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ORIGINAL ARTICLE

Transporter Genes and statin-induced Hepatotoxicity

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Abstract

Purpose Hepatotoxicity has emerged as a major cause of statin treatment interruption. Although organic anion-transporting polypeptide 1B1 (*SLCO1B1*), multidrug resistance protein 1 (*ABCB1*), and breast cancer resistance protein (*ABCG2*) have been identified as transporters of statins, knowledge of their role in statin-associated hepatotoxicity remains limited. Therefore, we aimed to conduct a comprehensive analysis to elucidate the association between hepatotoxicity and *SLCO1B1*, *ABCB1*, and *ABCG2* polymorphisms.

Methods This study retrospectively analyzed prospectively collected samples. We selected 10 single nucleotide polymorphisms (SNPs) of *SLCO1B1*, 9 SNPs of *ABCB1*, and 12 SNPs of *ABCG2*. We developed two models for multivariable analyses (Model I: clinical factors only; Model II: both clinical and genetic factors), and the attributable risk (%) of variables in Model II was determined.

Results Among 851 patients, 66 (7.8%) developed hepatotoxicity. In Model I, lipophilic statins, atrial fibrillation (Afib), and diabetes mellitus showed a significant association with hepatotoxicity. In Model II, lipophilic statins and Afib, *SLCO1B1* rs11045818 A allele, *SLCO1B1* rs4149035 T allele, and *ABCG2* rs2622629 TT genotype were associated with higher hepatotoxicity risk. Among them, the *SLCO1B1* rs11045818 A allele exhibited the highest attributable risk (93.2%). The area under the receiver operating characteristic curve in Model I was 0.62 (95% CI: 0.55–0.69), and it was increased to 0.71 in Model II (95% CI: 0.64–0.77).

Conclusion This study investigated the correlation between hepatotoxicity and polymorphisms of transporter genes in patients taking statins. The findings could help improve personalized treatments for patients receiving statin therapy.

Keywords Statins · Hepatotoxicity · SLCO1B1 · ABCB1 · ABCG2 · Pharmacogenomics

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Introduction

Hydroxymethyl glutaryl coenzyme A reductase (HMG-CoA) inhibitors, commonly referred to as statins, are widely used in the treatment of dyslipidemia for the management of atherosclerotic cardiovascular diseases (ASCVD) [1]. The pharmacological effects of statins include a reduction in plasma concentrations of total cholesterol (TC) and low-density lipoprotein cholesterol (LDL-C) and an increase in the level of high-density lipoprotein cholesterol [2]. Their lipid-lowering activity has been associated with a significant decrease in mortality, nonfatal acute myocardial infarction, stroke, and coronary revascularization for patients with high cardiovascular risk [3].

Statins are well-tolerated by most people; however, adverse drug events (ADEs) such as muscle symptoms, new-onset diabetes mellitus (DM), and hepatotoxicity have been observed [4]. In particular, liver toxicity has emerged as one of the major causes contributing to the interruption of statin treatment [5]. The symptoms of hepatic ADEs are diverse; although the most common symptoms are asymptomatic and usually involve the temporary elevation of transaminases [6], severe hepatotoxicity leading to liver failure or death has been reported in post-marketing surveillance [7].

Statins are substrates for transporter proteins from the solute carrier (SLC) and ATP-binding cassette (ABC) superfamilies [8]. Organic anion-transporting polypeptide 1B1 (OATP1B1), encoded by the *SLCO1B1* gene, is an influx transporter that facilitates the hepatic uptake of all statins, thereby regulating systemic exposure to statins. In particular, polymorphisms of *SLCO1B1* have been identified as a genetic factor for statin-induced myopathy in a genome-wide association study (GWAS) and systematic reviews [9, 10]. Multidrug resistance protein 1 (encoded by *ABCB1*) and breast cancer resistance protein (encoded by *ABCG2*) are efflux transporters associated with the hepatobiliary excretion of statins [8].

Inter-individual differences in the response to statins suggest a genetic factor as a potential contributor to the variable response to statin therapy [11]. However, there is limited information on the correlation between gene polymorphisms linked to transporters and hepatotoxicity. Various studies have focused on hepatotoxicity for one specific type of statin [12, 13]. Additionally, some studies have defined the primary outcome as ADEs, with hepatotoxicity included as part of composite outcomes [14, 15]. Therefore, we aimed to conduct a comprehensive pharmacogenomic investigation by examining the association between hepatotoxicity and polymorphisms of transporter genes, including *SLCO1B1*, *ABCB1*, and *ABCG2*.

