

3rd International Conference on Chemo and BioInformatics

Kragujevac, September 25-26, 2025, Serbia



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Identification of potential microRNA biomarkers for early diagnosis of hepatocellular carcinoma applying bioinformatics approaches

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Abstract: Hepatocellular carcinoma (HCC) is a leading cause of cancer-related mortality worldwide, largely due to limited tools for early detection and the asymptomatic nature of early-stage disease. Circulating microRNAs (miRNAs) have emerged as promising non-invasive biomarkers because of their high stability in body fluids and disease-specific expression patterns. In this study, we performed an *in silico* analysis of serum miRNA expression profiles using the Gene Expression Omnibus (GEO) dataset GSE113740, which included 40 patients with HCC and 10 healthy controls. A total of 257 differentially expressed miRNAs were identified, of which seven (hsa-miR-885-3p, hsa-miR-320a, hsa-miR-744-5p, hsa-miR-221-3p, hsa-miR-561-3p, hsa-miR-124-3p, and hsa-miR-637) were prioritized based on network metrics, including the number of single-line regulators (NSR) and transcription factor percentage (TFR) ($p < 0.05$). The majority have previously been reported as functionally associated with HCC. Meta-profile analysis across 40 cancer types revealed distinct liver cancer-specific expression for five of these miRNAs (hsa-miR-885-3p, hsa-miR-320a, hsa-miR-744-5p, hsa-miR-221-3p, and hsa-miR-124-3p). Network topology and pathway enrichment highlighted key regulatory hubs and cancer-related targets. Ultimately, four miRNAs (hsa-miR-885-3p, hsa-miR-320a, hsa-miR-744-5p, and hsa-miR-124-3p) emerged as promising diagnostic biomarkers for early HCC detection.

Keywords: hepatocellular carcinoma, microRNA, biomarker

1. Introduction

Hepatocellular carcinoma (HCC) is the most common primary liver cancer, originating from hepatocytes and frequently associated with chronic liver disease and cirrhosis. It ranks as the sixth most common cancer and the third leading cause of cancer-related deaths globally, underscoring the urgent need for reliable early diagnostic biomarkers [1]. Current surveillance methods, including serological tests and abdominal ultrasound, suffer from limited sensitivity and specificity, often missing early-stage

cases [2]. MicroRNAs (miRNAs), small, non-coding RNAs that regulate gene expression post-transcriptionally by binding to target mRNA 3' untranslated regions (3' UTRs), causing translation inhibition or mRNA degradation have emerged as promising biomarkers due to their stability and detectability in body fluids, alongside disease-reflective expression profiles [3].

2. Methodology

2.1. Microarray dataset selection

The GEO database (<http://www.ncbi.nlm.nih.gov/geo/>) was searched using keywords “hepatocellular carcinoma,” “HCC,” and “microRNA/miRNA/miR,” yielding 371 datasets. Filtering for “*Homo sapiens*” and “serum” narrowed this to 164 datasets. Further limiting to studies with over 50 samples resulted in 32 datasets. After excluding pre-/post-operative samples and incomplete data, GSE113740 was selected for analysis.

2.2. Identification of differentially expressed miRNAs (DEMs)

DEMs between HCC and controls were identified using GEO2R (<https://www.ncbi.nlm.nih.gov/geo/geo2r/>) with quantile normalization. Significant DEMs were defined by $|\log_2 \text{fold change}| \geq 1$ and adjusted p -value < 0.01 .

2.3. Biomarker prediction

Candidate miRNA biomarkers were predicted with miRNA-BD, prioritizing miRNAs based on the number of single-line regulations (NSR) and transcription factor percentage (TFP) within the miRNA–mRNA regulatory network. A p -value < 0.05 was considered significant for both metrics.

2.4. Biomarker selection

2.4.1. Diagnostic potential of predicted biomarkers

Statistical analyses were conducted using GraphPad Prism 10.5.0. Differences in miRNA expression between HCC and controls were assessed by the Mann–Whitney U test and visualized as scatter plots. Significance was set at $p < 0.01$.

2.4.2. Meta-profiling heatmap

To evaluate miRNA expression across multiple cancers and refine biomarker candidates, a meta-profiling heatmap was generated using dbDEMC 2.0, integrating data from 40 cancer types (<https://www.biosino.org/dbDEMC/index>).

2.4.3. miRNA–miRNA interaction network

The miRNA–miRNA interaction network was constructed using miRNet2.0 with validated target genes from miRTarBase v9.0 and TarBase v9.0, including disease associations (cut-off degree = 2) (<https://www.mirnet.ca/>). Network topology parameters, degree and betweenness centrality, were used to identify miRNA clusters.

KEGG pathway enrichment of target genes was performed using the hypergeometric test in miRNet 2.0.

