META-ANALYSIS

Statin liver safety in non-alcoholic fatty liver disease: A systematic review and metanalysis

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Aims: Statin liver safety in non-alcoholic fatty liver disease (NAFLD) patients is not well defined. We analysed differences in liver function tests, including alanine transaminase aminotransferase (ALT), aspartate transaminase (AST) and gamma-glutamyl transpeptidase (GGT) in NAFLD patients treated or not treated with statins.

Methods: We performed a systematic review of MEDLINE via PubMed and EMBASE databases and metanalysis of clinical studies investigating levels of ALT, AST and GGT in NAFLD according to statin treatment. Mean difference (MD) and percentage MD were calculated between the two groups.

Results: We included 22 studies with 2345 NAFLD patients. Overall, 16 were before-after interventional, five were cross-sectional and one was combined cross-sectional/interventional study. In all interventional studies, except one, patients had raised ALT, AST and GGT at baseline. Interventional studies showed reduced ALT values with an MD reduction of −27.2 U/L (95% CI −35.25/−19.15) and a percentage MD reduction of −35.41% (95% CI −44.78/−26.04). Also, AST values were reduced after statin treatment in interventional studies with an MD of −18.82 U/L (95% CI −25.63/−12.02) (percentage −31.78%, 95% CI −41.45/ −22.11). Similarly, GGT levels were reduced after statin treatment with an MD of −19.93 U/L (95% CI −27.10/−12.77) (percentage −25.57%, 95% CI −35.18/ −15.97). Cross-sectional studies showed no difference in AST and GGT values between patients treated with and without statins.

Conclusion: In interventional studies, ALT, AST and GGT were reduced after statin treatment with a percentage mean difference of −35.41%, −31.78% and −25.57%, respectively, while observational studies showed a null effect, suggesting liver safety of statins in NAFLD patients.

KEYWORDS
ALT, AST, GGT, liver, NAFLD, safety, statins

1 | INTRODUCTION

The prevalence of non-alcoholic fatty liver disease (NAFLD) is continuously increasing, especially in Western countries[1] and it is expected to become the leading cause of liver transplantation.[2]

Patients with NAFLD are frequently characterized by the presence of cardio-metabolic disorders, the most frequent including impaired fasting glucose/diabetes, overweight/obesity and dyslipidaemia. These conditions define the so-called metabolic syndrome (MetS), of which NAFLD has long been regarded as the hepatic manifestation.[3] The presence of MetS increases cardiovascular risk in NAFLD patients.[4–6] In particular, the presence of an atherogenic dyslipidaemia, with elevated levels of triglyceride-rich lipoproteins and low levels of high-density lipoprotein cholesterol (HDL-C), is a strong risk factor for cardiovascular events.[7,8]

For this reason, NAFLD patients are often prescribed statins, which are associated with a substantial reduction in cardiovascular mortality due to several cardio-metabolic diseases.[9–11]

Statin treatment is usually safe and well tolerated by patients.[12,13] However, a minority of patients may experience side effects, such as myalgia rarely associated to rhabdomyolysis, and less frequently, elevation of liver enzymes.[14,15] Thus, transient asymptomatic elevations in aminotransferases could occur in 0.1–3% of patients, while fulminant hepatic failure is an extremely rare event (2 in 1 million of treated patients).[16] The discontinuation rate of patients due to these effects is variable, ranging from 1.8%[17] up to 12%,[18] which is notably associated with a subsequent increased risk of cardiovascular complications.[19]

The prescription of statins may be challenging in patients with chronic liver disease, especially when an elevation of liver enzymes is present.[20,21] Despite a general agreement that statins may be safely prescribed to NAFLD patients,[22] firm data supporting this recommendation are still lacking.

We performed a systematic review and metanalysis of clinical studies investigating the safety of statin treatment in NAFLD patients. In particular, the effect of statin therapy on alanine aminotransferase (ALT), aspartate transaminase (AST) and gamma-glutamyl transferase (GGT) levels was analysed.

2 | METHODS

2.1 | Selection of studies for inclusion

We conducted a systematic review of literature searching MEDLINE via PubMed and EMBASE databases for observational, randomized (RCT) and before-after studies, using a combination of the following MESH terms and keywords for PubMed: "NAFLD", "hydroxymethylglutaryl-CoA reductase inhibitors", "statins", "pitavastatin", "lovastatin", "fluvastatin", "simvastatin", "atorvastatin", "transaminases", "aspartate aminotransferases", "alanine transaminase", "gamma-glutamyltransferase", "AST", "ALT", "GGT", "liver enzymes" and "liver function tests".

