

MiR-92a family: A Novel Diagnostic Biomarker and Potential Therapeutic Target in Human Cancers

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Supplementary appendix to the manuscript

Table S1 main characteristics of enrolled studies in diagnostic meta-analyses

Study ID	ethnicity	specime n	cas e	con trol		Cancer-t ype	Control- type	stage	miRNA	Reference miRNA	SEN (%)	SPE (%)
				N	age							
MiR-92a												
Liu HN 2018	Asian	serum	85	59.5	78	34.8	CRC	HC	I-IV	miR-92a, miR-29a, miR-21, cel-miR-39	84.7	98.7

Liu HN 2018	Asian	serum	85	59.5	78	34.8	CRC	HC	I -IV	miR-92a		cel-miR-39	78.8	71.8
Elshafei A 2017	Oceanian	serum	64	51.4	27	46.4	CRC	HC	I -IV	miR-92a		SNORD-68	84.4	100.0
Elshafei A 2017	Oceanian	serum	32	51.8	27	46.4	CRC	HC	I -II	miR-92a		SNORD-68	78.1	100.0
Elhamamsy A 2017	African	plasma	65	55.3	50	54.7	AML	HC	NA	miR-92a		U6	81.5	94.0
MotawKi TK 2016	Oceanian	plasma	70	56.2	62	57.2	BLC	HC	II -III	miR-92a		U6	97.0	76.7
MotawKi TK 2016	Oceanian	plasma	70	56.2	62	57.2	BLC	HC	II -III	miR-92a,miR-100 and miR-143		U6	94.3	83.3
Chang PY 2016	Asian	plasma	353	62.9	492	52.5	CRC	HC	I -IV	miR-92a,miR-223		cel-miR-238	96.8	75.0
Fan LH 2016	Asian	serum	94	60.5	58	58.1	NSCLC	HC	I -III	miR-92a		-	86.8	65.5
Huang S 2016	Asian	serum	30	NA	30	NA	GC	HC	I -IV	miR-21,miR-31, miR-181b, miR-203	miR-92a,	miR-16	90.0	96.7
Huang S 2016	Asian	serum	62	NA	59	NA	GC	HC	I -IV	miR-21,miR-31, miR-181b, miR-203	miR-92a,	miR-16	85.5	98.3
Wen Y 2015	Asian	plasma	67	48.5	82	48.6	HCC	BD	NA	miRNAs ^a		cel-miR-39	86.6	64.6
Zhu C 2014	Asian	plasma	40	53.8	40	53.6	GC	HC	I -II	miR-92a		cel-miR-39	97.5	85.0
Zhu C 2014	Asian	plasma	40	53.8	40	53.6	GC	HC	I -II	miR-16, miR-25, miR-451, miR-486-5p	miR-92a,	cel-miR-39	97.5	87.5
Zhu C 2014	Asian	plasma	48	56.6	102	54.0	GC	HC,BD	I -II	miR-92a		cel-miR-39	72.9	73.5
Zhu C 2014	Asian	plasma	48	56.6	102	54.0	GC	HC,BD	I -II	miR-16, miR-25, miR-451, miR-486-5p	miR-92a,	cel-miR-39	72.9	89.2
Du ML 2014	Asian	plasma	49	61.1	49	61.7	CRC	HC	II -III	miR-92a		cel-miR-39	18.4	95.9
Zheng G 2014	Asian	serum	117	56.3	175	52.6	CRC	BD,HC	I -IV	miR-19a-3p, miR-223-3p, miR-92a, miR-422a	miR-191-5p,	U6	84.3	91.6

Wang J 2014	Asian	serum	30	NA	30	NA	CRC	HC	I -IV	miR-21, let-7g, miR-31, miR-92a, miR-16 miR-181b, miR-203	83.3	96.7	
Wang J 2014	Asian	serum	83	NA	59	NA	CRC	HC	I -IV	miR-21, let-7g, miR-31, miR-92a, miR-16 miR-181b, miR-203	96.4	88.1	
Liu GH 2013	Asian	serum	200	NA	80	NA	CRC	HC	I -IV	miR-92a, miR-21	miR-16	68.0	91.2
Liu GH 2013	Asian	serum	200	NA	80	NA	CRC	HC	I -IV	miR-92a	miR-16	65.5	82.5
Wang SY 2013	Asian	tissue	25	NA	21	NA	CRC	BD	NA	miR-375, miR-424, miR-92a	U47	92.0	95.0
Wang SY 2013	Asian	tissue	25	NA	20	NA	CRC	BD	NA	miR-375, miR-424, miR-92a	U47	96.0	90.0
Wang SY 2013	Asian	tissue	33	NA	25	NA	CRC	BD	NA	miR-375, miR-424, miR-92a	U47	94.0	84.0
Luo XY 2013	Caucasian	plasma	80	68.0	144	62.5	CRC	BD	I -IV	miR-92a	miR-16	68.2	49.4
Torres A 2013	Caucasian	tissue	73	62.8	31	44.8	EEC	BD	I -IV	miR-92a	U48, U44, U75	78.0	90.0
Torres A 2013	Caucasian	tissue	73	62.8	31	44.8	EEC	BD	I -IV	miR-92a, miR-205, miR-410	U48, U44, U75	96.0	100.0
Torres A 2013	Caucasian	plasma	34	60.2	14	54.7	EEC	HC	I -IV	miR-92a	miRNAs ^b	61.0	93.0
Torres A 2013	Caucasian	plasma	34	60.2	14	54.7	EEC	HC	I -IV	miR-92a, miR-9	miRNAs ^b	73.0	100.0
Wu CW 2012	Asian	stool	88	67.2	101	60.5	CRC	HC	I -IV	miR-92a, miR-21	U6	81.8	57.4
Wu CW 2012	Asian	stool	88	67.2	101	60.5	CRC	HC	I -IV	miR-92a	U6	71.6	73.3
Wang QF 2012	Asian	plasma	90	62.0	58	58.0	CRC	HC	I -IV	miR-92a, miR-29a, miR-760	cel-miR-39	83.3	93.1
Baraniskin A 2011	Caucasian	CF	23	64.0	30	NA	PCNSL	BD	NA	miR-92a	miR-24	95.7	80.0
Ng EK 2009	Asian	plasma	90	NA	50	NA	CRC	HC	I -IV	miR-92a	U6	89.0	70.0
Huang ZH 2009	Asian	plasma	100	61.0	59	58.0	CRC	HC	I -IV	miR-92a, miR-29a	miR-16	83.0	84.7

