

Original Article

AI-Guided Selection of Circulating MicroRNA Panels for Early Detection of Hepatocellular Carcinoma in High-Risk Patients

Hufsa Raees¹, Fatima Khan Ghauri², Maryam Bibi³, Iqra Walayat⁴, Arshia Arbab Kasi⁵, Aaima Khan⁶, Fatima Ali⁷

¹ Masters in Biochemistry, Sapienza University of Rome, Rome, Italy

² Quaid e Azam Medical College, Bahawalpur, Pakistan

³ COMSATS University Islamabad, Vehari Campus, Vehari, Pakistan

⁴ Lecturer, Khwaja Fareed University of Engineering and Information Technology, Rahim Yar Khan, Pakistan

⁵ MPhil Scholar, Sardar Bahadur Khan Women's University, Quetta, Pakistan

⁶ Kinnaird College for Women University, Lahore, Pakistan

⁷ BS Medical Laboratory Technology, Riphah International University, Lahore, Pakistan.

✉ Correspondence: Hufsa Raees, hufsaraees@gmail.com

Received: 19 January 2026

Revised: 03 February 2026

Accepted: 10 February 2026

Published: 15 February 2026

HOW TO CITE

Hufsa Raees et al. 2026. AI-Guided Selection of Circulating MicroRNA Panels for Early Detection of Hepatocellular Carcinoma in High-Risk Patients. *Journal of Health, Wellness and Community Research*. 4, 3 (Feb. 2026), 1–9. DOI:<https://doi.org/10.61919/4x1xfr40>

ARTICLE INFORMATION

Author Contributions	Concept: HR; Design: HR, FKG, AK, FA; Data Collection: MB, AAK; Analysis: HR, IW; Drafting: HR, FKG, MB, IW, AAK, AK, FA.
Ethical Approval	The study was approved by research ethical board of Khwaja Fareed University of Engineering and Information Technology, Rahim Yar Khan, Pakistan
Informed Consent	Written informed consent was obtained from all participants
Conflict of Interest	The authors declare no conflict of interest.
Funding	No external funding.
Data Availability	Available from the corresponding author on reasonable request.
AI Declaration	No generative AI was used for conceptualization, analysis, or content generation. AI use was limited to language refinement, and the authors remain fully responsible for the accuracy, originality, validity, and integrity of the manuscript's content.

ABSTRACT

Background: Early detection of hepatocellular carcinoma (HCC) remains challenging in patients with cirrhosis because conventional ultrasonography and alpha-fetoprotein surveillance have limited sensitivity for early-stage disease. **Objective:** To evaluate the diagnostic performance of an artificial intelligence-selected five-microRNA panel added to standard HCC surveillance in high-risk adults with cirrhosis. **Methods:** This single-center, parallel-group randomized diagnostic-strategy trial was conducted at a tertiary referral hospital in Punjab, Pakistan, from May to December 2025. Eighty-four participants aged 35–65 years were randomized 1:1 to standard surveillance or standard surveillance supplemented with longitudinal qRT-PCR profiling of miR-21, miR-122, miR-192, miR-224, and miR-885-5p; 78 completed scheduled follow-up. Diagnostic performance, biomarker trajectories, lead time, and tumor size were evaluated using diagnostic-accuracy measures, t-tests, repeated-measures ANOVA, and Pearson correlation. **Results:** Sensitivity was 88.9% (8/9) with augmented surveillance and 55.6% (5/9) with standard surveillance (difference 33.3 percentage points, 95% CI –7.9 to 63.6; $p=0.294$), while specificity was 90.3% and 87.1%, respectively. AUC was 0.92 versus 0.68 ($p=0.004$), and diagnostic lead time was 4.8 versus 1.4 months (difference 3.4 months; $p=0.001$). Tumor size at detection was 1.4 versus 2.3 cm. **Conclusion:** The AI-selected five-miRNA panel showed potential as an adjunct to conventional HCC surveillance, although the imprecise sensitivity estimate and limited number of confirmed cases require cautious interpretation and further validation. **Keywords:** Artificial intelligence; circulating microRNA; diagnostic accuracy; hepatocellular carcinoma; liquid biopsy; surveillance.

INTRODUCTION

Hepatocellular carcinoma (HCC) remains a major cause of cancer-related morbidity and mortality and commonly develops in individuals with chronic liver disease, particularly those with viral hepatitis, metabolic liver disease, or established cirrhosis. Clinical outcomes are strongly influenced by the stage at which HCC is detected because patients diagnosed at an early stage are more likely to remain eligible for potentially curative treatments, including surgical resection, local ablative therapy, and liver transplantation. Consequently, timely identification of malignant transformation among high-risk individuals is a central objective of HCC surveillance and remains an important component of efforts to improve disease management and long-term outcomes (1).

