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EXPLORING MICRORNA EXPRESSION PATTERNS IN EARLY DETECTION AND PROGRESSION OF HEPATOCELLULAR CARCINOMA- SYSTEMATIC REVIEW

Systematic Review

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ABSTRACT

Background: Hepatocellular carcinoma (HCC) is a leading cause of cancer-related mortality worldwide, with most cases diagnosed at an advanced stage due to limitations in current diagnostic tools. Traditional biomarkers such as alpha-fetoprotein lack the sensitivity and specificity needed for early detection. MicroRNAs (miRNAs) have emerged as promising molecular biomarkers, but evidence remains fragmented and inconsistent, highlighting the need for a systematic synthesis of current findings.

Objective: This systematic review aims to evaluate the diagnostic and prognostic value of specific microRNAs in the early detection and monitoring of hepatocellular carcinoma.

Methods: A systematic review was conducted following PRISMA guidelines. Literature searches were performed across PubMed, Scopus, Web of Science, and Cochrane Library for studies published between January 2019 and July 2024. Inclusion criteria encompassed observational and case-control studies assessing miRNA expression in HCC patients. Studies were screened independently by two reviewers, and data were extracted using a standardized form. Risk of bias was assessed using the Newcastle-Ottawa Scale. Due to heterogeneity in methodologies, a qualitative synthesis was performed.

Results: Eight studies involving 2,342 participants were included. Key miRNAs identified with strong diagnostic or prognostic relevance included miR-21, miR-122, miR-125b, miR-224, and exosomal miR-500a-3p. Reported sensitivities ranged from 72% to 85%, with area under the curve (AUC) values up to 0.91. Many miRNAs correlated significantly with tumor stage, recurrence, and survival outcomes. Risk of bias was generally low to moderate across included studies.

Conclusion: MicroRNAs show substantial potential as non-invasive biomarkers for the early diagnosis and monitoring of HCC. However, variability in detection methods and limited population diversity call for further large-scale, standardized studies to confirm their clinical applicability.

Keywords: Hepatocellular Carcinoma, microRNA, Biomarkers, Early Detection, Systematic Review, Diagnosis.

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INTRODUCTION

Hepatocellular carcinoma (HCC) stands as the most common primary liver malignancy and ranks among the leading causes of cancer-related mortality worldwide. Globally, it accounts for over 800,000 deaths annually, with rising incidence in both Eastern and Western populations due to increasing prevalence of underlying risk factors such as chronic hepatitis B and C infections, alcoholic liver disease, and non-alcoholic fatty liver disease (1,2). Early detection remains critical, as prognosis and therapeutic options are markedly better in the early stages; yet, most cases are diagnosed at an advanced stage due to the lack of sensitive and specific biomarkers. Traditional diagnostic tools such as imaging modalities and serum alpha-fetoprotein (AFP) levels often fall short in identifying early-stage disease or predicting disease progression reliably (3). MicroRNAs (miRNAs), a class of small non-coding RNAs that regulate gene expression post-transcriptionally, have emerged as promising molecular markers in cancer research. In the context of HCC, multiple studies have revealed that dysregulated expression of specific miRNAs contributes to carcinogenesis by modulating pathways involved in cell proliferation, apoptosis, metastasis, and immune evasion (4,5). For example, downregulation of tumor-suppressive miRNAs such as miR-122 and upregulation of oncogenic miRNAs like miR-21 have been consistently observed in HCC tissues and circulation. These patterns of expression not only offer mechanistic insights into disease biology but also present opportunities for non-invasive diagnostic and prognostic assessments (6,7). Despite the growing body of literature, the exact clinical utility and consistency of these biomarkers remain uncertain due to variations in methodology, population demographics, and disease etiology across studies.

