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Pharmacogenomic insights into atorvastatin and rosuvastatin adverse effects: a prospective observational study in the UAE's multiethnic population

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Abstract

Background Statins are essential for managing cardiovascular disease (CVD), but adverse effects often lead to treatment discontinuation and non-adherence, underscoring the need for personalized approaches. This study aimed to evaluate the influence of pharmacogenomic (PGx) variants and demographic factors on statin-associated adverse effects in a multiethnic cohort from the United Arab Emirates (UAE).

Methods This sub-analysis of the EmHeart Study included 675 patients using rosuvastatin or atorvastatin. Patients were genotyped for *SLCO1B1* and *ABCG2* actionable variants using real-time PCR. Data on demographics, comorbidities, and statin use were extracted from electronic health records. Adverse events, including statin-associated muscle symptoms (SAMS) and liver enzyme elevation, were tracked over 12 months. Associations were analyzed using chi-square tests and logistic regression.

Results Rosuvastatin users carrying the *ABCG2 rs2231142* variant had a threefold increased risk of liver enzyme elevation, particularly among East Asian patients ($P < 0.005$). Atorvastatin users with the *SLCO1B1 rs4149056* variant exhibited a twofold increased risk of SAMS, with higher rates observed in females and Arabs ($P < 0.05$). The combination of rosuvastatin with ezetimibe further exacerbated risks of SAMS and liver enzyme elevation.

Conclusion This study highlights the importance of genetic testing and demographic factors, such as ethnicity and gender, in tailoring statin therapy to minimize adverse effects. Despite extensive research on PGx-guided statin prescribing, clinical implementation remains limited. Integrating PGx testing into routine practice and enhancing physician awareness of genetic and demographic risk factors can improve the safety, efficacy, and adherence of lipid-lowering therapies in diverse populations.

Keywords Cardiovascular disease, Statins, Pharmacogenomics, SLCO1B1, ABCG2, Atorvastatin, Rosuvastatin

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Introduction

Cardiovascular diseases (CVDs) are major and leading global and regional causes of morbidity and mortality. The estimated number of deaths caused by CVDs globally is approximately 17.9 million each year, representing ~ 32% of all global deaths [1]. In the United Arab Emirates (UAE), a country noted for its multiethnic and highly heterogeneous population, with Emiratis constituting only about 11% of the total [2]., CVDs are a significant health concern [3]. These diseases are responsible for approximately 40% of all deaths in the country, highlighting the significant healthcare challenges posed by demographic diversity [4]. The high prevalence of cardiovascular diseases has placed considerable economic and social strains on the country [3].

Statins (3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors) are the most prescribed medications for managing and preventing CVDs by lowering Low-density lipoprotein cholesterol (LDL-C), both in the UAE and globally [5]. The 2019 ESC/EAS guidelines strongly emphasized aggressively lowering LDL-C to reduce the risk of atherosclerotic cardiovascular disease (ASCVD) [6]. Lowering LDL is not merely a treatment goal but a fundamental aspect of the comprehensive management approach that targets multiple risk factors, including lipid levels, blood sugar, blood pressure, weight, and lifestyle habits [7]. Adherence to LDL-lowering therapies, such as statins, plays a crucial role in achieving the objectives of this integrated strategy, which aims to reduce cardiovascular events through coordinated interventions addressing these risk factors [8]. A study conducted in the UAE on the use of statins among 3,066 Emirati patients hospitalized with acute coronary syndrome (ACS) found that, despite cardiologists' recommendations for statin usage before or after experiencing ACS, only 58.1% of patients were on statins before or within 90 days following the incident [9]. These statistics underscore the need for broader use of statins among this demographic and highlight a significant gap between current prescribing behaviors and the established guidelines for Emirati patients [9].

Although statins are generally safe and well tolerated, they can sometimes be associated with side events of variable severity. The most reported side event is statin-associated muscle symptoms (SAMS), affecting about 27% of statin users [10]. SAMS can lead to noncompliance and premature discontinuation of the medication [11]. Hence, it is crucial to identify patients with true SAMS to ensure optimal statin use and to study the confounding factors affecting its incidence [12].

In this study, we utilized the well-established evidence linking pharmacogenomic variants in *SLCO1B1*, which encodes a solute carrier transport molecule essential for liver uptake of statins. Variants that have significant evidence of associations with statin pharmacokinetics (rs4149056 (521T > C), rs2306283 (388 A > G)) were selected [13, 14]. Additionally, we considered variant rs2231142 (421 C > A) in the ATP-binding cassette subfamily G member 2 (*ABCG2*) for its impact on rosuvastatin pharmacokinetics and the development of side effects [15], which led to the latest CPIC guidelines [16]. This manuscript reports an observational real-world study that explored the prevalence of SAMS within our cardiovascular disease cohort (*EmHeart Study*). The full description of the study can be found elsewhere [17]. It includes an ethnically diverse and heterogeneous patient population with varied medical histories, ethnicities, and nationalities. By analyzing data from such a population, we aimed to comprehensively understand these side events and their potential risk factors, including age, gender, BMI, ethnicity, genetic factors, combination therapy, duration of treatment, and statin intensity. Although genetic and other factors have been extensively studied in simvastatin users [18, 19], they remain less explored in those taking atorvastatin and rosuvastatin, highlighting the significance of this study. Identifying these associations can contribute to developing a more personalized approach to statin therapy. This approach would balance the established benefits of statin use in CVD prevention with minimizing potential adverse events for individual patients. Ultimately, this research seeks to optimize the risk-benefit profile of statin therapy, ensuring a safer and more effective CVD prevention strategy at the global multiethnic levels.

