can effectively prolong survival of patients, the survival rate of cancer is still very low, especially in GI cancer, being less than 20%[2]. One of the major reasons is the late diagnosis of cancer, in which patients are already with advanced and metastatic tumors. As a result, no therapies can effectively kill the cancer cells. The situation is even worse in pancreatic cancers at distant stage, with 5-year survival rate of only 3%[2].

Since more than half of the patients present with locally advanced or metastatic stage, early diagnosis and early treatment are fundamentally important for better prognosis. Therefore, many tumor makers have been developed, aiming at accurately detecting various types of cancer and monitoring the disease progression. Blood test of the tumor antigens carcinoembryonic antigen, carbohydrate antigen 19-9, and carbohydrate antigen 125 (known as CEA, CA19-9 and CA125 respectively) are commonly used for detection of many cancers, such as GI cancers, ovarian cancer and breast cancer[5-8]. However, the sensitivity of these cancer biomarkers is unsatisfactory[9-12]. Also, the fecal occult blood test of colorectal cancer and the invasion endoscopic detection of gastric and colon cancer represent a great inconvenience to the patients. Therefore, highly sensitive and non-invasive diagnostic markers are urgently needed for early detection of cancer.

Exosomes are microvesicles of 30-100 nm diameter, which are secreted by both normal cells and cancer cells. They are distributed in many body fluids such as blood, saliva and urine, and carry various types of biomolecules, including RNA, proteins and lipids, for inter-cellular communication[13-15]. During cancer development, cancer cells secrete more exosomes, with significant changes in composition[16-18]. These facilitate communication within the tumor environment, acquisition of drug resistance, and metastasis to distant organs[19-21]. Although many potential non-invasive biomarkers have been developed using liquid biopsy, such as serum and urine, studies have found that these biomarkers are commonly located in the exosomes[22,23]. Enriching these exosomal biomarkers could achieve a higher diagnostic and prognostic efficiency[24-26]. Thus, exosomal biomarkers can be novel targets in cancer diagnosis and prognosis.

The objective of this systemic review and meta-analysis is to evaluate the diagnostic and prognostic potential of exosomes in patients with various types of cancer, based on current available data. This information will help in the development of novel non-invasive biomarkers for sensitive and specific diagnosis and prognosis of cancer.

MATERIALS AND METHODS

Search strategy

Electronic literature search was performed using the PubMed database, without any language restriction. Articles related to exosomes in cancer from 2010 to September 11, 2018 were identified using the following key words: "exosome" and "cancer" and

""diagnosis" or "prognosis"".

Inclusion and exclusion criteria

Articles were reviewed by their titles, key words, abstracts and full text to identify eligible studies. Eligible studies were included based on the following inclusion criteria: (1) The original article was related to exosomal diagnostic or prognostic markers in cancer; (2) At least 10 patients and 10 matched controls were enrolled in the study; (3) For diagnostic markers, enough information, such as specificity and sensitivity, was provided to construct 2 × 2 table [true positive (TP), true negative (TN), false positive (FP), false negative (FN)]; and (4) For prognostic markers, enough information was provided to estimate the hazard ratios (HRs) and confidence intervals (CIs). The exclusion criteria were as follows: (1) Duplicate articles; (2) Review articles, abstracts, comments, letters, case-report; (3) Fundamental research or animal study; (4) Diagnostic or prognostic marker that was not specific to exosome; (5) Sample size was less than 10; (6) Performance of the biomarker was not statistically significant; or (7) Incomplete information to estimate diagnostic or prognostic accuracy.

Data extraction

Two reviewers (Chi-Hin Wong and Yang-Chao Chen) independently reviewed and extracted the data from the eligible studies according to the listed criteria. Any disagreement was resolved by consensus among the authors. The following data from included studies were extracted: first author's name, year of publication, sample size, cancer type, country of origin, source of exosome, isolation method of exosome, and detection method of biomarkers. For diagnostic studies, data for the cut-off value of tested targets, sensitivity, specificity, and area under the receiver operating characteristics curve (ROC) were also extracted. For prognostic studies, data for survival analysis, cut-off value, multivariable HR and its 95%CI were extracted. If odds ratio (OR) was reported, OR was converted to relative risk using the formula introduced by Zhang and Yu[27]. If either OR or HR was not reported, the method introduced by Tierney *et al*[28] was used to estimate the HR and its 95%CI from a Kaplan-Meier plot.

Quality assessment

For diagnostic studies, the Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) was used to assess the quality of studies for the meta-analysis[29]. Briefly, 14 questions covering the patient selection, patient flow, index test and reference standard test were applied to each study and an answer of "Yes", "No" or "Unclear" was given to each study. Only answers of "Yes" were given a score.

For prognostic study, the quality of studies was assessed according to reporting recommendations for tumor marker prognostic studies (REMARK)[30]. Briefly, a checklist of 20 items was generated, covering patients' characteristics, samples' source and storage, assay methods, statistical analysis, and data interpretation. A score was given when the study fulfilled the requirement of each item.

Statistical analysis

The statistical analysis of the diagnostic performance of biomarkers was performed using Meta-DiSc 1.4[31]. The 2 × 2 table of each study was used to assess the pooled sensitivity, specificity, positive likelihood ratio (PLR) and negative likelihood ratio (NLR). Also, the summary receiver operating characteristic (SROC) curve was plotted; the area under the curve (AUC) was calculated and Q* index was estimated to assess the overall performance in cancer diagnosis. An AUC of 0.5 suggested no diagnostic ability; 0.7-0.8 suggested acceptable diagnostic performance; 0.8-0.9 was considered excellent, and 0.9-1.0 suggested outstanding performance[32]. Q* was defined at a point in which sensitivity and specificity are equal. For statistical analysis of the prognostic performance of biomarkers, forest plots were constructed using the HR and its 95%CI of each biomarker to assess the overall prognostic performance of biomarkers on overall survival (OS), disease-free survival (DFS) and recurrence-free survival (RFS). Graphpad Prism 6 was used in constructing the forest plots. To elevate the heterogeneity between studies, Cochran-Q test and inconsistency index (I^2) statistics were calculated[33,34]. *P*-value of < 0.05 for Cochran-*Q* test or I^2 >50% suggested the presence of heterogeneity.

RESULTS

Literature search

Initially, 1233 articles were identified based on the search strategies. Based on title and

abstract screening, 705 were not related to exosome biomarkers in cancer diagnosis or prognosis, and 287 were review articles. Upon further full-text review, 56 studies were basic studies, 42 studies with sample size less than 10 in either group (test group or control group), 12 studies analyzed the performance of combined markers, 70 studies did not provide enough information for analysis, and 5 studies were without statistical significance. Finally, 56 eligible studies were included for systematic review (Figure 1). Of these, 22 candidate studies were related to diagnosis, 34 candidate studies were related to prognosis, and 8 studies were related to both diagnosis and prognosis.

Assessment of study quality

For diagnostic studies, the QUADAS-2 system was used to assess the study quality (Figure 2A). Most of the studies on diagnosis were with moderate-to-high quality, revealed by low risk of publication bias. However, there may be risk of bias in "patient selection" and "flow and timing". This may due to control-based design in most of the studies. Also, time between the index test and the reference test is poorly reported. Importantly, many studies did not provide enough information on how the patients were selected and classified. Patients excluded from the 2 × 2 table were often observed in some studies.

