The Diagnostic Value of MicroRNAs as a Biomarker for Hepatocellular Carcinoma: A Meta-Analysis

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Received 10 August 2019; Revised 15 October 2019; Accepted 5 November 2019; Published 29 November 2019

Academic Editor: Kosei Maemura

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Background. Recently, the role of microRNAs (miRNAs) in diagnosing cancer has been attracting increasing attention. However, few miRNAs have been applied in clinical practice. The purpose of this study was to evaluate the diagnostic efficacy of miRNAs for hepatocellular carcinoma (HCC) at early stages clinically.

Methods. A literature search was carried out using PubMed, Web of Science, and EMBASE databases. We explored the diagnostic value of miRNAs in distinguishing HCC from healthy individuals. The quality assessment was performed in Review Manager 5.3 software. The overall sensitivity and specificity and 95% confidence intervals (CIs) were obtained with random-effects models through Stata 14.0 software. And heterogeneity was assessed using Q and I² statistics. Meta-regression and subgroup analyses were conducted based on the sample, nation, quality of studies, and miRNA profiling. The publication bias was evaluated through Deeks’ funnel plot.

Results. A total of 34 studies, involving in 2747 HCC patients and 2053 healthy individuals, met the inclusion criteria in the 33 included literature studies. In the summary receiver operating characteristic (sROC) curve, AUC was 0.92 (95% CI, 0.90–0.94), with 0.84 (95% CI, 0.79–0.88) sensitivity and 0.87 (95% CI, 0.83–0.90) specificity. There was no publication bias (P = 0.48).

Conclusion. miRNAs in vivo can be acted as a potential diagnostic biomarker for HCC, which can facilitate the early diagnosis of HCC in clinical practice.

1. Introduction

Hepatocellular carcinoma (HCC) accounts for more than 90% of primary liver cancers. It is one of the most common malignant tumors in the world and the third leading cause of cancer-related death [1], with an increasing incidence rate in the United States [2]. However, HCC is often diagnosed at an advanced stage, leading to limited treatment [3, 4] and poor prognosis, with a median overall survival of 6–20 months and 5-year survival rate of 3% [5].

HCC is often confirmed by pathological biopsy [6] and immunohistochemistry [7]. However, these methods have high invasiveness, leading to limited clinical application for early HCC screening. The alpha-fetoprotein (AFP) is the most common serum marker in the clinic for HCC routinely screening. However, it is not accurate for the diagnosis of HCC [4]. Given the cutoff value of AFP was 20 μg/L [8], less than 400 μg/L [9], the AFP has limited diagnostic efficacy.

Besides, the imaging techniques are also usually used to early screen HCC patients, including ultrasound (US), computed tomography (CT), and magnetic resonance imaging (MRI) [10]. However, the diagnostic accuracy of the imaging techniques mainly relies on the size of the nodules, and these techniques are insensitive to small HCC nodules [10]. Because of the limited diagnostic value in the previous methods, it is urgent to discover a biomarker for the diagnosis of early HCC. Recently, many studies were focused on the role of microRNAs (miRNAs) in HCC.

miRNAs are highly conservative noncoding RNA, with 19–25 nucleotides [11, 12], resulting in mRNA degradation or inhibiting transcript through combining with mRNA [13, 14], which play an essential role in the formation mechanism of tumor [12, 15, 16]. Moreover, it is characterized by stable in serum or plasma [17], laying a foundation for serum/plasma miRNAs in the diagnosis of tumors. In recent years, miRNAs have higher diagnostic accuracy in...
2. Materials and Methods

2.1. Study Search Strategies. We searched the related studies about the diagnosis of miRNAs for HCC in the Web of Science, EMBASE, and PubMed databases. There was no limit to the published time, languages, and sample source, with the deadline of searching articles (October 08, 2019). To verify the effectiveness of the study, we also manually searched the review papers and other relevant references. The search terms were found in the website of http://fmrs.metstr.com/index.aspx. “Carcinoma, hepatocellular,” “microRNAs,” and “diagnosis” were inputted in http://mesh.metstr.com/, where the entrance words were obtained for literature retrieval.

2.2. Study Selection. Inclusion and exclusion criteria to screen the literature were developed. A study can be included if it met the following criteria: (1) the studies were focused on the expression of miRNAs between HCC patients and healthy controls (HCs); (2) the difference in miRNA expression levels was statistically significant; (3) the data in studies must be complete, including sample size of two groups and sensitivity and specificity evaluation indexes to calculate the value of true positive (TP), false positive (FP), false negative (FN), and true negative (TN) or TP, FP, FN, and TN were directly given in the studies; (4) the purpose of studies was related to the diagnosis of HCC. In addition, the exclusion criteria were described below: (1) the studies were review, systematic evaluation, or meta-analysis; (2) the studies were duplicate; (3) the studies were focused on animal studies and cell culture, without case-control groups of humans; (4) the studies were the abstract of literature, letter to editors, or meetings; (5) the studies lacked complete information; and (6) the papers concentrated only on the survival, treatment, and prognosis of HCC, without involving in the diagnosis of HCC.

2.3. Quality Assessment. The qualitative evaluation of quality assessment was performed using QUADAS-2 tools for diagnostic studies, which included four domains: Patient Selection, Index Test, Reference Standard, and Flow and Timing [29, 30]. And two reviewers (Yao Jiang and Yiqin Li) performed the assessment separately. When encountering the divergence on the same literature, we invited a third individual (Jimin He) to discuss and solve the problem together.

2.4. Data Extraction. The data were extracted by two reviewers (Yao Jiang and Yiqin Li). The following contents need to be extracted: the first author, publication year, country, sample size, age ± standard deviation (SD), proportion of males, miRNAs categories, area under the curve (AUC), sensitivity, specificity, detection method, internal reference, and cutoff value. Besides, we pooled multiple groups of miRNAs in a single study using Meta-disc 1.4 software (https://meta-disc.software.informer.com/1.4/). Finally, the data were obtained in each study on the basis of the same specimen source, including the value of TP, FP, FN, and TN.