The search strategy on EMBASE included the following Emtree and keywords "hydroxymethylglutaryl coenzyme a reductase inhibitor" AND "nonalcoholic fatty liver" AND "human"/de AND ("article"/it OR "article in press"/it) AND "clinical article"/de, resulting in the retrieval of 21 articles.

The last search was run on 24 April 2020. There was no time restriction for the inclusion of articles.

Figure S1 in the Supporting Information reports the study selection process, which was performed according to the PRISMA guidelines.

2.2 | Types of studies for inclusion

We included all clinical articles reporting liver transaminase values before and after statin administration and case–control studies reporting liver transaminase values in both case and control groups. We included only journal articles in English with full text available.

Studies including 15 or fewer patients were excluded. We excluded case reports/series, editorials/comments, letters, reviews and metanalyses, and experimental studies. Finally, we excluded interventional studies testing the effect of statins in association with other drugs. When a study reported data derived from both statins alone and statins combined with other drugs, only data from the statins alone arm were included in the metanalysis. No RCTs were found. We included 22 studies (16 before-after studies, five cross-sectional studies and one study reporting both cross-sectional and interventional data).

2.3 | Study selection

Two physicians (F.B. and D.P.) independently screened the titles and abstracts of manuscripts identified through the database searches to identify studies potentially eligible for further assessment. A third physician (M.D.B.) reviewed eligible studies for appropriateness and completeness. The study selection was performed in multiple phases. In the first phase, potentially relevant studies were obtained by combined searches of electronic databases using the selected abovementioned keywords. Then, studies not in English, not involving humans or not addressing the study question were excluded. In the second phase, studies were reviewed and selected according to the inclusion and exclusion criteria. Finally, F.B. and D.P. independently collected data from the reports.

2.4 | Risk of bias

The risk of bias was estimated by "Risk of Bias Assessment tool for Non-randomized Studies (RoBANS)" (https://abstracts.cochrane.org/2011-madrid/risk-bias-assessment-tool-non-randomized-studies-robans-development-and-validation-new), including six domains: item 1: selection of participants (selection bias); item 2: confounding variables

(confounding bias); item 3: measurement of intervention/exposure (performance bias); item 4: blinding of outcome assessment (detection bias); item 5: incomplete outcome data (attrition bias); and item 6: selective outcome reporting (reporting bias).

2.5 | Outcomes

The endpoints considered were the mean difference and percentual mean differences in AST, ALT and GGT levels between patients using or not using statins.

2.6 | Data analysis

The continuous variables were reported as means with standard deviations (SDs). When data were reported as median and interquartile range (IQR), means and SDs were approximately estimated by means of the method described by Wan et al.[23] Mean differences, percentage mean differences, and their standard error were calculated for cross-sectional studies. The delta method was used to calculate the asymptotic standard error of the percentage mean difference.[24] In before-after studies, the pre/post-intervention means were transformed to a mean difference and percentage mean difference; standard deviations were imputed according to Marinho et al.,[25] following the recommendations in the *Cochrane Handbook for Systematic Reviews of Interventions*.

Pooled estimates were obtained by means of a random-effects model. Results are shown in forest plots, with 95% confidence intervals (Cis). A subgroup analysis was performed after stratifying by study design (interventional *vs.* observational). Heterogeneity was assessed with the Q-statistic and Moran's I^2 and interpreted qualitatively as low (25–50%), moderate (50–75%) or high (75–100%).

All analyses were performed using the R (R Development Core Team) software version 3.6.1, with "rmeta" and "metafor" packages. All *P*-values were two-tailed, and the statistical significance level was set at .05.

3 | RESULTS

3.1 | Characteristics of included studies

Table 1 summarizes study characteristics, diagnosis of NAFLD and indication for statin treatment. No RCTs were found. We included 22 studies, 16 before-after studies, five cross-sectional and one study, reporting both baseline and interventional data (Table 1).

A total of 2345 NAFLD patients was included, 1000 from interventional and 1345 from observational studies (Table 1). In eight out of 16 interventional studies, diagnosis of NAFLD was biopsy-proven, in four studies it was based on imaging findings, in four studies by raised serum liver enzymes, and in two studies by combined liver biopsy, ultrasound and imaging or liver enzymes (Table 1).

