Research Article

Prognostic Role of MicroRNA-126 for Survival in Malignant Tumors: A Systematic Review and Meta-Analysis

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Background. Increasing studies found that miR-126 expression may be associated with the prognosis of cancers. Here, we performed a meta-analysis to assess the prognostic role of miR-126 in different cancers. Methods. Eligible studies were identified by searching in PubMed, Embase, the Cochrane Library, CNKI, and Wan Fang databases up to March 2015. Pooled hazard ratios (HRs) and their corresponding 95% confidence intervals (CIs) were calculated to investigate the correlation between miR-126 and survival of cancers. Results. Thirty studies including a total of 4497 participants were enrolled in this meta-analysis. The pooled results showed that high level of miR-126 was a predictor for favorable survival of carcinomas, with pooled HR of 0.77 (95% CI 0.64–0.93) for OS, 0.64 (95% CI 0.48–0.85) for DFS, and 0.70 (95% CI 0.50–0.98) for PFS/RFS/DSS. However, high level of circulating miR-126 predicted a significantly worse OS in patients with cancer (HR = 1.65, 95% CI 1.09–2.51). Conclusions. Our results indicated that miR-126 could act as a significant biomarker in the prognosis of various cancers.

1. Introduction

MicroRNAs (miRNAs), which are a new class of small noncoding RNAs (21–23 nucleotides), have emerged as crucial players regulating the magnitude of gene expression in a variety of organisms [1, 2]. Regulation of microRNAs is achieved via binding to the 3′ untranslated regions (3′ UTR) of target mRNAs, which leads to their inhibition of the expression of target genes in the translation level [3]. Mounting evidence suggests that microRNAs play crucial and complex roles in the initiation and progression of cancer [4], including cell proliferation, differentiation, apoptosis, and metabolism [5, 6]. Obviously, microRNAs may be exploited as new promising molecular biomarkers for early diagnosis and efficient treatment in human cancers [7].

MicroRNA-126 (miR-126), located within the 7th intron of EGFL7 (epidermal growth factor-like domain 7), plays an important role in cellular biology, including cancer biology [8, 9]. Many studies have demonstrated that miR-126 contributes to progression of angiogenesis, proliferation, migration, invasion, and cell survival in some cancers [8, 10–12]. As a tumor suppressor, miR-126 was shown to down-regulate expression in lung, breast, gastric, colon, pancreatic, oral, and some other cancers in previous studies [13–18]. Cancer patients with lower expression of miR-126 always had a worse prognostic outcome; however, the results from different studies indicated that miR-126 functioned as an oncogene and its expression was upregulated [19–22].

The majority of cancers at the time of initial diagnosis are often at an advanced stage and have poor prognosis, and therefore there is an urgent need for the identification of novel prognostic and predictive biomarkers to improve treatment of patients with various cancers [23]. In spite of some contradictory results, miR-126 is still a significant tumor biomarker and a potential therapeutic target [24]. Moreover, the result from individual study is inadequate to evaluate whether miR-126 can be considered as a promising biomarker. So we performed this meta-analysis to assess the prognostic value of tissue and blood-based miR-126 levels in various cancers.

2. Materials and Methods

This meta-analysis was performed following the guidelines of the Systematic Reviews and Meta-Analyses (PRISMA) and the Observational Studies in Epidemiology group (MOOSE) [25].
2.1. Search Strategy. Literatures were systematically searched through PubMed, Embase, the Cochrane Library, CNKI (China National Knowledge Infrastructure), and Wan Fang databases up to March 2015 without any language restrictions by two independent reviewers (Jie Bu and Hui Li). The search strategy of key words and their combination was the following terms: “microRNA-126 OR miR-126 OR miR-126-3p” AND “tumor OR tumour OR neoplasm OR cancer OR carcinoma” AND “prognosis OR survival OR outcome OR prognostic.” We also carefully performed a manual search in order to identify other potentially eligible studies.

2.2. Inclusion and Exclusion Criteria. The eligible studies in this systematic review must meet all the following criteria: (1) patients are included with any type of cancers, (2) the association between miR-126 expression and survival outcome was measured in cancerous tissues or circulatory system, and (3) sufficient data was provided to calculate the hazard ratio (HR) and 95% confidence intervals (CIs). Articles were excluded according to the following criteria: (1) letters, case reports, reviews, conference abstracts, and animal or laboratory studies, (2) studies analyzing a set of miRNAs altogether and nondichotomous miR-126 expression levels, and (3) studies with fewer than 30 patients. When the same patient cohort was reported from multiple published data, only the most recent or complete study was selected.

2.3. Quality Assessment and Data Extraction. Quality assessment of included studies was assessed by two researchers independently (Jie Bu and Hui Li) following a critical review checklist of the Dutch Cochrane Centre proposed by MOOSE [25]. The following items were included: first author’s name, publication year, country or area of origin, cancer type, sample type, TNM stage, method, total number of patients, cut-off value, follow-ups and HRs of miR-126 for overall survival (OS), disease-free survival (DFS), recurrence-free survival (RFS), progression-free survival (PFS), and disease-specific survival (DSS), with their 95% confidence intervals (CIs). Disagreements were resolved by discussion between these reviewers (Jie Bu, Hui Li, and Xiao-yang Li) or consultation with senior reviewer (Li-hong Liu). If both univariate and multivariate analysis results were reported for survival, the latter ones would be selected [26, 27].

We extracted the statistical variables according to the following methods. If HRs and 95% CIs were described in publications, we extracted them directly. Otherwise, survivals and deaths at specified times in each group were extracted to calculate HRs. If only Kaplan-Meier curves are available, they were extracted from the graphical survival plots to estimate the HRs following the previously described method [28, 29]. We used Engauge Digitizer version 4.1 to extract the data from Kaplan-Meier survival curves, and three independent researchers (Jie Bu, Hui Li, and Xiao-yang Li) read the curves to reduce reading variability. We also contacted the authors of eligible articles by email for additional information and the essential data needed for the meta-analytic calculations.

2.4. Statistical Analysis. HRs with their 95% CIs were combined to evaluated the effect of miR-126 expression on the survival outcome of cancer. Patients with overexpression of miR-126 indicated a better prognosis if HR < 1 and its 95% CI did not overlap with 1. Heterogeneity of pooled HRs was carried out using Cochran’s Q-test and Higgins I²-square (I²) statistic [30, 31]. If there was significant heterogeneity (P < 0.05 or I² > 50%), the random-effects model (Der Simonian and Laird method) was used [32]. Otherwise, a fixed-effects model (Mantel-Haenszel test) was applied [33]. Subgroup analysis and metaregression were further performed to explore possible explanations for heterogeneity. Begg’s funnel plot and Egger’s bias were used to evaluate the potential publication bias [34, 35]. Analysis of sensitivity was performed to evaluate the stability of the results. All statistical tests were two-sided, and P < 0.05 was regarded as statistically significant. All analyses were conducted using the Cochrane Collaboration RevMan 5.2 or STATA package version 12.0 (Stata Corporation, College Station, Texas, USA).