2.5. Statistical Analysis. Meta-disc 1.4 and Stata 14.0 software were used for all statistical analysis. And P value less than 0.05 was considered statistically significant. Pooled sensitivity and specificity statistical indicators were analyzed using a random-effects model. The overall diagnostic efficacy was evaluated by the summary receiver operating characteristic (sROC) curve. The threshold effect was investigated based on the Spearman correlation coefficient and P value. And the heterogeneity was assessed using I^2 and chi-square test. When the value of I^2 > 50% and P value < 0.05, the heterogeneity exits. The value of I^2 is 0–40%, 40–70%, and 70–100%, which indicate the low, medium, and high heterogeneity, respectively [31]. In addition, meta-regression and subgroup analyses were further applied to explore the potential sources of heterogeneity. The AUC was an index of diagnostic efficacy, the values ranging from 1.0 to 0.5. The closer the AUC is to 1.0, the better the diagnostic efficacy. At last, Deeks’ funnel plot was used to analyze the potential publication bias [32, 33].
3.3. Quality Assessment. According to the QUADAS-2 tools, we provided an overview of the quality assessment for these studies. In the Index Test aspect, there existed a high risk of bias and applicability concern due to presetting the threshold. Figure 2 shows the details of the quality assessment form.

3.4. Comprehensive Analysis. The threshold effect was evaluated by the Spearman correlation coefficient (−0.537), with the $P$ value of 0.001, showing that the threshold effect existed. Then we analyzed the pooled sensitivity and specificity of miRNAs, with 0.84 (95% CI, 0.79–0.88) sensitivity, 0.87 (95% CI, 0.83–0.90) specificity (Figure 3), and 0.92 (95% CI, 0.90–0.94) AUC in sROC curve (Figure 4). Heterogeneity was found, with $I^2$ of 88.13% in sensitivity and 82.22% in specificity, indicating that the heterogeneity was significant. Subsequently, subgroup analyses were conducted to explore the possible sources of heterogeneity.

3.5. Subgroup Analyses. We divided these studies into four subgroups, including sample, nation, quality, and miRNA profiling. In the nation subgroup, we divided the studies into three groups: China, non-China, and Egypt groups. We found the studies on the Egypt people had superior diagnostic efficacy, with 0.91 (95% CI, 0.79–0.96) sensitivity, 0.92 (95% CI, 0.84–0.97) specificity, 0.97 (95% CI, 0.95–0.98) AUC, 12.0 (95% CI, 5.2–27.5) positive likelihood ratio (PLR), 0.10 (95% CI, 0.04–0.24) negative likelihood ratio (NLR), and 119 (95% CI, 24–592) diagnostic odds ratio (DOR), showing miRNAs had better diagnostic ability for HCC in Egypt. The studies were divided into low- or high-quality subgroup according to the result of quality assessment. Figures 5(a)–5(j) show the diagnostic effect in China, non-China, Egypt, serum, plasma, low-quality, high-quality, single miRNA, multiple miRNAs, and miRNA panel subgroups. The diagnostic efficacy of serum- and plasma-derived miRNAs was the same, with 0.93 AUC (95% CI, 0.90–0.95). And the high-quality subgroup had 0.90 (95% CI, 0.86–0.94) sensitivity, 0.91 (95% CI, 0.85–0.94) specificity, 93 (95% CI, 40–214) DOR, and 0.96 (95% CI, 0.94–0.97) AUC, higher than low-quality subgroup. And miRNA panel had better diagnostic efficacy than single miRNA and multiple miRNAs subgroup, with sensitivity of 0.86 (95% CI, 0.79–0.91), specificity of 0.93 (95% CI, 0.85–0.97), PLR of 12.2 (95% CI, 5.7–27.0), NLR of 0.15 (95% CI, 0.10–0.23), DOR of 81 (95% CI, 28–236), and AUC of 0.95 (95% CI, 0.92–0.96). Table 2 shows the detailed results of subgroup analyses.
| Study          | Year | Country       | Specimen size | HCC ± SD (years) | Age ± SD (years) | Male (%) | Method       | Internal reference | Ref |
|---------------|------|---------------|---------------|-----------------|-----------------|----------|--------------|-------------------|-----|
| Ali, H. E. A. | 2017 | Egypt         | 34            | 25              | 50.03 ± 1.55    | 76.50    | qRT-PCR      | miR-16            | [34]|
| Ali, M. A.    | 2018 | Egypt         | 105           | 45              | 66.70           | 53.30    | qRT-PCR      | RNA U6            | [35]|
| Amr, K. S.    | 2017 | Egypt         | 40            | 20              | 52.03 ± 1.55    | 82.50    | RT-PCR       | RUN6B             | [36]|
| Bhattacharya, S. | 2016 | Columbia      | 39            | 14              | 58.00 ± 1.20    | 78.57    | qRT-PCR      | miR-39            | [37]|
| Chen, X.      | 2019 | China         | 120           | 118             | na              | 81.67    | qRT-PCR      | miR-16            | [38]|
| Chen, Y.      | 2015 | China         | 47            | 31              | na              | 93.62    | qPCR         | miR-16            | [39]|
| Dai, M.       | 2019 | China         | 50            | 50              | 48.60 ± 1.90    | 70.00    | RT-qPCR      | U6                | [40]|
| El Mahdy, H.  | 2019 | Egypt         | 60            | 60              | na              | 58.33    | RT-qPCR      | RNU6              | [41]|
| Bhattacharya, S. | 2017 | Columbia      | 155           | 14              | 58.00 ± 1.20    | 81.94    | RT-PCR       | U6snRNA/Cel-miR-39| [42]|
| Li, L. H.     | 2012 | China         | 86            | 60              | 54.00 ± 1.10    | 75.25    | qRT-PCR      | U6 snRNA          | [43]|
| Li, L. M.     | 2010 | China         | 55            | 50              | 52.83 ± 7.85    | 83.64    | qRT-PCR      | miR-168           | [44]|
| Luo, J.       | 2013 | China         | 85            | 85              | 53.60 ± 1.20    | 82.40    | qPCR         | U6RNA             | [45]|
| Li, L. H.     | 2018 | China         | 75            | 75              | 52.80 ± 9.70    | 94.70    | qRT-PCR      | miR-39            | [46]|
| Matboli, M.   | 2017 | Egypt         | 70            | 38              | na              | 74.30    | qPCR         | RNAU-6            | [47]|
| Ning, S.      | 2019 | China         | 30            | 30              | 50.70 ± 10.56   | 60.00    | qRT-PCR      | miR-16            | [48]|
| Shaheen, N. M. H. | 2017 | Egypt         | 40            | 40              | 58.00 ± 8.60    | 65.00    | qRT-PCR      | cel-miR-39        | [49]|
| Shaker, O.    | 2019 | Egypt         | 36            | 36              | 59.92 ± 7.47    | 77.78    | RT-qPCR      | SNORD68           | [50]|
| Shen, J.      | 2013 | New York      | 49            | 49              | 61.10 ± 11.70   | 84.00    | qRT-PCR      | U6snRNA           | [51]|
| Shen, X.      | 2018 | China         | 70            | 45              | na              | 65.71    | qRT-PCR      | U6                | [52]|
| Tan, Y.       | 2014 | China         | 103           | 60              | 52.01 ± 10.21   | 73.80    | qRT-PCR      | miRNA-24          | [53]|
| Tomimaru, Y.  | 2012 | China         | 126           | 50              | 63.00 ± 10.00   | 78.60    | qRT-PCR      | miR-16            | [54]|
| Wang, F.      | 2016 | China         | 76            | 55              | na              | 86.84    | qRT-PCR      | cel-miR-39        | [55]|
| Wang, Y.      | 2018 | China         | 50            | 50              | 56.32 ± 9.71    | 80.00    | qPCR         | na                | [56]|
| Xie, Y.       | 2014 | China         | 67            | 30              | 51.69 ± 10.43   | 85.10    | qRT-PCR      | cel-miR-39        | [57]|
| Xu, L. J.     | 2018 | China         | 100           | 100             | 54.90 ± 13.10   | 74.00    | qRT-PCR      | miR-U6            | [58]|
| Yang, L.      | 2016 | China         | 156           | 64              | na              | na       | qRT-PCR      | RUN6B             | [59]|
| Yin, J.       | 2015 | China         | 78            | 156             | 56.30 ± 6.70    | 37.18    | qRT-PCR      | U6snRNA           | [60]|
| Yu, F.        | 2015 | China         | 120           | 120             | 58.00 ± 10.40   | 62.5    | qRT-PCR      | miR-16            | [61]|
| Zhang, Z.     | 2014 | China         | 95            | 127             | 54.21 ± 6.95    | 63.16    | qRT-PCR      | U6                | [62]|
| Zhou, J.      | 2011 | China         | 196           | 66              | 53.00 ± 12.00   | 85.00    | qRT-PCR      | miR-1228          | [63]|
| Zhu, H. T.    | 2017 | China         | 121           | 62              | na              | 84.30    | qPCR         | na                | [64]|
| Zhu, S.       | 2018 | China         | 33            | 31              | 54.00 ± 11.00   | 81.82    | RT-qPCR      | U6 snRNA          | [65]|
| Zuo, D.       | 2016 | China         | 90            | 30              | 54.70 ± 9.80    | 75.56    | RT-qPCR      | RNA U6            | [66]|
3.6. Meta-Regression Analysis. Meta-regression analysis was used to investigate the possible sources of heterogeneity in Meta-Disc 1.4 software. Since all of $I^2$ in sensitivity, specificity, PLR, NLR, and DOR were more than 70% (Figure S2), we explored the source of heterogeneity. The $P$ values were 0.0410, 0.9808, 0.3906, and 0.5372 in quality, sample, nation, and miRNA profiling subgroups, respectively. We also separately analyzed the impact of quality on the meta-analysis. The variable of quality had a $P$ value with 0.0093, demonstrating the quality of studies was the main source of heterogeneity (Table 3). Meanwhile, we also performed meta-regression analysis using Stata 14.0 software. However, the difference in quality was not statistically significant in Figure 6.