Methods

Study Participants and data Collection

This study was conducted at Ewha Womans University Seoul Hospital and Ewha Womans University Mokdong Hospital. We identified patients aged ≥ 18 years who started taking statins (atorvastatin, fluvastatin, lovastatin, pitavastatin, pravastatin, rosuvastatin, or simvastatin) between January 2000 and May 2021 for the primary or secondary prevention of ASCVD. Genomic DNA samples were prospectively collected during regularly scheduled clinic visits from February to May 2021. Patients were excluded if they (1) received statins less than 3 months (2) lacked liver function test results, (3) presented with elevated aspartate aminotransferase (AST), alanine aminotransferase (ALT), or alkaline phosphatase (ALP) at statin initiation, (4) had underlying chronic liver diseases, (5) had inappropriate follow-up data, or (6) had insufficient DNA samples for analysis.

The primary endpoint was hepatotoxicity, defined as grade II or higher according to the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 [16]. The CTCAE defines grade II toxicity levels of AST, ALT, and ALP as 3.0–5.0, 3.0–5.0, and 2.5–5.0 times the upper limit of normal (ULN), respectively. As transaminase levels exceeding three times the ULN require additional tests or the discontinuation of statins in clinical settings, we set the cutoff for hepatotoxicity at grade II in this analysis [17, 18]. We retrospectively collected demographic and clinical information from electronic medical records, including data on age, height, weight, estimated glomerular filtration rate (eGFR), liver function tests (AST, ALT, ALP), serum lipid levels, statin prescription data (type, dosage, duration), alcohol and smoking status, comorbidities and comedications.

This study was approved by the Institutional Review Boards (IRBs) of Ewha Womans University Seoul Hospital and Ewha Womans University Mokdong Hospital (IRB numbers: 2020-11-014 and 2021-02-026, respectively). We followed the ethical guidelines outlined in the 1964 Declaration of Helsinki and its subsequent amendments. Prior to participation, all patients provided written informed consent.

Single Nucleotide Polymorphism (SNP) and Haplotype Selection

We selected 10 SNPs of *SLCO1B1* [19–21], 9 SNPs of *ABCB1* [22, 23], and 12 SNPs of *ABCG2* [24–27] based on previous findings. For *SLCO1B1*, further haplotype analysis was conducted using 4 haplotypes: *SLCO1B1**1A (c.388 A-c.521T), *1B (c.388G-c.521T), *5 (c.388 A-c.521 C), and *15 (c.388G-c.521 C). HaploReg v4.2 was used to assess the linkage disequilibrium

(LD) and minor allele frequency in Asian populations [28]. We obtained genetic information for these SNPs from the National Center for Biotechnology Information [29].

Genotyping Methods

Genomic DNA was extracted from the patients' blood samples using QIAamp DNA Blood Mini Kit (QIAGEN GmbH, Hilden, Germany) or saliva samples using Ora-Gene-600 (DNA Genotek, Ottawa, ON, Canada). The genotypes of 31 SNPs were analyzed by TaqMan SNP genotyping assay (Applied Biosystems, Foster City, CA, USA) or SNaPshot Multiplex Kit (Applied Biosystems, Foster City, CA, USA).

Statistical Analysis

Chi-squared test or Fisher's exact test was used to analyze categorical variables and unpaired *t*-test was used to compare continuous variables. Crude odds ratios (ORs) and adjusted ORs (AORs) with 95% confidence intervals (CIs) were calculated by univariate and multivariable regression analyses, respectively. A multivariable logistic regression model was used to identify independent risk factors for hepatotoxicity. The model incorporated variables with $p < 0.05$ in univariate analysis along with strong confounders such as age and sex. Attributable risk (%) was calculated by the equation $(1 - 1/\mathrm{AOR}) \times 100$.

The model fit of the prediction model was assessed by the Hosmer-Lemeshow goodness-of-fit test. The discrimination of the model was further evaluated by calculating the area under the receiver operating characteristic curve (AUROC). All statistical analyses were performed using SPSS v20.0 (IBM Corp., Armonk, NY, USA) and $p < 0.05$ was considered statistically significant.

Results

Among the 1,005 enrolled patients, 154 patients were excluded for the following reasons: received statins for less than 3 months (5 patients), did not have liver function test results (55 patients), had elevated liver enzyme levels before administration of statins (58 patients), had underlying liver diseases (29 patients), died during statin therapy (1 patient), had inappropriate follow-up data (2 patients), and had insufficient samples for DNA analysis (4 patients) (Fig. 1). Consequently, 851 patients were included, among whom 66 patients (7.8%) had CTCAE grade II or higher hepatotoxicity.