Huang ZH 2009	Asian	plasma	100	61.0	59	58.0	CRC	HC	I-IV	miR-92a		miR-16	84.0	71.2
MiR-25														
Li FX 2017	Asian	plasma	65	54.1	65	56.2	GC	HC	I-IV	miR-25		U6	87.6	76.9
Le Q 2017	Asian	serum	41	61.0	41	58.0	GC	HC	NA	miR-25		U6	78.1	61.0
Fujiwara I T 2017	Asian	serum	14	NA	22	NA	OS	HC, BD	NA	miR-25		cel-miR-39	71.4	92.3
Johansen JS 2016	Caucasian	serum	133	NA	51	NA	PC	HC	I-IV	miR-16, miR-27a, miR-25, miR-29c,		miR-292,	85.0	33.0
										miR-483-5p		miR-259		
Johansen JS 2016	Caucasian	serum	198	NA	153	NA	PC	HC	I-IV	miR-16, miR-27a, miR-25, miR-29c,		miR-292,	85.0	66.0
										miR-483-5p		miR-259		
Johansen JS 2016	Caucasian	serum	86	NA	44	NA	PC	HC	I-IV	miR-16, miR-27a, miR-25, miR-29c,		miR-292,	85.0	67.0
										miR-483-5p		miR-259		
Deng T 2016	Asian	serum	303	62.0	600	49.0	PC	HC	I-IV	miR-25		U6, 5S rRNAs	75.6	93.0
Cochetti G 2016	Caucasian	serum	64	63.0	60	NA	PRC	BD	NA	miR-25		miR-191-5p,	38.5	88.0
												miR-425-5p		
Cappellesso R 2016	Caucasian	cytologic	29	73.2	24	61.2	MM	BD	NA	miR-25		U6	54.0	72.0
Bryzgunova O 2016	Caucasian	Urine	14	72.0	20	59.0	PRC	HC	NA	miR-25		miR-16	71.0	60.0
		exosome												
Butz H 2016	Caucasian	urine	28	59.0	18	NA	RCC	HC	NA	miR-126-3p, miR-25		miR-16, miR-	62.1	85.0
		exosome										106a		
Butz H 2016	Caucasian	urine	81	NA	33	NA	RCC	HC	NA	miR-126-3p, miR-25		miR-16, miR-	52.5	86.2
		exosome										106a		
Zhou X 2015	Asian	plasma	101	NA	91	NA	GC	HC	I-IV	miR-185, miR-20a, miR-210,		cel-miR-39,	65.0	80.0

											miR-25, miR-92b	U6		
Wen Y 2015	Asian	plasma	67	48.5	82	48.6	HCC	BD	NA	miR-25		cel-miR-39	55.3	79.3
Wen Y 2015	Asian	plasma	67	48.5	82	48.6	HCC	BD	NA	miR-20a-5p, miR-25, miR-30a-5p, miR-92a-3p, miR-132-3p, miR-185-5p, miR-320a, miR-324-3p		cel-miR-39	86.6	64.6
Wang C 2015	Asian	serum	19	62.1	19	61.8	NSCLC	HC	I-IV	miR-483-5p, miR-193a-3p, miR-25, miR-214, miR-7		let-7d/g/i	100.0	84.0
Wang C 2015	Asian	serum	63	59.7	63	61.9	NSCLC	HC	I-IV	miR-483-5p, miR-193a-3p, miR-25, miR-214, miR-7		let-7d/g/i	89.0	68.0
Wang C 2015	Caucasian	serum	108	67.2	48	58.5	NSCLC	HC	I-IV	miR-483-5p, miR-193a-3p, miR-25, miR-214, miR-7		let-7d/g/i	95.0	84.0
Wang C 2015	Caucasian	serum	108	67.2	56	63.7	NSCLC	BD	I-IV	miR-483-5p, miR-193a-3p, miR-25, miR-214, miR-7		let-7d/g/i	95.0	95.0
Meng XD 2015	Caucasian	serum	180	60.0	66	59.0	EOC	HC	I-IV	miR-7, miR-25, miR-93, miR-429		cel-miR-39	93.0	92.0
Meng XD 2015	Caucasian	serum	180	60.0	66	59.0	EOC	HC	I-IV	miR-25		cel-miR-39	92.4	63.9
Li M 2015	Asian	plasma	56	NA	95	NA	PTC	BD	I-IV	miR-25		U6	92.8	68.8
Jia WH 2015	Asian	serum	123	46.0	94	47.8	CC	HC	I-IV	miR-21, miR-29a, miR-25, miR-200a, miR-486-5p		let-7d/j/i	81.0	88.6
Wang P 2015	Asian	serum	142	61.1	111	59.8	LC	HC	I-IV	miR-125a-5p, miR-25, miR-126		cel-miR-39	88.0	82.6
Wang P 2015	Asian	serum	94	NA	111	59.8	LC	HC	I-II	miR-125a-5p, miR-25, miR-126		cel-miR-39	87.5	87.5
Wang P 2015	Asian	serum	94	NA	111	59.8	LC	HC	I-II	miR-25		cel-miR-39	83.3	75.0

