Research Square

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Clinical and Histologic Characteristics and Longitudinal Liver Test Changes According to GLP1R rs10305420 Genotype in Biopsy-Proven MASLD With Type 2 Diabetes

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Research Article

Keywords: fibrosis, GLP1R, metabolic dysfunction-associated steatotic liver disease, pharmacogenetics, type 2 diabetes

Posted Date: October 18th, 2026

DOI: https://doi.org/10.21203/rs.3.rs-11184481/v1

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Abstract

Background

The clinical relevance of *GLP1R* rs10305420 in metabolic dysfunction-associated steatotic liver disease (MASLD) is uncertain. We evaluated associations with clinicopathological features and 12-month changes in alanine aminotransferase (ALT) and Fibrosis-4 (FIB-4) index during glucose-lowering therapy.

Methods

This retrospective study included 155 Japanese patients with type 2 diabetes and biopsy-proven MASLD. CT/TT genotypes were combined as T-allele carriers and compared with CC. Clinical and histologic multivariable logistic models assessed T-allele carriage; histologic variables were ordinal, with binary sensitivity analyses.

Results

The cohort comprised 109 CC, 41 CT, and 5 TT patients. T-allele carriers were less frequently male and had higher AST and FIB-4, different lobular inflammation grades, and more advanced fibrosis and at-risk MASH. In the clinical model, each 1-kg/m^2 increase in BMI was associated with lower odds of T-allele carriage (adjusted odds ratio [aOR], 0.89; 95% CI, 0.81–0.99), whereas higher AST (aOR per doubling, 2.00; 95% CI, 1.18–3.38) and at-risk MASH (aOR, 2.46; 95% CI, 1.01–6.02) were positively associated. In the histologic model, lobular inflammation (aOR per grade, 2.27; 95% CI, 1.15–4.49) and fibrosis stage (aOR per stage, 1.68; 95% CI, 1.11–2.53) were associated with T-allele carriage. Sensitivity analysis supported the association with advanced fibrosis but not high lobular inflammation. At 12 months, ALT decreased in CC, whereas FIB-4 increased in T-allele carriers; however, between-genotype differences and treatment-by-genotype interactions were nonsignificant.

Conclusions

GLP1R rs10305420 T-allele carriage was associated with lower BMI and more severe inflammatory and fibrotic histology. Longitudinal analyses did not establish a genotype-specific hepatic treatment response.

Introduction

Metabolic dysfunction-associated steatotic liver disease (MASLD) is highly prevalent among patients with type 2 diabetes and encompasses a broad spectrum of hepatic injury, from steatosis to metabolic dysfunction-associated steatohepatitis (MASH), progressive fibrosis, and cirrhosis. Glucagon-like peptide-1 receptor agonists (GLP-1RAs) address several metabolic drivers of MASLD through weight

loss and improved glycemic control. In the phase 3 ESSENCE trial, semaglutide improved both MASH resolution and fibrosis-related histologic outcomes in patients with noncirrhotic MASH and stage F2-F3 fibrosis.[1] Nevertheless, substantial interindividual variability remains in both metabolic and hepatic responses to GLP-1RA therapy.

Genetic variation in *GLP1R* may contribute to this heterogeneity. The rs10305420 variant is a missense variant in the *GLP1R* signal peptide that changes proline to leucine at amino acid 7 (p.Pro7Leu). A large genome-wide association study of 27,885 GLP-1 medication users identified the T allele as an efficacy allele, with an additional 0.641% reduction in body mass index and approximately 0.76 kg of additional weight loss per allele.[2] The investigators proposed that altered signal-peptide stability and receptor trafficking may contribute to the observed pharmacogenetic effect. Earlier smaller studies reported associations in the opposite direction, emphasizing the potential importance of drug type, disease context, ancestry, and sample size.[2, 3]

Whether rs10305420 is associated with the hepatic phenotype of MASLD or with changes in liver tests during glucose-lowering therapy remains unclear. This question is clinically relevant because lobular inflammation is a defining component of steatohepatitis and may influence serum aminotransferase levels. Moreover, an association between rs10305420 and liver-related treatment response could provide a biological link between pharmacogenetic variation in *GLP1R* and heterogeneity in hepatic outcomes.

We therefore examined the association of *GLP1R* rs10305420 with clinical and histologic features in patients with type 2 diabetes and biopsy-proven MASLD. We also explored 12-month changes in alanine aminotransferase (ALT) and Fibrosis-4 (FIB-4) index according to genotype and glucose-lowering treatment, with particular attention to GLP-1RA, sodium-glucose cotransporter 2 inhibitor, and other therapies.

Methods

Study design and participants

This retrospective, single-center cohort study included Japanese patients with type 2 diabetes mellitus (T2DM) and biopsy-proven metabolic dysfunction-associated steatotic liver disease (MASLD) who underwent liver biopsy at Toranomon Hospital between February 1987 and October 2021. Eligible patients were receiving pharmacologic treatment for T2DM and had clinical, laboratory, histologic, and genetic data available for the cross-sectional analysis. Patients with hepatitis B or C virus infection, autoimmune hepatitis, primary biliary cholangitis, drug-induced liver injury, alcohol consumption exceeding 30 g/day in men or 20 g/day in women, no pharmacologic treatment for T2DM, or insufficient clinical data were excluded. The final cross-sectional cohort comprised 155 patients. The final data extraction date, which defined the end of the study, was October 31, 2025.