3. Results

3.1. Eligible Studies and Characteristics. A flow chart of detailed searching process is illustrated in Figure 1. Using the described searching strategy above, a total of 549 articles were initially retrieved out of PubMed, Embase, the Cochrane Library, CNKI, and Wan Fang databases. After manually screening the titles, publication types, and abstracts and then checking the full texts by two investigators (Jie Bu and Hui Li), 30 articles were selected for the present meta-analysis [36–65]. Among these eligible studies, 20 studies evaluated the prognostic effect of miR-126 for OS, 8 studies for DFS, and 6/4/3 studies for PFS/RFS/DSS.

The main characteristics and basic information of eligible studies were listed in Table 1 and Table S1 (in Supplementary Material available online at http://dx.doi.org/10.1155/2015/739469). A total of 4497 patients from the United States [63, 65], Spain [53], Japan [36, 37, 57], China [43–48, 51, 52, 58, 62, 64], South Korea [41], Netherlands [38], Norway [40], France [39], Bosnia and Herzegovina [42], Serbia [42], Denmark [49, 50, 54–56], Sweden [55], Canada [61], and Germany [59, 60] were diagnosed with a wide range of carcinomas, including acute myeloid leukemia [36, 38], adult T-cell leukemia [37], non-small cell lung cancer [39–44], colorectal cancer [49, 50, 52, 54–56], laryngeal squamous cell carcinoma [48], esophageal squamous cell cancer [63], hepatocellular carcinoma [45, 46], colon cancer [51, 53], cervical cancer [47], prostate cancer [58], oral cancer [57], breast cancer [59], clear cell renal cell carcinoma [60, 61], esophageal squamous cell carcinoma [62–64], and glioblastoma multiforme [65]. The sample size ranged from 35 to 560. The expression of miR-126 was most often examined in cancerous tissue, while 5 studies examined it in serum/plasma and 1 study tested it in bone marrow. The majority of these studies assessed miR-126 expression by quantitative real-time PCR (qRT-PCR), and in situ hybridization (ISH) was applied in six studies. The most frequently used cut-off value was the median which was applied in 19 studies and the other values were different.

3.2. OS Associated with miR-126 Expression. The main results of this meta-analysis were displayed in Table 2. 20 studies
#### Table 1: Main characteristics of enrolled studies in the systematic review.

| Author          | Year | Country          | Cancer          | Number | Specimen   | Assay          | Cut-off value | Source of HR | Endpoint | Median follow-up (months) |
|-----------------|------|------------------|------------------|--------|------------|----------------|---------------|--------------|----------|--------------------------|
| Shibayama et al. [36] | 2015 | Japan            | AML              | 108    | Bone marrow | qRT-PCR        | Median        | R            | OS       | NR                       |
| Ishihara et al. [37] | 2012 | Japan            | ATL              | 35     | Plasma      | qRT-PCR        | Median        | SC          | OS       | NR                       |
| de L. euev et al. [38] | 2014 | Netherlands      | AML              | 92     | Blood       | qRT-PCR        | Median        | R            | OS, EFS, RFS | NR                       |
| Sanfiozoeno et al. [39] | 2013 | France           | NSCLC            | 52     | Plasma      | qRT-PCR        | Median        | R            | DFS      | 46                       |
| Donnem et al. [40] | 2011 | Norway           | NSCLC            | 332    | Tissue      | ISH Expression score ≥ 2 | Median        | DSS         | 86       | 31                       |
| Kim et al. [41] | 2014 | South Korea      | NSCLC            | 72     | Tissue      | qRT-PCR        | Median        | R            | OS       | 5.13                     |
| Jusufović et al. [42] | 2012 | Serbia           | NSCLC            | 50     | Tissue      | qRT-PCR        | Median        | R            | OS, DFS   | 24.39–29.28 |
| Yang et al. [43] | 2012 | China            | NSCLC            | 442    | Tissue      | qRT-PCR        | Median        | R            | OS       | 42.89                    |
| Donnem et al. [44] | 2012 | China            | NSCLC            | 49     | Tissue      | qRT-PCR        | Median        | SC          | OS, DFS   | 49                       |
| Han et al. [45] | 2012 | China            | NSCLC            | 105    | Tissue      | qRT-PCR Fold change = 2 | Median        | R            | OS       | 60 (max)                |
| Chet al. [46] | 2012 | China            | NSCLC            | 68     | Tissue      | qRT-PCR 0.70 (ROC curve) | SC          | OS          | 45.66–55.04 |
| Donnem et al. [47] | 2012 | China            | Cervical cancer  | 133    | Tissue      | qRT-PCR        | Median        | R            | OS       | 16.8–26.2               |
| Hansen et al. [48] | 2012 | Denmark          | CRC              | 89     | Tissue      | qRT-PCR        | Median        | SC          | OS       | 8.8–9.2                |
| Hansen et al. [49] | 2014 | Denmark          | CRC              | 63     | Plasma      | qRT-PCR        | Median        | R            | DFS      | 3–10 years              |
| Li et al. [51] | 2013 | China            | Colon cancer     | 53     | Tissue      | qRT-PCR        | Median        | R            | OS, DFS   | 7 years (max)            |
| Liu et al. [52] | 2014 | China            | CRC              | 92     | Tissue      | qRT-PCR        | Median        | SC          | OS       | 65                       |
| Diaz et al. [53] | 2014 | Spain            | Colon cancer     | 110    | Tissue      | qRT-PCR        | Median        | R            | OS, DFS   | 68                       |
| Hansen et al. [54] | 2014 | Denmark          | CRC              | 81     | Tissue      | qRT-PCR        | Median        | R            | OS, DFS   | NR                       |
| Hansen et al. [55] | 2014 | Denmark/Sweden   | CRC              | 89     | Tissue      | qRT-PCR        | Median        | R            | PFS      | NR                       |
| Hansen et al. [56] | 2015 | Denmark          | CRC              | 560    | Tissue      | qRT-PCR        | Median        | R            | OS, DSS   | 3.4 years               |
| Sasahira et al. [57] | 2012 | Japan            | Oral cancer      | 94     | Tissue      | qRT-PCR        | Means         | R            | DFS      | NR                       |
| Sun et al. [58] | 2015 | China            | Prostate cancer  | 128    | Tissue      | qRT-PCR        | Median        | SC          | RFS      | 48.6                     |
| Hoppe et al. [59] | 2013 | Germany          | Breast cancer    | 80     | Tissue      | qRT-PCR 6.20 (ROC curve) | R            | RFS        | 8.84 years              |
| Vergho et al. [60] | 2014 | Germany          | cRCC             | 37     | Tissue      | qRT-PCR        | 3.57 (ROC curve) | DSS         | 41.4                  |
| Khella et al. [61] | 2015 | Canada           | cRCC             | 257,481 | Tissue      | qRT-PCR        | 20th percentile | R            | OS, DFS, OS | 86                       |
| Liu et al. [62] | 2015 | China            | ESCC             | 185    | Tissue      | qRT-PCR        | Fold change > 3 | R            | DSS      | 32                       |
| Hu et al. [63] | 2015 | USA              | ESCC             | 158    | Tissue      | qRT-PCR        | 1–3+/0.5–0.5  | R            | OS, DFS   | 16.25                    |
| Wang et al. [64] | 2013 | China            | ESCC             | 116    | Tissue      | qRT-PCR        | ΔΔCT < −1     | SC          | DFS      | 21–32                   |
| Feng et al. [65] | 2012 | USA              | GBM              | 248    | Tissue      | qRT-PCR        | Median        | R            | PFS/RFS, OS | NR                       |

