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

Song Gao1,*
Zhi-Ying Zhao2,*
Rong Wu1
Yue Zhang3
Zhen-Yong Zhang1

1Second Department of Clinical Oncology, Shengjing Hospital of China Medical University, 2School of Computer Science and Engineering, Northeastern University, Shenyang, 3First Clinical Medical College, Shandong University of Traditional Chinese Medicine, Jinan, China

*These authors contributed equally to this work

Correspondence: Yue Zhang
First Clinical Medical College, Shandong University of Traditional Chinese Medicine, 16369 Jinghai Road, Lixia, Jinan, Shandong 250014, China
Tel +86 531 6861 6426
Fax +86 531 8260 2948
Email zhangyue0811@hotmail.com

Zhen-Yong Zhang
Second Department of Clinical Oncology, Shengjing Hospital of China Medical University, 39 Huaxiang Road, Tiaoxi, Shenyang, Liaoning 110022, China
Tel +86 189 4025 7577
Fax +86 24 2384 2568
Email zhangzy@sj-hospital.org

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...
base pairing to partially complementary sites, predominantly in the 3′-untranslated areas of mRNAs.\textsuperscript{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.\textsuperscript{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\textsuperscript{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 if the point estimation was outside the 95% CI after removal from the analysis. 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 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) |
|------|-----|--------------|------|-----|--------------|------|-----|--------------|------|-----|--------------|
| let7a-5p | 1   | 31           | 34a-5p | 1   | 99           | 143  | 6   | 59, 112, 150–153 | 211  | 1   | 197          |
| let7a-2 | 1   | 32           | 34a   | 1   | 100          | 144  | 1   | 154           | 212  | 1   | 198          |
| let7a  | 1   | 33           | 92a   | 3   | 64, 101, 102 | 145  | 5   | 33, 64, 150, 155, 156 | 214  | 1   | 199          |
| let7b  | 1   | 34           | 93    | 2   | 34, 103      | 148a | 5   | 157           | 215  | 4   | 58, 155, 179, 200 | 494  | 2   | 34, 235       |
| let7c  | 1   | 35           | 96-5p | 1   | 104          | 148a | 5   | 81, 158, 159   | 217  | 2   | 201, 202     |
| let7e  | 1   | 18           | 96    | 1   | 105          | 149  | 2   | 160, 161      | 218  | 2   | 203, 204     |
| let7g* | 1   | 36           | 99a-3p| 1   | 162          | 221-3p | 1   | 205           | 505a | 1   | 36           |
| let7g  | 1   | 37           | 99a   | 2   | 35, 106      | 153  | 1   | 163           | 221  | 1   | 106          |
| let7i  | 1   | 28           | 99b-5p| 1   | 110          | 182  | 3   | 171–173       | 320  | 1   | 214          |
| let7d | 1   | 34, 39, 40   | 100   | 2   | 106, 108     | 155  | 1   | 60            | 223  | 1   | 208          |
| let7e | 1   | 41           | 101   | 1   | 64           | 181a | 5   | 18, 165–168   | 229  | 1   | 542-3p       |
| let7c | 1   | 45           | 103-1 | 1   | 81           | 181b | 1   | 16, 169       | 296  | 1   | 556          |
| let7b | 1   | 46           | 103   | 1   | 109          | 181c | 1   | 170           | 320a | 1   | 570          |
| let7a | 1   | 46           | 106a-5p| 1   | 110         | 182  | 1   | 174           | 320  | 1   | 157          |
| let7a | 1   | 46           | 106b  | 3   | 58, 115, 116 | 185  | 1   | 133           | 326  | 1   | 243, 244     |
| let7a | 1   | 46           | 106c  | 1   | 136          | 187  | 2   | 175, 176      | 328  | 3   | 592          |
| let7b | 1   | 38           | 124-3p| 1   | 9            | 188-3p | 1   | 177           | 335  | 1   | 610          |
| let7b | 1   | 38           | 124  | 2   | 117, 118     | 191  | 1   | 178           | 337  | 1   | 625-3p       |
| let7a | 1   | 38           | 125b  | 5   | 33, 35, 106, 112, 119 | 192  | 2   | 179, 180     | 338  | 1   | 625          |
| let7a | 1   | 39, 40       | 126   | 6   | 120–125      | 193a | 5   | 181           | 340  | 1   | 219          |
| let7a | 1   | 40           | 128   | 2   | 126, 127     | 193b | 1   | 182           | 342  | 1   | 630          |
| let7a | 1   | 40           | 130a  | 1   | 81           | 194  | 3   | 38, 183, 184  | 361  | 1   | 652          |
| let7a | 1   | 40           | 130b  | 1   | 128          | 195-5p | 1   | 33            | 362  | 2   | 644-3p       |
| let7a | 1   | 40           | 131  | 2   | 129, 130     | 195b | 1   | 33, 34        | 365  | 1   | 720          |
| let7a | 1   | 40           | 131a  | 2   | 131, 132     | 196a | 1   | 185           | 365  | 1   | 802          |
| let7a | 1   | 40           | 132  | 3   | 133, 134     | 196b-3p | 1   | 186           | 365  | 1   | 885-3p       |
| let7a | 1   | 40           | 134  | 1   | 135          | 196c | 1   | 185           | 370  | 1   | 885-3p       |
| let7a | 1   | 40           | 135  | 1   | 136–138      | 197  | 1   | 32            | 372  | 1   | 889          |
| let7a | 1   | 40           | 136  | 2   | 139, 140     | 198  | 1   | 187           | 376  | 1   | 944          |
| let7a | 1   | 40           | 139  | 3   | 241, 142     | 199a-3p | 1   | 188           | 378  | 1   | 1260         |
| let7a | 1   | 40           | 139-3p| 1   | 144          | 199b | 1   | 189           | 378  | 1   | 1288         |
| let7a | 1   | 40           | 140  | 2   | 147, 148     | 200a | 3   | 82, 149, 190  | 378  | 1   | 1290         |
| let7a | 1   | 40           | 141  | 2   | 34, 149      | 200b | 3   | 23, 149, 191  | 422  | 2   | 141, 226     |
| let7a | 1   | 40           | 142  | 2   | 146          | 203  | 2   | 24, 192       | 424  | 1   | 1297         |
| let7a | 1   | 40           | 143  | 1   | 58           | 210  | 1   | 196           | 455  | 1   | 4775         |

