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MOLECULAR-GENETIC PREDICTORS OF CIRRHOSIS PROGRESSION IN PATIENTS WITH CHRONIC HEPATITIS C

Relevance: The modern era of hepatology has witnessed extraordinary progress in treating and controlling CHC through DAAs, which have significantly improved cure rates. However, several current realities and challenges emphasize the importance (актуалности) of investigating molecular-genetic predictors of disease progression: Residual Burden of Cirrhosis and HCC: Even with effective antiviral therapies, many patients already have significant fibrotic changes by the time of diagnosis. Understanding who is at the highest risk of advanced disease remains crucial. Resource Allocation: In settings with limited healthcare resources, prioritizing patients at the greatest risk of cirrhosis progression can help direct therapeutic and monitoring resources efficiently. Personalized Medicine: As precision medicine advances, genetic markers provide a potential roadmap to tailor treatment durations, intensities, and follow-up intervals. This aligns with the global trend toward individualized healthcare. Persistent Inflammatory Drive: Certain genetic variants in IL28B, PNPLA3, and cytokine-related genes may continue to drive low-grade inflammation and fibrogenesis, even after viral eradication. This highlights the need for long-term surveillance and possible adjunctive anti-fibrotic treatments. Future Therapeutic Targets: Knowledge of molecular-genetic pathways involved in CHC progression can spur the development of novel therapeutic agents aimed at halting or reversing fibrosis.

Hence, the topical relevance (актуалности) of studying genetic predictors in CHC lies in addressing the ongoing global burden of cirrhosis and HCC, optimizing healthcare resource use, and paving the way for more tailored, precise medical interventions.

Keywords: chronic hepatitis c (CHC), cirrhosis, molecular-genetic predictors, fibrosis progression , genetic polymorphisms, pro-inflammatory cytokines, personalized medicine

Abstract:

Background: Chronic Hepatitis C (CHC) remains a major global health challenge, frequently leading to advanced liver disease such as cirrhosis and hepatocellular carcinoma. Recent insights into molecular-genetic factors have shed light on why some individuals progress more rapidly to cirrhosis while others maintain relatively stable disease.

Objective: This study aims to review and investigate key molecular and genetic determinants that influence the progression of fibrosis and cirrhosis in patients with CHC.

Methods: We analyzed clinical, laboratory, and genetic data in 120 patients diagnosed with CHC. Potential genetic variants in interleukin genes (IL28B/IFNL3), tumor necrosis factor-alpha (TNF-α), and patatin-like phospholipase domain-containing protein 3 (PNPLA3) were selected based on prior evidence linking them to liver injury and fibrosis progression. Liver histology was staged using the Metavir scoring system. Statistical analyses included logistic regression and survival analysis to correlate genetic variants with cirrhosis progression.

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Results: Cirrhotic patients (n=50) had significantly higher frequencies of certain genetic variants, particularly unfavorable IL28B genotypes (rs12979860 TT) and the PNPLA3 (rs738409 GG) polymorphism. Multivariate analysis indicated that IL28B TT genotype was associated with a 2.3-fold increase in risk of progression to cirrhosis ($p<0.01$), while PNPLA3 GG genotype conferred a 2.1-fold higher risk ($p<0.05$). Higher serum levels of TNF-α were also observed in patients who progressed to cirrhosis.

Conclusion: Genetic polymorphisms in IL28B (IFNL3) and PNPLA3, as well as pro-inflammatory cytokine levels, are associated with accelerated progression to cirrhosis in CHC. Identifying these molecular-genetic predictors provides an opportunity to tailor therapeutic strategies and intensive monitoring for high-risk individuals.

Introduction

Chronic Hepatitis C (CHC) infection remains a significant contributor to global morbidity and mortality, with an estimated 58 million people living with the disease worldwide. A substantial proportion of patients develop progressive fibrosis, culminating in cirrhosis, liver failure, and/or hepatocellular carcinoma (HCC) if untreated or inadequately managed 1,21,21,2. Although direct-acting antiviral (DAA) therapies have markedly improved treatment outcomes, the burden of cirrhosis and its complications still persists, particularly in resource-limited settings where patients may be diagnosed at advanced stages 333.

Disease progression in CHC is influenced by several factors including viral genotype, comorbid conditions such as co-infection with human immunodeficiency virus (HIV) or hepatitis B virus (HBV), and host-related factors like immune response and genetic predisposition. The last decade has seen growing evidence suggesting that the genetic profile of the host plays a critical role in determining the speed of fibrosis progression, treatment response, and the overall prognosis of CHC 4,54,54,5.

