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ORIGINAL ARTICLE

The Diagnostic Accuracy of Liquid Exosomal miRNAs for Cancer Detection: a Meta-Analysis

Hongling Yin, Qian Zhang, Qunzhi Zhou, Chengwan Xia, Yumei Pu, Yuxin Wang

Department of Oral and Maxillofacial Surgery, Nanjing Stomatological Hospital, Medical School of Nanjing University, Nanjing, China

SUMMARY

Background: **Early diagnosis of cancer is related to a good prognosis. Noninvasive methods of body fluid diagnosis are receiving more and more attention. Many studies have shown that exosomal miRNAs in body fluids may be potential biomarkers. Therefore, we conducted a meta-analysis to assess the overall diagnostic value of liquid exosomal miRNAs for cancer.**

Methods: **Relevant research was retrieved from multiple electronic databases. The research quality was evaluated based on the QUADAS-2 scale in Review Manager 5.3. Diagnostic value was evaluated by data analysis using Stata 16.0, and Meta-DiSc 1.4.**

Results: **The meta-analysis included 23 articles and 79 research units. The pooled sensitivity was 0.74, specificity was 0.78, the diagnostic likelihood ratio positive was 3.55, the diagnostic likelihood ratio negative was 0.29, diagnostic OR was 14.26, and area under the curve was 0.8621. These results provide evidence for liquid exosomal miRNAs as potential biomarkers.**

Conclusions: **Liquid exosomal miRNAs are potential biomarkers for cancer diagnosis. In particular, diagnosis based on multiple miRNAs is more valuable than a single miRNA.**

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Correspondence:
Yuxin Wang
Department of Oral and Maxillofacial Surgery
Nanjing Stomatological Hospital
Medical School of Nanjing University
Nanjing
China
Email: wangyuxin0212@126.com

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Supplementary Tables and Figures

Table S1. Summary of the characteristics of included studies.

Author	Coun-try	Controls		Patients			Type of sample	Isolation method	miRNA profiling	TP	FP	FN	TN	Expression level
		Type	n	Cancer Type	n	TNM stage (n)								
Fengming Lan 2020 [20]	China	HC	50	glioma	91	I(12)II(20) III(22)IV(37)	serum	ultracentri-fugation	miRNA-210	76	3	15	47	up
Ya Jing Zhao 2019 [21]	China	HC	153	CRC	165	…	serum	ultracentri-fugation	miR-99b-5p	53	14	112	139	down
									miR-150-5p	124	63	41	90	down
		HC	153	CRC	72	I(16)II(56)	serum		miR-99b-5p	24	13	48	140	
									miR-150-5p	58	62	14	91	
Xuan Zou 2019 [22]	China	HC	107	pancreatic cancer	129	I(13)II(65)III(6)IV(29) NA(16)	serum	ExoQuick	let-7b-5p	103	43	26	64	up
									miR-192-5p	100	46	29	61	up
									miR-19a-3p	92	23	37	84	up
									miR-19b-3p	84	20	45	87	up
									miR-223-3p	101	9	28	98	up
									miR-25-3p	86	21	43	86	up
									cumulative	123	25	6	82	
		HC	30	pancreatic cancer	30	I(3)II(13) III(5)IV(8) NA(1)			cumulative	28	1	2	29	
Xiangxiang Liu 2018 [23]	China	HC	40	colorectal cancer	40	I(40)	plasma	ExoQuick	miR-27a	30	9	10	31	up
									miR-130a	33	15	7	25	up
									miR-27a+130a	33	10	7	30	
		HC	40	colorectal cancer	80	I(40)II(20) III(14)IV(6)	plasma	ExoQuick	miR-27a	64	9	16	31	
									miR-130a	56	8	24	32	
									miR-27a+miR-130a	64	4	16	36	

Table S1. Summary of the characteristics of included studies (continued).

