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A COMBINED MOLECULAR-GENETIC RISK SCORE FOR PREDICTING LIVER CIRRHOSIS IN CHRONIC HEPATITIS C: DEVELOPMENT AND CLINICAL VALIDATION

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Abstract

Liver cirrhosis (LC) develops in 15-30% of chronic hepatitis C (CHC) patients over 20-30 years, yet the trajectory of fibrosis progression varies substantially between individuals [1]. While clinical risk factors (age, alcohol use, HCV genotype) contribute to this variability, host genetic polymorphisms are now recognised as independent modulators of fibrosis kinetics. As R. Bataller and D.A. Brenner stated, "identifying patients at high risk of fibrosis progression remains the central unmet need in hepatitis C management, and genetic profiling represents the most promising avenue for this purpose" [2]. Despite extensive international data, a validated multi-locus genetic risk score integrated with clinical and instrumental parameters had not been developed for the Uzbek CHC population.

The aim of this study was to construct and validate a combined molecular-genetic risk stratification score for LC prediction in CHC patients in Uzbekistan, incorporating three significant genetic polymorphisms (IL-28B rs12979860,

TNFA rs1800629, SOD2 rs4880) alongside transient elastography, ultrasound parameters and serum fibrosis indices.

Materials and methods. A total of 92 CHC patients were enrolled: group 1 (n=47, F0-F2 fibrosis by METAVIR, no cirrhosis) and group 2 (n=45, verified LC, F4, Child-Pugh A-B). Genotyping for five single-nucleotide polymorphisms (SNPs) was performed by Real-time PCR (TaqMan, Applied Biosystems; QuantStudio 12K Flex). Fibrosis stage was assessed by transient elastography (FibroScan 502 Touch; threshold for LC >12.5 kPa) and histologically in 23 patients. Multivariate binary logistic regression was used to identify independent predictors of LC and to construct the predictive model. Model performance was assessed by receiver-operating characteristic (ROC) analysis (AUC with 95% CI). Comparison of AUC values between models was performed using the DeLong method. Net reclassification improvement (NRI) was calculated to quantify the incremental value of genetic predictors beyond the clinical model [3].

Results. Genotype distributions for all five SNPs satisfied Hardy-Weinberg equilibrium (all $p>0.05$). As shown in Table 1, FibroScan stiffness >12.5 kPa was the strongest single predictor of LC (OR=12.47; $p<0.001$), followed by APRI >1.0 (OR=5.86) and HCV duration >10 years (OR=4.53). Among genetic predictors, IL-28B TT genotype conferred the highest LC risk (OR=2.87; p=0.014), followed by TNFA allele A (OR=2.23; p=0.028) and SOD2 Val/Val (OR=2.11; p=0.047). The combined model (genetic + clinical-instrumental predictors) achieved AUC=0.847 [95%CI: 0.759-0.935], significantly outperforming the clinical-only model (AUC=0.741; p=0.031 by DeLong). The net reclassification improvement attributable to the three genetic predictors was

NRI=0.106 (p=0.022), indicating correct reclassification of an additional 10.6% of patients.

The three-tier algorithm assigned 38 patients (41.3%) to the low-risk group, 25 (27.2%) to the moderate-risk group and 29 (31.5%) to the high-risk group. None of the 38 low-risk patients had cirrhosis, confirming a high negative predictive value for exclusion of LC. All 29 high-risk patients either had established cirrhosis or progressed to F3-F4 within the observation period. In the subgroup of 9 patients carrying all three unfavourable genotypes simultaneously, median liver stiffness reached 24.3 kPa [17.8;33.2] - significantly higher than in carriers of all three favourable genotypes (15.7 kPa; p=0.017) - indicating an additive effect of the genetic predictors on fibrosis severity.

The clinical utility of integrating genetic data with instrumental findings is supported by the concept of personalised medicine in hepatology. As J.M. Pawlotsky noted, "risk-adapted treatment and surveillance strategies in CHC require biomarkers that reflect not only the current fibrosis stage but the underlying biological drivers of progression" [4]. Our combined score directly addresses this need by capturing both the current fibrosis burden (FibroScan, APRI) and the host's genetic propensity for ongoing fibrogenesis (IL-28B, TNFA, SOD2). The economic analysis demonstrated a cost-effectiveness ratio of 10.1 (net return of 278.3 million sum against 27.6 million sum investment in genotyping), supporting the feasibility of algorithm implementation in Uzbekistan's healthcare system.

The main limitation of this study is its single-centre design (n=92), which was adequate to detect ORs ≥2.1 for all three significant genetic predictors (power >68%) but may have underestimated effect sizes. External validation in an independent multi-centre cohort is required before widespread clinical implementation. The algorithm does not yet incorporate serum fibrosis

biomarkers (Pro-C3, ELF test), which could further refine risk stratification once these tests become available in Uzbekistan [5].

Conclusion

A validated three-tier molecular-genetic risk stratification algorithm for CHC-to-cirrhosis progression has been developed for the Uzbek population. The combined model (AUC=0.847) significantly outperforms clinical-only risk assessment and correctly reclassifies an additional 10.6% of patients. The algorithm provides clear, actionable management recommendations for each risk category and is supported by a favourable cost-effectiveness analysis. Multi-centre prospective validation is the essential next step towards its routine clinical implementation in Uzbekistan.

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