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ORIGINAL RESEARCH

Prognostic value of microRNAs in colorectal cancer: a meta-analysis

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Background: Numerous studies have shown that miRNA levels are closely related to the survival time of patients with colon, rectal, or colorectal cancer (CRC). However, the outcomes of different investigations have been inconsistent. Accordingly, a meta-analysis was conducted to study associations among the three types of cancers.

Materials and methods: Studies published in English that estimated the expression levels of miRNAs with survival curves in CRC were identified until May 20, 2017 by online searches in PubMed, Embase, Web of Science, and the Cochrane Library by two independent authors. Pooled HRs with 95% CIs were used to estimate the correlation between miRNA expression and overall survival.

Results: A total of 63 relevant articles regarding 13 different miRNAs, with 10,254 patients were ultimately included. CRC patients with high expression of blood miR141 (HR 2.52, 95% CI 1.68–3.77), tissue miR21 (HR 1.31, 95% CI 1.12–1.53), miR181a (HR 1.52, 95% CI 1.26–1.83), or miR224 (HR 2.12, 95% CI 1.04–4.34), or low expression of tissue miR126 (HR 1.55, 95% CI 1.24–1.93) had significantly poor overall survival ($P<0.05$).

Conclusion: In general, blood miR141 and tissue miR21, miR181a, miR224, and miR126 had significant prognostic value. Among these, blood miR141 and tissue miR224 were strong biomarkers of prognosis for CRC.

Keywords: microRNA, colorectal cancer, prognosis, meta-analysis

Introduction

Numerous researchers have studied the associations between miRNA expression and the survival outcomes of colorectal cancer (CRC) patients.[1–258] CRC has a 10% cancer incidence and mortality worldwide,[259] and thus, it is one of the most serious diseases threatening human health. Despite great success in the treatment of CRC, the prognosis of CRC patients is still poor. Therefore, it is fundamental for the diagnosis, treatment, and prognosis of CRC patients to understand its emphasized molecular origin.[260] Despite a comprehensive study about the mechanisms of CRC, there are still some challenges that require recognizing prognostic biomarkers with minimal invasion and sensitivity. Accordingly, it is of vital significance to improve the survival rate of CRC patients, utilizing rapid and reliable tumor-prognosis biomarkers.

miRNAs, small noncoding RNA gene products of approximately 22 nucleotides, are found in various types of organisms. They account for 2%–5% of the entire genome, number about 1,000, and regulate the expression of ≥20% of human genes.[261] In addition, they play crucial roles in regulating the translation and degradation of mRNAs via

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base pairing to partially complementary sites, predominantly in the 3′-untranslated areas of mRNAs.[262–264]

In the study of CRC, a large number of articles have covered the fact that miRNAs are closely related to the survival time of patients.[1–258] There were relatively small samples in these papers, and the present work aims to estimate the most accurate prognostic value between miRNA level and survival outcome of CRC patients, better to comprehend the miRNAs with prognostic pertinence that are potential candidates for clinical verification in the future.

Materials and methods

Search strategy

We used four online databases – PubMed, Embase, Web of Science, and the Cochrane Library – to find pertinent literature published until May 20, 2017. The combination term "miR and colorectal cancer" was employed for the literature search. Two authors (S Gao and ZY Zhao) independently performed this comprehensive online search.

Inclusion criteria

Articles qualified if they satisfied the following criteria: patients with colon/rectal cancer or CRC; miRNA levels in tissue, plasma, or serum and survival results were measured; at least one survival curve was measured of overall survival (OS), cause-specific survival (CSS), disease-free survival (DFS), recurrence-free survival (RFS), progression-free survival (PFS), and metastasis-free survival (MFS), with or without HRs/95% CIs; and full text published in English.

Exclusion criteria

Exclusion criteria were experimental studies, reviews, or letters without primary data and retracted papers; frequency of research evaluating prognostic value of miRNAs in tissue of four or less. Only the most comprehensive study was included for this meta-analysis if more than one paper had been published in the same research group.

Quality assessment

SG and ZY Zhao identified all qualifying studies analyzing the prognostic value of miRNAs in CRC, and YZ reevaluated uncertain data.

Study selection

A flow diagram of the study selection process is presented in Figure 1. Our study found 1,843 articles for consideration within this meta-analysis, and 322 articles suitable for assessment of prognostic miRNA signatures in CRC and full-text papers were acquired by evaluating titles and abstracts. On elaborate review of research methodologies, 64 investigations were excluded, the details of which are shown in Figure 1. On the basis of the exclusion criteria, 63 studies were finally included in this meta-analysis.

Study frequency

The frequency of studies estimating the prognostic value of miRNAs in CRC are shown in Tables 1 (blood) and 2 (tissue), including miRNA name, number of studies estimating prognostic value, and references.

Study characteristics

Literature with Kaplan–Meier survival curves for CRC are detailed in Table 3. If data were not provided visually and merely as curves, they were extracted from the curves, and estimated HRs with 95% CIs were subsequently calculated using the method of Tierney et al[265] with Engauge Digitizer version 4.1 software. In addition, if outcomes of both univariate and multiple covariates were covered, only the latter was chosen, because of adjustment for confounders.

Statistical analyses

All analyses were performed utilizing Stata version 13.0 (StataCorp, College Station, TX, USA). Merged HRs were regarded as significant at the $P<0.05$ level if 95% CIs did not contain the value 1. Effect values for HRs were regarded as large if ≥2. HRs for OS were regarded as the prime reference standard if OS *P*-values were inconsistent with other survival outcomes with respect to the associated miRNA level. All analyses employed random-effect models instead of fixed-effect models, because there existed differences among the studies, including tissue detected (frozen or formalin-fixed, paraffin-embedded), blood (plasma or serum), tumor stage (I–IV), cutoff values, and miRNA-analysis methods. Publication bias was measured by Begg's funnel plot, and a two-tailed *P*-value <0.05 was regarded as significant. The trim-and-fill method was performed if publication bias occurred. Sensitivity analysis was employed to weigh how powerful merged HRs were after a single study had been removed. An individual study was suspected of having excess of influence if the point estimation was outside the 95% CI after removal from the analysis.

Results

Meta-analysis

An overview of HRs appraised from comprehensive analysis of all the miRNAs is given in Table 4. Thirteen miRNAs were involved in this meta-analysis: miR21, miR92a, miR106a, miR125b, miR126, miR141, miR143, miR145, miR181a,

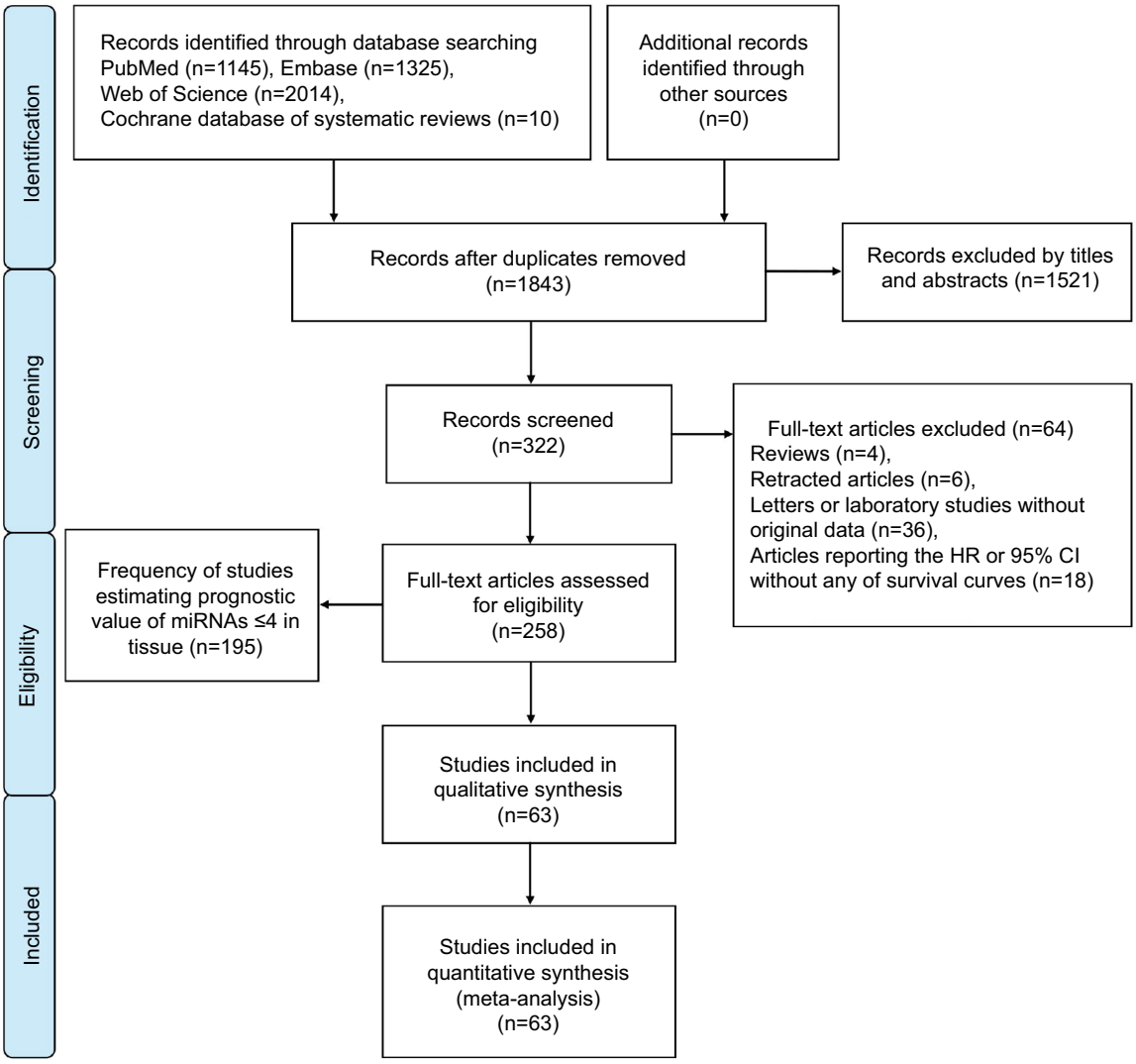

Figure 1 Flow diagram of literature search and selection.

