INTERNATIONAL JOURNAL OF MEDICAL SCIENCE AND DENTAL HEALTH
(ISSN: 2454-4191)
www.ijmsdh.org (2026)

Received: 28 July 2026
Revised: 30 Aug 2026
Accepted: 06 Sep 2026
Published: 23 Sep 2026

Volume 12 Issue 09, 2026
Page No - 222-227
DOI - 10.55640/ijmsdh-12-09-26

Article Citation: Kholikova, D. S., & Zhuraeva , M. A. (2026). Candidate Gene Polymorphisms Associated with Sarcopenia in HBV-, HCV-, and Alcohol-Related Liver Cirrhosis: CYP2C9, SOD2, and TGFβ1 in an Uzbek Cohort. International Journal of Medical Science and Dental Health, 12(09), 222-227. https://doi.org/10.55640/ijmsdh-12-09-26

Candidate Gene Polymorphisms Associated with Sarcopenia in HBV-, HCV-, and Alcohol-Related Liver Cirrhosis: CYP2C9, SOD2, and TGFβ1 in an Uzbek Cohort

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Abstract

Background: Sarcopenia is a frequent complication of liver cirrhosis, but the contribution of host genetic variability to muscle loss remains insufficiently characterized. This study evaluated candidate polymorphisms in CYP2C9, SOD2, and TGFβ1 in patients with cirrhosis of different etiologies, stratified by sarcopenia status.

Methods: A candidate-gene analysis was performed within a cohort of patients with HBV-, HCV-, and alcohol-related liver cirrhosis. According to the molecular-genetic tables in the dissertation, the analyzed subgroups comprised HBV cirrhosis with/without sarcopenia (n=40/60), HCV cirrhosis with/without sarcopenia (n=40/60), alcohol-related cirrhosis with/without sarcopenia (n=20/40), and healthy controls (n=40). Peripheral-blood DNA was isolated and polymorphisms were assessed by PCR-based methods. The investigated variants were CYP2C9 Ile359Leu, CYP2C9 Arg144Cys, SOD2 Ala16Val, and TGFβ1 Arg25Pro.

Results: Risk-allele enrichment was observed consistently in sarcopenic patients. The CYP2C9 Leu allele occurred in 30.0%, 33.8%, and 40.0% of sarcopenic HBV, HCV, and alcohol-related cirrhosis groups versus 12.5%, 15.0%, and 13.8% in the corresponding non-sarcopenic groups. The SOD2 Val allele occurred in 85.0%, 80.0%, and 85.0% versus 58.3%, 60.0%, and 65.0%, respectively. The TGFβ1 Pro allele showed the largest separation: 57.5%, 60.0%, and 70.0% in sarcopenia versus 26.7%, 28.3%, and 27.5% without sarcopenia (all reported $P<0.001$). In alcohol-related cirrhosis, the CYP2C9 Arg144Cys Cys allele was 27.5% in sarcopenia versus 12.5% without

sarcopenia and 1.2% in controls; the dissertation reported RR=22.0 and OR=29.97 for sarcopenia versus controls.

Conclusions: The dissertation data support an association between sarcopenia and enrichment of CYP2C9 Leu/Cys, SOD2 Val, and TGFβ1 Pro variants across major cirrhosis etiologies. These findings are hypothesis-generating and require external replication, adjustment for confounders, and reconciliation of subgroup denominators before journal submission.

Keywords: liver cirrhosis; sarcopenia; CYP2C9; SOD2; TGFβ1; genetic polymorphism; oxidative stress; fibrosis

Introduction

Background

Sarcopenia in cirrhosis reflects a complex interaction between hypercatabolism, inflammation, malnutrition, mitochondrial dysfunction, reduced anabolic signaling, and impaired muscle protein synthesis. Its clinical importance is increasingly recognized because loss of muscle mass and strength is associated with poorer functional status and adverse outcomes in cirrhosis [1–4].

Host genetic variation may modify several biological pathways that are relevant to the liver–muscle axis. SOD2 is a major mitochondrial antioxidant enzyme, and the Ala16Val polymorphism has been studied in oxidative-stress–related liver phenotypes, although published associations are not uniform [5–7]. TGFβ1 is a central profibrogenic and tissue-remodeling cytokine. Prior studies have linked codon 25 variation to hepatic fibrogenesis in selected populations, while other studies have reported null or context-dependent effects [8–11]. CYP2C9 polymorphisms are best established as pharmacogenetic variants influencing hepatic drug metabolism; their relationship to sarcopenia is substantially less established and should therefore be regarded as exploratory in the present candidate-gene analysis.

