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Corresponding author:
Chao Sun

sunchao.0819@163.com

Author Affiliation:
Soochow university.

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None declared.

Diagnostic and prognostic value of miRNAs in hepatoblastoma: A systematic review with meta-analysis

Wu, B[1]; Zhen, K[2]; Guo, L[3]; Sun, C[4].

Review question / Objective: Background and aim: Increasing evidence has revealed the valuable diagnostic and prognostic applications of dysregulated microRNAs (miRNAs) in hepatoblastoma (HB), the most common hepatic malignancy during childhood. However, these results are inconsistent and remain to be elucidated. In the present study, we aimed to systematically compile up-to-date information regarding the clinical value of miRNAs in HB. Methods: Articles concerning the diagnostic and prognostic value of single miRNAs for HB were searched from databases. The sensitivity (SEN), specificity (SPE), positive and negative likelihood ratios (PLR and NLR), diagnostic odds ratio (DOR), area under the curve (AUC), and hazard ratios (HRs) were separately pooled to explore the diagnostic and prognostic performance of miRNA. Subgroup and meta-regression analyses were further carried out only in the event of heterogeneity. Results: In all, 20 studies, involving 264 HB patients and 206 healthy individuals, met the inclusion criteria in the six included literature articles. For the diagnostic analysis of miRNAs in HB, the pooled SEN and SPE were 0.76 (95% CI: 0.72–0.80) and 0.75 (95% CI: 0.70–0.80), respectively. Moreover, the pooled PLR was 2.79 (95% CI: 2.12–3.66), NLR was 0.34 (95% CI: 0.26–0.45), DOR was 10.24 (95% CI: 6.55–16.00), and AUC was 0.83, indicating that miRNAs had moderate diagnostic value in HB. For the prognostic analysis of miRNAs in HB, the abnormal expressions of miR-21, miR-34a, miR-34b, miR-34c, miR-492, miR-193, miR-222, and miR-224 in patients were confirmed to be associated with a worse prognosis. The pooled HR was 1.74 (95% CI: 1.20–2.29) for overall survival (OS) and 1.74 (95% CI: 1.31–2.18) for event-free survival (EFS), suggesting its potential as a prognostic indicator for HB. Conclusion: To the best of our knowledge, this is the first comprehensive systematic review and meta-analysis that examines the diagnostic and prognostic role of dysregulated miRNAs in HB patients. The combined meta-analysis results supported the previous individual finds that miRNAs might provide a new, noninvasive method for the diagnostic and prognostic analyses ofHB.

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 14 November 2021 and was last updated on 14 November 2021 (registration number INPLASY2021110045).

INTRODUCTION

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childhood. However, these results are inconsistent and remain to be elucidated. In the present study, we aimed to systematically compile up-to-date information regarding the clinical value of miRNAs in HB. Methods: Articles concerning the diagnostic and prognostic value of single miRNAs for HB were searched from databases. The sensitivity (SEN), specificity (SPE), positive and negative likelihood ratios (PLR and NLR), diagnostic odds ratio (DOR), area under the curve (AUC), and hazard ratios (HRs) were separately pooled to explore the diagnostic and prognostic performance of miRNA. Subgroup and meta-regression analyses were further carried out only in the event of heterogeneity. Results: In all, 20 studies, involving 264 HB patients and 206 healthy individuals, met the inclusion criteria in the six included literature articles. For the diagnostic analysis of miRNAs in HB, the pooled SEN and SPE were 0.76 (95% CI: 0.72–0.80) and 0.75 (95% CI: 0.70–0.80), respectively. Moreover, the pooled PLR was 2.79 (95% CI: 2.12–3.66), NLR was 0.34 (95% CI: 0.26–0.45), DOR was 10.24 (95% CI: 6.55–16.00), and AUC was 0.83, indicating that miRNAs had moderate diagnostic value in HB. For the prognostic analysis of miRNAs in HB, the abnormal expressions of miR-21, miR-34a, miR-34b, miR-34c, miR-492, miR-193, miR-222, and miR-224 in patients were confirmed to be associated with a worse prognosis. The pooled HR was 1.74 (95% CI: 1.20–2.29) for overall survival (OS) and 1.74 (95% CI: 1.31–2.18) for event-free survival (EFS), suggesting its potential as a prognostic indicator for HB. Conclusion: To the best of our knowledge, this is the first comprehensive systematic review and meta-analysis that examines the diagnostic and prognostic role of dysregulated miRNAs in HB patients. The combined meta-analysis results supported the previous individual finds that miRNAs might provide a new, noninvasive method for the diagnostic and prognostic analyses ofHB.