The study protocol was approved by the institutional ethics committee of Toranomon Hospital (approval numbers 953 and 1135) and was conducted in accordance with the Declaration of Helsinki. Because of

the retrospective study design, informed consent was obtained using an opt-out approach.

Clinical and laboratory assessment

Demographic characteristics, anthropometric measurements, medical history, glucose-lowering treatment, and laboratory values were obtained from the medical records. Baseline variables included age, sex, body mass index (BMI), albumin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamyl transferase, creatinine, estimated glomerular filtration rate, platelet count, and hemoglobin A1c. The Fibrosis-4 (FIB-4) index was calculated as age (years) x AST (U/L) / [platelet count (10^9/L) x square root of ALT (U/L)].

Liver histopathology

Liver biopsy specimens were obtained using a 14-gauge modified Vim-Silverman needle (Tohoku University model, Kakinuma Factory, Tokyo, Japan), a 16-gauge core biopsy needle (Bard Peripheral Vascular Inc., Tempe, AZ, USA), or surgical resection. Specimens were fixed in 10% formalin and stained with hematoxylin and eosin, Masson's trichrome, silver, and periodic acid-Schiff after diastase digestion. Four experienced pathologists (K.K., F.K., T.F., and T.F.), who were blinded to the clinical data, evaluated the specimens. A specimen was considered adequate when it was at least 1.5 cm in length or contained at least 11 portal tracts.

Steatosis was graded as < 5% (grade 0), 5%-33% (grade 1), 34%-66% (grade 2), or > 66% (grade 3). Lobular inflammation was graded as no foci (grade 0), < 2 foci (grade 1), 2–4 foci (grade 2), or > 4 foci (grade 3) per x200 field. Hepatocellular ballooning was scored as none (0), few ballooned cells (1), or many cells/prominent ballooning (2). The NAFLD activity score (NAS) was calculated as the sum of steatosis, lobular inflammation, and ballooning scores (range, 0–8). Fibrosis was staged from F0 to F4 according to established criteria. MASH was defined as NAS > = 5, advanced fibrosis as F3-F4, and at-risk MASH as NAS > = 4 with fibrosis stage > = F2 [4, 5].

Genotyping

The TaqMan SNP Genotyping Assay (Applied Biosystems, Foster City, CA, USA) was used to genotype *GLP1R* rs10305420, *PNPLA3* rs738409, *HSD17B13* rs6834314, and *ALDH2* rs671. Because only five patients had the TT genotype for *GLP1R* rs10305420, patients with the CT or TT genotype were combined as T-allele carriers and compared with patients with the CC genotype under a dominant genetic model.

Glucose-lowering treatment and longitudinal outcomes

For the longitudinal analysis, treatment exposure was evaluated on an episode basis. Each treatment episode was classified according to the newly initiated glucose-lowering agent as GLP-1 receptor agonist (GLP-1RA), sodium-glucose cotransporter 2 inhibitor (SGLT2 inhibitor), or other glucose-lowering therapy. When an SGLT2 inhibitor was added during treatment with another glucose-lowering agent, the patient was classified in the SGLT2 inhibitor group from the date of its initiation, which was defined as month 0 for that episode. Similarly, when a GLP-1RA was subsequently added, a new GLP-1RA episode began on the date of its initiation. If an SGLT2 inhibitor and a GLP-1RA were initiated on the same date, the episode was prespecified to be classified in the GLP-1RA group; however, no simultaneous initiation occurred in this cohort. Thus, the same patient could contribute sequential treatment episodes to more than one treatment group, while background glucose-lowering therapy could be continued. Patients were required to have received the index treatment for at least 6 months and to have available measurements at treatment initiation and 12 months. The 12-month assessment was accepted when performed within 11–13 months after treatment initiation. Treatment selection, initiation, discontinuation, duration, switching, and combination therapy were determined by the treating physician.

The longitudinal outcomes were changes in ALT and FIB-4 index from treatment initiation to 12 months. Values at 12 months were expressed as ratios relative to baseline (12-month value / baseline value). Analyses were performed by rs10305420 genotype group, treatment group, and genotype within each treatment group. Because FIB-4 is derived from age, AST, ALT, and platelet count, a 12-month change in FIB-4 was interpreted as a change in the noninvasive index and not as direct evidence of histologic fibrosis progression.

Statistical analysis

Continuous variables are presented as medians with interquartile ranges and were compared between two groups using the Mann-Whitney U test. Categorical variables are presented as numbers and percentages. Binary categorical variables were compared using the Pearson chi-square test or Fisher exact test, as appropriate. Steatosis grade, ballooning grade, lobular inflammation grade, fibrosis stage, and NAS were treated as categorical variables in descriptive analyses. When expected cell counts were sparse, overall differences in multilevel histologic categories between genotype groups were assessed using Pearson's chi-square tests with Monte Carlo-simulated p values based on 500,000 replicates (seed, 20260924).