Table 1 Frequency of studies estimating prognostic value of blood miRNA expression in colorectal cancer

miR	n	Reference(s)	miR	n	Reference(s)	miR	n	Reference(s)
15b	1	1	122	1	16	221	1	26
17-3p	1	2	124-5p	1	9	324-3p	1	12
19a	1	3	135	1	17	345	1	12
21	4	4–7	139-5p	1	18	372	1	27
23b	1	8	141	2	14, 19	628-5p	1	12
26a	1	9	143	1	12	885-5p	1	28
29a	1	10	155	1	20	886-3p	1	12
29b	1	11	183	1	21	1290	1	29
34a*	1	12	194	1	11	4772-3p	1	30
92a	2	10, 13	196b	1	22	6826	1	17
96	1	14	200b	2	14, 16	6875	1	17
103	1	15	200c	1	23			
106a	1	2	203	2	24, 25			

Note: Highlighted studies were included in the present meta-analysis.

Table 2 Frequency of studies estimating prognostic value of tissue-miRNA expression in colorectal cancer

miR	n	Reference(s)	miR	n	Reference(s)	miR	n	Reference(s)	miR	n	Reference(s)	miR	n	Reference(s)
let7a-5p	1	31	34a-5p	1	99	143	6	59, 112, 150–153	211	1	197	487b	1	233
let7a-2	1	32	34a	1	100	144	1	154	212	1	198	490-3p	1	234
let7a	1	33	92a	3	64, 101, 102	145	5	33, 64, 150, 155, 156	214	1	199	491-5p	1	205
let7b	1	34	93	2	34, 103	148a*	1	157	215	4	58, 155, 179, 200	494	2	34, 235
let7c	1	35	96-5p	1	104	148a	3	81, 158, 159	217	2	201, 202	498	1	215
let7e	1	18	96	1	105	149	2	160, 161	218	2	203, 204	503	3	227, 236, 237
let7g*	1	36	99a-3p	1	36	150	1	162	221-3p	1	205	505*	1	36
let7g	1	37	99a	2	35, 106	153	1	163	221*	1	206	505	1	32
let7i	1	28	99b-5p	1	107	154	1	164	221	2	28, 207	506	2	238, 239
7	3	34, 39, 40	100	2	106, 108	155	1	60	223	1	208	515-5p	1	134
9	1	41	101	1	64	181a-1	1	32	224	5	206, 209–212	517a	1	240
10b	4	28, 42–44	103a	1	58	181a	5	18, 165–168	229-5p	1	36	542-3p	2	241, 242
15a-5p	1	45	103-1	1	81	181b	2	18, 169	296	1	213	556	1	67
15a	1	46	103	1	109	181c	1	170	320a	1	28	570	1	157
16	3	46–48	106a-5p	1	110	182	3	171–173	320e	1	214	573	1	134
17-5p	3	49–51	106a	7	49, 64, 67, 111–114	183	1	174	320	1	215	579	1	134
17	1	52	106b	3	58, 115, 116	185	1	133	326	1	216	590-5p	2	243, 244
18a	2	53, 54	107	1	36	187	2	175, 176	328	1	32	592	2	186, 245
19b	1	38	124-5p	1	9	188-3p	1	177	335	1	217	610	1	246
20a-5p	2	55, 56	124	2	117, 118	191	1	178	337-5p	1	36	625-3p	1	247
20a	2	57, 58	125b	5	33, 35, 106, 112, 119	192	2	179, 180	338-3p	1	218	625	1	248
21	17	5, 58–73	126	6	120–125	193a-5p	1	181	340	1	219	630	1	249
22	2	74, 75	128	2	126, 127	193b	1	182	342-3p	1	205	638	1	250
23b	2	76, 77	130a	1	81	194	3	38, 183, 184	361-5p	1	220	652	1	32
24-3p	2	78, 79	130b	1	128	195-5p	1	33	362-3p	1	157	664-3p	1	186
25	1	80	132	2	129, 130	195	2	33, 34	365-1	1	76	720	1	251
26a-2	1	81	133a	2	131, 132	196a	1	185	365-2	1	76	802	1	134
26b	1	82	133b	2	133, 134	196b-5p	1	186	365	1	221	875-5p	1	252
29a	2	83, 84	134	1	135	196b	1	185	370	1	36	885-5p	1	28
29b	1	85	135b	3	136–138	197	1	32	372	1	222	889	1	36
30a-5p	1	86	137	2	139, 140	198	1	187	376a	1	223	944	1	157
30a	1	87	138-5p	2	141, 142	199a-3p	1	188	378a-3p	1	224	1260b	1	253
30b	1	88	138	1	143	199b	1	189	378a-5p	1	224	1288	1	254
30d	1	89	139-3p	1	144	200a	3	82, 149, 190	378	1	225	1290	1	29
31-3p	2	90, 91	139-5p	2	18, 145	200c	3	23, 149, 191	422a	2	141, 226	1292	1	227
31-5p	3	91–93	139	1	146	203	2	24, 192	424-3p	1	227	1297	1	255
31	4	64, 94–96	140-5p	2	147, 148	204-5p	2	193, 194	429	5	149, 228–231	1826	1	256
32	2	32, 97	141	2	34, 149	206	1	195	450b-5p	1	232	4500	1	257
33b	1	98	143-5p	1	58	210	1	196	455-5p	1	186	4775	1	258

Note: Highlighted studies were included in the present meta-analysis.

Table 3 Characteristics of studies included on colorectal cancer

miRNA	Study	Country/source	Design	Sample	Number	Stage	Cutoff	Method	Follow-up (months)	Result	HR (L/H)	HR (H/L)	95% CI
21	Menéndez et al[4]	Spain	P	Serum	102	I–IV	1.00	qRT-PCR	36	OS[a]		0.50	0.25–1.02
										DFS[a]		0.51	0.25–1.06
21	Toiyama et al[5]	Japan	R	Serum	188	I–IV	<0.01	RT-qPCR	84	OS[a]		4.12	1.10–15.40
21	Monzo et al[6]	Spain	R	Plasma	52	I–IV	Median	TaqMan	48	DFS[b]		2.32	0.80–6.71
21	Tsukamoto et al[7]	Japan	R	Plasma	326	I–IV	Median	qRT-PCR	84	OS[a]		2.28	1.81–5.74
					259					DFS[a]		2.34	1.87–4.60
92a	Wang and Gu[10]	China	R	Serum	74	II–IV	<0.06	RT-qPCR	35	OS[b]		1.17	0.70–1.97
92a	Liu et al[13]	China	R	Serum	166	I–IV	<0.01	RT-qPCR	53	OS[a]		4.36	1.64–11.57
141	Cheng et al[19]	China, USA	R	Plasma	258	I–IV	Median	RT-qPCR	96	OS[a]		2.40	1.18–4.86
141	Sun et al[14]	USA	R	Plasma	168	I–IV	Mean	RT-qPCR	96	OS[b]		2.58	1.58–4.21
200b	Maierthaler et al[16]	Germany I	R	Plasma	308	I–IV	Median	RT-qPCR	>72	OS[a]		0.77	0.57–1.05
		Germany II			219					OS[a]		1.21	0.98–1.50
200b	Sun et al[14]	USA	R	Plasma	169	I–IV	Mean	RT-qPCR	96	OS[b]		2.46	1.57–3.85
203	Hur et al[24]	Japan	R	Serum	186	I–IV	ROC	RT-qPCR	70	OS[a]		2.14	1.09–4.21
203	Shi et al[25]	China	R	Serum	180	II–IV	Median	RT-qPCR	60	OS[b]		0.47	0.27–0.81
21	Kulda et al[59]	Czech Republic	R	Frozen	46	I–IV	8.10	RT-qPCR	56	DFS[b]		1.80	0.05–65.37
21	Shibuya et al[60]	Japan	R	Frozen	156	I–IV	Mean	TaqMan	84	OS[a]		1.95	1.05–4.48
					116					DFS[a]		2.53	1.15–5.59
21	Nielsen et al[61]	Denmark I	R	FFPE	129	II	65%	ISH	≥60	OS[b]		1.17	1.02–1.34
										DFS[a]		1.29	1.06–1.56
		Denmark II			67					OS[b]		0.97	0.83–1.13
										DFS[a]		0.85	0.73–1.01
21	Faltejskova et al[62]	Czech Republic	R	Tissue	44	I–IV	Median	RT-qPCR	86	OS[b]		2.72	0.63–11.83
21	Kjaer-Frifeldt et al[63]	Denmark	P	FFPE	520	II	Mean	ISH	84	OS[a]		1.08	0.97–1.22
										RF-CSS[a]		1.41	1.19–1.67
21	Schee et al[64]	Norway	P	Frozen	193	I–III	Median	qRT-PCR	>60	MFS[b]		1.17	0.59–2.32
21	Chen et al[65]	China	R	Tissue	195	I–IV	Mean	RT-qPCR	>100	OS[a]		2.56	1.43–4.57
21	Toiyama et al[5]	Japan	R	FFPE	166	I–IV	3.70	RT-qPCR	84	OS[a]		0.59	0.21–1.63
21	Oue et al[66]	Japan	R	FFPE	87	II–III	None	qRT-PCR	60	OS[a]		3.13	1.20–8.17
		Germany			145	II				OS[a]		2.65	1.06–6.66
21	Bullock et al[67]	UK	P	Frozen, FFPE	50	II	Mean	qRT-PCR	96	OS[b]		2.47	1.19–5.55
										DFS[b]		2.68	1.21–5.93
21	Fukushima et al[68]	Japan	R	Frozen	306	I–IV	Mean	RT-qPCR	90	OS[a]		2.88	1.70–5.08
					244					DFS[a]		2.94	1.68–5.36
21	Kang et al[69]	South Korea	R	FFPE	277	IIA–IIIC	Median	ISH	80	RFS[a]		2.24	1.25–4.02
21	Caritg et al[58]	Spain	R	Frozen	69	II	2.04	TaqMan	>140	DFS[b]		1.33	0.14–12.47
21	Feiersinger et al[70]	Germany	R	FFPE	29	I–IV	Median	qRT-PCR	205.15	OS[b]		1.45	0.39–5.43
										DFS[b]		1.76	0.75–4.11