Zhu C 2014	Asian	plasma	40	53.8	40	53.6	GC	HC	I-II	miR-25		cel-miR-39	87.5	97.5
Zhu C 2014	Asian	plasma	40	53.8	40	53.6	GC	HC	I-II	miR-16, miR-25, miR-92a, miR-451, miR-486-5p		cel-miR-39	97.5	87.5
Zhu C 2014	Asian	plasma	48	56.6	102	54.0	GC	HC,BD	I-II	miR-25		cel-miR-39	41.7	97.1
Zhu C 2014	Asian	plasma	48	56.6	102	54.0	GC	HC,BD	I-II	miR-16, miR-25, miR-92a, miR-451, miR-486-5p		cel-miR-39	72.9	89.2
Wu CY 2014	Asian	serum	63	62.0	63	59.7	ESCC	HC	I-IV	miR-25		let-7d/g/i	81.0	81.0
Pan WZ 2014	Asian	plasma	30	58.4	26	NA	PC	HC	I-IV	miR-25		cel-miR-39	73.3	73.1
Mengual LV 2013	Caucasian	urine	151	72.0	126	63.0	BLC	HC,BD	NA	miR-25, miR-18a, miR-187, miR-204,miR-142-3p, miR-140-3p		miR-103, miR-30c	84.8	86.5
Hu ZB 2012	Asian	serum	48	54.0	48	51.0	BC	HC	I-III	miR-16, miR-25, miR-222, miR-324-3p		miR-484, miR-191	91.7	89.6
Hu ZB 2012	Asian	serum	76	53.0	76	49.2	BC	HC	I-III	miR-16, miR-25, miR-222, miR-324-3p		miR-484, miR-191	92.1	93.4
li LM 2010	Asian	serum	55	52.8	50	47.7	HCC	HC	NA	miR-375, miR-25,let-7f		-	97.9	99.1
MiR-363														
Wu CW 2017	Caucasian	blood	29	61.2	115	66.2	CRC	HC	I-IV	miR-144-3p, miR-144-5p, miR-486-5p, miR-363		miR-451a, miR-20b-5p, cel-miR-39	66.0	95.0

a: miR-20a-5p, miR-25-3p, miR-30a-5p, miR-92a-3p, miR-132-3p, miR-185-5p, miR-320a, miR-324-3p.

b: miR-93, miR-26b, miR-192, miR-103a, miR-142-3p.

Abbreviation: AML, acute myeloid leukemia; BC, breast cancer; BLC, bladder cancer; CC, cervical cancer; CF, cerebrospinal fluid; CRC, colorectal cancer;

EEC, endometrioid endometrial carcinoma; EOC, epithelial ovarian cancer; ESCC, esophageal squamous cell carcinoma; GC, gastric cancer; HCC,

hepatocellular carcinoma; LC, lung cancer; LUAD, lung adenocarcinomas; MM, malignant mesothelioma; N, number; NMIBC, non-muscle invasive bladder

cancer; NSCLC, non-small cell lung cancer; OS, osteosarcoma; PCNSL, primary central nervous system lymphoma; PRC, prostate cancer; PTC, papillary

thyroid carcinoma; RCC, renal cell carcinoma; SEN, sensitivity; SPE, specificity.

Table S2 main characteristics of enrolled researches in prognostic meta-analyses

Study ID	No. of	No. of	ethnicity	speci	cancer	stage	miRNA	reference	outco	Median	HR	LL	UL	NO
	low	high		men			miRNA		me	Follow-u				S
										p				
										(month)				

MiR-92a

Ingelmo-Torres	M	NA	NA	Caucasian	Urinar	NMIBC	NA	miR-92a	miR-103-3p,	PFS	47	6.210	2.090	18.450	7
2017					y cell				miR-30c-5p						
Ren CL 2016		34	146	Asian	tissue	GC	I -	miR-92a	Scramble-miR	OS	85.2	3.340	1.670	6.700	6

