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SYSTEMATIC REVIEW

Current Evidence on miRNAs as Potential Theranostic Markers for Detecting Chemoresistance in Colorectal Cancer: A Systematic Review and Meta-Analysis of Preclinical and Clinical Studies

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Abstract

Background Findings from observational clinical studies examining the relationship between biomarker expression and theranosis in colorectal cancer (CRC) have been conflicting.

Objective We conducted this systematic review and meta-analysis to summarise the existing evidence to demonstrate the involvement of microRNAs (miRNAs) in chemoresistance and sensitivity in CRC through drug genetic pathways.

Methods Using PRISMA guidelines, we systematically searched PubMed and Science Direct for relevant studies that took place between 2012 and 2017. A random-effects model of meta-analysis was applied to evaluate the pooled effect size of hazard ratios (HRs) across the included studies. Cochran's Q test and the I^2 statistic were used to detect heterogeneity. A funnel plot was used to assess potential publication bias.

Results Of the 4700 studies found, 39 studies comprising 2822 patients with CRC met the inclusion criteria. The included studies used one or a combination of 14 chemotherapy drugs, including 5-fluorouracil and oxaliplatin. Of the 60 miRNAs, 28 were associated with chemosensitivity, 20 with chemoresistance, and one with differential expression and radiosensitivity; ten miRNAs were not associated with any impact on chemotherapy. The results outline the importance of 34 drug–regulatory pathways of chemoresistance and sensitivity in CRC. The mean effect size was 0.689 (95% confidence interval 0.428–1.110), indicating that the expression of miRNAs decreased the likelihood of death by about 32%.

Conclusion Studies have consistently shown that multiple miRNAs could act as clinical predictors of chemoresistance and sensitivity. An inclusion of supplementary miRNA estimation in CRC routine practice needs to be considered to evaluate the efficacy of chemotherapy after confirming our findings with large-scale prospective cohort studies.

PROSPERO registration number CRD42017082196.

Key Points

This is the first comprehensive systematic review to define the impact of microRNAs (miRNAs) in chemoresistance in colorectal cancer.

Our results aid in comparing the association of drug-related genetic pathways with chemoresistance in colorectal cancer.

This review highlights the critical role of biomarkers involved in colorectal cancer and will help determine their possible role in diagnosis and prognosis.

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s40291-019-00381-6) contains supplementary material, which is available to authorized users.

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1 Introduction

Colorectal cancer (CRC) is the third most common cancer in men, with 746,000 cases annually, and is the second most common in women, with 614,000 cases per year worldwide [1]. The conventional modalities of treatment for CRC include surgery [2], chemotherapy [3], radiation therapy [4], immunotherapy [5], targeted therapy [6], and precision medicine [7]. The commonly used chemotherapy drugs and monoclonal antibodies (mAbs) to treat CRC are 5-fluorouracil (5-FU) [8], oxaliplatin [9], cisplatin [10], doxorubicin [11], leucovorin [12], paclitaxel [13], mitomycin C (MMC) [14], tumour necrosis factor-related apoptosis-inducing ligand (TRAIL) [15], deoxycholic acid (DCA) [16], thapsigargin (Tg) and trichostatin A (TSA) [17], irinotecan [18], cetuximab [19], panitumumab, and bevacizumab [20]. However, chemoresistance is a significant hindrance to successful treatment in many CRC cases [21–23], and acquired drug resistance occurs with 90% of metastatic cancer [24]. Despite advances in treatment methods, the 5-year survival rate is 12.5% [24].

The involvement of microRNAs (miRNAs) in chemoresistance is associated with poor prognosis in several cancers [25–31]. Therefore, identification of biomarkers to detect possible chemoresistance in individual cases is a significant step towards specialised or personalised cancer treatment [32]. Emerging evidence has revealed that miRNAs can be considered as minimally invasive biomarkers useful for prognosis and as theranostic targets for monitoring treatment response (theranosis) [33]. Chemoresistance in CRC is mediated by the expression of a few specific miRNAs through drug-regulatory pathways [34, 35]. Both miRNA-19b and -21 were found to influence chemoresistance to 5-FU in human colon cells (DLD-1 and KM12C) [36]. 5-FU triggers A-disintegrin and metalloprotease domain-17 (ADAM-17), which causes growth factor shedding and growth factor receptor activation, leading to chemoresistance in CRC, which was found to be profoundly influenced by miRNA-222 [37, 38]. These drug-regulatory genes have been found to regulate cellular transformation and are influenced by miRNA expression [39].

Huang et al. [40] analysed 12 miRNAs (134, 146a, 17-3p, 181d, 191, 221, 222, 223, 25, 29a, 320a, and 92a) in plasma samples of both patients with CRC and healthy patients and found that levels of miRNA-29a and miRNA-92a were significantly higher in cancer tissues. miRNA was consistently upregulated in patients with CRC, with 21 of 30 patients expressing high levels throughout the 50 months of the post-treatment follow-up period [40]. The investigation of 5-FU resistance in 88 patients with CRC revealed that miRNA-10b expression was significantly higher in cancer tissues than in normal tissues and was connected to lymphatic invasion and poor prognosis, thus indicating miRNA-10b expression as a potential indicator of chemoresistance [41].

Cancer invasiveness and an increase in resistance to oxaliplatin and cisplatin were observed in both in vitro and in vivo studies; this mechanism was mediated by forkhead transcription factor forkhead box O3a (FOXO3a) and miRNA-induced metalloprotease enzyme, which indirectly promotes invasion [42]. Preclinical and clinical observational studies demonstrated that miRNA expression profiling could help to identify high-risk patients with CRC who may develop chemoresistance. Therefore, a comprehensive systematic review and meta-analysis was sought to review the published studies on miRNA-mediated chemoresistance in CRC (refer to the Electronic Supplementary Material [ESM] for the rationale of the study).

2 Methods

This systematic review and meta-analysis followed the 2015 PRISMA (Preferred Reporting Items for Systematic Review and Meta-analysis) guidelines [43] and was conducted following a previously established protocol (PROSPERO registration number: CRD42017082196).