(*Continued*)

Table 3 (*Continued*)

miRNA	Study	Country/source	Design	Sample	Number	Stage	Cutoff	Method	Follow-up (months)	Result	HR (L/H)	HR (H/L)	95% CI
21	Iseki et al[71]	Japan	R	FFPE	32	None	8.10	qRT-PCR	63.2	OS[a]		2.52	0.65–8.34
										PFS[a]		4.93	1.08–20.81
21	Lee et al[72]	South Korea	R	FFPE	170	I–IV	Median	ISH	105	OS[b]		0.93	0.54–1.60
21	Mima et al[73]	USA I	P	FFPE	190/192	I–IV	25%	RT-qPCR	207.6	OS[a]		0.99	0.75–1.31
										CSS[a]		0.88	0.58–1.31
		USA II			192/192		50%			OS[a]		1.03	0.78–1.35
										CSS[a]		1.10	0.75–1.60
		USA III			191/192		75%			OS[a]		1.40	1.07–1.84
										CSS[a]		1.42	0.98–2.04
106a	Díaz et al[49]	Spain	R	Frozen	110	I–IV	Median	RT-qPCR	99	OS[a]		0.53	0.26–1.08
										DFS[a]		0.36	0.17–0.78
106a	Feng et al[111]	China	R	Frozen	28	IIB–IIIB	Median	qRT-PCR	60	MFS[b]		3.63	0.56–23.68
106a	Schee et al[64]	Norway	P	Frozen	193	I–III	Median	qRT-PCR	>60	MFS[b]		0.81	0.41–1.59
106a	Ak et al[112]	Turkey	R	FFPE	40	I–IV	None	qRT-PCR	>200	OS[b]		0.94	0.35–2.56
106a	Bullock et al[67]	UK	P	Frozen, FFPE	50	II	Mean	qRT-PCR	96	OS[b]		2.25	1.00–5.04
										DFS[b]		2.91	1.32–6.42
106a	Hao et al[113]	China	R	Tissue	138	I–IV	66%	RT-qPCR	>60	OS[a]		1.87	1.13–3.09
										DFS[a]		1.22	0.70–2.12
106a	Hao et al[114]	China	R	FFPE	65	I–IV	Median	qRT-PCR	>60	OS[b]		2.00	0.51–7.85
125b	Nishida et al[119]	Japan	R	Frozen	89	None	Median	RT-qPCR	>96	OS[b]		2.42	0.99–5.91
125b	Ak et al[112]	Turkey	R	FFPE	40	I–IV	None	qRT-PCR	>200	OS[b]		0.90	0.32–2.56
125b	Cappuzzo et al[35]	Italy	R	FFPE	183	None	None	None	48	OS[a]		0.58	0.32–1.05
125b	Rokavec et al[106]	TCGA	R	Tissue	438	I–IV	None	Downloaded	>133	OS[b]		1.88	1.36–2.60
125b	Sun et al[33]	TCGA	R	Tissue	107	I–IV	Median	Downloaded	141.1	OS[b]		2.29	1.33–3.92
126	Hansen et al[120]	Denmark	R	FFPE	89	None	Median	ISH	58	OS[b]	1.93		1.13–3.29
					83					PFS[b]	2.69		1.42–5.08
126	Hansen et al[121]	Sweden, Denmark	P	FFPE	89	None	Median	qRT-PCR	>30	PFS[a]	2.04		1.19–3.45
126	Hansen et al[122]	DCCG	P	FFPE	560	II	Median	qRT-PCR	84	OS[a]	1.32		1.00–1.72
										RF-CSS[a]	1.04		0.71–1.52
126	Liu et al[123]	China	R	Frozen	92	I–IV	None	qRT-PCR	92	OS[b]	2.65		1.00–6.98
126	Ebrahimi et al[124]	Australia	R	FFPE	132	I–IV	<1/>2	qRT-PCR	>100	OS[b]	1.81		0.82–4.00
126	Yuan et al[125]	China	R	Tissue	75	I–IV	0/>0	ISH	68	OS[b]	2.35		0.91–6.06
143	Kulda et al[59]	Czech Republic	R	Frozen	46	I–IV	11.40	RT-qPCR	56	DFS[b]	0.45		0.07–2.78
143	Drebber et al[150]	Germany	R	FFPE	40	I–IV	1.00	RT-qPCR	76.8	OS[b]	1.52		0.32–7.22
143	Pichler et al[151]	Austria	R	FFPE	77	II–IV	None	qRT-PCR	>125	CSS[a]	1.86		1.06–3.25
					52					PFS[b]	1.55		0.91–2.66
143	Guo et al[152]	China	R	Tissue	79	I–IV	Median	qRT-PCR	122	OS[b]	1.45		0.69–3.07
143	Ak et al[112]	Turkey	R	FFPE	40	I–IV	1.76	qRT-PCR	>200	OS[b]	2.69		0.80–9.08
143	Simmer et al[153]	DCCG	P	FFPE	55	I–IV	Median	TaqMan	42	PFS[a]	0.45		0.24–0.85

(*Continued*)

Table 3 (*Continued*)

miRNA	Study	Country/source	Design	Sample	Number	Stage	Cutoff	Method	Follow-up (months)	Result	HR (L/H)	HR (H/L)	95% CI
145	Drebber et al[150]	Germany	R	FFPE	40	I–IV	0.10	RT-qPCR	76.8	OS[b]	1.95		0.43–8.79
145	Schee et al[64]	Norway	P	Frozen	193	I–III	Median	qRT-PCR	>60	MFS[b]	0.61		0.30–1.22
145	Pecqueux et al[155]	Germany	R	Frozen	47	None	Median	RT-qPCR	>60	OS[b]	3.73		1.45–9.55
145	Zhou et al[156]	China	R	Frozen	60	I–IV	Median	qRT-PCR	80	OS[b]	2.57		1.12–5.90
										DFS[b]	2.58		1.12–5.94
145	Sun et al[33]	TCGA	R	Tissue	107	I–IV	Median	Downloaded	>144	OS[b]	0.52		0.30–0.77
181a	Nishimura et al[165]	Japan	R	Frozen	162	I–IV	Median	qRT-PCR	>144	OS[b]		2.00	1.05–3.80
										DFS[b]		2.26	1.10–4.61
181a	Ji et al[166]	China I	R	Tissue	137	I–IV	Median	RT-qPCR	100	OS[a]		1.87	1.08–3.25
		China II		FFPE	294		1.00	ISH		OS[a]		1.38	1.11–1.72
181a	Pichler et al[167]	Austria	R	FFPE	80	II–IV	None	qRT-PCR	>125	CSS[a]		0.63	0.37–1.21
					54					PFS[b]		0.57	0.36–0.91
181a	Li et al[168]	China	R	Frozen	72	I–IV	None	RT-qPCR	>60	OS[b]		2.06	1.00–4.23
181a	Miyoshi et al[18]	TCGA	R	Tissue	93	II–III	None	Downloaded	135	RFS[b]		2.85	1.24–6.55
224	Liao et al[209]	China	R	Frozen	110	I–IV	Median	qRT-PCR	87	OS[b]		1.82	0.88–3.79
224	Yuan et al[206]	China	R	Tissue	108	I–III	None	qRT-PCR	60	OS[a]		0.27	0.14–0.51
					54					DFS[a]		0.07	0.02–0.25
224	Zhang et al[210]	China	R	Frozen	108	I–II	25.72	qRT-PCR	62.5	DFS[b]		1.87	0.79–4.41
224	Adamopoulos et al[211]	Greece	R	Frozen	104	I–IV	56%	qRT-PCR	120	OS[a]		4.41	1.72–11.34
					91					DFS[a]		4.61	1.41–15.09
224	Ling et al[212]	TCGA	R	Tissue	143	I–IV	None	Downloaded	72	OS[a]		2.88	0.97–8.56
		Italy I			54			qRT-PCR	115	OS[a]		2.77	0.95–8.11
		Italy II			68			qRT-PCR	115	OS[a]		4.14	0.96–17.76
		Romania			38			qRT-PCR	70	OS[a]		1.76	0.36–8.64
		Austria			74			qRT-PCR	130	OS[a]		2.36	1.32–4.21
		UK			41			qRT-PCR	60	OS[b]		4.92	1.31–18.46
										MFS[b]		6.51	1.97–21.51
429	Li et al[228]	China	R	Frozen	107	I–III	Median	qRT-PCR	82	OS[b]		2.09	0.84–5.17
429	Diaz et al[149]	Spain	R	Frozen	127	I–III	None	TaqMan	113	OS[b]		0.35	0.16–0.77
429	Sun et al[229]	China	R	Frozen	84	I–IV	None	qRT-PCR	96	OS[b]		0.29	0.16–0.55
429	Dong et al[230]	China	R	Frozen	78	I–IV	Median	qRT-PCR	60	OS[b]		2.66	1.25–5.68
429	Han et al[231]	China	R	Frozen	71	I–IV	Median	qRT-PCR	60	OS[a]		1.85	1.02–3.33