Note: Highlighted studies were included in the present meta-analysis.
| 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<sup>a</sup> | Spain          | P      | Serum  | 102    | I–IV  | 1.00     | qRT-PCR        | 36                | OS<sup>a</sup> | 0.50    | 0.25–1.02 |          |        |
| 21    | Toiyama et al<sup>b</sup> | Japan          | R      | Serum  | 188    | I–IV  | <0.01    | RT-qPCR        | 84                | OS<sup>b</sup> | 4.12    | 1.10–15.40 |          |        |
| 21    | Monzo et al<sup>c</sup>  | Spain          | R      | Plasma | 52     | I–IV  | Median   | TaqMan         | 48                | DFS<sup>c</sup> | 2.32    | 0.80–6.71 |          |        |
| 21    | Tsukamoto et al<sup>d</sup> | Japan          | R      | Plasma | 326    | I–IV  | Median   | qRT-PCR        | 84                | OS<sup>d</sup> | 2.28    | 1.81–5.74 |          |        |
| 92a   | Wang and Gu<sup>e</sup>   | China          | R      | Serum  | 74     | II–IV | <0.06    | RT-qPCR        | 35                | OS<sup>e</sup> | 1.17    | 0.70–1.97 |          |        |
| 92a   | Liu et al<sup>f</sup>     | China          | R      | Serum  | 166    | I–IV  | <0.01    | RT-qPCR        | 53                | OS<sup>f</sup> | 4.36    | 1.64–11.57 |          |        |
| 141   | Cheng et al<sup>g</sup>   | China, USA     | R      | Plasma | 258    | I–IV  | Median   | RT-qPCR        | 96                | OS<sup>g</sup> | 2.40    | 1.18–4.86 |          |        |
| 141   | Sun et al<sup>h</sup>     | USA            | R      | Plasma | 168    | I–IV  | Mean     | RT-qPCR        | 96                | OS<sup>h</sup> | 2.58    | 1.58–4.21 |          |        |
| 200b  | Maierthalier et al<sup>i</sup> | Germany I     | R      | Plasma | 308    | I–IV  | Median   | RT-qPCR        | >72               | OS<sup>i</sup> | 0.77    | 0.57–1.05 |          |        |
| 200b  | Sun et al<sup>h</sup>     | USA            | R      | Plasma | 169    | I–IV  | Mean     | RT-qPCR        | 96                | OS<sup>h</sup> | 1.21    | 0.98–1.50 |          |        |
| 203   | Hur et al<sup>j</sup>     | Japan          | R      | Serum  | 186    | I–IV  | ROC      | RT-qPCR        | 70                | OS<sup>j</sup> | 2.14    | 1.09–4.21 |          |        |
| 203   | Shi et al<sup>k</sup>     | China          | R      | Serum  | 180    | II–IV | Mean     | RT-qPCR        | 60                | OS<sup>k</sup> | 0.47    | 0.27–0.81 |          |        |
| 21    | Kulda et al<sup>l</sup>   | Czech Republic | R      | Frozen | 46     | I–IV  | 8.10     | RT-qPCR        | 56                | DFS<sup>l</sup> | 1.80    | 0.05–65.37 |          |        |
| 21    | Shibuya et al<sup>m</sup> | Japan          | R      | Frozen | 156    | I–IV  | Mean     | TaqMan         | 84                | OS<sup>m</sup> | 1.95    | 1.05–4.48 |          |        |
| 21    | Nielsen et al<sup>n</sup> | Denmark I      | R      | FFPE   | 129    | II    | 65% ISH  | ≥60             | OS<sup>n</sup>   | 1.17    | 1.02–1.34 |          |        |
| 21    | Faltejskova et al<sup,o</sup> | Czech Republic | R      | Tissue | 44     | I–IV  | Median   | RT-qPCR        | 86                | OS<sup,o</sup> | 2.72    | 0.63–11.83 |          |        |
| 21    | Kjaer-Frifeldt et al<sup>p</sup> | Denmark II    | P      | FFPE   | 520    | II    | Mean     | ISH            | 84                | OS<sup>p</sup> | 1.08    | 0.97–1.22 |          |        |
| 21    | Schi et al<sup>q</sup>    | Norway         | P      | Frozen | 193    | I–III | Median   | qRT-PCR        | >60               | DFS<sup>q</sup> | 3.58    | 0.59–23.22 |          |        |
| 21    | Chen et al<sup>r</sup>    | China          | R      | Tissue | 195    | I–IV  | Mean     | RT-qPCR        | >100              | OS<sup>r</sup> | 2.56    | 1.43–4.57 |          |        |
| 21    | Toiyama et al<sup>s</sup> | Japan          | R      | FFPE   | 166    | I–IV  | 3.70     | RT-qPCR        | 84                | OS<sup>s</sup> | 0.59    | 0.21–1.63 |          |        |
| 21    | Oue et al<sup>t</sup>     | Japan          | R      | FFPE   | 87     | II–III | None     | qRT-PCR        | 60                | DFS<sup>t</sup> | 3.13    | 1.20–8.17 |          |        |
| 21    | Bullock et al<sup>u</sup> | UK              | P      | Frozen, FFPE | 50 | II    | Mean     | qRT-PCR        | 96                | DFS<sup>u</sup> | 2.47    | 1.19–5.55 |          |        |
| 21    | Fukushima et al<sup>v</sup> | Japan         | R      | Frozen | 306    | I–IV  | Mean     | RT-qPCR        | 90                | OS<sup>v</sup> | 2.88    | 1.70–5.08 |          |        |
| 21    | Kang et al<sup>w</sup>    | South Korea    | R      | FFPE   | 277    | II–III | Median   | ISH            | 80                | DFS<sup>w</sup> | 2.24    | 1.25–4.02 |          |        |
| 21    | Caritg et al<sup>x</sup>  | Spain          | R      | Frozen | 69     | II    | 2.04     | TaqMan         | >140              | DFS<sup>x</sup> | 1.33    | 0.14–12.47 |          |        |
| 21    | Feiersinger et al<sup>z</sup> | Germany       | R      | FFPE   | 29     | I–IV  | Median   | qRT-PCR        | 205,15            | DFS<sup>z</sup> | 1.45    | 0.39–5.43 |          |        |