The dissertation underlying this article examined a large Uzbek cohort with HBV-, HCV-, and alcohol-related cirrhosis and included a dedicated molecular-genetic chapter. The present manuscript isolates that genetic component to evaluate whether the distribution of CYP2C9, SOD2, and TGFβ1 variants differs according to sarcopenia status and cirrhosis etiology.

Materials and Methods

Study design and participants

This was a cross-sectional candidate-gene analysis nested within the dissertation cohort of 260 patients with liver cirrhosis and 40 healthy controls. The clinical cohort comprised 100 patients with HBV-related cirrhosis, 100 with HCV-related cirrhosis, and 60 with alcohol-related cirrhosis. Sarcopenia was assessed using muscle mass, muscle strength, and functional/nutritional parameters described in the dissertation.

For the molecular-genetic chapter, the dissertation tables used the following denominators: HBV cirrhosis, 40 patients with sarcopenia and 60 without; HCV cirrhosis, 40 with sarcopenia and 60 without; alcohol-related cirrhosis, 20 with sarcopenia and 40 without; and 40 healthy controls. These denominators were retained for the present manuscript because they are the explicit denominators attached to the genotype tables.

Sarcopenia assessment

The dissertation assessed skeletal muscle mass by bioimpedance-derived skeletal muscle index, muscle strength by handgrip dynamometry, and nutritional status by the Nutritional Risk Index. These measures were used together with the clinical evaluation to classify patients according to sarcopenia status.

DNA extraction and genotyping

Genomic DNA was isolated from peripheral-blood lymphocytes using the Diatom™ DNA Prep 200 system according to the dissertation protocol. Polymerase chain reaction–based molecular-genetic methods were used to evaluate candidate polymorphisms. The variants selected for this article were CYP2C9 Ile359Leu, CYP2C9 Arg144Cys, SOD2 Ala16Val, and TGFβ1 Arg25Pro. The supplied dissertation text does not provide complete assay-specific primer sequences or a full laboratory validation table for each SNP; these details should be added from the original laboratory protocol before submission.

Statistical analysis

The dissertation reports use of Microsoft Excel (2024), Student's t tests for quantitative variables, chi-square tests for qualitative variables, calculation of relative risk (RR) and odds ratios (OR) with 95% confidence intervals for candidate-gene analyses, and Pearson correlation for continuous associations. In this manuscript, no new inferential statistics were generated; reported frequencies, χ^2 values, P values, RR, and OR were transcribed or summarized from the dissertation.

Results

Study groups

Etiology	Sarcopenia	No sarcopenia	Control
HBV cirrhosis	n=40	n=60	n=40 shared control
HCV cirrhosis	n=40*	n=60*	n=40 shared control
Alcohol-related cirrhosis	n=20	n=40	n=40 shared control

**The clinical chapter reports 37/63 for HCV sarcopenia/no sarcopenia, whereas the molecular-genetic tables use 40/60. This discrepancy requires reconciliation before submission.*

CYP2C9 Ile359Leu

The Leu allele was consistently more frequent in patients with sarcopenia. In HBV cirrhosis, Leu frequency was 30.0% with sarcopenia versus 12.5% without sarcopenia (χ^2=9.36, P<0.01; RR=2.40; OR=3.00). In HCV cirrhosis, frequencies were 33.8% versus 15.0% (χ^2=9.68, P<0.01). In alcohol-related cirrhosis, Leu occurred in 40.0% versus 13.8% (χ^2=10.54, P<0.001; RR=2.909; OR=4.182). The control Leu frequency reported in the dissertation was 1.2%.

CYP2C9 Arg144Cys

The Cys allele was also enriched in the sarcopenia subgroups. Reported frequencies were 25.0% versus 11.7% in HBV cirrhosis, 28.75% versus 13.3% in HCV cirrhosis, and 27.5% versus 12.5% in alcohol-related cirrhosis. In the alcohol-related group, the Cys-allele comparison was significant (χ^2=4.16, P<0.05); compared with the 1.2% control frequency, the dissertation reported RR=22.0 and OR=29.966.