Current surveillance of patients at increased risk of HCC relies predominantly on abdominal ultrasonography, with or without measurement of serum alpha-fetoprotein (AFP). Although this strategy is widely used, its effectiveness for detecting small or early-stage tumors is limited by several factors. Ultrasonography is operator-dependent and may be technically compromised in patients with obesity, advanced fibrosis, cirrhotic architectural distortion, or small lesions, while AFP lacks sufficient sensitivity and specificity to function as an independent early diagnostic marker. These limitations create the possibility that clinically important tumors remain undetected until they become radiologically apparent at a more advanced stage. The resulting diagnostic gap has increased interest in minimally invasive circulating biomarkers that may identify molecular changes associated with hepatocarcinogenesis before conventional surveillance produces definitive findings (1).

Among the emerging circulating biomarkers, microRNAs (miRNAs) have attracted particular attention because these small non-coding RNAs regulate post-transcriptional gene expression and can be detected in circulating biological samples. Their relative stability in blood and cancer-associated alterations in expression make them potential candidates for minimally invasive early detection assays (2). More broadly, advances in liquid-biopsy technologies have created opportunities to combine circulating molecular signals with computational approaches for cancer screening and early detection (3). In HCC specifically, genomic and molecular liquid-biopsy strategies have been investigated as complementary approaches to conventional imaging and serum-based surveillance, with the aim of improving diagnostic sensitivity while preserving clinically acceptable specificity (4). Recent work has therefore increasingly focused on the potential role of circulating biomarkers in the early detection, prognostic assessment, and therapeutic monitoring of HCC (5).

A major challenge, however, is that HCC is biologically heterogeneous and no single circulating biomarker is likely to capture the full spectrum of molecular changes occurring during early hepatocarcinogenesis. Artificial intelligence and machine-learning approaches may help address this limitation by evaluating high-dimensional biomarker data, identifying informative combinations of molecular features, and constructing multi-marker signatures that cannot be readily selected through conventional univariable approaches (6). This computational strategy is particularly relevant to HCC, in which improvements in molecular characterization are increasingly being explored alongside conventional diagnostic and therapeutic pathways (7). Previous work has demonstrated that machine-learning methods can be applied to circulating miRNA profiles to identify candidate signatures for early HCC detection, supporting the biological and computational feasibility of multi-miRNA diagnostic models (8). At the same time, the wider HCC biomarker literature emphasizes that promising candidate markers require rigorous clinical validation before they can be incorporated into diagnostic pathways (9). Similar concerns apply to precision-medicine approaches based on liquid biopsy, for which model development, clinical validation, reproducibility, and generalizability remain essential steps before routine implementation (10).

Despite growing interest in AI-assisted liquid biopsy, an important gap remains between computational identification of candidate miRNA signatures and their prospective evaluation within an active HCC surveillance pathway. Diagnostic performance demonstrated during biomarker discovery or retrospective model development does not by itself establish whether an AI-selected panel provides clinically meaningful additional detection when applied prospectively to high-risk patients alongside standard surveillance. Evaluation should therefore determine not only whether an augmented strategy increases sensitivity for early-stage HCC, but also whether specificity remains acceptable and whether gains are reflected in other diagnostic measures, including predictive values, receiver-operating-characteristic performance, and the timing of tumor detection (6,10). Prospective comparison with conventional surveillance is particularly important because any potential benefit of an additional biomarker panel must be interpreted in the context of the diagnostic strategy that high-risk patients would otherwise receive.

Accordingly, the present randomized controlled trial was designed to evaluate an artificial intelligence-selected five-microRNA panel comprising miR-21, miR-192, miR-224, and miR-885-5p as an adjunct to standard HCC surveillance in high-risk adults with cirrhosis. The study compared standard surveillance supplemented by longitudinal circulating miRNA profiling with standard surveillance alone. The primary objective was to compare the sensitivity and specificity of the two surveillance strategies for detecting very-early or early-stage HCC confirmed by the study reference standard. Secondary objectives were to compare the area under the receiver operating characteristic curve, positive and negative predictive values, and diagnostic lead time between the two strategies. The study therefore sought to determine whether adding an AI-selected circulating miRNA panel to conventional surveillance could improve early HCC detection while maintaining acceptable diagnostic specificity.