Table 1 shows the baseline characteristics of the study population. Among the patients, 67.3% of them were male, and the median age was 63 years (interquartile range (IQR): 27–91 years). The median follow-up period was 2.0 years (IQR 1.2–3.2 years). In comparison with patients without comorbidities, patients with DM and atrial fibrillation (Afib) were more susceptible to hepatotoxicity ($p = 0.013$ and $p = 0.037$, respectively). Among the patients, 60.2% of them used lipophilic statins (including atorvastatin, fluvastatin, lovastatin, pitavastatin, and simvastatin), and 39.8% of them used hydrophilic statins (such as pravastatin and rosuvastatin). There was more

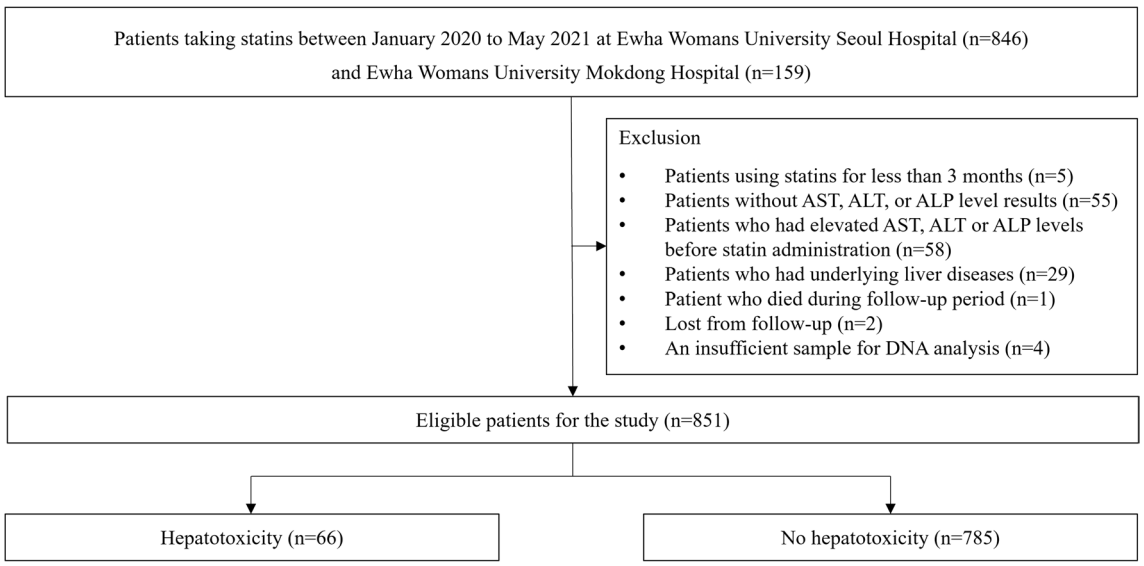

Fig. 1 Flowchart of patient selection

Table 1 Baseline characteristics of the study patients

Characteristics	Hepatotoxicity		*p*
	Presence ($n=66$)	Absence ($n=785$)	
Sex			0.694
Male	43 (65.2)	530 (67.5)	
Female	23 (34.8)	255 (32.5)	
Age (years)			0.172
<65	31 (47.0)	437 (55.7)	
≥65	35 (53.0)	348 (44.3)	
Mean ± SD	64.8 ± 9.3	62.8 ± 11.1	0.154
BMI (kg/m^2)			0.525
<30	61 (93.8)	749 (95.7)	
≥30	4 (6.2)	34 (4.3)	
eGFR (mL/min/1.73m^2) [a]			0.312
<60	7 (12.3)	59 (8.0)	
≥60	50 (87.7)	683 (92.0)	
LDL-C (mg/dL)	98.7 ± 34.4	107.6 ± 37.2	0.081
HDL-C (mg/dL)	47.9 ± 11.7	46.4 ± 11.0	0.357
TG (mg/dL)	126.5 ± 65.7	128.4 ± 80.7	0.857
TC (mg/dL)	167.5 ± 36.3	175.9 ± 47.9	0.097
Type of statins [b]			0.030
Lipophilic	48 (72.7)	464 (59.1)	
Hydrophilic	18 (27.3)	321 (40.9)	
Intensity of statins			0.554
High	20 (30.3)	266 (33.9)	
Moderate to low	46 (69.7)	519 (66.1)	
Alcohol history	32 (48.5)	304 (39.0)	0.129
Smoking history	26 (39.4)	275 (35.3)	0.500
Comorbidities			
Atrial fibrillation	14 (21.2)	96 (12.2)	0.037
Cancer	6 (9.1)	45 (5.7)	0.275
Chronic kidney disease	5 (7.6)	25 (3.2)	0.075
Congestive heart failure	2 (3.0)	13 (1.7)	0.327
Diabetes mellitus	30 (45.5)	241 (30.7)	0.013
Dyslipidemia	39 (59.1)	402 (51.2)	0.218
Hypertension	48 (72.7)	560 (71.3)	0.810
Stroke	57 (86.4)	635 (80.9)	0.273
Comedications			
ACEIs/ARBs	30 (45.5)	413 (52.6)	0.264
Acetaminophen	1 (1.5)	31 (3.9)	0.504
Anticoagulants	14 (21.2)	110 (14.0)	0.111
Antiplatelets	55 (83.3)	641 (81.7)	0.735
Beta-blockers	14 (21.2)	109 (13.9)	0.104
Calcium channel blockers	24 (36.4)	302 (38.5)	0.735
Diuretics	7 (10.6)	91 (11.6)	0.809
Ezetimibe	11 (16.7)	131 (16.7)	0.996
Fibric acid	0 (0.0)	9 (1.1)	1.000
H_2 blockers/PPIs	10 (15.2)	202 (25.7)	0.056