Author	Coun-try	Controls		Patients			Type of sample	Isolation method	miRNA profiling	TP	FP	FN	TN	Expression level
		Type	n	Cancer Type	n	TNM stage (n)								
Yurong Wang 2018 [24]	China	HC	50	HCC	50		serum	PEG-base	miR-122	50	5	0	45	up
Xianyin Lai 2017 [25]	USA	HC	6	PDAC	29		plasma	ultracentri-fugation	miR-10b	29	0	0	6	up
									miR-21	29	0	0	6	up
									miR-30c	29	0	0	6	up
									miR-106b	18	0	11	6	up
									miR-20a	24	0	5	6	up
									miR-181a	29	0	0	6	up
									miR-let7a	29	0	0	6	
									miR-122	27	0	2	6	
Olga E 2016 [26]	Russian	HC	20	PCa	14		urine	ultracentri-fugation	miR-19b	11	1	3	19	down
Marta Rodríguez 2017 [27]	Norway	HC	9	PCa	20		urine	ultracentri-fugation	miR-196a	18	0	2	9	down
Divya Bhagirath 2018 [28]	USA	HC	8	PCa	44		serum	ExoQuick	miR-1246	33	0	11	8	up
Shuli Tang 2020 [29]	China	HC	50	GC	50	I(30)II(20)	serum	ExoQuick	miR-92b-3p	29	10	21	40	down
									let-7g-5p	27	6	23	44	down
									miR-146b-5p	23	9	27	41	down
									miR-9-5p	25	8	25	42	down
									miR-92b-3p+let-7g-5p	32	11	18	39	
Shangqing Song 2019 [30]	China	HC	30	ccRCC	70	I(5)IIA(51) IIB(15)	urine	ultracentri-fugation	miR-30c-5p	48	0	22	30	down

Table S1. Summary of the characteristics of included studies (continued).

Author	Country	Controls		Patients			Type of sample	Isolation method	miRNA profiling	TP	FP	FN	TN	Expression level
		Type	n	Cancer Type	n	TNM stage (n)								
Yuntao Shi 2019 [31]	China	HC	50	GC	85	I(28)II(32) III(14)IV(11)	serum	ExoQuick	miR-1246	70	7	15	43	up
		HC	50	GC	28	I			miR-1246	24	13	4	37	
Naiyuan Shao 2018 [32]	China	HC	24	glioma	24		serum	ExoQuick	miR-454-3p	19	2	5	22	up
Alessandra Santangelo 2017 [33]	Italy	HC	30	GBM	44		serum	ExoQuick	miR-21	37	7	7	23	up
									miR-222	25	0	19	30	up
									miR-124-3p	39	11	5	19	up
									cumulative	37	7	7	23	
		HC	30	HGG	60				miR-21	49	7	11	23	
									miR-222	36	1	24	29	
									miR-124-3p	50	11	10	19	
									cumulative	50	7	10	23	
			30	LGG	32				miR-21	24	16	8	14	
									miR-222	22	8	10	22	
									miR-124-3p	19	7	13	23	
									cumulative	28	17	4	13	
		HC	30	Brain metastases	11				miR-21	9	2	2	28	
									miR-222	9	13	2	17	
									miR-124-3p	1	1	10	29	
									cumulative	9	7	2	23	

Table S1. Summary of the characteristics of included studies (continued).

Author	Country	Controls		Patients			Type of sample	Isolation method	miRNA profiling	TP	FP	FN	TN	Expression level
		Type	n	Cancer Type	n	TNM stage (n)								
Patricia M. M. Ozawa 2019 [34]	Brazil	HC	16	BC	31		serum	ExoQuick	miR-320a	29	5	2	11	up
									miR-142-5p	27	3	4	13	up
									miR-4433b-5p	27	4	4	12	up
									cumulative	29	5	2	11	
Tatsuya Machida 2016 [35]	Japan	HC	13	pancreatobiliary tract cancer	12		saliva	ExoQuick	miR-1246	8	0	4	13	up
									miR-4644	9	3	3	10	up
									cumulative	10	1	2	12	
Maria Barceló 2019 [36]	Spain	HC	8	PCa	24		semen	ultracentri-fugation	miR-142-3p+miR-142-5p	20	3	4	5	
Yi Zhang 2019 [37]	China	HC	47	NSCLC	72		serum	ExoQuick	miR-17-5p	48	11	24	36	up
Wei Zhang 2019 [38]	China	HC	80	ccRCC	82		serum	EpCAM beads	miR-210	57	30	25	50	up
									miR-1233	66	20	16	60	up
Xuegang Wang 2018 [39]	China	HC	30	ccRCC	45		serum	ExoQuick	miR-210	37	6	8	24	up
Poroyko V 2018 [40]	USA	HC	10	SCLC	9		serum	ExoQuick	miR-1180	7	1	2	9	
									miR-451a	7	0	2	10	
									miR-486-5p	9	1	0	9	
									miR-363-3p	7	0	2	10	
			10	NSCLC	11				miR-660-5p	9	0	2	10	
									miR-15b-5p	9	1	2	9	

Table S1. Summary of the characteristics of included studies (continued).