2.1 Search Strategy and Selection Criteria

We searched the PubMed and Science Direct databases on October 2017 from 1 January 2012 to 25 October 2017, restricting the search to papers in the English language and to the last 5 years so the use of chemotherapeutic drugs was relatively current. The literature search was performed using the Medical Subject Heading (MeSH) search terms miRNA or microRNA, chemoresistance/sensitivity, and colorectal cancer in combination. The search strategy is presented in Table 1 in the ESM. We also manually searched the reference lists of all included publications for additional relevant studies. The titles and abstracts of all relevant studies were carefully examined and screened before full-text articles were retrieved. All search results were collated in a reference manager database (EndNote) to avoid duplication. Eligible studies had to meet the following inclusion criteria: involved miRNA and CRC, involved both clinical samples and in vitro preclinical analyses for patients with CRC, focused on resistance to CRC therapy, reported miRNA profiling platforms, and reported the genes or pathways involved in chemoresistance or sensitivity. We excluded the following: studies in languages other than English; reviews, editorials, opinions, case studies, and reports; unpublished materials, uninterpretable data, conference proceedings, or thesis; studies focusing only on long non-coding (lnc) RNA, and studies involving *Fusobacterium nucleatum* and its association with CRC chemoresistance.

Table 1 Description of the 39 included studies

Study	Patient information		Chemotherapy	Clinical stages	Patients (*N*)	Samples (*N*; cancer/normal)	Cell lines	miRNA	miRNA profiling platform	Pathways associated/gene
	Country (ethnicity)	Sex (M/F)								
Su et al. [17]	USA (White)	NR	Tg and TSA	NR	10	10[a]	Normal fibroblast LD419, UROtsa, NK2464, C42B, UM-UC-3, J82, HCT-116, HL-60	30d, 181a, 199a-5p	MiRNA Taqman assays (Applied Biosystems, Foster City, CA, USA)	78-kDa glucose-regulated protein (GRP78)
Zhang et al. [42]	UK (White British)	NR	Cisplatin and OHP	4 (stages 1–4)	100	100[a]	SW620, HCT116, DLD-1, HT29, SW480, COLO205, Caco-2	153	One-colour mirVana miRNA Bioarrays V2 (Applied Biosystems)	Forkhead transcription factor Forkhead box O3a (FOXO3a)
Cheng et al. [85]	China (Asian)	NR	5-FU and OHP	NR	20	20/20	NCM460, HT-29, Caco-2, DLD-1, SW480, SW620	219-5p	One Step PrimeScript miRNA cDNA synthesis kit (D350A; Takara, Otsu, Shiga, Japan)	Sal-like protein 4 (Sall-4) gene
Fu et al. [57]	China (Asian)	NR	5-FU	NR	26	26/26	HCT-116	20b	TaqMan microRNA reverse transcription kit (Applied Biosystems)	ADAM9/EGFR
Guo et al. [50]	China (Asian)	82/55	Cisplatin, 5-FU, and TRAIL	2 (stages 1–2, 3–4)	147	147/147	HCT-116, HCT-28, LoVo, Colon205, SW480, SW620, CRL-1831	15a,15b, 16, 195, 424, 497	miRNA microarray chip (Agilent Technologies, Inc.)	PI3K/Akt signalling and IGF1R
Li et al. [66]	China (Asian)	40/23	5-FU based (FOLFOX, FOLFIRI and 5-FU/LV)	3 (stages 2–4)–4	63	63/63	HT-29, HCT-116	218	PrimeScript RT reagent kit (Takara, Dalian, China)	Baculoviral IAP repeat-containing protein-5 (BIRC5)
Wang et al. [47]	China (Asian)	NR	5-FU	3 (stages 1, 2,& 3–4)	62	62/62	SW1116, HEK293T	497	TaqMan real-time PCR assay	Kinase suppressor of Ras 1 (KSR1)

Table 1 (continued)

Study	Patient information		Chemotherapy	Clinical stages	Patients (*N*)	Samples (*N*; cancer/normal)	Cell lines	miRNA	miRNA profiling platform	Pathways associated/gene
	Country (ethnicity)	Sex (M/F)								
Liu et al. [46]	China (Asian)	NR	Paclitaxel, 5-FU, and cisplatin	NR	10	10/10	CCD-18Co, CCD-33Co, LoVo, CaCo-2, T-84, SW480, DLD-1, NCI-N87, SKBR3, LNCaP, SK-MEL-30,,SW 1271, SKOV3	203	TaqMan microRNA reverse transcription kit and TaqMan microRNA assays kit (Applied Biosystems)	Salt-inducible kinase-2 (SIK-2)
Qian et al. [48]	China (Asian)	NR	OHP	3 (stage 1, 2, & 3–4)	113	175[a]	SW1116, HEK293T	143	PrimeScript RT Reagent Kit (Takara)	IGFIR
Sui et al. [49]	China (Asian)	19/11	OHP, MMC, and 5-FU	NR	210	30/30, whole blood from tumour (120) & healthy individuals (30)	HCT-8, HCT-116, SGC7901, Bel7402	200c	miRcute miRNA Isolation Kit (Tiangen, Co. Ltd.)	c-Jun N-terminal kinases (JNK2)/c-Jun signalling
Qu et al. [51]	China (Asian)	NR	Doxorubicin	4 (stages 1–4)	NR	NR	HT-29, LoVo	21, 22, 127, 137, 195, 592	SuperTaq Polymerase and a mirVana qRT-PCR miRNA Detection Kit (Ambion, Austin, TX, USA)	BCL2-Like 2 (BCL2L2)
Zhou et al. [52]	China (Asian)	57/17	(XELOX [capecitabine + OHP] or FOLFOX [5-FU, LV, OHP])	2 (stages 3–4)	74	74[a]	HCT-116	506	ImPro-II Reverse Transcriptase (Promega, Madison, WI, USA)	Multidrug resistance gene (MDR1)/P-glycoprotein (P-gp) expression
Huang et al. [53]	China (Asian)	NR	TRAIL	NR	110	30/30, 80 serum samples (40 CRC patients & 40 controls)	FHC, SW480, SW948, NCI-H508, HT-29	20a	stem-loop RT primer using the PrimeScript RT reagent kit (Takara, Dalian, China)	(BH3 interacting-domain) BID-BCL2
Kong et al. [54]	China (Asian)	23/17	DCA	2 (stages 1–2, 3–4)	40	40/40	HCT-8, human PCECs	199a-5p	mirVanaTM qRT-PCR miRNA detection kit (Ambion)	Cdk-Associated Cullin1 (CAC1)