MATERIALS AND METHODS

This single-center, parallel-group randomized controlled diagnostic-strategy trial was conducted at a tertiary referral hospital in the Industrial and Urban Core of Punjab, Pakistan, from May to December 2025. The trial was designed to determine whether supplementing conventional hepatocellular carcinoma (HCC) surveillance with an artificial intelligence-selected circulating microRNA panel could improve early-stage HCC detection compared with standard surveillance alone. The target population comprised adults at high risk of HCC because of established liver cirrhosis. Patients presenting to the study center during the recruitment period were screened for eligibility. Adults aged 35–65 years with cirrhosis secondary to chronic hepatitis B virus infection, chronic hepatitis C virus infection, or metabolic dysfunction-associated steatohepatitis were eligible for inclusion. Patients were excluded if they had a previous history of malignancy, active acute hepatitis, previous liver transplantation, or a concurrent severe systemic illness. Baseline demographic and clinical information included age, biological sex, etiology of cirrhosis, Child–Pugh class, serum alpha-fetoprotein (AFP) concentration, and other routinely assessed liver-related clinical characteristics.

A total sample of 84 participants, with 42 participants allocated to each study arm, was planned. The sample-size calculation was based on preliminary diagnostic-accuracy evidence for circulating microRNA panels in patients with chronic liver disease and assumed an anticipated 15-percentage-point difference in diagnostic sensitivity between the two surveillance strategies, 80% statistical power, a two-sided significance level of 0.05, and an anticipated dropout rate of 10%. Following confirmation of eligibility and provision of written informed consent, enrolled participants were randomly assigned in a 1:1 ratio to either the AI-guided microRNA surveillance group or the standard-surveillance control group. Randomization was performed using a computer-generated allocation sequence. Allocation concealment was maintained using sequentially numbered, opaque, sealed envelopes, which were opened by an independent study coordinator after enrollment. Random assignment served as the principal strategy for balancing measured and unmeasured baseline characteristics between the two groups.

Each participant underwent a 24-week active surveillance period. Participants assigned to the control group received standard HCC surveillance consisting of abdominal ultrasonography and measurement of serum AFP at 12-week intervals. Participants assigned to the intervention group received the same conventional surveillance protocol supplemented by molecular profiling of an AI-selected five-microRNA panel comprising miR-21, miR-192, miR-224, and miR-885-5p. MicroRNA profiling was performed using real-time quantitative reverse-transcription chain reaction at baseline, week 12, and week 24. Longitudinal microRNA expression was recorded as fold-change measurements and was additionally summarized using the five-miRNA panel index reported for evaluation of biomarker trends. Participant adherence to the scheduled surveillance pathway was monitored through biweekly telephone contact and automated tracking of scheduled clinic visits.

Because the intervention involved different diagnostic-surveillance pathways, participants and treating clinicians were not blinded to group allocation. To reduce ascertainment and laboratory-related bias, outcome assessors, laboratory personnel conducting microRNA extraction and profiling, and radiological reviewers responsible for diagnostic assessment were blinded to randomized group assignment. The principal comparison was between standard surveillance supplemented with the AI-selected microRNA panel and standard surveillance alone; therefore, all clinical and diagnostic outcomes were interpreted according to the originally assigned surveillance strategy. Primary analyses were specified according to the intention-to-treat principle, with participants retained in their original randomized groups regardless of non-compliance or subsequent loss to follow-up.

The primary outcome was diagnostic accuracy for detection of very-early or early-stage HCC, defined according to the Barcelona Clinic Liver Cancer staging classification. Diagnostic performance was principally evaluated using sensitivity and specificity. Suspected HCC was confirmed using dynamic contrast-enhanced magnetic resonance imaging or histopathological examination, which constituted the study reference standard. Secondary diagnostic outcomes included positive predictive value, negative predictive value, area under the receiver operating characteristic curve, and diagnostic lead time. Diagnostic lead time was defined as the interval, expressed in months, by which detection through the augmented surveillance strategy preceded radiological confirmation. Tumor size at detection was also recorded, and the relationship between longitudinal changes in individual microRNA expression and tumor diameter at diagnostic confirmation was evaluated. Outcome assessment focused on the end of the 24-week surveillance period while incorporating longitudinal biomarker measurements obtained at baseline, week 12, and week 24.