Table 3 Characteristics of studies included on colorectal cancer (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 | OSa | 2.52 | 0.65–8.34 | |
| 21    | Lee et al 72 | South Korea | R | FFPE | 170 | I–IV | Median | ISH | 105 | OSa | 0.93 | 0.54–1.60 | |
| 21    | Mima et al 73 | USA I | P | FFPE | 190/192 | I–IV | 25% | RT-qPCR | 207.6 | OSa | 0.99 | 0.75–1.31 | |
|       | USA II | 192/192 | 50% | 192/192 | 75% | OSa | 1.03 | 0.78–1.35 | |
|       | USA III | 191/192 | 75% | 191/192 | 75% | OSa | 1.40 | 1.07–1.84 | |
| 106a  | Díaz et al 89 | Spain | R | Frozen | 110 | I–IV | Median | RT-qPCR | 99 | OSa | 0.53 | 0.26–1.08 | |
|       | Feng et al 111 | China | R | Frozen | 28 | IIIB–IIIB | Median | qRT-PCR | 60 | OSb | 2.69 | 1.07–6.89 | |
|       | Schee et al 84 | Norway | P | Frozen | 193 | I–III | Median | qRT-PCR | >60 | OSb | 2.04 | 1.22–3.36 | |
|       | Ak et al 112 | Turkey | R | FFPE | 40 | I–IV | None | qRT-PCR | >200 | OSb | 0.94 | 0.35–2.56 | |
|       | Bullock et al 87 | UK | P | Frozen, FFPE | 50 | II | Mean | qRT-PCR | 96 | OSb | 2.25 | 1.00–5.04 | |
|       | Hao et al 113 | China | R | Tissue | 138 | I–IV | 66% | RT-qPCR | >60 | OSb | 1.87 | 1.13–3.09 | |
|       | Hao et al 114 | China | R | FFPE | 65 | I–IV | Median | RT-qPCR | >60 | OSb | 2.00 | 0.51–7.85 | |
| 125b  | Nishida et al 119 | Japan | R | Frozen | 89 | None | Median | RT-qPCR | >96 | OSb | 2.42 | 0.99–5.91 | |
| 125b  | Ak et al 121 | Turkey | R | FFPE | 40 | I–IV | None | qRT-PCR | >200 | OSb | 0.90 | 0.32–2.56 | |
| 125b  | Cappuzzo et al 125 | Italy | R | FFPE | 183 | None | None | None | 48 | OSb | 0.58 | 0.32–1.05 | |
| 125b  | Rokavec et al 106 | TCGA | R | Tissue | 438 | I–IV | None | Downloaded | >133 | OSb | 1.88 | 1.36–2.60 | |
| 125b  | Sun et al 123 | TCGA | R | Tissue | 107 | I–IV | Median | Downloaded | 141.1 | OSb | 2.29 | 1.33–3.92 | |
| 126   | Hansen et al 120 | Denmark | R | FFPE | 89 | None | Median | ISH | 58 | OSb | 1.93 | 1.13–3.29 | |
| 126   | Hansen et al 121 | Sweden, Denmark | P | FFPE | 89 | None | Median | qRT-PCR | >30 | OSb | 2.69 | 1.42–5.08 | |
| 126   | Hansen et al 122 | DCCG | P | FFPE | 560 | II | Median | qRT-PCR | 84 | OSb | 1.93 | 1.13–3.29 | |
| 126   | Liu et al 123 | China | R | Frozen | 92 | I–IV | None | qRT-PCR | 92 | OSb | 2.65 | 1.00–6.98 | |
| 126   | Ebrahimi et al 124 | Australia | R | FFPE | 132 | I–IV | <1/>2 | qRT-PCR | >100 | OSb | 1.81 | 0.82–4.00 | |
| 126   | Yuan et al 125 | China | R | Tissue | 75 | I–IV | 0/>0 | ISH | 68 | OSb | 2.35 | 0.91–6.06 | |
| 143   | Kulda et al 129 | Czech Republic | R | Frozen | 46 | I–IV | 11.40 | RT-qPCR | 56 | DFSb | 0.45 | 0.07–2.78 | |
| 143   | Drebber et al 130 | Germany | R | FFPE | 40 | I–IV | 1.00 | RT-qPCR | 76.8 | OSb | 1.52 | 0.32–7.22 | |
| 143   | Pichler et al 131 | Austria | R | FFPE | 77 | II–IV | None | qRT-PCR | >125 | CSSb | 1.86 | 1.06–3.25 | |
| 143   | Guo et al 132 | China | R | Tissue | 79 | I–IV | Median | qRT-PCR | 122 | OSb | 1.45 | 0.69–3.07 | |
| 143   | Ak et al 121 | Turkey | R | FFPE | 40 | I–IV | 1.76 | qRT-PCR | >200 | OSb | 2.69 | 0.80–9.08 | |
| 143   | Simmer et al 133 | DCCG | P | FFPE | 55 | I–IV | Median | TaqMan | 42 | DFSb | 0.45 | 0.24–0.85 | |
### Prognostic value of miRNAs in colorectal cancer

| 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<sup>145</sup> | Germany | R | FFPE | 40 | I–IV | 0.10 | RT-qPCR | 76.8 | OS<sup>b</sup> | 1.95 | 0.43–8.79 |
| 145   | Schee et al<sup>144</sup> | Norway | P | Frozen | 193 | I–III | Median | qRT-PCR | >60 | MFS<sup>b</sup> | 0.61 | 0.30–1.22 |
| 145   | Pecqueux et al<sup>155</sup> | Germany | R | Frozen | 47 | None | Median | RT-qPCR | >60 | OS<sup><i>a</i></sup> | 3.73 | 1.45–9.55 |
| 145   | Zhou et al<sup>156</sup> | China | R | Frozen | 60 | I–IV | Median | qRT-PCR | 80 | OS<sup>b</sup> | 2.57 | 1.12–5.90 |
| 145   | Sun et al<sup>143</sup> | TCGA | R | Tissue | 107 | I–IV | Median | Downloaded | >144 | OS<sup>b</sup> | 0.52 | 0.30–0.77 |
| 181a  | Nishimura et al<sup>165</sup> | Japan | R | Frozen | 162 | I–IV | Median | qRT-PCR | >144 | OS<sup><i>a</i></sup> | 2.00 | 1.05–3.80 |
| 181a  | Ji et al<sup>146</sup> | China I | R | Tissue | 137 | I–IV | Median | RT-qPCR | 100 | OS<sup><i>a</i></sup> | 1.87 | 1.08–3.25 |
| 181a  | Pichler et al<sup>167</sup> | Austria | R | FFPE | 80 | II–IV | None | qRT-PCR | >125 | CSS<sup><i>a</i></sup> | 0.63 | 0.37–1.21 |
| 181a  | Li et al<sup>168</sup> | China | R | Frozen | 72 | I–IV | None | RT-qPCR | >60 | OS<sup><i>a</i></sup> | 2.06 | 1.00–4.23 |
| 181a  | Miyoshi et al<sup>169</sup> | TCGA | R | Tissue | 93 | II–III | None | Downloaded | 135 | RFS<sup><i>b</i></sup> | 2.85 | 1.24–6.55 |
| 224   | Liao et al<sup>170</sup> | China | R | Frozen | 110 | I–IV | Median | qRT-PCR | 87 | OS<sup><i>a</i></sup> | 1.82 | 0.88–3.79 |
| 224   | Yuan et al<sup>171</sup> | China | R | Tissue | 108 | I–III | None | qRT-PCR | 60 | OS<sup><i>a</i></sup> | 0.27 | 0.14–0.51 |
| 224   | Zhang et al<sup>172</sup> | China | R | Frozen | 108 | I–II | 25.72 | qRT-PCR | 62.5 | DFS<sup><i>b</i></sup> | 1.87 | 0.79–4.41 |
| 224   | Adamopoulos et al<sup>173</sup> | Greece | R | Frozen | 104 | I–IV | 56% | qRT-PCR | 120 | OS<sup><i>a</i></sup> | 4.41 | 1.72–11.34 |
| 224   | Ling et al<sup>174</sup> | TCGA | R | Tissue | 143 | I–IV | None | Downloaded | 72 | OS<sup><i>a</i></sup> | 2.88 | 0.97–8.56 |
| 429   | Li et al<sup>175</sup> | China | R | Frozen | 107 | I–III | Median | qRT-PCR | 82 | OS<sup><i>a</i></sup> | 2.09 | 0.84–5.17 |
| 429   | Díaz et al<sup>176</sup> | Spain | R | Frozen | 127 | I–III | None | TaqMan | 113 | OS<sup><i>a</i></sup> | 0.35 | 0.16–0.77 |
| 429   | Sun et al<sup>177</sup> | China | R | Frozen | 84 | I–IV | None | qRT-PCR | 96 | OS<sup><i>a</i></sup> | 0.29 | 0.16–0.55 |
| 429   | Dong et al<sup>178</sup> | China | R | Frozen | 78 | I–IV | Median | qRT-PCR | 60 | OS<sup><i>a</i></sup> | 2.66 | 1.25–5.68 |
| 429   | Han et al<sup>179</sup> | China | R | Frozen | 71 | I–IV | Median | qRT-PCR | 60 | OS<sup><i>a</i></sup> | 1.85 | 1.02–3.33 |

### Notes:
- <sup>m</sup>multiple-covariate analysis; <sup>u</sup>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; R-F-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.
miR200b, miR203, miR224, and miR429. Results of survival analyses of these miRNAs are given in Figures 2–8.

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

| miRNA        | Survival analysis | Articles | Studies included | HR   | 95% CI       | Figure | P-value | Heterogeneity | 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                 | 8        | 5, 60, 63, 65, 66, 68, 71, 73 | 1.47 | 1.16–1.87 | 3A     | <0.01  | 71.7%, P < 0.02 | 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 miR203  | OS                 | 4        | 5, 60, 63, 65, 66, 68, 71, 73 | 1.13 | 0.96–1.34 | 4B     | 0.15   | 71.6%, P < 0.01 | 467         |
| 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   | DFS/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: *Multiple-covariate analysis; †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.