Methods

Patient characteristics

Eligible participants were adult patients aged 18 years or older who had been prescribed either atorvastatin or rosuvastatin, agreed to participate in a 12-month follow-up study, and signed an informed consent form. Exclusion criteria for the study were as follows: patients who were pregnant or breastfeeding; those who planned to use the study drug for less than seven days; individuals with hepatic insufficiency, defined as alanine aminotransferase (ALT) or aspartate aminotransferase (AST) levels more than twice the upper limit of the normal range, or those with liver cirrhosis; patients with renal insufficiency, where serum creatinine was more than 1.5 times the upper limit of the normal range, or serum creatinine exceeded 2.5 mg/dl in the last seven days, or those with severe renal function impairment requiring dialysis; subjects with an active tumor, a recent cancer diagnosis, or those undergoing chemotherapy treatment; patients with hematologic issues, such as a white blood cell count less than 2 x 10^9/L, or platelet counts under 100 x 10^9/L and patients suffering from sepsis. We initially enrolled 712 patients. To minimize confounding, 20 atorvastatin

users and 17 rosuvastatin users were excluded due to underlying musculoskeletal disorders, hypothyroidism, or chronic pain syndromes. The final cohort included 675 patients who were eligible for the 12-month follow-up analysis.

All the recruited patients have been genotyped for *SLCO1B1 rs4149056 (521T > C), SLCO1B1 rs2306283 (388 A > G), and ABCG2 rs2231142 (421 C > A*) variants as part of the *EmHeart Study*.

Data collection, ethical approvals, and Follow-up

The study was conducted per the declaration of Helsinki and received approval from The Abu Dhabi Health Research and Technology Ethical Committee, reference numbers (DOH/CVDC/2020/1187), (DOH/CVDC/2021/1519), (DOH/CVDC/2022/1458), (MCME.CR.213.MAIN.2021), and (SNA/FA/2020-14). All the baseline and follow-up data were recorded using the Castor-EDC software (Netherlands) (www.castoredc.com). Castor EDC is a web-based platform designed to capture data entered via an electronic Case Report Form (eCRF) at clinical sites, which is then uploaded into a centralized database. Access to the software was limited to authorized users who log in using their credentials, ensuring the confidentiality of study participant data. Additionally, this tool simplified the process of exporting and analyzing the data, enhancing the efficiency and accuracy of research analysis.

Clinical information was gathered from electronic medical records (EMR); data collected included the reasons for prescribing statins, such as cardiovascular disease, and comorbid conditions that could influence the risk of SAMS, like thyroid disorders, were identified using the International Classification of Diseases (ICD). Medication details, such as levothyroxine prescriptions, helped confirm diagnoses like hypothyroidism. Demographics like age, gender, height, weight, smoking status, alcohol consumption, ethnicity, concomitant medications, family history, and comorbidities. Besides laboratory results, prescriptions, and noted drug allergies. Follow-ups were made by reviewing the medical records and conducting phone calls to confirm the occurrence of SAMS within one year of recruitment. Outcomes include the occurrence of SAMS while using atorvastatin or rosuvastatin (the only two statins prescribed in UAE).

Sample collection and DNA isolation

Peripheral blood samples (3 mL) were collected in EDTA-containing vacutainer tubes (BD Inc., UK) and stored at -20 °C until further analysis. Genomic DNA isolation from whole blood was achieved using the FlexiGene® DNA kit (Qiagen, Germany) or the QIAamp® DNA kit (Qiagen, Germany), following the manufacturer's instructions. DNA quality and quantity were evaluated using a Nanodrop One Spectrophotometer (Thermo Fisher Scientific, USA).

Genotyping of genetic variants

Genotyping for three specific genetic variants was performed using TaqMan® SNP assays for *SLCO1B1* rs4149056 (521T > C), *SLCO1B1* rs2306283 (388 A > G), *ABCG2* rs2231142 (421 C > A) (catalogue numbers C__8898463_10, C_30633988_10, and C_15854163_70, respectively) in conjunction with TaqMan SNP master mix on a Realtime-QuantStudio 7 Flex PCR machine (Applied Biosystems, ThermoFisher Scientific). The resulting genotypes were validated using TaqMan Genotyper software version 1.6.0 (Applied Biosystems, ThermoFisher Scientific). The genotypes of a representative sample were confirmed by Sanger sequencing, which showed 100% concordance.

Statin Associated Muscle Symptoms (SAMS)

The diagnosis of statin-induced myalgia and other milder forms of statin-associated muscle symptoms (SAMS) relies predominantly on clinical criteria due to the absence of specific diagnostic tests [20]. These criteria recognize symptoms such as muscle pain, cramps, and weakness as common indicators of SAMS. Symptoms typically affect large muscle groups like the thighs, buttocks, back, and shoulders, presenting bilaterally and early after initiating or increasing the statin dosage. Contrarily, muscle cramps often occur unilaterally and might affect smaller muscles in the hands and feet, with symptoms commonly emerging about one month after starting treatment. We applied the SAMS-CI tool [21], which gives a score indicating the probability of the muscle pain symptoms being induced by statins. However, in this study, we included all patients who suffered from SAMS regardless of the values of these scores. We have evaluated the EMR for other medical conditions that could cause muscle pain, such as hypothyroidism, vitamin D deficiency, or underlying muscle disease. Moreover, we asked the patients via phone calls if the pain was synchronous with excessive physical work, changes in exercise patterns, concurrent illnesses, hypothyroidism, or underlying muscle diseases. Those patients were excluded from the SAMS diagnosis.

Transaminase elevation

Using medical records, we checked the laboratory results for alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels. The study's clinical laboratory data focused on three key measures: AST, ALT, and creatinine, which were adjusted for age, sex, race, and creatinine level to control for potential confounders affecting liver enzyme levels. For analytical purposes, the value closest to the genotyping date for each variable was used.