IV

Yang W 2015	53	53	Asian	tissue	HCC	I -	miR-92a	U6	OS	38,7	2.283	1.104	4.717	8	
						IV									
Zhou T 2013	41	41	Asian	tissue	CRC	I -	miR-92a	U6	OS	NA	2.342	1.072	5.115	7	
						IV									
Nilsson S 2012	59	58	Caucasian	tissue	BC	I	miR-92a	NA	RFS	78	0.375	0.145	0.972	7	
						-III									
MiR-25															
Jacob H 2017	48	63	Caucasian	tissue	CRC	II-III	miRNAs ^a	miRNAs ^b	DFS	NA	21.40	4.210	108.700	7	
Jacob H 2017	90	119	Caucasian	tissue	CRC	II-III	miRNAs ^a	miRNAs ^b	DFS	NA	2.000	1.040	3.890	8	
Goossens-Beumer	I	29	21	Caucasian	tissue	CRC	II-III	miR-25	miR-16-5p,mi	RFS	51.2	2.370	0.930	6.030	8
2015								R-26a-5p							
Goossens-Beumer	I	26	17	Caucasian	tissue	CRC	II-III	miR-25	miR-16-5p,mi	RFS	83.5	5.760	1.820	18.200	8
2015								R-26a-5p							
Wu CY 2014	12	51	Asian	serum	ESCC	I -	miR-25	let-7d/g/i	OS	19.6	3.840	1.020	14.410	6	
						IV									
Wu CH 2014	73	121	Asian	serum	ESCC	I -	miR-25	U6, miR-16	OS	31.3	1.127	0.778	1.637	7	
						IV									
Wang X 2014	NA	NA	Asian	tissue	EOC	I -	miR-25	U6	OS	NA	2.119	1.568	3.221	6	
						IV									
Su ZX 2014	NA	NA	Asian	tissue	HCC	I -	miR-25	U6	OS	47	2.179	1.876	4.335	6	
						IV									
Li XJ 2014	78	108	Asian	tissue	CRC	I -	miR-25	U44	OS	NA	1.900	1.220	2.970	8	

IV

Xu FX 2014 49 51 Asian tissue LUAD I - miR-25 U6 OS 34 2.340 1.020 5.350 6

IV

Jonsdottir K 2012 119 84 Caucasian tissue BC NA miR-25 U6 MFS 122 2.400 1.100 5.300 8

a: miR-143-5p, miR-27a-3p, miR-31-5p, miR-181a-5p, miR-30b-5p, miR-30d-5p, miR-146a-5p, miR-23a-3p, miR-150-5p, miR-210-3p, miR-25-3p,

miR-196a-5p, miR-148a-3p, miR-222-3p, miR-30c-5p and miR-223-3p; b: UniSp3, cel-miR-39-3p, UniSp2, UniSp4, UniSp5, UniSp6; Abbreviation: HR,

hazard ratio; LL, lower limit; UL, upper Limit; NOS, Newcastle-Ottawa Scale; NMIBC, non-muscle invasive bladder cancer; GC, gastric cancer; HCC,

hepatocellular carcinoma; CRC, colorectal cancer; BC, breast cancer; ESCC, esophageal squamous cell carcinoma; EOC, epithelial ovarian cancer; LUAD,

lung adenocarcinoma; OS, overall survival; PFS, progression-free survival; RFS, relapse free survival; DFS, disease free survival; MFS, metastasis free

survival.

Table S3 NOS scores for each study included in the prognosis meta-analysis

Items	Representativeness of the exposed cohort (1)	Selection of the non-exposed cohort (1)	Ascertainment of exposure (1)	Demonstration that outcome of interest was not present at start of study (1)	Comparability of cohorts on the basis of the design or analysis (2)	Assessment of outcome (1)	Was follow-up long enough for outcomes to occur (1)	Adequacy of follow up of cohorts (1)	total scores (9)
Jacob H 2017	0	1	1	1	1	1	1	1	7
Jacob H 2017	0	1	1	1	2	1	1	1	8
Ingelmo-Torres M 2017	0	1	1	1	1	1	1	1	7
Ren CL 2016	0	0	1	1	1	1	1	1	6
Yang W 2015	1	1	1	1	1	1	1	1	8
Goossens-Beumer I 2015	1	1	1	1	1	1	1	1	8
Wu CY 2014	1	1	1	1	1	1	0	0	6
Wu CH 2014	1	1	1	1	1	1	0	1	7
Wang X 2014	1	0	1	1	1	0	1	1	6
Su ZX 2014	1	0	1	1	1	0	1	1	6
Li XJ 2014	1	1	1	1	1	1	1	1	8
Zhou T 2013	1	0	1	1	1	1	1	1	7
Nilsson S 2012	1	0	1	1	1	1	1	1	7

Jonsdottir K 2012	1	1	1	1	1	1	1	1	8
Xu FX 201	1	1	1	1	1	1	0	0	6
Ranade AR 2010	1	1	1	1	0	1	1	1	7

NOS, newcastle - ottawa quality assessment.