Author	Coun-try	Controls		Patients			Type of sample	Isolation method	miRNA profiling	TP	FP	FN	TN	Expression level
		Type	n	Cancer Type	n	TNM stage (n)								
Poroyko V 2018 [40]	USA								miR-25-3p	9	1	2	9	
									miR-16-2-3p	9	0	2	10	
									miR-221-3p	11	2	0	8	
Ning Wang 2017 [41]	China	HC	20	gastric cancer	20		serum	ExoQuick	miR-19b-3p+ miR-106a-5p	19	2	1	18	
Lihong He 2020 [42]	China	HC	10	OSCC	45		saliva	ExoQuick	miR-24-3p	29	2	16	8	up

Abbreviations: CRC - colorectal cancer, HCC - hepatocellular carcinoma, PDAC - pancreatic ductal adenocarcinoma, BC - breast cancer, PCa - prostatic cancer, ccRCC - clear-cell renal cell carcinoma, SCLC - small cell lung cancer, NSCLC - non-small cell lung cancer, OSCC - oral squamous cell carcinoma, GC - gastric cancer, GBM - glioblastoma multiforme, HGG - high grade gliomas, LGG - low grade gliomas.

Table S2. Summary results of subgroup analysis.

Subgroups	Number of studies	SEN (95% CI)	I^2	SPE (95% CI)	I^2	DLR+(95% CI)	I^2	DLR-(95% CI)	I^2	DOR (95% CI)	I^2	AUC
Country												
China	35	0.714 (0.696 - 0.731)	90.2	0.775 (0.758 - 0.792)	84.5	3.449 (2.894 - 4.110)	76.6	0.334 (0.276 - 0.403)	89	11.144 (8.316 - 14.934)	73.1	0.8442
Other	44	0.815 (0.792 - 0.837)	73.5	0.800 (0.770 - 0.828)	71.7	3.916 (3.045 - 5.035)	58.2	0.228 (0.173 - 0.301)	81.4	20.080 (13.971 - 28.861)	34.1	0.8862
Sample type												
Serum	57	0.728 (0.712 - 0.744)	87.2	0.773 (0.757 - 0.788)	81.7	3.361 (2.887 - 3.913)	71.4	0.307 (0.258 - 0.366)	87.5	12.410 (9.597 - 16.046)	65	0.8507
Plasma	14	0.834 (0.802 - 0.864)	82.6	0.809 (0.759 - 0.853)	58.9	3.961 (2.826 - 5.552)	33.2	0.220 (0.157 - 0.310)	60.5	24.884 (12.789 - 48.415)	50.8	0.9098
Urine	3	0.740 (0.645 - 0.821)	54.7	0.983 (0.909 - 1.000)	9	20.638 (5.272 - 80.792)	0	0.258 (0.154 - 0.432)	31.1	101.23 (20.912 - 490.04)	0	0.9584
Saliva	4	0.691 (0.579 - 0.789)	0	0.878 (0.752 - 0.954)	43.7	4.319 (2.113 - 8.829)	0	0.376 (0.260 - 0.544)	0	14.424 (5.084 - 40.922)	0	0.8087
Semen	1											
Isolation method												
Ultracentri-fugation	17	0.698 (0.668 - 0.728)	94.3	0.795 (0.765 - 0.823)	89.3	5.054 (3.099 - 8.244)	78.6	0.247 (0.167 - 0.365)	90.8	27.190 (12.741 - 58.024)	75.3	0.9353
Isolation kit	59	0.755 (0.738 - 0.771)	74.7	0.780 (0.762 - 0.798)	72.1	3.417 (2.949 - 3.960)	61.8	0.301 (0.258 - 0.351)	78.3	13.111 (10.357 - 16.597)	51.8	0.8528
Others	3	0.808 (0.749 - 0.859)	92.7	0.738 (0.673 - 0.796)	84.8	3.515 (1.629 - 7.580)	88.3	0.242 (0.084-0.698)	87.6	17.276 (3.068 - 97.279)	88.4	0.6934
Patient size												
≤ 50	55	0.783 (0.761-0.803)	80.2	0.808 (0.785 - 0.830)	67.4	3.815 (3.132 - 4.647)	55.6	0.252 (0.201 - 0.316)	81.2	18.091 (12.971 - 25.233)	49.1	0.881
> 50	24	0.719 (0.700 - 0.737)	91.2	0.764 (0.745 - 0.783)	88.5	3.301 (2.687 - 4.055)	80.6	0.326 (261 - 0.406)	91	11.024 (7.930 - 15.325)	75.4	0.8367
Control size												
≤ 50	66	0.777 (0.759 - 0.794)	78.2	0.815 (0.796 - 0.834)	67.8	3.942 (3.307 - 4.697)	57.6	0.265 (0.222 - 0.317)	79.4	17.670 (13.395 - 23.309)	48.9	0.8775
> 50	13	0.695 (0.671 - 0.718)	94.6	0.744 (0.722 - 0.766)	91.9	2.829 (2.263 - 3.537)	82.8	0.371 (0.276 - 0.498)	93.2	8.135 (5.531 - 11.966)	78.6	0.8091