Continuous variables were assessed for approximate normality using the Shapiro–Wilk test and were summarized as means with standard deviations when the normality assumption was satisfied. Categorical variables were summarized using frequencies and percentages. Diagnostic performance was summarized using sensitivity, specificity, positive predictive value, negative predictive value, and receiver operating characteristic curve analysis, with confidence intervals reported for principal diagnostic estimates.

Within-group changes in continuous biomarker measurements between assessment points were evaluated using paired-samples t-tests, whereas between-group comparisons of biomarker concentrations and diagnostic lead time were performed using independent-samples t-tests. Repeated measures analysis of variance was used to evaluate longitudinal changes in microRNA expression across baseline, week 12, and week 24 and to assess the interaction between time and randomized group. Pearson correlation analysis was used to examine the relationship between changes in individual microRNA expression and tumor diameter at diagnostic confirmation. All statistical tests were two-sided, and statistical significance was defined as a p-value <0.05. Statistical analyses were performed using IBM SPSS Statistics version 28.0.

Ethical approval was obtained from the Institutional Ethics Review Committee before participant recruitment and data collection. All eligible participants received information about the study procedures and provided written informed consent before enrollment. Participant allocation and diagnostic assessment procedures were structured to preserve confidentiality, minimize assessment bias, and ensure that clinical surveillance was conducted within the predefined study protocol.

RESULTS

A total of 102 patients with chronic liver disease were screened between May and December 2025. Eighteen patients did not proceed to randomization because of ineligibility or non-consent, leaving 84 participants who were randomized equally to the intervention and control groups (42 per group). During the 24-week surveillance period, six participants were lost from follow-up, three from each group, resulting in 78 participants who completed the scheduled assessments, with 39 remaining in each study arm. Baseline demographic and clinical characteristics were similar between the randomized groups. Mean age was 51.9 ± 7.6 years in the intervention group and 52.9 ± 8.1 years in the control group ($p=0.561$), while baseline AFP concentrations were 17.9 ± 11.8 and 19.3 ± 13.1 ng/mL, respectively ($p=0.608$). The distributions of sex, cirrhosis etiology, and Child–Pugh class were also comparable between groups (Table 1).

Table 1. Baseline Demographic and Clinical Characteristics of Randomized Participants

Characteristic	Total (N=84)	Intervention (n=42)	Control (n=42)	p-value
Age, years	52.4 ± 7.8	51.9 ± 7.6	52.9 ± 8.1	0.561
Male sex	54 (64.3)	28 (66.7)	26 (61.9)	0.649
Female sex	30 (35.7)	14 (33.3)	16 (38.1)	
Cirrhosis due to hepatitis B	38 (45.2)	19 (45.2)	19 (45.2)	0.798
Cirrhosis due to hepatitis C	34 (40.5)	18 (42.9)	16 (38.1)	
Cirrhosis due to MASH	12 (14.3)	5 (11.9)	7 (16.7)	
Child–Pugh class A	68 (81.0)	35 (83.3)	33 (78.6)	0.578
Child–Pugh class B	16 (19.0)	7 (16.7)	9 (21.4)	
Serum AFP, ng/mL	18.6 ± 12.4	17.9 ± 11.8	19.3 ± 13.1	0.608

Data means SD or n (%). Continuous variables were compared using independent-samples t-tests. Categorical variables were compared using Pearson χ^2 tests. AFP, alpha-fetoprotein; MASH, metabolic dysfunction-associated steatohepatitis.

Table 2. Diagnostic Performance of the Two Surveillance Strategies

Diagnostic measure	Intervention, n/N (%) [95% CI]	Control, n/N (%) [95% CI]	Absolute difference, percentage points (95% CI)	p-value
Sensitivity	8/9 (88.9) [56.5–98.0]	5/9 (55.6) [26.7–81.1]	33.3 (–7.9 to 63.6)	0.294
Specificity	28/31 (90.3) [75.1–96.7]	27/31 (87.1) [71.1–94.9]	3.2 (–13.9 to 20.4)	1.000
Positive predictive value	8/11 (72.7) [43.4–90.3]	5/9 (55.6) [26.7–81.1]	17.2 (–21.7 to 51.0)	0.642
Negative predictive value	28/29 (96.6) [82.8–99.4]	27/31 (87.1) [71.1–94.9]	9.5 (–6.3 to 25.7)	0.355

Individual 95% CIs were calculated using Wilson score intervals. Confidence intervals for absolute differences were calculated using the Newcombe score method. Between-group p-values were calculated using two-sided Fisher exact tests.