3. Results and Discussion

This study aimed to identify serum miRNA biomarkers for early HCC diagnosis. We analyzed the GEO dataset GSE113740 (40 HCC, 10 controls; platform GPL21263) and identified 257 differentially expressed miRNAs (DEMs). Network metrics (NSR and TFP) prioritized seven candidates: hsa-miR-885-3p, hsa-miR-320a, hsa-miR-744-5p, hsa-miR-221-3p, hsa-miR-561-3p, hsa-miR-124-3p, and hsa-miR-637. Notably, some are already functionally linked to HCC [4-7]. Conversely, hsa-miR-221-3p and hsa-miR-561-3p were expressed at very low levels in this dataset and excluded from differential expression analysis. This is likely due to technical limitations of microarray sensitivity or differences in serum stability compared to tissue [8]. Five miRNAs (hsa-miR-885-3p, hsa-miR-320a, hsa-miR-744-5p, hsa-miR-124-3p, and hsa-miR-637) showed the strongest discriminatory power between HCC and controls ($p < 0.0001$; **Fig. 1**).

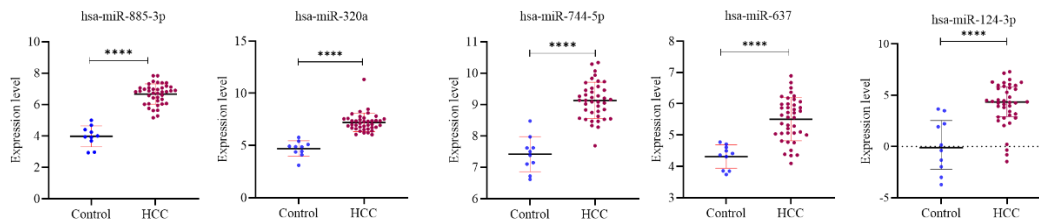


Figure 1. Expression levels of five miRNAs in HCC and control sera obtained from GEO dataset (GSE113740). HCC - hepatocellular carcinoma; **** p value < 0.0001 .

Meta-profile heatmap analysis of the seven candidate miRNAs across 40 cancer types showed that five (hsa-miR-885-3p, hsa-miR-320a, hsa-miR-744-5p, hsa-miR-221-3p, and hsa-miR-124-3p) had distinct expression patterns in HCC, each with a z-score of +4. This highlights their strong serum-based discrimination and liver cancer-specific expression, supporting their diagnostic potential and biological relevance in HCC. A miRNA-miRNA interaction network was comprised 3,081 nodes (3,074 genes and 7 miRNAs) and 10,327 edges. Topology analysis based on node degree and betweenness centrality identified four clusters: top hubs (hsa-miR-124-3p, hsa-miR-221-3p), mid-tier (hsa-miR-744-5p), medium-low (hsa-miR-885-3p, hsa-miR-320a), and peripheral (hsa-miR-561-3p, hsa-miR-637). These clusters correspond to their known roles in HCC [4-7], with cluster 4 likely representing niche or context-specific regulatory functions. Among the 3,074 gene targets (**Fig. 2A**), KEGG analysis identified 101 genes involved in cancer pathways (**Fig. 2B**). The miRNA-disease network linked hsa-miR-637 to multiple conditions, while hsa-miR-885-3p was specifically associated with malignant mesothelioma, a rare liver malignancy [9]. These findings suggest that hsa-miR-885-3p may assist not only in HCC detection but also in distinguishing rare hepatic malignancies, emphasizing the importance of disease-specific biomarker context. Based on differential expression, meta-heatmap profiling, and network topology, four

miRNAs: hsa-miR-885-3p, hsa-miR-320a, hsa-miR-744-5p, and hsa-miR-124-3p, emerged as promising diagnostic candidates, either individually or within a multi-miRNA panel.

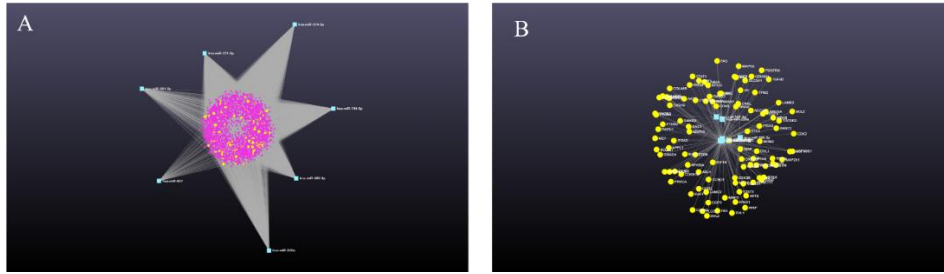


Figure 2. (A) miRNA-gene interaction network of the seven predicted miRNA biomarkers (B) Cancer-related genes extracted from the miRNA-gene interaction network.

4. Conclusion

Hsa-miR-885-3p, hsa-miR-320a, hsa-miR-744-5p, and hsa-miR-124-3p are promising HCC biomarkers with key roles in cancer development. Further validation and panel integration may improve early detection beyond alpha-fetoprotein, the most established serological biomarker in HCC diagnostics.

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