The REMARK system was used to assess the quality of prognostic studies (Figure 2B). Most of the studies (> 90%) clearly stated the objective, biomarkers examined, source of exosomes, and methodology of isolation and detection. Also, most of the studies clearly defined the clinical endpoints and the period of the follow-up time. However, details in patient's characteristics during the follow-up period, such as the use of post-operative adjuvant therapy which significantly affects the OS and DFS, were lacking in most of the studies. Importantly, some studies did not clearly report the clinicpathological characteristics of the patients enrolled. Also, some studies did not show the relationship of the tested biomarkers to prognostic variables, including tumor stages and tumor differentiation. Twelve prognostic marker studies did not perform univariable or multivariable analysis. Twenty-eight of the enrolled studies reported multivariable analysis in prognostic markers, but only five studies clearly stated the adjustment factors.

Diagnostic markers

Diagnostic markers from 30 studies were included in the meta-analysis (Table 1). More than a half of these studies were related to GI cancers (4 studies were about colon cancer; 5 studies were related to liver cancer; 4 studies were about pancreatic or pancreatobiliary tract cancer; and 4 studies were related to gastric cancer). A total of 2240 patients were included in the meta-analysis, with 12 studies having enrolled < 50 patients, 16 studies having enrolled 50-100 patients, and 6 studies having enrolled > 100 patients. There were 47 diagnostic biomarkers analyzed in the meta-analysis. There were 42.6% of the biomarkers as miRNAs, followed by lncRNAs (36.2%) and proteins (19.1%). Notably, 6 studies analyzed the diagnostic performance of exosomal miR-21 in various types of cancer. Also, 61.3%, 16.1%, 12.9%, 3.2% and 3.2% of the biomarkers were detected in serum, plasma, urine, saliva and bile respectively.

Since a wide range of cancers was studied by different groups, we separated the diagnostic biomarkers according to cancer types and meta-analyzed cancer types with more than three biomarkers studied. Therefore, we focused on colorectal cancer (4 studies with 11 biomarkers), gastric cancer (4 studies with 5 biomarkers), pancreatic cancer (4 studies with 8 biomarkers), liver cancer (4 studies with 7 biomarkers), and prostate cancer (4 studies with 7 biomarkers (Figures 3-7). We observed that the pooled biomarkers had a good specificity of 0.87 but poor sensitivity of 0.57 in colorectal cancer diagnosis (Figure 3A and B). The PLR and NLR were 2.02 and 0.21 respectively (Figure 3C and D). The diagnostic OR was 20.35 (Figure 3E). Importantly, the AUC of the SROC curve was 0.89 and the Q* was 0.82 (Figure 3F). In diagnosis of gastric cancer, we observed that the pooled biomarkers had a good sensitivity of 0.77 and specificity of 0.73 with PLR, NLR, AUC of the SROC curve and Q* of 2.94, 0.32, 9.88, 0.84 and 0.77 respectively (Figure 4). For diagnosis of pancreatic cancer, we also observed the pooled biomarkers had an excellent sensitivity of 0.91 and specificity of 0.90 with PLR, NLR, AUC of the SROC curve and Q* of 6.35, 0.19, 40.71, 0.94 and 0.88 respectively (Figure 5). In liver cancer, the pooled biomarkers had a good diagnostic sensitivity of 0.76 and specificity of 0.80 with PLR, NLR, AUC of the SROC curve and Q* of 3.51, 0.32, 12.45, 0.85 and 0.78 respectively (Figure 6). The pooled biomarkers also had a good sensitivity of 0.77 and specificity of 0.79 in detecting prostate cancer with PLR, NLR, AUC of the SROC curve and Q* of 3.84, 0.28, 17.88, 0.88 and 0.80 respectively (Figure 7). The high sensitivity, specificity and Q* demonstrated that the pooled biomarkers could effectively discriminate cancer patients from healthy people or non-cancer patients.

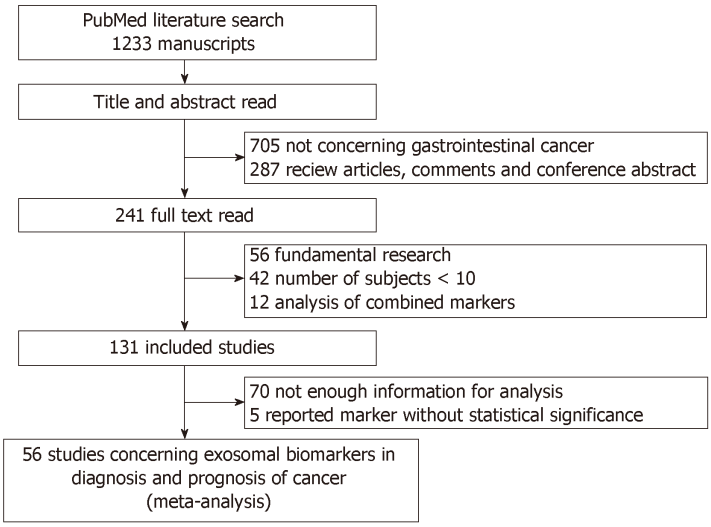

Figure 1 Literature search process to select studies which evaluated the diagnostic or prognostic performance of exosomal biomarkers in cancer.

Prognostic markers

Prognostic biomarkers from 42 studies were included in the systematic review (Table 2). In total, 4797 patients were represented among the studies, with 7 studies having enrolled < 50 patients, 15 studies having enrolled 50-100 patients, and 20 studies having enrolled > 100 patients. There were 50 prognostic biomarkers analyzed in the systematic review, with 60% of the biomarkers being miRNAs, followed by lncRNAs (18%) and proteins (16%). Also, 50%, 43%, 2.4%, 2.4% and 2.4% of the biomarkers were detected in serum, plasma, bile, ascetic fluid and cell-free effusion supernatant respectively. For the included studies, 92.9%, 26.2% and 9.5% used OS, DFS and RFS respectively as the primary endpoints. In addition, a wide range of cancers was studied by the different groups. More than one-half of the included studies were related to GI cancers (11 studies were about colorectal or colon cancer, 5 studies were related to liver cancer, 5 studies were about pancreatic cancer, and 4 studies were related to gastric cancer). In this meta-analysis, we separated studies according to clinical endpoints and focused on cancer types with more than three biomarkers studied.

For 13 biomarkers with OS reported in colon cancer, the pooled HR was 1.833 with $I2$ of 62.14% and P = 0.002 (Figure 8A). Also, for 5 biomarkers with DFS reported in colon cancer, the pooled HR was 3.035 with $I2$ of 0.00% and P = 0.536 (Figure 8B). Furthermore, for 4 biomarkers with RFS reported in colon cancer, the pooled HR was 1.645 with $I2$ of 89.61% and P = 0.000 (Figure 8C). Apart from colon cancer, for the 4 biomarkers with OS reported in gastric cancer, the pooled HR was 1.836 with $I2$ of 96.71 and P = 0.000 (Figure 9). In addition, for the 4 biomarkers with OS reported in pancreatic cancer, the pooled HR was 1.537 with $I2$ of 81.50 and P = 0.001 (Figure 10). For 5 biomarkers, the pooled HR was 1.828, $I2$ of 84.48% and P = 0.000 for prognosing OS in liver cancer (Figure 11). Also, 9 biomarkers with the pooled HR of 0.895, $I2$ of 89.50% and P = 0.000 were reported to function as prognostic biomarkers of OS in lung cancer (Figure 12). These results demonstrated that exosomes were associated with OS, DFS and RFS in various types of cancer.