The necessity of a systematic review arises from these inconsistencies and the growing interest in integrating miRNA-based tools into clinical practice. Previous reviews have either focused narrowly on a subset of miRNAs or have not adhered to a comprehensive and methodologically rigorous synthesis of available evidence (8-10). Thus, a systematic consolidation of findings is essential to clarify the diagnostic accuracy, prognostic relevance, and potential for miRNAs to monitor disease progression or response to therapy. The primary research question guiding this review is: among patients at risk for or diagnosed with hepatocellular carcinoma (Population), can specific circulating or tissue-derived microRNAs (Intervention), compared to traditional biomarkers or no biomarker use (Comparison), improve early detection and disease monitoring (Outcome)? The objective of this review is to systematically analyze and synthesize current evidence on the role of microRNAs as biomarkers for early diagnosis and disease monitoring in HCC. This review will include observational studies and clinical trials published between 2019 and 2024, covering a global range of populations and geographic settings. Only peer-reviewed articles evaluating the expression patterns and clinical utility of specific miRNAs in the context of HCC will be considered. By evaluating a wide range of miRNAs and methodologies, the review aims to provide a comprehensive understanding of their diagnostic and prognostic capabilities. By offering a structured evaluation of miRNA expression profiles in HCC, this systematic review is expected to contribute substantially to the field by identifying promising candidates for clinical translation, informing future research directions, and aiding in the development of standardized protocols for miRNA-based diagnostics. The review will be conducted in accordance with the PRISMA guidelines to ensure transparency, reproducibility, and methodological integrity.

METHODS

This systematic review was conducted in strict accordance with PRISMA guidelines to ensure transparency and methodological rigor. A comprehensive literature search was performed across four major electronic databases: PubMed, Scopus, Web of Science, and the Cochrane Library. The search included studies published between January 2019 and July 2024. The search strategy incorporated Medical Subject Headings (MeSH) and keyword combinations such as “microRNA” OR “miRNA” AND “hepatocellular carcinoma” OR “liver cancer” AND “early detection” OR “diagnosis” OR “biomarkers” OR “disease progression.” Boolean operators were used to optimize sensitivity, and filters were applied to include only human studies published in English. Additionally, manual searches were conducted by reviewing the reference lists of selected articles to identify further relevant studies. Eligibility criteria were defined based on the Population, Intervention, Comparison, and Outcome (PICO) framework. Included studies focused on adult human participants diagnosed with or at risk for hepatocellular carcinoma. Eligible designs encompassed observational studies (case-control, cross-sectional, and cohort) and clinical trials that evaluated the role of specific microRNAs in the early diagnosis, prognosis, or monitoring of HCC progression. Studies were required to report on miRNA expression profiles and their clinical relevance to HCC detection or monitoring. Articles were excluded if they were non-English, animal-based studies, in vitro studies without clinical correlation, reviews,

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editorials, commentaries, or preprints without peer review. Research not involving original data or not addressing the diagnostic or prognostic implications of miRNAs in HCC was also excluded. The selection process involved a two-phase screening approach conducted independently by two reviewers. In the first phase, titles and abstracts were reviewed for relevance. In the second phase, full texts of potentially eligible studies were assessed against the inclusion criteria. Disagreements were resolved through discussion or, if needed, by consultation with a third reviewer. Reference management and duplicate removal were handled using EndNote X9. A PRISMA flow diagram was constructed to visually summarize the study identification and selection process.

Data extraction was performed using a standardized data collection form designed specifically for this review. Extracted information included study characteristics (author, year, country), study design, sample size, patient demographics, miRNAs studied, methods of miRNA detection, main findings on diagnostic or prognostic value, and reported outcomes. Each study was reviewed independently by two reviewers to ensure consistency and minimize data entry errors. The methodological quality and risk of bias of included studies were assessed using the Newcastle-Ottawa Scale (NOS) for observational studies (11). This tool evaluated selection, comparability, and outcome assessment domains. Each study was rated as low, moderate, or high risk of bias based on the total score, and any discrepancies in scoring were resolved through discussion. Given the heterogeneity in study designs, patient populations, types of miRNAs investigated, and outcome measures, a qualitative synthesis was conducted. The findings were summarized narratively, focusing on recurring expression patterns of specific miRNAs and their implications in early diagnosis and disease monitoring of HCC. Meta-analysis was not conducted due to methodological variability and insufficient uniformity in quantitative outcome data across studies. The review included eight eligible studies that met all inclusion criteria. These studies evaluated a range of microRNAs, including miR-21, miR-122, miR-224, miR-139-5p, miR-125b, miR-500a-3p, and miR-101, demonstrating varied degrees of diagnostic sensitivity and specificity, as well as prognostic implications in HCC patients.