BMI: body mass index; eGFR: estimated glomerular filtration rate; LDL-C: low-density lipoprotein cholesterol; HDL-C: high-density lipoprotein cholesterol; TG: triglyceride; TC: total cholesterol; ACEIs: angiotensin converting enzyme inhibitors; ARBs: angiotensin II receptor blockers; PPIs: proton-pump inhibitors. [a] eGFR was calculated using the MDRD equation. [b] Lipophilic statins include atorvastatin, fluvastatin, lovastatin, pitavastatin, and simvastatin, while hydrophilic statins include pravastatin and rosuvastatin

hepatotoxicity among patients taking lipophilic statins than among those taking hydrophilic statins (9.4% vs. 5.3%, $p=0.030$). The most commonly used comedication was antiplatelets (81.8%), followed by angiotensin-converting enzyme inhibitors (ACEIs)/angiotensin II receptor blockers (ARBs) (52.1%) and calcium channel blockers (38.3%). None of the patients used nicotinic acid.

The results of genotype analysis for *SLCO1B1* are presented in Table 2. For *SLCO1B1* rs11045818, A allele carriers had an increased risk of hepatotoxicity compared with that of GG genotype carriers (41.7% vs. 7.1%, $p=0.001$). There was a higher incidence of hepatotoxicity among patients with the T allele of rs4149035 than among those with the CC genotype (11.3% vs. 6.4%, $p=0.019$). None of the *SLCO1B1* haplotypes demonstrated statistical significance for hepatotoxicity (Table 2). Within the *ABCG2* gene, there was increased hepatotoxicity among individuals with the rs2622629 TT genotype compared with those with the C allele (12.6% vs. 7.0%, $p=0.041$) (Table 3). In the case of rs4367138, hepatotoxicity was more common among patients with wild-type homozygotes (GG) than among those carrying the variant (A) allele (14.9% vs. 7.0%, $p=0.020$). However, no significant differences were found between the two groups in *ABCB1*.

Two models were constructed for multivariable logistic regression analyses; Model I included clinical factors only, and Model II included both clinical and genetic factors (Table 4). In Model I, lipophilic statins, Afib, and DM showed a significant association with hepatotoxicity. In Model II, lipophilic statins increased the risk of hepatotoxicity by 2.1 times (95% CI: 1.2–3.9), and Afib increased the risk by 2.2 times (95% CI: 1.1–4.4). Regarding genetic factors, A allele of *SLCO1B1* rs11045818 had the most significant impact on hepatotoxicity risk (AOR: 14.7, 95% CI: 4.1–53.1) compared to the GG genotype. Individuals carrying the *SLCO1B1* T allele showed a 1.9-fold higher risk of liver toxicity (95% CI: 1.1–3.3) than those with the CC genotype. Furthermore, compared with individuals carrying the variant allele, *ABCG2* rs2622629 TT genotype carriers exhibited a 2.4-fold (95% CI: 1.2–4.6) increased risk of hepatotoxicity.