Notes: [a]multiple-covariate analysis; [b]Univariate analysis;

Abbreviations: L/H, low versus high miRNA expression; H/L, high versus low miRNA expression; P, prospective; qRT-PCR, quantitative real-time polymerase chain reaction; OS, overall survival; DFS, disease-free survival; R, retrospective; RT-qPCR, reverse transcription qRT-PCR; RF-CSS, recurrence-free cause-specific survival; ROC, receiver-operating characteristic; FFPE, formalin-fixed, paraffin-embedded; ISH, in situ hybridization; MFS, metastasis-free survival; RFS, recurrence-free survival; PFS, progression-free survival; CSS, cause-specific survival; TCGA, the Cancer Genome Atlas; DCCG, Dutch Colorectal Cancer Group.

Table 4 Meta-analysis results for miRNA expression in colorectal cancer

miRNA	Survival analysis	Articles	Studies included	HR	95% CI	Figure	*P*-value	Heterogeneity (Higgins's I^2)	Patients, n
High miR21	OS	3	4, 5, 7	1.56	0.47–5.23	2	0.47	85.2%, *P*<0.01	616
High miR21	DFS	3	4, 6, 7	1.39	0.49–3.96	2	0.53	84.4%, *P*<0.01	480
High miR92a	OS	2	10, 13	2.11	0.59–7.61	2	0.25	81.6%, *P*=0.02	240
High miR141	OS	2	14, 19	2.52	1.68–3.77	2	<0.01	0.0%, *P*=0.87	426
High miR200b	OS	2	14, 16	1.28	0.75–2.19	2	0.36	88.8%, *P*<0.01	696
High miR203	OS	2	24, 25	0.99	0.22–4.37	2	0.99	91.4%, *P*<0.01	366
High miR21	OS	13	5, 60–68, 70–73	1.31	1.12–1.53	3A	<0.01	65.3%, *P*<0.01	2,861
High miR21	OS[a]	8	5, 60, 63, 65, 66, 68, 71, 73	1.47	1.16–1.87	3A	<0.01	71.7%, *P*<0.01	2,372
High miR21	DFS	7	58–61, 67, 68, 70	1.64	1.11–2.41	3D	0.01	79.2%, *P*<0.01	554
High miR21	RFS/CSS/MFS/PFS	5	63, 64, 69, 71, 73	1.33	1.06–1.67	3D	0.01	48.6%, *P*=0.07	1,787
High miR21	OS, adjusted[b]			1.13	0.96–1.34	4B	0.15	71.6%, *P*<0.01	
High miR106a	OS	5	49, 67, 112–114	1.31	0.72–2.36	5	0.38	62.2%, *P*=0.03	403
High miR106a	DFS/MFS	5	49, 64, 67, 111, 113	1.14	0.55–2.36	5	0.72	75.8%, *P*<0.01	519
High miR125b	OS	5	33, 35, 106, 112, 119	1.43	0.83–2.47	5	0.19	74.6%, *P*<0.01	857
Low miR126	OS	5	120, 122–125	1.55	1.24–1.93	6	<0.01	1.2%, *P*=0.40	948
Low miR126	PFS/RFS/CSS	3	120–122	1.72	0.95–3.10	6	0.07	75.2%, *P*=0.02	732
Low miR143	DFS/CSS/PFS	3	59, 151, 153	1.00	0.47–2.13	6	1.00	77.7%, *P*<0.01	230
Low miR143	OS	3	112, 150, 152	1.69	0.94–3.04	6	0.08	0.0%, *P*=0.69	159
Low miR145	OS	4	33, 150, 155, 156	1.68	0.55–5.12	7	0.36	85.4%, *P*<0.01	254
Low miR145	MFS/DFS	2	64, 156	1.23	0.30–5.06	7	0.77	85.1%, *P*<0.01	253
High miR181a	OS	3	165, 166, 168	1.52	1.26–1.83	7	<0.01	0.0%, *P*=0.45	665
High miR181a	DFS/CSS/PFS/RFS	3	18, 165, 167	1.17	0.53–2.59	7	0.69	84.0%, *P*<0.01	309
High miR224	OS	4	206, 209, 211, 212	2.12	1.04–4.34	8	0.04	80.9%, *P*<0.01	740
High miR224	DFS/MFS	4	206, 210–212	1.43	0.23–8.77	8	0.70	90.6%, *P*<0.01	294
High miR429	OS	5	146, 228–231	1.00	0.39–2.58	8	1.00	88.7%, *P*<0.01	467

Notes: [a]Multiple-covariate analysis; [b]adjusted with trim-and-fill method.
Abbreviations: OS, overall survival; DFS, disease-free survival; RFS, recurrence-free survival; CSS, cause-specific survival; MFS, metastasis-free survival; PFS, progression-free survival.

miR200b, miR203, miR224, and miR429. Results of survival analyses of these miRNAs are given in Figures 2–8.

CRC patients with high blood miR141, high tissue miR181a and miR224, or low tissue miR126 expression have significantly shorter OS

Two studies[14,19] focused on associations between high blood miR141 levels and OS, indicating that CRC patients with high blood miR141 levels had significantly shorter OS than those with low miR141 expression (HR 2.52, 95% CI 1.68–3.77, *P*<0.01; Figure 2). Five papers[120,122–125] stressed connections between low tissue miR126 levels and OS, suggesting that CRC patients with low expression of tissue miR126 levels had significantly poorer OS than those with high miR126 expression (HR 1.55, 95% CI 1.24–1.93, *P*<0.01; Figure 6).

Three articles concentrated on the relationship between high tissue miR181a levels and OS, demonstrating that CRC patients with high miR181a levels had significantly worse OS than those with low miR181a expression (HR 1.52, 95% CI 1.26–1.83, *P*<0.01; Figure 7). Four studies paid attention to correlations between high expression of tissue miR224 levels and OS, showing that CRC patients with high tissue miR224 levels had significantly shorter OS than those with low miR224 expression (HR 2.12, 95% CI 1.04–4.34, *P*=0.04; Figure 8).

There was no significant relationship between high expression levels of blood miR21, miR92a, miR200b, miR203, tissue miR106a, miR125b, or miR429 or low expression levels of tissue miR143 or miR145 and OS

Details are given in Table 4 and Figures 2 and 5–8.

High tissue miR21 expression forecasts poor OS

Thirteen investigations[5,60–68,70–73] analyzed the connection between high tissue miR21 levels and OS, showing that CRC patients with high tissue miR21 levels had significantly worse OS than those with low miR21 expression (HR 1.31, 95% CI 1.12–1.53, *P*<0.01; Figure 3A).