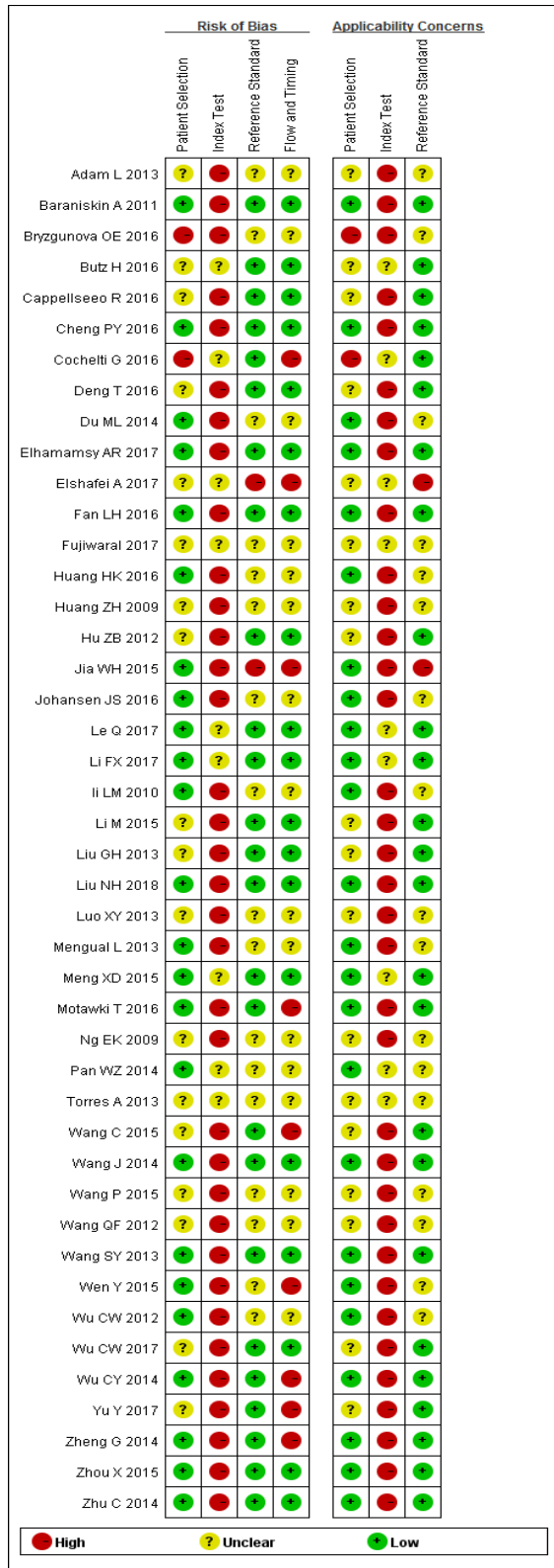


Figure S1: Risk of bias graph: a plot of the distribution of judgments (Yes, No, Unclear) across studies for each

risk of bias entry for each enrolled literature in the diagnostic meta-analysis.

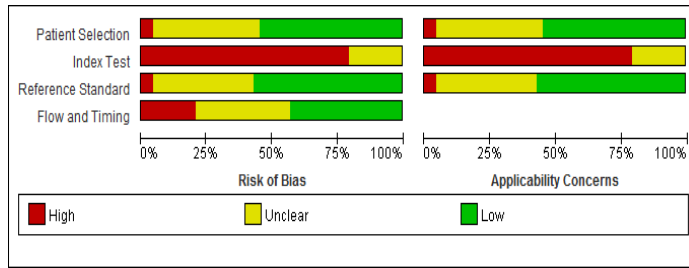


Figure S2: Risk of bias summary: a summary table of review authors' judgments for each risk of bias entry for each study in the diagnostic meta-analysis: proportion of articles with risk of bias (left) and proportion of articles with regarding applicability (right).

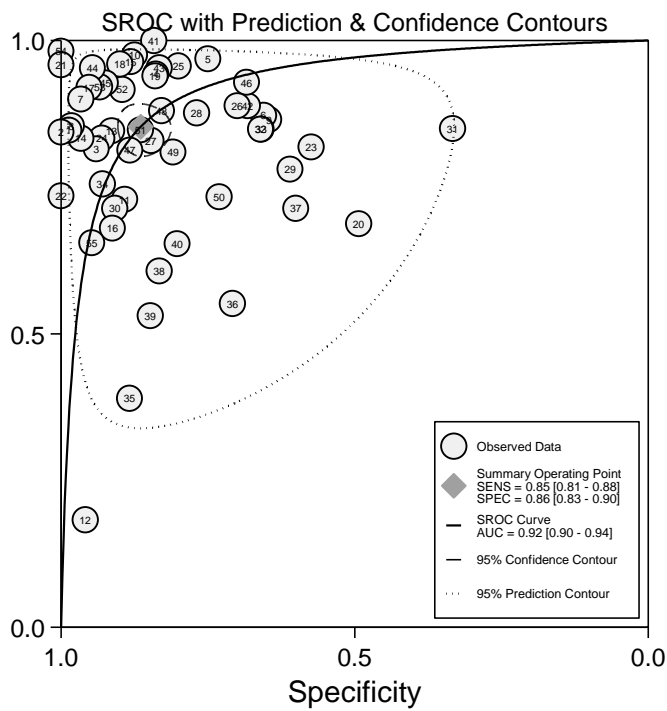


Figure S3: SROC curve of the whole miR-92a family for cancer diagnostic meta-analysis. SENS, sensitivity; SPEC, specificity; SROC, summary receiver operating characteristic; AUC, the area under the SROC curve.

