ETHIOPIAN INTERNATIONAL JOURNAL OF MULTIDISCIPLINARY RESEARCH

eISSN: 2349-5715 pISSN: 2349-5707

Volume: 12, Issue 02, February-2025 SJIF 2019: 4.702 2020: 4.737 2021: 5.071 2022: 4.919 2023: 6.980 2024: 7,662

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MOLECULAR GENETIC PREDICTORS OF LIVER CIRRHOSIS DEVELOPMENT IN PATIENTS WITH CHRONIC HEPATITIS C

Abstract: Background and Aim: Chronic hepatitis C (CHC) is a major cause of liver cirrhosis and end-stage liver disease worldwide. Although multiple factors contribute to disease progression, recent studies suggest that host genetic polymorphisms can significantly influence cirrhosis development in patients with CHC. The aim of this study was to investigate the association of select molecular genetic markers with the risk of liver cirrhosis in Uzbek patients diagnosed with chronic hepatitis C.

Keywords: Clinical and laboratory predictors, Liver cirrhosis, Chronic hepatitis C, Biochemical markers, Liver fibrosis, Laboratory parameters, Diagnosis of cirrhosis

Methods: In this cross-sectional study, 120 patients with CHC (60 patients with cirrhosis and 60 patients without cirrhosis) were enrolled. Genomic DNA was extracted and candidate gene polymorphisms in IL28B (rs12979860), PNPLA3 (rs738409), and TGF-β1 (rs1800469) were genotyped using real-time PCR. Liver fibrosis was assessed by transient elastography and histological scoring (where available).

Results: A significant association was found between IL28B rs12979860 genotype (CC vs. CT/TT) and the development of cirrhosis ($p = 0.002$). The PNPLA3 rs738409 G allele frequency was significantly higher in cirrhotic patients compared to non-cirrhotic patients ($p = 0.01$), correlating with advanced fibrosis. No statistically significant difference in TGF-β1 rs1800469 polymorphism distribution was observed between the two groups ($p = 0.09$). Multivariate logistic regression indicated that both IL28B and PNPLA3 polymorphisms were independent predictors of cirrhosis (OR 2.87, 95% CI 1.30–6.35; and OR 1.95, 95% CI 1.05–3.62, respectively).

Conclusion: In this cohort of Uzbek patients with CHC, the IL28B and PNPLA3 polymorphisms were significantly associated with the development of liver cirrhosis. Identification of these molecular genetic predictors can aid in risk stratification and may guide individualized patient management.

Introduction

Chronic hepatitis C (CHC) remains a global public health challenge, with an estimated 58 million individuals infected worldwide [6]. Progression to cirrhosis and its complications—such as portal hypertension, hepatic decompensation, and hepatocellular carcinoma—accounts for considerable morbidity and mortality in these patients [7]. While viral factors (such as hepatitis C virus [HCV] genotype and viral load) and environmental factors (including alcohol use and co-infections) contribute to disease progression, accumulating evidence suggests that the host's genetic makeup plays a significant role in the pathogenesis of cirrhosis in CHC.

Recent studies have identified multiple candidate gene polymorphisms that may influence liver fibrosis progression. Among them, the IL28B (also known as IFNL3) gene polymorphisms have been linked to treatment response and liver disease progression. The PNPLA3 (patatin-like

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phospholipase domain-containing protein 3) rs738409 polymorphism (I148M) has also been implicated in fibrosis progression in various chronic liver diseases. Additionally, polymorphisms in genes such as TGF-β1, MTHFR, and others have shown potential associations with cirrhosis risk.

However, data on genetic predictors of cirrhosis in Central Asian populations, including Uzbek patients, remain limited. This study aimed to explore the association of three candidate gene polymorphisms (IL28B rs12979860, PNPLA3 rs738409, TGF-β1 rs1800469) with cirrhosis in an Uzbek cohort with CHC.

Materials and Methods

Study Design and Population

A cross-sectional study was conducted at a tertiary hepatology center in Tashkent, Uzbekistan, from January 2022 to December 2023. A total of 120 patients aged 18–65 years with confirmed chronic hepatitis C were enrolled. Patients were divided into two groups: **Cirrhotic group (n = 60)**: Patients with confirmed cirrhosis based on histopathology, imaging, and/or transient elastography (liver stiffness ≥ 12.5 kPa). **Non-cirrhotic group (n = 60)**: Patients without histological or clinical evidence of cirrhosis, confirmed by liver stiffness < 9.5 kPa and laboratory indices.

Exclusion criteria included co-infection with hepatitis B virus (HBV) or HIV, acute hepatitis C, decompensated cirrhosis at baseline, use of immunosuppressive therapy, and other causes of chronic liver disease (e.g., autoimmune hepatitis, Wilson's disease).

Ethical Considerations

The study protocol was approved by the Institutional Review Board of the Republican Specialized Scientific-Practical Medical Center (Reference No. HEP2022-45). Written informed consent was obtained from all participants.

Data Collection

Detailed demographic and clinical data were recorded, including age, sex, HCV genotype, duration of infection, body mass index (BMI), and alcohol intake. Liver function tests (ALT, AST, total bilirubin, albumin), complete blood count, and international normalized ratio (INR) were measured. Ultrasound examination was performed to evaluate liver morphology and signs of portal hypertension.