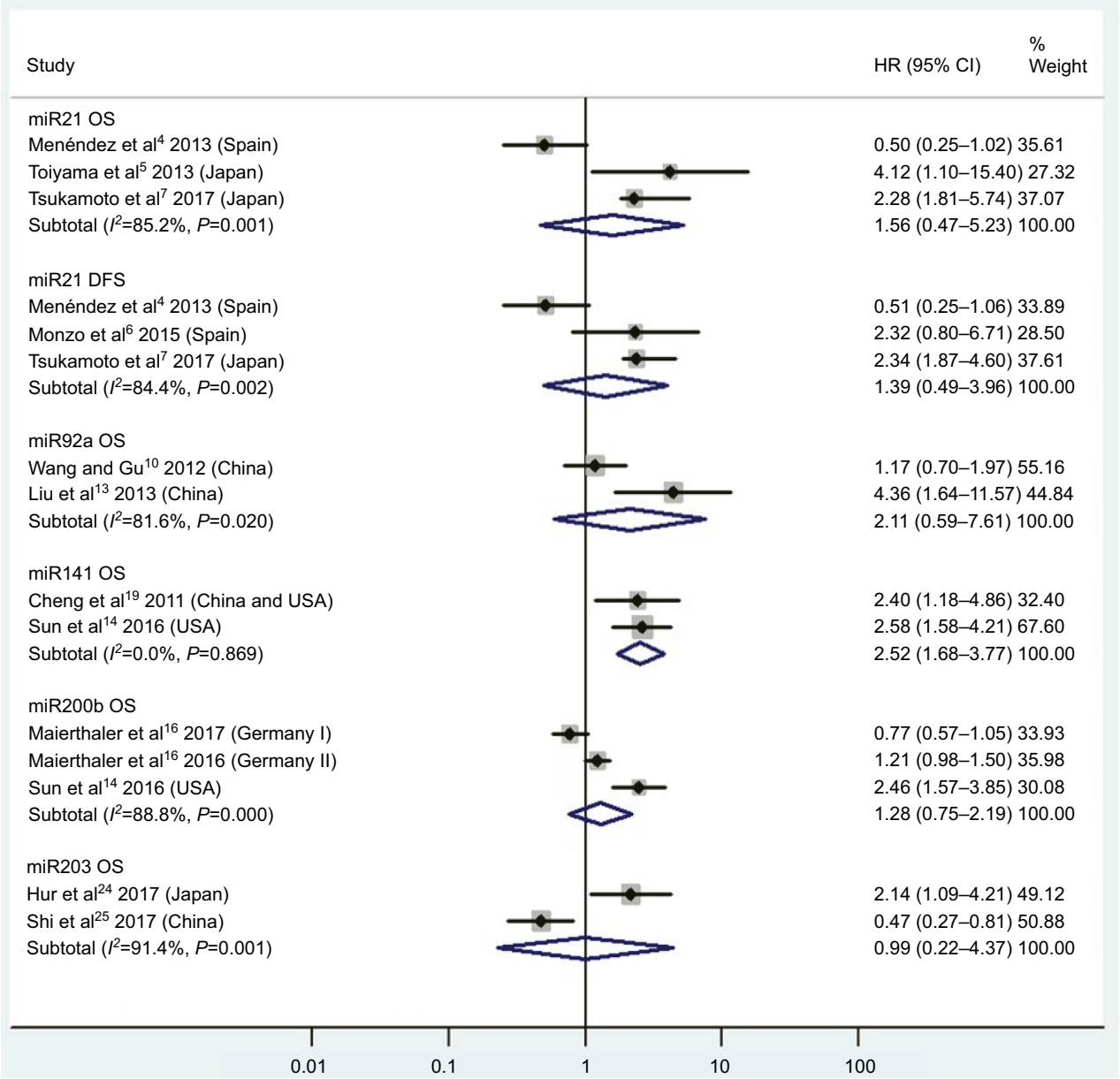

Figure 2 Pooled analyses of OS or DFS in association with high blood miR21-, miR92a-, miR141-, miR200b-, and miR203-expression levels.
Note: Weights are from random-effect analysis.
Abbreviations: OS, overall survival; DFS, disease-free survival.

Publication bias

To assess publications showing some degree of bias for OS of CRC patients with high tissue miR21 levels, our study used Begg's funnel plot (Figure 3B). The *P*-value was less than 0.01, indicating the presence of publication bias. As such, the trim-and-fill method was performed and the pooled HR recalculated with presumed missing studies to estimate asymmetry in the funnel plot (Figure 4A), indicating no publication bias (*P*=0.73). The recalculated HR changed significance for OS (HR 1.13, 95% CI 0.96–1.34, *P*=0.15; Figure 4B).

Sensitivity analysis

For research on OS of CRC patients with high tissue miR21 levels, the sensitivity analysis did not manifest alterations during outcomes on the basis of the exclusion of any single investigation (Figure 3C), showing that no sole study significantly affected the merged HR or 95% CI. This also

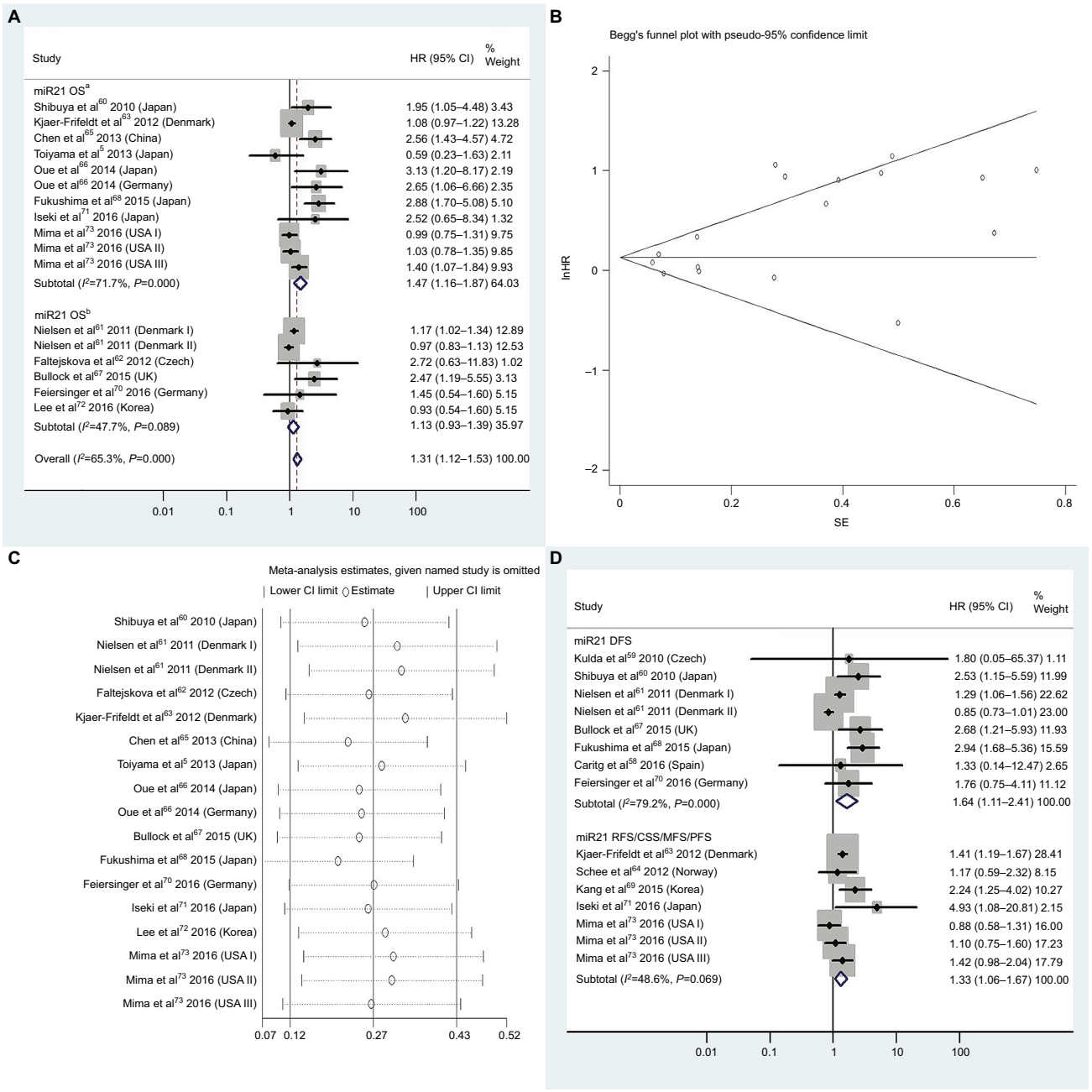

Figure 3 (**A**) Forest plots of pooled analyses of OS or OS (multiple-covariate analysis) in association with high tissue miR21-expression levels; (**B**) Begg's funnel plot of publication bias for pooled analysis of OS in association with high tissue miR21-expression levels; (**C**) sensitivity analysis of pooled analysis of OS in association with high tissue miR21-expression levels; (**D**) forest plots of pooled analyses of DFS or RFS/CSS/MFS/PFS in association with high tissue miR21-expression levels. Weights are from random-effects analysis in A and D. [a]Multiple-covariate analysis; [b]univariate analysis.

Abbreviations: OS, overall survival; DFS, disease-free survival; RFS, recurrence-free survival; CSS, cause-specific survival; MFS, metastasis-free survival; PFS, progression-free survival.

proved true for the outcome of OS adjusted with the trim-and-fill method (Figure 4C).

Key findings

We carried out a meta-analysis of 13 miRNAs and OS. Serving as the most investigated miRNA, miR21 (high tissue levels) in CRC showed significantly shorter OS than low tissue miR21 levels (P<0.05). However, there was no significant relationship between high blood miR21 levels and OS (P=0.47). The different detected sample types and relatively small sample capacity of the miR21 blood group (only three studies analyzing the relationship between blood miR21 levels and OS) may have been potential clinical reasons and caused the statistical significance between tissue and blood miR21 levels.