DISCUSSION

Exosomes play important roles in cancer development *via* intercellular communication, promoting cell metastasis and developing drug resistance[19-21]. Importantly, exosomes are frequently secreted by the cancers and are widely distributed in many body fluids. Therefore, they can be detected in blood, saliva and urine. Exosomal biomarkers have better performance in cancer diagnosis and prognosis than liquid biopsy used alone[24-26]. However, the methods of isolating exosomes from liquid biopsy varies between studies. Ultracentrifugation or the use of commercial isolation kits are common methods in extracting exosomes. Ultracentrifugation gives highly pure exosomes but the isolation efficiency is relatively low; whereas, the use of commercial kits maximizes the efficiency with the

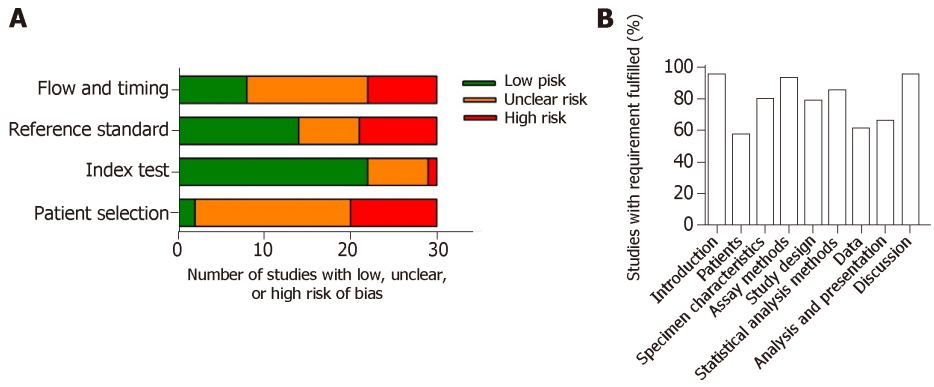

Figure 2 Quality assessment of the studies in this meta-analysis. A: QUADAS-2 system was used to assess the quality of diagnostic studies; B: REMARK checklist was used to assess the quality of prognostic studies.

loss of purity[95,96]. Therefore, a standardized protocol of detecting exosomal biomarkers is greatly needed.

There are some limitations of our meta-analysis. We excluded studies that utilized combined biomarkers because this cannot tell the performance of individual biomarkers[97,98]. For example, a six-microRNA panel was developed for diagnosis of lung cancer but miR-409-3p, miR-425-5p and miR-584-5p were not significantly dysregulated in patients' exosomes[98]. This may reduce the diagnostic performance of other biomarkers in the same panel. Since many of the individual biomarkers in the panel were significantly differentially expressed in cancer exosomes, further studies may be needed to explore the correlation of these potential biomarkers with patients' characteristics and their performances in cancer diagnosis and prognosis.

A further limitation is that we focused on exosomal markers only in cancer diagnosis and prognosis and excluded tissue-based biomarkers from this meta-analysis. In fact, many studies have reported that expression levels in exosomes and in tissues are highly associated[35,66]. This suggests that many exosomal markers can reflect the situation in cancer cells, and this notion has been developed for potential biomarkers in various cancers. Importantly, this strong association may also suggest that many tissue-based biomarkers can be developed into non-invasive exosomal biomarkers in cancer diagnosis.

Notably, most of the included studies are retrospective, having been performed on stored samples. However, the main disadvantage of the retrospective study is its lack of complete clinicpathological information[30], which lowers the quality of study. Despite the above limitations, our meta-analysis indicates that exosomes can be potential biomarkers in cancer diagnosis and prognosis. Further large prospective studies are greatly needed to clarify the performance of exosomal biomarkers in cancer diagnosis and prognosis.

Table 1 Studies included for meta-analysis of exosomal biomarkers in cancer diagnosis

Ref.	Country	Cancer type	Stage	Control	Number of Control	Number of patients	Sample	Isolation method of exosome	Marker	Detection method	Cut-off	TP	TN	FP	FN
Sun *et al*[35]	China	Colorectal	All	Healthy	32	92	Plasma	UC	CPNE3	ELISA	0.143 pg/μg exosome	62	27	5	30
Ogata-Kawata *et al*[36]	Japan	Colorectal	All	Healthy	11	88	Serum	UC	miR-1246	qRT-PCR	1.45	84	10	4	1
									miR-23a		0.3100	81	11	7	0
									miR-21		1.08	54	10	34	1
									miR-150		0.08	49	11	39	0
									let-7a		0.9	44	10	44	1
									miR-223		1.72	41	10	47	1
									miR-1224-5p		0.5	28	11	60	0
									miR-1229		0.06	20	11	68	0
Liu *et al*[37]	China	Colorectal	All	Healthy and benign	320	148	Serum	ExoQuick	CRNDE-h	qRT-PCR	0.02	104	302	18	44
Uratani *et al*[38]	Japan	Colorectal	NR	Healthy	47	26	Serum	ExoQuick	miR-21	qRT-PCR	Youden index	18	38	9	8
Lin *et al*[39]	China	Gastric	All	Healthy	60	51	Plasma	UC	lncUEGC1	qRT-PCR	NR	45	50	10	6
									lncUEGC2		NR	46	34	26	17
Zhao *et al*[40]	China	Gastric	All	Healthy	120	126	Serum	NR	HOTTIP	qRT-PCR	1.72	88	102	18	38
Pang *et al*[41]	China	Gastric	All	Healthy	37	40	Serum	ExoQuick	ZFAS1	qRT-PCR	NR	32	28	9	8
Yang *et al*[42]	China	Gastric	All	Healthy	80	80	Serum	ExoQuick	miR-423-5p	qRT-PCR	NR	65	46	34	15
Goto *et al*[43]	Japan	Pancreatic	All	Healthy and advanced pancreatic cancer	22	23	Serum	ExoQuick	miR-191	qRT-PCR	Distance = (1-sensitivity)^2 + (1-specificity)^2 in ROC curve	18	17	5	5
									miR-21			20	18	4	3
									miR-451a			16	18	4	7
Melo *et al*[44]	Germany	Pancreatic	All	Healthy	100	190	Serum	UC	GPC1	Flow cytometry	Youden index	190	100	0	0
Que *et al*[45]	China	Pancreatic	All	Non-PDAC	27	22	Serum	UC	miR-17-5p	qRT-PCR	6.826	20	20	7	2
									miR-21		7.693	18	26	1	4
Machida *et al*[46]	Japan	Pancreatobiliary tract	II-IV	Healthy	13	12	Saliva	Total exosome isolation kit	miR-1246	qRT-PCR	13.77	8	13	0	4
									miR-4644		-5.205	9	10	3	3
Xu *et al*[47]	China	Liver	All	Chronic hepatitis B	68	88	Serum	Total exosome isolation kit	hnRNPH1	qRT-PCR	0.67	75	52	16	13