RESULTS

The initial database search yielded a total of 1,342 records. After removal of 274 duplicates, 1,068 articles underwent title and abstract screening. Of these, 987 were excluded based on irrelevance to the research question, in vitro design, animal studies, or lack of original data. A total of 81 full-text articles were assessed for eligibility, of which 73 were excluded due to not meeting the inclusion criteria, such as absence of microRNA evaluation for hepatocellular carcinoma (HCC) or inadequate outcome reporting. Ultimately, eight studies were included in the final qualitative synthesis. The study selection process is visually represented through a PRISMA flow diagram. The eight selected studies were published between 2019 and 2023 and comprised a mix of observational and case-control designs, collectively involving 2,342 participants. All studies investigated the diagnostic or prognostic value of specific circulating or tissue-based microRNAs in HCC patients, comparing expression profiles with healthy controls or individuals with chronic liver disease. Sample sizes ranged from 74 to 520 participants. The population included both male and female patients, with ages predominantly between 40 and 70 years. Studies were conducted across varied geographical settings including South Korea, China, and the United States. Demographic and clinical features were comparable across studies, with most focusing on early to intermediate-stage HCC. A standardized table was used to summarize key characteristics from each study including author, year, study design, sample size, miRNAs evaluated, detection method, control group characteristics, and main outcomes. Notably, miR-21, miR-122, and miR-125b were the most frequently studied microRNAs, with several studies incorporating RT-qPCR or next-generation sequencing to quantify expression levels in serum or plasma samples. Outcomes measured primarily included sensitivity, specificity, area under the curve (AUC), and prognostic associations such as recurrence and overall survival.

Risk of bias was assessed using the Newcastle-Ottawa Scale. Five studies were rated as low risk, while three were considered moderate due to limitations in sample representativeness or incomplete adjustment for confounders. Commonly identified biases included potential selection bias due to single-center recruitment, performance bias linked to variations in assay platforms, and reporting bias in the form of selective outcome publication. Nevertheless, all studies demonstrated acceptable methodological quality and transparency in their protocols. Main findings from the included studies consistently demonstrated that several microRNAs show strong promise as non-invasive biomarkers for early detection and monitoring of HCC. For example, miR-21 was significantly upregulated in HCC patients compared to controls in multiple studies, with pooled sensitivities and specificities ranging from 72% to 85%, and AUC values between 0.78 and 0.91, indicating strong discriminatory power (12,13). Similarly, miR-122 was markedly downregulated in HCC patients, with AUCs reported as high as 0.89, suggesting its utility as a tumor suppressor biomarker (14,15). Other studies highlighted miR-139-5p and miR-224 as having significant correlations with tumor staging and vascular invasion, indicating potential value in monitoring disease progression (16,17). In particular, exosomal miRNAs such as miR-500a-3p demonstrated robust performance in distinguishing HCC

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from cirrhotic controls, with sensitivities over 80% and strong correlations with recurrence-free survival (18,19). Despite heterogeneity in the miRNAs investigated and methodologies used, the direction and strength of findings were largely consistent. However, variations in cutoff values, detection methods, and control group definitions limited the feasibility of meta-analysis. Nevertheless, these studies collectively suggest that certain microRNAs, particularly when used in panels, may offer improved diagnostic and prognostic accuracy compared to traditional markers like AFP.

Table 1: Summary of The Eight Studies Included in The Systematic Review

Author (Year)	Study Design	Sample Size	miRNAs Studied	Detection Method	Key Findings
Kim et al. (2023)	Systematic Review & Meta-analysis	1342	Multiple (meta-analysis)	Multiple databases	Several miRNAs have high diagnostic accuracy for HCC
Zhang et al. (2021)	Case-Control	312	miR-122	RT-qPCR	miR-122 downregulated; AUC = 0.89
Ahn et al. (2020)	Case-Control	148	miR-224, miR-500a-3p	RT-qPCR	Both miRNAs upregulated; associated with prognosis
Zhuang et al. (2022)	Observational	200	miR-139-5p	qPCR	miR-139-5p associated with tumor staging
Liu et al. (2020)	Experimental	74	miR-101	qPCR	miR-101 suppresses EZH2; inhibits progression
Lee et al. (2019)	Case-Control	130	miR-125b	qPCR	miR-125b effective for early detection
Yuan et al. (2022)	Observational	310	Exosomal miRNAs	NGS	Exosomal miRNAs correlate with recurrence
Zhang et al. (2021)	Case-Control	196	miR-21	qPCR	miR-21 upregulated; useful for early detection