3.7. Publication Bias. In order to evaluate the underlying publication bias, Deeks’ funnel plot was designed in Stata 14.0 software. The $P$ value was 0.48, indicating the probability of publication bias was fairly small (Figure 7).

4. Discussion

Early HCC patients are usually asymptomatic [67], which made the diagnosis of HCC more difficult. When the HCC patients have obvious symptoms, such as liver pain, jaundice, refractory ascites, progressive weight loss, fever, cachexia, or very serious complications (hepatic encephalopathy), indicating that early HCC may progress into advanced stages [68, 69], then the treatments will be limited. The radical hepatic resection in early HCC is one of the most effective treatments [70]. However, only 30% to 40% of HCC patients can perform radical treatment at the time of diagnosis [63]. Therefore, the early diagnosis of HCC is rather important for improving the five-year survival rate of HCC patients. In recent years, miRNAs have been found to be potential biomarkers for the diagnosis of HCC [44, 63]. However, the conclusions are inconsistent. Therefore, we conducted this study to evaluate whether miRNAs can be used as diagnostic biomarkers for early HCC.

In this study, the overall sensitivity, specificity, and AUC were 0.84, 0.87, and 0.92, respectively, indicating that the overall accuracy was high using the circulating miRNAs as diagnostic biomarkers for HCC. In addition, the 6.5 PLR showed better diagnostic efficacy for distinguishing HCC patients from healthy individuals. The 0.18 NLR showed miRNAs had the probability of excluding the participants without HCC. The value of DOR (36, 95% CI: 20–64) showed high diagnostic efficacy in 34 studies. Subsequently, we analyzed the main source of heterogeneity and divided these studies into four subgroups. It was reported that the circulating miRNA concentrations might be associated with different ethnic groups [71]. Then, we found the studies in Egypt had better diagnostic accuracy than China. And Shaker et al. found the incidence of HCC in Egypt is overall increasing, from 4% in 1993 to 7.3% in 2003 [67]. Besides, the incidence rate of HCC among the cirrhosis patients in Egypt was approximately 21% [41], which might play an important role in the diagnosis of HCC. In addition, Yang, Y et al. found the miRNAs had higher diagnostic efficacy in Asians with 22 DOR than Caucasians [72]. Therefore,
Figure 3: The forest plot of miRNAs for overall diagnostic efficacy in HCC. The solid squares represent the point estimates for the sensitivity and specificity of each study. Error bars indicate 95% confidence interval (CI).