The *SLCO1B1* rs11045819 A allele was associated with a high attributable risk for hepatotoxicity at 93.2%, followed by *ABCG2* rs2622629 TT genotype (58.1%) and *SLCO1B1* rs4149035 T allele (46.3%) (Table 4). The Hosmer-Lemeshow test revealed a satisfactory fit for Model I and Model II ($\chi^2=2.11$, $p=0.72$ and $\chi^2=2.60$, $p=0.86$, respectively). The AUROC in Model I (0.62, 95% CI: 0.55–0.69), the AUROC was increased in Model II (0.71, 95% CI: 0.64–0.77) by adding genetic factors (Fig. 2).

Table 2 Effects of *SLCO1B1* polymorphisms on hepatotoxicity

dbSNP rsID	Genotypes	Hepatotoxicity		*p*
		Presence (*n* = 66)	Absence (*n* = 785)	
rs11045879 (T > C)	TT	24 (36.4)	259 (33.1)	0.592
	TC, CC	42 (63.6)	523 (66.9)	
rs4149056 (T > C)	TT	45 (68.2)	592 (75.4)	0.193
	TC, CC	21 (31.8)	193 (24.6)	
rs4149015 (G > A)	GG	43 (67.2)	584 (74.6)	0.194
	GA, AA	21 (32.8)	199 (25.4)	
rs4149057 (T > C)	TT	34 (52.3)	420 (53.7)	0.828
	TC, CC	31 (47.7)	362 (46.3)	
rs34671512 (A > C)	AA	57 (95.0)	716 (98.5)	0.084
	AC, CC	3 (5.0)	11 (1.5)	
rs4363657 (T > C)	TT	24 (36.4)	259 (33.2)	0.602
	TC, CC	42 (63.6)	521 (66.8)	
rs2306283 (A > G)	AA	5 (7.7)	62 (7.9)	0.951
	AG, GG	60 (92.3)	722 (92.1)	
rs11045818(G > A)	GG	58 (92.1)	759 (99.1)	0.001
	GA, AA	5 (7.9)	7 (0.9)	
rs4149035 (T > C)	TT, TC	25 (38.5)	196 (25.1)	0.019
	CC	40 (61.5)	584 (74.9)	
rs4149032 (C > T)	CC, CT	50 (75.8)	529 (67.5)	0.166
	TT	16 (24.2)	255 (32.5)	
*1A carrier	Yes	31 (47.7)	377 (48.1)	0.951
	No	34 (52.3)	407 (51.9)	
*1B carrier	Yes	60 (92.3)	704 (89.8)	0.517
	No	5 (7.7)	80 (10.2)	
*5 carrier	Yes	6 (9.2)	64 (8.2)	0.764
	No	59 (90.8)	720 (91.8)	
*15 carrier	Yes	21 (32.3)	192 (24.5)	0.162
	No	44 (67.7)	592 (75.5)	

SNP: single nucleotide polymorphism

Discussion

Identifying the clinical and genetic risk factors associated with hepatotoxicity is essential for preventing ADEs in patients receiving statin therapy [30]. This study indicated that *SLCO1B1* rs11045818, *SLCO1B1* rs4149035, *ABCG2* rs2622629, lipophilic statins, and Afib were significantly associated with hepatotoxicity. The AUROC for predicting statin-associated hepatotoxicity, which included clinical and genetic factors, was satisfactory.

The *SLCO1B1* gene, located on chromosome 12, is predominantly expressed in the liver and is responsible for the uptake of endogenous substances or drugs such as statins and anti-bacterial agents into hepatocytes [31]. As the active transportation of statins into hepatocytes is mediated mainly by OATP1B1, polymorphisms of the *SLCO1B1* gene could affect statin disposition, potentially contributing to the development of hepatotoxicity [8, 32]. Further supporting this, Jin et al. demonstrated that SNPs and haplotypes of *SLCO1B1* were critical predisposing factors for methimazole-induced hepatotoxicity [32].