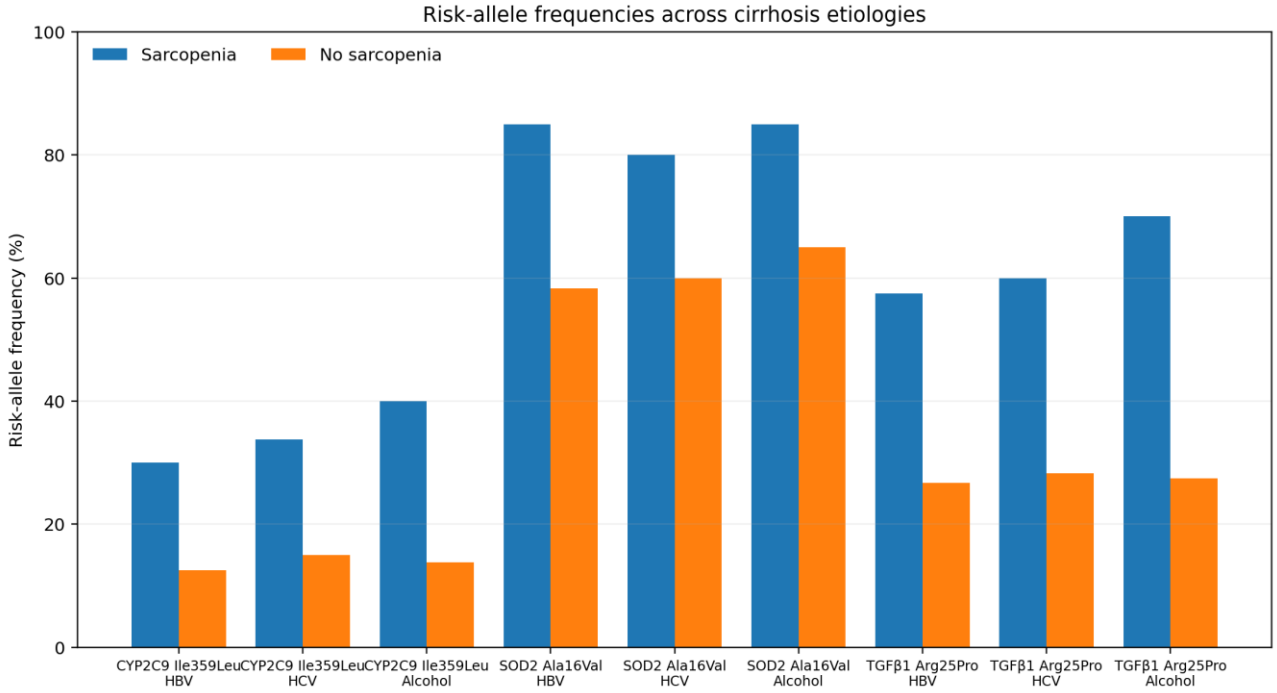

Figure 1. Frequency of selected risk alleles in cirrhosis with and without sarcopenia.

All values are reproduced from the dissertation's molecular-genetic chapter. No new P values were calculated for this figure.

SOD2 Ala16Val

The Val allele was present in 85.0% of HBV-cirrhosis patients with sarcopenia versus 58.3% without sarcopenia (χ^2=15.96, P<0.01), in 80.0% versus 60.0% in HCV cirrhosis (χ^2=8.82, P<0.01), and in 85.0% versus 65.0% in alcohol-related cirrhosis (χ^2=5.25, P<0.05). The healthy-control Val frequency was 17.5%. Val/Val genotype frequency among sarcopenic

patients was reported as 80.0% for HBV, 67.5% for HCV, and 75.0% for alcohol-related cirrhosis.

TGFβ1 Arg25Pro

The Pro allele showed a pronounced association with sarcopenia status in all etiologic groups. Frequencies were 57.5% versus 26.7% in HBV cirrhosis (χ^2=19.18, P<0.001), 60.0% versus 28.3% in HCV cirrhosis (χ^2=19.90, P<0.001), and 70.0% versus 27.5% in alcohol-related cirrhosis (χ^2=19.82, P<0.001). The control Pro frequency was 3.8%. The dissertation reported Pro/Pro genotype frequencies among sarcopenic patients of 35.0%, 37.5%, and 50.0%, respectively.

