Original Article

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Impact of statins on liver transaminases in patients with metabolic dysfunction–associated steatotic liver disease: A 12-month retrospective review

Running Head: Statins and liver enzymes in MASLD: A 12-month review

Paul Jen Wui Wong[1], Sau Chyun Ng[1], Samuel George[2], Rasnaizam bin Rasdi[1]

[1]Department of Gastroenterology, Medical Hospital Tengku Ampuan Afzan, Kuantan, Malaysia

[2]Klinik Kesihatan Bentong, Bentong, Malaysia

Paul Jen Wui Wong: https://orcid.org/0009-0004-3630-1953

Sau Chyun Ng: https://orcid.org/0009-0005-6653-1298

Samuel George: https://orcid.org/0000-0002-6518-8150

Rasnaizam bin Rasdi: https://orcid.org/0009-0009-3380-3364

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Corresponding author:

Paul Jen Wui Wong

Department of Medical, Gastroenterology Unit, Hospital Tengku Ampuan Afzan, Kuantan, Malaysia

Phone: +6 016 658 03 13 Email: thejww@gmail.com

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Abstract

Background and Aim: Metabolic dysfunction-associated steatotic liver disease (MASLD) is the most common chronic liver disease worldwide and is strongly linked to metabolic comorbidities such as diabetes mellitus, hypertension, dyslipidemia, and coronary artery disease. Despite their cardiovascular benefits, statins are historically underused in patients with MASLD because of concerns regarding hepatotoxicity. This study aimed to evaluate the impact of statins on liver transaminase levels in patients with MASLD and assess whether statin type or dose influences these outcomes.

Materials and Methods: We conducted a retrospective review of 104 patients with MASLD who attended outpatient clinics between January 2023 and December 2024. Patients on statins for ≥12 months were included, while those with viral hepatitis, autoimmune liver disease, or significant alcohol intake were excluded. The data collected included comorbidities, statin type/dose, and liver transaminase levels at baseline, 3, 6, and 12 months. Patients without baseline transaminase levels available at the time of statin initiation were excluded. Of the 104 patients recruited, only 21 underwent transient elastography, of which two had advanced chronic liver disease.

Results: The mean BMI was 34.26 kg/m². Most patients had diabetes mellitus (86%), hypertension (88.5%), and dyslipidemia (98.1%). Transaminase levels remained stable over 12 months (ALT, $\chi^2(3)=0.340$, $p=0.952$; AST, $\chi^2(3)=0.342$, $p=0.926$). Statin type and dose had no significant effects on transaminase levels.

Conclusion: Statins of different types and doses did not significantly affect transaminases in patients with MASLD, indicating that statins are safe for use in patients with MASLD who meet the criteria for lipid-lowering therapy. Further studies are warranted to explore the long-term hepatic effects of statins in patients with metabolic dysfunction-associated steatohepatitis (MASH), focusing on histological outcomes.

Keywords: Liver transaminases; MASLD; statins.

Introduction

Metabolic dysfunction-associated fatty liver disease (MASLD), previously termed non-alcoholic fatty liver disease (NAFLD), is the most common chronic liver disorder worldwide.[1] It is characterized by hepatic steatosis in the presence of metabolic risk factors, such as obesity, type 2 diabetes mellitus, and dyslipidemia. MASLD not only carries the risk of progression to steatohepatitis, fibrosis, and cirrhosis, but also significantly increases cardiovascular morbidity and mortality,[2] which is the leading cause of death in this population.

Statins are widely prescribed lipid-lowering agents that have been proven to reduce cardiovascular risk in patients with dyslipidemia. Given the high prevalence of dyslipidemia and atherosclerotic cardiovascular disease among patients with MASLD, statins are frequently indicated.[3] However, concerns regarding potential hepatotoxicity and elevated liver transaminase levels often lead to the hesitancy or discontinuation of statins in patients with chronic liver disease.[4] Studies have shown that statins are under-prescribed in patients with MASLD despite the indication for statins in these patients, with Del Ben et al.[5] demonstrating that 50% of their patients with MASLD with indications for statins did not receive any statins. Blais et al.[6] showed that patients whose primary care providers recognized the presence of MASLD were less likely to receive statins than those with undetected MASLD.