Figure 4: The summary receiver operator characteristic (sROC) curve of miRNAs for the diagnosis of HCC. The numerical value in each circle represents the number of the included studies in the meta-analysis. And the regression sROC curve indicates overall diagnostic accuracy.
Observed data
Summary operating point
SENS = 0.82 [0.77–0.86]
SPEC = 0.85 [0.81–0.89]

95% confidence contour
sROC curve
AUC = 0.91 [0.88–0.93]

95% prediction contour
sROC with prediction and confidence contours

Observed data
Summary operating point
SENS = 0.89 [0.77–0.95]
SPEC = 0.91 [0.85–0.95]

95% confidence contour
sROC curve
AUC = 0.96 [0.94–0.97]

95% prediction contour
sROC with prediction and confidence contours

Observed data
Summary operating point
SENS = 0.91 [0.79–0.96]
SPEC = 0.92 [0.84–0.97]

95% confidence contour
sROC curve
AUC = 0.97 [0.95–0.98]

95% prediction contour
sROC with prediction and confidence contours

Observed data
Summary operating point
SENS = 0.86 [0.79–0.90]
SPEC = 0.87 [0.82–0.90]

95% confidence contour
sROC curve
AUC = 0.93 [0.90–0.95]

95% prediction contour
sROC with prediction and confidence contours

Observed data
Summary operating point
SENS = 0.82 [0.70–0.89]
SPEC = 0.89 [0.82–0.94]

95% confidence contour
sROC curve
AUC = 0.88 [0.85–0.91]

95% prediction contour
sROC with prediction and confidence contours

Observed data
Summary operating point
SENS = 0.78 [0.71–0.83]
SPEC = 0.84 [0.79–0.88]

95% confidence contour
sROC curve
AUC = 0.88 [0.71–0.83]

95% prediction contour
sROC with prediction and confidence contours

Figure 5: Continued.
Multiple-central studies are needed to verify our findings. Furthermore, the miRNAs were reported that they were differentially expressed in plasma and serum [73]. We speculated that serum- or plasma-derived miRNAs might have little difference on the diagnosis of HCC. However, due to the lack of consensus on whether plasma or serum is more suitable for sample detection, there exist limitations to analyzing the expression level of miRNAs in both plasma and serum [74]. Subsequently, we found the high-quality studies had better diagnostic efficacy than low-quality studies, showing the quality of studies...
was one of the most essential factors influencing the overall heterogeneity. And in the meta-regression, we found the difference in quality was statistically significant using Meta-disc 1.4 software, with \( P \) value < 0.05. Besides, we also showed that miRNA panel had a higher diagnostic value than multiple miRNAs or single miRNA subgroup. Hung et al. showed that miRNA panel had 84.8% sensitivity and 50.0% specificity, better than single miRNA (miR-122 and let-7b) [75]. Zhou et al. also reported that miRNA panel (miR-122, miR-192, miR-21, miR-223, miR-26a, miR-27a, and miR-801) can distinguish early HCC from healthy individuals with 82.5% sensitivity, 83.5% specificity, and 0.888 AUC [63]. And Zhang et al. also showed that 3-miRNA panels (miR-92a-3p, miR-107, and miR-3126-5p) had better diagnostic accuracy with 0.975 AUC [76]. Ning et al. also demonstrated miRNA panel (miR-155, miR-96, and miR-99a) had 0.931 AUC, higher than single miRNA [48]. Meanwhile, Pascut et al. provided comprehensive profiling of miRNome in HCC patient blood and serum, which provided useful molecular markers for the diagnosis of HCC [77].

Our study had some advantages compared with previous studies. Firstly, we integrated multiple single miRNAs or

### Table 2: The results of subgroup analysis.

| Subgroup | Sensitivity (95% CI) | Specificity (95% CI) | PLR (95% CI) | NLR (95% CI) | DOR (95% CI) | AUC (95% CI) |
|----------|----------------------|----------------------|--------------|--------------|--------------|--------------|
| Sample   |                      |                      |              |              |              |              |
| Serum    | 0.86 (0.79, 0.90)    | 0.87 (0.82, 0.90)    | 6.5 (4.6, 9.1) | 0.17 (0.11, 0.25) | 39 (19, 78) | 0.93 (0.90, 0.95) |
| Plasma   | 0.82 (0.70, 0.89)    | 0.89 (0.82, 0.94)    | 7.8 (4.0, 14.9) | 0.20 (0.12, 0.36) | 38 (12, 117) | 0.93 (0.90, 0.95) |
| Nation   |                      |                      |              |              |              |              |
| China    | 0.82 (0.77, 0.86)    | 0.85 (0.81, 0.89)    | 5.7 (4.1, 7.8) | 0.21 (0.16, 0.28) | 27 (15, 48) | 0.91 (0.88, 0.93) |
| Non-China| 0.89 (0.77, 0.95)    | 0.91 (0.85, 0.95)    | 10.3 (5.3, 20.1) | 0.12 (0.05, 0.27) | 89 (22, 236) | 0.96 (0.94, 0.97) |
| Egypt    | 0.91 (0.79, 0.96)    | 0.92 (0.84, 0.97)    | 12.0 (5.2, 27.5) | 0.10 (0.04, 0.24) | 119 (24, 592) | 0.97 (0.95, 0.98) |
| Quality  |                      |                      |              |              |              |              |
| Low-quality | 0.78 (0.71, 0.83) | 0.84 (0.79, 0.88) | 4.9 (3.5, 6.9) | 0.27 (0.19, 0.37) | 18 (10, 34) | 0.88 (0.85, 0.91) |
| High-quality | 0.90 (0.86, 0.94) | 0.91 (0.85, 0.94) | 9.7 (6.0, 15.9) | 0.11 (0.07, 0.16) | 93 (40, 214) | 0.96 (0.94, 0.97) |
| miRNA profiling |   |                      |              |              |              |              |
| Single miRNA | 0.84 (0.77, 0.89) | 0.88 (0.83, 0.92) | 6.9 (4.6, 10.4) | 0.18 (0.12, 0.27) | 39 (18, 83) | 0.93 (0.90, 0.95) |
| Multiple miRNAs | 0.84 (0.75, 0.90) | 0.86 (0.80, 0.90) | 5.9 (3.9, 8.9) | 0.19 (0.11, 0.31) | 32 (13, 75) | 0.91 (0.89, 0.94) |
| miRNA panel | 0.86 (0.79, 0.91) | 0.93 (0.85, 0.97) | 12.2 (5.7, 27.0) | 0.15 (0.10, 0.23) | 81 (28, 236) | 0.95 (0.92, 0.96) |

PLR: positive likelihood ratio; NLR: negative likelihood ratio; DOR: diagnostic odds ratio; AUC: area under the curve.