Sun *et al*[48]	China	Liver	All	Healthy	56	56	Serum	Total exosome isolation kit	LINC00161	qRT-PCR	NR	42	41	15	14
Xu *et al*[49]	China	Liver	All	Chronic hepatitis B	96	60	Serum	Total exosome isolation kit	ENSG00000258332.1	qRT-PCR	1.345	43	80	16	17
					60	55			ENSG00000258332.1		1.366	40	48	12	15
					96	60			LINC00635		1.69	46	75	21	14
					60	55			LINC00635		1.532	44	45	15	11
Goldvaser *et al*[50]	Israel	Pan-cancer (not include liver)		Healthy	45	98	Serum	Total exosome isolation kit	hTERT	qRT-PCR	NR	61	45	0	37
		Liver	NR	Healthy	45	35					NR	21	45	0	14
Zhang *et al*[51]	China	Lung	All	Healthy	30	77	Serum	ExoQuick	MALAT-1	qRT-PCR	NR	62	21	9	15
Sun *et al*[52]	China	Lung	All	Healthy	15	15	Plasma	UC	14-3-3ζ	ELISA		9	12	3	6
Li *et al*[53]	NR	Ovarian		Benign	21	50	Serum	UC	ephrinA2	ELISA	20.4 ng/L	44	17	4	6
Meng *et al*[54]	NR	Ovarian	All	Benign	20	163	Serum	Total exosome isolation kit	miR-200a	PCR+qRT-PCR	Youden index	135	18	2	28
									miR-200b			86	20	0	77
									miR-200c			51	20	0	112
Pan *et al*[55]	Germany	Ovarian	All	Healthy	29	106	Plasma	ExoQuick	miR-21	PCR+qRT-PCR	Youden index	65	24	5	41
									miR-100			66	21	8	40
									miR-200b			68	25	4	38
									miR-320			59	20	9	47
Bryzgunova *et al*[56]	Russia	Prostate	All	Healthy	20	14	Urine	UC	miR-125	qRT-PCR	NR	12	13	7	2
									miR-19b		NR	11	19	1	3
Wang *et al*[57]	China	Prostate	II-IV	Healthy	30	34	Plasma	Total exosome isolation kit	SAP30L-AS1	qRT-PCR	NR	21	25	5	13
									SChLAP1		NR	30	23	7	4
Øverbye *et al*[58]	NR	Prostate	All	Healthy	15	16	Urine	UC	ADIRF	Mass spectrometry	Youden index	12	16	0	3
									TMEM256			14	16	0	1
Işın *et al*[59]	NR	Prostate	All	BPH	49	30	Urine	Urine Exosome RNA Isolation Kit	LincRNA-p21	qRT-PCR	0.181	20	31	18	10
Wang *et al*[60]	China	Laryngeal	All	Vocal cord polyps	49	52	Serum	ExoQuick	miR-21	qRT-PCR	0.043	36	40	9	16
									HOTAIR		0.032	48	28	21	4
Alegre *et al*[61]	NR	Melanoma	NR	Healthy	25	53	Serum	ExoQuick	exo-MIA	ELISA	1.4 μg/L	42	20	5	11
									exo-S100B	ELISA	0.015 μg/L	42	20	5	11
Manterola *et al*[62]	France	GBM	NR	Healthy	30	50	Serum	ExoQuick	RNU6	qRT-PCR	0.372	33	20	10	17
Chen *et al*[63]	Taiwan	Bladder	All	hernia	81	140	Urine	UC	TACSTD2	ELISA	2.47 ng/mL	103	62	19	37

Ge *et al*[64]	China	Cholangiocarcinoma	All	Biliary obstruction	56	35	Bile	UC	ENST00000588480.1	qRT-PCR	NR	22	41	15	13

UC: Ultracentrifugation; NR: Not reported.

Table 2 Studies included for meta-analysis of exosomal biomarkers in cancer prognosis

Ref.	Period	Country	Sample Size	Cancer Type	Stage	Sample	Isolation method of exosome	Marker	Detection method	Cut-off value	Survival analysis	HR (95%CI)
Peng *et al*[65]	2008-2014	China	108	Colorectal	All	Serum	Total exosome isolation kit	miR-548c-5p	qRT-PCR	NR	OS	3.40 (1.02 11.27)
Sun *et al*[35]	2012-2017	China	92	Colorectal	All	Plasma	UC	CPNE3	ELISA	≥ 0.143 pg/μg exosome	OS	3.0 (1.0-8.9)
										≥ 0.143 pg/μg exosome	DFS	2.5 (1.1-5.5)
Tsukamoto *et al*[66]	2002-2012	Japan	326	Colorectal	II-IV	Plasma	UC	miR-21	qRT-PCR	> median	OS	2.28 (1.81-5.74)
											DFS	2.34 (1.87-4.60)
Liu *et al*[37]	2007-2010	China	148	Colorectal	All	Serum	ExoQuick	CRNDE-h	qRT-PCR	> 0.02	OS	2.000 (1.269-3.154)
Liu *et al*[67]	2006-2011	United States	84	Colorectal	II-III	Serum	ExoQuick	miR-4772-3p	qRT-PCR	≥ 27.88	OS	6.19 (1.50-25.5)
										≥ 27.88	RFS	5.48 (2.49-12.1)
Liu *et al*[24]	2013-2014	China	158	Colorectal	All	Plasma	UC	lncRNA GAS5	qRT-PCR	NR	OS	0.265 (0.082 - 0.844)
											RFS	0.449 (0.194-0.909)
								miR-221	qRT-PCR	NR	OS	2.141 (1.368-3.054)
											RFS	1.600 (1.162-2.007)
Gao *et al*[68]	2011-2014	China	108	Colorectal	All	Serum	ExoQuick	91H	qRT-PCR	≥ 0.85	RFS	7.14 (1.23-21.35)
Yan *et al*[69]	NR	NR	168	Colorectal	All	Serum	Total Exosome Isolation kit	miR-6803	qRT-PCR	NR	OS	2.93 (1.35-6.37)
											DFS	3.26 (1.56-6.81)
Li *et al*[70]	2013-2015	China	85	Colorectal	III	Plasma	ExoCapTM	GPC1	Flow cytometry	> mean	OS	1.89 (1.23-2.89)
Silva *et al*[71]	2003-2009	Spain	91	Colorectal	All	Plasma	UC	Exosome	Flow cytometry of EpCAM	High	OS	0.87 (0.57-1.32)
Matsumura *et al*[72]	1992-2007	Japan	209	Colorectal	All	Serum	UC	miR-19	qRT-PCR	> mean	O	2.49 (1.12-6.61)
											DFS	2.49 (1.12-6.61)
Yan *et al*[73]	2012-2015	China	142	Colorectal	All	Serum	Total Exosome Isolation kit	miR-6869-5p	qRT-PCR	< mean	OS	2.32 (1.08-4.99)

Santasusagna *et al*[25]	2009-2013	Spain	32	Colon	I-III	Plasma	UC	miR-141	qRT-PCR	High	OS	1.89 (0.93-3.83)
Zhao *et al*[40]	2011-2012	China	126	Gastric	All	Serum	NR	HOTTIP	qRT-PCR	> 1.72	OS	2.037 (1.085-3.823)
Liu *et al*[74]	2012-2017	China	76	Gastric	All	Serum	Total Exosome Isolation kit	miR-451	qRT-PCR	> median	5yr-OS	4.344 (2.853 5.721)
Yang *et al*[42]	NR	China	80	Gastric	All	Serum	ExoQuick	miR-423-5p	qRT-PCR	> median	DFS	1.93 (1.25-2.99)
											OS	1.42 (0.92-2.20)
Kumata *et al*[75]	2006-2013	Japan	232	Gastric	All	Plasma	UC	miR23b	qRT-PCR	> 0.78	OS	0.57 (0.370.78)
											DFS	0.64 (0.410.91)
Zhou *et al*[76]	2010-2014	China	152	Pancreatic	All	Plasma	ExoQuick	miR-125b-5p	qRT-PCR	< median	OS	0.285 (0.108-0.75)
Li *et al*[77]	2012-2016	China	87	Pancreatic	All	Plasma	NR	circPDE8A	qRT-PCR	> median	OS	1.764 (1.064-2.925)
Goto *et al*[43]	2013-2015	Japan	32	Pancreatic	All	Serum	ExoQuick	miR-21	qRT-PCR	> median	OS	4.071 (1.832-11.996)
Takahasi *et al*[78]	2013-2017	Japan	50	Pancreatic	I-II	Plasma	UC	miR-451a	qRT-PCR	> 1.75	OS	3.20 (1.07-11.94)
											DFS	2.87 (1.23-7.23)
Xu *et al*[49]	2012-2016	China	60	Liver	All	Serum	Total Exosome Isolation kit	ENSG00000258332.1	qRT-PCR	> 1.845	OS	2.22 (1.34-3.68)
								LINC00635	qRT-PCR	> 2.100	OS	1.46 (0.88-2.43)
Shi *et al*[79]	2008-2011	China	126	Liver	All	Serum	Total Exosome Isolation kit	miR-638	qRT-PCR	NR	3yr-OS	3.52 (1.37-6.02)
											5yr-OS	2.80 (1.24-4.31)
Liu *et al*[26]	2012	China	128	Liver	All	Serum	ExoQuick	miR-125b	qRT-PCR	< median	RFS	0.14 (0.07-0.29)
											OS	0.36 (0.18-0.74)
Xue *et al*[80]	2015-2017	China	85	Liver	All	Serum	Total Exosome Isolation kit	miR-93	qRT-PCR	NR	OS	1.47 (0.96-2.25)
Liu *et al*[81]	2008-2013	China	32	Hepatoblastoma (children)	All	Serum	ExoQuick	miR-21	qRT-PCR	NR	EFS	1.434 (1.257-2.766)
Matsumoto *et al*[82]	2011-2012	Japan	66	Esophageal	All	Plasma	Total Exosome Isolation kit	exosome	AChE activity	< 600 x 108/mL	OS	2.177 (1.085-3.605)
Lu *et al*[83]	2007-2015	China	110	Nasopharyngeal	All	Plasma	UC	miR-9	qRT-PCR	NR	OS	1.5 (1.03-2.18)
Ye *et al*[84]	2011-2013	China	83	Nasopharyngeal	II-IV	Serum	UC	protein concentration	BCA assay	> 11 μg/mL	DFS	214.22 (139.27-329.49)
Huang *et al*[85]	NR	NR	23	Prostate	All	Plasma	ExoQuick	miR-1290	qRT-PCR	> mean	OS	1.79(1.30-2.48)
								miR-375	qRT-PCR	> mean	OS	2.69(1.52-4.77)
Tang *et al*[86]	NR	NR	35	Ovarian	All	Ascitic fluid	UC	E-cadherin	NR	> 10 μg/mL	OS	1.82 (0.53-3.58)
Vaksman *et al*[87]	1998-2003		86	Ovarian	III-IV	Effusion supernatant	ExoQuick	miR-21	qRT-PCR	> median	OS	1.70 (1.1-2.59)

