Effects of apolipoprotein E and solute carrier organic anion transporter family member 1B1 gene polymorphisms on statin efficacy and safety in dyslipidemic patients

Xiaohong Wu, Yumei Cai, Yonglong Su, Xianni Wei, Tingting Nan, Xiaoyun Ye, Siheng Lian and Jinbao Wei

Objective **To investigate the distribution of the apolipoprotein E (*ApoE*) and solute carrier organic anion transporter family member 1B1 (*SLCO1B1*) polymorphisms in dyslipidemia patients and their impact on statin efficacy and safety.**

Methods **A retrospective analysis was conducted on dyslipidemic inpatients (April 2024–March 2025) who received statin therapy and genetic testing for *SLCO1B1* (rs4149056) and *ApoE* (rs429358 and rs7412), to analyze the association of genotypes with lipid levels and safety indicators.**

Results **The final analysis included 238 hospitalized patients with dyslipidemia (156 males and 82 females) who met the inclusion criteria. The study population had a mean age of 60.61 ± 0.91 years (mean ± SEM). The allele frequencies for both *ApoE* and *SLCO1B1* polymorphisms were in Hardy–Weinberg equilibrium ($P > 0.05$). Analysis of statin efficacy revealed a significant association between *ApoE* genotype and atorvastatin response: E3 carriers demonstrated higher low-density lipoprotein cholesterol levels posttreatment compared to E2 carriers (2.85 ± 1.00 mmol/l vs. 2.28 ± 0.96 mmol/l, $P = 0.026$). However, no such association was found in patients administered rosuvastatin. For safety outcomes, comparisons of creatine kinase and alanine aminotransferase levels between carriers of the *SLCO1B1* TC and TT genotypes showed no statistically significant differences.**

Conclusion ***APOE*** **polymorphisms influence statin efficacy. The E2 genotype is associated with better atorvastatin efficacy in lipid management. At low-to-moderate doses, the *SLCO1B1* TC genotype did not increase safety risk, supporting its clinical safety.**

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Department of Pharmacy, Xiamen Medical College Affiliated Haicang Hospital, Xiamen, Fujian, China

Correspondence to Jinbao Wei, MD, Department of Pharmacy, Xiamen Medical College Affiliated Haicang Hospital/Xiamen Haicang Hospital, 89 Haiyu Road, Haicang District, Xiamen 361026, Fujian Province, China
Tel: +86 18817893031; e-mail: vigeepaul@163.com

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Introduction

Dyslipidemia emerges as a critical contributor to cardiovascular disease and type 2 diabetes. Patients with dyslipidemia present with dysregulated lipid profiles, characterized by markedly increased total cholesterol (TC) and triglyceride levels. The prevalence of dyslipidemia has increased significantly in recent decades, affecting even children and adolescents [1,2]. It was predicted that increased serum cholesterol levels could lead to approximately 9.2 million additional cardiovascular events in China between 2010 and 2030 [3]. Both domestic and international guidelines [4–7] uniformly designate statins as a first-line therapy for cholesterol management, barring contraindications.

Although statins share a common mechanism of action, they exhibit distinct lipid-lowering efficacy, safety, and pharmacokinetic profiles, implicating genetic modulation of therapeutic response. This heterogeneity underscores the significant role of genetic factors in modulating statin response. Genome-wide association studies have identified several key genes involved in statin pharmacodynamics and pharmacokinetics, particularly those encoding drug transporters such as cytochromes P450 and members of the organic anion transporting polypeptide (OATP) family. Among these, apolipoprotein E (*ApoE*), which exhibits high affinity for cell-surface lipoprotein receptors, plays a critical role in regulating tissue and plasma lipid homeostasis. The three common *ApoE* alleles – E2, E3, and E4 – influence lipid metabolism and plasma levels, contributing to interindividual variability in statin efficacy. On the other hand, solute carrier organic anion transporter family member 1B1 (*SLCO1B1*), which encodes the *OATP1B1* transporter, is predominantly expressed on the sinusoidal membrane of

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hepatocytes and mediates the hepatic uptake of statins. Single nucleotide polymorphisms (SNPs) in *SLCO1B1* can reduce transporter activity, leading to diminished hepatic uptake, elevated systemic statin concentrations, and an increased risk of statin-associated myopathy [8].