Table 3. Longitudinal Five-miRNA Panel Index and Serum AFP Concentrations

Measure	Group	Baseline, mean $\pm$ SD	Week 24, mean $\pm$ SD	Within-group change (95% CI)	Within-group p-value	Week-24 between-group difference (95% CI)	Between-group p-value	Hedges g
Five-miRNA panel index	Intervention (n=39)	1.02 $\pm$ 0.18	2.84 $\pm$ 0.62	1.82 (1.61–2.03)	<0.001	1.66 (1.44–1.88)	<0.001	3.35
	Control (n=39)	1.05 $\pm$ 0.19	1.18 $\pm$ 0.31	0.13 (0.02–0.24)	0.022			
Serum AFP, ng/mL	Intervention (n=39)	18.2 $\pm$ 11.5	34.6 $\pm$ 22.1	16.4 (9.1–23.7)	<0.001	6.80 (–2.38 to 15.98)	0.144	0.33
	Control (n=39)	19.1 $\pm$ 12.8	27.8 $\pm$ 18.4	8.7 (2.4–15.0)	0.012			

Within-group comparisons used paired-samples t-tests. Week-24 between-group comparisons were recalculated from the reported means, SDs, and group sizes using independent-group Welch t-tests. Hedges g represents the standardized between-group difference at week 24. AFP, alpha-fetoprotein; miRNA, microRNA.

Table 4. Repeated-Measures Analysis of Five-miRNA Expression

Effect	F statistic	Degrees of freedom	p-value	Partial η^2
Time	18.42	2, 152	<0.001	0.195
Group	24.15	1, 76	<0.001	0.241
Time $\times$ group	12.87	2, 152	<0.001	0.145

Partial η^2 values were derived from the reported F statistics and degrees of freedom.

Table 5. Secondary Diagnostic Outcomes

Outcome	Intervention	Control	Between-group difference (95% CI)	p-value
Area under the ROC curve	0.92 (0.85–0.99)	0.68 (0.54–0.82)	0.24 (0.08–0.40)	0.004
Diagnostic lead time, months	4.8 $\pm$ 1.6	1.4 $\pm$ 1.2	3.4 (1.8–5.0)	0.001
Tumor size at detection, cm	1.4 $\pm$ 0.3	2.3 $\pm$ 0.6	–0.9 (–1.4 to –0.4)	

Data are mean $\pm$ SD or estimate (95% CI), as reported. ROC, receiver operating characteristic.

Using the diagnostic counts reported for participants with and without confirmed early-stage HCC, the intervention strategy detected 8 of 9 confirmed cases, corresponding to a sensitivity of 88.9% (95% CI 56.5–98.0%), compared with 5 of 9 cases detected by standard surveillance, corresponding to a sensitivity of 55.6% (95% CI 26.7–81.1%). The absolute difference in sensitivity was 33.3 percentage points (95% CI –7.9 to 63.6); however, this difference was not statistically significant using an exact comparison ($p=0.294$). Specificity was 90.3% (28/31; 95% CI 75.1–96.7%) in the intervention group and 87.1% (27/31; 95% CI 71.1–94.9%) in the control group, giving an absolute difference of 3.2 percentage points (95% CI –13.9 to 20.4; $p=1.000$). Positive and negative predictive values were numerically greater with the intervention strategy, but the corresponding confidence intervals were wide and the between-group differences were not statistically significant (Table 2).

Among the 39 participants per group with longitudinal biomarker measurements, the mean five-miRNA panel index increased from 1.02 $\pm$ 0.18 at baseline to 2.84 $\pm$ 0.62 at week 24 in the intervention group, representing a mean within-group change of 1.82 (95% CI 1.61–2.03; $p<0.001$). In the control group, the corresponding values were 1.05 $\pm$ 0.19 and 1.18 $\pm$ 0.31, with a mean change of 0.13 (95% CI 0.02–0.24; $p=0.022$). At week 24, the mean panel index was 1.66 units greater in the intervention group than in the control group (95% CI 1.44–1.88; $p<0.001$), corresponding to a

large, standardized difference (Hedges $g=3.35$). Serum AFP increased in both groups. At week 24, mean AFP was 34.6 ± 22.1 ng/mL in the intervention group and 27.8 ± 18.4 ng/mL in the control group; the between-group difference of 6.80 ng/mL was not statistically significant (95% CI -2.38 to 15.98 ; $p=0.144$; Hedges $g=0.33$) (Table 3).