Table 1 Patients demographics and Statin indications

Baseline characteristics (*N* = 675)	Number of patients (%)
Gender	
Female	208 (30.8%)
Male	467 (69.2%)
Ethnicity	
Arabs	263 (38.9%)
Indians	186 (27.5%)
East Asians	128 (19%)
Europeans	38 (5.7%)
Others	60 (8.8%)
Statin dose	
Moderate intensity Rosuvastatin (5-10 mg)	186 (27.5%)
Moderate intensity Atorvastatin (10-20 mg)	180 (26.6%)
High intensity Rosuvastatin (20-40 mg)	137 (20.3%)
High intensity Atorvastatin (40-80 mg)	172 (25.5%)
Indication	
Secondary Prevention (Previous Cardiac event)	187 (27.6%)
Diabetes	270 (40%)
Primary Prevention [Dyslipidaemia defined as LDL > 190 mg/dL (4.92 mmol/L)].	127 (18.8%)
Primary Prevention [ASCVD > 7.5%]	91 (53.6%)
Other diseases	
Hypertension	202 (30%)

ASCVD; Atherosclerotic cardiovascular diseases, CVD; Cardiovascular diseases, LDL; low-density lipoprotein

Transaminase elevation was defined as ALT levels greater than three times the upper limit of normal, a threshold that helps identify significant hepatocellular injury potentially related to statin use. Physicians specifically noted cases where elevated liver enzymes were attributed probably to statin use, leading to the cessation of statin therapy to monitor enzyme levels, thus confirming the clinical pathway followed in response to suspected adverse drug reactions.

Statistical analysis

The statistical analysis was designed to investigate the associations between statin use and the incidence of adverse effects, specifically SAMS and transaminase elevation. Initially, univariate analyses, including Chi-square tests, explored the frequencies and comparison of adverse events between patients treated with atorvastatin and rosuvastatin. Then we investigated factors affecting the occurrence of adverse events including genetic variations. This step helped identify potential variables of interest based on the observed distributions in the cohort.

Subsequently, multivariate logistic regression models were employed to elucidate further the relationships between patient demographics, genetic profiles, and the occurrence of adverse events. These models adjusted for multiple confounding factors such as age, sex, BMI, and ethnicity to ensure the robustness of the results. Variables with a p-value < 0.1 in the univariate analysis were entered into the multivariate logistic regression model to identify independent predictors of adverse events. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated to quantify the impact of various predictors, including the intensity of statin therapy and the presence of pharmacogenomic variants like *SLCO1B1* rs4149056 and *ABCG2* rs2231142. Statistical significance was established at a p-value of less than 0.05, using SPSS (version 29.0, IBM Corporation, Armonk, NY, USA) for all analyses.

Results

Our cohort included 675 patients treated with statins (352 with atorvastatin and 323 with rosuvastatin) as monotherapy or in combination with ezetimibe (*N* = 264). The average age of our cohort was 52.43 years (± 11.52). Table 1 lists the demographics of patients and indications for statins.

Genotyping results were analyzed, and Table 2 lists the minor allele frequencies (MAF) of the studied variants among the different ethnicities of the study cohort.

The frequencies of adverse events were compared between atorvastatin and rosuvastatin users. Table 3 lists these frequencies and the p-value of the Chi-square test, illustrating the significance of differences between the observed frequencies. A significant difference was detected in the frequencies of gastrointestinal (GI) symptoms and elevation in liver enzymes.

SAMS were the most frequent side effects prevalent in our cohort affecting around 30% of statins users.

Table 2 Minor allele frequencies of the studied variants among different ethnicities in the study cohort

Variant	Minor Allele Frequencies (*N*)					
	Total (675)	Arabs (260)	Indians (186)	East Asians (128)	Europeans (38)	Others (63)
SLCO1B1 rs4149056 (521T > C)	0.081	0.16	0.027	0.055	0.0216	0.003
SLCO1B1 rs2306283 (388 A > G)	0.390	0.560	0.133	0.680	0.12	0.022
ABCG2 rs2231142 (421 C > A)	0.051	0.040	0.018	0.156	0.0185	0.003

Table 3 Comparison of adverse events occurrence between Atorvastatin and Rosuvastatin

Adverse Drug Reaction	Atorvastatin (*N* = 352)	Rosuvastatin (*N* = 323)	*P*- value
SAMS	96 (27.27%)	96 (29.7%)	0.4811
Headache	14 (4%)	12 (3.8%)	0.772
Fatigue	14 (4%)	21 (6.5%)	0.135
GI Symptoms (Constipation, Diarrhea, Indigestion)	16 (4.5%)	33 (10.2%)	**0.0035**
New incidence of T2DM	30 (8.5%)	41(12.7%)	0.0730
Elevated Liver Enzymes	12(3.4%)	44(13.6%)	**< 0.0001**

GI; gastrointestinal, T2DM; Type II Diabetes, SAMS; Statin induced muscle symptoms

Although the overall incidence of SAMS did not significantly differ between atorvastatin and rosuvastatin users, we analyzed them separately due to differences in pharmacogenomic associations and co-medication profiles (e.g., ezetimibe use), which could affect the risk of adverse effects in a drug-specific manner. The percentage of patients and odds ratios of SAMS in each group, with 95% confidence intervals and p-values, are listed in Table 4 for the atorvastatin group and Table 5 for the rosuvastatin group. Gender, BMI, Arab ethnicity, and carrying the minor allele at *SLCO1B1*:rs4149056 were all significant variables in the atorvastatin group. In comparison, a similar analysis yielded different significant variables in the rosuvastatin group (Table 5). The combination of ezetimibe therapy and *ABCG2* variant was significant and nearly significant in this group, respectively.

Thereafter, regression analysis revealed that *SLCO1B1 rs4149056* was the most significant predictor of SAMS among atorvastatin users as shown in Table 6. In contrast, in the rosuvastatin group, ezetimibe co-therapy emerged as a significant contributor while the *ABCG2 rs2231142* variant showed a trend toward significance (Table 7). Elevated transaminase levels were significantly associated with the use of combination ezetimibe therapy and the *ABCG2* variant in rosuvastatin users, as shown in Table 8. These findings were further supported by regression analysis (Table 9).