Factors independently associated with *GLP1R* rs10305420 T-allele carriage were evaluated using multivariable binary logistic regression, with CC coded as 0 and CT/TT coded as 1. Two prespecified models were analyzed. Panel A was a clinical model that included age (per 10 years), sex, BMI (per 1 kg/m^2), log_2-transformed AST, creatinine (per 0.1 mg/dL), *PNPLA3* rs738409 G-allele carrier status, and at-risk MASH. The odds ratio for AST therefore represents a doubling of AST. Panel B was a histology-focused model that included age, sex, BMI, lobular inflammation, and fibrosis stage. The models were separated to avoid entering at-risk MASH, a composite based on NAS and fibrosis, together with its

histologic components. *PNPLA3* was not included in Panel B because of the prespecified concern regarding its relationship with both hepatic histology and the *GLP1R* genotype distribution.

In the primary Panel B analysis, lobular inflammation and fibrosis stage were modeled as ordinal variables; odds ratios represent a one-grade or one-stage increase. In a sensitivity analysis, lobular inflammation was categorized as low (grades 0–1) or high (grades 2–3), and fibrosis was categorized as F0-F2 or advanced fibrosis (F3-F4). Results are reported as adjusted odds ratios with 95% confidence intervals. Panel A included 151 patients, including 45 T-allele carriers, and Panel B included all 155 patients, including 46 T-allele carriers.

Within-episode changes in ALT and FIB-4 index from treatment initiation to 12 months were assessed using paired Wilcoxon signed-rank tests. Differences in 12-month ratios between genotype groups were assessed using Mann-Whitney U tests, and overall differences among the three treatment groups were assessed using Kruskal-Wallis tests. Treatment-by-genotype interactions for the 12-month ratios were assessed in regression models that included treatment group, genotype group, and their interaction, with clustering by patient because an individual patient could contribute more than one treatment episode. All tests were two-sided, and $p < 0.05$ was considered statistically significant. Because the longitudinal and subgroup analyses were exploratory, no adjustment for multiple comparisons was performed. Statistical analyses were performed using R version 4.3.1 and EZR version 1.68 (Saitama Medical Center, Jichi Medical University, Saitama, Japan) [6].

Results

Patient characteristics

The analysis included 155 patients: 109 (70.3%) with the CC genotype, 41 (26.5%) with CT, and 5 (3.2%) with TT. The T-allele frequency was 16.5%. Compared with patients with the CC genotype, T-allele carriers were less frequently male (45.7% vs. 67.9%; p = 0.012), had higher AST (56 [38–80] vs. 41.5 [31.3–59.5] U/L; p = 0.004), lower creatinine (0.61 [0.52–0.80] vs. 0.75 [0.62–0.89] mg/dL; p = 0.006), and higher FIB-4 index (2.11 [1.60–2.72] vs. 1.74 [1.01–2.42]; p = 0.012). The distribution of lobular inflammation grades differed between genotype groups (global p = 0.021), whereas the distributions of steatosis, ballooning, fibrosis stage, and NAS did not differ significantly. T-allele carriers more frequently had advanced fibrosis (73.9% vs. 56.9%; p = 0.049) and at-risk MASH (76.1% vs. 56.0%; p = 0.020) (Table 1).

Table 1
Baseline characteristics according to *GLP1R* rs10305420 genotype

Characteristic	CC n = 109	CT/TT n = 46	p value
Demographic and clinical characteristics			
Age, years	59 [50–69]	58.5 [51-66.8]	0.902
Male sex, n (%)	74 (67.9)	21 (45.7)	0.012
BMI, kg/m^2	28.9 [26.0-31.6]	26.7 [24.5–30.4]	0.055
Laboratory findings			
Albumin, g/dL	4.1 [3.9–4.4]	4.1 [3.86–4.3]	0.484
AST, U/L	41.5 [31.3–59.5]	56 [38–80]	0.004
ALT, U/L	54.5 [36.3–97.5]	71 [38–108]	0.287
GGT, U/L	62.5 [40.5-111.8]	73 [46–102]	0.342
Creatinine, mg/dL	0.75 [0.62–0.89]	0.61 [0.52–0.80]	0.006
eGFR, mL/min/1.73 m2	78.7 [65.1–87.8]	81.5 [68.1–95.0]	0.474
Platelet count, x10^4/uL	19.6 [15.6–23.6]	19.6 [12.7–23.6]	0.515
HbA1c, %	6.9 [6.2–7.9]	7.2 [6.43–7.88]	0.556
FIB-4 index	1.74 [1.01–2.42]	2.11 [1.60–2.72]	0.012
Genetic variants			
PNPLA3 rs738409 G carrier, n (%)	85 (78.0)	42 (91.3)	0.066
HSD17B13 rs6834314 G carrier	46/94 (48.9)	25/43 (58.1)	0.360
ALDH2 rs671 A carrier, n (%)	48/100 (48.0)	24/45 (53.3)	0.593
Histological findings			
Steatosis, grade 0/1/2/3, n	2/35/43/29	0/17/18/11	0.804
Ballooning, grade 0/1/2, n	5/64/40	2/19/25	0.110

Data are median [interquartile range] or n (%); the percent sign is omitted within cells. Multi-category histology is shown as counts in the category order specified in each row; p values are global comparisons. Continuous variables: Mann-Whitney U test; binary categorical variables: Fisher exact or Pearson chi-square test; multi-level histology: Pearson's chi-square test with Monte Carlo-simulated p values (500,000 replicates; seed, 20260924). Advanced fibrosis: F3-F4. At-risk MASH: NAS > = 4 and fibrosis stage > = F2. Missing denominators are shown where applicable.