In view of the individual differences in lipid levels and safety after statin treatment, *ApoE* and *SLCO1B1* gene polymorphisms may play crucial roles in the treatment of dyslipidemia. This study investigated *ApoE* and *SLCO1B1* gene polymorphisms in a cohort of Han Chinese patients with dyslipidemia. We analyzed the distribution characteristics and frequency of these polymorphisms and assessed their effects on the efficacy and safety of statin therapy, which were help to provide clinically relevant evidence.

Materials and methods

Study design

This single-center, retrospective cohort study was conducted at a tertiary general hospital in Xiamen City, Fujian Province, China. We reviewed the medical records of all hospitalized patients with dyslipidemia who received statin therapy and underwent clinically indicated genotyping for *SLCO1B1* and *ApoE* at our institution between April 2024 and March 2025. The genotyping was performed as part of routine clinical care for pharmacogenetic guidance, and results were available in the electronic health records.

Study participants

Inclusion criteria were: (a) a documented clinical diagnosis of dyslipidemia or atherosclerotic cardiovascular disease (ASCVD) that warranted statin therapy per current guidelines; (b) continuous statin treatment for at least 4 weeks prior to data collection; and (c) availability of complete *SLCO1B1* and *ApoE* genotype data. Note on lipid criteria: while the diagnosis established the indication for statins, all included patients also had at least one qualifying lipid profile [fasting TC ≥ 5.2 mmol/l, or low-density lipoprotein cholesterol (LDL-C) ≥ 3.4 mmol/l, or triglycerides ≥ 1.7 mmol/l, or high-density lipoprotein cholesterol (HDL-C) < 1.0 mmol/l] documented in their medical records, further confirming their eligibility. These values were obtained from the earliest available time point, typically prior to or near statin initiation.

Exclusion criteria were: (a) hepatic or renal impairment: alanine aminotransferase (ALT)/aspartate aminotransferase (AST) ≥ 3× upper limit of normal or estimated glomerular filtration rate < 60 ml/min/1.73 m^2; (b) documented poor adherence to statin therapy; (c) incomplete clinical data; and (d) comorbidities potentially confounding results (e.g. uncontrolled thyroid disorders, nephrotic syndrome, and active autoimmune diseases) or recent use of interfering medications.

Genotyping of solute carrier organic anion transporter family member 1B1 and apolipoprotein E

Venous blood samples (2 ml) were collected from dyslipidemic patients using EDTA-K2 anticoagulant vacuum tubes (purple top). Fasting was not required prior to sampling. Following collection, the tubes were gently inverted 8–10 times to ensure thorough mixing of the blood with the anticoagulant.

For DNA preparation, 10 µl of whole blood was added to 400 µl of sample extraction solution (CQ-ENH type). The pipette tip was immersed 3–4 mm below the liquid surface during dispensing to minimize aerosol generation. After standing for 1 min until the sample turned brown, 1.0 µl of the mixture was aliquoted onto the wall of a reagent tube for subsequent centrifugation and mixing.

Genotyping was performed using a ligase detection reaction assay on a MA-011780 fluorescent quantitative PCR instrument (Suzhou Yairui Biotechnology Co., Ltd., Suzhou, Jiangsu, China). The *ApoE* SNPs (rs7412 and rs429358) were detected, which allows for the identification of six genotypes categorized into three phenotypic isoforms: E2 (E2/E2 and E2/E3), E3 (E2/E4 and E3/E3), and E4 (E3/E4 and E4/E4). Similarly, the *SLCO1B1* (rs4149056, T > C) was genotyped, classifying individuals into TT, TC, or CC genotypes.

Assessment of efficacy and safety parameters

After 4 weeks of continuous statin therapy, fasting venous blood samples (2 ml) were collected from participants in the morning using serum-separating tubes. The samples were centrifuged for 5 min to isolate serum. Serum levels of efficacy biomarkers – including TC, triglycerides, high-density lipoprotein cholesterol, and low-density lipoprotein cholesterol, as well as safety biomarkers, such as total bilirubin, ALT, alkaline phosphatase, and creatine kinase – were measured using a Beckman Coulter fully automated biochemical immunoassay analyzer.

Statistical analysis

Data analysis was performed using SPSS Statistics software (version 29.0, IBM Corp.). Hardy–Weinberg equilibrium (HWE) was assessed by χ^2 test, with a P value of greater than 0.05 indicating population representativeness. Normally distributed continuous variables are expressed as mean ± SD ($\bar{x}$± SD). Intergroup comparisons were analyzed using Student's t-test (two groups) or one-way analysis of variance (≥3 groups). Statistical significance was defined as a Pvalue less than 0.05.