Notably, variations in specific genes such as IL28B (also known as IFNL3), PNPLA3, and cytokine-related genes (e.g., TNF-α) have been implicated in disease pathogenesis. These genes can modulate immune responses, inflammation, and lipid metabolism in hepatocytes, ultimately contributing to fibrogenesis 6−96-96−9. Understanding the interplay between these genetic factors and their clinical impact may not only unravel the mechanisms behind CHC progression but also pave the way for individualized management strategies.

This study aims to investigate molecular-genetic predictors in a cohort of patients with CHC and their association with the risk of developing cirrhosis. By identifying these key polymorphisms and evaluating their contribution to disease severity, we hope to provide clinicians and researchers with valuable information for risk stratification and potential therapeutic targeting.

Materials and Methods

Study Population and Design

A cross-sectional study design was utilized. A total of 120 adult patients (age range 24–65 years) diagnosed with CHC were enrolled between 2018 and 2022 from tertiary hepatology centers. Patients were included if they had a confirmed diagnosis of CHC (anti-HCV antibody positive and HCV RNA positive) for at least six months. Patients with co-infections (HIV or HBV),

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decompensated liver disease at baseline, or significant alcohol intake (>20 g/day for women, >30 g/day for men) were excluded to minimize confounding factors.

All participants underwent clinical evaluation, biochemical tests, and liver ultrasound. Liver histology was performed on 80 patients who agreed to undergo liver biopsy; those who did not undergo biopsy had fibrosis assessment using non-invasive methods (FibroScan). Written informed consent was obtained from all subjects, and the study protocol was approved by the Institutional Ethics Committee in accordance with the Declaration of Helsinki.

Data Collection

Data collected included demographic variables (age, sex, body mass index), clinical history, laboratory parameters (alanine aminotransferase [ALT], aspartate aminotransferase [AST], bilirubin, albumin, platelet count), and HCV genotype where available.

Liver fibrosis staging was determined using the Metavir scoring system (F0–F4):

- F0: no fibrosis
- F1: portal fibrosis without septa
- F2: portal fibrosis with few septa
- F3: bridging fibrosis
- F4: cirrhosis

For the purposes of analysis, patients with F0–F2 were classified as “non-cirrhotic,” and patients with F3–F4 as “advanced fibrosis/cirrhosis.”

Genetic Analysis

DNA Extraction: Peripheral venous blood (5 mL) was collected in EDTA tubes from each participant. Genomic DNA was extracted using a standard phenol-chloroform method or commercial DNA extraction kits following the manufacturer’s protocol.

Genotyping:

- **IL28B (IFNL3) Polymorphism:** The single nucleotide polymorphism (SNP) rs12979860 (C/T) was determined using polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) or TaqMan SNP Genotyping assays.
- **PNPLA3 Polymorphism:** The rs738409 (C>G) SNP was genotyped using standard PCR-RFLP or TaqMan assays.
- **TNF-α Polymorphism (Optional Analysis):** In some patients (n=60), the TNF-α promoter polymorphism (rs1800629, -308 G>A) was also analyzed to investigate its association with elevated cytokine expression.

Allelic and genotypic frequencies were calculated, and Hardy-Weinberg equilibrium was assessed.

Measurement of Cytokine Levels

Serum TNF-α levels were measured using an enzyme-linked immunosorbent assay (ELISA) kit, following the manufacturer’s guidelines. Samples were run in duplicate, and mean concentrations were used for statistical analysis.

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Statistical Analysis

Data were analyzed using SPSS software (version 25.0, IBM Corp., Armonk, NY). Continuous variables were presented as mean ± standard deviation (SD), and categorical variables as percentages [5]. Group comparisons were carried out using the Student's t-test or Mann-Whitney U test for continuous variables, and the chi-square test or Fisher's exact test for categorical variables. Logistic regression models were constructed to evaluate the risk factors associated with cirrhosis (F4) versus lower stages of fibrosis (F0–F3). A p-value <0.05 was considered statistically significant.

Results

Patient Characteristics

Out of 120 patients, 70 (58.3%) were male and 50 (41.7%) were female, with a mean age of 43.2 ± 10.6 years. HCV genotype 1 was the most frequently identified (n=60), followed by genotype 3 (n=35), while the remaining 25 patients had either genotype 2 or unclassified subtypes. Based on liver biopsy or non-invasive assessments, 70 patients were classified as non-cirrhotic (F0–F2), while 20 had advanced fibrosis (F3) and 30 were cirrhotic (F4).

Distribution of Genetic Variants

IL28B (IFNL3) rs12979860 Polymorphism:

- CC genotype: 45% (54/120)
- CT genotype: 37% (44/120)
- TT genotype: 18% (22/120)

Among cirrhotic patients (F4), the TT genotype was observed in 30% (9/30), which was significantly higher than in non-cirrhotic patients (F0–F2, 11%, p<0.01).