The mean age of patients ranged from 43 to 60 years, and the proportion of women ranged from 0.0% to ∼60% (Table 1). The type of statin was atorvastatin 10–20 mg in ten studies, pitavastatin 2–4 mg in two studies, rosuvastatin 2.5 and 10 mg in two studies, two studies used simvastatin 20 mg, and two studies more than one statin. The duration of intervention ranged from 3 to 24 months.

3.2 | Risk of bias of the included studies

Risk of bias for before-after and cross-sectional studies is reported in Figure 1. All observational studies were deemed to have an overall high risk of bias, primarily driven by lack of blinding of outcome assessment (detection bias), and bias in selection of the reported result (reporting bias).

3.3 | ALT, AST and GGT

All patients included in the interventional studies had a mean value of ALT >40 U/L, AST > 35 U/L and GGT > 50 U/L, except for Maroni[35] (see Table 2).

In patients treated with statins, the global mean difference of ALT values was −21.82 U/L (95% CI −29.06/−14.58) with a percentage mean difference reduction of −29.38% (95% CI −37.81/−20.95). This difference was most evident in interventional studies showing an ALT mean reduction of −27.2 U/L (95% CI −35.25/−19.15) and a percentage mean difference reduction of −35.41% (95% CI −44.78/−26.04), while it was less significant in cross-sectional ones −5.85 U/L (95% CI −12.19/0.49) (percentage −12.18 U/L, 95% CI −21.60/−2.75) (Figure 2).

The global mean difference of AST values in patients on statins was −15.25 U/L (95% CI −21.40/−9.11) with a percentual reduction of −25.91% (95% CI −35.17/−16.65). This difference was significant in interventional studies −18.82 U/L (95% CI −25.63/−12.02) (percentage −31.78%, 95% CI −41.45/−22.11) but not in cross-sectional ones (Figure 3).

Regarding GGT, in patients treated with statins, the global mean difference was −15.78 U/L (95% CI −23.16/−8.40) with a percentual reduction of −20.29% (95% CI −30.24/−10.35). This difference was most evident in interventional studies −19.93 U/L (95% CI −27.10/−12.77) (percentage −25.57%, 95% CI −35.18/−15.97) while it was non-significant in observational ones (Figure 4).

4 | DISCUSSION

This metanalysis provides pooled data on the safety of statin treatment in patients with NAFLD. Our results show that NAFLD patients prescribed statins in before-after interventional studies had a reduction of baseline values for all safety outcomes analysed, such as ALT, AST and GGT. This evidence is even more important considering that

TABLE 1 Characteristics of studies included in the metanalysis

Year/Author	Study design	NAFLD diagnosis	Setting/indication to statin	Type and dose of statin	Age (y)	Women (%)	Total patients
Panel A: Observational studies							
2003 Kiyici[26]	Before–after interventional study	Liver biopsy	NAFLD treatment; ALT elevation	Atorvastatin 10 mg	50.2	55.56	27
2004 Hatzitolios[27]	Before–after interventional study	Liver biopsy, ultrasound and CT scan	Mixed dyslipidaemia (Fredrickson type IIb); ALT elevation	Atorvastatin 20 mg	53.0	53.57	28
2006 Antonopoulos[28]	Before–after interventional study	Liver ultrasound	Hyperlipidaemic patients	Rosuvastatin 10 mg	56.0	28.30	23
2006 Athyros[29]	Before–after interventional study	Liver ultrasound	Non-diabetic	Atorvastatin 20 mg	60.0	35.00	63
2008 Hyogo[30]	Before–after interventional study	Liver biopsy	-	Atorvastatin 10 mg	52.5	35.48	31
2009 Abel[31]	Before–after interventional study	ALT >40 U/L or AST > 37 U/L in men; ALT or AST > 31 U/L in women	Well-controlled diabetes	Simvastatin 20 mg	58.6	46.15	26
2010 Kimura[32]	Before–after interventional study	Liver biopsy	Dyslipidaemia	Atorvastatin 10 mg	50.2	32.56	43
2010 GREACE[33]	Post-hoc analysis RCT	ALT >45 and <135 U/L or AST > 37 and <101 U/L	Secondary prevention	Atorvastatin 10 to 80 mg	60	21	227
2011 Hyogo[34]	Before–after interventional study	Liver biopsy	-	Pitavastatin 2 mg	50.6	55.00	20
2011 Maroni[35]	Retrospective	Liver ultrasound and abnormal liver enzyme values (AST ≥ 33 U/L and/or ALT ≥33 U/L; and/or GGT ≥ 49 U/L).	Dyslipidaemia	Atorvastatin (n = 19) Simvastatin (n = 11) Rosuvastatin (n = 10) Fluvastatin (n = 2) Lovastatin (n = 1)	54.5	30.23	43
2012 Han-1[36]	Before–after interventional study	ALT elevation ≥1.25 times and ≤2.5 times 40 IU/L	Hyperlipidaemic patients	Atorvastatin 10–20 mg	54.9	46.03	85
2012 Han-2[36]	Before–after interventional study	ALT elevation ≥1.25 times and ≤2.5 times 40 IU/L	Hyperlipidaemic patients	Pitavastatin 2–4 mg	55.8	46.97	88
2012 Hyogo[37]	Before–after interventional study	Liver biopsy	Hyperlipidaemic patients	Atorvastatin 10 mg	50.0	33.30	42