Table 1 (continued)

Study	Patient information		Chemotherapy	Clinical stages	Patients (*N*)	Samples (*N*; cancer/normal)	Cell lines	miRNA	miRNA profiling platform	Pathways associated/gene
	Country (ethnicity)	Sex (M/F)								
To et al. [55]	China (Asian)	13/13	5-FU and irinotecan	2 (stages 3 & 4)	52	26/26	Human colon cell line S1, Caco-2, HT-29, SW620	519c	Stem-loopRT (Applied Biosystems)	ATP-binding cassette sub-family G member 2 (ABCG2)
Liu et al. [58]	China (Asian)	NR	5-FU	NR	31	31/31	HCT-8, LoVo	135b, 182	SYBR Green qRT-PCR master mix (Takara)	ST6GALNAC2 via PI3K/AKT pathway
Liu et al. [59]	China (Asian)	NR	5-FU	NR	24	24/24	HCT-116, HT-29	302a	PrimeScript RT reagent kit (Takara)	IGF1R, Akt signalling
Fu et al. [60]	China (Asian)	NR	OHP	NR	NR	NR	HEK293T, HCT-116	218	TaqMan miRNA reverse transcription kit and TaqMan Human miRNA assay kit	YEATS domain containing 4 (YEATS4)
Sun et al. [61]	China (Asian)	NR	OHP	NR	60	30[a] & 30 blood samples	HT-29	34a	mirVana miRNA Isolation Kit (Ambion)	TGF-β/ Small mothers against decapentaplegic-4 (Smad4) pathway
Shang et al. [65]	China (Asian)	21/17	5-FU + OHP + calcium folinate	4 (stages 1–4)	38	38[a]	HC-116, HT-29	23a	Stem-loop reverse transcription	Apoptosis-activating factor-1 (APAF-1)/caspase-9 apoptotic pathway
Li et al. [67]	China (Asian)	NR	5-FU and OHP	NR	258	204/54	HT-29, HT-116, SW480, SW620, RKO, COLO205, Ls174T, LoVo	139-5p	PrimeScriptTM RT Master Mix (Perfect Real Time) Kit (RR036A, Takara, China)	BCL-2
Liu et al. [68]	China (Asian)	10/10	5-FU	4 (stages 1, 2, 3, & 4)	30	30[a]	HCT-116, LoVo, HCT-8	139-5p	Stem-loop qRT-PCR assays	Neurogenic locus notch homolog protein 1 (NOTCH-1)
Fang et al. [70]	China (Asian)	153/142	5-FU	2 (stages 1–2, 3–4)	295	295[a]	COLO205 (CCL-222), SW480 (CCL-228)	7,17-5p,19b, 20a, 93, 592	One-step PrimeScript miRNA cDNA Synthesis Kit (Takara)	Phosphatase and tensin homolog (PTEN)

Table 1 (continued)

Study	Patient information		Chemotherapy	Clinical stages	Patients (*N*)	Samples (*N*; cancer/normal)	Cell lines	miRNA	miRNA profiling platform	Pathways associated/gene
	Country (ethnicity)	Sex (M/F)								
Rasmussen et al. [71]	Denmark (Danes)	20/6	OHP/5-FU (XELOX/FOLFO)	NR	26	26[a]	HCT-116, LoVo	27b, 181b, 625-3p	miRCURY Human panel I and II V.2 (Exiqon) real-time PCR platform	NR
	NR	54/40	Irinotecan (XELIRI/FOLFIR)	NR	94	94[a]				NR
	Denmark (Danes)	61/56	OHP-based treatment	2 (stages 2–3)	117	117[a]				NR
	Denmark, Poland, Australia (Danes, Polish, English)	28/18	OHP-based treatment	1 (stage 2)	46	46[a]				NR
Yin et al. [72]	China (Asian)	NR	OHP	4 (stages 1–4)	140	136/136	Caco-2, DLD-1, HCT8, HCT116, HT29, LoVo, SW480, SW620	204-5p	SYBR Premix Ex Taq (Takara)	RAB22A (member RAS oncogene family)
Suto et al. [73]	Japan (Asian)	62/43	Cetuximab	2 (stages 1–2, 3 & 4)	105	105/105	HCT-116, SW480, HT-29	7/RNU6B	Specific stem-loop reverse transcription primers (Applied Biosystems)	EGFR and v-raf-1 murine leukemia viral oncogene homolog 1 (RAF-1)
Han et al. [74]	China (Asian)	17/15	5-FU	2 (stages 1–2, 3– 4)	32	32/32	LoVo, SW1116, SW480, HCT116, NCM460	874	miScript reverse transcription kit (Qiagen, Germany)	X-linked inhibitor of apoptosis protein (XIAP)
Wang et al. [117]	China (Asian)	34/16	NR	4 (stages 1–4)	50	50/50	HEK 293, HCT116, LOVO, LS174T, SW480, CCD-18Co	552, 592	Stem-loop RT-PCR method	ADAM28
Wang et al. [118]	China (Asian)	NR	5-FU	NR	30	15/15	HCT-116, 293TN	Lin28A	SYBR Green PCR Mix (BIORESEARCHER, Beijing, China)	H2A histone family, member X (H2AX)

Table 1 (continued)