### Table 3: The meta-regression of covariates.

| Variable | Coefficient | Standard error | \( P \) value | RDOR (95% CI) |
|----------|-------------|----------------|--------------|--------------|
| **Model 1: the variables are quality, sample, nation, and miRNA profiling** |           |               |              |              |
| Cte.     | 2.358       | 1.1800         | 0.0555       | —            |
| S        | 0.123       | 0.2919         | 0.6768       | —            |
| Quality  | 0.641       | 0.2993         | 0.0410       | 1.90 (1.03, 3.51) |
| Sample   | −0.012      | 0.5037         | 0.6746       | 0.99 (0.35, 2.77) |
| Nation   | 0.320       | 0.3668         | 0.3906       | 1.38 (0.65, 2.92) |
| miRNA profiling | −0.335 | 0.5356         | 0.5372       | 0.72 (0.24, 2.14) |
| **Model 2: the variables are quality, nation, and miRNA profiling** |           |               |              |              |
| Cte.     | 2.336       | 0.9455         | 0.0196       | —            |
| S        | 0.12        | 0.2838         | 0.6746       | —            |
| Quality  | 0.642       | 0.2872         | 0.0334       | 1.90 (1.06, 3.42) |
| Nation   | 0.316       | 0.3519         | 0.3762       | 1.37 (0.67, 2.82) |
| miRNA profiling | −0.332 | 0.5243         | 0.5316       | 0.72 (0.25, 2.10) |
| **Model 3: the variables are quality and nation** |           |               |              |              |
| Cte.     | 1.89        | 0.627          | 0.0052       | —            |
| S        | 0.11        | 0.2798         | 0.6981       | —            |
| Quality  | 0.643       | 0.2830         | 0.0304       | 1.90 (1.07, 3.39) |
| Nation   | 0.301       | 0.3465         | 0.3921       | 1.35 (0.67, 2.74) |
| **Model 4: the variable is quality** |           |               |              |              |
| Cte.     | 2.155       | 0.5404         | 0.0004       | —            |
| S        | 0.09        | 0.2765         | 0.7473       | —            |
| Quality  | 0.728       | 0.2626         | 0.0093       | 2.07 (1.21, 3.54) |

RDOR: relative diagnostic odds ratios. \( P \) value < 0.05 showing the significant difference.
miRNA panels into a single miRNA in a study for improving the diagnostic efficacy of miRNAs. Secondly, we evaluated the diagnostic performance of circulating miRNAs in serum or plasma for early HCC patients. Thirdly, we combined the Stata 14.0 software, Review Manager 5.3 [78], and Meta-Disc 1.4 software to perform the meta-analysis. And we also analyzed the difference of diagnosis for HCC among single miRNA, multiple miRNAs, and miRNA panel. Ultimately, our results were promising and implied that miRNAs might be potential noninvasive biomarkers for the diagnosis of early HCC.

Nevertheless, there existed several limitations to the present study. First of all, there existed a threshold effect, which might be related to the cutoff values. For example, Hea et al. set the cutoff value of miR-126 and miR-21 to 0.462 and 4.26, respectively [34]. Secondly, the subgroup classifications of HCC based on the different background, such as chronic hepatitis B, chronic hepatitis C, other types of nonviral hepatitis, and liver cirrhosis, were not conducted because some studies lack the detailed information. Furthermore, these studies lacked united internal reference in RNA quantification [79]. In the included articles, most of the studies used RNA U6 (also called snRNA U6 or U6), while some studies used miR-16, miR-39, or other miRNAs as internal reference.

In conclusion, our results have shown miRNAs in vivo can be acted as a potential diagnostic biomarker for HCC, which can promote the diagnosis of early HCC in clinical practice. Additionally, we also found miRNA panel in serum or plasma may have better diagnostic efficacy than single miRNA. In addition, more high-quality and multiple-central studies are needed to verify our findings.
Data Availability

The data used to support the findings of this study are included within the article.

Disclosure

Hualin Tao and Yongcan Guo contributed equally to this work. The funding agencies had no role in study design, analysis, interpretation of results, decision to publish, or preparation of the manuscript. The content is solely the responsibility of the authors and does not necessarily represent the official views of the funding agency.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Acknowledgments

This research was supported by a Key Project of Health and Family Planning Commission of Sichuan Province (no. 16ZD036) and a Research Project of Traditional Chinese Medicine Hospital Affiliated to Southwest Medical University funded research project (no. 2016-JYT009). The authors would like to appreciate Shaozhi Fu, PhD, and Zhihua Zuo, MD, who carefully revised our manuscript.

Supplementary Materials

Table S1: the diagnostic efficacy of miRNAs in the included studies (Supplementary Material 1). Figure S2: the pooled (a) sensitivity, (b) specificity, (c) PLR, (d) NLR, and (e) DOR were obtained using Meta-disc 1.4 software (Supplementary Material 2). (Supplementary Materials)

References

[1] F. F. J. S. Bray, “Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries,” CA: A Cancer Journal for Clinicians, vol. 68, no. 6, pp. 394–424, 2018.
[2] J. Wands, “Hepatocellular carcinoma and sex,” New England Journal of Medicine, vol. 357, no. 19, pp. 1974–1976, 2007.
[3] G. K. Abou-Alfa, T. Meyer, A.-L. Cheng et al., “Cabozantinib in patients with advanced and progressing hepatocellular carcinoma,” New England Journal of Medicine, vol. 379, no. 1, pp. 54–63, 2015.
[4] European Association for the Study of the Liver and European Organisation for Research and Treatment of Cancer, “EASL-EORTC clinical practice guidelines: management of hepatocellular carcinoma,” Journal of Hepatology, vol. 56, no. 4, pp. 908–943, 2012.
[5] N. Yang, N. R. Ekanem, C. A. Sakyi, and S. D. Ray, “Hepatocellular carcinoma and microRNA: new perspectives on therapeutics and diagnostics,” Advanced Drug Delivery Reviews, vol. 81, pp. 62–74, 2015.
[6] C. H. Wong, K. P. Chan, L. Y. Chan, and K. W. Tsui, “The molecular diagnosis of hepatitis B virus-associated hepatocellular carcinoma,” Critical Reviews in Clinical Laboratory Sciences, vol. 43, no. 1, pp. 69–101, 2006.
[7] M. Ronot, S. Bahrami, J. Calderaro, D. C. Valla, and P. Bedossa, “Hepatocellular adenomas: accuracy of magnetic resonance imaging and liver biopsy in subtype classification,” Hepatology, vol. 53, no. 4, pp. 1182–1191, 2011.
[8] J. A. Marrero and A. S. Lok, "Newer markers for hepatocellular carcinoma," *Gastroenterology*, vol. 127, no. 5, pp. S113–S119, 2004.