TABLE 1 (Continued)

Panel A: Observational studies

Year/Author	Study design	NAFLD diagnosis	Setting/indication to statin	Type and dose of statin	Age (y)	Women (%)	Total patients
2012 Nakahara[38]	Before-after interventional study	Liver biopsy	Hyperlipidaemic patients	Rosuvastatin 2.5 mg	46.3	57.89	19
2015 Derosa[39]	Before-after interventional study	Liver ultrasound	Hypertensive normo-cholesterolemic patients	Simvastatin 20 mg	-	49.6	139
2017 Bril[40]	Before-after interventional study	Liver biopsy	Prediabetes/diabetes	Simvastatin (67%) Rosuvastatin (21%) Atorvastatin and Pravastatin (12%)	-	-	19
2017 Cioboata[41]	Before-after interventional study	Liver biopsy	Hyperlipidaemic patients	Atorvastatin 20 mg	-	-	57
2018 Hadzi-Petrushev[42]	Before-after interventional study	Liver ultrasound	-	Atorvastatin 20 mg	43.0	0.00	20

Panel B: Cross-sectional studies

Year/Author	NAFLD diagnosis	Setting/indication to statin	Type and dose of statin	Age (y)	Women (%)	Total patients	On statin (n)	Not on statin (n)
2006 Dallas Heart Study[43]	MR spectroscopy	General population screened for the presence of liver steatosis	Simvastatin (48%) Atorvastatin (32%) Pravastatin (12%) Fluvastatin (6%) Cerivastatin (1%) Lovastatin (1%)	45.7	-	638	54	584
2007 Ekstedt[44]	Liver biopsy	Chronic elevation of ALT and AST	Simvastatin (n = 11) Atorvastatin (n = 5) Pravastatin (n = 1)	60.7	29.41	68	17	51
2016 Nascimbeni[45]	Liver biopsy	Diabetes	Atorvastatin (n = 82) Rosuvastatin (n = 24) Simvastatin (n = 23) Pravastatin (n = 10) Fluvastatin (n = 3) Statin + ezetimibe (n = 10)	53.0	60.00	343	154	192
2017 Bril[40]	Liver biopsy	Prediabetes/diabetes	8% on high-intensity and 79% on moderate intensity therapy.	50.6	29.70	101	38	63
2017 Del Ben[21]	Liver ultrasound	ASCVD	Not reported	59.9	35.29	442	230	212
2020 Khoo[46]	Liver ultrasound/CT/MR	NAFLD	Simvastatin (68.6%) Atorvastatin (21.6%) Rosuvastatin (8.6%) Lovastatin (0.5%) Pravastatin (0.5%)	54.3	47.90	428	185	243

ALT: alanine aminotransferase; ASCVD: atherosclerotic cardiovascular disease; AST: aspartate transaminase; CT: computed tomography; GGT: gamma-glutamyl transferase; MR: magnetic resonance; NAFLD: non-alcoholic fatty liver disease.