Characteristic	CC n = 109	CT/TT n = 46	p value
Demographic and clinical characteristics			
Lobular inflammation, 0/1/2/3, n	3/54/51/1	1/14/27/4	0.021
Fibrosis stage, 0/1/2/3/4, n	3/28/16/46/16	0/4/8/24/10	0.106
Advanced fibrosis (F3-F4), n (%)	62 (56.9)	34 (73.9)	0.049
NAS, 0/1/2/3/4/5/6/7/8, n	1/1/4/18/21/31/23/10/0	0/1/0/7/7/12/9/9/1	0.429
MASH, n (%)	64 (58.7)	31 (67.4)	0.369
At-risk MASH, n (%)	61 (56.0)	35 (76.1)	0.020
Glucose-lowering treatment			
SGLT2i and/or GLP-1RA use, n (%)	59 (54.1)	20 (43.5)	0.291

Data are median [interquartile range] or n (%); the percent sign is omitted within cells. Multi-category histology is shown as counts in the category order specified in each row; p values are global comparisons. Continuous variables: Mann-Whitney U test; binary categorical variables: Fisher exact or Pearson chi-square test; multi-level histology: Pearson's chi-square test with Monte Carlo-simulated p values (500,000 replicates; seed, 20260924). Advanced fibrosis: F3-F4. At-risk MASH: NAS > = 4 and fibrosis stage > = F2. Missing denominators are shown where applicable.

Factors associated with T-allele carriage

In the Panel A clinical model, each 1 kg/m^2 increase in BMI was associated with lower odds of T-allele carriage (adjusted odds ratio [aOR], 0.89; 95% CI, 0.81–0.99; p = 0.028); higher AST (aOR per doubling, 2.00; 95% CI, 1.18–3.38; p = 0.010), and at-risk MASH (aOR, 2.46; 95% CI, 1.01–6.02; p = 0.048) were independently associated with T-allele carriage. Age, sex, creatinine, and *PNPLA3* rs738409 G-carrier status were not independently associated with T-allele carriage (Table 2).

Table 2
Factors associated with *GLP1R* rs10305420 T-allele carriage Panel A Primary multivariable model

Variable	Adjusted OR	95% CI	p value
Age, per 10 years	0.84	0.59–1.21	0.360
Male sex	0.51	0.20–1.35	0.176
BMI, per 1 kg/m^2	0.89	0.81–0.99	0.028
AST, per doubling	2.00	1.18–3.38	0.010
Creatinine, per 0.1 mg/dL	0.90	0.72–1.14	0.385
PNPLA3 G carrier	2.20	0.66–7.38	0.202
At-risk MASH	2.46	1.01–6.02	0.048
Panel B Histological model Primary per-grade analysis			

In the primary per-grade Panel B model, each 1 kg/m^2 increase in BMI was associated with lower odds of T-allele carriage (aOR, 0.86; 95% CI, 0.77–0.95; p = 0.004); male sex (aOR, 0.44; 95% CI, 0.20-1.00; p = 0.049), higher lobular inflammation grade (aOR per grade, 2.27; 95% CI, 1.15–4.49; p = 0.019), and higher fibrosis stage (aOR per stage, 1.68; 95% CI, 1.11–2.53; p = 0.014) were independently associated with T-allele carriage. In the binary sensitivity analysis, advanced fibrosis remained significantly associated with T-allele carriage (aOR, 2.41; 95% CI, 1.02–5.66; p = 0.044), whereas high lobular inflammation showed a nonsignificant association (aOR, 2.09; 95% CI, 0.94–4.66; p = 0.071) (Table 2).

Longitudinal changes in ALT and FIB-4 index

At 12 months, the median ALT ratio decreased in the CC group (0.843 [0.657–1.167]; n = 105; p = 0.026) but not in T-allele carriers (0.986 [0.681–1.250]; n = 46; p = 0.754). The direct between-genotype comparison was not significant (p = 0.389). The median FIB-4 ratio was 0.983 [0.851–1.354] in the CC group (n = 103; p = 0.053) and increased to 1.146 [0.916–1.542] in T-allele carriers (n = 40; p = 0.005); however, the between-genotype comparison was not significant (p = 0.110) (Fig. 1).