However, the hesitation to use statin therapy in patients with MASLD due to potential hepatotoxicity is mostly unwarranted. The current consensus recommends that statins (if required for the treatment of dyslipidemia or CVD risk reduction) should be prescribed for patients with MASLD, even with modestly elevated serum liver enzyme levels (< 3× the upper limit of normal).[7]

One study showed that statins are not only safe but may also exert beneficial effects on liver histology and reduce the risk of fibrosis in patients with MASLD.[8] Nonetheless, real-world data examining the longitudinal effects of statins on transaminase trends in patients with MASLD, especially across different statin types and doses, remain limited and inconsistent.

This study aimed to address this gap by retrospectively analyzing the impact of statin therapy on liver transaminase levels over time in patients with MASLD and by exploring whether these effects vary based on the type or dose of statin used. Understanding this relationship is crucial for informing clinical decision-making and optimizing both hepatic and cardiovascular outcomes in this high-risk population.

This study aimed to investigate the effects of statin therapy on liver transaminases and lipid profiles in patients with metabolic dysfunction–associated steatotic liver disease (MASLD). Specifically, changes in alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels over time in patients with MASLD receiving statins were recorded. In addition, this study evaluated whether various statin types and doses had varying impacts on liver transaminase levels and examined the influence of statin type and dose on low-density lipoprotein (LDL) cholesterol reduction.

Materials and Methods

Study Population and Setting

We retrospectively reviewed the records of patients from the medical and gastroenterology outpatient clinics between January 2023 and December 2024. Patients with MASLD and those who had been on statins for ≥12 months were included.

Patients diagnosed with MASLD confirmed by liver ultrasonography and meeting any one of the following cardiometabolic criteria were included:

Cardiometabolic risk factors in adults include overweight or obesity, defined by a BMI >25 kg/m² (or >23 kg/m² in Asian populations), and central obesity, defined by ethnicity-specific waist circumference cut-offs (≥94 cm for European men and ≥80 cm for women; ≥90 cm for South Asian/Chinese men and ≥80 cm for women; ≥85 cm for Japanese men and ≥90 cm for women). Dysglycemia was characterized by prediabetes (HbA1c 5.7–6.4%, fasting plasma glucose 5.6–6.9 mmol/L, or 2-hour OGTT plasma glucose 7.8–11 mmol/L) or type 2 diabetes (HbA1c ≥6.5%, fasting plasma glucose ≥7.0 mmol/L, 2-hour OGTT plasma glucose ≥11.1 mmol/L, or treatment for type 2 diabetes). Dyslipidemia is defined as plasma triglycerides >1.7 mmol/L or HDL-cholesterol <1.0 mmol/L in men and <1.3 mmol/L in women, or on lipid-lowering treatment. Elevated blood pressure was defined as ≥130/85 mmHg or the use of antihypertensive therapy.[9]

Patients who were less than 18 years old, or who had hepatitis B or C, autoimmune hepatitis, Wilson's disease, primary biliary cholangitis, primary sclerosing cholangitis, hemochromatosis, congenital liver diseases, drug-induced hepatitis, and significant alcohol intake were excluded. Patients with no baseline liver transaminases available at the time of statin initiation were excluded. Of the 104 patients recruited, only 21 underwent transient elastography, of which two had advanced chronic liver disease (ACLD).

Study Design

The first time statins were prescribed to the patient was set as the baseline (0 months), and the liver transaminases and baseline lipid profiles were recorded. Liver transaminases and lipid profiles were recorded again at 3, 6, and 12 months. Other data collected included patient demographics, weight, BMI, statin type and dose, HbA1c levels, and ultrasonography findings.
The data were anonymized, and no identifiable information was reported.