**Notes:** CRC: colorectal cancer; HCC: hepatocellular carcinoma; NSCLC: non-small cell lung cancer; cRCC: clear renal cell carcinoma; ESCC: esophageal squamous cell carcinoma; AML: acute myeloid leukemia; ATL: adult T-cell leukemia; LSCC: laryngeal squamous cell carcinoma; GBM: glioblastoma multiforme; qRT-PCR: quantitative real-time PCR; ISH: in situ hybridization; OS: overall survival; DFS: disease-free survival; RFS: recurrence-free survival; PFS: progression-free survival; DSS: disease-specific survival; HR: hazard ratio; SC: survival curve; NR: not reported; R: reported.

*a* DSS included any of the following: DSS, CSS (cancer-specific survival). *b* Data extracted from TCGA (The Cancer Genome Atlas) in the paper.
Table 2: Meta-analysis results.

| Outcome | Variables | Number of studies | Number of patients | Model   | HR (95% CI)     | Heterogeneity | Publication bias |
|---------|-----------|-------------------|--------------------|---------|-----------------|---------------|------------------|
|         |           |                   |                    |         |                 | $I^2$ (%)      | Begg's $P$       | Egger's $P$       |
| OS      | All       | 20                | 3232               | Random  | 0.77 (0.64, 0.93) | 56.8          | 0.001           | 0.381            | 0.358            |
|         | Tumor type|                   |                    |         |                 |               |                 |                  |                  |
|         | NSCLC     | 4                 | 613                | Random  | 0.42 (0.17, 1.08) | 82.2          | 0.001           | 1.000            | 0.340            |
|         | HCC       | 2                 | 173                | Fixed   | 0.65 (0.49, 0.86) | 2.60          | 0.311           |                  |                  |
|         | CRC       | 5                 | 896                | Fixed   | 0.85 (0.69, 1.04) | 0             | 0.584           | 0.806            | 0.679            |
|         | RCC       | 2                 | 738                | Fixed   | 0.65 (0.38, 1.12) | 0             | 0.624           |                  |                  |
|         | AML       | 2                 | 200                | Fixed   | 1.77 (1.15, 2.72) | 0             | 0.666           |                  |                  |
|         | Ethnicity |                   |                    |         |                 |               |                 |                  |                  |
|         | Asian     | 12                | 1353               | Fixed   | 0.76 (0.66, 0.88) | 37.0          | 0.129           | 0.837            | 0.668            |
|         | Caucasian | 8                 | 1879               | Random  | 0.77 (0.57, 1.05) | 73.8          | <0.001          | 0.536            | 0.479            |
| Sample  | Circulation| 4                | 273                | Fixed   | 1.65 (1.09, 2.51) | 0             | 0.647           | 0.734            | 0.162            |
|         | Tissue    | 16                | 2959               | Random  | 0.71 (0.60, 0.85) | 51.1          | 0.01            | 0.137            | 0.068            |
|         | Assay method|               |                    |         |                 |               |                 |                  |                  |
|         | qRT-PCR   | 17                | 2940               | Random  | 0.72 (0.58, 0.90) | 61.2          | <0.001          | 0.303            | 0.250            |
|         | ISH       | 3                 | 292                | Fixed   | 1.00 (0.75, 1.34) | 0             | 0.804           | 1.000            | 0.646            |
| Analysis type |          |                   |                    |         |                 |               |                 |                  |                  |
|         | Multivariate|    | 7                 | 1870    | Fixed   | 0.81 (0.72, 0.90) | 11.0          | 0.344           | 0.072            | 0.095            |
|         | Univariate| 7                 | 1530               | Random  | 0.89 (0.79, 1.00) | 66.4          | 0.007           | 1.000            | 0.990            |
| HR estimated |          |                   |                    |         |                 |               |                 |                  |                  |
|         | HRs reported|       | 14                | 2897    | Random  | 0.78 (0.64, 0.96) | 67.8          | <0.001          | 0.274            | 0.461            |
|         | K-M curve | 6                 | 335                | Fixed   | 0.79 (0.53, 1.18) | 0             | 0.666           | 1.000            | 0.705            |
| DFS     | All       | 7                 | 755                | Fixed   | 0.64 (0.48, 0.85) | 0             | 0.780           | 0.133            | 0.203            |
|         | Tumor type|                   |                    |         |                 |               |                 |                  |                  |
|         | NSCLC     | 2                 | 101                | Fixed   | 0.49 (0.26, 0.93) | 0             | 0.983           |                  |                  |
|         | ESCC      | 2                 | 274                | Fixed   | 0.77 (0.48, 1.24) | 0             | 0.629           |                  |                  |
| Ethnicity | Asian     | 4                 | 417                | Fixed   | 0.64 (0.44, 0.94) | 0             | 0.532           | 0.308            | 0.081            |
|         | Caucasian | 3                 | 419                | Fixed   | 0.63 (0.41, 0.97) | 0             | 0.599           | 1.000            | 0.874            |
| Analysis type |          |                   |                    |         |                 |               |                 |                  |                  |
|         | Multivariate|    | 3                 | 509     | Fixed   | 0.65 (0.45, 0.94) | 0             | 0.384           | 0.296            | 0.360            |
|         | Univariate| 4                 | 619                | Random  | 0.67 (0.50, 0.90) | 88.0          | <0.001          | 0.734            | 0.586            |
| RFS/PFS/DSS |          |                   |                    |         |                 |               |                 |                  |                  |
|         | All       | 13                | 2014               | Random  | 0.70 (0.50, 0.98) | 84.8          | <0.001          | 0.360            | 0.288            |
|         | Tumor type|                   |                    |         |                 |               |                 |                  |                  |
|         | CRC       | 5                 | 882                | Fixed   | 0.74 (0.59, 0.94) | 47.3          | 0.108           | 1.000            | 0.514            |
|         | NSCLC     | 2                 | 382                | Random  | 0.43 (0.03, 7.25) | 97.2          | <0.001          |                  |                  |
| Ethnicity | Asian     | 2                 | 313                | Fixed   | 0.69 (0.48, 0.99) | 0             | 0.417           |                  |                  |
|         | Caucasian | 11                | 1701               | Random  | 0.69 (0.46, 1.02) | 87.1          | <0.001          | 0.213            | 0.267            |
| Analysis type |          |                   |                    |         |                 |               |                 |                  |                  |
|         | Multivariate|    | 7                 | 1531    | Random  | 0.71 (0.50, 1.02) | 83.2          | <0.001          | 0.230            | 0.281            |
|         | Univariate| 5                 | 651                | Random  | 0.89 (0.77, 1.02) | 81.4          | <0.001          | 0.462            | 0.872            |