Encouragingly, the HR from analysis of the association between high tissue miR21 levels and OS (multiple-covariate analysis)[5,60,63,65,66,68,71,73] was 1.47, which was greater than that

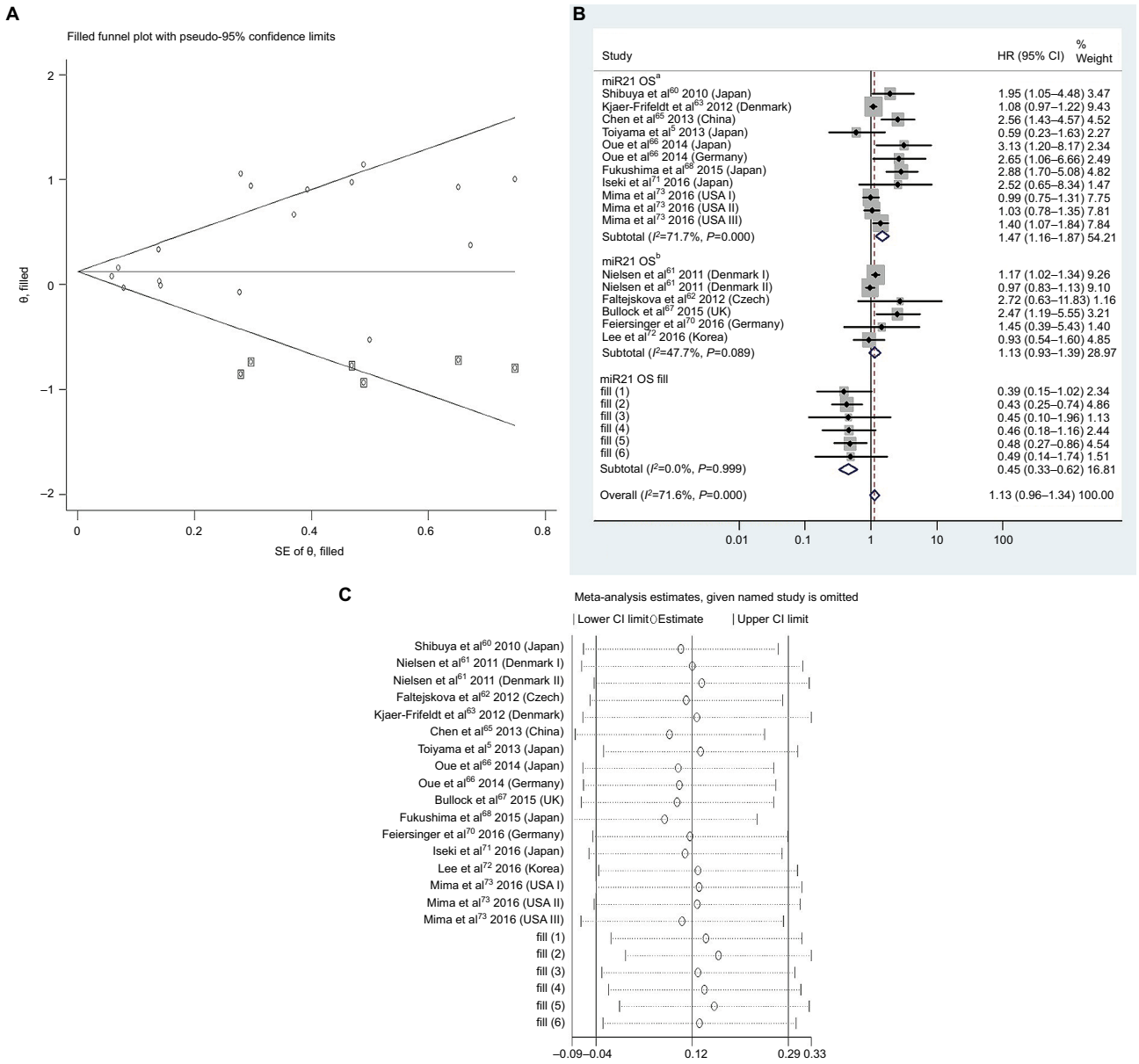

Figure 4 (**A**) Funnel plot of pooled analysis adjusted with the trim-and-fill method of OS in association with high tissue miR21-expression levels. Circles, included studies; diamonds, presumed missing studies. (**B**) Forest plot of pooled analysis adjusted with the trim-and-fill method of OS in association with high tissue miR21-expression levels. (**C**) Sensitivity analysis of pooled analysis adjusted with the trim-and-fill method of OS in association with high tissue miR21-expression levels. Weights are from random-effects analysis. [a]Multiple-covariate analysis; [b]univariate analysis.

Abbreviation: OS, overall survival.

reported in any of the 13 articles.[5,60–78,70–73] Nevertheless, the significance did not remain in accordance with the forest plot, which was adjusted with the trim-and-fill method because publication bias existed ($P<0.01$; Figure 3B). This result indicated that the prognostic value of tissue miR21 was not stable in CRC patients. There were other miRNAs with significant prognostic value in CRC, including blood miR141 and tissue miR21, miR181a, miR224, and miR126 ($P<0.05$). Among these, blood miR141 and tissue miR224 were powerful prognostic candidates in CRC (HR ≥2).

Discussion

Present situation

Increasing numbers of studies have indicated that diverse miRNAs are connected with survival results in CRC patients.[1–258] Nevertheless, no systematic review or meta-analysis has evaluated HRs between miRNA levels and survival outcomes of CRC patients. Therefore, it was of vital significance to launch a meta-analysis to comprehend the relationship between expression levels of miRNAs and prognoses of CRC patients.

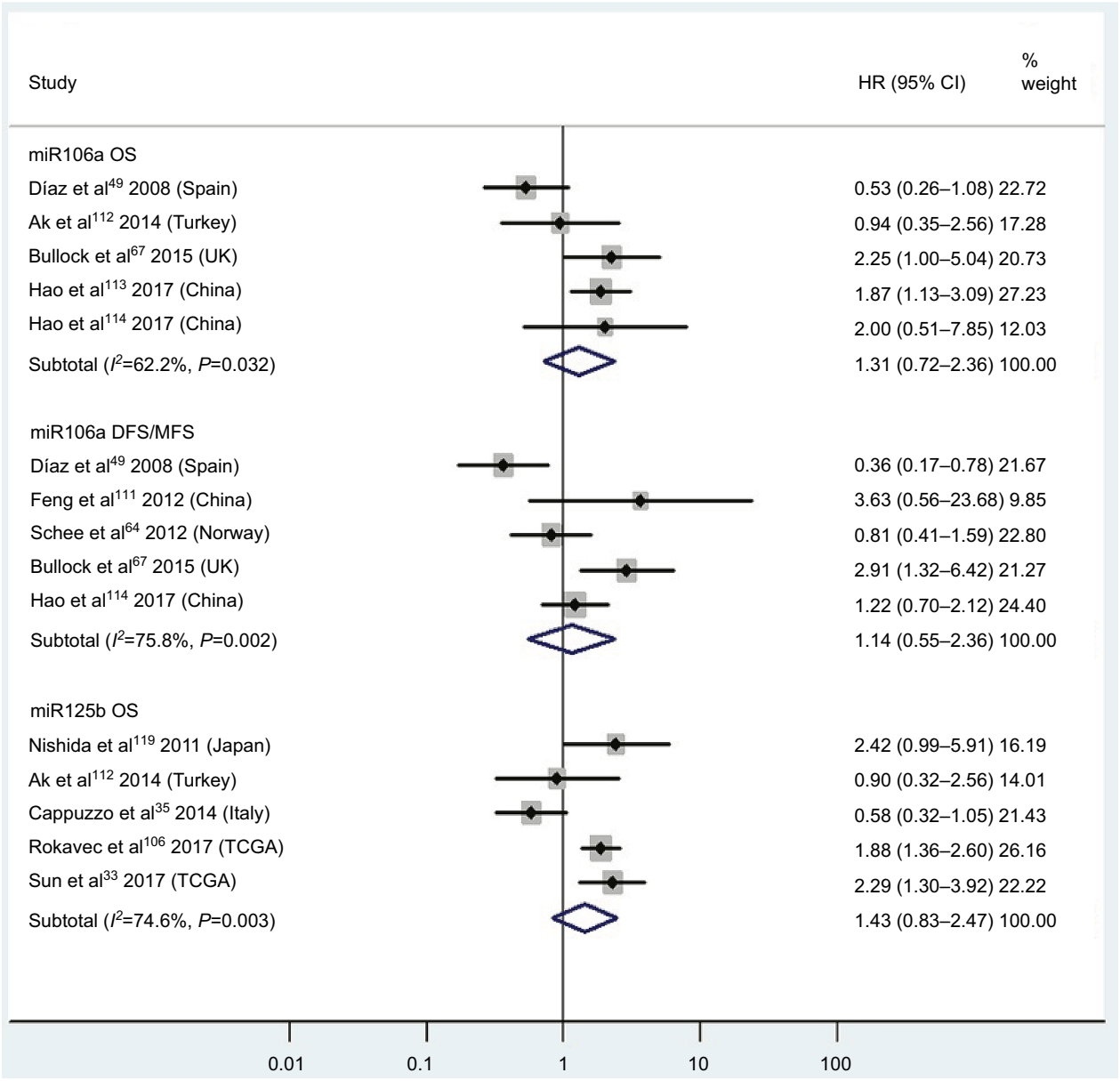

Figure 5 Pooled analyses of OS or DFS/MFS in association with high tissue miR106a- and miR125b-expression levels. Weights are from random-effects analysis.
Abbreviations: OS, overall survival; DFS, disease-free survival; MFS, metastasis-free survival; TCGA, the Cancer Genome Atlas.

Molecular mechanisms for miRNAs researched

An overview of miRNAs with dysregulated expression and their potential targets and pathways of entry is detailed in Figure 9. There was noticeable functional overlap and relationships among the miRNAs. Seven miRNAs (miR21, miR106a, miR126, miR143, miR181a, miR224, and miR429) touched upon cell functions, including cell apoptosis, cell cycle, and death. To sum up, these associations may refer to CRC progression.