Before-After Sudies						
Author (year)	Item 1	Item 2	Item 3	Item 4	Item 5	Item 6
Kiyici, 2003	🟡	🟢	🟢	🔴	🟢	🟡
Hatzitollos, 2004	🟢	🟢	🟢	🟡	🟢	🔴
Antonopulos, 2006	🟡	🟢	🟢	🔴	🟢	🟡
Athyros, 2006	🟢	🟢	🟢	🟢	🟢	🟢
Hyogo, 2008	🟡	🟢	🟢	🔴	🟢	🟡
Abel, 2009	🟡	🟢	🟢	🟢	🟢	🔴
Kimura, 2010	🟡	🟢	🟢	🔴	🟢	🟡
GREACE, 2010	🟢	🟢	🟢	🟢	🟢	🟢
Hyogo, 2011	🟡	🟢	🟢	🟡	🟢	🟡
Maroni, 2011	🔴	🟢	🟢	🟢	🟡	🟡
Han, 2012	🟢	🟢	🟢	🟡	🟢	🟢
Hyogo, 2012	🟡	🟢	🟢	🟡	🟢	🟡
Nakahara, 2012	🟡	🟢	🟢	🟡	🔴	🔴
Derosa, 2015	🟢	🟢	🟢	🟢	🟢	🟢
Bril, 2017	🟡	🟢	🟢	🟢	🟢	🔴
Cioboată, 2017	🟡	🟢	🟢	🟡	🟢	🔴
Hadzi-Petrushev, 2018	🟡	🟢	🟢	🟢	🟢	🔴
Cross sectional Studies						
Author (year)	Item 1	Item 2	Item 3	Item 4	Item 5	Item 6
Dallas Heart Study, 2006	🟢	🔴	🔴	🟢	🟢	🟢
Ekstedt, 2007	🟢	🟢	🟢	🟡	🔴	🟡
Nascimbeni, 2016	🟢	🟢	🟢	🟡	🟢	🟡
Bril, 2017	🟡	🟢	🟢	🟢	🟢	🔴
Del Ben, 2017	🟢	🟢	🟢	🟢	🟡	🟡
Khoo, 2020	🟢	🟢	🟢	🟡	🟡	🟡

FIGURE 1 The Risk of Bias Assessment tool for Non-randomized Studies (RoBANS) (red: high risk; yellow: unclear risk; green: low risk)

almost all patients treated with statins had baseline raised levels of liver enzymes, reinforcing the evidence that statin therapy may be safe in NAFLD patients also when liver damage is almost clinically evident.

Our results add to previous evidence from a retrospective study including 4024 hyperlipidaemic patients which showed no excess in the risk of hepatotoxicity in statin-treated patients with elevated liver enzymes.[47] Furthermore, data on more than 11 000 patients from randomized clinical trials showed that statins, in particular atorvastatin, improved NAFLD/NASH and reduced cardiovascular events twice as much as in those with normal liver function.[48] Finally, in 2013, a Cochrane meta-analysis, including only two small RCTs, showed a reduction in liver enzymes by statin use.[20]

Our data indicate that clinicians should not be discouraged from prescribing statins to NAFLD patients, even when a mild elevation of serum liver enzymes is present. Indeed, a clinically significant drug-induced liver injury (DILI) by statins is very rare. Björnsson et al.,[49] extracting data from the Swedish Adverse Reactions Advisory Committee, found that, in the period 1988–2010, only one patient prescribed with statin required a liver transplantation and two patients died as a consequence of a DILI. In addition, the estimated incidence of DILI (defined as aminotransferases more than five times the upper limit normal value [ULN], and/or alkaline phosphatase more than twice the ULN or bilirubin more than twice the ULN) was 1.6×10^{-4} person-years. The majority of DILIs induced by statins are a consequence of idiosyncratic effect. However, as most of the statins are metabolized by CYP3A4, the concomitant use of a drug inhibiting CYP3A4 could elevate serum concentration of atorvastatin, simvastatin and lovastatin and may favour liver enzyme elevation.[50,51] Furthermore, physicians should perform a laboratory and instrumental work-up to exclude other possible causes responsible for raised serum liver enzymes.[52]

The mechanisms responsible for the beneficial association between statin use and reduced liver enzymes may be several. The reduction of hepatic lipid content induced by statins might result in less hepatic inflammation and oxidative stress, with lower lipidic per-oxidation and ox-LDL formation, which are increased in NAFLD patients and potentially contributing to disease progression.[53] In an experimental study, atorvastatin was associated with an increased activity of some antioxidant enzymes, such as superoxide dismutase and glutathione peroxidase.[54] In addition, NAFLD patients with dyslipidaemia prescribed atorvastatin showed increased levels of the anti-inflammatory adiponectin with a reduction of tumour necrosis factor-alpha.[30]

Statins may also exert a direct effect on the liver, as suggested by experimental studies showing a modulation of liver fibrosis and inflammation by statins.[55] All these mechanisms may account for the lower risk of hepatic decompensation and hepatocellular carcinoma described in liver disease patients on statins.[56] Finally, discontinuation of statin treatment resulted in an increased cardiovascular risk in several clinical settings,[57] suggesting that the benefits of continuing statin treatment outweigh putative risks.