CRC: colorectal cancer; HCC: hepatocellular carcinoma, NSCLC: non-small cell lung cancer; cRCC: clear renal cell carcinoma; ESCC: esophageal squamous cell carcinoma; AML: acute myeloid leukemia; K-M curve: Kaplan-Meier curve; fixed: fixed-effects model; random: random-effects model.
including 3232 cancer patients investigated the relationship between miR-126 expression and the prognosis. For these studies evaluating OS for miR-126, a random-effects model was utilized to calculate the pooled HR and its 95% CI due to the high heterogeneity among these studies ($I^2 = 57.0\%$, $P = 0.001$). The result showed that high miR-126 level may predict a favorable OS with the combined HR of 0.77 (95% CI: 0.64–0.93, $P_{\text{heterogeneity}} = 0.001$) (Table 2, Figure 2(a)).

Furthermore, six subgroup analyses of overall survival were performed which stratified patients by tumor type, ethnicity, sample, assay method, analysis type, and HR estimated (Table 2). Subgroup analyses by tumor type showed that high miR-126 levels were significantly associated with a favorable OS in HCC (HR = 0.65, 95% CI 0.49–0.86, $P_{\text{heterogeneity}} = 0.311$). However, AML indicated the opposite result (HR = 1.77, 95% CI 1.15–2.72, $P_{\text{heterogeneity}} = 0.666$). In the subgroup analyses by sample type, high miR-126 levels were predictive of better outcome OS in tissue sample (HR = 0.71, 95% CI 0.60–0.85, $P_{\text{heterogeneity}} = 0.01$). While elevated miR-126 yielded a worse OS in circulation sample (HR = 1.65, 95% CI 1.09–2.51, $P_{\text{heterogeneity}} = 0.647$). With further analyses of studies evaluating OS by ethnicity, we found that the high expression of miR-126 was a significantly favorable predictor for OS in Asians (HR = 0.76, 95% CI 0.66–0.88, $P_{\text{heterogeneity}} = 0.129$). Similarly, this conclusion was also found in other subgroups of qRT-PCR assay (HR = 0.72, 95% CI 0.58–0.90, $P_{\text{heterogeneity}} < 0.001$), multivariate analysis (HR = 0.81, 95% CI 0.72–0.90, $P_{\text{heterogeneity}} = 0.344$), and HRs reported (HR = 0.78, 95% CI 0.64–0.96, $P_{\text{heterogeneity}} \leq 0.001$) (Table 2).

3.3. DFS Associated with miR-126 Expression. 7 studies included 755 cancer patients evaluated DFS for miR-126, a fixed-effects model was used to assess the pooled effect size due to no heterogeneity among the studies ($I^2 = 0\%$, $P = 0.983$) (Table 2), and we found that high expression of miR-126 was demonstrated to predict favorable DFS in various cancer (HR = 0.64, 95% CI 0.48–0.85, $P_{\text{heterogeneity}} = 0.780$) (Table 2, Figure 2(b)).

Similar to OS analyses, we also performed subtotal investigation for DFS analyses (Table 2). In the subgroup analyses by tumor type, high miR-126 levels were significantly associated with a favorable DFS in NSCLC (HR = 0.49, 95% CI 0.26–0.93, $P_{\text{heterogeneity}} = 0.983$). And for ethnicity and analysis type, the high expression of miR-126 was still a significantly better prognosis for DFS (Asian: HR = 0.64, 95% CI 0.44–0.94, $P_{\text{heterogeneity}} = 0.532$; Caucasian: HR = 0.63, 95% CI 0.41–0.97, $P_{\text{heterogeneity}} = 0.599$; multivariate: HR = 0.65, 95% CI 0.45–0.94, $P_{\text{heterogeneity}} = 0.384$; univariate: HR = 0.67, 95% CI 0.50–0.90; $P_{\text{heterogeneity}} < 0.001$).

3.4. PFS/RFS/DSS Associated with miR-126 Expression. We combined the results for PFS, RFS, and DSS together as PFS/RFS/DSS. A total of 13 studies including 2014 tumor patients focused on PFS/RFS/DSS analysis with significant
Figure 2: Forest plots of studies evaluating the pooled HR of elevated miR-126 levels for overall survival (OS) (a), disease-free survival (DFS) (b), and recurrence-free survival/progression-free survival/disease-specific survival (PFS/RFS/DSS) (c). Fixed-effects (b) and random-effects (a, c) models were used as the pooling method, respectively.
heterogeneity among them ($I^2 = 67.8\%, P < 0.001$). A random-effects model was applied, and elevated expression of miR-126 was a significant predictor of favorable PFS/RFS/DSS (HR = 0.70, 95% CI 0.50–0.98, $P_{\text{heterogeneity}} = 0.161$) (Table 2, Figure 2(c)).

In the subgroup analysis of patients with tumor type, the pooled HR indicated that the high expression of miR-126 was a favorable prognostic marker in CRC (HR = 0.74, 95% CI 0.59–0.94, $P_{\text{heterogeneity}} = 0.108$) (Table 2). The same trend was found in subgroup of Asians (HR = 0.69, 95% CI 0.48–0.99, $P_{\text{heterogeneity}} = 0.417$) (Table 2).