Other CRC molecular pathways

In addition to miRNAs, there are some other molecular data that can be confounders, related to mortalities, such as the chromosomal instability pathway, the DNA mismatch repair system, and microsatellite instability (MSI). Features of distinctive pathways are different models of genetic instability, succeeding clinical presentations, and features of pathological behavior. A majority of CRC follows the chromosomal instability pathway, features of which are extensive loss of heterozygosis and gross chromosomal

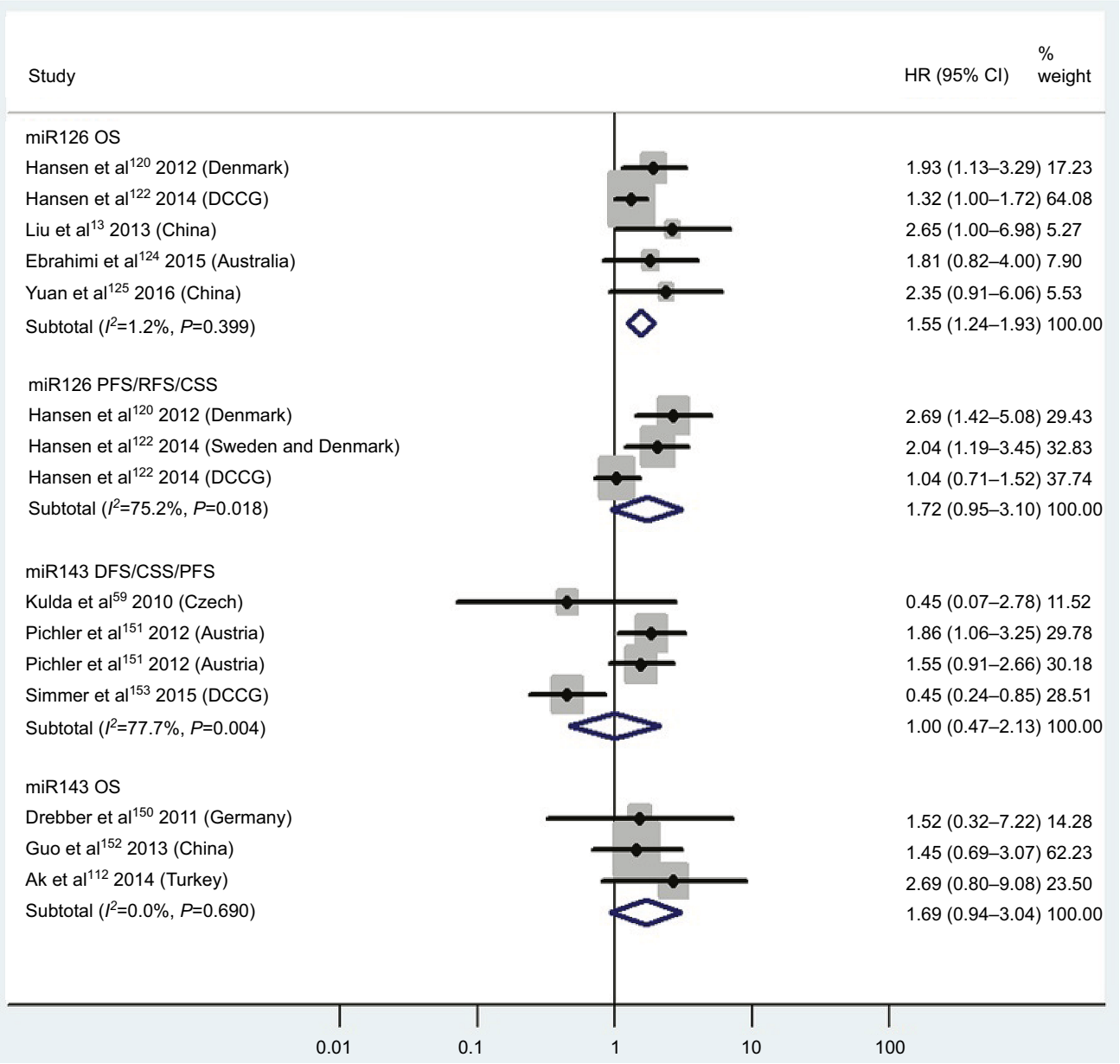

Figure 6 Pooled analyses of OS, PFS/RFS/CSS, or DFS/CSS/PFS in association with low tissue miR126- and miR143-expression levels. Weights are from random-effects analysis.

Abbreviations: OS, overall survival; DCCG, Dutch Colorectal Cancer Group; PFS, progression-free survival; RFS, recurrence-free survival; CSS, cause-specific survival; DFS, disease-free survival.

abnormalities.[266,267] Second, about 15% of CRC is due to the derangement of the DNA mismatch repair system and consequential MSI. The former is in charge of protein production, which identifies and directly repairs mononucleotide mismatches at MS sequences that escape the proofreading system of DNA polymerase. Furthermore, a previous meta-analysis indicated that MSI-high CRC patients had a 40% better OS rate compared with MS-stable CRC patients.[268]

Molecular pathological epidemiology (MPE)

MPE is a multidisciplinary research field of associations between endogenous and exogenous ingredients, molecular cancer biomarkers, and cancer progression and also a comprehensive interdisciplinary science on the strength of the characteristic principal and continuum theory of diseases.[269,270] Other than miRNAs, DNA mutation and methylation and other diagnostics, such as blood tests, also play crucial roles in cancer prognosis and MPE, which deeply investigates environmental exposure, intermediate phenotypes, such as blood biomarkers, and molecular changes in cancer using molecular pathologic analyses. MPE helps precision medicine by providing robust evidence for exposure–outcome associations, such as with drugs.

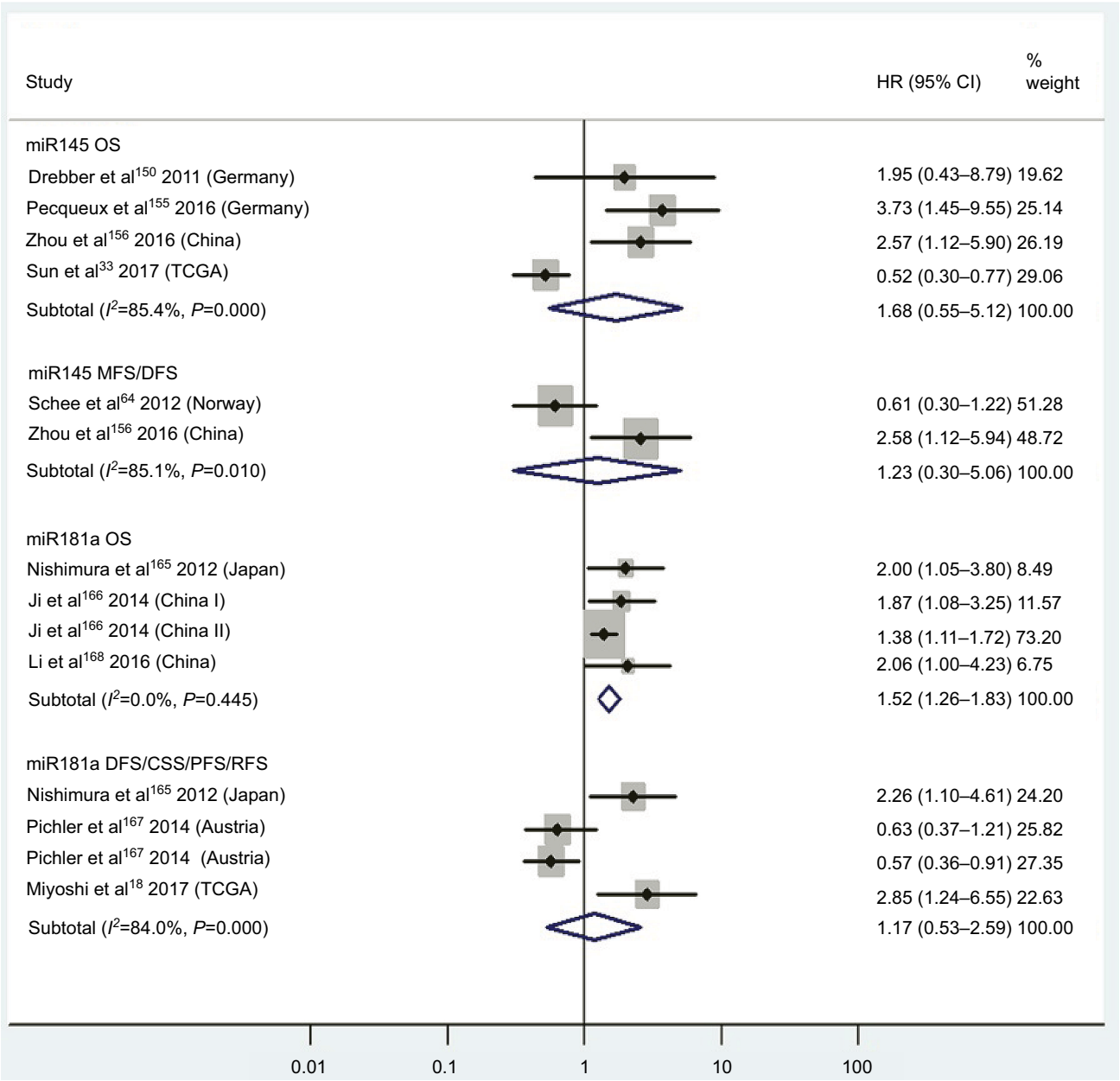

Figure 7 Pooled analyses of OS, MFS/DFS or DFS/CSS/PFS/RFS in association with high tissue miR145-expression levels or low tissue miR181a-expression levels. Weights are from random-effects analysis.