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

Two studies 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 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 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).
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

| Study | HR (95% CI) | Weight |
|-------|-------------|--------|
| miR21 OS | | |
| Menéndez et al4 2013 (Spain) | 0.50 (0.25–1.02) | 35.61 |
| Toiyama et al5 2017 (Japan) | 4.12 (1.10–15.40) | 27.32 |
| Tsukamoto et al7 2017 (Japan) | 2.28 (1.81–5.74) | 37.07 |
| Subtotal (I²=85.2%, P=0.001) | 1.56 (0.47–5.23) | 100.00 |
| miR21 DFS | | |
| Menéndez et al4 2013 (Spain) | 0.51 (0.25–1.06) | 33.89 |
| Monzo et al6 2015 (Spain) | 2.32 (0.80–6.71) | 28.50 |
| Tsukamoto et al7 2017 (Japan) | 2.34 (1.87–4.60) | 37.61 |
| Subtotal (I²=84.4%, P=0.002) | 1.39 (0.49–3.96) | 100.00 |
| miR92a OS | | |
| Wang and Gu10 2012 (China) | 1.17 (0.70–1.97) | 55.16 |
| Liu et al11 2013 (China) | 4.36 (1.64–11.57) | 44.84 |
| Subtotal (I²=81.6%, P=0.020) | 2.11 (0.59–7.61) | 100.00 |
| miR141 OS | | |
| Cheng et al12 2011 (China and USA) | 2.40 (1.18–4.86) | 32.40 |
| Sun et al14 2016 (USA) | 2.58 (1.58–4.21) | 67.60 |
| Subtotal (I²=0.0%, P=0.869) | 2.52 (1.68–3.77) | 100.00 |
| miR200b OS | | |
| Maiertaler et al16 2017 (Germany I) | 0.77 (0.57–1.05) | 33.93 |
| Maiertaler et al16 2016 (Germany II) | 1.21 (0.98–1.50) | 35.98 |
| Sun et al14 2016 (USA) | 2.46 (1.57–3.85) | 30.08 |
| Subtotal (I²=88.8%, P=0.000) | 1.28 (0.75–2.19) | 100.00 |
| miR203 OS | | |
| Hur et al24 2017 (Japan) | 2.14 (1.09–4.21) | 49.12 |
| Shi et al25 2017 (China) | 0.47 (0.27–0.81) | 50.88 |
| Subtotal (I²=91.4%, P=0.001) | 0.99 (0.22–4.37) | 100.00 |

**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.
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) was 1.47, which was greater than that estimated by analysis of the association between high tissue miR21 levels and OS (multiple-covariate analysis).
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.
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

| Study | HR (95% CI) | % weight |
|-------|-------------|----------|
| miR106a OS | | |
| Diaz et al 2008 (Spain) | 0.53 (0.26–1.08) | 22.72 |
| Ak et al 2014 (Turkey) | 0.94 (0.35–2.56) | 17.28 |
| Bullock et al 2015 (UK) | 2.25 (1.00–5.04) | 20.73 |
| Hao et al 2017 (China) | 1.87 (1.13–3.09) | 27.23 |
| Hao et al 2017 (China) | 2.00 (0.51–7.85) | 12.03 |
| Subtotal (I²=62.2%, P=0.032) | 1.31 (0.72–2.36) | 100.00 |
| miR106a DFS/MFS | | |
| Diaz et al 2008 (Spain) | 0.36 (0.17–0.78) | 21.67 |
| Feng et al 2012 (China) | 3.63 (0.56–23.68) | 9.85 |
| Schee et al 2012 (Norway) | 0.81 (0.41–1.59) | 22.80 |
| Bullock et al 2015 (UK) | 2.91 (1.32–6.42) | 21.27 |
| Hao et al 2017 (China) | 1.22 (0.70–2.12) | 24.40 |
| Subtotal (I²=75.8%, P=0.002) | 1.14 (0.55–2.36) | 100.00 |
| miR125b OS | | |
| Nishida et al 2011 (Japan) | 2.42 (0.99–5.91) | 16.19 |
| Ak et al 2014 (Turkey) | 0.90 (0.32–2.56) | 14.01 |
| Cappuzzo et al 2014 (Italy) | 0.58 (0.32–1.05) | 21.43 |
| Rokavec et al 2017 (TCGA) | 1.88 (1.36–2.60) | 26.16 |
| Sun et al 2017 (TCGA) | 2.29 (1.30–3.92) | 22.22 |
| Subtotal (I²=74.6%, P=0.003) | 1.43 (0.83–2.47) | 100.00 |

*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.
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.

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. 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.

| Study | HR (95% CI) | % weight |
|-------|-------------|----------|
| miR126 OS | 1.93 (1.13–3.29) | 17.23 |
| Hansen et al2012 (Denmark) | 1.32 (1.00–1.72) | 64.08 |
| Hansen et al2014 (DCCG) | 2.65 (1.00–6.98) | 5.27 |
| Liu et al2013 (China) | 1.81 (0.82–4.00) | 7.90 |
| Ebrahimi et al2015 (Australia) | 2.35 (0.91–6.06) | 5.53 |
| Yuan et al2016 (China) | | |
| Subtotal (I²=1.2%, P=0.399) | 1.55 (1.24–1.93) | 100.00 |
| miR126 PFS/RFS/CSS | 2.69 (1.42–5.08) | 29.43 |
| Hansen et al2012 (Denmark) | 2.04 (1.19–3.45) | 32.83 |
| Hansen et al2014 (DCCG) | 1.04 (0.71–1.52) | 37.74 |
| Subtotal (I²=75.2%, P=0.018) | 1.72 (0.95–3.10) | 100.00 |
| miR143 DFS/CSS/PFS | 0.45 (0.07–2.78) | 11.52 |
| Kulda et al2010 (Czech) | 1.86 (1.06–3.25) | 29.78 |
| Pichler et al2012 (Austria) | 1.55 (0.91–2.66) | 30.18 |
| Pichler et al2012 (Austria) | 0.45 (0.24–0.85) | 28.51 |
| Simmer et al2015 (DCCG) | | |
| Subtotal (I²=77.7%, P=0.004) | 1.00 (0.47–2.13) | 100.00 |
| miR143 OS | 1.52 (0.32–7.22) | 14.28 |
| Drebber et al2011 (Germany) | 1.45 (0.69–3.07) | 62.23 |
| Guo et al2013 (China) | 2.69 (0.80–9.08) | 23.50 |
| Ak et al2014 (Turkey) | 1.69 (0.94–3.04) | 100.00 |

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.
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, 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),\textsuperscript{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 ($I^2 \geq 50\%$). Statistical assessment of publication
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 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.
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.