3.5. Heterogeneity Analysis. Obvious heterogeneity of subjects was observed among 13 of the 30 analysis groups, as shown in Table 2. We performed a meta-regression analysis to investigate the sources of this heterogeneity in the OS analysis group ($P = 0.001$, $I^2 = 57\%$). The obvious heterogeneity was induced by tumor sample ($P = 0.017$) rather than tumor type ($P = 0.751$), miR-126 assay method ($P = 0.306$), patients origin ($P = 0.631$), cut-off values ($P = 0.772$), publication year ($P = 0.971$), and HRs estimate ($P = 0.836$).

3.6. Publication Bias and Sensitivity Analysis. Begg’s funnel plot and Egger’s test were used to assess the potential publication bias of the included studies. The funnel plots of the OS, DFS, and PFS/RFS/DSS analyses based on tissue and blood miR-126 did not reveal any evidence of obvious asymmetry. Moreover, the $P$ values of Egger’s and Begg’s tests were all greater than 0.05 in the 30 analysis groups (Table 2, Figure 3, and Figures S1 and S3). Hence, there was no obvious risk of publication bias in our meta-analysis.

Furthermore, we performed sensitivity analysis to investigate the influence of each individual study on the overall meta-analysis estimate, which computes the pooled HRs by omitting one study in each turn. And there was no obvious influence of individual study on the pooled HRs (Figure 4 and Figures S2 and S4).

4. Discussion

Cancer is considered one of the leading causes of death worldwide. The occurrence of cancer is increasing because of the growth and aging of the population, as well as increasing prevalence of established risk factors [66]. Despite the advances in technology and its access, to date, there are few defined prognostic and diagnostic biomarkers available in cancers. Essentially, high cancer mortality rates have remained high, mainly due to the late diagnosis and lack of prognostic markers for various cancers [67]. Hence, many research groups are carrying out studies to develop biomarkers, which can be applied to early detection and correlation of treatment efficacy and prognosis [68].

MiR-126, which is highly expressed in vascular endothelial cells, is one of the most commonly observed cancer-related miRNAs and is dysregulated in most cancers. As one of the major targets of miR-126, EGFL7 is known to be involved in cell migration and the process of angiogenesis. The conclusion suggests that one of the main functions of miR-126 is to inhibit angiogenesis to reduce blood vessels, which is facilitated by cell migration [69, 70]. Additionally, previous studies have demonstrated that miR-126 may play a role in tumorigenesis and growth by regulating the vascular endothelial growth factor (VEGF)/phosphoinositols 3-kinase (PI3K)/AKT signaling pathways [43, 71]. miR-126 also maintains its role as a suppressor of metastasis that could reduce metastatic rate and size of carcinoma [14, 72]. Furthermore, interactions of miR-126 and ADAM9 are related to epithelial-mesenchymal transition and the invasive growth of pancreatic cancer cells [73]. In most of the cancers studied, miR-126 functioned as a tumor suppressor and its expression was suppressed; however, several reports using different types of samples have described an oncogenic role for miR-126. Notably, several studies have shown that miR-126 is upregulated in some malignancies due to high tissue specificity, such as gastric cancer, liver cancer, ovarian cancer, and acute myeloid leukemia [19, 20, 74, 75]. In addition, miR-126 acting as an oncogene, which was found to downregulate HOXA9/PLK, was often upregulated in myeloid leukemia and associated with poor prognosis [22, 76]. Moreover, higher expression of miR-126 was shown to be a poor prognostic factor in NSCLC and promote metastasis in prostate cancer [77, 78]. Obviously, it is controversial that miR-126 expression can be used as a prognostic biomarker in different cancers. Hence, in order to evaluate the prognostic role of miR-126 expression in various cancers, we systematically reviewed the published studies and performed a meta-analysis for the first time.

In terms of this, a total of 4497 participants from 30 studies finally were included into the meta-analysis. This result showed that high expression of miR-126 was a significant marker for predicting better outcomes of various cancers (HR was 0.77, 0.64, and 0.70 for OS, DFS, and RFS/PFS/DSS, resp.). For OS, stratified analyses displayed that high expression of miR-126 was a better prognostic marker in HCC, Asians, tissue sample, qRT-PCR assay, multivariate analysis, and HRs reported. However, AML and circulation sample indicated the opposite result. For DFS, subgroup analyses revealed that high expression of miR-126 could predict a favorable DFS in NSCLC, Asian, Caucasian, multivariate, and univariate subgroups. Furthermore, we found that high
expression of miR-126 significantly relates to a favorable RFS/PFS/DSS in CRC and Asian subgroup, but no statistical significance is shown in NSCLC, Caucasian, multivariate, and univariate analysis. Additionally, there was no obvious risk of publication bias in our meta-analysis. From the above results, we found that high expression of tissue miR-126 was a positive prognostic factor in cancer patients. But high circulating miR-126 levels predicted a significantly worse OS in patients with cancer. As we know, circulating samples are more convenient to collect and keep monitored, which can effectively evaluate prognosis during or after clinical therapy. Therefore, circulating miR-126 may be an efficacious method for dynamically monitoring the prognosis and therapeutic effects in cancer patients. In this study, only four studies investigated circulating samples, and more studies on these cancers are needed in the future.

Although the present meta-analysis revealed that the expression of miR-126 in cancer patients could be a valuable prognostic biomarker for patients, some limitations should be noticed. Firstly, there was significant heterogeneity existing in our meta-analysis, which was probably attributed to the differences in baseline demographic characters of population, characteristics of patients, the types of cancer, the samples of cancer, the disease stages, the cut-off criteria, the duration of follow-up, and so on. Secondly, several HRs were calculated based on the data extracted from the survival curve; some minor differences exist between the exact HRs and the extrapolated data. Thirdly, due to the lack of a unified cut-off value in miR-126 expression, cut-off values were not consistent among included studies. The different cut-off values may influence the availability of miR-126 as a prognostic biomarker in human cancer. Fourth, in subgroup analyses by sample type and subtype analyses, the number of studies was relatively small. More studies on these cancers are needed in the future. Finally, treatments may influence the expression of miR-126 in cancer samples; however, few researches referred to the treatment effect on HRs or miR-126 expression.

5. Conclusion

In sum, in this meta-analysis, we concluded that overexpression of miR-126 was effectively predictive of better prognosis in various carcinomas. Increased miR-126 level in cancerous tissues was associated with favorable OS, DFS, and PFS/RFS/DSS, while elevated circulating miR-126 was indicative of poor OS. However, our results should be regarded cautiously due to the limitations of the present analysis listed above. Further prospective multicenter studies with larger sample size are needed to focus on the relationship between miR-126 and cancer prognosis as well as to explore effective therapies.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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References

[1] J. Lu, G. Getz, E. A. Miska et al., "MicroRNA expression profiles classify human cancers," *Nature*, vol. 435, no. 7043, pp. 834–838, 2005.