Unfortunately, there was too little available data to investigate whether liver enzyme reduction paralleled cholesterol lowering or if this effect was related to a direct/pleiotropic effect of statins. Furthermore, we also hypothesized that liver enzyme improvement might be related to body weight loss. However, available data do not support this hypothesis, as in only one interventional study did BMI improve after statin therapy,[29] and in all other studies no BMI change after statin therapy was reported.

TABLE 2 Liver function tests before and after statin treatment in interventional studies (Panel A) and in patients taking or not taking statins in cross-sectional studies (Panel B)

Year/Author	ALT before statin	ALT after statin	AST before statin	AST after statin	GGT before statin	GGT after statin
Panel A. Interventional studies						
2003 Kiyici[26]	81.8	44.8	45.4	32.1	64.2	37.2
2004 Hatzitolios[27]	115.0	76.6	68.0	46.0	98.0	33.0
2006 Antonopoulos[28]	90.9	28.30	38.0	30.4	52.0	39.7
2006 Athyros[29]	54.0	32.0	38.0	25.0	52.0	33.0
2008 Hyogo[30]	89.4	35.9	51.1	25.8	87.0	51.0
2009 Abel[31]	66.6	29.5	51.1	25.8	87.0	51.0
2010 Kimura[32]	61.8	56.2	48.9	33.1	90.3	65.0
2010 GREACE[33]	57.0	37.0	49.0	26.0	70.0	38.0
2011 Hyogo[34]	102.1	68.2	62.6	41.8	94.5	59.6
2011 Maroni[35]	37.6	44.7	26.3	34.3	59.0	86.5
2012 Han-1[36]	58.7	53.3	44.5	41.5	79.9	68.8
2012 Han-2[36]	56.4	51.3	39.5	39.0	75.7	64.8
2012 Hyogo[37]	89.0	56.6	48.0	33.0	90.4	65.1
2012 Nakahara[38]	68.7	50.3	40.1	33.8	78.7	61.4
2015 Derosa-1[39]	58.0	36.0	36.0	38.0	-	-
2015 Derosa-2[39]	55.0	38.0	58.0	39.0	-	-
2017 Bril[40]	66.0	38.0	48.0	31.00	-	-
2017 Cioboată[41]	82.6	43.6	83.1	43.3	53.0	43.1
2018 Hadzi-Petrushev[42]	41.9	30.8	42.7	24.2	-	-
Panel B. Cross-sectional studies						
	ALT on statin	ALT not on statin	AST on statin	AST not on statin	GGT on statin	GGT not on statin
2006 Dallas Heart Study[43]	30.0	25.0	-	-	-	-
2007 Ekstedt[44]	61.0	63.0	35.0	36.0	-	-
2016 Nascimbeni[45]	42.0	39.0	32.0	31.0	50.0	54.0
2017 Bril[40]	75.0	57.0	53.0	43.0	-	-
2017 Del Ben[21]	34.5	29.0	25.8	23.9	44.5	43.8
2020 Khoo[46]	44.3	46.6	31.2	36.8	45.8	54.5