[9] C. M. Sturgeon, M. J. Duffy, B. R. Hofmann, R. Lamerz, and H. A. Fritsche, "National Academy of Clinical Biochemistry Laboratory Medicine Practice Guidelines for use of tumor markers in liver, bladder, cervical, and gastric cancers," *Clinical Chemistry*, vol. 56, no. 6, pp. e1–e48, 2010.

[10] B. Choi and J. Lee, "Advancement in HCC imaging: diagnosis, staging and treatment efficacy assessments: imaging diagnosis and staging of hepatocellular carcinoma," *Journal of Hepato-Biliary-Pancreatic Surgery*, vol. 17, no. 4, pp. 369–373, 2010.

[11] L. F. R. Gebert and I. J. MacRae, "Regulation of microRNA function in animals," *Nature Reviews Molecular Cell Biology*, vol. 20, no. 1, pp. 21–37, 2019.

[12] I. Berindan-Neagoe, P. D. C. Monroig, B. Pasculli, and G. A. Calin, "MicroRNAome genome: a treasure for cancer diagnosis and therapy," *CA: A Cancer Journal for Clinicians*, vol. 64, no. 5, pp. 311–336, 2014.

[13] R. Rupaimoole and F. J. Slack, "MicroRNA therapeutics: towards a new era for the management of cancer and other diseases," *Nature Reviews Drug Discovery*, vol. 16, no. 3, pp. 203–222, 2017.

[14] M. Ha and V. N. Kim, "Regulation of microRNA biogenesis," *Nature Reviews Molecular Cell Biology*, vol. 20, no. 1, pp. 5–20, 2019.

[15] S. Giordano and A. Columbano, "MicroRNAs: new tools for diagnosis, prognosis, and therapy in hepatocellular carcinoma?*, *Hepatology*, vol. 57, no. 2, pp. 840–847, 2013.

[16] A. E. Frampton, L. Castellano, T. Colombo, E. Giovannetti, and J. Krell, "Integrated molecular analysis to investigate the role of microRNAs in pancreatic tumour growth and progression," *The Lancet*, vol. 385, p. S37, 2015.

[17] M. Karakas, C. Schulte, S. Appelbaum, F. Ojeda, and K. J. Lackner, "Circulating microRNAs strongly predict cardiovascular death in patients with coronary artery disease-results from the large AtheroGene study," *European Heart Journal*, vol. 38, no. 7, pp. 516–523, 2017.

[18] Q. Wang, P. Li, A. Li, and K. Xie, "Plasma specific miRNAs as predictive biomarkers for diagnosis and prognosis of glioma," *Journal of Experimental and Clinical Cancer Research*, vol. 31, no. 1, p. 97, 2012.

[19] E. Endzeli, A. Berger, V. Melne, C. Bajosantos, and K. S. Evska, "Detection of circulating miRNAs: comparative analysis of extracellular vesicle-incorporated miRNAs and cell-free miRNAs in whole plasma of prostate cancer patients," *BMC Cancer*, vol. 17, no. 1, p. 730, 2017.

[20] M. Swellam, H. M. El, N. M. Hassan, M. M. Hefny, and M. E. Sobeh, "Potential diagnostic role of circulating MiRNAs in breast cancer: implications on clinicopathological characters," *Clinical Biochemistry*, vol. 56, pp. 47–54, 2018.

[21] C. Wang, J. Hu, M. Lu, H. Gu, and X. Zhou, "A panel of five serum miRNAs as a potential diagnostic tool for early-stage renal cell carcinoma," *Scientific Reports*, vol. 5, no. 1, p. 7610, 2015.

[22] G. Basati, A. E. Razavi, I. Pakzad, and F. A. Malayeri, "Circulating levels of the miRNAs, miR-194, and miR-29b, as clinically useful biomarkers for colorectal cancer," *Tumor Biology*, vol. 37, no. 2, pp. 1781–1788, 2016.

[23] C. Zhou, Z. Chen, J. Dong, J. Li, and X. Shi, "Combination of serum miRNAs with Cyfra21-1 for the diagnosis of non-small cell lung cancer," *Cancer Letters*, vol. 367, no. 2, pp. 138–146, 2015.

[24] 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.

[25] Y. Rana, J. Han, J. Chen et al., "Plasma miRNAs as early biomarkers for detecting hepatocellular carcinoma," *International Journal of Cancer*, vol. 137, no. 7, pp. 1679–1690, 2015.

[26] M. Shaker, M. Alhelf, G. Morcos, and A. Elsharkawy, "miRNA-101-1 and miRNA-221 expressions and their polymorphisms as biomarkers for early diagnosis of hepatocellular carcinoma," *Infection, Genetics and Evolution*, vol. 51, pp. 173–181, 2017.

[27] A.-R. N. Zekri, A. S. E.-D. Youssef, E. D. El-Desouky et al., "Serum microRNA panels as potential biomarkers for early detection of hepatocellular carcinoma on top of HCV infection," *Tumor Biology*, vol. 37, no. 9, pp. 12273–12286, 2016.

[28] C. Zhuang, W. Jiang, D. Huang et al., "Serum miR-21, miR-26a and miR-101 as potential biomarkers of hepatocellular carcinoma," *Clinics and Research in Hepatology and Gastroenterology*, vol. 40, no. 4, pp. 386–396, 2016.

[29] A. Venazzi, W. Swardfager, B. Lam, and H. Cogo-Moreira, "Validity of the QUADAS-2 in assessing risk of bias in Alzheimer’s disease diagnostic accuracy studies," *Frontiers in Psychiatry*, vol. 9, p. 221, 2018.

[30] P. F. Whiting, A. Rutjes, M. Westwood et al., "QUADAS-2: a revised tool for the quality assessment of diagnostic accuracy studies," *Annals of Internal Medicine*, vol. 155, no. 8, pp. 529–536, 2011.