Table 4 Characteristics of patients with and without SAMS among Atorvastatin users (*N* = 352)

Factor	SAMS (*N* = 96)	No SAMS (*N* = 256)	O.*R* (95% CI)	*P*-value
Gender				
Male (*N* = 264)	64(24.24%)	200 (75.76%)	1.7857 (1.0642 to 2.996)	**0.0281**
Female (*N* = 88)	32 (36.36%)	56 (63.64%)		
Age				
21–55 (*N* = 175)	45 (25.7%)	130 (74.3%)	1.1693(0.7310 to 1.8706)	0.5141
56–82 (*N* = 177)	51 (28.8%)	105 (71.2%)		
Obese				
BMI > 30 (*N* = 111)	39 (35.14%)	72 (64.9%)	1.748 (1.0712 to 2.854)	**0.0254**
< 30 (*N* = 241)	57 (23.7%)	184 (76.3%)		
Arabs				
Arabs (*N* = 120)	45 (37.5%)	75 (62.5%)	2.1294 (1.314 to 3.451)	**0.0022**
Non-Arabs (*N* = 232)	51 (22%)	181 (78%)		
Smoking				
Smokers (*N* = 130)	30 (23%)	100 (77%)	1.41 (0.85 to 2.29)	0.2149
Non-smokers (*N* = 222)	66 (29.7%)	156 (70.3%)		
Combination therapy				
Ezetimibe (*N* = 125)	33 (26.4%)	92 (73.6%)	0.9337 (0.5682 to 1.524)	0.8040
No Ezetimibe (*N* = 227)	63 (27.75%)	164 (72.25%)		
Atorvastatin dose				
Moderate intensity (*N* = 180)	41 (22.77%)	139 (77.22%)	1.593 (0.9928 to 2.5558)	0.0536
High intensity (*N* = 172)	55 (32%)	117 (68%)		
Duration of therapy				
Less than one year (*N* = 244)	61 (25%)	183 (75%)	1.438 (0.87 to 2.378)	0.1512
More than one year (*N* = 108)	35(32.4%)	73 (67.6%)		
SLCO1B1 rs4149056				
C allele Carriers (*N* = 69)	28 (40.6%)	41 (59.4%)	2.202 (1.287 to 3.811)	**0.0063**
Non-carriers (*N* = 283)	68 (24.03%)	215 (76.3%)		
SLCO1B1 rs2306283				
G allele Carriers (*N* = 252)	71 (28.2%)	181 (71.8%)	1.177 (0.70 to 1.959)	0.5970
Non-carriers (*N* = 100)	25 (24.03%)	75 (75.97%)		

Table 5 Characteristics of patients with and without SAMS among Rosuvastatin users (*N* = 323)

Factor		SAMS (*N* = 96)	No SAMS (*N* = 227)	O.*R* (95% CI)	*P*-value
Gender	Male (*N* = 203)	55(27%)	148(73%)	1.397 (0.8698 to 2.286)	0.2079
	Female (*N* = 120)	41(34%)	79(65.8%)		
Age	21–55 (*N* = 205)	62(30.2%)	143(69.7%)	1.071 (0.6482 to 1.772)	0.8019
	56–82 (*N* = 118)	34(28.8%)	84(71.2%)		
Obese BMI > 30	> 30 (*N* = 123)	42(34%)	81(65.8%)	1.402 (0.8495 to 2.288)	0.2098
	< 30 (*N* = 200)	54(27%)	146(73%)		
Arabs	Arabs (*N* = 143)	47(32.8%)	96(67.2%)	1.309 (0.8091 to 2.116)	0.2734
	Non-Arabs (*N* = 180)	49(27.2%)	131(72.8%)		
Smoking	Smokers (*N* = 79)	24(30.4%)	55(69.6%)	1.042 (0.5981 to 1.774)	0.8881
	Non-smokers (*N* = 244)	72(29.5%)	172(70.5%)		
Combination therapy	Ezetimibe (*N* = 123)	46(37.4%)	77(62.6%)	1.792 (1.093 to 2.937)	0.0238
	No Ezetimibe (*N* = 200)	50(25%)	150(75%)		
Rosuvastatin dose	Moderate intensity (5 or 10 mg (*N* = 186)	50(26.8%)	136(73.2%)	1.375 (0.8468 to 2.227)	0.2185
	High intensity (20 or 40 mg) (*N* = 137)	46 (33.6%)	91(66.4%)		
Duration of therapy	Less than one year(*N* = 226)	70(31%)	156 (69%)	1.225 (0.7259 to 2.072)	0.5077
	More than one year(*N* = 97)	26 (26.8%)	71(73.2%)		
SLCO1B1 rs4149056 (521T > C)	Carriers (*N* = 77)	25(32.5%)	52(67.5%)	1.185 (0.6859 to 2.017)	0.5691
	Non- carriers (*N* = 246)	71(28.8%)	175(71.2%)		
ABCG2 rs2231142 (421 C > A)	Carriers (*N* = 69)	27 (39%)	42 (60.8%)	1.724 (0.9969 to 2.998)	0.0739
	Non- carriers (*N* = 254)	69 (27%)	185 (73%)		

Table 6 Logistic regression analysis identifying factors associated with muscle symptoms among Atorvastatin users

Independent Variables	*P*-Value	Adjusted Odds Ratio (OR)	95% CI (Lower)	95% CI (Upper)
High intensity (40 or 80 mg)	0.143	1.445	0.883	2.366
***SLCO1B1 rs4149056*Carriers**	**0.013**	2.047	1.162	3.608
BMI > 30	0.285	1.325	0.791	2.219
Arabs	0.048	1.667	1.005	2.766
Gender (Female)	**0.002**	2.395	1.366	4.199

Table 7 Logistic regression analysis of factors associated with muscle symptoms among Rosuvastatin users