Table S2. Summary results of subgroup analysis (continued).

Subgroups	Number of studies	SEN (95% CI)	I^2	SPE (95% CI)	I^2	DLR+(95% CI)	I^2	DLR-(95% CI)	I^2	DOR (95% CI)	I^2	AUC
Cancer type												
Lung cancer	10	0.767 (0.694 - 0.829)	40.2	0.876 (0.809 - 0.926)	42.3	4.348 (2.897 - 6.526)	0	0.300 (0.218 - 0.412)	7.2	27.873 (11.625 - 66.830)	22.1	0.8636
Gastric cancer	8	0.650 (0.600 - 0.6980)	84.5	0.822 (0.779 - 0.859)	0	3.453 (2.740 - 4.353)	0	0.423 (0.305 - 0.585)	78.3	9.362 (5.151 - 17.015)	61.2	0.8747
Pancreatic cancer	19	0.798 (0.774 - 0.820)	87.1	0.778 (0.749 - 0.806)	81.5	4.355 (3.045 - 6.229)	76.3	0.239 (0.179 - 0.318)	75.4	25.821 (13.859 - 48.110)	76.8	0.9201
OSCC	1											
Breast cancer	4	0.903 (0.837 - 0.949)	0	0.734 (0.609 - 0.837)	0	3.318 (2.208 - 4.987)	0	0.138 (0.079 - 0.240)	0	27.274 (11.797 - 63.055)	0	0.8944
Colorectal cancer	10	0.646 (0.613 - 0.679)	94.1	0.757 (0.727 - 0.785)	90.9	2.894 (2.236 - 3.746)	69.8	0.373 (0.265 - 0.526)	91.6	7.867 (5.449 - 11.359)	50.6	0.8064
Glioma	18	0.767 (0.734 - 0.798)	72.6	0.771 (0.733 - 0.805)	82.1	3.232 (2.332 - 4.480)	74.4	0.310 (0.213 - 0.451)	88.4	12.636 (8.057 - 19.817)	48.1	0.8503
Hepatocarci-noma	1											
Prostate cancer	4	0.804 (0.714 - 0.876)	0	0.911 (0.788 - 0.975)	64.6	7.345 (1.671 - 32.283)	58.1	0.240 (0.161 - 0.358)	0	31.077 (0.295 - 116.43)	15.5	0.8925
Renal carcinoma	4	0.746 (0.690 - 0.796)	44.8	0.745 (0.683 - 0.802)	87.4	3.182 (1.682 - 6.022)	78.6	0.325 (0.234 - 0.451)	55.7	11.850 (4.104 - 34.219)	75.9	0.835
miRNA number												
One	66	0.725 (0.710 - 0.741)	86.2	0.782 (0.766 - 0.798)	80.8	3.529 (3.020 - 4.123)	67.8	0.313 (0.268 - 0.366)	84.9	12.715 (9.931 - 16.279)	59.8	0.8525
Cumulative	13	0.856 (0.824 - 0.884)	66.4	0.775 (0.733 - 0.813)	66.2	3.658 (2.586 - 5.173)	69.9	0.190 (0.129 - 0.281)	66	21.941 (11.997 - 40.129)	59.3	0.8987
miRNA profiling												
Up	46	0.772 (0.754 - 0.788)	79.2	0.773 (0.752 - 0.792)	76.6	3.463 (2.891 - 4.147)	67.9	0.292 (0.245 - 0.350)	79.8	13.819 (10.321 - 18.502)	60.3	0.856
Down	11	0.566 (0.530 - 0.601)	91.7	0.786 (0.758 - 0.813)	91.7	3.033 (2.203 - 4.176)	70.4	0.494 (0.394 - 0.619)	84.2	5.983 (4.193 - 8.537)	39	0.7533