References

1. Li J, Chen Y, Guo X, et al. Inhibition of miR-15b decreases cell migration and metastasis in colorectal cancer. Tumour Biol. 2016;37(7):8765–8773.
2. Li J, Liu Y, Wang C, et al. Serum miRNA expression profile as a prognostic biomarker of stage II/III colorectal adenocarcinoma. Sci Rep. 2015;5:12921.
3. Matsumura T, Sugimachi K, Inuuma H, et al. Exosomal microRNA in serum is a novel biomarker of recurrence in human colorectal cancer. Br J Cancer. 2015;113(2):275–281.
4. Menéndez P, Padilla D, Villarejo P, et al. Prognostic significances of serum microRNA-21 in colorectal cancer. J Surg Oncol. 2013;108(6):369–373.
5. Toiyama Y, Takahashi M, Hur K, et al. Serum miR-21 as a diagnostic and prognostic biomarker in colorectal cancer. J Natl Cancer Inst. 2013;105(12):849–859.
6. Monzo M, Martinez-Rodenas F, Moreno I, et al. Differential MIR-21 expression in plasma from mesenteric versus peripheral veins: an observational study of disease-free survival in surgically resected colon cancer patients. Medicine (Baltimore). 2015;94(1):e145.
7. Tsukamoto M, Inuuma H, Yagi T, Matsuda K, Hashiguchi Y. Circulating exosomal microRNA-21 as a biomarker in each tumor stage of colorectal cancer. Oncology. 2017;92(6):360–370.
8. Kou CH, Zhou T, Han XL, Zhuang HJ, Qian HX. Downregulation of mir-23b in plasma is associated with poor prognosis in patients with colorectal cancer. Oncol Lett. 2016;12(6):4838–4844.
9. Jinushi T, Shibayama Y, Kinoshita I, et al. Low expression levels of microRNA-124-5p correlated with poor prognosis in colorectal cancer via targeting of SMC4. Cancer Med. 2014;3(6):1544–1552.
10. Wang LG, Gu J. Serum microRNA-29a is a promising novel marker for early detection of colorectal liver metastasis. Cancer Epidemiol. 2012;36(1):e61–e67.
11. Basati G, Razavi AE, Pakzad I, Malayeri FA. Circulating levels of the miRNAs, miR-194, and miR-29b, as clinically useful biomarkers for colorectal cancer. Tumour Biol. 2016;37(2):1781–1788.

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.
12. Schou JV, Rossi S, Jensen BV, et al. miR-345 in metastatic colorectal cancer: a non-invasive biomarker for clinical outcome in non-KRAS mutant patients treated with 3rd line cetuximab and irinotecan. *PloS One*. 2014;9(6):e99886.

13. Liu GH, Zhou ZG, Chen R, et al. Serum miR-21 and miR-92a as biomarkers in the diagnosis and prognosis of colorectal cancer. *Tumour Biol*. 2013;34(4):2175–2181.

14. Sun Y, Liu X, Cogdell D, et al. Examining plasma microRNA markers for colorectal cancer at different stages. *Oncotarget*. 2016;7(10):11434–11449.

15. Mao L, Feng W, Yu Y, Xu X. Serum expression of miRNA-103, a potential diagnostic and prognostic biomarker for colorectal cancer. *Int J Clin Med*. 2016;9(7):14212–14218.

16. Maerithera M, Benner A, Hoffmeister M, et al. Plasma miR-122 and miR-200 family are prognostic markers in colorectal cancer. *Int J Cancer*. 2017;140(1):176–187.

17. Kijima T, Hazama S, Tsunedomi R, et al. MicroRNA-6826 and-6875 in plasma are valuable non-invasive biomarkers that predict the efficacy of vaccine treatment against metastatic colorectal cancer. *Oncol Rep*. 2017;37(1):23–30.

18. Miyoshi J, Toden S, Yoshida K, et al. MiR-139-5p as a novel serum biomarker for recurrence and metastasis in colorectal cancer. *Sci Rep*. 2017;7:43393.

19. Cheng H, Zhang L, Cogdell D, et al. Circulating plasma MiR-141 is a novel biomarker for metastatic colon cancer and predicts poor prognosis. *PloS One*. 2011;6(3):e17745.

20. Lv ZC, Fan YS, Chen HB, Zhao DW. Investigation of microRNA-155 as a serum diagnostic and prognostic biomarker for colorectal cancer. *Tumour Biol*. 2015;36(3):1619–1625.

21. Yuan D, Li K, Zhu K, Yan R, Dang C. Plasma miR-183 predicts recurrence and prognosis in patients with colorectal cancer. *Cancer Biol Ther*. 2015;16(2):268–275.

22. Xu C, Gu L. The diagnostic effect of serum miR-199b as biomarker in colorectal cancer. *Biomed Rep*. 2017;6(1):39–45.

23. Toiyama Y, Hur K, Tanaka K, et al. Serum miR-200c is a novel prognostic and metastasis-predictive biomarker in patients with colorectal cancer. *Ann Surg*. 2014;259(4):735–743.

24. Hur K, Toiyama Y, Okugawa Y, et al. Circulating microRNA-203 predicts prognosis and metastasis in human colon cancer. *Gut*. 2017;66(6):654–665.

25. Shi SQ, Ke JJ, Wu WQ, Xu QS. Serum miRNA-203 expression is associated with chemo-response to standard FOLFOTX treatment of patients with colorectal cancer. *Int J Exp Pathol*. 2017;100(1):105–116.

26. Pu XX, Huang GL, Guo HQ, et al. Circulating miR-221 directly amplified from plasma is a potential diagnostic and prognostic marker of colorectal cancer and is correlated with p53 expression. *J Gastroenterol Hepatol*. 2010;25(10):1674–1680.

27. Yu J, Jin L, Jiang L, et al. Serum miR-372 is a diagnostic and prognostic biomarker in patients with early colorectal cancer. *Anticancer Agents Med Chem*. 2016;16(4):424–431.

28. Hur K, Toiyama Y, Schetter AJ, et al. Identification of a metastasis-specific microRNA signature in human colorectal cancer. *J Natl Cancer Inst*. 2015;107(3):djv492.

29. Imaoka H, Toiyama Y, Fujikawa H, et al. Circulating microRNA-1290 as a novel diagnostic and prognostic biomarker in human colorectal cancer. *Ann Oncol*. 2016;27(10):1879–1886.

30. Liu C, Eng C, Shen J, et al. Serum exosomal miR-4772-3p is a predictor of tumor recurrence in stage II and III colon cancer. *Oncotarget*. 2016;7(46):76250–76260.

31. Liu TP, Huang CC, Yeh KT, et al. Down-regulation of let-7a-5p predicts lymph node metastasis and prognosis in colorectal cancer: implications for chemotherapy. *Surg Oncol*. 2016;25(4):429–434.

32. Xu M, Kuang Y, Wang M, Han X, Yang Q. A microRNA expression signature as a predictor of survival for colon adenocarcinoma. *Neo-plasma*. 2017;64(1):56–64.
54. Wu CW, Dong YJ, Liang QY, et al. MicroRNA-18a attenuates DNA damage repair through suppressing the expression of ataxia telangiectasia mutated in colorectal cancer. PLoS One. 2013;8(2):e57036.

55. Chen X, Shi K, Wang Y, et al. Clinical value of integrated-signature miRNAs in colorectal cancer: miRNA expression profiling analysis and experimental validation. Oncotarget. 2015;6(35):37544–37556.

56. Cheng D, Zhao S, Tang H, et al. MicroRNA-20a-5p promotes colorectal cancer invasion and metastasis by downregulating Smad4. Oncotarget. 2016;7(29):45199–45213.

57. Zhang GJ, Li Y, Zhou H, Xiao HX, Zhou T. miR-20a is an independent prognostic factor in colorectal cancer and is involved in cell metastasis. Mol Med Rep. 2014;10(1):283–291.

58. Carigt O, Navarro A, Moreno I, et al. Identifying high-risk stage II colon cancer patients: a three-microRNA-based score as a prognostic biomarker. Clin Colorectal Cancer. 2016;15(4):e175–e182.