Repeated-measures analysis demonstrated significant effects of time ($F[2,152]=18.42$, $p<0.001$; partial $\eta^2=0.195$) and group ($F[1,76]=24.15$, $p<0.001$; partial $\eta^2=0.241$), together with a significant time-by-group interaction ($F[2,152]=12.87$, $p<0.001$; partial $\eta^2=0.145$). These results indicate that the longitudinal pattern of the measured five-miRNA index differed between the two study groups across the reported assessment period (Table 4).

The reported area under the receiver operating characteristic curve was 0.92 (95% CI 0.85–0.99) for the AI-guided surveillance strategy compared with 0.68 (95% CI 0.54–0.82) for standard surveillance, with a reported between-group difference of 0.24 (95% CI 0.08–0.40; $p=0.004$). Diagnostic lead time was reported as 4.8 ± 1.6 months in the intervention group and 1.4 ± 1.2 months in the control group, corresponding to a mean difference of 3.4 months (95% CI 1.8–5.0; $p=0.001$). Tumors were detected at a mean size of 1.4 ± 0.3 cm in the intervention group and 2.3 ± 0.6 cm in the control group, with a reported difference of -0.9 cm (95% CI -1.4 to -0.4) (Table 5). In addition, week-24 miR-21 fold-change was positively correlated with radiologically determined tumor diameter ($r=0.68$, $p=0.002$).

DISCUSSION

The present study evaluated whether adding an AI-selected circulating five-miRNA panel to conventional HCC surveillance could improve early detection among adults with cirrhosis at high risk of HCC. The augmented surveillance strategy showed a numerically higher sensitivity than standard surveillance, while specificity remained broadly comparable between the groups. However, after exact reanalysis of the reported diagnostic counts, the difference in sensitivity was not statistically significant and was accompanied by wide confidence intervals, reflecting the small number of confirmed HCC cases. In contrast, the reported overall discrimination measured by the area under the receiver operating characteristic curve was greater with the augmented strategy, and participants in that group had an earlier reported diagnostic lead time and smaller tumors at detection. Taken together, these findings suggest a potentially useful diagnostic signal, but the magnitude and reliability of that signal require cautious interpretation.

The observed pattern is broadly compatible with the growing literature supporting molecular biomarkers as adjuncts to conventional HCC surveillance rather than replacements for established imaging and serum-based approaches. Contemporary reviews of point-of-care and circulating biomarker strategies emphasize that early HCC detection is unlikely to depend on a single analyte and increasingly involves combinations of molecular markers, computational interpretation, and conventional clinical assessment (11). Earlier tumor recognition may be clinically relevant because patients detected at early stages are more likely to remain candidates for potentially curative or disease-modifying interventions; however, the clinical value of an earlier diagnostic signal ultimately depends on whether it leads to appropriate confirmation and treatment rather than simply shifting the date of diagnosis (12). The present finding of a 3.4-month reported difference in diagnostic lead time is therefore potentially important, but it should not be interpreted as evidence of improved survival or reduced mortality because neither outcome was assessed in this study.

The numerical increase in sensitivity observed with the five-miRNA panel is also directionally consistent with previous computational research showing that machine-learning methods can integrate multidimensional molecular information in HCC and identify patterns that may not be captured by individual conventional biomarkers (8). AI and machine-learning approaches are increasingly being investigated across HCC precision oncology for biomarker selection, classification, prognosis, and integration of heterogeneous molecular datasets (13). Nevertheless, diagnostic-model performance depends heavily on reproducibility, analytical standardization, model locking, independent validation, and avoidance of overfitting. Similar translational concerns have been emphasized for other circulating biomarker platforms, including extracellular-vesicle-derived markers, where promising discrimination in discovery studies has not automatically translated into routine clinical utility (14). Molecular-signature research in HCC likewise indicates that tumor heterogeneity can generate substantial variability across populations and stages of disease, reinforcing the need for externally validated multivariable signatures rather than reliance on isolated molecular changes (15).

A plausible biological basis for circulating RNA-based detection is that hepatocarcinogenesis involves progressive alterations in gene regulation, signaling pathways, cellular stress responses, and tumor-microenvironment interactions, some of which may be reflected in circulating nucleic-acid profiles before a lesion becomes readily identifiable through routine imaging. Molecularly informed approaches have therefore become increasingly important in the broader development of HCC theranostics and precision medicine (16). Systems-biology and multi-omics frameworks similarly emphasize that dynamic molecular networks may provide information not captured by anatomic imaging alone, although the translation of such complex signatures into clinically reproducible assays remains challenging (17). The expanding study of other circulating small-RNA classes, including transfer RNA-derived small RNAs, further illustrates the wider biological interest in non-coding RNA signatures as potential diagnostic and prognostic biomarkers in HCC (18). At the same time, the marked molecular heterogeneity of HCC, including pathway-specific subtypes such as β -catenin-associated disease, makes it unlikely that any single molecular panel will perform uniformly across all patients and etiological backgrounds (19).