All values expressed as U/L.
ALT: alanine aminotransferase; AST: aspartate transaminase; GGT: gamma-glutamyl transferase.
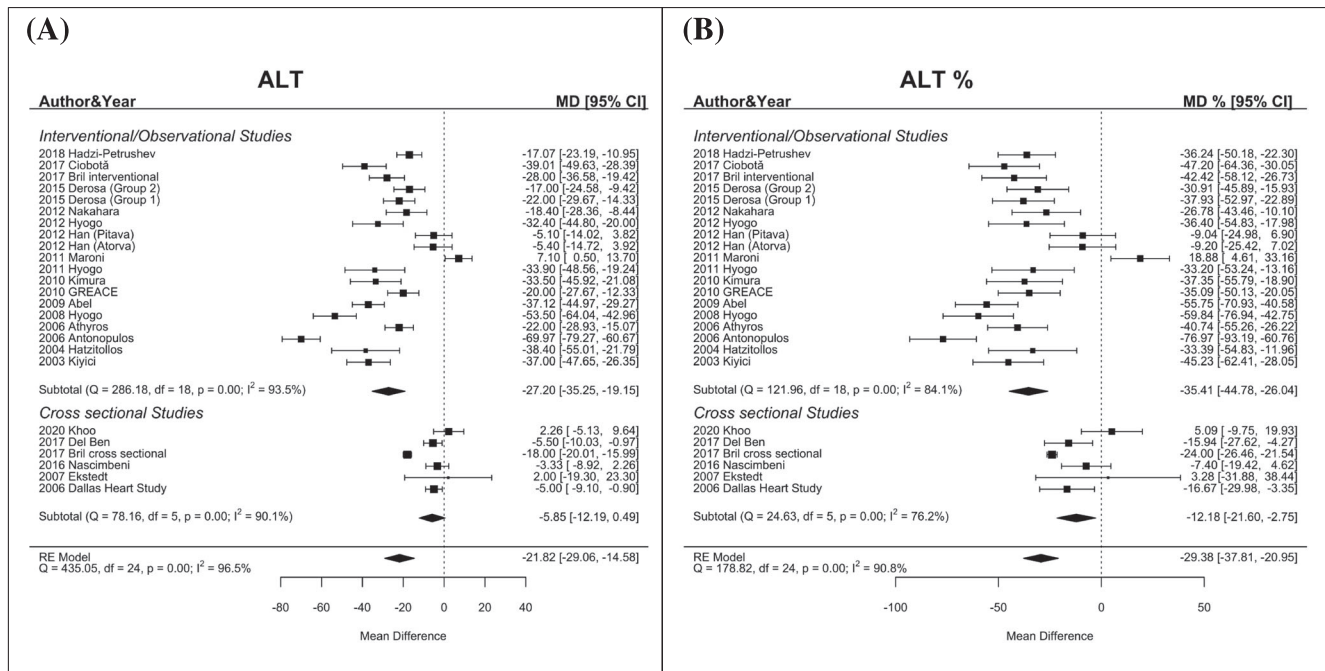
FIGURE 2 Changes in ALT levels (mean difference, Panel A; percentual difference, Panel B) according to statin treatment
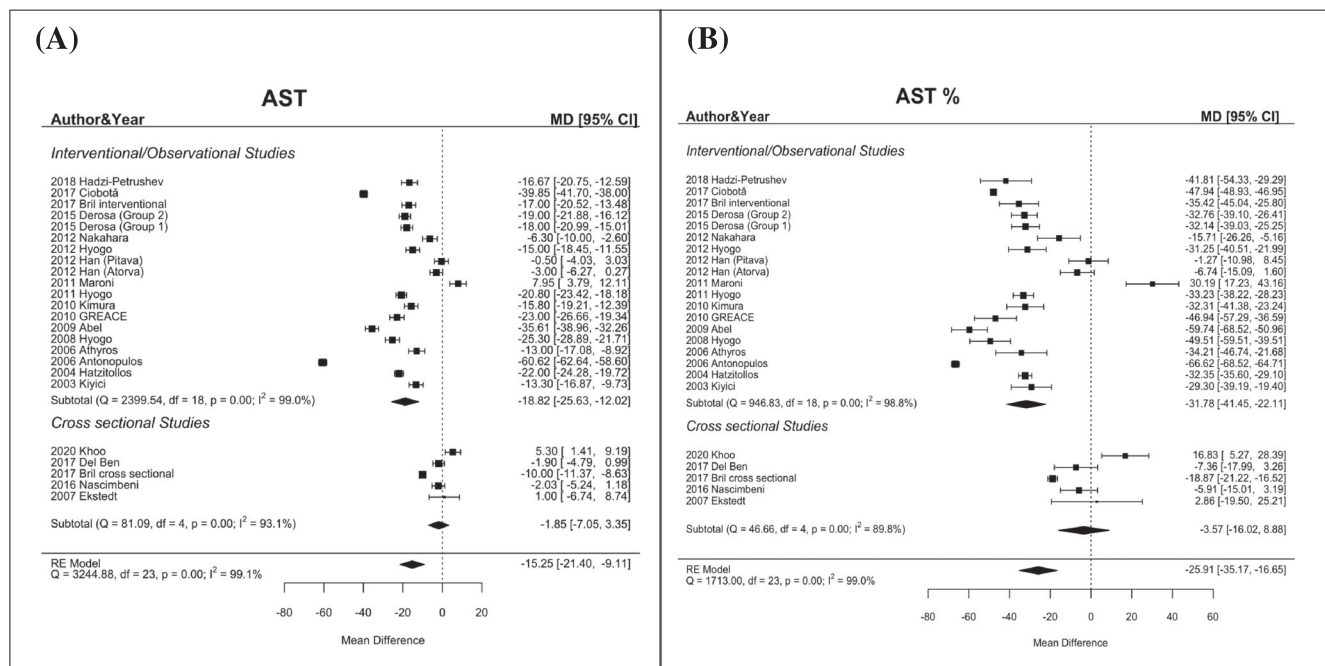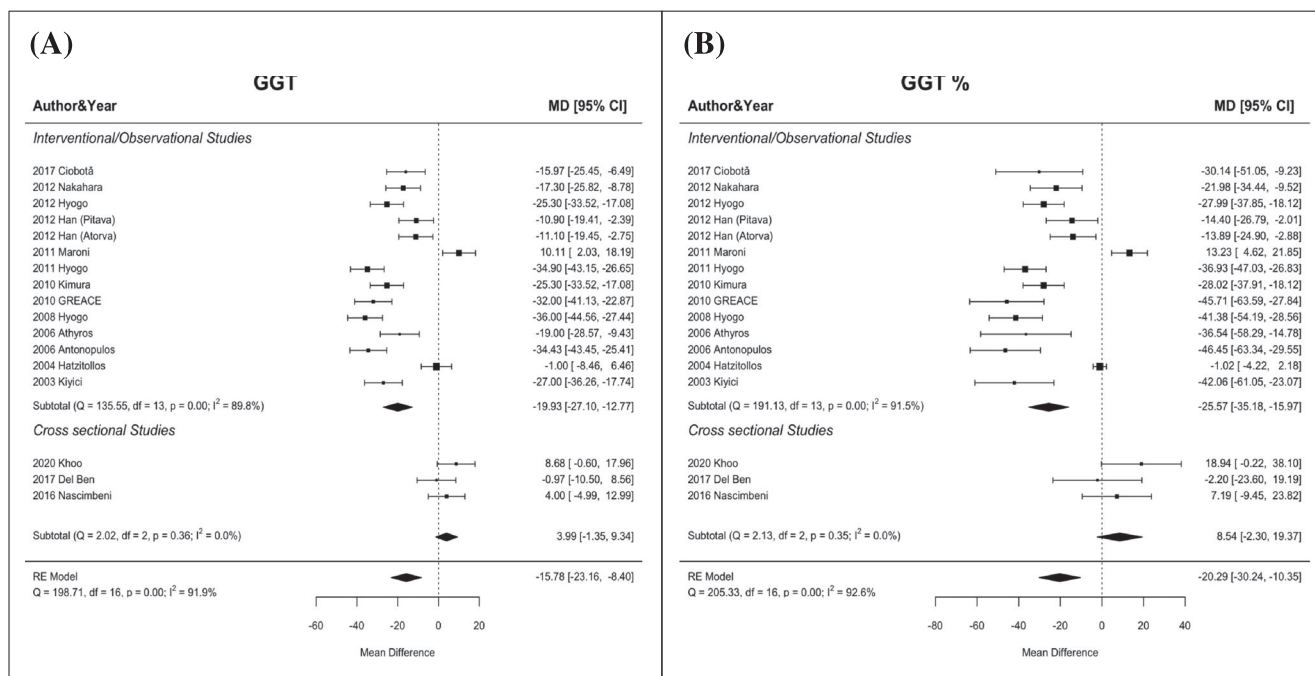