59. Kaula V, Pesta M, Topolcan O, et al. Relevance of miR-21 and miR-143 expression in tissue samples of colorectal carcinoma and its liver metastases. Cancer Gene Cyto gene. 2010;200(2):154–160.

60. Shibuya H, Inuma H, Shimada R, Horituchi A, Watanabe T. Clinicopathological and prognostic value of microRNA-21 and microRNA-155 in colorectal cancer. Oncology. 2010;79(3–4):313–320.

61. Nielsen BS, Jorgensen S, Fog JU, et al. High levels of microRNA-21 in the stroma of colorectal cancers predict short disease-free survival in stage II colon cancer patients. Clin Exp Metastasis. 2011;28(1):27–38.

62. Faltejskova P, Besse A, Sevcikova S, et al. Clinical correlations of miR-21 expression in colorectal cancer patients and effects of its inhibition on DLD1 colon cancer cells. Int J Colorectal Dis. 2012;27(11):1401–1408.

63. Kjaer-Frifeldt S, Hansen TF, Nielsen BS, et al. The prognostic importance of miR-21 in stage II colon cancer: a population-based study. Br J Cancer. 2012;107(7):1169–1174.

64. Schek K, Boye K, Abrahamsson TW, Fodstad O, Flatmark K. Clinical relevance of microRNA miR-21, miR-31, miR-92a, miR-101, miR-106a and miR-145 in colorectal cancer. BMC Cancer. 2012;12:505.

65. Chen TH, Chang SW, Huang CC, et al. The prognostic significance of APC gene mutation and miR-21 expression in advanced-stage colorectal cancer. Colorectal Dis. 2013;15(11):1367–1374.

66. Oue N, Anami K, Schetter AJ, et al. High miR-21 expression from FFPE tissues is associated with poor survival and response to adjuvant chemotherapy in colon cancer. Int J Cancer. 2014;134(8):1926–1934.

67. Bullock MD, Pickard K, Mittler R, et al. Stratifying risk of recurrence in stage II colorectal cancer using deregulated stromal and epithelial microRNAs. Oncotarget. 2015;6(9):7262–7279.

68. Fukushima Y, Inuma H, Tsukamoto M, Matsuda K, Hashiguchi Y. Clinical significance of microRNA-21 as a biomarker in each Dukes’ stage of colorectal cancer. Oncol Rep. 2015;33(2):573–582.

69. Kang WK, Lee JK, Oh ST, Lee SH, Jung CK. Stromal expression of miR-21 in T3a-T4a colorectal cancer is an independent predictor of early tumor relapse. BMC Gastroenterol. 2015;15:2.

70. Feiersinger F, Nolte E, Wach S, et al. MiRNA-21 expression decreases from primary tumors to liver metastases in colorectal carcinoma. PLoS One. 2016;11(2):e0148580.

71. Iseki Y, Shibutani M, Maeda K, et al. Prognostic significance of microRNA-21 expression in patients with unresectable metastatic colon cancer. Anticancer Res. 2016;36(10):5145–5151.

72. Lee KS, Nam SK, Ko J, et al. Stromal expression of microRNA-21 in advanced colorectal cancer patients with distant metastases. J Pathol Transl Med. 2016;50(4):270–277.

73. Mima K, Nishihara R, Yang J, et al. MicroRNA MIR21 (miR-21) and PTGS2 expression in colorectal cancer and patient survival. Clin Cancer Res. 2016;22(15):3841–3848.

74. Zhang G, Xia S, Tian H, Liu Z, Zhou T. Clinical significance of miR-22 expression in patients with colorectal cancer. Med Oncol. 2012;29(5):3108–3112.

75. Li B, Li B, Sun H, Zhang H. The predicted target gene validation, function, and prognosis studies of miRNA-22 in colorectal cancer tissue. Tumour Biol. 2017;39(3):1010428317692257.
97. Wu W, Yang P, Feng X, et al. The relationship between and clinical significance of microRNA-32 and phosphatase and tensin homologue. *Genes Chromosomes Cancer*. 2013;52(12):1133–1140.

98. Liao W, Gu C, Huang A, Yao J, Sun R. MicroRNA-33b inhibits tumor cell growth and is associated with prognosis in colorectal cancer patients. *Clin Transl Oncol*. 2016;18(5):449–456.

99. Gao J, Li N, Dong Y, et al. miR-34a-5p suppresses colorectal cancer metastasis and predicts recurrence in patients with stage II/III colorectal cancer. *Oncogene*. 2015;34(31):4142–4152.

100. Hyoshiz Y, Schetter AJ, Okayama H, et al. Increased microRNA-34b and 34c predominantly expressed in stromal tissues is associated with poor prognosis in human colon cancer. *PLoS One*. 2015;10(4):e0124899.

101. Zhou T, Zhang G, Liu Z, Xia S, Tian H. Overexpression of miR-92a correlates with tumor metastasis and poor prognosis in patients with colorectal cancer. *Int J Colorectal Dis*. 2013;28(1):19–24.

102. Ke TW, Wei PL, Yeh KT, Chen WT, Cheng YW. MiR-92a promotes cell metastasis of colorectal cancer through PTEN-mediated PI3K/akt pathway. *Ann Surg Oncol*. 2015;22(8):2649–2655.

103. Xiao ZG, Deng ZS, Zhang YD, Zhang Y, Huang ZC. Clinical significance of microRNA-93 downregulation in human colorectal cancer. *Eur J Gastroenterol Hepatol*. 2013;25(3):290–301.

104. Reis AL, Stieglitzauer V, Winter E, et al. MiR-96-5p influences cellular growth and is associated with poor survival in colorectal cancer patients. *Mol Carcinog*. 2015;54(11):1442–1450.

105. Rapti SM, Kontos CK, Papadopoulou IN, Scorilas A. High miR-96 level in colorectal adenocarcinoma predict poor prognosis, particularly in patients without distant metastasis at the time of initial diagnosis. *Tumour Biol*. 2016;37(9):11815–11824.

106. Rokavec M, Horst D, Herrmeing H. Cellular model of colon cancer progression reveals signatures of miRNAs, mRNAs, IncRNAs, and epigenetic modifications associated with metastasis. *Cancer Res*. 2017;77(8):1854–1867.

107. Li W, Chang J, Wang S, et al. miRNA-99b-5p suppresses liver metastasis of colorectal cancer by down-regulating mTOR. *Oncotarget*. 2015;6(27):24448–24462.

108. Chen P, Qi X, Wang Q, Wei P. Downregulation of microRNA-100 correlates with tumor progression and poor prognosis in colorectal cancer. *Med Oncol*. 2014;31(10):235.

109. Zheng YB, Xiao K, Xiao GC, et al. MicroRNA-103 promotes tumor growth and metastasis in colorectal cancer by directly targeting LATS2. *OncoLett*. 2016;12(3):2194–2200.

110. Yue B, Sun B, Liu C, et al. Long non-coding RNA Fer-1 like protein 4 suppresses oncogenicity and exhibits prognostic value by associating with miR-106a-5p in colon cancer. *Cancer Sci*. 2015;106(10):1323–1332.

111. Feng B, Dong TT, Wang LL, et al. Colorectal cancer migration and invasion initiated by microRNA-106a. *PLoS One*. 2012;7(8):e43452.

112. Ak S, Tunca B, Tezcan G, et al. MicroRNA expression patterns of tumors in early-onset colorectal cancer patients. *J Surg Res*. 2014;191(1):113–122.

113. Hao H, Liu L, Zhang D, et al. Diagnostic and prognostic value of miR-106a in colorectal cancer. *Oncotarget*. 2017;8(3):5038–5047.