Statistical Analysis

Statistical analyses were performed using SPSS version 30 (IBM, Chicago, IL, USA). Basic descriptive statistics, including means and standard deviations, were used to characterize the study patients. In this study, age, BMI, ALT, AST, LDL-C, total cholesterol, and HbA1c were treated as continuous variables for both descriptive and inferential analyses, with the means, standard deviations, and ranges reported. ALT and AST trends over time were analyzed as continuous variables using Friedman's test, given their non-parametric distribution. LDL-C was similarly analyzed as a continuous variable. The Kruskal-Wallis test was performed to determine whether there was any correlation between statin type and dose with ALT/AST trends, and the relationship between statin type and dose with the LDL trend.

For subgroup analyses, statin doses were categorized into standard clinical dose ranges (e.g., simvastatin 20–40 mg, atorvastatin 20–80 mg, and rosuvastatin 10–40 mg) to facilitate comparisons between potency levels. Multivariate analyses were performed with adjustments for potential confounders, including age, BMI, diabetes mellitus, hypertension, and chronic kidney disease, when assessing the effects of statin therapy on ALT and AST levels.

Ethics Approval and Consent

This study was conducted in accordance with the ethical principles outlined in the Declaration of Helsinki. Patient confidentiality and data privacy were strictly maintained throughout the study.
Ethics approval was obtained from the Medical Ethics Research Committee of Hospital Tengku Ampuan Afzan. Informed consent was not required for this retrospective study.

Results

Participants' Baseline Characteristics

A total of 104 patients were included in this study. The mean age was 53.97±13.66 years, and the mean BMI was 34.26±12.40 kg/m². Most participants had multiple metabolic comorbidities: 86.0% had diabetes mellitus, 88.5% had hypertension, and 98.1% had dyslipidemia. Additionally, 14.4% had ischemic heart disease, 12.5% had a history of stroke, and 27.9% had chronic kidney disease. In terms of demographics, this study included three main ethnic groups in Malaysia (79 Malay – 76%, 13 Chinese – 12.5%, 12 Indian – 11.5%), and gender was equally distributed (52 male, 52 female).

The statins used were simvastatin (n=23: 20 mg, n=9; 40 mg, n=14), atorvastatin (n=69: 10 mg, n=1; 20 mg, n=15; 40 mg, n=48; 60 mg, n=4; 80 mg, n=1), rosuvastatin (n=11: 10 mg, n = 3; 20 mg, n=7; 40 mg, n=1), pravastatin (n=1: 40 mg, n=1).

(Table 1)

Impact of Statin Use on Liver Transaminases

Friedman's test demonstrated no significant change in ALT levels across the study period (baseline, 3, 6, and 12 months): $\chi^2(3)=0.340$, $p=0.952$. Post-hoc pairwise comparisons with Bonferroni correction revealed no significant differences between any of the time points (all adjusted $p>0.60$). Similarly, AST levels remained stable over time ($\chi^2(3)=0.342$, $p=0.926$; all adjusted $p>0.50$) (Fig. 1,2).

Effect of Statin Types and Doses on LDL-C

Kruskal-Wallis analysis showed no significant difference in LDL-C levels at 0, 3, 6, and 12 months among the different statin types and doses ($H=15.507$, $df=9$, $p=0.078$). Although there was a trend towards lower LDL-C levels with higher doses and higher-potency statins, this was not statistically significant (Fig. 3).

Effect of Statin Types and Doses on Liver Transaminases

For liver transaminases, statin types and doses demonstrated no significant effect on ALT and AST level trends in multivariate analysis after adjusting for age, BMI, diabetes mellitus, and chronic kidney disease ($p=0.512$) (Fig. 4).