Condition being studied: To our knowledge, this is the first time to use meta-analysis to verify the diagnostic value of hepatoblastoma from the perspective of microRNA.

METHODS

Search strategy: In order to retrieve all of the articles analyzing the diagnostic and prognostic value of miRNAs in patients with HB, a comprehensive literature search (updated on December 01, 2019) in PubMed, Cochrane Library, EMBASE, and Web of Science databases was performed. The following medical subject headings (MeSHs) and free words in the literature retrieval were used: “hepatoblastoma” and “miRNA” or “microRNAs” or “miRNA” or “microRNA” or “RNA, micro” or “miR” or “primary microRNA” or “circulating microRNAs” or “circulating miRNA” and “diagnosis” and “prognosis” or “sensitivity” and “specificity”. We searched for relevant articles whenever possible to evaluate the text.

Participant or population: As shown in Figure 1, in all, 332 articles were initially identified using the major literature retrieval strategies, from PubMed, EMBASE, Cochrane Library, and Web of Science. Duplicate records (n = 158) were removed. After a review of their abstracts and titles, 151 articles were deleted as they were reviews, letters, animal research, or irrelevant studies. After careful full-text reading, we found that 17 articles lacked sufficient data for the meta-analysis or were unrelated to the diagnosis or prognosis. As a result, 20 studies (including 10 for the diagnostic analysis and 10 for the prognostic analysis) from six articles were included in the current meta-analysis. For example, in Jiao’s article, we could conclude that there were three included miRNA (miR-34a, -34b, -34c) that could be pooled in diagnostic meta-analysis. That means three different study not only with different microRNA, but also maybe with different sample size, ratio of sex, and diagnostic accuracy.

Intervention: The diagnostic studies were consistent with the criteria in QUADAS-2, suggesting that the enrolled studies were suitable for quantitative integration. The

bias risk and applicability concerns are detailed in Figure 2. NOS was used to evaluate the prognostic studies, with an average score of 6.6, indicating that the enrolled studies were of a high quality.

Comparator: The overall Spearman's correlation coefficient across the 10 studies considered in the diagnosis analysis was 0.248 (P = 0.49), which indicated no threshold effect.

Study designs to be included: (1) the relationship between miRNA and HB was analyzed in the study; (2) a definitive diagnosis of HB was conducted using the gold standard (such as histological confirmation); and (3) the articles provided sufficient data. In addition, we only included publications in English.

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Information sources: A comprehensive literature search (updated on December 01, 2019) in PubMed, Cochrane Library, EMBASE, and Web of Science databases was performed.

Main outcome(s): Results: In all, 20 studies, involving 264 HB patients and 206 healthy individuals, met the inclusion criteria in the six included literature articles. For the diagnostic analysis of miRNAs in HB, the pooled SEN and SPE were 0.76 (95% CI: 0.72–0.80) and 0.75 (95% CI: 0.70–0.80), respectively. Moreover, the pooled PLR was 2.79 (95% CI: 2.12–3.66), NLR was 0.34 (95% CI: 0.26–0.45), DOR was 10.24 (95% CI: 6.55–16.00), and AUC was 0.83, indicating that miRNAs had moderate diagnostic value in HB. For the prognostic analysis of miRNAs in HB, the abnormal expressions of miR-21, miR-34a, miR-34b, miR-34c, miR-492, miR-193, miR-222, and miR-224 in patients were confirmed to be associated with a worse prognosis. The pooled HR was 1.74 (95% CI: 1.20–2.29) for overall survival (OS) and 1.74 (95% CI: 1.31–2.18) for event-free survival (EFS), suggesting its potential as a prognostic indicator for HB. Conclusion: To the best of our knowledge, this is the first comprehensive systematic review and meta-analysis that examines the diagnostic and prognostic role of dysregulated miRNAs in HB patients. The combined meta-analysis results supported the previous individual finds that miRNAs might provide a new, noninvasive method for the diagnostic and prognostic analyses of HB.