By treatment group, ALT decreased during GLP-1RA treatment (0.802 [0.627-1.000]; n = 42; p = 0.021) and SGLT2 inhibitor treatment (0.756 [0.617–0.997]; n = 58; p < 0.001), but not during other therapies (1.111 [0.746–1.303]; n = 64; p = 0.440; overall p = 0.003). FIB-4 did not change significantly during GLP-1RA treatment (0.930 [0.874–1.184]; n = 39; p = 0.696) or SGLT2 inhibitor treatment (0.958 [0.820–1.275]; n = 55; p = 0.241), but increased during other therapies (1.227 [0.932–1.489]; n = 61; p < 0.001; overall p = 0.020) (Fig. 2).

Within each treatment group, no significant CC-versus-CT/TT difference was observed for ALT (GLP-1RA, p = 0.469; SGLT2 inhibitor, p = 0.850; other therapies, p = 0.540) or FIB-4 (GLP-1RA, p = 0.062; SGLT2

inhibitor, p = 0.621; other therapies, p = 0.392) (Fig. 3). Treatment-by-genotype interactions were not significant for ALT (p = 0.905) or FIB-4 (p = 0.665).

Discussion

In this biopsy-defined cohort of patients with MASLD and type 2 diabetes, *GLP1R* rs10305420 T-allele carriers had higher AST and FIB-4 values, a different distribution of lobular inflammation grades, and higher prevalences of advanced fibrosis and at-risk MASH than patients with the CC genotype. In Panel A, lower BMI, higher AST, and at-risk MASH were independently associated with T-allele carriage. In the primary per-grade analysis of Panel B, both lobular inflammation and fibrosis stage were independently associated with T-allele carriage. In the binary sensitivity analysis, advanced fibrosis remained significant, whereas high lobular inflammation showed only a nonsignificant trend. Thus, the fibrosis association was consistent across model specifications, whereas the lobular-inflammation association depended on how the ordinal score was modeled.

The lobular-inflammation finding is biologically relevant but requires cautious interpretation. Lobular inflammation reflects inflammatory-cell infiltration accompanying hepatocellular injury and may contribute to aminotransferase release. T-allele carriers had significantly higher AST at baseline, although ALT did not differ significantly between genotype groups. Lobular inflammation was significant both in the global categorical comparison and in the per-grade multivariable model. However, the association was attenuated after dichotomization into grade 0–1 versus 2–3. This difference is compatible with loss of ordinal information and statistical power after dichotomization, but it also indicates that the finding is less robust than the association with fibrosis. A direct causal effect of rs10305420 cannot be inferred from this cross-sectional analysis.

Our findings extend the pharmacogenetic observations reported by Su et al.[2] In that study, the rs10305420 T allele was associated with greater weight loss during treatment with GLP-1 medications, with consistent directionality in an independent electronic health record cohort. The T-allele frequency in our Japanese cohort was approximately 16%, similar to the East Asian frequency reported in that study. The coexistence of a greater GLP-1 medication-related weight-loss response in the prior study and greater baseline hepatic inflammatory activity in our cohort raises the hypothesis that T-allele carriers may have both a more inflammatory liver phenotype and greater potential metabolic responsiveness to pharmacologic *GLP1R* stimulation. This hypothesis is clinically attractive but was not directly demonstrated by our longitudinal liver-test analysis.

Specifically, ALT decreased significantly in the CC group but not in T-allele carriers, and the direct between-genotype comparison was not significant. FIB-4 increased within the T-allele carrier group, but the between-genotype difference was also not significant. When treatment groups were examined separately, no significant CC-versus-CT/TT difference was detected for either ALT or FIB-4 within the GLP-1RA, sodium-glucose cotransporter 2 inhibitor, or other-therapy groups. Furthermore, treatment-by-genotype interactions were not significant for ALT or FIB-4. Accordingly, the present data do not establish

that rs10305420 predicts hepatic response to GLP-1RA therapy, nor do they establish that genotype effects are specific to GLP-1RA rather than other glucose-lowering treatments.

The absence of a detectable pharmacogenetic effect on liver tests does not necessarily conflict with the Nature report.[2] Weight loss and aminotransferase change represent different phenotypes, and hepatic response may depend on baseline inflammatory activity, fibrosis stage, diabetes status, treatment dose, duration, and the magnitude of weight loss. In addition, only 11 T-allele carriers contributed to the ALT analysis and 9 to the FIB-4 analysis in the GLP-1RA subgroup. The study was therefore underpowered to detect the modest per-allele effect reported for weight loss or a genotype-by-treatment interaction. Direct analysis of body-weight change, drug exposure, dose, and adherence will be required to determine whether the T allele modifies the relationship between GLP-1RA-induced weight loss and improvement in liver injury.

The treatment-level findings provide complementary clinical context. ALT decreased during GLP-1RA and sodium-glucose cotransporter 2 inhibitor treatment, whereas FIB-4 increased during other therapies. These observations are consistent with a favorable liver-test trajectory during contemporary metabolic therapy, but treatment allocation was not randomized. Differences in baseline characteristics, treatment era, indication, and concomitant therapy may therefore account for part of the observed associations. Moreover, a change in FIB-4 over 12 months should not be interpreted as histologic fibrosis progression because FIB-4 is influenced by age, AST, ALT, and platelet count.