Study	Patient information		Chemotherapy	Clinical stages	Patients (*N*)	Samples (*N*; cancer/normal)	Cell lines	miRNA	miRNA profiling platform	Pathways associated/gene
	Country (ethnicity)	Sex (M/F)								
Zhang et al. [98]	China (Asian)	NR	Radiotherapy (10 Gy) and chemotherapy	NR	24	24/24	SW480, SW620, LoVo, HCT-116, LS-174T, HT29	124	qSYBR-green-containing PCR kit (GenePharma, Shanghai, China).	Paired related homeobox 1 (PRRX1)
Lu et al. [119]	China (Asian)	35/22	5-FU, cisplatin, OHP, and paclitaxel	2 (stages 1–2, 3– 4)	57	57[a]	HCT-116, SW480, RKO, DLD1, LS174T, Caco2, HCT-8, HT-29, LoVo, SW620	128	SYBR Green detection (Applied Biosystems)	Galectin-3
Karaayvaz et al. [120]	Germany (Deutsche)	NR	5-FU	NR	22	22/22	HCT-116, RKO, SW480	129	TaqMan Gene Expression Assay (Applied Biosystems)	BCL-2
		NR	NR	4 (stages 1–4)	61	31 /30				
Ye et al. [121]	China (Asian)	NR	5-FU and OHP	NR	8	8[a]	Human colon cancer cell line, HT-29, SW620	141	Affymetrix miRNA array (Affymetrix GeneChip miRNA 2.0 array; Affymetrix, Inc., Santa Clara, CA, USA)	Cyclin D2
Han et al. [122]	China (Asian)	39/25	OHP and 5-FU	2 (stages 1–2, 3–4)	64	64/64	HCT116, SW480	181a-5p	SYBR PrimeScript™ miRNA RT-PCR Kit (Takara Biotech)	Wnt/β-catenin, colorectal neoplasia differentially expressed (CRNDE)
Wan et al. [123]	China (Asian)	NR	5-FU, OHP and 2 Gy radiation	NR	50	50/50	HCT-116, HT-29	320	qPCR SuperMix (Invitrogen, USA)	Forkhead box protein M1 (FOXM1)
Tan et al. [124]	China (Asian)	NR	OHP	NR	30	20/10	LoVo, HCT-116, DLD-1, SW480, HT-29, RKO, FHC, CCD-18Co	409-3p	TaqMan microRNA reverse transcription kit (Applied Biosystems)	Beclin-1 mediated autophagy
Jin et al. [125]	China (Asian)	NR	5-FU	NR	40	40/40	SW480, SW620, HT-29, HT-116	450b-5p	TaqMan miRNA assays (Applied Biosystems)	Sex determining region Y-box 2 (SOX-2)

Table 1 (continued)

Study	Patient information		Chemotherapy	Clinical stages	Patients (*N*)	Samples (*N*; cancer/normal)	Cell lines	miRNA	miRNA profiling platform	Pathways associated/gene
	Country (ethnicity)	Sex (M/F)								
Amankwatia et al. [126]	UK (White British)	18/23	5-FU, OHP, and irinotecan	4 (stages 1–4)	41	53[a]	HCT-116, NIH3T3 embryonic fibroblast cell line	224	7900 TaqMan real-time system (Applied Biosystems)	Kirsten RAS (KRAS)-dependent and independent
Zhou et al. [56]	China (Asian)	NR	Cetuximab	NR	12	9/3	HT-29, SW480, SW620, Caco-2, HCT-116	133b	SYBR-Green qPCR assay (Takara Bio, Inc.)	EGFR

ADAM A disintegrin and metalloprotease, *BCL-2* B-cell lymphoma 2, *cDNA* complementary DNA, *CRC* colorectal cancer, *DCA* deoxycholic acid, *EGFR* epidermal growth factor receptor, *F* female, *IGF1R* insulin-like growth factor-1 receptor, *LV* leucovorin, *M* male, *miRNA* microRNA, *MMC* mitomycin C, *NR* not reported, *OHP* oxaliplatin, *PCECs* primary colonic epithelial cells, *PCR* polymerised chain reaction, *PI3K/Akt* phosphatidylinositol 3-kinase/protein kinase B, *qPCR* quantitative polymerised chain reaction, *RT-PCR* reverse transcription polymerase chain reaction, *Tg* thapsigargin, *TGF* transforming growth factor, *TRAIL* tumour necrosis factor-related apoptosis-inducing ligand, *TSA* trichostatin A, *5-FU* 5-fluorouracil

[a]Total samples

2.2 Data Extraction and Quality Assessment

Two authors (RJ and MRM) independently evaluated and extracted the data from the screened articles using the selection criteria. Corresponding authors were contacted for supplementary materials if any necessary data were unavailable from the full text. Any disagreements between reviewers were resolved through discussion between the authors or by team decision or by consultation with the third reviewer (CK). The following data were collected and recorded for each study: first author and year of publication, patient information, location of the study, sex, ethnicity, tumour stage, number of samples, lymph node metastasis/nodal status, cell lines used, miRNAs involved, miRNA profiling platform, chemotherapy drugs used, drug-regulatory pathways, and associated genes. We described the effect size of the prognosis using the hazard ratio (HRs) and 95% confidence interval (CI) of survival of patients with CRC.

Two investigators (RJ and MRM) independently assessed each study for methodological quality using the MOOSE (Meta-analysis Of Observational Studies in Epidemiology) checklist by the Dutch Cochrane Centre [44]. A study checklist with predefined criteria prepared from the MOOSE study criteria list was used to assess the methodological quality of the studies included in the systematic review.

2.3 Statistical Analysis

Reporting of the sections, meta-analysis, subgroup analysis, and publication bias follows guidelines from the *Meta-analysis concepts and applications workshop manual* by Michael Borenstein. We used the Comprehensive Meta-Analysis (CMA) software (version 3.0, USA) to analyse the HRs and 95% CIs. The survival data, in the form of Kaplan–Meier curves, were transformed into HRs and 95% CIs. The forest plot was generated with combined outcome data to elucidate the clinical outcome effects of patient survival in CRC. Heterogeneity was obtained using Cochran's Q test and Higgins I^2 statistic [45]. Z-statistics were generated to analyse the standard deviations from the mean of all included studies if the pooled study results deviated. We used the subgroup analysis to compare the effect size in studies that employed a high expression and low expression of miRNAs.

2.4 Publication Bias

The inverted funnel plot depicts the level of publication bias. Publication bias was quantified using Egger's bias indicator test, the Orwin and classic fail-safe N test, the Begg and Mazumdar rank collection test, and Duval and Tweedie's trim-and-fill calculation.

3 Results

3.1 Study Search and Characteristics

The initial search yielded 4700 studies. By implementing the search strategy, we identified a total of 2450 studies from PubMed ($n = 200$) and Science Direct ($n = 2250$) (Fig. 1). After removing duplicates, 163 potentially eligible studies were scrutinised for selection criteria. Crosschecking the existing reference lists of narrative and systematic reviews revealed no further relevant articles. Careful review of the 163 articles against the PRISMA guidelines identified 43 full-text studies that contained available data items. Of these 43, four were excluded because three studies evaluated lnc RNA expression in CRC and one investigated the association between *F. nucleatum* and CRC chemoresistance. We identified 39 studies involving 2822 patients with CRC, eligible for our systematic review. Seven studies were ultimately included in the meta-analysis.