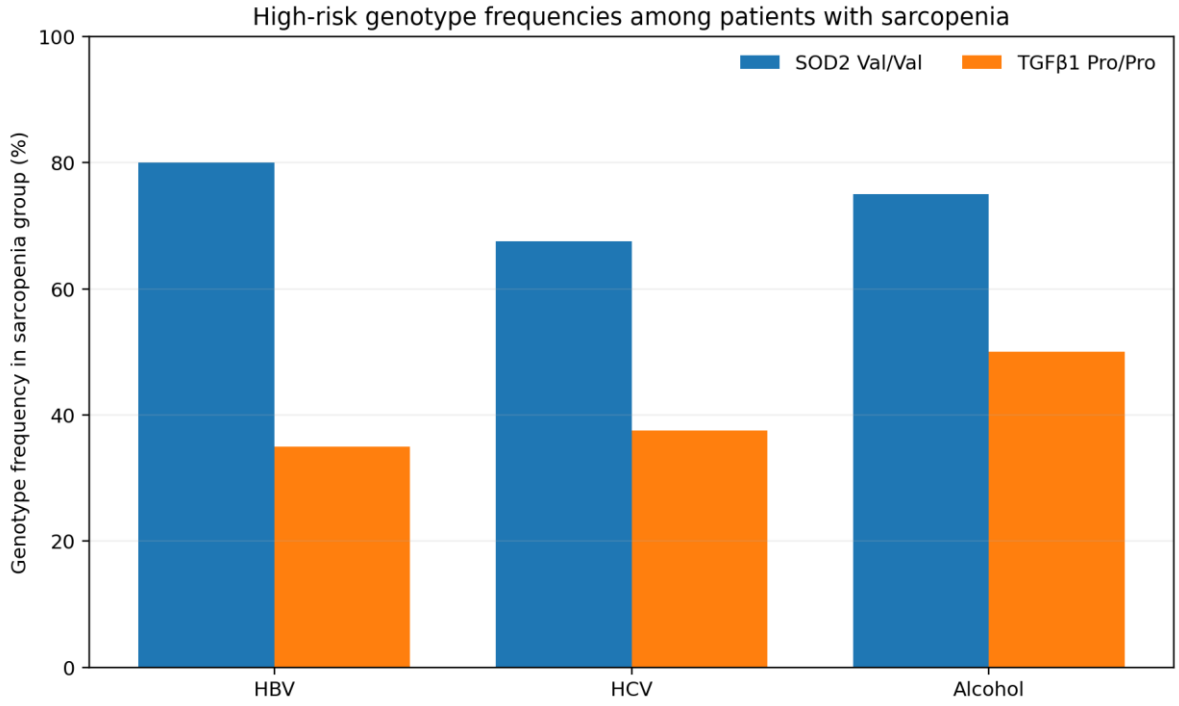

Figure 2. High-risk SOD2 Val/Val and TGFβ1 Pro/Pro genotype frequencies among sarcopenic patients by cirrhosis etiology.

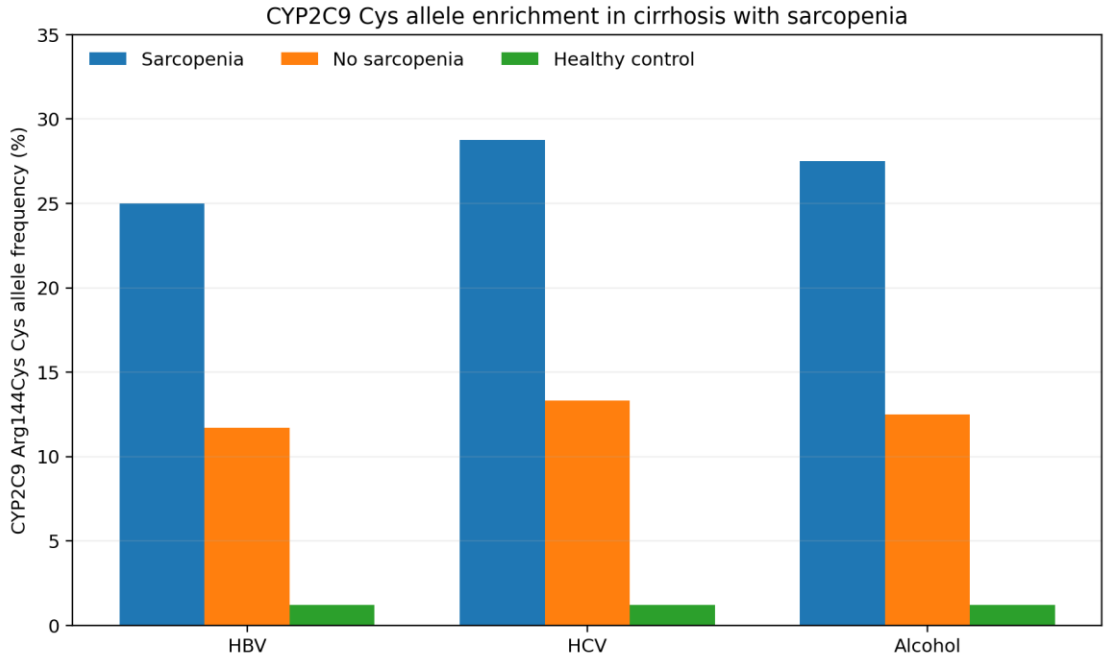

Figure 3. CYP2C9 Arg144Cys Cys-allele frequency in sarcopenic, non-sarcopenic, and healthy control groups.