SLCO1B1 rs11045818, a synonymous variant, exhibited the highest attributable risk in our study [33]. This finding is in agreement with Alhawari et al., which revealed that the rs11045818 A allele was associated with a 27% increase in ALT levels in type 2 DM patients taking atorvastatin ($p < 0.05$) [34]. Furthermore, rs11045818 is in complete LD ($r^2 = 1$) with *SLCO1B1* rs11045819 (c.463 C > A), a missense variant [28, 35]. Rs11045819 is part of the *SLCO1B1**14 haplotype, which enhances the function of OATP1B1 [35]. Due to the increased influx of statins, patients with a variant allele of rs11045819 were found to have a decreased area under the plasma concentration-time curve for simvastatin acid. In addition, the efficacy of statins in lowering LDL-C and TC levels was observed to be better for these patients than for those with wild-type homozygotes [36]. Therefore, *SLCO1B1* rs11045818 could potentially affect OATP1B1 function, resulting in the enhanced

Table 3 Effects of *ABCB1* and *ABCG2* polymorphisms on hepatotoxicity

dbSNP rsID	Genotypes	Hepatotoxicity		*p*
		Presence ($n=66$)	Absence ($n=785$)	
ABCB1				
rs3747802 (A > G)	AA	52 (80.0)	681 (86.8)	0.129
	AG, GG	13 (20.0)	104 (13.2)	
rs3842 (T > C)	TT	29 (43.9)	379 (48.3)	0.492
	TC, CC	37 (56.1)	405 (51.7)	
rs2032583 (A > G)	AA	60 (92.3)	716 (91.4)	0.810
	AG, GG	5 (7.7)	67 (8.6)	
rs3789243 (A > G)	AA	9 (13.6)	123 (15.7)	0.655
	AG, GG	57 (86.4)	660 (84.3)	
rs3213619 (A > G)	AA	52 (80.0)	682 (87.3)	0.094
	AG, GG	13 (20.0)	99 (12.7)	
rs2032582 (A > C)	AA	16 (24.2)	235 (29.9)	0.330
	AC, CC	50 (75.8)	550 (70.1)	
rs1128503 (A > G)	AA, AG	56 (84.8)	634 (81.1)	0.450
	GG	10 (15.2)	148 (18.9)	
rs1045642 (A > G)	AA, AG	36 (54.5)	442 (56.4)	0.765
	GG	30 (45.5)	341 (43.6)	
rs2235047 (A > C)	AA, AC	47 (71.2)	617 (78.7)	0.158
	CC	19 (28.8)	167 (21.3)	
ABCG2				
rs72552713 (G > A)	GG	62 (93.9)	760 (96.8)	0.273
	GA, AA	4 (6.1)	25 (3.2)	
rs2231142 (G > T)	GG	36 (54.5)	419 (53.6)	0.880
	GT, TT	30 (45.5)	363 (46.4)	
rs2622604 (T > C)	TT, TC	24 (36.4)	224 (28.6)	0.181
	CC	42 (63.6)	560 (71.4)	
rs2622629 (T > C)	TT	14 (21.2)	97 (12.4)	0.041
	TC, CC	52 (78.8)	686 (87.6)	
rs3114018 (A > C)	AA, AC	39 (59.1)	408 (52.0)	0.271
	CC	27 (40.9)	376 (48.0)	
rs4367138 (G > A)	GG	10 (15.4)	57 (7.3)	0.020
	GA, AA	55 (84.6)	728 (92.7)	
rs6532049 (C > T)	CC	43 (66.2)	583 (74.6)	0.138
	CT, TT	22 (33.8)	199 (25.4)	
rs2231164 (C > T)	CC, CT	41 (62.1)	539 (68.9)	0.254
	TT	25 (37.9)	243 (31.1)	
rs2231137 (C > T)	CC, CT	57 (87.7)	737 (94.1)	0.058
	TT	8 (12.3)	46 (5.9)	
rs4148157 (G > A)	GG	38 (57.6)	459 (58.5)	0.878
	GA, AA	28 (42.4)	325 (41.5)	
rs2622624 (T > C)	TT, TC	38 (58.5)	387 (49.5)	0.164
	CC	27 (41.5)	395 (50.5)	
rs2622628 (A > C)	AA, AC	18 (27.3)	289 (37.0)	0.116
	CC	48 (72.7)	493 (63.0)	

SNP: single nucleotide polymorphism

Table 4 Univariate and multivariable regression analyses to identify predictors for hepatotoxicity in patients receiving statins