This study has several strengths, including histologic confirmation of MASLD, categorical presentation of histologic scores, preservation of ordinal information in the primary per-grade regression, and analysis of two widely used metabolic drug classes. The principal limitations are the retrospective single-center design, inclusion of Japanese patients only, which may limit generalizability to other ancestral populations, the small number of T-allele carriers in treatment-stratified analyses, nonrandom treatment selection, and the use of aminotransferases and FIB-4 rather than repeat biopsy as longitudinal outcomes. The per-grade model assumes a constant change in the log odds across adjacent grades or stages, whereas dichotomization reduces information and statistical power. We therefore used the per-grade model as the primary histologic analysis and the clinically defined binary model as a sensitivity analysis. Multiple comparisons and the number of covariates relative to the number of T-allele carriers also increase the risk of unstable estimates.

In conclusion, *GLP1R* rs10305420 T-allele carriage was independently associated with higher lobular inflammation grade and fibrosis stage in the primary ordinal analysis of biopsy-proven MASLD with type 2 diabetes. The binary sensitivity analysis confirmed the association with advanced fibrosis, whereas the association with high lobular inflammation was attenuated. These results support an association with hepatic disease phenotype but require validation in larger cohorts. The longitudinal analyses did not demonstrate a genotype-specific hepatic response to GLP-1RA or other glucose-lowering therapies.
Ethics approval and consent to participate

This study was approved by the Institutional Review Board of Toranomon Hospital (approval numbers 953 and 1135). The requirement for written informed consent was waived because of the retrospective study design. An opt-out approach was used in accordance with the institutional policy and the Declaration of Helsinki.

Registry and the Registration No. of the study/trial:

This study was not a prospective interventional clinical trial and was therefore not registered in a public clinical trial registry.

Animal Studies:

Not applicable.

Research involving recombinant DNA:

Not applicable.

Declarations

Funding Statement:

This work was supported by the Japan Agency for Medical Research and Development (AMED, Grant No. JP26fk0210174, JP26fk0210149, JP24fk0210113, JP24fk0210129, JP25fk0210129, JP24fk0210149, JP25fk0210149, JP25fk0210174) and the Ministry of Health, Labour and Welfare of Japan (Grant No. 23HC2002, 24HC0101). The funders had no role in study design, data collection, analysis, interpretation, or manuscript preparation.

Conflict of Interest Statement:

1, Tetsuya Hosaka has received honoraria from Gilead Sciences and Eisai Co., Ltd. 2, Fumitaka Suzuki has received honoraria from Gilead Sciences. The remaining authors declare that they have no competing interests.

Acknowledgement:

Not applicable.

Author Contribution:

S.G. and N.A. conceived and designed the study. S.G. collected and analyzed the data and drafted the manuscript. Y.E., S.Y., Y.T., H.S., T.H., S.S., K.I., Y.S., and F.S. contributed to data collection. N.A. supervised the study. All authors critically reviewed the manuscript and approved the final version.

Data availability statement:

The data that support the findings of this study are available from the corresponding author upon reasonable request, because the data contain potentially identifiable clinical information