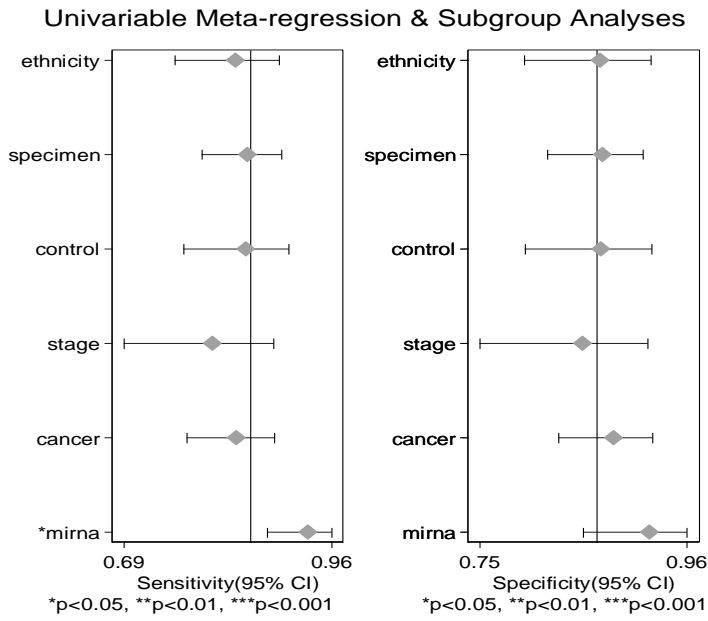


Figure S4: Forest plots for the diagnostic meta-regression analysis: sensitivity (left) and specificity (right). The factors included ethnicity, specimen, control types (healthy controls or patients with benign diseases), stage, cancer types and miRNA-profilings (single miRNA or multiple miRNAs)

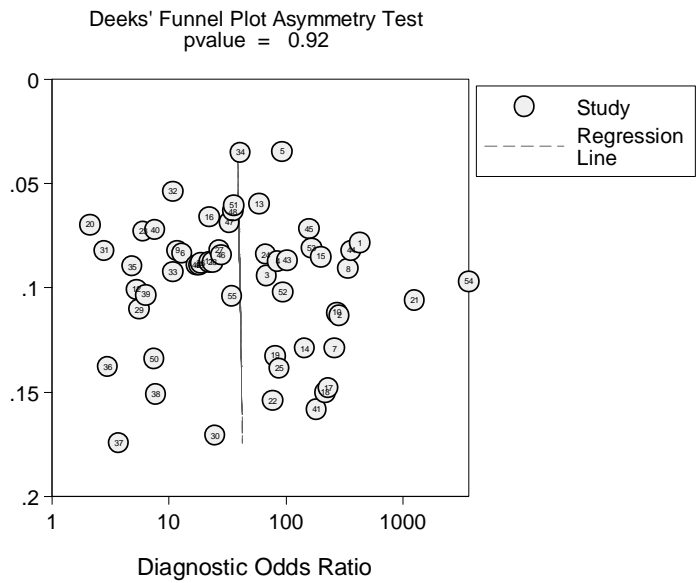


Figure S5: The Deek's test for assessing the publication bias for miR-92a family in the detection of human cancers.

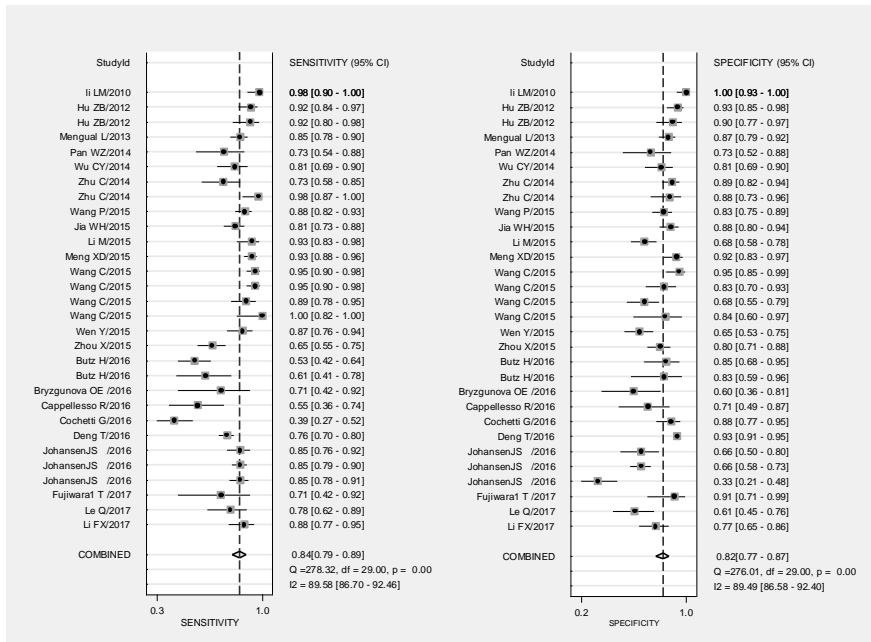


Figure S6: Forest plots of sensitivity and specificity for the cancer diagnosis of miR-25. Both the sensitivity and specificity of each study were showed by square with its 95% Confidence interval showed by the error bars.