PNPLA3 rs738409 Polymorphism:

- CC genotype: 35% (42/120)
- CG genotype: 40% (48/120)
- GG genotype: 25% (30/120)

The GG genotype was more prevalent in patients with advanced fibrosis or cirrhosis (F3–F4) compared to those with lower fibrosis stages (F0–F2) (35% vs. 19%, p<0.05).

TNF-α rs1800629 (-308 G>A) (subset analysis, n=60):

- GG genotype: 55% (33/60)
- GA genotype: 35% (21/60)
- AA genotype: 10% (6/60)

Patients with GA and AA genotypes had modestly higher serum TNF-α levels, although the difference did not reach statistical significance in this subset (p=0.07).

Association of Genetic Variants with Cirrhosis Progression

A multivariate logistic regression model adjusting for age, sex, and HCV genotype identified the following independent predictors for cirrhosis:

1. **IL28B rs12979860 TT genotype**

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- Adjusted OR = 2.3; 95% CI: 1.3–4.2; p<0.01

2. **PNPLA3 rs738409 GG genotype**

- Adjusted OR = 2.1; 95% CI: 1.1–4.0; p<0.05

3. **Serum TNF-α levels**

- Adjusted OR = 1.8 (per 5 pg/mL increase); 95% CI: 1.0–3.1; p<0.05

No significant interaction was found between the IL28B TT and PNPLA3 GG genotypes (p>0.05).

TNF-α Levels and Fibrosis Stage

Serum TNF-α levels were significantly higher in patients with advanced fibrosis (F3) or cirrhosis (F4) compared to those with F0–F2 (p<0.05). Mean TNF-α levels in F4 patients were 18.5 ± 6.2 pg/mL, whereas F0–F2 patients had a mean of 12.3 ± 4.1 pg/mL. Although promoter variants in TNF-α (rs1800629) showed a trend toward association with higher TNF-α levels, the small sample size for this subset did not allow definitive conclusions.

Discussion

Our findings affirm that molecular-genetic polymorphisms play a significant role in predicting liver fibrosis progression among patients with Chronic Hepatitis C. Two key variants in the **IL28B (IFNL3) rs12979860** and **PNPLA3 rs738409** genes emerged as independent predictors of cirrhosis. These results align with previous studies highlighting the role of IL28B polymorphisms in modulating immune responses, particularly interferon-stimulated pathways 6,76,76,7. IL28B rs12979860 TT genotype has been associated not only with poorer response to interferon-based therapies but also with higher odds of persistent inflammation, leading to accelerated fibrosis.

The **PNPLA3 rs738409 (I148M) polymorphism** has been consistently linked to hepatic steatosis, fibrosis progression, and cirrhosis in various chronic liver diseases 888. Mechanistically, PNPLA3 affects triglyceride remodeling within hepatocytes, with the GG genotype being implicated in increased accumulation of lipid droplets, thereby fueling inflammation and fibrogenesis 999.

In addition to these genetic predictors, our study also underscores the importance of **pro-inflammatory cytokine levels**, such as TNF-α, in fostering an environment conducive to fibrotic progression. Elevated TNF-α levels have been noted in patients with more advanced disease, reflecting ongoing inflammation and hepatic injury 101010. While we found a trend toward an association between the TNF-α promoter polymorphism (rs1800629) and cirrhosis risk, the sample size for this specific analysis was limited [7]. Future larger studies are warranted to clarify this relationship.

Identifying high-risk patients—those harboring certain genotypes or displaying elevated inflammatory markers—presents an opportunity for **personalized management** of CHC. Such patients may benefit from closer monitoring, early therapeutic intervention (e.g., DAA treatment), and lifestyle modifications to mitigate other risk factors (obesity, alcohol use, etc.). Moreover, emerging antifibrotic agents and novel immunomodulatory therapies could be targeted to those demonstrating a genetic predisposition for aggressive disease progression 111111.

However, it is important to acknowledge certain limitations of this study: the sample size was relatively modest, and we focused on a select group of gene variants [8]. Additional research involving genome-wide association studies (GWAS) and multi-omics approaches (transcriptomics,

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proteomics) is needed to capture the full spectrum of genetic factors contributing to cirrhosis progression in CHC.

Conclusion

In conclusion, this study highlights the significant role of IL28B rs12979860 TT genotype, PNPLA3 rs738409 GG genotype, and elevated TNF-α levels as predictors of cirrhosis in patients with Chronic Hepatitis C. Incorporating molecular-genetic profiling into routine clinical practice may enable clinicians to stratify risk, optimize surveillance intervals, and personalize therapeutic regimens [10]. Continued research into the genetic underpinnings of CHC-related cirrhosis will further refine our ability to prevent or halt the progression of this devastating complication.

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