Predictors	Crude OR (95% CI)	Adjusted OR (95% CI)		Attributable risk[b] (%)
		Model I	Model II	
Female	1.11 (0.66–1.89)			
Age (≥65 years)	1.42 (0.86–2.35)			
Lipophilic statins[a]	1.85 (1.05–3.23)*	1.89 (1.07–3.34)*	2.14 (1.16–3.94)*	53.3
Atrial fibrillation	1.93 (1.03–3.62)*	2.06 (1.09–3.90)*	2.22 (1.14–4.35)*	55.0
Diabetes mellitus	1.88 (1.13–3.13)*	1.77 (1.07–2.96)*	1.61 (0.94–2.77)	37.9
SLCO1B1 rs11045818 A allele	9.34 (2.88–30.37)**		14.73 (4.09–53.07)**	93.2
SLCO1B1 rs4149035 T allele	1.86 (1.10–3.15)*		1.86 (1.06–3.27)*	46.3
ABCG2 rs2622629 TT	1.90 (1.02–3.57)*		2.39 (1.23–4.64)*	58.1
ABCG2 rs4367138 GG	2.32 (1.12–4.80)*			

CI: confidence interval; OR: odds ratio. Model I included variables of sex, age, lipophilic statins, atrial fibrillation, and diabetes mellitus. Model II included variables of sex, age, lipophilic statins, atrial fibrillation, diabetes mellitus, *SLCO1B1* rs11045818, *SLCO1B1* rs4149035, *ABCG2* rs2622629, and *ABCG2* rs4367138. [a]Lipophilic statins include atorvastatin, fluvastatin, lovastatin, pitavastatin, and simvastatin. [b]Attributable risk of Model II was calculated using formula 1–(1/adjusted OR). * $p < 0.05$, ** $p < 0.01$

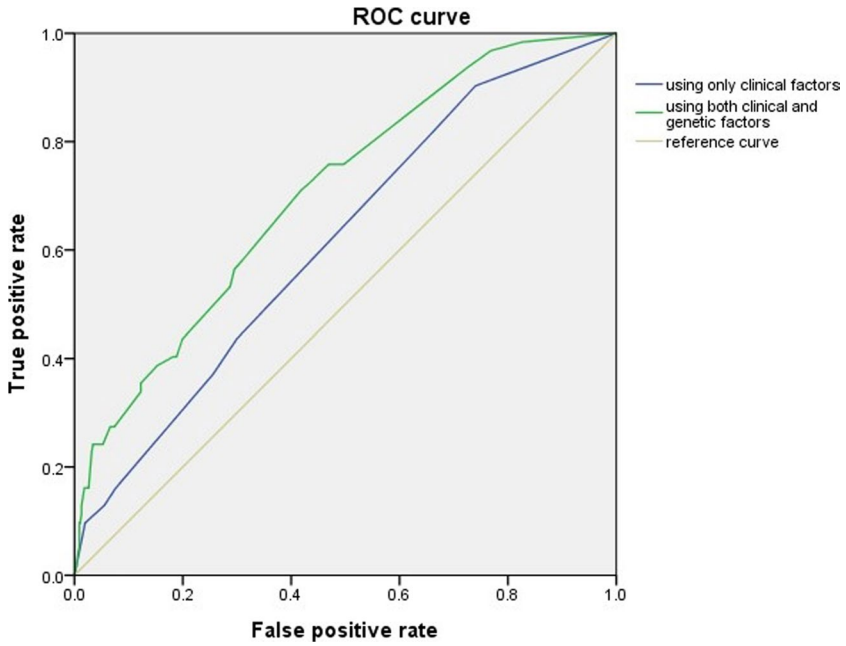

Fig. 2 The receiver operating characteristic (ROC) curve for hepatotoxicity using clinical and genetic factors. The blue line represents the predicted probability of Model I, while the green line represents that of Model II. The yellow line is the reference

hepatic uptake of statins, thereby increasing the risk of hepatotoxicity.

Analysis of *SLCO1B1* rs4149035, an intron variant, showed a correlation between the wild-type allele (T allele) and increased liver toxicity risk. A Spanish cohort study of 384 pediatric patients with acute lymphoblastic leukemia revealed that a variant-type homozygote (CC) of rs4149035 was associated with increased methotrexate plasma concentration and nephrotoxicity [37]. In addition, *SLCO1B1* rs4149035 was found to be highly correlated with *SLCO1B1* rs4149033 ($r^2 = 0.98$) [28]. A variant allele of rs4149033 increased the risk of rhabdomyolysis by 1.4 times (95% CI: 1.06 – 1.87) in cerivastatin-treated patients [38]. Another study identified a variant allele of rs4149033 as one of the risk factors associated with sudden cardiac death caused by coronary artery disease (OR: 1.30, 95% CI: 1.03 – 1.64) [39]. These studies collectively suggest that these SNPs could reduce the hepatic uptake of statins, leading to an increased risks of systemic complications [31, 40].