[2] Y. Suarez and W. C. Sessa, "MicroRNAs as novel regulators of angiogenesis," *Circulation Research*, vol. 104, no. 4, pp. 442–454, 2009.

[3] R. Garzon, M. Fabbri, A. Cimmino, G. A. Calin, and C. M. Croce, "MicroRNA expression and function in cancer," *Trends in Molecular Medicine*, vol. 12, no. 12, pp. 580–587, 2006.
[4] Z. Li and T. M. Rana, “Therapeutic targeting of microRNAs: current status and future challenges,” Nature Reviews Drug Discovery, vol. 13, no. 8, pp. 622–638, 2014.

[5] L. P. Lim, N. C. Lau, P. Garrett-Engele et al., “Microarray analysis shows that some microRNAs downregulate large numbers of target mRNAs,” Nature, vol. 433, no. 7027, pp. 769–773, 2005.

[6] V. Ambros, “The functions of animal microRNAs,” Nature, vol. 431, no. 7006, pp. 350–355, 2004.

[7] M. Ferracin, A. Veronese, and M. Negrini, “Micromarkers: miRNAs in cancer diagnosis and prognosis,” Expert Review of Molecular Diagnostics, vol. 10, no. 3, pp. 297–308, 2010.

[8] J. E. Fish, M. M. Santoro, S. U. Morton et al., “miR-126 regulates angiogenic signaling and vascular integrity,” Developmental Cell, vol. 15, no. 2, pp. 272–284, 2008.

[9] J. Meister and M. H. H. Schmidt, “miR-126 and miR-126: new players in cancer,” TheScientificWorldJournal, vol. 10, pp. 2090–2100, 2010.

[10] S. Wang, A. B. Aurora, B. A. Johnson et al., “The endothelial-specific microRNA miR-126 governs vascular integrity and angiogenesis,” Developmental Cell, vol. 15, no. 2, pp. 261–271, 2008.

[11] T. A. Harris, M. Yamakuchi, M. Ferlito, J. T. Mendell, and C. J. Lowenstein, “MicroRNA-126 regulates endothelial expression of vascular cell adhesion molecule 1,” Proceedings of the National Academy of Sciences of the United States of America, vol. 105, no. 5, pp. 1516–1521, 2008.

[12] Y. Zhou, X. Feng, Y.-L. Liu et al., “Down-regulation of miR-126 is associated with colorectal cancer cells proliferation, migration and invasion by targeting IRS-1 via the AKT and ERK1/2 signaling pathways,” PLoS ONE, vol. 8, no. 11, Article ID e81203, 2013.

[13] B. Liu, X.-C. Peng, X.-L. Zheng, J. Wang, and Y.-W. Qin, “MiR-126 restoration down-regulate VEGF and inhibit the growth of lung cancer cell lines in vitro and in vivo,” Lung Cancer, vol. 66, no. 2, pp. 169–175, 2009.

[14] S. F. Tavazoie, C. Alarcón, T. Oskarsson et al., “Endogenous human microRNAs that suppress breast cancer metastasis,” Nature, vol. 451, no. 7175, pp. 147–152, 2008.

[15] R. Feng, X. Chen, Y. Yu et al., “miR-126 functions as a tumour suppressor in human gastric cancer,” Cancer Letters, vol. 298, no. 1, pp. 50–63, 2010.

[16] Z. Li, N. Li, M. Wu, X. Li, Z. Luo, and X. Wang, “Expression of miR-126 suppresses migration and invasion of colon cancer cells by targeting CXCR4,” Molecular and Cellular Biochemistry, vol. 381, no. 1-2, pp. 233–242, 2013.

[17] L. R. Jiao, A. E. Frampton, J. Jacob et al., “Micronas targeting oncogenes are down-regulated in pancreatic malignant transformation from benign tumors,” PLoS ONE, vol. 7, no. 2, Article ID e32068, 2012.

[18] X. Yang, H. Wu, and T. Ling, “Suppressive effect of microRNA-126 on oral squamous cell carcinoma in vitro,” Molecular Medicine Reports, vol. 10, no. 1, pp. 125–130, 2014.

[19] T. Otsubo, Y. Akiyama, Y. Hashimoto, S. Shimada, K. Goto, and Y. Yuasa, “Microrna-126 inhibits SOX2 expression and contributes to gastric carcinogenesis,” PLoS ONE, vol. 6, no. 1, Article ID e16617, 2011.

[20] I. Barshack, E. Meiri, S. Rosenwald et al., “Differential diagnosis of hepatocellular carcinoma from metastatic tumors in the liver using microRNA expression,” International Journal of Biochemistry and Cell Biology, vol. 42, no. 8, pp. 1355–1362, 2010.

[21] Z. Li and J. Chen, “In vitro functional study of miR-126 in leukemia,” Methods in Molecular Biology, vol. 676, pp. 185–195, 2011.

[22] W.-F. Shen, Y.-L. Hu, L. Uttarwar, E. Passegue, and C. Larmian, “microRNA-126 regulates HOX9A by binding to the homeobox,” Molecular and Cellular Biology, vol. 28, no. 14, pp. 4609–4619, 2008.

[23] M. V. Iorio and C. M. Croce, “MicroRNA dysregulation in cancer: diagnostics, monitoring and therapeutics. A comprehensive review,” EMBO Molecular Medicine, vol. 4, no. 3, pp. 143–159, 2012.

[24] F. Ebrahimi, V. Gopalan, R. A. Smith, and A. K. Lam, “miR-126 in human cancers: clinical roles and current perspectives,” Experimental and Molecular Pathology, vol. 96, no. 1, pp. 98–107, 2014.

[25] D. F. Stroup, J. A. Berlin, S. C. Morton et al., “Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis of Observational Studies in Epidemiology (MOOSE) group,” The Journal of the American Medical Association, vol. 283, no. 15, pp. 2008–2012, 2000.

[26] Y. Shao, Y. Geng, W. Gu, J. Huang, H. Wei, and J. Jiang, “Prognostic role of tissue and circulating microRNA-200c in malignant tumors: a systematic review and meta-analysis,” Cellular Physiology and Biochemistry, vol. 35, no. 3, pp. 1188–1200, 2015.

[27] Z. Zhang, T. Wang, J. Zhang et al., “Prognostic value of epidermal growth factor receptor mutations in resected non-small cell lung cancer: a systematic review with meta-analysis,” PLoS ONE, vol. 9, no. 8, Article ID e106053, 2014.

[28] J. F. Tierney, L. A. Stewart, D. Gershi, and M. R. Sydes, “Practical methods for incorporating summary time-to-event data into meta-analysis,” Trials, vol. 8, article 16, 2007.