114. Hao H, Xia G, Wang C, Zhong F, Liu L, Zhang D. miR-106a suppresses tumor cells death in colorectal cancer through targeting ATG7. *Med Mol Morphol*. 2017;50(2):76–85.

115. Wang YX, Lang F, Liu YX, Yang QG, Gao HJ. In situ hybridization analysis of the expression of miR-106b in colorectal cancer. *Int J Clin Exp Pathol*. 2015;8(1):786–792.

116. Zhang GJ, Li JS, Zhou H, Xiao HX, Li Y, Zhou T. MicroRNA-106b promotes colorectal cancer cell migration and invasion by directly targeting Dlc1. *J Exp Clin Cancer Res*. 2015;34:73.

117. Wang MJ, Li Y, Wang R, et al. Downregulation of microRNA-124 is an independent prognostic factor in patients with colorectal cancer. *Int J Colorectal Dis*. 2013;28(2):183–189.

118. Qiu Z, Guo W, Wang Q, et al. MicroRNA-124 reduces the pentose phosphate pathway and proliferation by targeting PRPS1 and RP1A mRNAs in human colorectal cancer cells. *Gastroenterology*. 2015;149(6):1587.e11–1598.e11.

119. Nishida N, Yokobori T, Mimori K, et al. MicroRNA miR-120b is a prognostic marker in human colorectal cancer. *Int J Oncol*. 2011;38(5):1437–1443.

120. Hansen TF, Sorensen FB, Lindhebjerg J, Jakobsen A. The predictive value of microRNA-126 in relation to first line treatment with capecitabine and oxaliplatin in patients with metastatic colorectal cancer. *BMC Cancer*. 2012;12:83.

121. Hansen TF, Christensen RD, Andersen RF, Sorensen FB, Johnsson A, Jakobsen A. MicroRNA-126 and epidermal growth factor-like domain 7-an angiogenic couple of importance in metastatic colorectal cancer: results from the Nordic ACT trial. *Br J Cancer*. 2013;109(5):1243–1251.

122. Liao W, Guo YQ, Li XY, et al. MicroRNA-126 inhibits colon cancer cell proliferation and invasion by targeting the chemokine (C-X-C motif) receptor 4. *Oncotarget*. 2016;7(37):60230–60244.

123. Takahashi Y, Iwaya T, Sawada G, et al. Up-regulation of NEK2 by microRNA-128 methylation is associated with poor prognosis in colorectal cancer. *Ann Surg Oncol*. 2014;21(1):205–212.

124. Zhou T, Zheng G, Liu Z, Tian H. Overexpression of miR-92a correlates with tumor metastasis and poor prognosis in patients with colorectal cancer. *Int J Colorectal Dis*. 2013;28(1):19–24.

125. Ke TW, Wei PL, Yeh KT, Chen WT, Cheng YW. MiR-92a promotes cell metastasis of colorectal cancer through PTEN-mediated PI3K/akt pathway. *Ann Surg Oncol*. 2015;22(8):2649–2655.

126. Hao H, Xia G, Wang C, Zhong F, Liu L, Zhang D. miR-106a suppresses tumor cells death in colorectal cancer through targeting ATG7. *Med Mol Morphol*. 2017;50(2):76–85.

127. Wang YX, Lang F, Liu YX, Yang QG, Gao HJ. In situ hybridization analysis of the expression of miR-106b in colorectal cancer. *Int J Clin Exp Pathol*. 2015;8(1):786–792.

128. Zhang GJ, Li JS, Zhou H, Xiao HX, Li Y, Zhou T. MicroRNA-106b promotes colorectal cancer cell migration and invasion by directly targeting Dlc1. *J Exp Clin Cancer Res*. 2015;34:73.

129. Wang MJ, Li Y, Wang R, et al. Downregulation of microRNA-124 is an independent prognostic factor in patients with colorectal cancer. *Int J Colorectal Dis*. 2013;28(2):183–189.
180. Shan B, Chen P, Li S, Xu L, Yu H. Decreased expression of microRNA-192 correlates with tumor progression and poor prognosis in patients with colorectal cancer. *Int J Clin Exp Pathol.* 2017;10(1):595–602.

181. Zhang P, Ji DB, Han HB, Shi YF, Du CZ, Gu J. Downregulation of miR-193a-5p correlates with lymph node metastasis and poor prognosis in colorectal cancer. *World J Gastroenterol.* 2014;20(34):12241–12248.

182. Guo F, Luo Y, Mu YF, et al. miR-193b directly targets STMN1 and inhibits the malignant phenotype in colorectal cancer. *Am J Cancer Res.* 2016;6(1):2463–2475.

183. Zhao HJ, Ren LL, Wang ZH, et al. MiR-194 deregulation contributes to colorectal carcinogenesis via targeting AKT2 pathway. *Theranostics.* 2014;4(12):1193–1208.

184. Wang B, Shen ZL, Gao ZD, et al. MiR-194, commonly repressed in colorectal cancer, suppresses tumor growth by regulating the MAPK4/c-Jun/MDM2 signaling pathway. *Cell Cycle.* 2015;14(7):1046–1058.

185. Ge J, Chen Z, Li R, Lu T, Xiao G. Upregulation of microRNA-196a and microRNA-196b cooperatively correlate with aggressive progression and unfavorable prognosis in patients with colorectal cancer. *Cancer Cell Int.* 2014;14(1):128.

186. Boisen MK, Dehlendorff C, Linemann D, et al. Tissue microRNAs as predictors of outcome in patients with metastatic colorectal cancer treated with first line capecitabine and oxaliplatin with or without bevacizumab. *PLoS One.* 2014;9(10):e109430.

187. Wang M, Wang J, Kong X, et al. MiR-198 represses tumor growth and metastasis in colorectal cancer by targeting fucosyltransferase 8. *Sci Rep.* 2014;4:6145.

188. Wan D, He S, Xie B, et al. Aberrant expression of miR-199a-3p and its clinical significance in colorectal cancer. *Med Oncol.* 2013;30(1):378.

189. Shen ZL, Wang B, Jiang KW, et al. Downregulation of miR-199b is associated with distant metastasis in colorectal cancer via activation of SIRT1 and inhibition of CREB/KISS1 signaling. *Oncotarget.* 2016;7(23):35092–35105.

190. Pichler M, Ress AL, Winter E, et al. MiR-200a regulates epithelial to mesenchymal transition-related gene expression and determines prognosis in colorectal cancer patients. *Br J Cancer.* 2014;110(6):1614–1621.

191. Xi Y, Formentini A, Chien M, et al. Prognostic values of microRNAs in colorectal cancer. *Biomark Insights.* 2006;2:113–121.

192. Deng B, Wang B, Fang J, et al. MiRNA-203 suppresses cell proliferation, migration and invasion in colorectal cancer via targeting of EIF5A2. *Sci Rep.* 2016;6:28301.

193. Sümült AT, Göğebakan B, Ergün S, et al. miR-204-5p expression in colorectal cancer: an autophagy-associated gene. *Tumour Biol.* 2014;35(12):12713–12719.

194. Yin Y, Zhang B, Wang et al. miR-204-5p inhibits proliferation and invasion and enhances chemotherapeutic sensitivity of colorectal cancer cells by downregulating RAB22A. *Clin Cancer Res.* 2014;20(23):6187–6199.

195. Sun P, Sun D, Wang X, Liu T, Ma Z, Duan L. MiR-206 is an independent prognostic factor and inhibits tumor invasion and migration in colorectal cancer. *Cancer Biomark.* 2015;15(4):391–396.