Independent Variables	*P*-Value	Adjusted Odds Ratio (OR)	95% CI (Lower)	95% CI (Upper)
Combination therapy (Ezetimibe)	**0.033**	1.778	1.046	3.020
***ABCG2 rs2231142* Carriers**	0.280	1.379	0.770	2.469

Finally, we stratified the incidence of transaminase elevation according to ethnicity, hypothesizing that some side effects may occur more frequently in some ethnic groups. East Asians demonstrated a higher susceptibility to these adverse events, with 36.30% of the liver enzyme elevation group being East Asian, of whom 73.7% were carriers of the *ABCG2 rs2231142* variant. Additionally, in the SAMS group, 52% of participants were Arab (25% of whom carried the variant), and 21.80% were East Asian, with 51.85% carrying the variant. The frequencies of elevated liver enzymes and SAMS are plotted in different ethnic groups (Fig. 1). The percentage of *ABCG2*: rs2231142 (421 C > A) was further illustrated on the same plot to illustrate the positive trend between the carrier status of this variant and ethnic group.

Discussion

This observational real-time cohort study provides valuable insights into the comparative safety profiles of atorvastatin and rosuvastatin in a multiethnic population. It

Table 8 Transaminase elevation relations with the patients' characteristics among Rosuvastatin users (*N* = 323)

Factor		Transaminase Elevation (*N* = 44)	No transaminase elevation (*N* = 279)	O.*R* (95% CI)	*P*-value
Gender	Male (*N* = 203)	28(13.8%)	175(86.2%)	1.040 (0.5425 to 2.027)	0.9999
	Female (*N* = 120)	16(13.3%)	104(86.7%)		
Age	21–55 (*N* = 205)	31(15%)	174 (85%)	1.439 (0.7255 to 2.975)	0.3186
	56–82 (*N* = 118)	13(11%)	105(89%)		
Body mass index (BMI)	> 30 (*N* = 123)	19(15.5%)	104 (84.5%)	1.279 (0.6833 to 2.427)	0.5051
	< 30 (*N* = 200)	25(12.5%)	175(87.5%)		
Ethnicity	Arabs (*N* = 143)	13(9%)	130 (91%)	2.081 (1.054 to 4.279)	0.0353
	Non- Arabs (*N* = 180)	31(17.3%)	149(82.7%)		
Smoking	Smokers (*N* = 79)	15(19%)	64(81%)	1.808 (0.9203 to 3.636)	0.1256
	Non-smokers (*N* = 244)	28(11.5%)	216(88.5%)		
Alcohol Use	Yes (55)	12 (21.8%)	43(78.2%)	2.058 (0.9902 to 4.222)	0.0812
	No (268)	32(11.9%)	236(88.1%)		
Combination therapy	Ezetimibe (*N* = 123)	23(18.7%)	100(81.3%)	1.960 (1.024 to 3.711)	0.0449
	No Ezetimibe (*N* = 200)	21(10.5%)	179(89.5%)		
Rosuvastatin dose	Moderate intensity (5 or 10 mg (*N* = 186)	29(15.6%)	157(84.4%)	1.502 (0.7804 to 2.850)	0.2539
	High intensity (20 or 40 mg) (*N* = 137)	15(11%)	122(89%)		
SLCO1B1 rs4149056 (521T > C)	Carriers (*N* = 77)	13(16.8%)	64(83.2%)	1.409 (0.6981 to 2.880)	0.3447
	Non-carriers (*N* = 246)	31(12.6%)	215(87.4%)		
ABCG2 rs2231142 (421 C > A)	Carriers (*N* = 69)	19(27.5%)	50(72.5%)	3.481 (1.771 to 6.574)	**0.0005**
	Non-carriers (*N* = 254)	25(9.8%)	229(90.2%)		

Table 9 Logistic regression analysis of factors associated with transaminase elevation among Rosuvastatin users (*N* = 323)

Independent Variables	*P*-Value	Adjusted Odd Ratio (OR)	95% CI (Lower)	95% CI (Upper)
Combination therapy (Ezetimibe)	**0.040**	2.053	1.032	4.087
***ABCG2 rs2231142* Carriers**	**0.002**	3.222	1.554	6.680
Ethnicity (Arab)	0.373	0.697	0.315	1.541
Alcohol use	0.260	1.589	0.710	3.560

focuses on statin-associated muscle symptoms (SAMS), the most reported adverse event, and transaminase elevation, surprisingly more frequently observed among rosuvastatin users in our cohort. The study highlights differences in these adverse events across a multi-ethnic heterogeneous population. It evaluates confounding factors such as age, gender, obesity, ethnicity, genetic variants, duration of statin therapy, and combination therapies.

The structural differences between atorvastatin and rosuvastatin significantly impact their pharmacological properties [22]. Our results indicate that gastrointestinal symptoms are significantly more common in rosuvastatin patients than atorvastatin patients. Specifically, 10.2% of rosuvastatin users experienced gastrointestinal symptoms compared to 4.5% of atorvastatin users ($P = 0.0035$). The administration of rosuvastatin in mice leads to significant alterations in gut microbiota composition, bile acid metabolism, and local gene expression profiles related to inflammation and gut homeostasis [23]. Another study showed that rosuvastatin has a limited effect on human gut microbiome composition [24]. Roy and colleagues compared high-dose atorvastatin (80 mg/day) and rosuvastatin (40 mg/day) among post-percutaneous coronary