Discussion

In this study, we investigated the effects of statin therapy on liver transaminases and lipid profiles in patients with MASLD. Our findings indicate that statin use for >12 months did not lead to significant elevations in ALT or AST levels. Furthermore, we observed no significant differences in ALT or AST trends when comparing different statin types or doses, even after adjusting for potential confounders, including age, BMI, diabetes mellitus, hypertension, and chronic kidney disease.

MASLD is now recognized not only as the most common chronic liver disease worldwide but also as an important cardiovascular risk factor. The cardiovascular burden among patients with MASLD is well established. Previous studies have shown that MASLD is independently associated with subclinical atherosclerosis, electrocardiographic abnormalities, and an increased prevalence of ischemic heart disease, cerebrovascular disease, and peripheral vascular disease.[10,11] For example, a large study in Taiwan involving over 2,000 middle-aged male workers found that individuals with ultrasound-confirmed MASLD were more likely to exhibit ischemic changes on resting

ECG, independent of traditional risk factors such as lipid profiles and smoking status.[12] Similarly, Targher et al.[13] demonstrated that patients with type 2 diabetes mellitus and MASLD had a higher prevalence of coronary and cerebrovascular diseases than diabetic patients without MASLD.

Despite the strong association between MASLD and cardiovascular disease, statins, which are widely proven to reduce cardiovascular morbidity and mortality, are often under-prescribed in this population.[6] This is largely due to concerns regarding potential hepatotoxicity.

In a large-scale cohort study, the incidence rate of statin-induced liver injury was rare and was estimated to be 13–15 events per 100,000 person-years.[14] In our study, three patients had transient elevation of liver transaminases, which improved over time; these transient elevations were not statistically significant. We did not observe any significant statin-induced liver injury, which could be partly due to our relatively small sample size. However, it is important to note that our findings contribute to the growing body of evidence indicating that statins do not adversely affect liver transaminases in patients with MASLD, supporting their use in this group of patients.

These results are consistent with emerging evidence suggesting that statins are safe for use in patients with MASLD. Several studies have shown that statins do not increase the risk of hepatotoxicity in this population and may even have potential hepatoprotective effects by improving steatosis and reducing inflammation.[15,16] Our findings reinforce that statins should not be withheld from patients with MASLD when lipid-lowering therapy is indicated, such as in patients at high risk of cardiovascular disease.[17]

However, the effectiveness of statins in treating metabolic dysfunction-associated steatohepatitis (MASH) remains unclear, as no large randomized controlled trials have evaluated their impact on histological outcomes.[9]

Although we noted a trend in which higher doses and higher-potency statins (e.g., atorvastatin 40–80 mg and rosuvastatin 20–40 mg) were associated with lower LDL-C levels, these differences did not achieve statistical significance in our sample. This may be attributed to the limited sample sizes in certain statin subgroups and variability in patient adherence or lifestyle factors, which were not controlled for in this retrospective analysis. Nevertheless, our observations align with other pharmacological data showing a dose-dependent LDL-lowering effect of statins.[18]

Limitations

A major strength of our study is the real-world setting involving patients with multiple comorbidities representative of those observed in clinical practice. The 12-month follow-up and multivariate adjustment for key confounders (age, BMI, diabetes mellitus, hypertension, chronic kidney disease, and baseline liver transaminase levels) enhanced the validity of our findings.

However, our study had some limitations. The relatively small sample size, particularly within certain statin dose groups, reduced the power to detect small differences in outcomes. Liver histology was not available; therefore, we could not assess the impact of statins on fibrosis or steatosis progression. In addition, transient elastography was only performed for a small number of patients in this study, and the degree of fibrosis could not be determined for other patients.

Since this was a retrospective study conducted in the outpatient clinics of a single center, there is a possibility of selection bias. This could lead to the overrepresentation of patients who were more adherent to follow-up or more engaged in care. Unmeasured confounders (e.g., lifestyle factors such as diet, exercise, and alcohol intake below the exclusion threshold) could have influenced liver transaminases or lipid profiles independently of statin use. Medication adherence was not directly measured; therefore, statin exposure may have been overestimated if prescriptions were not consistently taken. We acknowledge this in the study limitations and recommend future prospective studies to assess adherence.