[31] H. Wei, K. Pu, X. G. Liu, B. X. Li, and H. S. Zhang, "The diagnostic value of circulating microRNAs as a biomarker for gastric cancer: a meta-analysis," *Oncology Reports*, vol. 41, no. 1, pp. 87–102, 2019.

[32] J. J. Deeks, P. Macaskill, and L. Irwig, "The performance of tests of publication bias and other sample size effects in systematic reviews of diagnostic test accuracy was assessed," *Journal of Clinical Epidemiology*, vol. 58, no. 9, pp. 882–893, 2005.

[33] L. Lin, H. Chu, M. H. Murad et al., "Empirical comparison of publication bias tests in meta-analysis," *Journal of General Internal Medicine*, vol. 33, no. 8, pp. 1260–1267, 2018.

[34] H. E. A. Ali, H. R. Abdel, H. Efati, E. K. Ahmed, and A. A. Atef, "Circulating microRNAs panel as a diagnostic tool for discrimination of HCV-associated hepatocellular carcinoma," *Clinics and Research in Hepatology and Gastroenterology*, vol. 41, no. 4, pp. e51–e62, 2017.

[35] M. A. Ali, M. Mattoli, N. El-Khazragy, O. Saber, and S. El-Nakeep, "Investigating miRNA-661 and ATG4-B mRNA expression as potential biomarkers for hepatocellular carcinoma," *Biomarkers in Medicine*, vol. 12, no. 3, pp. 245–256, 2018.

[36] K. S. Amr, H. Atia, R. Elbnhawy, and W. M. Ezzat, "Early diagnostic evaluation of miR-122 and miR-224 as biomarkers for hepatocellular carcinoma," *Genes and Diseases*, vol. 4, no. 4, pp. 215–221, 2017.

[37] S. Bhattacharya, R. Steele, S. Shrivastava, S. Chakraborty, and A. Biscoglie, "Serum miR-30e and miR-223 as Novel Non-invasive Biomarkers for Hepatocellular Carcinoma," *The American Journal of Pathology*, vol. 186, no. 2, pp. 242–247, 2016.

[38] X. Chen and A. Wang, "Clinical significance of miR-195 in hepatocellular carcinoma and its biological function in tumor progression," *OncoTargets and Therapy*, vol. 12, pp. 527–534, 2019.

[39] C. Yi, C. Jin, Y. Liu, S. Li, and H. Ping, "Plasma miR-15b-5p, miR-338-5p, and miR-764 as biomarkers for hepatocellular carcinoma," *Medical Science Monitor*, vol. 21, pp. 1864–1871, 2015.
Y. Tan, G. Ge, T. Pan, D. Wen, and L. Chen, “A serum microRNA panel as potential biomarkers for hepatocellular carcinoma,” *Digestive Diseases and Sciences*, vol. 57, no. 11, pp. 2910–2916, 2012.

L.-M. Li, Z.-B. Hu, Z.-X. Zhou et al., “Serum microRNA profiles serve as novel biomarkers for HBV infection and diagnosis of HBV-positive hepatocarcinoma,” *Cancer Research*, vol. 70, no. 2, pp. 9798–9807, 2010.

J. Luo, M. Chen, H. Huang, T. Yuan, M. Zhang, and S. Deng, “Circulating microRNA-122a as a diagnostic marker for hepatocellular carcinoma,” *Oncotarget*, vol. 6, pp. 577–583, 2013.

Z. Lv, Y. Tao, and X. Cai, “Cluster of specified microRNAs in tissues and serum as biomarkers for early diagnosis of hepatocellular carcinoma,” *International Journal of Clinical and Experimental Pathology*, vol. 11, no. 2, pp. 990–997, 2018.

M. Mathboli, A. E. Shafei, H. H. Shehata, N. Nabil, and N. Hassam, “Clinical significance of miRNA-autophagy transcript expression in patients with hepatocellular carcinoma,” *Biomarkers in Medicine*, vol. 11, no. 8, pp. 641–656, 2017.

S. Ning, H. Liu, B. Gao, and L. Zhang, “miR-155, miR-96 and miR-99a as potential diagnostic and prognostic tools for the clinical management of hepatocellular carcinoma,” *Oncology Letters*, vol. 18, no. 3, pp. 3381–3387, 2019.

N. Shaheen, N. Zayed, N. Riad, and R. Khalifa, “Role of circulating miR-182 and miR-150 as biomarkers for cirrhosis and hepatocellular carcinoma post HCV infection in Egyptian patients,” *Virus Research*, vol. 255, pp. 77–84, 2018.

O. Shaker, M. Abdelwahed, N. Ahmed, and S. Ayoub, “Evaluation of serum long noncoding RNA NEAT and miR-129-5p in hepatocellular carcinoma,” *IUBMB Life*, vol. 71, no. 10, pp. 1571–1578, 2019.

S. Jing, A. Wang, W. Qiao, I. Gurvich, and A. B. Siegel, “Exploration of genome-wide circulating MicroRNA in hepatocellular carcinoma (HCC): MiR-483-5p as a potential biomarker,” *Cancer Epidemiology, Biomarkers and Prevention*, vol. 22, no. 12, pp. 2364–2373, 2013.

X. Shen, Y. Xue, H. Cong, X. Wang, and S. Ju, “Dysregulation of serum miR-574-3p and its clinical significance in hepatocellular carcinoma,” *Annals of Clinical Biochemistry: International Journal of Laboratory Medicine*, vol. 55, no. 4, pp. 478–484, 2018.

Y. Tan, G. Ge, T. Pan, D. Wen, and L. Chen, “A serum microRNA panel as potential biomarkers for hepatocellular carcinoma related with hepatitis B virus,” *PloS One*, vol. 9, no. 10, Article ID e107986, 2014.

Y. Tomimaru, H. Eguchi, H. Nagano, H. Wada, and S. Kobayashi, “Circulating microRNA-21 as a novel biomarker for hepatocellular carcinoma,” *Journal of Hepatology*, vol. 56, no. 1, pp. 167–175, 2012.

F. Wang, H. Ying, B. He, Y. Pan, and H. Sun, “Circulating miR-148/152 family as potential biomarkers in hepatocellular carcinoma,” *Tumor Biology*, vol. 37, no. 4, pp. 4945–4953, 2016.