Data management: Articles concerning the diagnostic and prognostic value of single miRNAs for HB were searched from databases. The sensitivity (SEN), specificity (SPE), positive and negative likelihood ratios (PLR and NLR), diagnostic odds ratio (DOR), area under the curve (AUC), and hazard ratios (HRs) were separately pooled to explore the diagnostic and prognostic performance of miRNA. Subgroup and meta-regression analyses were further carried out only in the event of heterogeneity.

Quality assessment / Risk of bias analysis: This meta-analysis was performed following the guidelines of the preferred reporting items for systematic reviews and meta-analysis (PRISMA) statement. For the diagnosis meta-analysis, the QUADAS-2 (Quality Assessment of Diagnostic Accuracy Studies 2) was performed to evaluate the methodological quality assessment of the included articles. For the prognosis meta-analysis, the quality of the included studies was evaluated with the Newcastle Ottawa Scale (NOS)18, 19. NOS scores were calculated on the basis of selection, comparability, and outcome. Studies with a final score of >6 were considered to be of a high quality.

Strategy of data synthesis: The statistical analyses of this study were performed using the Review Managers V5.3 and the Meta Disc 1.40 software. The numbers of patients with true positives (TP), false negatives (FN), false positives (FP), and true negatives (TN) from the included

studies were extracted. We calculated the combined specificity, sensitivity, the combined positive likelihood ratio (PLR), the combined negative likelihood ratio (NLR), the diagnostic odds ratio (DOR), and the AUC of the summary receiver operating characteristic (SROC) using Meta Disc20. Firstly, we calculate the spearman correlation coefficient to determine whether there is threshold effect in our meta-analysis. If P > 0.05, it indicates that there is no threshold effect, and then the study effect quantity can be combined. Additionally, the heterogeneity among studies was estimated with the Q test and I2 statistics. The I2 value was more than 50%, which indicated the existence of significant heterogeneity. Subgroup and meta-regression analyses were performed to explore the potential sources of inter-study heterogeneity. Different sample size, race from Europe or Asia, various examining measurements and different resouced specimen maybe resulted significant heterogeneity. Thus we performed the subgroup and meta-regression analyses to explore the potential sources of inter-study heterogeneity. Deeks' funnel plot was used to evaluate the potential publication bias, and a P-value of 1 indicated poor prognosis in patients with a high miRNA expression. Conversely, an observed HR of <1 indicated the good prognosis in patients with a high miRNA expression. The heterogeneity assessment was performed with a Q test and I2 statistics. The values of I2 ≥ 50% and P < 0.1 indicated the existence of significant heterogeneity21. Because of samples from different HB patients (formalin-fixed samples, frozen tissue samples, serum samples, and plasma samples) and cut-off values in individual studies, the random-effects model was adopted preferentially. Subgroup and meta-regression analyses were performed to explore the source of heterogeneity. We drew Deeks' funnel plots to test the publication bias in this meta-analysis. The value of P < 0.05 was considered statistically significant.

Subgroup analysis: Subgroup and meta-regression analyses were performed to explore the potential sources of inter-study heterogeneity.

Sensitivity analysis: We conducted the sensitivity analysis in the prognostic part of microRNAs, and the results could be as the supplemented file.

Language: English.

Country(ies) involved: China.

Keywords: microRNAs, diagnosis, prognosis, hepatoblastoma, meta-analysis.

Contributions of each author:

Author 1 - Bin Wu drafted the manuscript.
Email: wb97245@sina.com
Author 2 - Kaikai Zhen provided statistical expertise.
Email: zkk326@163.com
Author 3 - Lixia Guo - The author contributed to the development of the selection criteria, and the risk of bias assessment strategy.
Email: 1263297568@qq.com
Author 4 - Chao Sun - The author read, provided feedback and approved the final manuscript.
Email: sunchao.0819@163.com