The longitudinal difference in the five-miRNA panel index should be interpreted carefully. Diagnostic testing itself would not be expected to biologically alter circulating miRNA expression; therefore, the observed divergence should be viewed as a difference in measured biomarker trajectories rather than a therapeutic effect of allocation to the surveillance strategy. The large standardized difference in the week-24 panel index suggests that the selected markers separated the observed groups strongly at that time point, but this finding does not by itself establish clinical utility. Conversely, serum AFP concentrations increased in both groups and did not differ significantly at week 24, supporting the rationale for exploring molecular information beyond AFP alone. The positive correlation between miR-21 fold-change and tumor diameter is biologically interesting, but it should be considered exploratory because the number of participants with confirmed tumors was small and no multivariable analysis was reported.

The reported AUC difference warrants separate consideration from the single-threshold sensitivity comparison. AUC summarizes discrimination across a range of possible thresholds, whereas sensitivity and specificity in Table 2 represent performance at the applied classification threshold. It is therefore possible for an ROC analysis to suggest better overall discrimination even when a comparison at one diagnostic cutoff is statistically imprecise. In the current study, however, the small number of HCC cases limits confidence in both forms of analysis. Similarly, the observation that tumors were smaller when detected under the augmented surveillance strategy may be clinically relevant because HCC treatment options depend strongly on stage and tumor characteristics, and continued innovation in early diagnosis complements the rapidly developing therapeutic landscape of HCC (20). Nonetheless, an apparent diagnostic lead-time advantage can be affected by lead-time and surveillance-related biases, and this study did not evaluate whether earlier recognition translated into greater treatment eligibility, improved recurrence-free survival, overall survival, quality of life, or cost-effectiveness.

Several features strengthen the study. The prospective randomized allocation created contemporaneous comparison groups receiving the same conventional surveillance schedule, while allocation concealment and blinding of laboratory and diagnostic assessors were intended to reduce selection and ascertainment bias. The study also assessed multiple clinically interpretable diagnostic metrics rather than relying on accuracy alone and incorporated longitudinal molecular measurements across the surveillance period. In addition, evaluation in a high-risk cirrhotic population reflects the group in whom supplementary HCC surveillance tools would be most clinically relevant.

Important limitations substantially temper the interpretation of the findings. The trial was conducted at a single center and included a modest overall sample with very few confirmed HCC events, resulting in wide confidence intervals and limited statistical power for diagnostic comparisons. The recalculated sensitivity difference was not statistically significant, and the positive and negative predictive values were similarly imprecise. The available manuscript also does not provide sufficient detail regarding the derivation and locking of the AI-selected five-miRNA panel, the classification threshold, or the analytical procedures required for complete qRT-PCR reproducibility. External validation was not performed, and the etiologically mixed cirrhotic population was too small for reliable subgroup analyses according to hepatitis B, hepatitis C, or metabolic dysfunction-associated steatohepatitis. The 24-week surveillance period limits assessment of longer-term diagnostic performance, interval cancers, treatment consequences, and patient-centered outcomes. In addition, the study did not evaluate

mortality, cost-effectiveness, implementation feasibility, or downstream harms arising from false-positive investigations.

Overall, the results support continued evaluation of AI-selected circulating miRNA signatures as an adjunct to established HCC surveillance rather than immediate clinical replacement of conventional testing. The combination of numerically greater sensitivity, greater reported ROC discrimination, and earlier detection is sufficiently encouraging to justify further validation, but the current evidence remains preliminary because of the limited event count and uncertainty surrounding several diagnostic estimates. Larger multicenter studies using prespecified and independently validated molecular algorithms, standardized laboratory procedures, clearly defined diagnostic thresholds, complete reference-standard assessment, and longer follow-up will be necessary to determine whether the apparent diagnostic advantage is reproducible and whether it results in meaningful improvements in clinical management.

CONCLUSION

The addition of an AI-selected five-miRNA panel to standard HCC surveillance showed a numerically higher sensitivity and greater reported overall diagnostic discrimination than standard surveillance alone, while specificity remained similar between the strategies. The augmented approach was also associated with an earlier reported diagnostic lead time and smaller tumor size at detection; however, the recalculated sensitivity difference was not statistically significant and the estimates were limited by the small number of confirmed HCC cases. These findings indicate that circulating multi-miRNA profiling may have potential as an adjunctive early-detection strategy in high-risk patients with cirrhosis, but larger independently validated studies are required before its diagnostic performance or clinical utility can be established.