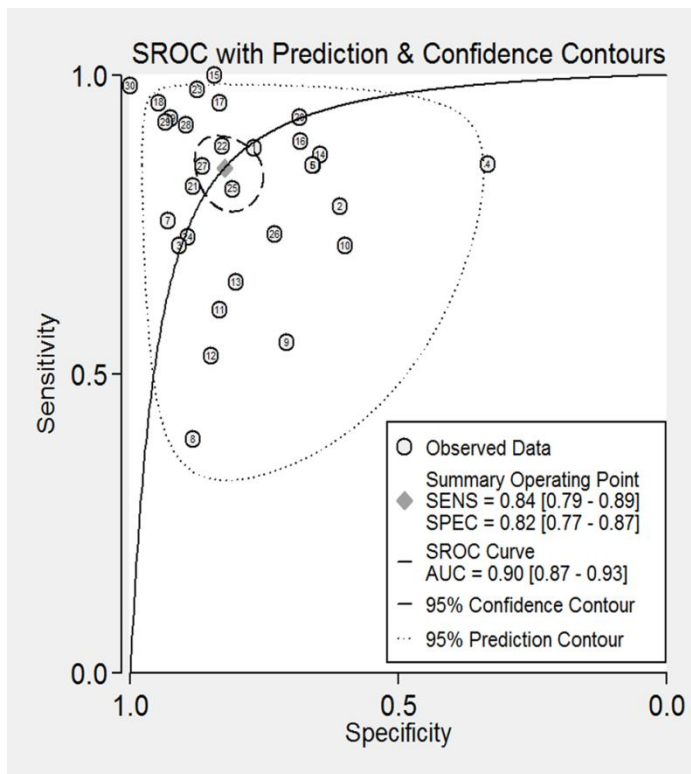


Figure S7: SROC curve of miR-25 for cancer diagnostic meta-analysis. SENS, sensitivity; SPEC, specificity; SROC, summary receiver operating characteristic; AUC, the area under the SROC curve.

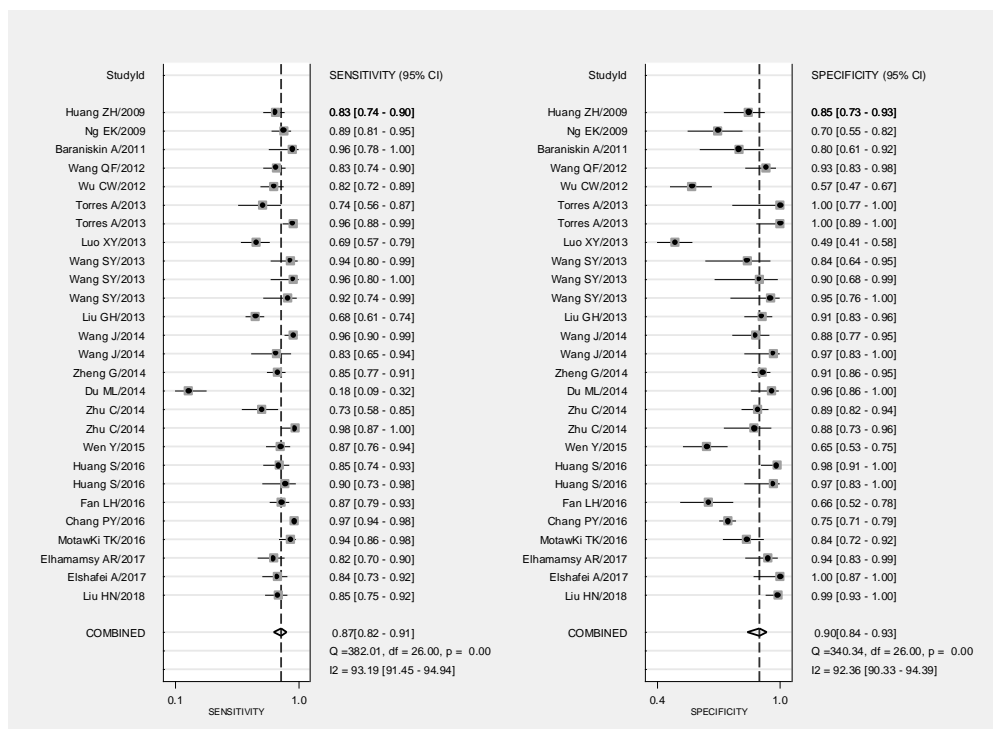


Figure S8: Forest plots of sensitivity and specificity for the cancer diagnosis of miR-92a. Both the sensitivity and specificity of each study were showed by square with its 95% Confidence interval showed by the error bars.

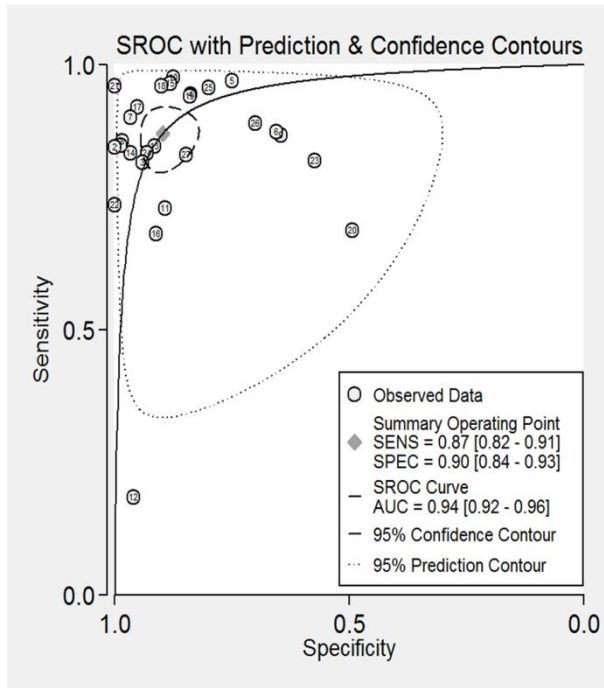


Figure S9: SROC curve of miR-92a for cancer diagnostic meta-analysis. SENS, sensitivity; SPEC, specificity; SROC, summary receiver operating characteristic; AUC, the area under the SROC curve.