Conclusion

Our study provides further evidence that statin therapy in patients with MASLD is not associated with significant liver transaminase elevation or hepatotoxicity over 12 months of treatment. Statins of varying types and doses did not result in significant differences in ALT or AST levels. Trends in LDL-C reduction with higher-potency statins were observed, but were not statistically significant in this cohort. Statins are safe for use in patients with MASLD who meet the criteria for lipid-lowering therapy. Further studies are warranted to explore the long-term hepatic effects of statins in patients with MASH by measuring histological outcomes.

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Table 1. Baseline characteristics of the study participants

Parameter	Mean ± SD	Range
Age (years)	53.97±13.66	27–86
Weight (kg)	85.21±25.43	40.0–186.0
BMI (kg/m²)	34.26±12.40	10.6–72.5
ALT (U/L)	31.49±19.11	6–107
AST (U/L)	29.96 ±14.32	8–83
LDL-C (mmol/L)	2.89±1.14	1.24–6.37
Total cholesterol (mmol/L)	4.97±1.41	2.29–9.55
HDL-C (mmol/L)	1.25±0.28	0.45–1.89
Triglycerides (mmol/L)	1.80±0.94	0.67–5.59
HbA1c (%)	8.79±2.45	5.3–15.6
BMI: Body mass index; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; LDL: Low-density lipoprotein; HbA1c: Hemoglobin A1c.		

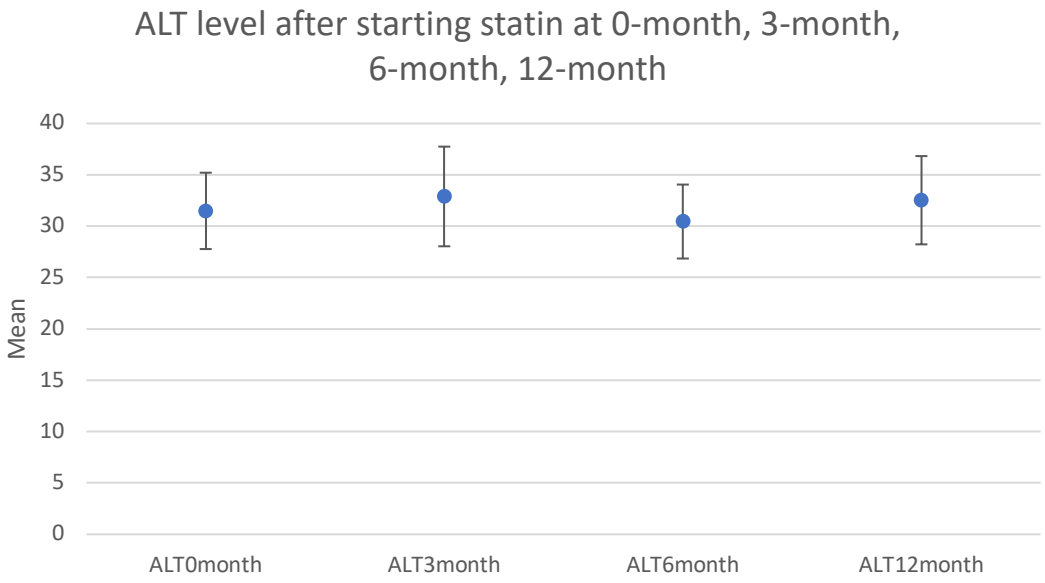

Figure 1. ALT level after starting statin at 0-month, 3-month, 6-month, 12-month
ALT: Alanine aminotransferase.