REFERENCES

1. Johnson P, Zhou Q, Dao DY, Lo YD. Circulating biomarkers in the diagnosis and management of hepatocellular carcinoma. *Nat Rev Gastroenterol Hepatol*. 2022;19(10):670–81.
2. Metcalf GAD. MicroRNAs: circulating biomarkers for the early detection of imperceptible cancers via biosensor and machine-learning advances. *Oncogene*. 2024;43(28):2135–42.
3. Wu D, Yu Q, Wu Q, Wang X, Wei H, Li F, et al. Liquid biopsy, multi-cancer early detection, and artificial intelligence: new frontiers in cancer screening from a technological and immunological perspective. 2026;17:1854718.
4. Moldogazieva NT, Zavadskiy SP, Terentiev AA. Genomic landscape of liquid biopsy for hepatocellular carcinoma personalized medicine. *Cancer Genomics Proteomics*. 2021;18(3 Suppl):369–83.
5. Alrumaihi F. Role of liquid biopsy for early detection, prognosis, and therapeutic monitoring of hepatocellular carcinoma. *Diagnostics*. 2025;15(13):1655.
6. AbdelHamid SG, Halawa EM, Ibrahim EM, ElHefnawi M. Artificial intelligence-powered liquid biopsy in cancer: a paradigm shift in cancer detection and personalized care. *Cancer Cell Int*. 2026.
7. Li C, Lu B, Deng B. New insights into the diagnosis and treatment of hepatocellular carcinoma. *Biomedicines*. 2025;13(5):1244.
8. Sayed GI, Solyman M, El Gedawy G, Moemen YS, Aboul-Ella H, Hassanien AE. Circulating miRNA's biomarkers for early detection of hepatocellular carcinoma in Egyptian patients based on machine learning algorithms. *Sci Rep*. 2024;14(1):4989.
9. Chan YT, Zhang C, Wu J, Lu P, Xu L, Yuan H, et al. Biomarkers for diagnosis and therapeutic options in hepatocellular carcinoma. *Mol Cancer*. 2024;23(1):189.
10. Akabane M, Imaoka Y, Kawashima J, Pawlik TM. Advancing precision medicine in hepatocellular carcinoma: current challenges and future directions in liquid biopsy, immune microenvironment, single nucleotide polymorphisms, and conversion therapy. *Hepat Oncol*. 2025;12(1):2493457.

11. Liu M, Wen Y. Point-of-care testing for early-stage liver cancer diagnosis and personalized medicine: biomarkers, current technologies and perspectives. *Heliyon*. 2024;10(19).
12. Cui Y, Du Z, Xu J, Gu L, Du J, Wang M, et al. Surgery-centered integrated strategies for personalized hepatocellular carcinoma care. 2026.
13. Manan A, Ilyas S. Navigating the labyrinth of hepatocellular carcinoma: leveraging AI/ML for precision oncology. *Oncol Res*. 2026;34(5):9.
14. Zhuang Y, Zeng W, Long T, Gao N, Zhong W, Mu H, et al. Developing blood extracellular vesicle protein biomarkers for hepatocellular carcinoma: mechanisms, methods, and translation. *J Nanobiotechnology*. 2026;24:515.
15. Wahb A, Abdel-Aleem GA, Shawky NO, El-Kassas M. Emerging roles of hepatocellular carcinoma gene signatures in prognosis and immunotherapy: challenges and opportunities. *Gene Expr*. 2026;25(2).
16. Nagaraju GP, Vadde R, editors. *Theranostics and precision medicine for the management of hepatocellular carcinoma. Volume 2: Diagnosis, therapeutic targets, and molecular mechanisms*. Academic Press; 2022.
17. Colonna G. Advancing liver cancer treatment through dynamic genomics and systems biology: a path toward personalized oncology. 2025.
18. Youness A. Emerging role of transfer RNA-derived small RNAs (tsRNAs) in hepatocellular carcinoma.
19. Lehrich B. Precision medicine for β -catenin-mutated hepatocellular carcinoma: targets, immune microenvironment, and biomarkers. University of Pittsburgh School of Medicine; 2025.
20. Gao Y. Cutting-edge therapies for hepatocellular carcinoma (HCC): perspectives from patents. University of Macau; 2023.