Summary of candidate-gene findings

Variant / risk allele	HBV sarc vs no sarc	HCV sarc vs no sarc	Alcohol sarc vs no sarc	Control	Reported significance
CYP2C9 Ile359Leu / Leu	30.0 vs 12.5%	33.8 vs 15.0%	40.0 vs 13.8%	1.2%	P<0.01; P<0.01; P<0.001
CYP2C9 Arg144Cys / Cys	25.0 vs 11.7%	28.75 vs 13.3%	27.5 vs 12.5%	1.2%	HBV/HCV/Alcohol: significant as reported; alcohol P<0.05
SOD2 Ala16Val / Val	85.0 vs 58.3%	80.0 vs 60.0%	85.0 vs 65.0%	17.5%	P<0.01; P<0.01; P<0.05
TGFβ1 Arg25Pro / Pro	57.5 vs 26.7%	60.0 vs 28.3%	70.0 vs 27.5%	3.8%	All P<0.001

Discussion

The molecular-genetic results show a consistent pattern: several candidate risk alleles were more frequent in cirrhotic patients with sarcopenia than in etiologically matched patients without sarcopenia. The most pronounced separation was observed for TGFβ1 Arg25Pro, followed by SOD2 Ala16Val. CYP2C9 variants also differed according to sarcopenia status, although the biological pathway connecting CYP2C9 genotype to muscle loss is less direct and requires particularly cautious interpretation.

The TGFβ1 findings are biologically plausible in the context of hepatic fibrogenesis and tissue remodeling. Prior studies have shown that codon 25 variation may influence fibrosis progression in chronic hepatitis C and other chronic liver diseases, although results have differed across populations and etiologies [8–11]. The present dissertation extends this candidate-gene question from hepatic fibrosis to the sarcopenic phenotype, with the Pro allele reaching 70% in alcohol-related cirrhosis with sarcopenia.

The SOD2 results are also consistent with a potential oxidative-stress contribution. SOD2 regulates mitochondrial superoxide handling, and Ala16Val variation has been evaluated in chronic liver disease and oxidative-stress phenotypes. Importantly, published work has been inconsistent regarding which allele confers risk and in which clinical setting [5–7]. Therefore, the high Val-allele frequency observed in the present sarcopenia groups should be treated as a population-specific association rather than a universally established functional direction.

CYP2C9 Ile359Leu and Arg144Cys were associated with sarcopenia in all three etiologic strata in the dissertation. CYP2C9 is primarily recognized for interindividual variability in hepatic xenobiotic metabolism. The present observations may reflect linkage, treatment-related selection, population structure, or another unmeasured mechanism rather than a direct muscle-catabolic effect. Replication with multivariable modeling and independent genotyping is needed before CYP2C9 variants can be considered predictive biomarkers of cirrhosis-related sarcopenia.

Several strengths deserve emphasis: the study evaluated three major cirrhosis etiologies within the same population, used etiologically matched non-sarcopenic comparison groups, and included a healthy control group. The principal limitations are the candidate-gene design, absence of genome-wide correction, uncertain adjustment for age/sex/disease severity, incomplete assay-specific genotyping details in the supplied dissertation, and a discrepancy between the HCV sarcopenia counts reported in the clinical and genetic chapters.

Clinical and Research Implications

The genetic findings may help define a hypothesis for future risk-stratification studies in cirrhosis. A practical next step would be a prospectively designed validation cohort using prespecified sarcopenia criteria, blinded genotyping, Hardy-Weinberg testing, multivariable logistic regression, and correction for multiple comparisons. A combined genetic score should not be proposed clinically until these steps are completed.

Conclusions

Across HBV-, HCV-, and alcohol-related cirrhosis, sarcopenia was associated with higher frequencies of the CYP2C9 Leu and Cys alleles, the SOD2 Val allele/Val-Val genotype, and the TGFβ1 Pro allele/Pro-Pro genotype. TGFβ1 Arg25Pro demonstrated the strongest and most consistent separation between sarcopenic and non-sarcopenic groups. These findings support further investigation of host genetic susceptibility to cirrhosis-related muscle wasting, but should be considered exploratory until externally validated.

Ethics Approval and Informed Consent

The study protocol was reviewed and approved by the Ethics Committee of Andijan State Medical University. The study was conducted in accordance with the ethical principles of the Declaration of Helsinki. All participants were informed about the objectives, procedures, potential risks, and intended scientific use of the collected data. Written informed consent was obtained from all participants before enrollment. Participant confidentiality was maintained throughout the study.

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