Abbreviations: OS, overall survival; TCGA, the Cancer Genome Atlas; MFS, metastasis-free survival; DFS, disease-free survival; CSS, cause-specific survival; PFS, progression-free survival; RFS, recurrence-free survival.

Strengths

This study has some strengths. Almost all the articles with survival consequences in CRC patients with disparate miRNAs were searched. Furthermore, the current expression profile of miRNAs is explicitly detailed in Tables 1 and 2 according to miRNAs and types of detected samples (blood or tissue). Papers assessing at least one of the survival curves of OS, CSS, DFS, RFS, PFS, and MFS were eventually included, and papers covering merely HRs or 95% CIs without any of the survival curves were excluded. Meta-analyses were performed on miRNAs investigated five or more times in CRC tissues. Virtually all the studies included had sample sizes ≥30 (except two),[70,111] reinforcing the usability and enlarging the feasibility of consequences to CRC patients.

Limitations

Nevertheless, we cannot overemphasize the following limitations. There was much heterogeneity in designs of studies, and most of the outcomes from our meta-analyses contained high heterogeneity (I^2≥50%). Statistical assessment of publication

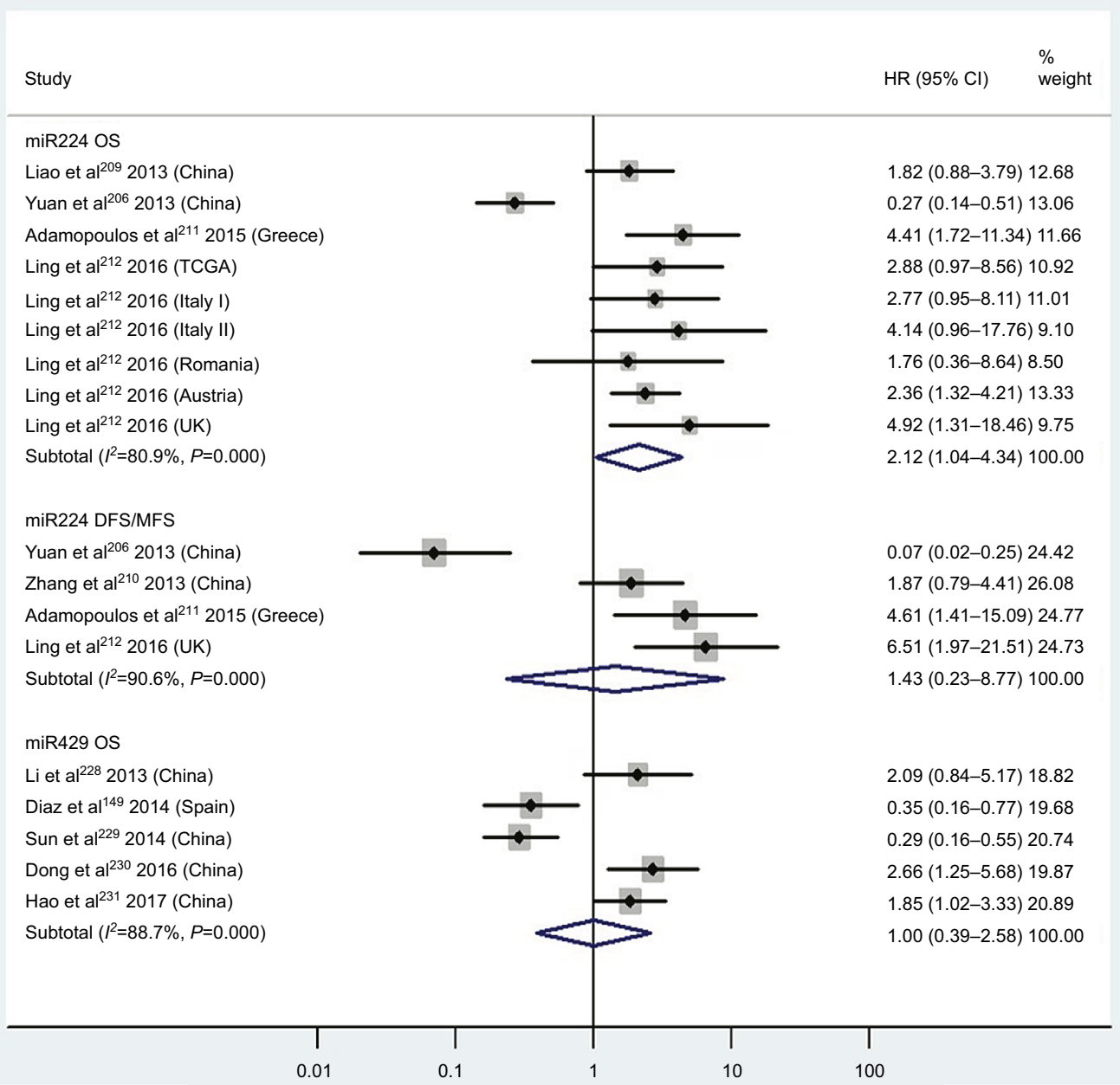

Figure 8 Pooled analyses of OS or DFS/MFS in association with high tissue miR224- and miR429-expression levels. Weights are from random-effects analysis.
Abbreviations: OS, overall survival; TCGA, the Cancer Genome Atlas; DFS, disease-free survival; MFS, metastasis-free survival.

bias was suboptimal. There existed differences among the studies, including tissue-detected (frozen or formalin-fixed, paraffin-embedded), blood (plasma or serum), tumor stage (I–IV), cutoff values, and miRNA methods. The present meta-analysis simply included papers published in English, perhaps excluding potential studies published in other languages with respect to miRNA level and prognosis of CRC patients. Papers covering only HRs or 95% CIs without survival curves were excluded, lowering the sample sizes of the papers included. Because of the massive interrelation between papers and data about CRC, we subjectively and selectively included specific studies on the basis of the inclusion and exclusion criteria, bringing about the omission of several possible miRNAs with prognostic value and a relatively small number of included studies. The studies included contained three types of cancers (colon and rectal cancer and CRC), which blurred the division between tumor types. Some blood miRNAs were from cell-free RNA, while others were from exosome isolates. These were considered the same to some degree and may have caused some deviations in the final results.

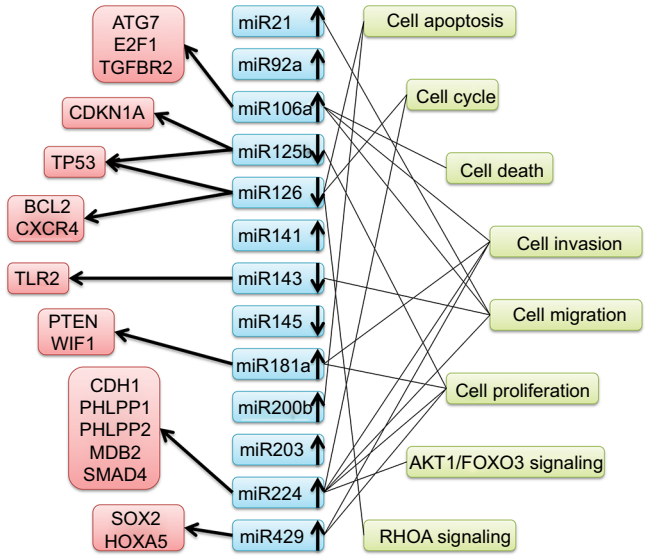

Figure 9 Summary of microRNAs with altered expression and potential targets and pathways entered in this study.
Abbreviations: ATG7, autophagy related 7; E2F1, E2F transcription factor 1; TGFBR2, transforming growth factor beta receptor 2; CDKN1A, cyclin dependent kinase inhibitor 1A; TP53, tumor protein p53; BCL2, apoptosis regulator; CXCR4, C-X-C motif chemokine receptor 4; TLR2, toll like receptor 2; PTEN, phosphatase and tensin homolog; WIF1, WNT inhibitory factor 1; CDH1, cadherin 1; PHLPP1, PH domain and leucine rich repeat protein phosphatase 1; PHLPP2, PH domain and leucine rich repeat protein phosphatase 2; MBD2, methyl-CpG binding domain protein 2; SMAD4, SMAD family member 4; SOX2, SRY-box 2; HOXA5, homeobox A5; AKT1, AKT serine/threonine kinase 1; FOXO3, forkhead box O3; RHOA, ras homolog family member A.

Implications for prospective clinical and scientific study

It should be mentioned that the current meta-analysis is the first system assessment of the pertinence of miRNA level to the prognosis of CRC patients. This study presents foundations for prospective clinical and scientific study with respect to clinical staff and other health care providers, for whom simultaneous determination of miRNA expression is able greatly to reinforce assessment of life expectancy of CRC patients, thus enabling prompt therapy, and for scientific researchers. Current research progress and trends in connections between miRNAs and prognosis of CRC patients are shown in Tables 1 and 2. Selectively basic experiments can be conducted using these details (Figure 9). Conflicting results on the prognosis of miRNAs may be addressed based on the present meta-analysis.

Conclusion

In general, blood miR141 and tissue miR21, miR181a, miR224, and miR126 have significant prognostic value. Among these, blood miR141 and tissue miR224 are strong biomarkers of prognosis in CRC.

Author contributions

All authors contributed toward data analysis, drafting and critically revising the paper and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

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