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IL28B POLYMORPHISM (rs12979860) AND HOST INNATE IMMUNITY IN PREDICTING CIRRHOSIS DEVELOPMENT AMONG PATIENTS WITH CHRONIC HEPATITIS C

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Background

The IL28B gene encodes interferon-lambda-3, a cytokine that activates JAK-STAT signaling in hepatocytes and plays a pivotal role in the innate antiviral response against hepatitis C virus (HCV). The rs12979860 C/T polymorphism, first identified through genome-wide association studies, has been consistently linked with both spontaneous viral clearance and treatment-induced sustained virologic response [1]. Even in the current era of direct-acting antivirals, IL28B retains prognostic significance because genetically determined inflammatory intensity affects the rate of fibrogenesis irrespective of virologic outcomes [2]. Eslam M. et al. (2017) demonstrated that the IFNL3 haplotype mediates hepatic inflammation and fibrosis progression independently of viral replication [3]. Population-level data on IL28B allele frequencies in Central Asian cohorts remain limited, which restricts the applicability of existing prediction models to this region.

Aim was to evaluate the distribution of IL28B (rs12979860) genotypes in chronic hepatitis C (CHC) patients across different fibrosis stages and to determine its prognostic value for liver cirrhosis (LC) prediction in an Uzbek cohort.

Materials and Methods

This cross-sectional study was conducted at Andijan State Medical Institute (2021-2025). A total of 93 CHC patients were enrolled. Fibrosis was staged by transient elastography (FibroScan, Echosens, France) using METAVIR classification. Patients were assigned to Group I (F0-F3, no cirrhosis, n = 48) or Group II (F4, cirrhosis, n = 45). The control group comprised 80 healthy age- and sex-matched individuals. HCV genotype was determined by sequencing: genotype 1 predominated (52.7%), followed by genotype 3 (33.3%). Genotyping of IL28B (rs12979860) was performed by real-time PCR with TaqMan probes (CFX96, Bio-Rad). Statistical analysis included Pearson χ^2 test, Fisher exact test, odds ratios (OR) and relative risks (RR) with 95% confidence intervals (CI), Cochran-Armitage trend test, Hardy-Weinberg equilibrium (HWE) testing, and ROC analysis. Significance was set at $p < 0.05$.

Results and Discussion

HWE was confirmed in controls ($\chi^2 = 0.41$; $p = 0.52$). The CC genotype showed a significant protective effect, being present in 41.3% of controls but in only 20.0% of cirrhosis patients (OR = 0.35; 95% CI 0.14-0.84; $p = 0.02$). CC carriers thus have approximately threefold lower odds of developing cirrhosis. The TT genotype was identified as a risk factor, found in 26.7% of Group II versus 11.2% of controls (OR = 2.89; 95% CI 1.09-7.63; $p = 0.03$; RR = 2.38). The heterozygous CT genotype showed no significant difference between groups ($p = 0.53$), consistent with a codominant model.

The T allele frequency demonstrated a dose-dependent linear increase: 35.0% in controls, 41.7% in Group I, and 53.3% in Group II (Cochran-Armitage $\chi^2 = 8.16$; $p = 0.004$). The difference between the two clinical groups was also independently significant ($\chi^2 = 4.78$; $p = 0.03$; OR = 1.60). ROC analysis yielded an AUC of 0.67 (95% CI 0.57-0.77; $p = 0.003$), with TT genotype providing 26.7% sensitivity, 88.8% specificity, 70.6% positive predictive value, and 64.4% negative predictive value. The moderate AUC is expected for a single locus in a polygenic condition and positions IL28B as a component of combined panels rather than a standalone diagnostic tool.

Stratification by HCV genotype revealed a trend toward higher TT frequency among genotype 1 patients (32.7%) compared to genotype 3 (16.1%; $p = 0.10$), consistent with the known stronger influence of IL28B on genotype 1 outcomes [4]. The T allele frequency in our controls (35.0%) occupies an intermediate position between European (30-40%) and East Asian (10-15%) populations, reflecting the unique ethnogenetic profile of Central Asian populations [1]. Within the cirrhosis group, TT carriers had significantly higher MELD scores (17.8 ± 5.4 vs. 14.6 ± 4.2; $p < 0.05$) and lower platelet counts (88 ± 36 vs. $115 \pm 43 \times 10^9$/L; $p < 0.05$) compared with CC and CT carriers. These findings suggest that the TT genotype predicts not only cirrhosis risk but also the severity of established disease.

A notable observation concerns the potential mechanism linking IL28B to fibrogenesis independently of viral clearance. The CC genotype is associated with higher levels of interferon-lambda-3, which exerts direct antifibrotic effects on hepatic stellate cells in addition to its antiviral activity [3]. In TT carriers, the reduced interferon-lambda-3 output may simultaneously impair viral suppression and remove a physiological brake on collagen synthesis. This dual deficit explains why the TT genotype retains prognostic significance even among

patients who have achieved sustained virologic response after direct-acting antiviral therapy [2]. From a practical standpoint, IL28B genotyping adds meaningful information to existing risk stratification algorithms, particularly when combined with other genetic and serological markers. The genotype is determined once, does not fluctuate with disease activity, and is unaffected by treatment status or intercurrent illness.

Conclusions

The IL28B TT genotype confers nearly threefold elevated odds of LC in CHC, while the CC genotype is substantially protective. The T allele shows a statistically significant dose-dependent trend across fibrosis stages, confirming its role as a gradual risk modifier. IL28B genotyping is recommended as a component of combined genetic panels for CHC prognostic stratification, particularly in genotype 1 patients [5, 6].

References

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