Results

Baseline patient characteristics

Of the dyslipidemia inpatients who received statins and underwent *SLCO1B1* and *ApoE* genotyping at

our hospital (April 2024–March 2025), one patient on simvastatin was excluded because of incomplete data. Two hundred thirty eight patients were included in the final analysis, all of whom were treated exclusively with either atorvastatin 20 mg daily (n = 182; 76.50%) or rosuvastatin 10 mg daily (n = 56; 23.50%). All participants were of Han Chinese ethnicity. Most patients were recruited from the Department of Cardiology and presented with multiple comorbidities, including hypertension, diabetes, and coronary artery disease. Detailed demographic and clinical characteristics are summarized in Table 1.

Apolipoprotein E and solute carrier organic anion transporter family member 1B1 genotype frequencies and conformation to Hardy–Weinberg equilibrium

Consistency with HWE was confirmed for all genotyped loci. The minor allele frequency for *ApoE* rs429358 (T > C) was 6.09% (χ^2 = 1.61, P = 0.447) and for *ApoE* rs7412 (C > T) was 5.46% (χ^2 = 0.13, P = 0.94). The *SLCO1B1* rs4149056 (T > C) variant had a minor allele frequency of 7.76% (χ^2 = 1.59, P = 0.451). The observed genotype distributions for all tested SNPs were consistent with HWE expectations (all P > 0.05), supporting the genetic representativeness of the study population. See Table 2 for detailed genotype distributions.

Apolipoprotein E gene polymorphism and allele frequency distribution

The *ApoE* genotype E3 group (E2/E4 and E3/E3) had the highest proportion, accounting for 77.31%; the E2 group (E2/E2 and E2/E3) accounted for 11.76%; the E4 group (E3/E4 and E4/E4) accounted for 10.92%. Please refer to Table 3.

Table 1 Basic clinical characteristics of the patients included in the study ($\bar{x}$± SD) or (n, %)

Clinical features	n = 38
Age (average; years)	60.61 ± 0.91
Male/female	156 (65.55)/82 (34.45)
Alcohol consumption history	37 (15.55)
Hypertension	107 (44.96)
Diabetes	1 (0.42)
Coronary artery disease	92 (38.66)

Distribution of apolipoprotein E genotype by sex

The E3 phenotype was predominant in both sexes (male: 77.60%, female: 76.80%). Females exhibited a slightly higher proportion of the E2 phenotype (13.40% vs. 10.90%) and a moderately lower proportion of the E4 phenotype (9.80% vs. 11.50%) compared to males. However, no statistically significant differences were observed between sexes (P > 0.05), as detailed in Table 4.

Distribution of solute carrier organic anion transporter family member 1B1 genotype by sex

Only two *SLCO1B1* genotypes (TT and TC) were identified in this cohort, with the CC genotype not being detected. The TT genotype was predominant, with comparable frequencies in both males (85.90%) and females (82.90%). The χ^2 test confirmed no statistically significant difference in genotype distribution between genders (P > 0.05). Detailed data are presented in Table 5.

Comparative analysis of lipid levels by apolipoprotein E genotype

The patient's blood lipid levels were monitored after taking atorvastatin calcium 20 mg daily or rosuvastatin calcium 10 mg daily for 4 weeks. Significant intergroup differences in LDL-C levels were observed among *ApoE* genotypes in the atorvastatin cohort (F = 3.743, P = 0.026), with the E3 genotype exhibiting the highest levels (2.85 ± 1.00 mmol/l) and E2 the lowest (2.28 ± 0.96 mmol/l). TC showed borderline significance (P = 0.073), with numerically higher values in E3 versus E2/E4 genotypes. In contrast, no statistically significant differences in lipid parameters were observed across *ApoE* genotypes in the rosuvastatin group (P > 0.05). Complete data are presented in Table 6.