ABCG2, expressed in the liver, small intestines, and kidneys, resides on chromosome 4 [41]. It plays a vital role in regulating intestinal absorption and the biliary excretion of drugs. The reduced activity of ABCG2 has been shown to increase the absorption of statins in the gastrointestinal tract

and decrease drug efflux in the biliary ducts [8]. Therefore, we hypothesized that these dual effects may result in drug accumulation in hepatocytes, possibly leading to hepatotoxicity. *ABCG2* rs2622629, located in the intronic region of *ABCG2*, was associated with hepatotoxicity risk in this study. Although the specific function of this SNP in hepatotoxicity has not been characterized in detail, an eQTL analysis performed by GTEx demonstrated that C allele of rs2622629 was associated with higher ABCG2 expression in the thyroid and esophageal mucosa ($p = 7.9 \times 10^{-7}$) [42]. However, as no significant difference was detected in the liver ($p = 0.7$) [42], further studies are necessary to elucidate the role of this SNP.

In comparison with hydrophilic statins, lipophilic statins were associated with greater susceptibility to hepatotoxicity in our study. This result was consistent with previous findings showing that lipophilic statins were associated with the majority of statin-induced liver injuries, whereas hydrophilic statins accounted for a small proportion [7]. Moreover, a meta-analysis demonstrated a higher risk of ALT elevation among patients taking lipophilic statins compared with those taking hydrophilic statins (OR: 2.69, 95% CI: 1.84–3.95) [43]. These lipophilicity-dependent effects highlight key differences in the pharmacokinetic properties of statins. For example, lipophilic statins can easily penetrate the hepatic and intestinal membrane by passive diffusion, whereas hydrophilic statins depend on specific transporters [8, 44]. In addition, lipophilic statins undergo hepatic metabolism via cytochrome P450 (CYP), whereas hydrophilic statins are mainly excreted unchanged [45]. CYP-dependent metabolism generates reactive oxygen species (ROS) and is involved in cell apoptosis [30]. Therefore, the use of lipophilic statins can promote ROS production and lipid peroxidation, decreasing the mitochondrial membrane potential and subsequently inducing cytotoxicity [30, 46]. Taken together, the findings explain the association between lipophilic statins and hepatotoxicity.

Patients with Afib showed approximately a 2-fold increase in hepatotoxicity in this study. Makar et al. revealed that 27.6% of study participants with Afib experienced ALT elevation above the ULN (40 IU/L), and 2.8% of them had ALT levels exceeding three times the ULN [47]. These findings suggest that Afib patients have an increased risk of elevated liver enzymes. Additionally, a recent study has identified persistent Afib as a significant factor associated with elevated liver fibrosis markers [48]. However, research examining the mechanism underlying the effects of Afib on hepatotoxicity is lacking, underscoring the need for further investigation.

This study is the first to comprehensively investigate various types of statins to evaluate the genetic polymorphisms of transporters as potential risk factors for statin-associated hepatotoxicity. However, the present study has a risk of bias due to the retrospective study design. Moreover, this study included only Asian participants with a relatively small sample size, which would limit the generalizability of the findings. Further prospective large cohort studies are needed to validate our findings.

Conclusion

Our study elucidated the relationship between *SLCO1B1*, *ABCB1*, and *ABCG2* gene polymorphisms and hepatotoxicity. The findings could contribute to a better understanding of the causes of statin-induced hepatotoxicity and facilitate the development of personalized treatments for patients receiving statin therapy.

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Authors' Contributions All the authors have made substantial contributions to the conception of the study. SAC, JSK, TJS, and HSG contributed to designing the study. YC and TJS contributed to material preparation and YAP, DHL, MP and JY contributed to data collection. SAC and JSK performed data analysis and interpretation. SAC and JSK contributed to the drafting of the manuscript. TJS and HSG contributed to the critical revision of the manuscript. All authors approved the final manuscript.

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Data Availability The datasets analyzed during the current study are presented as a supplementary file.

Code Availability Not applicable.

Declarations

Ethics Approval The study was conducted in accordance with the Declaration of Helsinki, and the protocol was approved by the Ethics Committee of Ewha Womans University Seoul Hospital and Ewha Womans University Mokdong Hospital (IRB number: 2020-11-014 and 2021-02-026, respectively).

Consent for Publication All authors approved the final manuscript and the submission to this journal.

Consent to Participate Written informed consent was obtained from all patients.

Conflict of Interest The authors declare no competing interests.

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