Table 1 provides the main characteristics of the 39 included studies. The study period of the included studies was between 1999 and 2015. The most commonly used chemotherapy agents were 5-FU and oxaliplatin. Frozen CRC tissue samples were used in 23 studies, and four studies used formalin-fixed paraffin-embedded (FFPE) tissues; 17 studies did not specify the sampling type. A total of 3868 CRC tissue samples and 231 blood samples were included for analysis, 94 in stage I, 312 in stage II, 548 in stage III, and 114 samples in stage IV. Furthermore, 228 samples were observed from stage I to II, and 342 samples from stage III to IV. miRNA expression was analysed via microarray in a few studies, and all 39 studies used reverse transcription polymerase chain reaction (RT-PCR) for miRNA expression profiling.

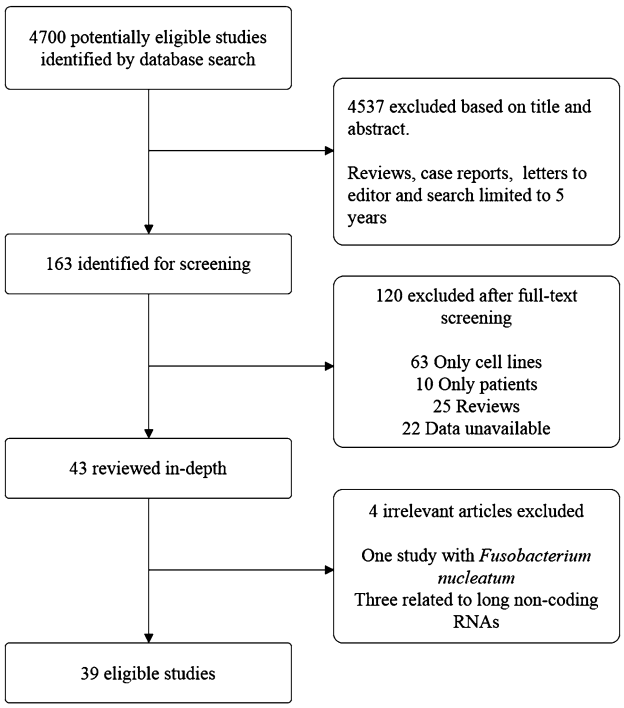

Fig. 1 Flowchart of the literature study process and selection

3.2 Preclinical Investigation of MicroRNA (miRNA) Expression

In total, 39 studies reported a total of 40 cell lines utilised in the in vitro analysis to evaluate miRNA expression and its association with drug-regulatory genetic pathways. Figure 1 in the ESM presents the number of studies illustrating the most common assays. The most common cell lines were HCT-116, HCT-29, LoVo, SW480, and SW620. HCT-116 was used in 27 studies. The highest number of cell lines used in a single study was 13 [46]. The in vivo and in vitro assays from the studies included in our systematic review were the MTT/cell viability assay, luciferase assay, cell proliferation, western blotting, chemotherapy sensitivity assay, cell migration, cell invasion, apoptotic assay, clonogenic assay, tumorigenesis, colony formation, caspase-3 assay, BrdU assay, and radiosensitivity assay.

3.3 Clinical Investigation of miRNA Expression

3.3.1 Association Between miRNA Expression and Chemoresistance/Chemosensitivity

Of 60 miRNAs reported in the systematic review, 34 were downregulated and 24 were upregulated in patients with CRC (Fig. 2). Five upregulated miRNAs were associated with chemosensitivity, and 13 upregulated miRNAs were associated with chemoresistance. Similarly, 22 downregulated miRNAs were associated with chemosensitivity, and six downregulated miRNAs were associated with chemoresistance. Our report showed that miRNA-224 was differentially expressed and not related to either chemoresistance or sensitivity. Overall, the role of these miRNAs was investigated individually, as enhancers of chemoresistance ($n = 20$ miRNAs) or chemosensitivity ($n = 28$ miRNAs). We observed five miRNAs that were predominantly studied in ten different studies, with all being downregulated in patients with CRC. The internal control used was glyceraldehyde 3-phosphate dehydrogenase (GAPDH) (ten studies) and U6 small nuclear RNA (U6 snRNA) (27 studies) for normalising the expression of miRNAs in the pooled studies. Some studies used both GAPDH and U6 snRNA.

3.4 Colorectal Cancer (CRC) Chemotherapy

Information about the CRC chemotherapy was available for 2822 patients across 37 studies. The included studies

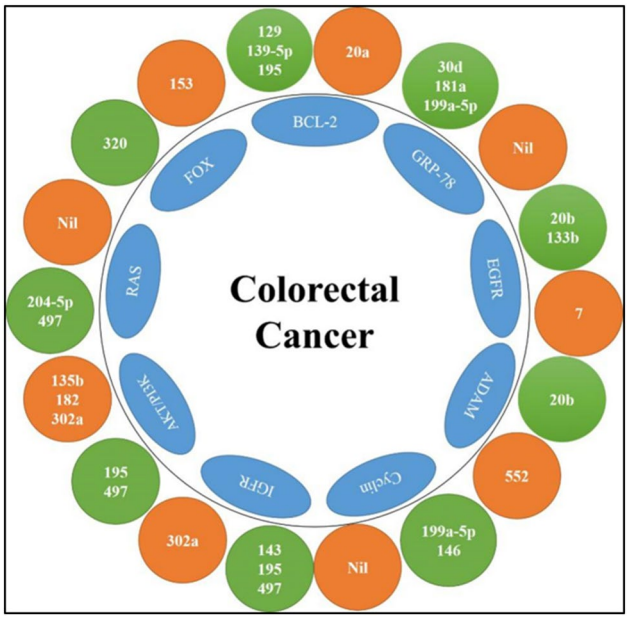

Fig. 2 Nine hallmarks of colorectal cancer chemotherapy BCL-2, GRP-78, EGFR, ADAM, cyclin, IGFR, AKT/PI3K, RAS, and FOX. Each hallmark shows specific miRNA that influences particular cellular function in CRC; some miRNAs control more than one hallmark, indicating multiple pathways regulated by them. Orange colour refers upregulated miRNAs; green colour indicates downregulated miRNAs. *BCL-2* B-cell lymphoma-2, *GRP-78* glucose-regulated protein 78 kDa, *EGFR* epidermal growth factor receptor, *ADAM* A disintegrin and metalloproteinase domain, *IGFR* insulin-like growth factor 1 receptor, *AKT/PI3K* protein kinase B/phosphoinositide 3-kinase, *FOX* forkhead box