Y. Wang, C. Zhang, P. Zhang, G. Guo, and T. Jiang, “Serum exosomal microRNAs combined with alpha-fetoprotein as diagnostic markers of hepatocellular carcinoma,” *Cancer Medicine*, vol. 7, no. 5, pp. 1670–1679, 2018.

Y. Xie, Q. Yao, A. M. Butt, J. Guo, and Z. Tian, “Expression profiling of serum microRNA-101 in HBV-associated chronic hepatitis, liver cirrhosis, and hepatocellular carcinoma,” *Cancer Biology and Therapy*, vol. 15, no. 9, pp. 1248–1255, 2014.

L. Xu, B. Wei, H. Hui, and Y. Liu, “Association of serum microRNA-125b and HBV-related hepatocellular carcinoma in Chinese Han patients,” *International Journal of Clinical and Experimental Medicine*, vol. 11, no. 4, pp. 3699–3703, 2018.

L. Yang, Q. Xu, H. Xie, G. Gu, and J. Jiang, “Expression of serum miR-218 in hepatocellular carcinoma and its prognostic significance,” *Clinical and Translational Oncology*, vol. 18, no. 8, pp. 841–847, 2016.

J. Yin, P. Hou, Z. Wu, T. Wang, and Y. Nie, “Circulating miR-375 and miR-199a-3p as potential biomarkers for the diagnosis of hepatocellular carcinoma,” *Tumor Biology*, vol. 36, no. 6, pp. 4501–4507, 2015.

F. Yu, Z. Lu, B. Chen, P. Dong, and J. Zheng, “microRNA-150: a promising novel biomarker for hepatitis B virus-related hepatocellular carcinoma,” *Diagnostic Pathology*, vol. 10, no. 1, p. 129, 2015.

Z. Q. Zhang, H. Meng, N. Wang, L. N. Liang, and L. N. Liu, “Serum microRNA 143 and microRNA 215 as potential biomarkers for the diagnosis of chronic hepatitis and hepatocellular carcinoma,” *Diagnostic Pathology*, vol. 9, no. 1, p. 135, 2014.

J. Zhou, L. Yu, X. Gao et al., “Plasma microRNA panel to diagnose hepatitis B virus-related hepatocellular carcinoma,” *Journal of Clinical Oncology*, vol. 29, no. 36, pp. 4781–4788, 2011.

H. T. Zhu, R. B. Liu, Y. Y. Liang, A. Hasan, and H. Y. Wang, “Serum microRNA profiles as diagnostic biomarkers for HBV-positive hepatocellular carcinoma,” *Liver International*, vol. 37, no. 6, pp. 888–896, 2017.

S. Zhu, W. Liu, B. Fu, Z. Yuan, and Y. Zhou, “Association of serum miR-205 with liver cirrhosis and cancer and its diagnostic significance,” *International Journal of Clinical and Experimental Medicine*, vol. 11, no. 11, pp. 12375–12380, 2018.

D. Zuo, L. Chen, X. Liu, X. Wang, and Q. Xi, “Combination of miR-125b and miR-27a enhances sensitivity and specificity of AFP-based diagnosis of hepatocellular carcinoma,” *Tumor Biology*, vol. 37, no. 5, pp. 6539–6549, 2016.

M. K. Shaker, H. M. Abdella, M. O. Khalifa, and A. Dorry, “Epidemiological characteristics of hepatocellular carcinoma in Egypt: a retrospective analysis of 1313 cases,” *Liver International*, vol. 33, no. 10, pp. 1601–1606, 2013.

B. A. Di, “Epidemiology and clinical presentation of hepatocellular carcinoma,” *Journal of Vascular and InterventionalRadiology*, vol. 13, no. 9, pp. S169–S171, 2002.

B. A. Cahill and D. Braccia, “Current treatment for hepatocellular carcinoma,” *Clinical Journal of Oncology Nursing*, vol. 8, no. 4, pp. 393–399, 2004.

Q.-Y. He, R. Zhu, T. Lei et al., “Toward the proteomic identification of biomarkers for the prediction of HBV related hepatocellular carcinoma,” *Journal of Cellular Biochemistry*, vol. 103, no. 3, pp. 740–752, 2008.
for haematological cancers: a systematic review and meta-analysis,” *Cancer Management and Research*, vol. 11, pp. 4313–4326, 2019.

[72] Y. Yang and R. Zhu, “Diagnostic value of circulating microRNAs for hepatocellular carcinoma,” *Molecular Biology Reports*, vol. 41, no. 10, pp. 6919–6929, 2014.

[73] G. E. Qinyu, Y. Shen, F. Tian, L. U. Jiafeng, and Y. Bai, “Profiling circulating microRNAs in maternal serum and plasma,” *Molecular Medicine Reports*, vol. 12, no. 3, pp. 3323–3330, 2015.

[74] G. Li, Q. Shen, C. Li, and M. He, “Identification of circulating MicroRNAs as novel potential biomarkers for hepatocellular carcinoma detection: a systematic review and meta-analysis,” *Clinical and Translational Oncology*, vol. 17, no. 9, pp. 684–693, 2015.

[75] C. Hung, T. Hu, S. Lu, F. Kuo, and C. Chen, “Circulating microRNAs as biomarkers for diagnosis of early hepatocellular carcinoma associated with hepatitis B virus,” *International Journal of Cancer*, vol. 138, no. 3, pp. 714–720, 2015.

[76] Y. Zhang, T. Li, Y. Qiu, and L. Han, “Serum microRNA panel for early diagnosis of the onset of hepatocellular carcinoma,” *Medicine*, vol. 96, no. 2, p. e5642, 2017.

[77] D. Pascut, H. Krmac, F. Gilardi, and C. Tiribelli, “A comparative characterization of the circulating miRNome in whole blood and serum of HCC patients,” *Scientific Reports*, vol. 9, no. 1, p. 8265, 2019.

[78] J. P. T. Higgins and S. Green, *Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0*, John Wiley & Sons, Ltd., Hoboken, NJ, USA, 2011.

[79] L. Jiang, Q. Cheng, B. Zhang, and M. Zhang, “Circulating MicroRNAs as biomarkers in hepatocellular carcinoma screening: a validation set from China,” *Medicine Baltimore*, vol. 94, no. 10, p. e603, 2015.