Kanaoka *et al*[88]	2012-2017	Japan	285	Lung	I-III	Plasma	UC	miR-451a	qRT-PCR	> 1.45	OS	6.06 (2.61-15.94)
											DFS	2.55 (1.44-4.65)
Liu *et al*[89]	2012-2014	China	196	Lung	All	Plasma	ExoQuick	miR-23b-3p	qRT-PCR	High	OS	2.42 (1.45-4.04)
								miR-21-5p	qRT-PCR		OS	2.12(1.28-3.49)
								miR-10b-5p	qRT-PCR		OS	2.22 (1.18-4.16)
Liu *et al*[90]	2012-2014	China	208	Lung	All	Plasma	ExoQuick	Exosome	AChE activity		OS	1.72 (1.05-2.83)
Sandfeld-Paulsen *et al*[91]	2011-2014	Denmark	276	Lung	All	Plasma	/	CD171	ELISA	NR	OS	0.56 (0.41-0.79)
								Flotilin1	ELISA	NR	OS	0.63 (0.46-0.86)
								HER3	ELISA	NR	OS	0.63 (0.46-0.86)
								GRP78	ELISA	NR	OS	0.69 (0.51-0.91)
Manier *et al*[92]	2006-2008	France	156	Multiple myeloma	All	Plasma	ExoQuick	let-7b	qRT-PCR	< median	OS	2.83 (1.07-7.50)
								let-7b	qRT-PCR	< median	DFS	1.90 (1.22-2.94)
								let-7e	qRT-PCR	< median	DFS	2.01 (1.30-3.11)
								miR-106a	qRT-PCR	< median	DFS	2.34 (1.52-3.61)
								miR-106b	qRT-PCR	< median	DFS	3.54 (2.21-5.68)
								miR-155	qRT-PCR	< median	OS	2.41 (0.96-6.05)
								miR-155	qRT-PCR	< median	DFS	1.76 (1.15-2.69)
								miR-16	qRT-PCR	< median	DFS	2.21 (1.41-3.47)
								miR-17	qRT-PCR	< median	DFS	2.29 (1.48-3.55)
								miR-18a	qRT-PCR	< median	DFS	4.52 (1.57-12.98)
								miR-18a	qRT-PCR	< median	OS	2.76 (1.79-4.26)
								miR-20a	qRT-PCR	< median	DFS	2.31 (1.52-3.53)
Alegre *et al*[61]	NR	NR	53	Melanoma	NR	Serum	ExoQuick	MIA	ELISA	2.5 μg/L	OS	1.28 (0.65-2.51)
Lan *et al*[93]	2011-2012	China	60	Glioma	All	Serum	ExoQuick	miR-301a	qRT-PCR	>median	OS	4.4 (3.1-9.6)
Ge *et al*[64]	NR	China	35	Cholangio carcinoma	All	Bile	UC	ENST00000588480.1	qRT-PCR	> median	OS	2.40 (1.24-4.66)
								ENST00000517758.1	qRT-PCR		OS	1.55 (0.80-3.01)
Fujii *et al*[94]	2005-2014	Japan	108	Renal cell	I-III	Serum	Total Exosome Isolation kit	miR-224	qRT-PCR	> median	OS	9.1 (1.8-166.1)

UC: Ultracentrifugation; OS: Overall survival; DFS: Disease-free survival; RFS: Recurrence free survival; EFC: Event-free survival; NR: Not reported.