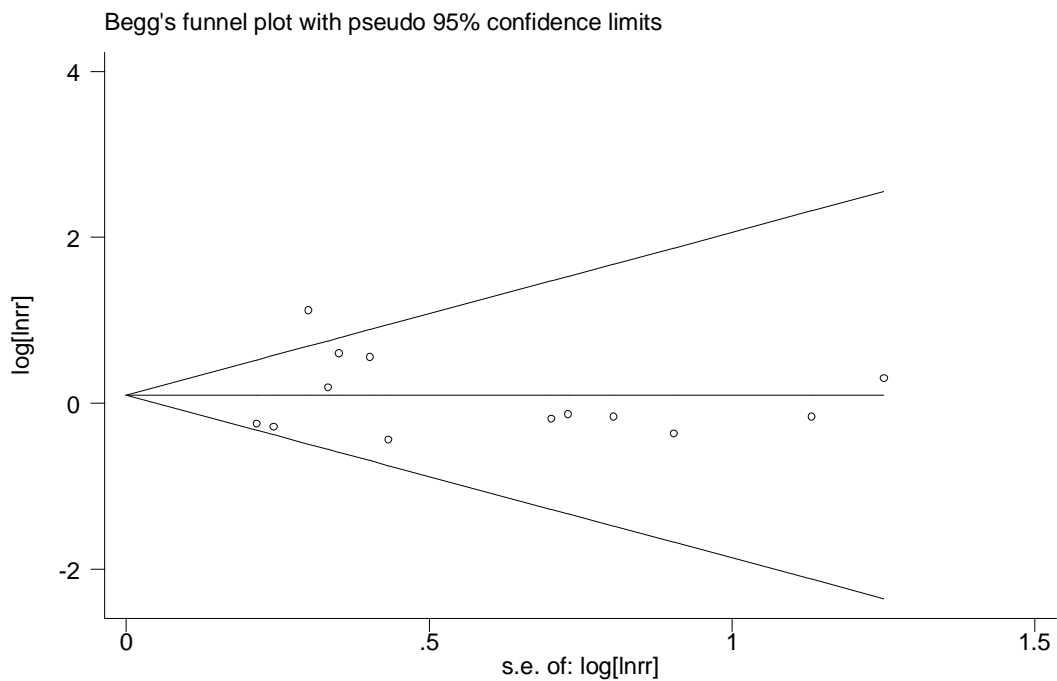


Figure S10: The Begg's funnel plot to assess the publication bias for miR-92a family in cancer prognosis prediction.

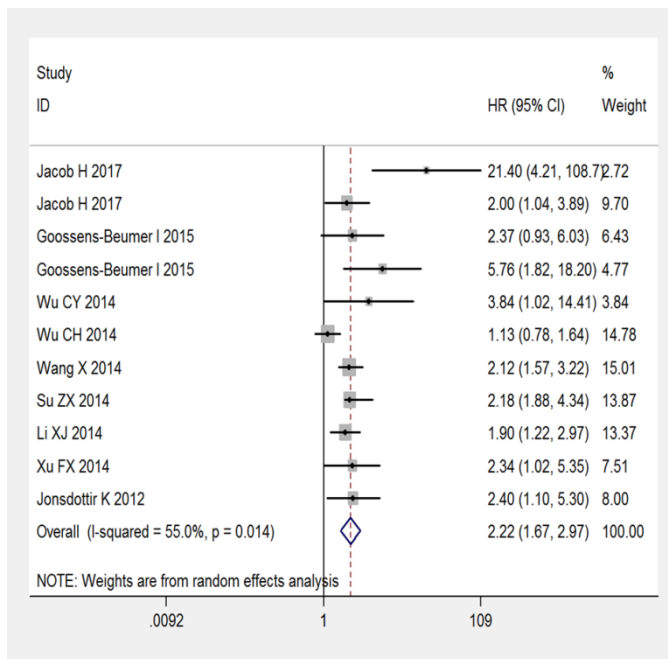


Figure S11: Forest plot of the prognostic meta-analysis of the association between miR-25 and the risk of cancers. HR, hazard ratio; 95% CI, 95% confidence interval.

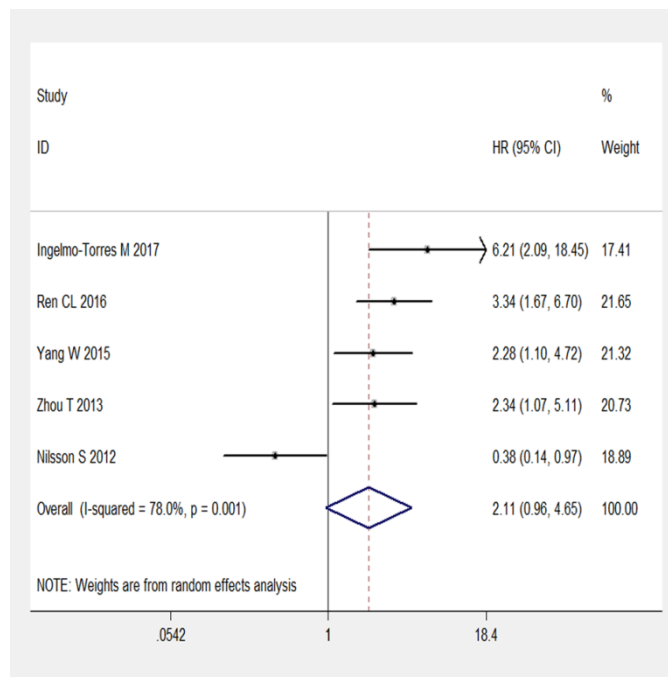


Figure S12: Forest plot of the prognostic meta-analysis of the association between miR-92a and the risk of cancers. HR, hazard ratio; 95% CI, 95% confidence interval.

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