196. Qu A, Du L, Yang Y, et al. Hypoxia-inducible MiR-210 is an independent prognostic factor and contributes to metastasis in colorectal cancer. *PLoS One.* 2014;9(3):e90952.

197. Sümült AT, Göğebakan B, Bayram S, Batmaci CY, Ortuzucu S. MicroRNA 211 expression is upregulated and associated with poor prognosis in colorectal cancer: a case-control study. *Tumour Biol.* 2015;36(12):9703–9709.

198. Meng X, Wu P, Pan C, et al. Genetic and epigenetic down-regulation of miR-212 promotes colorectal tumor metastasis via dysregulation of MsoRD. *Gastroenterology.* 2013;145(2):426.e1–436.e1–e6.

199. Chen DL, Wang QZ, Zeng ZL, et al. Identification of microRNA-214 as a negative regulator of colorectal cancer liver metastasis by way of regulation of fibroblast growth factor receptor 1 expression. *Hepatology.* 2014;60(2):598–609.
241. Ye C, Yue G, Shen Z, et al. miR-542-3p suppresses colorectal cancer progression through targeting survivin. *Transl Cancer Res*. 2016;5(6):817–826.

242. Yuan L, Yuan P, Yuan H, et al. miR-542-3p inhibits colorectal cancer cell proliferation, migration and invasion by targeting OTUB1. *Am J Cancer Res*. 2017;7(1):159–172.

243. Zhou Q, Zhu Y, Wei X, et al. MiR-590-5p inhibits colorectal cancer angiogenesis and metastasis by regulating nuclear factor 90 vascular endothelial growth factor A axis. *Cell Death Dis*. 2016;7(10):e2413.

244. Ou C, Sun Z, Li X, et al. MiR-590-5p, a density-sensitive microRNA, inhibits tumorigenesis by targeting YAP1 in colorectal cancer. *Cancer Lett*. 2017;399:53–63.

245. Liu M, Zhi Q, Wang W, Zhang Q, Fang T, Ma Q. Up-regulation of miR-592 correlates with tumor progression and poor prognosis in patients with colorectal cancer. *Biomed Pharmacother*. 2015;69:214–220.

246. Shi F, Li R, Guo P. Expression and prognostic value of miR-610 in patients with colorectal cancer. *Biomed Res*. 2017;28(3):1321–1324.

247. Rasmussen MH, Jensen NF, Tarpgaard LS, et al. High expression of microRNA-625-3p is associated with poor response to first-line oxaliplatin based treatment of metastatic colorectal cancer. *Moh Oncol*. 2013;7(3):637–646.

248. Lou X, Qi X, Zhang Y, Long H, Yang J. Decreased expression of microRNA-625 is associated with tumor metastasis and poor prognosis in patients. *J Surg Oncol*. 2013;108(4):230–235.

249. Chu D, Zheng J, Li J, et al. MicroRNA-630 is a prognostic marker for patients with colorectal cancer. *Tumour Biol*. 2014;35(10):9787–9792.

250. Zhang J, Fei B, Wang Q, et al. MicroRNA-638 inhibits cell proliferation, invasion and regulates cell cycle by targeting tetraspanin 1 in human colorectal carcinoma. *Oncotarget*. 2014;5(52):12083–12096.

251. Wang X, Kuang Y, Shen X, et al. Evaluation of miR-720 prognostic significance in patients with colorectal cancer. *Tumour Biol*. 2015;36(2):719–727.

252. Zhang T, Cai X, Li Q, et al. Hsa-miR-875-5p exerts tumor suppressor function through down-regulation of EGFR in colorectal carcinoma (CRC). *Oncotarget*. 2016;7(27):42225–42240.

253. Liu DR, Gnan QL, Gao MT, Jiang L, Kang HX. miR-1260b is a potential prognostic biomarker in colorectal cancer. *Med Sci Monit*. 2016;22:2417–2423.

254. Gopalan V, Pillai S, Ebrahimi F, et al. Regulation of microRNA-1288 in colorectal cancer: altered expression and its clinicopathological. *Mol Carcinog*. 2014;53(Suppl 1):E36–E44.

255. Tu HQ, Lu YY, Chen DL, et al. Redox regulation of stem-like cells through the CD44v-xCT Axis in colorectal cancer: mechanisms and therapeutic implications. *Theranostics*. 2016;6(8):1160–1175.

256. Hu Y, Yi B, He S, et al. Clinical significance of miR-1826 as a novel prognostic biomarker in colorectal cancer. *Anticancer Agents Med Chem*. 2016;16(9):1109–1116.

257. Yu FY, Tu Y, Deng Y, et al. MiR-4500 is epigenetically downregulated in colorectal cancer and functions as a novel tumor suppressor by regulating HMGAA2. *Cancer Biol Ther*. 2016;17(11):1149–1157.

258. Zhao S, Sun H, Jiang W, et al. miR-4775 promotes colorectal cancer invasion and metastasis via the Smad7/TGFβ-mediated epithelial to mesenchymal transition. *Mol Cancer*. 2017;16(1):12.

259. Jemal A, Siegel R, Xu J, Ward E. Cancer statistics, 2010. *CA Cancer J Clin*. 2010;60(5):277–300.

260. Valeri N, Croce CM, Fabbri M. Pathogenic and clinical relevance of microRNAs in colorectal cancer. *Cancer Genomics Proteomics*. 2009;6(4):195–204.

261. Forman JJ, Legesse-Miller A, Coller HA. A search for conserved sequences in coding regions reveals that the let-7 microRNA targets Dicer within its coding sequence. *Proc Natl Acad Sci U S A*. 2008;105(39):14879–14884.

262. Lagos-Quijanta M, Rauhut R, Lendeckel W, Tuschl T. Identification of novel genes coding for small expressed RNAs. *Science*. 2001;294(5543):853–858.

263. Lau NC, Lim LP, Weinstein EG, Bartel DP. An abundant class of tiny RNAs with probable regulatory roles in *Caenorhabditis elegans*. *Science*. 2001;294(5543):858–862.

264. Lee RC, Ambros V. An extensive class of small RNAs in *Caenorhabditis elegans*. *Science*. 2001;294(5543):862–864.
265. Tierney JF, Stewart LA, Ghersi D, Burdett S, Sydes MR. Practical methods for incorporating summary time-to-event data into meta-analysis. *Trials*. 2007;8:16.

266. Lin JK, Chang SC, Yang YC, Li AF. Loss of heterozygosity and DNA aneuploidy in colorectal adenocarcinoma. *Ann Surg Oncol*. 2003;10(9):1086–1094.

267. Leary RJ, Lin JC, Cummins J, et al. Integrated analysis of homozygous deletions, focal amplifications, and sequence alterations in breast and colorectal cancers. *Proc Natl Acad Sci U S A*. 2008;105(42):16224–16229.

268. Guastadisegni C, Colafranceschi M, Ottini L, Dogliotti E. Microsatellite instability as a marker of prognosis and response to therapy: a meta-analysis of colorectal cancer survival data. *Eur J Cancer*. 2010;46(15):2788–2798.

269. Ogino S, Chan AT, Fuchs CS, Giovannucci E. Molecular pathological epidemiology of colorectal neoplasia: an emerging transdisciplinary and interdisciplinary field. *Gut*. 2011;60(3):397–411.

270. Ogino S, Nishihara R, van der Weele T, et al. The role of molecular pathological epidemiology in the study of neoplastic and non-neoplastic diseases in the era of precision medicine. *Epidemiology*. 2016;27(4):602–611.