used a total of 14 drugs and their combinations, including 5-FU (1404 patients) [47], oxaliplatin (890 patients) [48], mitomycin C (180 patients) [49], cisplatin (314 patients) [50], doxorubicin (number of patients not reported) [51], leucovorin (137 patients) [52], paclitaxel (67 patients) [46], TRAIL (257 patients) [53], DCA (40 patients) [54], irinotecan (173 patients) [55], capecitabine (74 patients) [52], cetuximab (117 patients) [56], and thapsigargin (Tg) and TSA (ten patients) [17]. Of the 14 chemotherapy drugs studied individually and in combinations, 5-FU [57–59] was the most studied, followed by oxaliplatin [60, 61]. 5-FU is a non-specific drug treatment for all types of cancers [47, 62–64] and is also used in combination with oxaliplatin [65], leucovorin, and irinotecan [66]. The four studies investigated miRNA-139-5p [67, 68] and -497 [47, 50] twice in 5-FU treatment, whereas the remaining miRNAs were studied with other chemotherapy only once. Studies using cohort populations in the USA and China indicated a correlation between chemoresistance to 5-FU and increased miRNA-21 expression [69].

3.5 CRC Chemoresistance and Drug-Regulated Genetic Pathways

In the 39 studies, 34 unique miRNA-mediated drug-regulatory pathway-associated genes were reported (Fig. 2). We collated the drug-regulated gene pathways in CRC, with epidermal growth factor receptor (EGFR) ($n = 3$), phosphatidylinositol 3-kinase/protein kinase B (PI3K/AKT) ($n = 2$), ADAM ($n = 2$), B-cell lymphoma 2 (BCL-2) ($n = 3$), and insulin like growth factor 1 receptor (IGF1R; $n = 7$) being the most common pathways explored.

Tables 2 and 3 present the upregulation and downregulation of miRNAs contributing to chemosensitivity and resistance in patients with CRC through drug-regulated genetic pathways.

Table 2 Genetic pathways involving colorectal cancer chemoresistance

Downregulated			Upregulated		
Drugs	miRNA	Pathway	Drugs	miRNA	Pathway
5-FU	181a-5p	Wnt/β-Catenin/CRNDE	5-FU	7	PTEN
	497	KSR1/IGF/AKT		17-5p	PTEN
	519c	ABCG2		19b	PTEN
	181a-5p	Wnt/β-Catenin/CRNDE		93	PTEN
OHP	34a	TGF-β/Smad4		135b	PI3K/AKT
	181a-5p	Wnt/β-Catenin/CRNDE		182	PI3K/AKT
TRAIL	497	IGF/AKT	OHP	27b	NR
Cisplatin	497	IGF/AKT		153	FOXO3a
Irinotecan	519c	ABCG2		181b	NR
				625-3p	NR
			TRAIL	20a	BID-BCL2
			Cisplatin	153	FOXO3a
			Doxorubicin	592	NR

miRNA microRNA, *NR* not reported, *OHP* oxaliplatin, *PI3K/Akt* phosphatidylinositol 3-kinase/protein kinase B, *TGF* transforming growth factor, *TRAIL* tumour necrosis factor-related apoptosis-inducing ligand, *5-FU* 5-fluorouracil

Table 3 Genetic pathways involving colorectal cancer chemosensitivity

Downregulated			Upregulated		
Drugs	miRNA	Pathways	Drugs	miRNA	Pathways
5-FU	20b	ADAM 9/EGFR	5-FU	23a	APAF-1
	128	Galectin-3		218	BIRC5
	129	BCL-2		Lin28A	H2AX
	139-5p	NOTCH-1/BCL-2	Cetuximab	7	EGFR
	141	Cyclin D2	Doxorubicin	592	NR
	195	BCL-2			
	200c	C-Jun			
	203	SIK-2			
	219-5p	Sall-4			
	302a	IGF1R			
	320	FOXM1			
	506	MDR-1/P-gp			
	874	XIAP			
OHP	128	Galectin-3			
	139-5p	NOTCH-1/BCL-2			
	141	Cyclin D2			
	143	IGF1R			
	181a	GRP78			
	200c	C-Jun			
	204-5p	RAB224			
	218	YEATS-4			
	219-5p	Sall-4			
	320	FOXM1			
	409-3p	Beclin-1 mediated autophagy			
	506	MDR-1/P-gp			
Cisplatin and paclitaxel	128	Galectin-3			
	203	SIK-2			
Cetuximab	133b	EGFR			
TRAIL	195	BCL-2			
DCA	199a-5p	CAC1			
MMC	200c	C-Jun			
Tg & TSA	30d	GRP78			
	199a-5p	GRP78			

ADAM A disintegrin and metalloprotease, *BCL-2* B-cell lymphoma 2, *DCA* deoxycholic acid, *EGFR* epidermal growth factor receptor, *IGF1R* insulin-like growth factor-1 receptor, *miRNA* microRNA, *MMC* mitomycin C, *OHP* oxaliplatin, *Tg* thapsigargin, *TRAIL* tumour necrosis factor-related apoptosis-inducing ligand, *TSA* trichostatin A, *5-FU* 5-fluorouracil

3.6 Meta-Analysis

3.6.1 Does miRNA Expression Affect Survival of Patients with CRC?

HRs and 95% CIs were explicitly reported in only four [42, 70–72] of the 39 studies and could be estimated from three studies [66, 71, 73] covering a total of 697 patients with CRC (Fig. 3). The mean effect size was 0.689, indicating that the expression of miRNAs decreased the likelihood of death by about 32%. The 95% CI for the HR was 0.428–1.110, which tells us the mean HR in the universe of studies could fall anywhere in this range.