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Figures

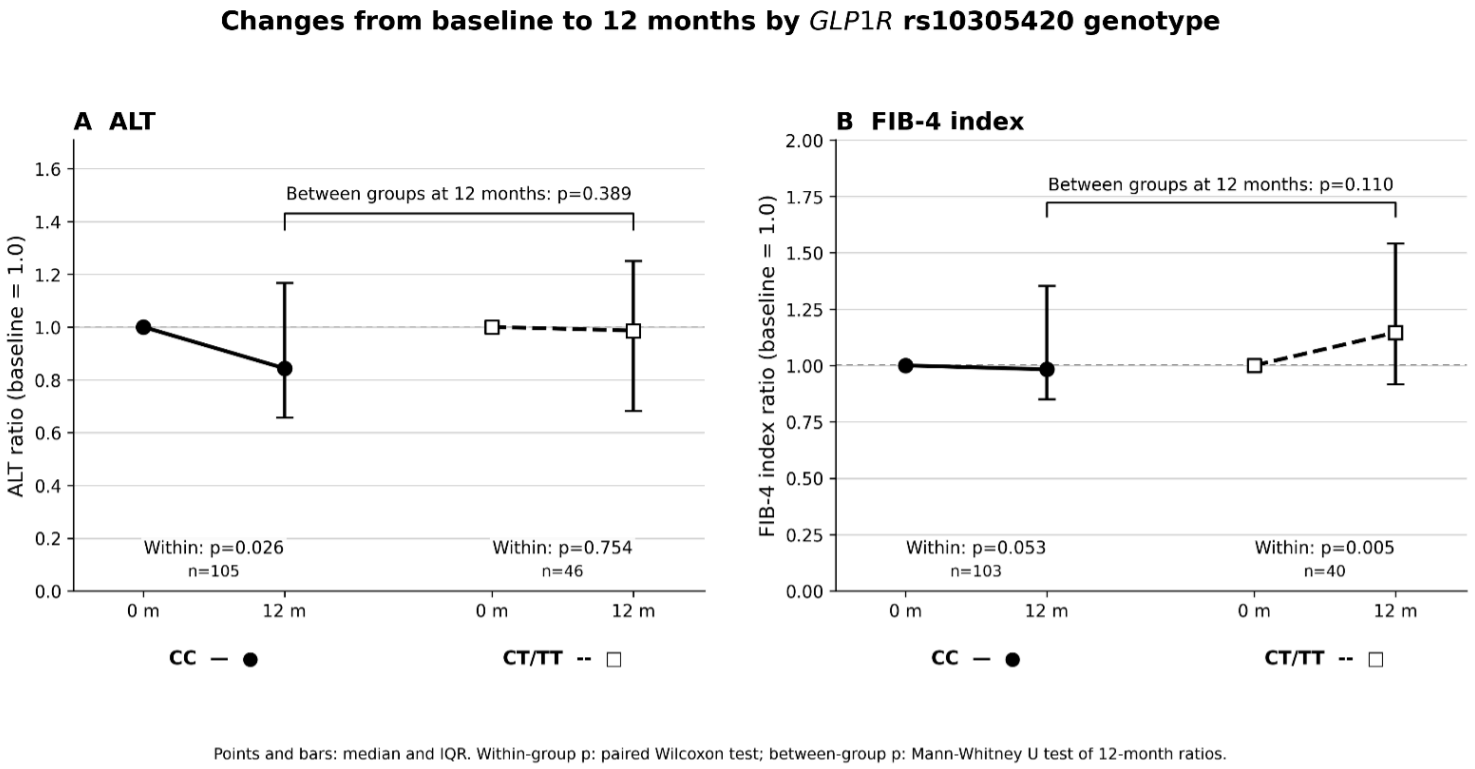

Figure 1

Changes in ALT and FIB-4 index according to *GLP1R* rs10305420 genotype

Values are shown as median and interquartile range. Within-group p values were calculated using paired Wilcoxon tests. Between-group p values compare 12-month ratios using Mann-Whitney U tests.

