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Expression Profile of Long Noncoding RNAs for Early Detection of Hepatocellular Carcinoma in Cirrhotic Patients

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Abstract:

Hepatocellular carcinoma is the most common primary liver cancer and one of the leading causes of cancer-related deaths worldwide. It develops mainly in patients with liver cirrhosis, a chronic condition marked by fibrosis, structural distortion, and nodular regeneration. Cirrhosis arises from long-term liver injury caused by hepatitis B and C infections, alcohol use, or aflatoxin exposure. These factors drive inflammation, oxidative stress, and DNA damage that promote malignant transformation of hepatocytes.In Egypt and many developing countries, hepatitis C infection remains the dominant cause of cirrhosis and hepatocellular carcinoma, creating a major health burden. Early detection of hepatocellular carcinoma is difficult because symptoms appear late and the available diagnostic tools are limited. Alpha-fetoprotein, the most used blood marker, lacks sensitivity and specificity, as it may stay normal in early stages or rise in benign liver diseases.New molecular approaches focus on long noncoding RNAs, which are RNA molecules longer than 200 nucleotides that do not code for proteins but regulate gene expression. These molecules influence cell growth, apoptosis, and tumor development. Several long noncoding RNAs, including HULC, HOTAIR, MALAT1, and PVT1, are involved in liver fibrosis and hepatocarcinogenesis by activating stellate cells, remodeling tissue, and promoting angiogenesis.Among them, PVT1 has shown strong association with tumor development and progression. It promotes cell proliferation, invasion, and survival through pathways such as Wnt/β-catenin, PI3K/AKT, and TGF-β. Its expression levels are higher in both liver tissue and blood of patients with hepatocellular carcinoma compared with cirrhotic or healthy individuals. High PVT1 levels also correlate with larger tumor size, advanced stage, and poor prognosis.These findings indicate that circulating long noncoding RNA PVT1 may serve as a sensitive and specific non-invasive biomarker for detecting hepatocellular carcinoma in cirrhotic patients, improving diagnostic accuracy beyond traditional markers like alpha-fetoprotein

Key words: Long noncoding RNA PVT1, hepatocellular carcinoma, liver cirrhosis, diagnostic biomarker, AFP, molecular detection, cirrhosis progression, non-invasive test, gene expression, tumor marker.

Introduction

Hepatocellular carcinoma (HCC) is the most common primary malignancy of the liver, accounting for more than 80% of all liver cancer cases. It ranks among the leading causes of cancer-related mortality worldwide (Liang et al., 2024). Despite improvements in diagnosis and therapy, survival remains low because most cases are diagnosed at advanced stages. The five-year survival rate of advanced HCC is below 20% (Abou-Alfa et al., 2023). The disease burden is especially high in regions with a high prevalence of viral hepatitis such as East Asia, sub-Saharan Africa, and Egypt.

Pathogenesis and Risk Factors

Liver cirrhosis represents the final stage of chronic liver injury caused by various etiologies, including chronic viral hepatitis (HBV and HCV), alcohol abuse, and aflatoxin B1 exposure (Shah, 2024; Xu et al., 2024). Cirrhosis involves continuous cycles of inflammation, hepatocellular necrosis, and regeneration, leading to fibrosis, nodular formation, and genetic instability. These pathological changes create a fertile ground for malignant transformation (Mallela et al., 2023). In Egypt, where chronic HCV infection remains highly prevalent, cirrhosis and HCC pose a major public health challenge. Persistent viral replication and immune-mediated injury drive the progression from fibrosis to hepatocellular carcinoma (Tonon et al., 2024).

Limitations of Current Diagnostic Tools

Early diagnosis of HCC is crucial for curative management, yet it remains difficult due to the asymptomatic nature of early-stage disease. The most widely used biomarker, alpha-fetoprotein (AFP), has limited sensitivity and specificity. AFP levels can be normal in up to 40% of patients with early HCC and can be elevated in non-malignant conditions such as chronic hepatitis and cirrhosis (Park et al., 2017; Hu et al., 2018). Imaging techniques such as ultrasonography and CT scan are useful for tumor detection but are expensive and operator-dependent. This diagnostic gap highlights the need for reliable, non-invasive biomarkers capable of identifying HCC at earlier stages.

Long Noncoding RNAs and Hepatocarcinogenesis

Long noncoding RNAs (lncRNAs) are RNA molecules longer than 200 nucleotides that do not encode proteins but play critical regulatory roles in gene expression (Chen, 2025). They function at multiple levels including chromatin modification, transcriptional activation, and RNA processing. Dysregulation of lncRNAs contributes to various pathological processes, including carcinogenesis (Vij et al., 2024). In the liver, several lncRNAs such as HULC, HOTAIR, MALAT1, and PVT1 have been linked to the activation of hepatic stellate cells, extracellular matrix deposition, angiogenesis, and immune modulation—all key processes in fibrosis and tumor progression (Shah, 2024; Xu et al., 2024).

lncRNA PVT1 as an Oncogenic Driver

The lncRNA PVT1 (Plasmacytoma Variant Translocation 1) is located on chromosome 8q24, near the MYC oncogene. It has been identified as a major oncogenic lncRNA in several cancers, including HCC (Rashad et al., 2022; Ding et al., 2015). PVT1 promotes hepatocyte proliferation, suppresses apoptosis, and enhances migration and invasion. It exerts these effects by regulating pathways such as Wnt/β-catenin, PI3K/AKT, and TGF-β, all of which are central to tumor development and metastasis (Vij et al., 2024).

Clinical Relevance of lncRNA PVT1 in HCC

Multiple studies have shown that PVT1 is significantly upregulated in HCC tissues and in the serum of affected patients compared with cirrhotic patients and healthy controls (Jiang et al., 2020; Zhang et al., 2021). Elevated PVT1 expression correlates with tumor size, vascular invasion, advanced stage, and poor prognosis (Ding et al., 2014; Rojas et al., 2022). PVT1 overexpression has also been linked to HBV-related carcinogenesis, suggesting a potential role in virus-mediated oncogenic transformation (Wang et al., 2019).

Circulating lncRNAs, including PVT1, show high stability in body fluids and resistance to RNase degradation, making them promising non-invasive biomarkers (Dos Santos et al., 2025; Samir et al., 2024). Their early deregulation during carcinogenesis may provide diagnostic insight before radiological detection of tumors.

Study Aim

This study aims to evaluate the diagnostic value of circulating lncRNA PVT1 for detecting hepatocellular carcinoma among patients with liver cirrhosis, and to compare its performance with alpha-fetoprotein (AFP). It also explores the association between PVT1 expression and clinical, biochemical, and radiological features, including tumor characteristics, Child–Pugh classification, and Barcelona Clinic Liver Cancer (BCLC) stage.

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