The impact of solute carrier organic anion transporter family member 1B1 gene polymorphism on the safety of statins

Across the *SLCO1B1* TT and TC genotypes (CC genotype undetected), no statistically significant differences were observed in any safety parameters (ALT and creatine kinase) between atorvastatin- and rosuvastatin-treated

Table 2 Genotypes of apolipoprotein E and solute carrier organic anion transporter family member 1B1 and Hardy–Weinberg equilibrium test

Gene	Gene locus	Genotype	n, %	Allele	n, %	χ^2	P value
ApoE	388 T > C	TT	211 (88.66)	T	447 (93.91)	1.61	0.447
		TC	25 (10.50)	C	29 (6.09)		
	526 C > T	CC	213 (89.50)	C	450 (94.54)	0.13	0.936
		CT	24 (10.08)	T	26 (5.46)		
		TT	1 (0.42)				
SLCO1B1	521 T > C	TT	202 (84.87)	T	440 (92.44)	1.59	0.451
		TC	36 (15.13)	C	36 (7.56)		
		CC	0 (0.00)				

ApoE, apolipoprotein E; *SLCO1B1*, solute carrier organic anion transporter family member 1B1.

patients ($P > 0.05$ for all comparisons). Complete safety data are presented in Table 7.

Discussion

Dyslipidemia represents a major modifiable risk factor for cardiovascular disease. Statins, inhibitors of 3-hydroxy-3-methylglutaryl CoA reductase, exert pharmacological effects by reducing plasma concentrations of TC and LDL-C, while elevating HDL-C levels. These lipid-modifying properties translate into significant reductions in cardiovascular mortality, nonfatal myocardial infarction, stroke, and coronary revascularization among high-risk patients [9].

Statins undergo systemic absorption via intestinal passive diffusion and active transport mediated by ATP-binding cassette and solute carrier organic anion transporter (SLC) gene families. Their metabolism is primarily catalyzed by cytochrome P450 and uridine diphosphate-glucuronosyltransferase enzymes, with ATP-binding cassette transporters facilitating major clearance pathways [10]. Pharmacogenomic studies confirm that *ApoE* and *SLCO1B1* polymorphisms significantly modulate drug efficacy and the risk of associated adverse outcomes (e.g. myopathy for *SLCO1B1*) or underlying disease progression [11]. The *ApoE* gene regulates lipoprotein metabolism and facilitates β-amyloid clearance. Its E4 allele is linked to higher baseline LDL-C levels and a potentially diminished lipid-lowering response to statins like atorvastatin [12]. This elevated baseline risk coupled with suboptimal therapeutic correction may accelerate the trajectory of ASCVD. Conversely, the E2 allele is associated with a more favorable lipid profile and enhanced response to atorvastatin in our study, which could translate into a slower disease progression with appropriate treatment. In contrast, *SLCO1B1* polymorphisms primarily modulate disease progression indirectly through treatment safety. The rs4149056 C allele, which reduces hepatic statin uptake and increases systemic exposure, elevates the risk of statin-associated myopathy [13]. Patients harboring this allele may experience interruptions in effective lipid-lowering therapy, leading to poor LDL-C control and potentially hastening ASCVD progression. The Dutch Pharmacogenetics Working Group has also confirmed that the *SLCO1B1* polymorphism, which shows a significant clinical effect in reducing the risk of myopathy for statins, is c.521 T > C [14].

Table 3 Apolipoprotein E *g*enotypes and frequencies in patients with dyslipidemia

Genotyping	Allele	*n*, %	Total (*n*, %)
E2	E2/E2 (TT/TT)	1 (0.42)	28 (11.76)
	E2/E3 (TT/CT)	27 (11.34)	
E3	E2/E4 (TC/TC)	1 (0.42)	184 (77.31)
	E3/E3 (TT/CC)	183 (76.89)	
E4	E3/E4 (CT/CC)	24 (10.08)	26 (10.92)
	E4/E4 (CC/CC)	2 (0.84)	
Total (n,%)		238 (100.00)	

The study cohort comprised Han Chinese individuals. No significant sex-based differences were observed in *ApoE* or *SLCO1B1* genotype distributions ($P > 0.05$), indicating consistent genetic influences on dyslipidemia across sexes [15]. In our study, the T alleles of *ApoE* (388 T > C) and C alleles (526 C > T), as well as the T allele of *SLCO1B1* (521 T > C), were identified as the main alleles. This result was similar to those of most domestic studies [16,17]. It indicates that the genotype distribution in this study conforms to HWE ($P > 0.05$), supporting the quality and internal consistency of the genotyping data.