[29] M. K. B. Parmar, V. Torri, and L. Stewart, “Extracting summary statistics to perform meta-analyses of the published literature for survival endpoints,” Statistics in Medicine, vol. 17, no. 24, pp. 2815–2834, 1998.

[30] J. Lau, J. P. A. Ioannidis, and C. H. Schmid, “Quantitative synthesis in systematic reviews,” Annals of Internal Medicine, vol. 127, no. 9, pp. 820–826, 1997.

[31] J. P. Higgins and S. G. Thompson, “Quantifying heterogeneity in a meta-analysis,” Statistics in Medicine, vol. 21, no. 11, pp. 1539–1558, 2002.

[32] R. DerSimonian and N. Laird, “Meta-analysis in clinical trials,” Controlled Clinical Trials, vol. 7, no. 3, pp. 177–188, 1986.

[33] N. Mantel and W. Haenszel, “Statistical aspects of the analysis of data from retrospective studies of disease,” Journal of the National Cancer Institute, vol. 22, no. 4, pp. 719–748, 1959.

[34] C. B. Begg and M. Mazumdar, “Operating characteristics of a rank correlation test for publication bias,” Biometrics, vol. 50, no. 4, pp. 1088–1091, 1994.

[35] M. Egger, G. D. Smith, M. Schneider, and C. Minder, “Bias in meta-analysis detected by a simple, graphical test,” Biometrics, vol. 51, no. 2, pp. 1191–1199, 1995.

[36] Y. Shibayama, T. Kondo, H. Ohya, S. Fujisawa, T. Teshima, and K. Iseki, “Upregulation of microRNA-126-5p is associated with drug resistance to cytarabine and poor prognosis in AML patients,” Oncology Reports, vol. 33, no. 5, pp. 2176–2182, 2015.

[37] K. Ishihara, D. Sasaki, K. Tsuruda et al., “Impact of miR-135 and miR-126 as novel biomarkers on the assessment of disease progression and prognosis in adult T-cell leukemia,” Cancer Epidemiology, vol. 36, no. 6, pp. 560–565, 2012.
[38] D. C. de Leeuw, F. Denkers, M. C. Olthof et al., “Attenuation of microRNA-126 expression that drives CD34+38 stem/progenitor cells in acute myeloid leukemia leads to tumor eradication,” Cancer Research, vol. 74, no. 7, pp. 2094−2105, 2014.

[39] C. Sanfiorenzo, M. I. Ilie, A. Belaid et al., “Two panels of plasma microRNAs as non-invasive biomarkers for prediction of recurrence in resectable NSCLC,” PLoS ONE, vol. 8, no. 1, Article ID e54596, 2013.

[40] T. Donnem, K. Lonvik, K. Ekelo et al., “Independent and tissue-specific prognostic impact of miR-126 in non-small cell lung cancer: coexpression with vascular endothelial growth factor A predicts poor survival,” Cancer, vol. 117, no. 14, pp. 3193–3200, 2011.

[41] M. K. Kim, S. B. Jung, J.-S. Kim et al., “Expression of microRNA miR-126 and miR-200c is associated with prognosis in patients with non-small cell lung cancer,” Virchows Archiv, vol. 465, no. 4, pp. 463−471, 2014.

[42] E. Jusufović, M. Rijavec, D. Keser et al., “Let-7b and miR-126 are down-regulated in tumor tissue and correlate with microvessel density and survival outcomes in non-small-cell lung cancer,” PLoS ONE, vol. 7, no. 9, Article ID e45577, 2012.

[43] J. Yang, H. Lan, X. Huang, B. Liu, and Y. Tong, “MicroRNA-126 inhibits tumor cell growth and its expression level correlates with poor survival in non-small cell lung cancer patients,” PLoS ONE, vol. 7, no. 8, Article ID e42978, 2012.

[44] X. Li, G. Wan, Y. Liang, C. Sun, and H. Dong, “Effect of miR-126 on cell cycle regulation and prognosis of lung cancer patients,” Journal of Practical Oncology, vol. 23, no. 5, pp. 440−445, 2014.

[45] Z. B. Han, L. Zhong, M. J. Teng et al., “Identification of recurrence-related microRNAs in hepatocellular carcinoma following liver transplantation,” Molecular Oncology, vol. 6, no. 4, pp. 445−457, 2012.

[46] H. Chen, R. Miao, J. Fan et al., “Decreased expression of miR-126 correlates with metastatic recurrence of hepatocellular carcinoma,” Clinical & Experimental Metastasis, vol. 30, no. 5, pp. 651−658, 2013.

[47] Y. Yang, K. L. Song, H. Chang, and L. Chen, “Decreased expression of microRNA-126 is associated with poor prognosis in patients with cervical cancer,” Diagnostic Pathology, vol. 9, no. 1, article 220, 2014.

[48] X. Sun, Z.-M. Wang, Y. Song, X. U.-H. Tai, W.-Y. Ji, and H. Gu, “MicroRNA-126 modulates the tumor microenvironment by targeting calmodulin-regulated spectrin-associated protein 1 (Camsap1),” International Journal of Oncology, vol. 44, no. 5, pp. 1678−1684, 2014.

[49] T. F. Hansen, F. B. Sørensen, J. Lindebjerg, and A. Jakobsen, “The predictive value of microRNA-126 in relation to first line treatment with capcitabine and oxaliplatin in patients with metastatic colorectal cancer,” BMC Cancer, vol. 12, article 83, 2012.

[50] T. F. Hansen, S. Kjaer-Frifeldt, S. Morthenthaler et al., “The prognostic value of microRNA-126 and microvessel density in patients with stage II colon cancer: results from a population cohort,” Journal of Translational Medicine, vol. 12, no. 1, article 254, 2014.

[51] N. Li, X. Li, S. Huang, S. Shen, and X. Wang, “miR-126 inhibits colon cancer proliferation and invasion through targeting IRS1, SLC7A5 and TOM1 gene,” Zhong Nan Da Xue Xue Bao Yi Xue Ban, vol. 38, no. 8, pp. 809−817, 2013.

[52] Y. Liu, Y. Zhou, X. Feng et al., “Low expression of MicroRNA-126 is associated with poor prognosis in colorectal cancer,” Genes Chromosomes and Cancer, vol. 53, no. 4, pp. 358−365, 2014.

[53] R. Díaz, J. Silva, J. M. García et al., “Deregulated expression of miR-106a predicts survival in human colon cancer patients,” Genes, Chromosomes and Cancer, vol. 47, no. 9, pp. 794−802, 2008.