Similarly, the Z value for test null hypothesis (that the mean risk ratio is 1.0) was -1.531, $p = 0.126$. Therefore, we can reject the null that the risk of an event is the same in both upregulated and downregulated groups and conclude that the risk is higher in the upregulated group.

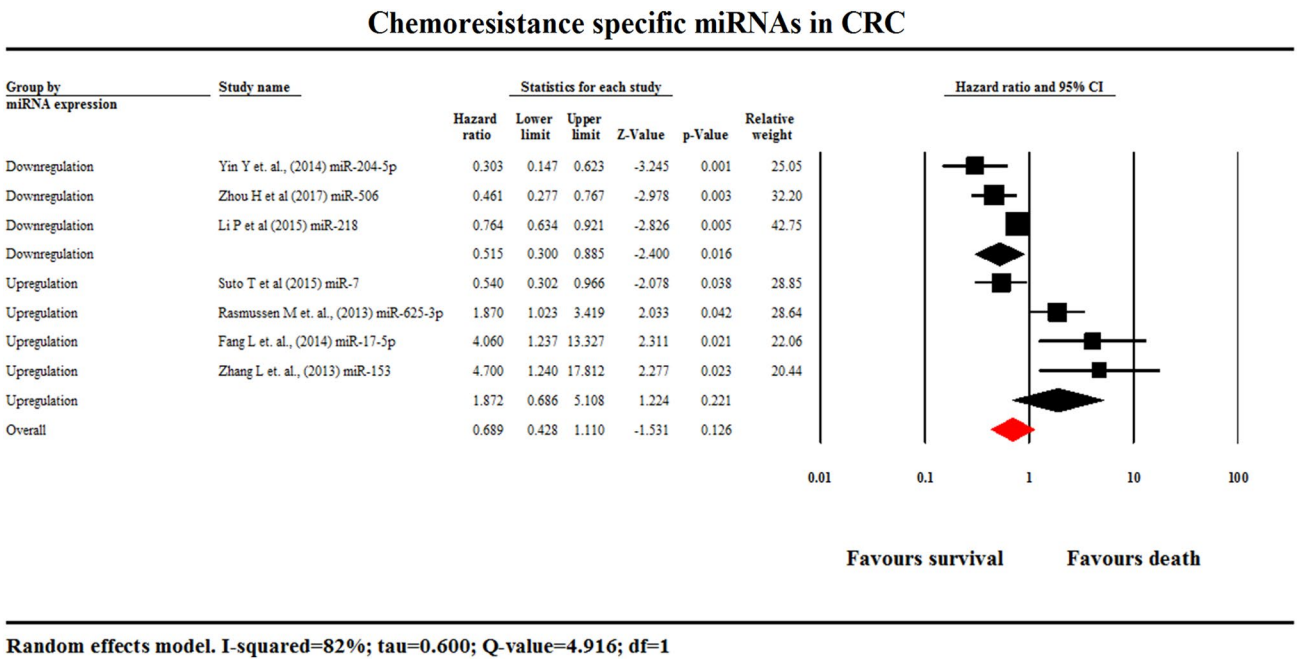

Fig. 3 Forest plot of pooled hazard ratio values from studies correlating the overall patient survival and miRNA expression with regards to chemotherapy. The pooled hazard ratios of hazard ratio values for colorectal cancer prognostic data were calculated and analysed using CMA software (version 3.3.070, USA). The red diamond represents the pooled effect estimate of survival for patients with colorectal cancer randomly assigned to miRNA evaluation. The black square line indicates the effect size of miRNA of the included studies with 95% confidence interval. The hazard ratio of 1 suggests no difference in survival risk of patients with colorectal cancer. A hazard ratio >1 indicates an increased risk of patients' survival, whereas a hazard ratio <1 suggests a reduced risk of patients' survival

3.6.2 How Much Does the Effect Size Vary Across Studies?

The Q value was 34.640, $df = 6$, $p = 0.000$. Since the observed variance falls within the range that can be attributed to sampling error, we cannot reject the null that the true effect size is the same in all studies. Here, I^2 was 82.679%. T^2 is the variance of true effect sizes (in log units). Here, T^2 was 0.360. T is the standard deviation of true effects (in log units). Here, T was 0.600.

3.6.3 Does the Effect Size Vary by Subgroup?

While the mean effect size across all studies is modest (HR 0.689), it is possible that the mean HR varies by subgroup. The mean HR in the upregulated and downregulated groups was 1.812 and 0.515, respectively. The Q value for the differences was 4.916, $df = 1$, $p = 0.027$. Therefore, there was no evidence that the HR varied according to survival of patients with CRC.

3.7 Publication Bias

Figure 4 presents the funnel plot correlating overall patient survival and miRNA expression with regards to chemotherapy.

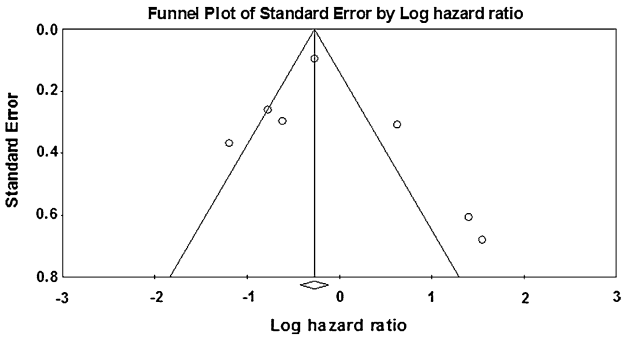

Fig. 4 Funnel plot of studies correlating the overall patient survival and miRNA expression with regards to chemotherapy. *Dots* represent the individual study; two studies on the bottom and three studies on the left-hand side of the plot. Given most of this area contains regions of high significance, publication bias would be unlikely to cause that asymmetry. This would reflect the fact that smaller studies (which appear toward the bottom) are more likely to be published if they have larger than average effects, which makes them more likely to meet the criterion for statistical significance

3.7.1 Classic Fail-Safe N

This meta-analysis includes data from seven CRC studies, which yield a Z value of -1.70300 and a corresponding 2-tailed $p = 0.08857$. Since the combined result was not statistically significant, the fail-safe N was irrelevant.