Consistent with prior studies [12], the *ApoE* E3 genotype predominated in our cohort (77.31%; n = 184/238), with the E3/E3 (rs429358-TT/rs7412-CC) diplotype being most prevalent (76.89%; n = 183). The established association between E4 carriage and elevated cardiovascular risk [16] was reaffirmed. Under fixed-dose atorvastatin 20 mg daily, E3 carriers exhibited significantly higher LDL-C levels versus E2 carriers (Δ = 0.57 mmol/l; $P < 0.05$). This aligns with evidence that E2 confers superior statin response while E4 reduces efficacy [18]. The rosuvastatin group did not observe differences in genotypes ($P > 0.05$), which may be attributed to the hydrophilic nature of rosuvastatin, less reliance on *ApoE*-mediated hepatocyte uptake, and reduced dependence on the lipid metabolism pathway through dual-channel excretion (liver and kidney pathways), while the E4 variant may result in reduced transport capacity because of abnormal expression or functional decline of transport proteins, thereby affecting the efficacy of statins [19]. However, because of the small sample size of rosuvastatin group (n = 56), the results may be biased.

In this study, no statistically significant differences in liver function biomarkers (TBil, ALT, and alkaline phosphatase) were observed across *SLCO1B1* rs4149056 genotypes (TT vs. TC; $P > 0.05$) within the current sample size. The primary pharmacogenetic role of *SLCO1B1* rs4149056 is well established in modulating systemic statin exposure and the risk of myopathy. Its

Table 4 The distribution results and differences of apolipoprotein E genotypes among different genders (*n*, %)

Sex	E2	E3	E4	χ^2	*P* value
Male ($n = 156$)	17 (10.90)	121 (77.60)	18 (11.50)	0.45	0.799
Female ($n = 82$)	11 (13.40)	63 (76.80)	8 (9.80)		
Total ($n = 238$)	28 (11.80)	184 (77.30)	26 (10.90)		

Table 5 The distribution results and differences of solute carrier organic anion transporter family member 1B1 genotypes among different genders (*n*, %)

Sex	TT	TC	CC	χ^2	*P* value
Male ($n = 156$)	134 (85.90)	22 (14.10)	0 (0.00)	0.37	0.543
Female ($n = 82$)	68 (82.90)	14 (17.10)	0 (0.00)		
Total ($n = 238$)	202 (84.90)	36 (15.10)	0 (0.00)		

relationship with hepatotoxicity is less clear mechanistically, as reduced hepatic uptake could theoretically alter the intrahepatic balance of parent drug and metabolites [14]. Contrary to the established literature, we did not replicate the association between the *SLCO1B1* c.521 T > C variant (TC genotype) and elevated creatine kinase. The canonical mechanism proposes that reduced OATP1B1 transporter function (mediated by rs4149056-C) increases systemic statin exposure [20]. Elevated plasma concentrations may impair muscle mitochondrial function, leading to myocyte damage and subsequent creatine kinase release [21]. This discrepancy may be attributed to our use of moderate statin dosing (atorvastatin 20 mg/rosuvastatin 10 mg), where dose-dependent protective effects likely prevented plasma concentrations from reaching myotoxicity thresholds.

Our study has some limitations. First, its retrospective design precluded the systematic collection of pretreatment lipid profiles. Consequently, the efficacy was assessed using absolute on-treatment levels at 4 weeks rather than the change from baseline (Δ), which may affect the precision of estimating genotype-dependent effects. Furthermore, the absence of *SLCO1B1* CC genotype and the small number of *ApoE* E4 carriers (n = 26) restricted the analysis of high-risk genotypes. Second, the single-center design and moderate sample size (n = 238), particularly the underpowered TC subgroup (n = 36), may have limited the statistical power to detect associations with low-incidence adverse events such as statin-induced myopathy or significant hepatotoxicity, despite being sufficient for the primary efficacy analysis. Third, potential confounders, including smoking, alcohol use, and unmeasured comorbidities, were not fully controlled and may have influenced the outcomes. Furthermore, the exclusion of patients with significant hepatic impairment at baseline, while aligning with clinical guidelines, limits the generalizability of our safety findings to that population. Future studies should focus on the following directions: prospectively incorporating standardized baseline assessments; conducting larger, multicenter trials with diverse cohorts to validate the gene-therapy associations; incorporating pharmacokinetic assessments (e.g. plasma drug concentrations) to elucidate genotype–metabolism relationships; and evaluating pharmacogenetic interactions specifically in patients with coexisting conditions such as hepatic impairment.