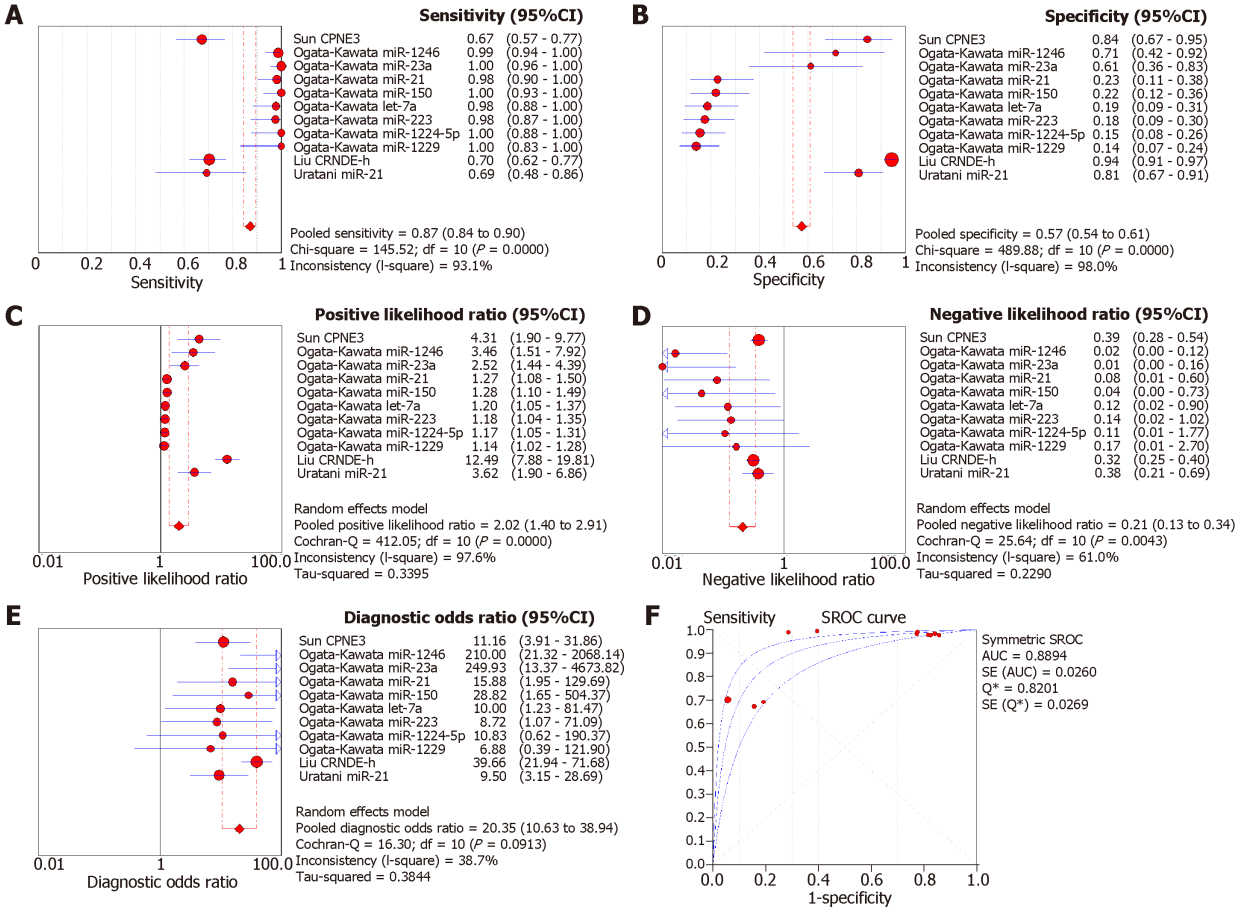

Figure 3 Forest plot of pooled (A) sensitivity, (B) specificity, (C) positive likelihood ratio, (D) negative likelihood ratio, (E) diagnostic odds ratio and (F) SROC curve of exosomal biomarkers in diagnosis of colon cancer. SROC: Summary receiver operating characteristic.

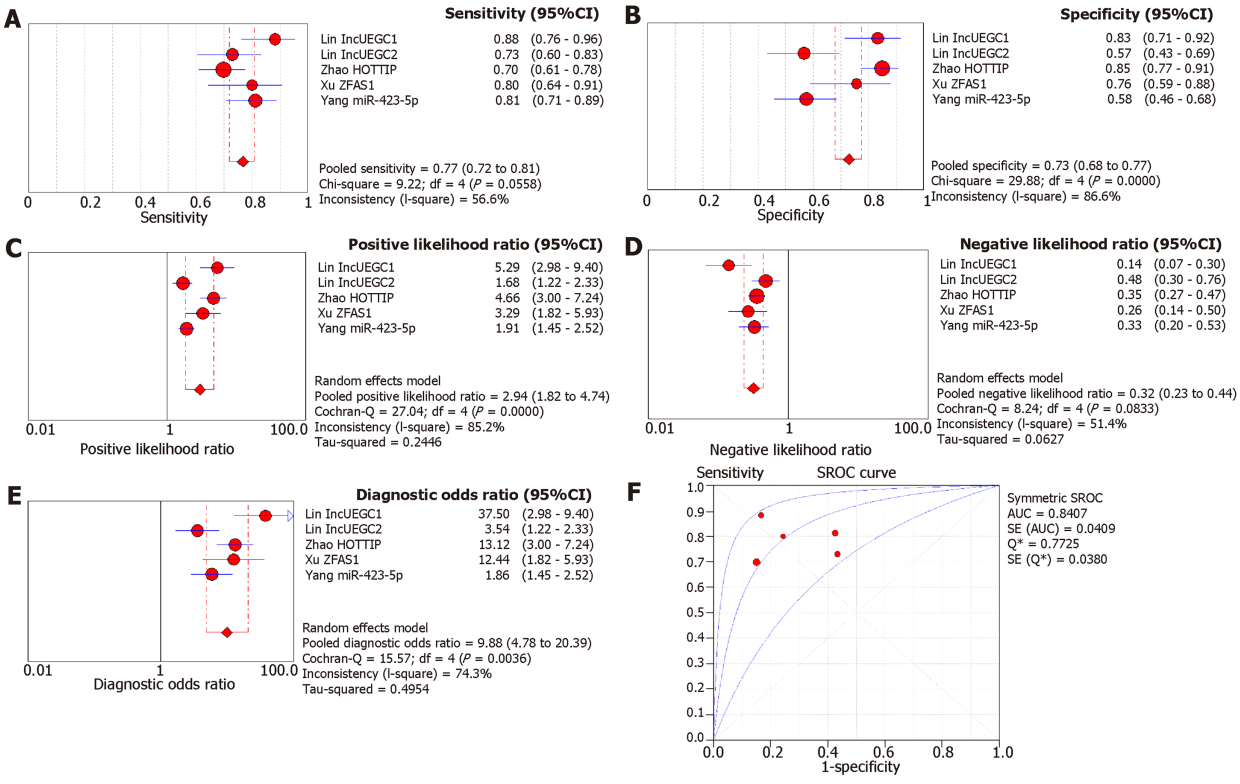

Figure 4 Forest plot of pooled (A) sensitivity, (B) specificity, (C) positive likelihood ratio, (D) negative likelihood ratio, (E) diagnostic odds ratio, and (F)

SROC curve of exosomal biomarkers in diagnosis of gastric cancer. SROC: Summary receiver operating characteristic.