FIGURE 3 Changes in AST levels (mean difference, Panel A; percentual difference, Panel B) according to statin treatment

4.1 | Strengths and limitations

In the majority of interventional studies, NAFLD was diagnosed by liver biopsy or second-level imaging techniques such as CT or MR spectroscopy, giving robustness to their results. Conversely, the diagnosis of NAFLD was more heterogeneous in observational studies, ranging from liver ultrasound to biochemical variables (liver enzymes, FLI). This is mainly due to the impossibility of performing liver biopsy on large populations and may account for the different result between the two types of studies. A limitation of this analysis lies in the lack of data from RCTs, as all interventional studies were unblinded single-arm interventions or post-hoc analysis of RCTs. Furthermore, despite

FIGURE 4 Changes in GGT levels (mean difference, Panel A; percentual difference, Panel B) according to statin treatment

most studies used atorvastatin, we cannot draw any conclusions on the effect of different statins on liver enzymes. In addition, no study investigated the effect of very high-intensity statins (i.e., atorvastatin 40 mg or rosuvastatin 20 mg) or directly compared the effect of different statins. Finally, our data should be interpreted with caution given the high heterogeneity found among studies.

5 | CONCLUSIONS

Our analysis shows that NAFLD patients prescribed statins have a significant reduction in liver enzymes. These data support the safe use of statins in these patients.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.