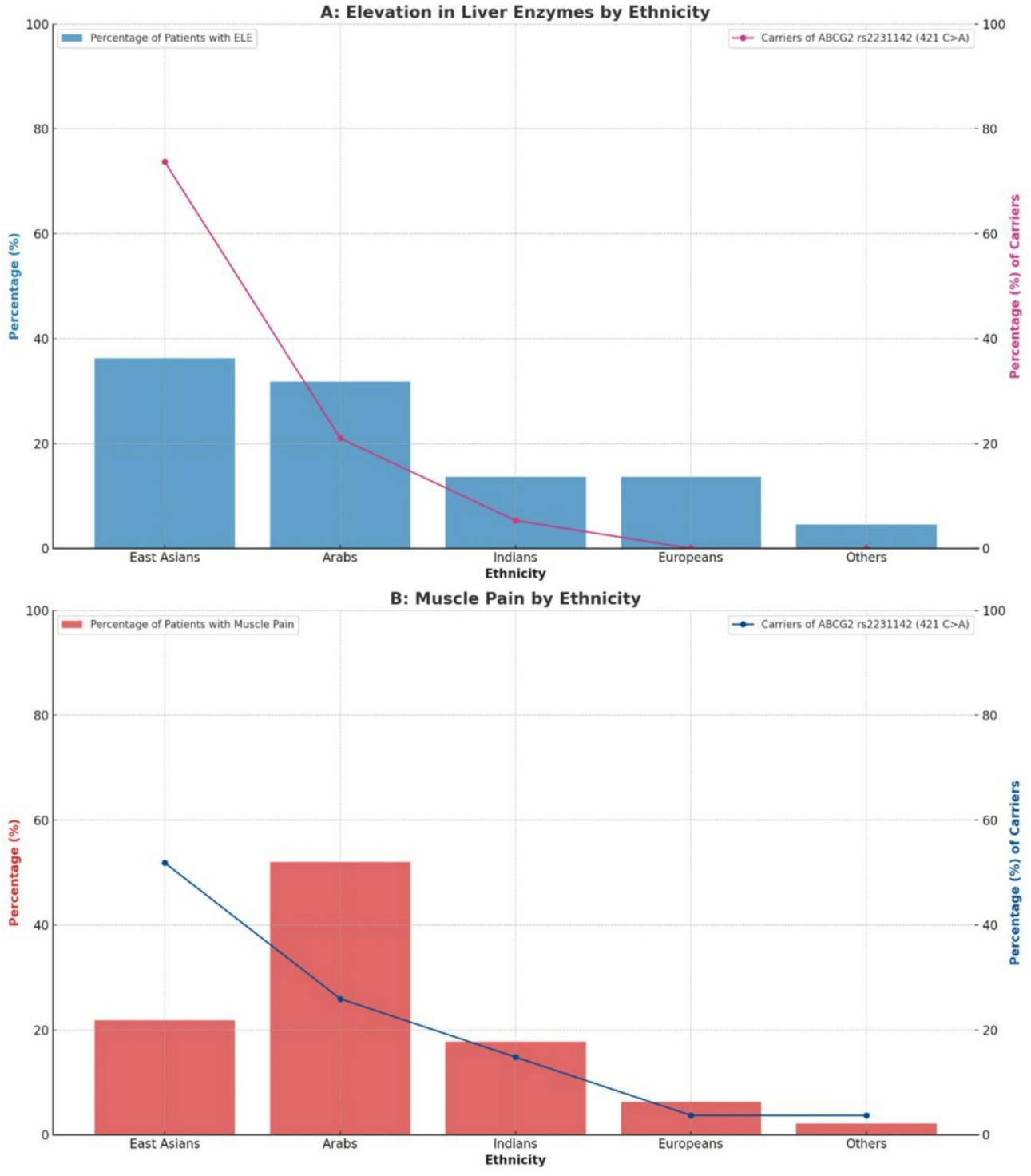

Fig. 1 Percentage of patients with elevated liver enzymes and SAMS across different ethnicities among rosuvastatin users. The line presents the percentage of carriers of the ABCG2:rs2231142 (421 C > A) variant

intervention (PCI) patients, focusing on their effects on gastroesophageal reflux disease (GERD) and gastritis. It was found that GERD and gastritis occurred in 2.18% of patients taking atorvastatin versus 4.83% in those taking rosuvastatin during a three-month follow-up [25]. Our data revealed that statin therapy led to a 10.51% increased risk of developing diabetes, with a 12.7% increased risk in rosuvastatin users, and 8.5% in the case of atorvastatin ($P = 0.0730$).

Additionally, elevated liver enzymes were observed in 13.6% of rosuvastatin users compared to 3.4% of atorvastatin users ($P < 0.0001$). This rate of elevated liver enzymes observed in rosuvastatin users in our study is notably higher than typical rates reported in the literature, which generally consider clinically significant transaminase increases with statins to be rare. This finding suggests that genetic predispositions or demographic factors may elevate the risk in certain populations. These results are contrary to those of a significant drug-level network meta-analysis of 165,534 individuals, which indicated that atorvastatin (OR, 2.55; 95% CI 1.71–3.74) was more likely to cause transaminase elevation than rosuvastatin (OR, 1.59; 95%CI, 1.02–2.50) [26]. The discrepancy may be due to the multi-ethnic composition of our cohort, particularly since most of the transaminase elevation cases were linked to East Asians carrying the *ABCG2 rs2231142* minor allele. So rosuvastatin might still be safer for specific ethnicities regarding transaminase elevation and atorvastatin might be safer for East Asians. This was discussed in our previous whole exome analysis for an Emirati cohort, and we stated that the integration of population-specific pharmacogenomic data into medical decisions to optimize drug efficacy while minimizing adverse effects is an appealing approach in personalized medicine [27]. Additionally, the smaller sample size of our study compared to the meta-analysis could have influenced these findings. Moreover, transaminase elevation in statin users is influenced by multiple factors [28]. Although our study included comprehensive medical reviews, it faced limitations in fully assessing all potential contributors to transaminase elevations. Specifically, we were unable to evaluate the impact of alcohol consumption, over-the-counter medications (e.g., acetaminophen), and herbal products on these laboratory parameters.