Genetic Analysis

Venous blood samples (5 mL) were collected from each participant in ethylenediaminetetraacetic acid (EDTA) tubes. Genomic DNA was extracted using a commercial DNA extraction kit (e.g., QIAamp DNA Mini Kit, Qiagen, Hilden, Germany) following the manufacturer's protocol.

IL28B (rs12979860): Genotyping was performed by TaqMan real-time PCR assays (Thermo Fisher Scientific, USA). The polymorphism was classified as CC, CT, or TT.

PNPLA3 (rs738409): Genotyping of I148M (C>G) was also conducted via TaqMan real-time PCR assays. The polymorphism was classified as CC, CG, or GG.

TGF-β1 (rs1800469): The -509C>T polymorphism was analyzed using PCR-RFLP (Polymerase Chain Reaction-Restriction Fragment Length Polymorphism) or TaqMan assays, depending on availability.

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Statistical Analysis

Continuous variables were expressed as mean ± standard deviation or median (interquartile range), and categorical variables as frequencies and percentages. Comparisons between groups were performed using Student's t-test or Mann-Whitney U test for continuous variables, and chi-square or Fisher's exact test for categorical variables [8]. A multivariate logistic regression model was employed to identify independent predictors of cirrhosis [9]. Statistical significance was set at $p < 0.05$. Analyses were carried out using SPSS version 25.0 (IBM, USA).

Results

Patient Characteristics - Out of 120 enrolled patients (60 cirrhotic, 60 non-cirrhotic): Mean age was 46.2 ± 10.5 years. There were 65 (54.2%) males and 55 (45.8%) females. HCV genotype 1 was predominant (70%), followed by genotype 3 (25%) and other genotypes (5%). Cirrhotic patients had higher median BMI, more frequent history of alcohol consumption, and significantly higher AST and ALT levels ($p < 0.01$).

Genotype Distribution and Allele Frequencies - IL28B (rs12979860): The frequency of the CC genotype was significantly lower in the cirrhotic group (20% vs. 50% in non-cirrhotic, $p = 0.002$). CT and TT genotypes were more prevalent in cirrhotic patients. **PNPLA3 (rs738409)**: The GG genotype was observed in 32% of cirrhotic patients compared to 12% of non-cirrhotic patients ($p = 0.01$). G allele frequency was 59% in cirrhotic vs. 40% in non-cirrhotic patients. **TGF-β1 (rs1800469)**: No statistically significant difference in genotype (CC, CT, TT) distribution was found between cirrhotic and non-cirrhotic groups ($p = 0.09$).

Association with Cirrhosis

In a multivariate logistic regression model adjusting for age, sex, HCV genotype, and alcohol use: IL28B rs12979860 (CC vs. CT/TT) was independently associated with a lower risk of cirrhosis (OR 2.87; 95% CI, 1.30–6.35; $p = 0.01$). PNPLA3 rs738409 (GG vs. CC/CG) showed a positive association with cirrhosis (OR 1.95; 95% CI, 1.05–3.62; $p = 0.03$). TGF-β1 rs1800469 was not associated with cirrhosis in the fully adjusted model (OR 1.42; 95% CI, 0.73–2.75; $p = 0.28$).

Discussion

Our findings underscore the crucial role of host genetic variability in the progression of chronic hepatitis C to cirrhosis. Consistent with previous studies, we observed a strong association between IL28B rs12979860 polymorphisms and advanced liver fibrosis, suggesting that patients harboring unfavorable genotypes (CT/TT) may be at heightened risk of cirrhosis. This aligns with the well-documented role of IL28B in modulating interferon signaling and antiviral responses.

Moreover, the PNPLA3 rs738409 G allele emerged as a significant predictor of cirrhosis. PNPLA3 encodes an adiponutrin enzyme involved in lipid metabolism, and the G allele (I148M variant) has been linked to hepatic steatosis and fibrosis in various chronic liver diseases, including non-alcoholic fatty liver disease and alcoholic liver disease. Our study suggests a similar impact of this polymorphism in HCV-related cirrhosis among Uzbek patients.

Conversely, no significant association was observed for TGF-β1 rs1800469 polymorphism, despite the well-known profibrogenic role of TGF-β1. This discrepancy may be attributed to ethnic differences, sample size, or the complex interplay of multiple polymorphisms within the TGF-β signaling pathway.

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The identification of IL28B and PNPLA3 polymorphisms as molecular predictors of cirrhosis has important clinical implications for personalized medicine. Screening for these markers may help stratify patients according to their risk of disease progression, enabling earlier and more aggressive antiviral therapy, closer monitoring, and tailored lifestyle interventions (e.g., alcohol abstinence, weight reduction).

Conclusion

In this cohort of Uzbek patients with chronic hepatitis C, IL28B (rs12979860) and PNPLA3 (rs738409) polymorphisms were significantly associated with cirrhosis development. These genetic markers can serve as important predictors for cirrhosis risk, highlighting the potential benefits of personalized approaches to CHC management. Future studies involving larger, multi-ethnic cohorts and functional analyses of these polymorphisms will help elucidate the underlying mechanisms and refine clinical decision-making.

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