Conclusion

This study demonstrates that in this cohort of Han Chinese patients with dyslipidemia, the efficacy of atorvastatin is associated with *ApoE* genotypes, with E2 carriers achieving superior LDL-C reduction compared to E3 carriers. In contrast, no such association was observed for rosuvastatin. Regarding safety, the *SLCO1B1* TC genotype did not confer a significantly increased risk of myopathy or hepatotoxicity over the TT genotype during low-to-moderate dose statin therapy. These findings provide evidence for the *ApoE*-guided selection of atorvastatin and support the relative

Table 6 Comparison of blood lipid levels among apolipoprotein E genotypes ($\bar{x}$± SD)

Medication	Genotype	Age	TC (mmol/l)	TG (mmol/l)	HDL-C (mmol/l)	LDL-C (mmol/l)
Atorvastatin calcium tablets (20 mg, daily)	E2 (n = 22)	59.14 ± 12.02	4.16 ± 1.27	2.25 ± 1.49	1.23 ± 0.27	2.28 ± 0.96
	E3 (n = 143)	61.41 ± 14.01	4.76 ± 1.29	1.91 ± 1.79	1.27 ± 0.32	2.85 ± 1.00
	E4 (n = 17)	56.35 ± 13.13	4.32 ± 1.18	2.58 ± 1.86	1.08 ± 0.27	2.50 ± 1.00
	F	1.190	2.656	1.309	2.695	3.743
	P	0.307	0.073	0.273	0.070	0.026
Rosuvastatin calcium tablets (10 mg, daily)	E2 (n = 6)	62.83 ± 19.83	4.55 ± 0.83	1.70 ± 1.01	1.23 ± 0.34	2.71 ± 0.86
	E3 (n = 41)	61.27 ± 15.12	4.71 ± 1.52	1.47 ± 1.05	1.35 ± 0.38	2.81 ± 1.27
	E4 (n = 9)	55.11 ± 14.13	4.72 ± 2.19	2.13 ± 1.26	1.21 ± 0.36	2.95 ± 1.66
	F	0.663	0.030	1.384	0.681	0.070
	P	0.519	0.971	0.260	0.510	0.932

HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TC, total cholesterol; TG, triglycerides.

Table 7 Impact of solute carrier organic anion transporter family member 1B1 gene polymorphism on the safety of statin drugs in patients ($\bar{x}$± SD)

Medication	Genotype	Age (years)	TBil (μmol/l)	ALT (U/l)	ALP (U/l)	CK (U/l)
Atorvastatin calcium tablets (20 mg, daily)	TT (n = 155)	60.72 ± 14.06	13.58 ± 5.67	33.05 ± 56.04	80.35 ± 26.14	105.07 ± 70.68
	TC (n = 27)	60.37 ± 11.84	12.62 ± 5.36	25.78 ± 18.47	77.85 ± 20.19	110.92 ± 73.54
	CC	–	–	–	–	–
	F	0.015	0.666	0.443	0.224	0.155
	P	0.904	0.416	0.506	0.637	0.694
Rosuvastatin calcium tablets (10 mg, daily)	TT (n = 47)	59.96 ± 14.15	14.43 ± 7.65	35.20 ± 46.81	78.43 ± 20.77	139.43 ± 226.03
	TC (n = 9)	63.00 ± 21.65	17.50 ± 4.49	52.94 ± 66.51	74.46 ± 12.74	107.07 ± 32.13
	CC	–	–	–	–	–
	F	0.291	1.343	0.943	0.305	0.181
	P	0.592	0.252	0.336	0.583	0.672

ALT, alanine aminotransferase; ALP, alkaline phosphatase; CK, creatine kinase; TBil, total bilirubin.

safety of the *SLCO1B1* TC genotype in this specific therapeutic context.

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This study was performed in accordance with the principles of the Declaration of Helsinki and was approved by the Medical Ethics Committee of Xiamen Haicang Hospital (approval no.: IIT-2025009).

The data that support the findings of this study are included within the article.

All participants provided oral informed consent.

The Ethics Committee approved the waiver of informed consent for this study because it involved a retrospective analysis of anonymized patient records.

During manuscript preparation, artificial intelligence-assisted translation tools were utilized to enhance readability and linguistic expression. The authors have meticulously reviewed and edited the translated content and take full responsibility for the accuracy and integrity of the final manuscript.

Conflicts of interest

There are no conflicts of interest.

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