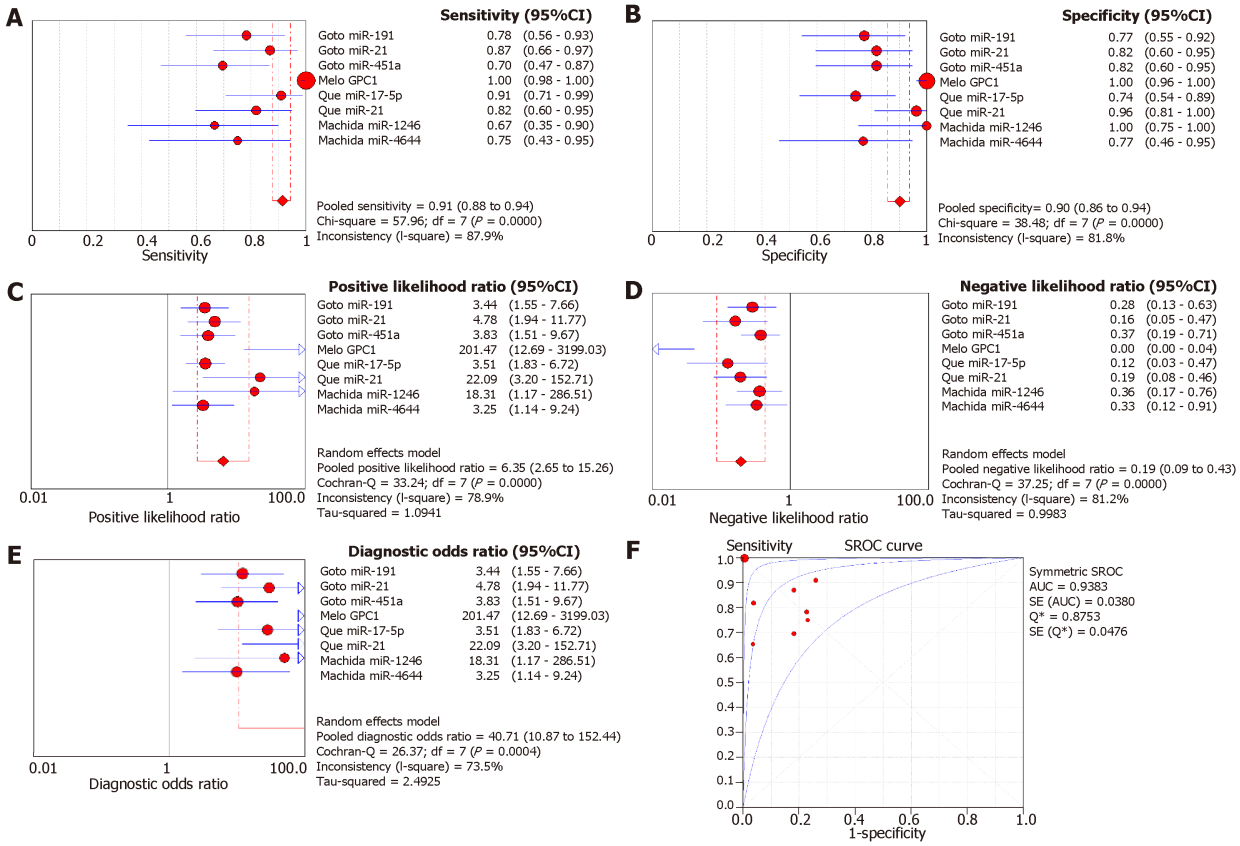

Figure 5 Forest plot of pooled (A) sensitivity, (B) specificity, (C) positive likelihood ratio, (D) negative likelihood ratio, (E) diagnostic odds ratio and (F) SROC curve of exosomal biomarkers in diagnosis of pancreatic cancer. SROC: Summary receiver operating characteristic.

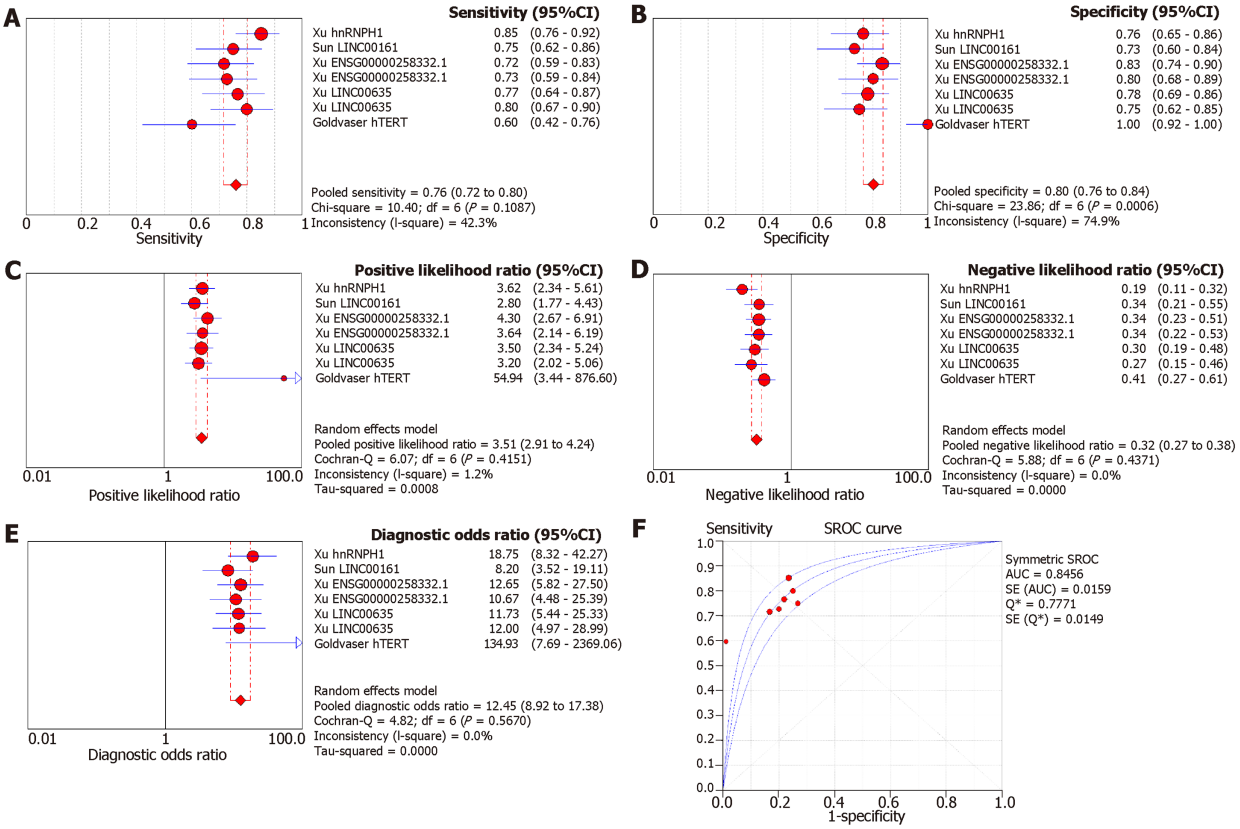

Figure 6 Forest plot of pooled (A) sensitivity, (B) specificity, (C) positive likelihood ratio, (D) negative likelihood ratio, (E) diagnostic odds ratio, and (F) SROC curve of exosomal biomarkers in diagnosis of liver cancers. SROC: Summary receiver operating characteristic.

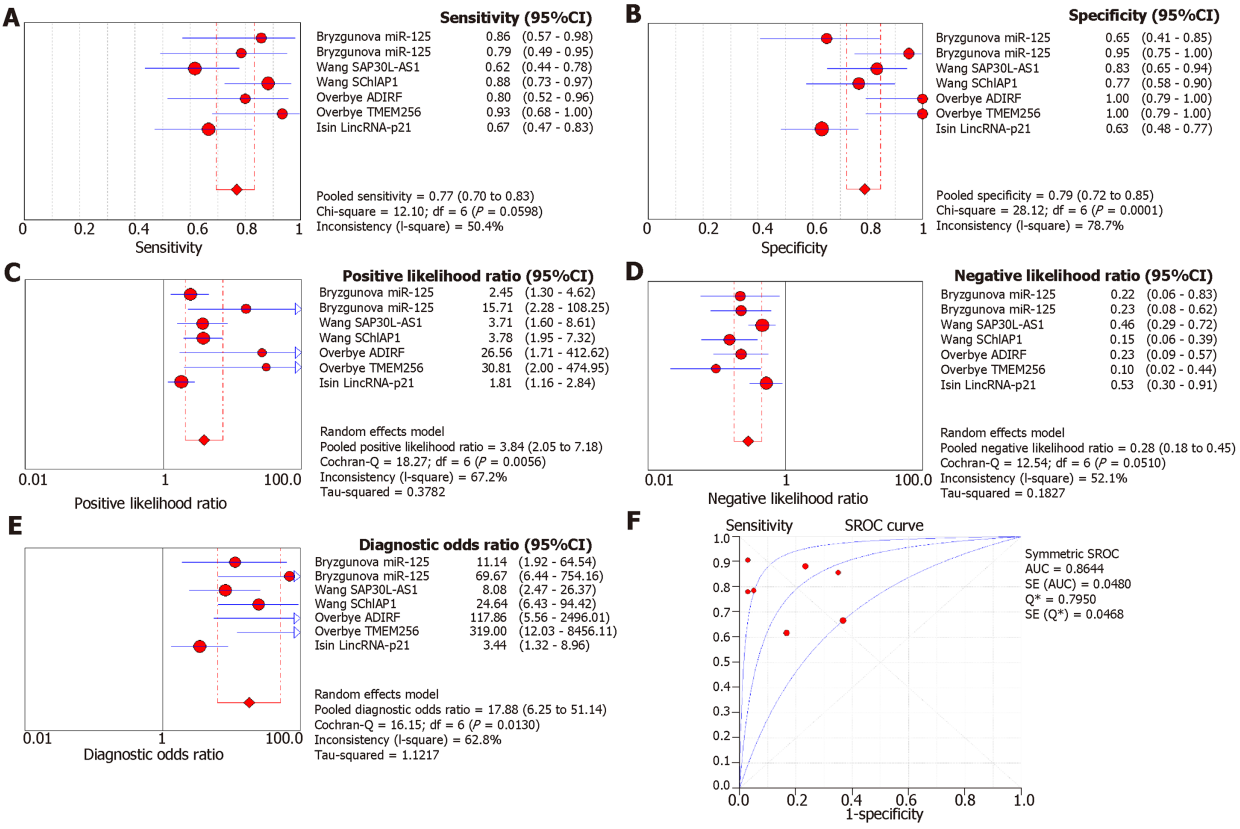

Figure 7 Forest plot of pooled (A) sensitivity, (B) specificity, (C) positive likelihood ratio, (D) negative likelihood ratio, (E) diagnostic odds ratio, and (F) SROC curve of exosomal biomarkers in diagnosis of prostate cancers. SROC: Summary receiver operating characteristic.