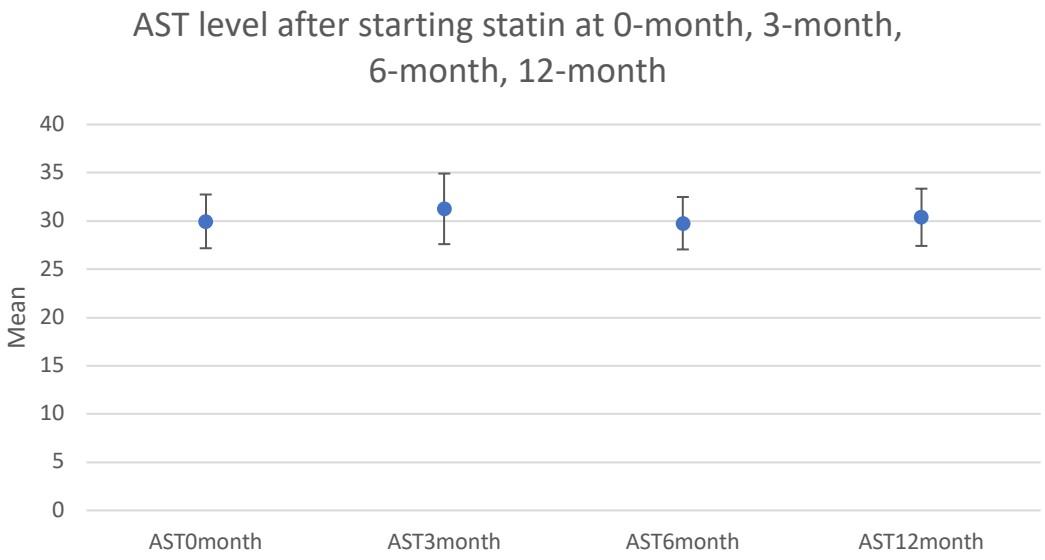

Figure 2. AST level after starting statin at 0-month, 3-month, 6-month, 12-month
AST: Aspartate aminotransferase.