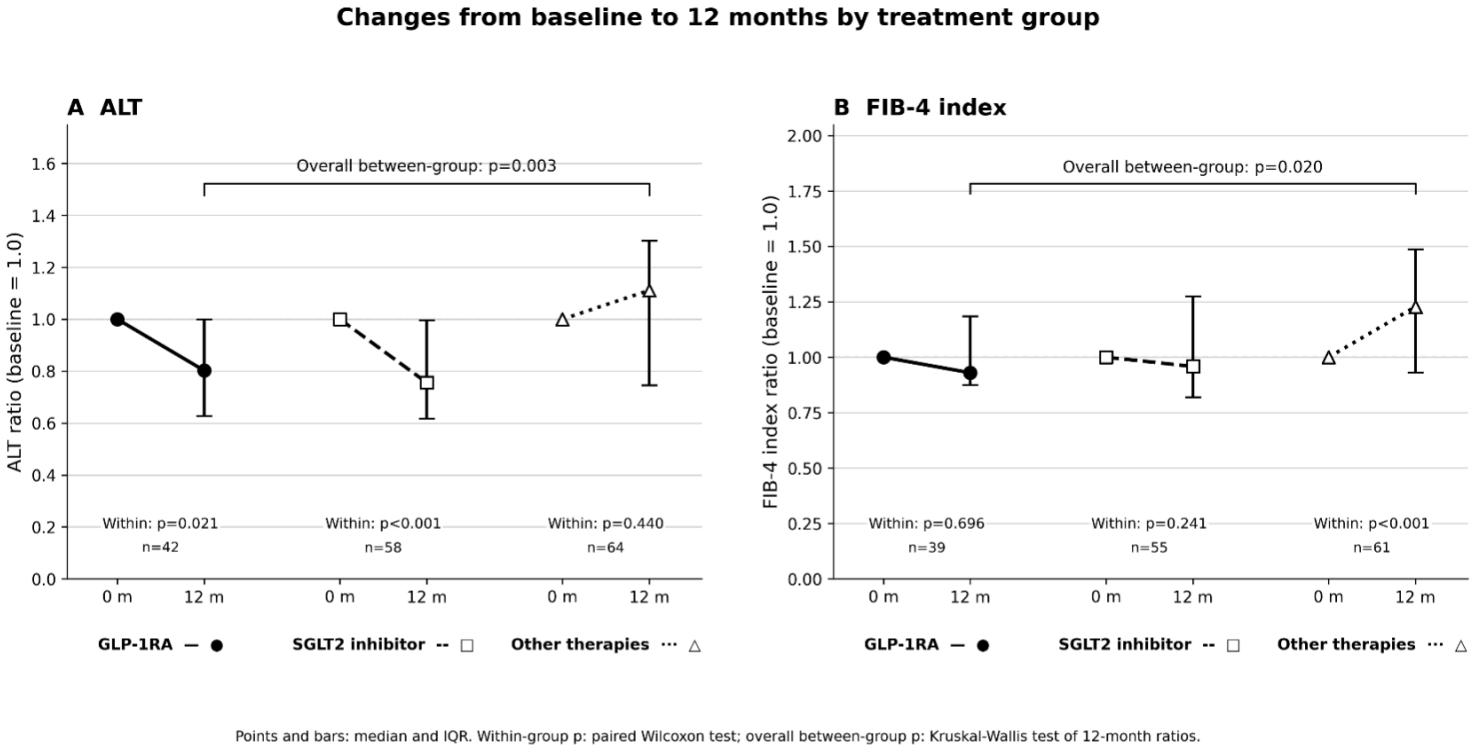

Figure 2

Changes in ALT and FIB-4 index according to treatment group

Values are shown as median and interquartile range. Within-group p values were calculated using paired Wilcoxon tests. Overall between-group p values compare 12-month ratios using Kruskal-Wallis tests.

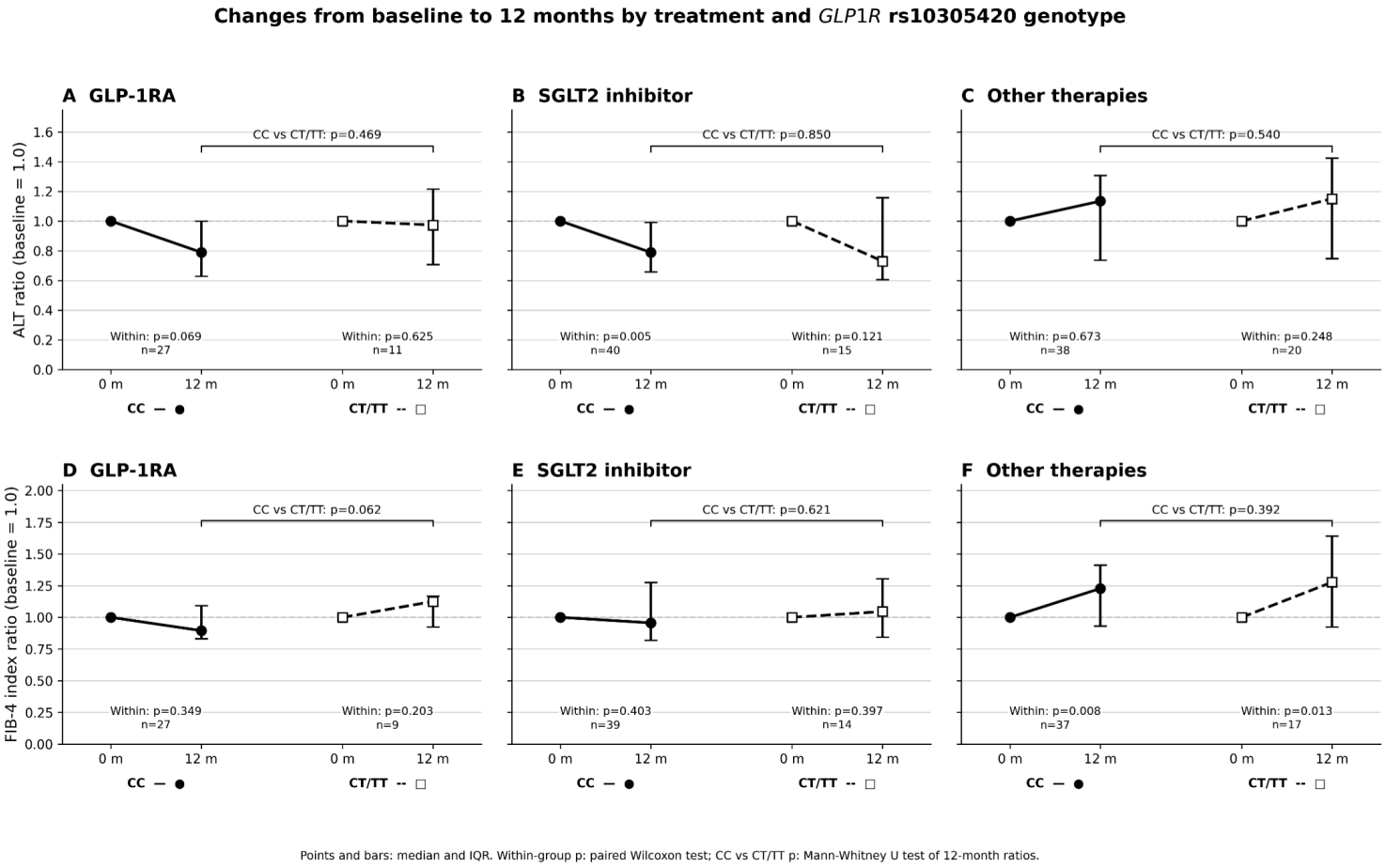

Figure 3

Genotype-stratified changes in ALT and FIB-4 index within each treatment group

Values are shown as median and interquartile range. Within-group p values were calculated using paired Wilcoxon tests. CC versus CT/TT p values compare 12-month ratios using Mann-Whitney U tests.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- GLP1RSNPTables.docx
- OnlineGotoGraphicalAbstract.png