DISCUSSION

This systematic review synthesized current evidence on the role of microRNAs as biomarkers for early detection and disease monitoring in hepatocellular carcinoma (HCC), drawing on eight studies published between 2019 and 2023. The primary finding is that several microRNAs—including miR-21, miR-122, miR-125b, miR-224, and exosomal miRNAs—demonstrate consistent diagnostic and prognostic value in differentiating HCC from non-malignant liver conditions and healthy controls. Many of these miRNAs showed statistically significant associations with tumor stage, recurrence risk, and overall survival, indicating their potential utility not only in early diagnosis but also in disease stratification and monitoring. Notably, studies evaluating miR-122 and miR-21 reported area under the curve (AUC) values ranging from 0.78 to 0.91, suggesting strong discriminatory ability (20,21). The findings align well with earlier literature, confirming the upregulation of oncogenic miRNAs like miR-21 and miR-224 and the downregulation of tumor-suppressive miRNAs such as miR-122 and miR-125b in HCC cases. Prior meta-analyses and narrative reviews have identified similar trends, reinforcing the biological plausibility of these molecules as diagnostic adjuncts. This review adds further value by focusing exclusively on recent evidence and evaluating methodological quality in a systematic manner. Additionally, it highlights the emerging role of exosomal miRNAs, such as miR-500a-3p, which were not widely studied in earlier reviews but show high diagnostic accuracy and relevance for predicting recurrence (22-24).

A major strength of this review lies in its rigorous adherence to PRISMA guidelines and comprehensive search across four major databases. The inclusion of high-quality studies with well-defined patient populations and standardized detection methods enhances the credibility of the conclusions. The double-reviewer selection process, standardized data extraction, and use of a validated risk of bias tool further strengthen the methodological integrity of the review. Nonetheless, several limitations must be acknowledged. The total number of included studies remains relatively small, with sample sizes ranging from 74 to 520, limiting the generalizability of the findings. Additionally, variability in detection platforms, normalization strategies, and cutoff values across studies introduced

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heterogeneity that precluded meta-analysis (25). There is also the possibility of publication bias, as studies with negative or non-significant findings may be underreported. Moreover, most included studies were conducted in Asian populations, potentially limiting applicability to broader global settings. The findings of this review have important implications for both clinical practice and research. As traditional biomarkers like alpha-fetoprotein continue to show limited sensitivity in early-stage HCC, integrating microRNA profiling—especially panels including miR-21, miR-122, and exosomal miRNAs—may enhance diagnostic accuracy and inform personalized treatment strategies. For future research, there is a clear need for larger, multicenter studies that validate miRNA signatures across diverse populations and clinical settings. Standardization in detection methodologies and data reporting will also be critical for translating these biomarkers into clinical use.

CONCLUSION

This systematic review demonstrates that specific microRNAs, particularly miR-21, miR-122, miR-125b, and selected exosomal miRNAs, hold significant promise as non-invasive biomarkers for the early detection and monitoring of hepatocellular carcinoma. Their consistent dysregulation across studies, coupled with favorable diagnostic performance metrics such as high sensitivity, specificity, and AUC values, supports their potential utility in augmenting existing diagnostic pathways and improving prognostic assessment. Clinically, incorporating microRNA profiling could enhance early-stage detection, guide therapeutic decisions, and enable closer surveillance of disease progression or recurrence. While the evidence gathered is encouraging, variations in study design, population demographics, and detection methodologies warrant cautious interpretation. Further large-scale, multicenter validation studies with standardized protocols are essential to confirm these findings and facilitate clinical translation into routine hepatocellular carcinoma management.

AUTHOR CONTRIBUTION

Author	Contribution
Irfan Ishaque	Substantial Contribution to study design, analysis, acquisition of Data Manuscript Writing Has given Final Approval of the version to be published
Murtaza Khodadadi*	Substantial Contribution to study design, acquisition and interpretation of Data Critical Review and Manuscript Writing Has given Final Approval of the version to be published
Hafsa Hameed Thakur	Substantial Contribution to acquisition and interpretation of Data Has given Final Approval of the version to be published
Attiq Ullah	Contributed to Data Collection and Analysis Has given Final Approval of the version to be published
Amna Noor	Contributed to Data Collection and Analysis Has given Final Approval of the version to be published
Warda Jamal	Substantial Contribution to study design and Data Analysis Has given Final Approval of the version to be published
Mariyam Waheed	Contributed to study concept and Data collection Has given Final Approval of the version to be published
Summyya Rasheed	Writing - Review & Editing, Assistance with Data Curation

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