A

Model	Study name	Statistics for each study			Hazard ratio and 95%CI
		Hazard ratio	Upper limit	Lowet limit	0.01 0.10 1.00 10.00 100.00
	Peng miR-548c-5p	3.400	11.302	1.023	
	Sun CPNE3	3.000	8.950	1.006	
	Tsukamoto miR-21	2.800	5.740	1.366	
	Liu CRNDE-h	2.000	3.153	1.269	
	Liu miR-4772-3p	6.190	25.522	1.501	
	Liu IncRNA GAS5	0.265	0.850	0.083	
	Liu miR-221	2.141	3.054	1.501	
	Yan miR-6803	2.930	6.365	1.349	
	Li GPC1	1.890	2.897	0.233	
	Silva Exosome	0.870	1.324	0.572	
	Matsumura miR-19	2.490	6.610	0.938	
	Yan miR-6869-5p	2.320	4.987	1.079	
	Santasusagna miR-141	1.890	3.835	0.931	
Fixed		1.833	2.171	1.548	

B

Model	Study name	Statistics for each study			Hazard ratio and 95%CI
		Hazard ratio	Upper limit	Lowet limit	0.01 0.10 1.00 10.00 100.00
	Sun CPNE3	2.500	5.590	1.118	
	Tsukamoto miR-21	2.340	4.600	1.190	
	Liu miR-4772-3p	5.480	12.080	2.486	
	Yan miR-6803	3.260	6.811	1.560	
	Matsumura miR-19	2.490	6.610	0.938	
Fixed		3.035	4.302	2.142	

C

Model	Study name	Statistics for each study			Hazard ratio and 95%CI
		Hazard ratio	Upper limit	Lowet limit	0.01 0.10 1.00 10.00 100.00
	Liu miR-4772-3P	5.480	12.080	2.486	
	Liu IncRNA GAS5	0.449	0.909	0.222	
	Liu miR-221	1.600	2.007	1.276	
	Gao 91H	7.140	21.350	2.388	
Fixed		1.645	2.018	1.341	

Figure 8 Forest plot evaluating the effect of exosomal markers on overall survival (A), disease-free survival (B), and (C) recurrence-free survival of patients with colon cancer.

Model	Study name	Statistics for each study			Hazard ratio and 95%CI
		Hazard ratio	Upper limit	Lowet limit	0.01 0.10 1.00 10.00 100.00
	Zhao HOTTIP	2.037	3.824	1.085	
	Liu miR-451	4.344	5.721	3.298	
	Yang miR-423-5p	1.930	2.985	1.248	
	Kumata miR-23b	0.570	0.780	0.417	
Fixed		1.836	2.196	1.534	

Figure 9 Forest plot evaluating the effect of exosomal markers on overall survival of patients with gastric cancer.

Model	Study name	Statistics for each study			Hazard ratio and 95%CI
		Hazard ratio	Upper limit	Lowet limit	0.01 0.10 1.00 10.00 100.00
	Zhou miR-125b-5p	0.285	0.751	0.108	
	Li circPDE8A	1.764	2.925	1.064	
	Goto miR-21	4.071	11.996	1.382	
	Takahasi miR-451a	3.200	11.940	0.858	
Fixed		1.537	2.282	1.036	

Figure 10 Forest plot evaluating the effect of exosomal markers on overall survival of patients with pancreatic cancer.

Model	Study name	Statistics for each study			Hazard ratio and 95%CI
		Hazard ratio	Upper limit	Lowet limit	0.01 0.10 1.00 10.00 100.00
	Xu ENSG00000258332.1	2.220	3.679	1.340	
	Xu LINC00635	1.460	2.426	0.879	
	Shi miR-638 [3-yr]	3.520	6.020	2.058	
	Shi miR-638 [5-yr]	2.800	4.310	1.819	
	Liu miR-125b	0.360	0.730	0.178	
	Xue miR-93	1.470	2.250	0.960	
Fixed		1.828	2.241	1.492	

Figure 11 Forest plot evaluating the effect of exosomal markers on overall survival of patients with liver cancer.

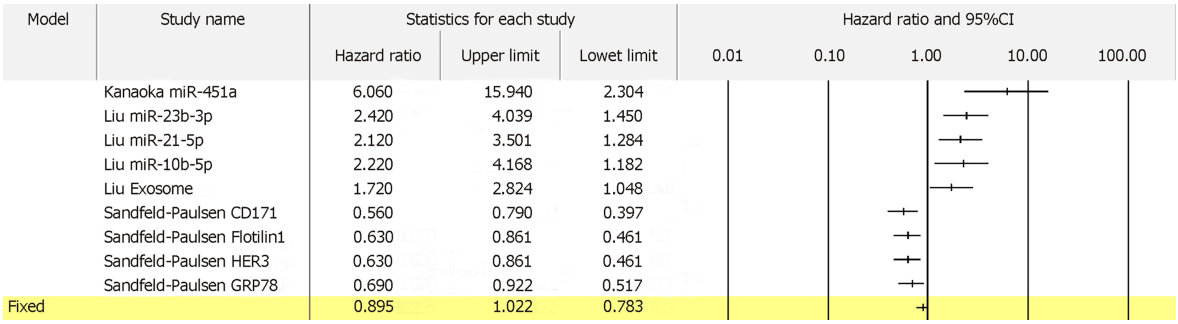

Figure 12 Forest plot evaluating the effect of exosomal markers on overall survival of patients with lung cancer.

ARTICLE HIGHLIGHTS

Research background

Exosomes, which are widely distributed in body fluids, including blood, bile, urine and saliva, are microvesicles of 30-100 nm diameter in size. Cancer-derived exosomes carry a wide variety of DNA, RNA, proteins and lipids, and may serve as novel biomarkers in cancer.

Research motivation

Exosomes may function as exosomal biomarkers in cancer diagnosis and prognosis.

Research objectives

To summarize the performance of exosomal biomarkers in cancer diagnosis and prognosis.

Research methods

Relevant studies in the literature were identified using the PubMed database. QUADAS-2 and REMARK were used to assess the quality of the included studies. For diagnostic biomarkers, 47 biomarkers and 2240 patients from 30 studies were included.

Research results

These exosomal biomarkers had excellent diagnostic ability in various types of cancer, with good sensitivity and specificity. A total of 50 biomarkers and 4797 patients from 42 studies were included for the prognostic markers. We observed that exosomal biomarkers had prognostic values in overall survival, disease-free survival and recurrence-free survival.

Research conclusions

Exosomes could be potential biomarkers in cancer diagnosis and prognosis.

Research perspectives

Further large prospective studies are needed to clarity the performance of exosomal biomarkers in cancer diagnosis and prognosis, through exosomes can be potential biomarkers in cancer diagnosis and prognosis.

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