Our analysis detected no significant association between SAMS and transaminase elevation across different age groups. Although randomized controlled trials (RCTs) assessing the safety of rosuvastatin remain scarce. The JUPITER trial, which involved 5,695 participants aged over 70 years at enrolment, reported no specific safety concerns for this age group compared to younger individuals [29]. Another recent study showed that the relationship between cholesterol levels and cardiovascular mortality is more significant in younger individuals compared to older ones [30].

Our study specifically examined the impact of combining ezetimibe with rosuvastatin among 323 users and found significant effects on liver enzyme levels. Notably, ethnicity and the use of ezetimibe were prominent factors. The combination of rosuvastatin and ezetimibe showed higher odds of transaminase elevation when compared to statin monotherapy. A recent study by González-Iglesias et al. found that *ABCG2* polymorphisms had a greater impact on rosuvastatin levels than *SLCO1B1* variants, supporting our findings on *ABCG2 rs2231142*. However, they also reported that ezetimibe co-administration lowered rosuvastatin levels, contrasting with our observed increase in SAMS and liver enzyme elevation [31]. This may reflect complex pharmacokinetic-pharmacodynamic interactions, where lower plasma levels don't always mean lower toxicity. Tissue distribution, transporter inhibition, pharmacodynamic effects, and genetic and clinical factors may influence outcomes. Further studies are needed to clarify these mechanisms. Zhu and colleagues conducted a metanalysis ($N = 3{,}105$), and they found no significant difference in the safety profile, specifically, transaminase elevation between double-dose statin monotherapy and combination therapy with ezetimibe [32]. The safety and tolerability of ezetimibe/rosuvastatin therapy were comparable with those of rosuvastatin monotherapy, as indicated by Hong and colleagues [33]. The SaveSAMS trial compares the impact of intensive statin monotherapy versus combination therapy on SAMS and transaminase elevation in elderly patients with established atherosclerotic cardiovascular disease. Their results have not yet been published [34].

The presence of the *ABCG2* rs2231142 variant was also notable, particularly in the context of elevated liver enzymes ($O.R = 3.481$, $P = 0.0005$). This suggests that genetic screening could play a crucial role in choosing the appropriate statin for each patient, in this case, avoiding rosuvastatin as this variant influences its excretion [35]. In contrast, factors such as age, gender, obesity, smoking, and alcohol consumption did not significantly impact liver enzyme levels, suggesting a more complex interplay that warrants further investigation to understand the mechanisms behind statin-related liver enzyme elevation. Although asymptomatic elevation of liver enzymes does not require discontinuation of statin therapy according to the FDA guidelines [36], many studies have shown that patients are often concerned about these elevations, which can contribute to discontinuation [37] and lower adherence rates [38]. This concern is especially significant because mild enzyme elevations have been associated with higher rates of statin discontinuation against clinical recommendations. While elevated transaminase levels can have various causes, it is worth noting that the *ABCG2 rs2231142 (421 C > A)* variant, which has been linked to higher uric acid levels, is more frequent in certain populations [39]. Although we aimed to exclude patients with symptomatic gout, some participants carried the minor allele and therefore had a higher risk of hyperuricemia. However, there is limited evidence linking hyperuricemia itself to transaminase elevation,

suggesting that other factors may also contribute to liver enzyme changes in these individuals.

Arab patients exhibited lower rates of enzyme elevation compared to non-Arabs. Furthermore, that might be due to the low frequency of *ABCG2 rs2231142* among Arabs, which explains fewer cases of gout hyperuricemia and elevated liver enzyme cases, which drove us to the same conclusion of the suitability of rosuvastatin for individuals of Emirati origin [27]. These findings are consistent with previous studies that have reported a higher incidence of gastrointestinal issues and liver enzyme elevations with rosuvastatin, potentially due to its greater potency and different metabolic pathways [40]. A study published in 2016 highlighted that the maximum dose of rosuvastatin should be restricted to 20 mg in East Asians to mitigate the risk of liver enzyme elevation and rhabdomyolysis [41]. This recommendation stems from the observation that East Asians have approximately double the plasma levels of rosuvastatin compared to Western populations at the same dosage [42]. Nevertheless, the current study did not identify an association between higher doses of rosuvastatin and the Incidence of adverse events (SAMS or transaminase elevation).

The analysis of SAMS revealed that female gender, Arab ethnicity, and the *SLCO1B1 rs4149056* variant are significant risk factors for developing SAMS while using atorvastatin. The odds ratio for SAMS in females was 1.7857 ($P = 0.0281$), indicating a more than 1.5-fold increase in risk compared to males. Gender-related differences are evident in the impact of SLCO1B1 genetic variation [43]. Female patients with the *SLCO1B1 c.521T > C* variant are more likely to experience higher cholesterol levels, reduced statin efficacy, increased SAMS, potentially influenced by variability in OATP1B1 activity [44] and smaller volumes of distribution relative to males [18]. Arab ethnicity was associated with a higher risk (O.$R = 2.129$, $P = 0.0022$), which may be due to genetic predispositions or cultural differences in reporting symptoms. The *SLCO1B1 rs4149056* variant also showed a significant association (O.$R = 2.202$, $P = 0.0063$), corroborating previous findings that link this variant to SAMS [14, 45, 46]. A study published in the Lancet 2022 elucidates that although a marginal increase in muscle pain occurs initially with statin use, most muscle-related complaints are not attributable to statins [47]. Importantly, the minor risk of SAMS is substantially outweighed by the cardiovascular advantages of statin therapy.

While more studies are warranted, a preliminary conclusion suggests that rosuvastatin should not be prescribed at high doses to East Asians. We noticed that physicians in the UAE do not consider ethnicity when prescribing statins. Instead, moderate-intensity atorvastatin might be a better choice for them. This recommendation is particularly pertinent because the MAF of the *ABCG2 rs2231142 (421 C > A)* variant is approximately 30% in East Asians. In contrast, it is about 10.3% in Europeans and much lower in African populations at around 2.7% (gnomad.broadinstitute.org). It is contributing to increased sensitivity to rosuvastatin and its adverse events.