[54] T. F. Hansen, C. L. Andersen, B. S. Nielsen et al., “Elevated microRNA-126 is associated with high vascular endothelial growth factor receptor 2 expression levels and high microvessel density in colorectal cancer,” Oncology Letters, vol. 2, no. 6, pp. 1101−1106, 2011.

[55] T. F. Hansen, R. D. P. Christensen, R. F. Andersen, F. B. Sørensen, A. Johnsson, and A. Jakobsen, “MicroRNA-126 and epidermal growth factor-like domain 7-angiogenic couple of importance in metastatic colorectal cancer. Results from the Nordic ACT trial,” British Journal of Cancer, vol. 109, no. 5, pp. 1243−1251, 2013.

[56] T. F. Hansen, A. L. Carlsen, N. H. H. Heegaard, F. B. Sørensen, and A. Jakobsen, “Changes in circulating microRNA-126 during treatment with chemotherapy and bevacizumab predicts treatment response in patients with metastatic colorectal cancer,” British Journal of Cancer, vol. 112, no. 4, pp. 624−629, 2015.

[57] T. Sasahira, M. Kurihara, U. K. Bhandal et al., “Downregulation of miR-126 induces angiogenesis and lymphangiogenesis by activation of VEGF-A in oral cancer,” British Journal of Cancer, vol. 107, no. 4, pp. 700−706, 2012.

[59] H. W. Khella, A. Scorilas, R. Mozes et al., “Low expression of miR-126 is a prognostic marker for metastatic clear cell renal cell carcinoma,” The American Journal of Pathology, vol. 185, no. 3, pp. 693−703, 2015.

[60] R. Hoppe, J. Achinger-Kawecka, S. Winter et al., “Increased expression of miR-126 and miR-10a predict prolonged relapse-free time of primary oestrogen receptor-positive breast cancer following tamoxifen treatment,” European Journal of Cancer, vol. 49, no. 17, pp. 3598−3608, 2013.

[61] D. C. Vergho, S. Knetz, C. Kalogirou et al., “Impact of miR-21, miR-126 and miR-221 as prognostic factors of clear cell renal cell carcinoma with tumor thrombus of the inferior vena cava,” PLoS ONE, vol. 9, no. 10, Article ID e109877, 2014.

[62] H. W. Khella, A. Scorilas, R. Mozes et al., “Low expression of miR-126 is a prognostic marker for metastatic clear cell renal cell carcinoma,” Journal of International Oncology, vol. 12, article 83, 2011.

[63] Y. Hu, A. M. Correa, A. Hoque et al., “Prognostic significances of microRNA-126 and microRNA-7 in esophageal squamous cell carcinoma,” International Journal of Oncology, vol. 49, no. 4, pp. 1320−1326, 2011.

[64] J. Wang, Z. Ling, and W. Mao, “Expression and clinical significances of microRNA-126 and microRNA-7 in esophageal squamous cell carcinoma,” Journal of International Oncology, vol. 40, no. 12, pp. 936−940, 2013.

[65] J. Feng, S.-T. Kim, W. Liu et al., “A integrated analysis of germline and somatic, genetic and epigenetic alterations at 9p21.3 in glioblastoma,” Cancer, vol. 118, no. 1, pp. 232−240, 2012.

[66] L. A. Torre, F. Bray, R. L. Siegel, J. Ferlay, J. Lortet-Tieulent, and A. Jemal, “Global cancer statistics, 2012,” CA: A Cancer Journal for Clinicians, vol. 65, no. 2, pp. 87−108, 2015.
[67] D. Paul, A. Kumar, A. Gajbhiye, M. K. Santra, and R. Srikanth, “Mass spectrometry-based proteomics in molecular diagnostics: discovery of cancer biomarkers using tissue culture,” BioMed Research International, vol. 2013, Article ID 783131, 16 pages, 2013.

[68] C. A. Gonzalez and A. Agudo, “Carcinogenesis, prevention and early detection of gastric cancer: where we are and where we should go,” International Journal of Cancer, vol. 130, no. 4, pp. 745–753, 2012.

[69] Y.-Q. Sun, F. Zhang, Y.-F. Bai, and L.-L. Guo, “miR-126 modulates the expression of epidermal growth factor-like domain 7 in human umbilical vein endothelial cells in vitro,” Nan Fang Yi Ke Da Xue Xue Bao, vol. 30, no. 4, pp. 767–770, 2010.

[70] K. J. Png, N. Halberg, M. Yoshida, and S. F. Tavazoie, “A microRNA regulon that mediates endothelial recruitment and metastasis by cancer cells,” Nature, vol. 481, no. 7380, pp. 190–194, 2012.

[71] N. Zhu, D. Zhang, H. Xie et al., “Endothelial-specific intron-derived miR-126 is down-regulated in human breast cancer and targets both VEGFA and PIK3R2,” Molecular and Cellular Biochemistry, vol. 351, no. 1-2, pp. 157–164, 2011.

[72] C. Du, Z. Lv, L. Cao et al., “MiR-126-3p suppresses tumor metastasis and angiogenesis of hepatocellular carcinoma by targeting LRP6 and PIK3R2,” Journal of Translational Medicine, vol. 12, article 259, 2014.

[73] S. Hamada, K. Satoh, W. Fujibuchi et al., “MiR-126 acts as a tumor suppressor in pancreatic cancer cells via the regulation of ADAM9,” Molecular Cancer Research, vol. 10, no. 1, pp. 3–10, 2012.

[74] K. E. Resnick, H. Alder, J. P. Hagan, D. L. Richardson, C. M. Croce, and D. E. Cohn, “The detection of differentially expressed microRNAs from the serum of ovarian cancer patients using a novel real-time PCR platform,” Gynecologic Oncology, vol. 112, no. 1, pp. 55–59, 2009.

[75] G. Cammarata, L. Augugliaro, D. Salemi et al., “Differential expression of specific microRNA and their targets in acute myeloid leukemia,” American Journal of Hematology, vol. 85, no. 5, pp. 331–339, 2010.

[76] Z. Li, J. Lu, M. Sun et al., “Distinct microRNA expression profiles in acute myeloid leukemia with common translocations,” Proceedings of the National Academy of Sciences of the United States of America, vol. 105, no. 40, pp. 15535–15540, 2008.

[77] T. Donnem, C. G. Fenton, K. Lonvik et al., “MicroRNA signatures in tumor tissue related to angiogenesis in non-small cell lung cancer,” PLoS ONE, vol. 7, no. 1, Article ID e29671, 2012.

[78] A. Watahiki, Y. Wang, J. Morris et al., “MicroRNAs associated with metastatic prostate cancer,” PLoS ONE, vol. 6, no. 9, Article ID e24950, 2011.