3.7.2 Orwin Fail-Safe N

The criterion value must be set between the other two values for the Orwin fail-safe N to be computed. Here, the HR in observed studies was 0.689, which did not fall between the mean HR in the missing studies, so we could not calculate the Orwin fail-safe N.

3.7.3 Begg and Mazumdar Rank Correlation Test

In this case, Kendall's tau b (corrected for ties, if any) was 0.09524, with a 1-tailed *p* value (recommended) of 0.38195 or a 2-tailed *p* value of 0.76389 (based on continuity-corrected normal approximation).

3.7.4 Egger's Test of the Intercept

In this case, the intercept (B0) was 1.11103 (95% CI −2.98430 to 5.20636), with t=0.69738, $df = 5$. The 1-tailed *p* value (recommended) was 0.25833, and the 2-tailed *p* value was 0.51665.

3.7.5 Duval and Tweedie's Trim and Fill

This method suggests that two studies are missing (Fig. 2 in the ESM). Under the fixed-effects model, the point estimate for the combined studies was 0.76243 (95% CI 0.65272–0.89057). Using trim and fill, the imputed point estimate was 0.72164 (95% CI 0.61924–0.84096). Under the random-effects model, the point estimate for the combined studies was 0.92213 (95% CI 0.54705–1.55438). Using trim and fill, the imputed point estimate was 0.67177 (95% CI 0.39161–1.15234).

4 Discussion

Recent studies have demonstrated that specific miRNA expressions in CRC modulate chemosensitivity and resistance through regulation of drug-related genetic pathways [47, 58, 70, 74]. miRNA-mediated chemoresistance mechanisms in CRC have been explored in individual studies but have not been comprehensively characterised. Therefore, this systematic review and meta-analysis aimed to provide insights into miRNA expression patterns in the chemotherapy–drug mechanistic relationship as well as the regulation of genes associated with chemoresistance/sensitivity. This is the first systematic review to include different ethnic groups in various clinical settings.

Numerous studies have focused on the effect of miRNAs on chemoresistance, including in breast [75], cervical [76], colorectal [77], gastric [78], lung [79], oral [80], ovarian [81], pancreatic [82], prostate [83], and skin [84] cancers. Our systematic review showed that 60 miRNAs were upregulated as well as downregulated in CRC cell lines and tissues. Most of the studies investigated only one miRNA [47, 68, 85], whereas only seven studies focused on two or more miRNAs.

Previous reports have demonstrated crucial clinical functions of miRNAs that were consistent with our findings, particularly miRNA-21, which is used as a diagnostic and prognostic marker for several cancers, such as lung [86], breast [87] pancreas [88], CRC [89], and prostate [90]; miRNA-10b, -141, and -155 are used as diagnostic markers for lung cancer [91]; miRNA-143 is used as a diagnostic marker for CRC [92]; and, more importantly, miRNA-21 [93], -22 [94], -23a [95], -27b [96], -34a [97], -124 [98], and -135b [99] are being proposed as diagnostic markers in CRC. However, reports have also demonstrated conflicting expression patterns for miRNAs: miRNA-27a was found to be downregulated in one study [100] but upregulated in another [101].

Our systematic review highlights the importance of 34 drug-regulatory pathways, including the EGFR, IGF1R, and AKT/PI3K pathways, in CRC chemoresistance and susceptibility. Research has revealed that EGFR is involved in the prediction of overall survival and prognosis of cancers such as gastric [102], lung [103], head and neck cancer (HNC) [104], and CRC [105]. IGF1R plays an essential role in the regulation of cell proliferation, differentiation, and survival of tumour development [106] and has been well-studied in breast cancer [107], CRC [108], and prostate cancer [109]; it directly promotes angiogenesis via the PI3K/AKT pathway. Alternation in the PI3K pathway helps in identification of clinical outcomes in breast cancer [110], gastric cancer [111], CRC, and HNC [112]. The AKT pathway is a frequent target for lung cancer [113], breast cancer [110], CRC [114], and gastric cancer [115]. Our results highlighted the involvement of EGFR in increased chemosensitivity through miRNA-7, -20b, and -133b. Our results are consistent with another study on EGFR-targeted therapy [116]. Furthermore, miRNA-34a was observed as the direct target of Wnt signalling pathways, similar to other reports [39].

Our meta-analysis showed an overall pooled effect size could be a good predictor of patient survival. However, it is essential to note that we used only seven studies because insufficient data were reported in 32 studies. We noticed that several factors, including study strategy, inadequate information, and sample size might be responsible for the high level of heterogeneity.

4.1 Limitation and Strengths

Lack of statistical data in many included studies, including clinicopathological parameters, odds ratios (ORs), HR values, and quantitative data for various assays, limited our quantitative data synthesis. As the HR and CI values were

retrieved from Kaplan–Meier curves, there could be some marginal errors, as values were not reported explicitly in the articles. The heterogeneity and differences in study design between different studies could have restricted both the analysis and a clinical hypothesis. A solution to this issue in future studies evaluating miRNA as theragnostic biomarkers would be to perform large collaborative studies in patients with CRC in established clinical settings.

One of the strengths of our study is the detailed correlation of the specific miRNAs with the regulation of chemoresistance in CRC. The clinical sources for miRNA profiling were investigated in our study using different clinical samples, including tissue and plasma. This study may be useful as a repository tabulating the miRNA gene regulatory pathways and its associations with chemotherapy in CRC. Furthermore, this study will provide lists of potential miRNA targets that could help to detect early chemoresistance and sensitivity in patients during treatment, encouraging individualised treatment.

5 Conclusions

This comprehensive systematic review and meta-analysis of published studies from around the world indicates the associations between the molecular mechanisms of chemoresistance and specific miRNAs in CRC. We anticipate that the interpretation of the molecular mechanisms of miRNAs in CRC will lead to improvements in the theranosis-based cancer therapy and oligonucleotide drugs currently under development.

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Author Contributions RJ contributed to the conceptualisation, study design, search strategy, protocol development, and review by revising different versions. RJ, MRM, CK, SB, AG, NR and KMG provided input into the study design, supervision, ensured the absence of errors, and arbitrated in case of disagreement. MRM and CK engaged in initial searches to determine the feasibility and in the data collection, analysis, and drafting of the manuscript. All authors read and approved the final version of the manuscript.

Compliance with Ethical Standards

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