The study highlights the need to re-evaluate the choice of statin-type therapy in patients who experience statin-related events, as most patients can tolerate long-term statin use if rechallenged [48]. Clinicians may consider evaluating known risk factors, including genetic markers, when choosing among statins rather than relying on empirical trial-and-error approaches. This approach is vital for preventing avoidable cardiovascular events and deaths that could result from the permanent cessation of statin therapy. Based on the factors discussed in this study, it is possible to prevent discontinuation due to side effects from the beginning by choosing the appropriate statin for each individual. These factors include gender and *SLCO1B1* genotyping among atorvastatin users, ezetimibe therapy, and *ABCG2* for rosuvastatin. Atorvastatin might be safer for individuals with fatty livers and other liver risk factors. A trial to implement pharmacogenetic testing in the healthcare system in the UAE, conducted from 2021 to 2024, is underway [17]. We are currently analyzing the data collected to refine further and tailor our approaches to statin therapy based on genetic profiles. Longitudinal studies are also needed to assess personalized statin therapy's long-term safety and efficacy. In addition to transporter gene variants, other factors, such as *CYP3A* enzyme activity, also influence statins plasma levels and metabolism, as highlighted [49]. Including *CYP3A* activity in future analyses could provide a more comprehensive understanding of pharmacokinetic variability and aid in optimizing personalized dosing strategies for atorvastatin and rosuvastatin.

Study limitations

While this study provides valuable insights, several limitations must be acknowledged. First, the observational design restricts our ability to draw causal inferences. Additionally, the reliance on self-reported symptoms may introduce reporting bias. Future research should validate these findings through randomized controlled trials and investigate the mechanisms underlying the observed genetic associations. We excluded patients whose muscle pain could be attributed to factors such as recent strenuous physical activity, changes in exercise patterns, concurrent illnesses, hypothyroidism, or underlying muscle conditions. However, for some patients who did not return for follow-up visits, we relied solely on medical records. Furthermore, our data on muscle pain relied on phone calls and patient-reported symptoms, which could introduce subjectivity. Secondly, our approach to

diagnosing statin-associated muscle symptoms (SAMS) may not effectively differentiate subjective reports from objectively confirmed cases, potentially impacting the accuracy of muscle symptom prevalence estimates related to statin use. Thirdly, Creatine kinase (CK) was not included as a muscle damage indicator, as CK lab tests were unavailable in the medical records for our cohort. Future studies could incorporate CK measurements to assess muscle-related effects with statins better. Fourth, high stratification and multiple testing may limit the generalizability and robustness of some findings. Fifth, although our study included comprehensive medical reviews, limitations existed in assessing all potential contributors to transaminase elevations. Specifically, we were unable to evaluate the impact of over-the-counter medications (e.g., acetaminophen) and herbal products on these laboratory values. Finally, although our analysis focused on *SLCO1B1 and ABCG2* variants supported by strong evidence of association with statins pharmacokinetics, we acknowledge that the inclusion of additional polymorphisms in the same genes may offer a more comprehensive evaluation of transporter functionality.

Conclusions

Our study highlights significant differences in adverse effects between atorvastatin and rosuvastatin, influenced by genetic variants and demographic factors. Given that genetic factors are the most confounding elements affecting the incidence of adverse events, these findings support genetic screening to guide statin therapy and minimize adverse effects, paving the way for more personalized and effective management of dyslipidemia in diverse populations. By integrating these findings into clinical practice, healthcare providers can enhance patient outcomes and reduce the incidence of statin-related adverse events, ultimately improving the quality of care for patients with cardiovascular disease. While our study highlights associations between specific genetic variants (such as *SLCO1B1 c.521T>C and ABCG2 rs2231142*) and adverse reactions to statin therapy, it is possible that these associations are also influenced by ethnicity-related factors beyond the tested genetic markers. Ethnic groups may carry additional genetic variations or environmental exposures that impact drug metabolism and response, which were not specifically examined in this study. Therefore, while our findings suggest genetic influences on statin intolerance, they may not fully account for the complexities of interethnic variability. Further research involving broader genetic testing and multiethnic analyses is warranted to better understand these associations and to refine pharmacogenomic recommendations for diverse populations.

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Author contributions
Authorship Contribution Mais N. Alqasrawi: Conceptualization, Data curation, Formal analysis, Visualization, Investigation, Methodology & Writing the original draft. Zeina N. Al-Mahayri: Conceptualization, Validation, Methodology & Writing– review and editing. Areej S. AlBawa'neh: Data curation, Investigation, Formal analysis & writing the original draft. Lubna Q. Khasawneh: Data curation & Investigation. Lilas Dabaghie: Data curation. Sahar M. Altoum: Data curation. Dana Hamza: Investigation. Virendra Misra: Investigation & Writing– review and editing, Husam Ouda: Investigation& Writing– review and editing. Salahdein Aburuz: Methodology, Formal Analysis & Writing– review and editing, Fatima Al-Maskari: Conceptualization, Funding acquisition & Writing– review and editing. Juma AlKaabi: Conceptualization, Funding acquisition & Writing– review and editing, George P. Patrinos: Conceptualization, Funding acquisition & Writing– review and editing. Bassam R. Ali: Conceptualization, Funding acquisition, Writing– review and editing, Data Curation, supervision, validation &Project administration.All co-authors contributed to the final manuscript and approved it.

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Data availability
The data from the current study (EMHEART) are not publicly available due to regulations of the local ethical committee but are available from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate
This study was conducted in compliance with the Declaration of Helsinki and was approved by the Abu Dhabi Health Research and Technology Ethical Committee (Institutional Review Board - IRB) (Ref. DOH/CVDC/2020/1187). All participants provided written informed consent before enrolment in the study.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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