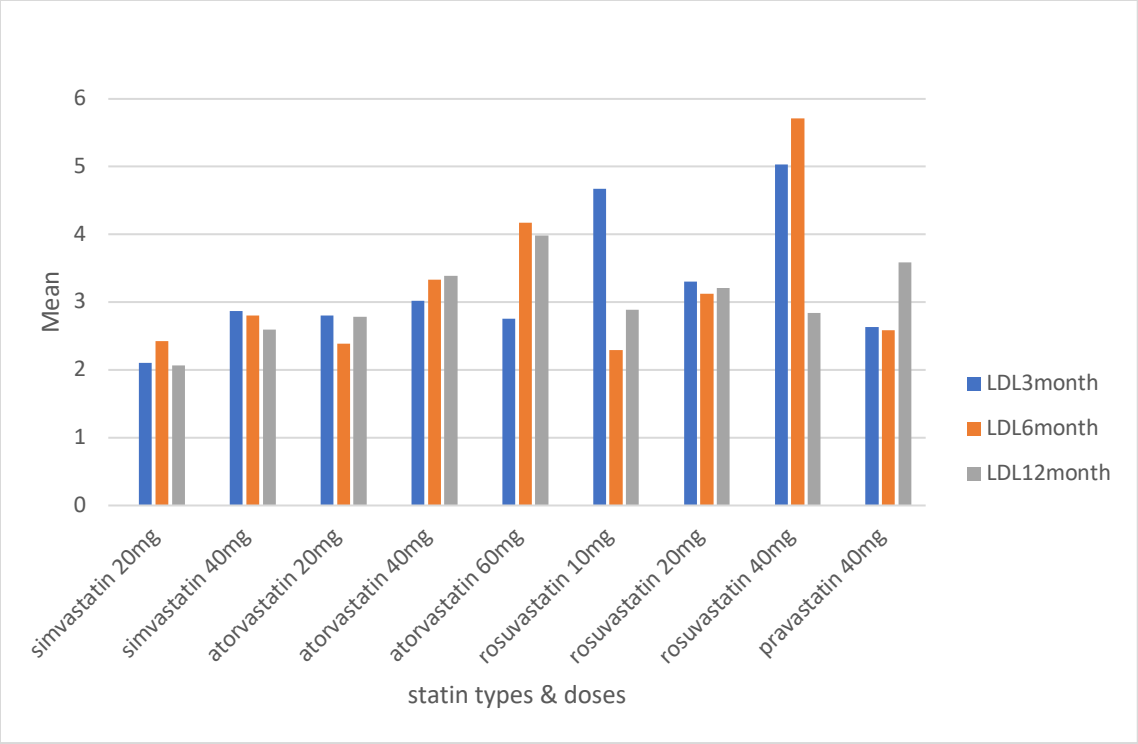

Figure 3. LDL level at 3, 6, 12-month post statin initiation among various statin types and doses
LDL: Low-density lipoprotein.

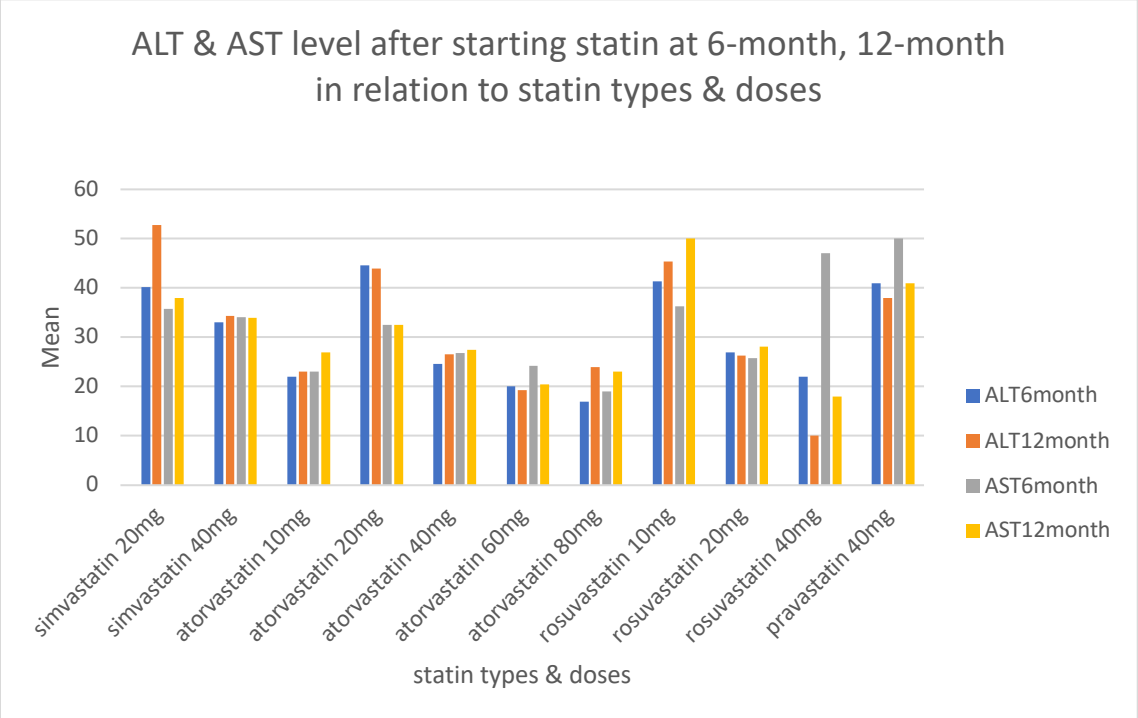

Figure 4. ALT & AST level after starting statin at 6-month, 12-month in relation to statin types & doses
ALT: Alanine aminotransferase; AST: Aspartate aminotransferase.