Table S2. Summary results of subgroup analysis (continued).

Subgroups	Number of studies	SEN (95% CI)	I^2	SPE (95% CI)	I^2	DLR+(95% CI)	I^2	DLR-(95% CI)	I^2	DOR (95% CI)	I^2	AUC
Others	**22**	**0.855 (0.825 - 0.881)**	**51.8**	**0.801 (0.765 - 0.835)**	**63.8**	**4.267 (3.112 - 5.851)**	**60.3**	**0.201 (0.153 - 0.265)**	**44**	**25.926 (16.049 - 41.880)**	**38.6**	**0.909**
Cancer stage												
Early stage	**12**	**0.631 (0.591 - 0.669)**	**85**	**0.780 (0.749 - 0.809)**	**84.7**	**2.902 (2.331 - 3.612)**	**46.2**	**0.437 (0.345 - 0.553)**	**78.4**	**7.031 (5.295 - 9.336)**	**5.8**	**0.7955**
Others	**67**	**0.766 (0.751 - 0.780)**	**84.8**	**0.782 (0.764 - 0.798)**	**78.1**	**3.789 (3.201 - 4.487)**	**70.5**	**0.257 (0.214 - 0.308)**	**86**	**17.375 (13.120 - 23.011)**	**64.9**	**0.8777**

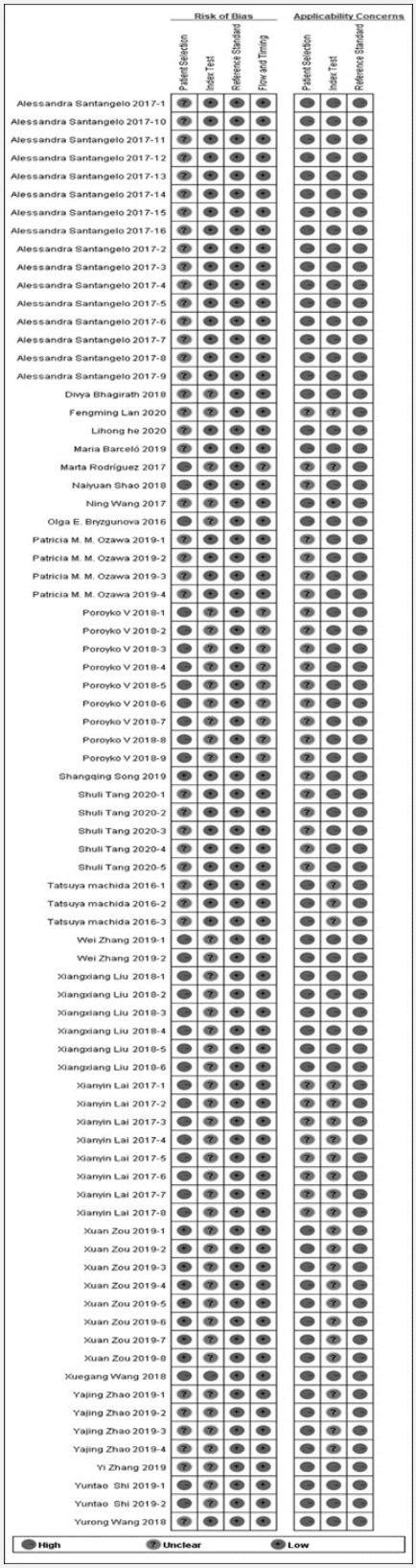

Figure S1. Summary of risk of bias and applicability concerns of each of the studies.