


Antifibrotic effect and long-term outcome of SGLT2 inhibitors in patients with NAFLD complicated by diabetes mellitus

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Abstract

The aim of this retrospective multicenter study was to clarify the antifibrotic effect and long-term outcome of sodium glucose cotransporter 2 inhibitors (SGLT2-Is) in patients with nonalcoholic fatty liver disease (NAFLD) complicated by type 2 diabetes mellitus (T2DM). Of the 1262 consecutive patients with T2DM who recently received SGLT2-Is, 202 patients with NAFLD had been receiving SGLT2-Is for more than 48 weeks and were subjected to this analysis. Furthermore, 109 patients who had been on SGLT2-I therapy for more than 3 years at the time of analysis were assessed for the long-term effects of SGLT2-Is. Significant decreases in body weight, liver transaminases, plasma glucose, hemoglobin A1c, and Fibrosis-4 (FIB-4) index were found at week 48. Overall, the median value of FIB-4 index decreased from 1.42 at baseline to 1.25 at week 48 ($p < 0.001$). In the low-risk group (FIB-4 index < 1.3), there was no significant change in the FIB-4 index. In the intermediate-risk (≥ 1.3 and < 2.67) and high-risk (≥ 2.67) groups, the median levels significantly decreased from 1.77 and 3.33 at baseline to 1.58 and 2.75 at week 48, respectively ($p < 0.001$ for both). Improvements in body weight, glucose control, liver transaminases, and FIB-4 index were found at 3 years of SGLT2-I treatment. In the intermediate-risk and high-risk groups (≥ 1.3 FIB-4 index), the FIB-4 index maintained a significant reduction from baseline throughout the 3 years of treatment. **Conclusion:** This study showed that SGLT2-Is offered a favorable effect on improvement in FIB-4 index as

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a surrogate marker of liver fibrosis in patient with NAFLD complicated by T2DM, especially those with intermediate and high risks of advanced fibrosis, and this antifibrotic effect is sustained for the long term.

INTRODUCTION

Nonalcoholic fatty liver disease (NAFLD) is the most frequent chronic liver disease, and its morbidity rate in adults is approximately 25% worldwide.^[1] NAFLD progresses to liver cirrhosis and hepatocellular carcinoma (HCC), along with the deterioration of liver fibrosis.^[2] Therefore, liver fibrosis is the most critical liver-related prognostic factor in patients with NAFLD. It is also associated with extrahepatic complications, specifically cardiovascular disease and extrahepatic cancers. These account for most extrahepatic causes of death^[3–8] because NAFLD is a multifactorial disease that is mutually correlated with metabolic syndrome, a common risk factor for cardiovascular disease and cancer.^[9] In particular, type 2 diabetes mellitus (T2DM) facilitates the progression of liver fibrosis and the development of HCC in patients with NAFLD.^[10,11] To date, no drug therapy has been established to improve liver fibrosis in patients with NAFLD. However, recent studies indicated the antifibrotic effect of antidiabetic drugs,^[12–17] especially in sodium glucose cotransporter 2 inhibitors (SGLT2-Is).^[14–17]

SGLT2-Is reduce blood glucose levels by inhibiting glucose resorption in the proximal kidney tubule and consequently increasing urinary glucose excretion. Several studies suggested that SGLT2-Is improve liver enzymes by reducing hepatic steatosis in patients with NAFLD complicated by T2DM.^[14–20] However, these studies were small in the sample size (<60 patients) and/or short in the treatment period (≤ 48 weeks). No large-scale study has examined the long-term effects of SGLT2-Is in patients with NAFLD. Furthermore, only a few prospective studies reported their effects on liver fibrosis based on biopsy-proven histological findings.^[14–16]

Liver biopsy is the gold standard for NAFLD diagnosis or liver fibrosis staging, but it has some limitations, including sampling errors, being costly, invasive and time-consuming procedures, and complication risks. As a noninvasive alternative to liver biopsy, transient elastography has been used to evaluate liver fibrosis-reducing effects; however, the obtained findings remain uncertain due to the limited number of patients and short observation periods.^[17] Alternatively, the usefulness of the fibrosis-4 index (FIB-4 index) for the assessment of liver fibrosis has been established.^[21–23] Moreover, several studies reported that the FIB-4 index is associated with extrahepatic complications, such as cardiovascular events and extrahepatic cancers, as

well as liver-related complications.^[6,7,24] These findings suggest that an improvement in the FIB-4 index by treatment reflects a decrease in liver fibrosis and may lead to a reduction in the risk of complications and improvement in the prognosis of patients with NAFLD.

This study aimed to investigate the antifibrotic effect of SGLT2-Is using the FIB-4 index and the long-term treatment outcomes in patients with NAFLD complicated by T2DM.

METHODS

Study design

This study was a retrospective, multicenter study to investigate the effect of SGLT2-Is on patients with NAFLD complicated by T2DM. A flowchart of the study is shown in [Figure 1](#). Among patients who visited Nippon Medical School Hospital, Nippon Medical School Chiba Hokusoh Hospital, Kikkoman General Hospital, and Kitasato University Hospital between May 2014 and April 2020, 1262 patients newly received SGLT2-Is for T2DM with inadequately controlled hyperglycemia as determined by their physicians. Of the 1262 patients, 237 were diagnosed with NAFLD and did not fulfill the exclusion criteria. NAFLD was diagnosed by (1) the presence of steatosis in $\geq 5\%$ of hepatocytes on liver biopsy specimens or fat deposition on imaging modalities, such as ultrasonography, computed tomography, and magnetic resonance imaging; (2) daily alcohol consumption <30 g for men and <20 g for women; (3) negative for hepatitis B surface antigen and hepatitis C virus antibody; and (4) absence of other chronic liver diseases, such as autoimmune hepatitis, primary biliary cholangitis, Wilson disease, and hemochromatosis, as determined by specific laboratory and imaging examinations, as well as the patients' medical histories. The main exclusion criteria were as follows: (1) age <20 years and (2) concomitant medication with pioglitazone, GLP-1 analogues, and insulin. Of the 237 patients with NAFLD, 202 had been receiving SGLT2-Is for more than 48 weeks and were subjected to this study analysis. Furthermore, 109 patients who had been on SGLT2-Is therapy for more than 3 years at the time of analysis were assessed for the long-term effects of SGLT2-Is. This study was conducted in accordance with the ethical guidelines of the Declaration of Helsinki and was approved by the institutional review board of each participating institution.

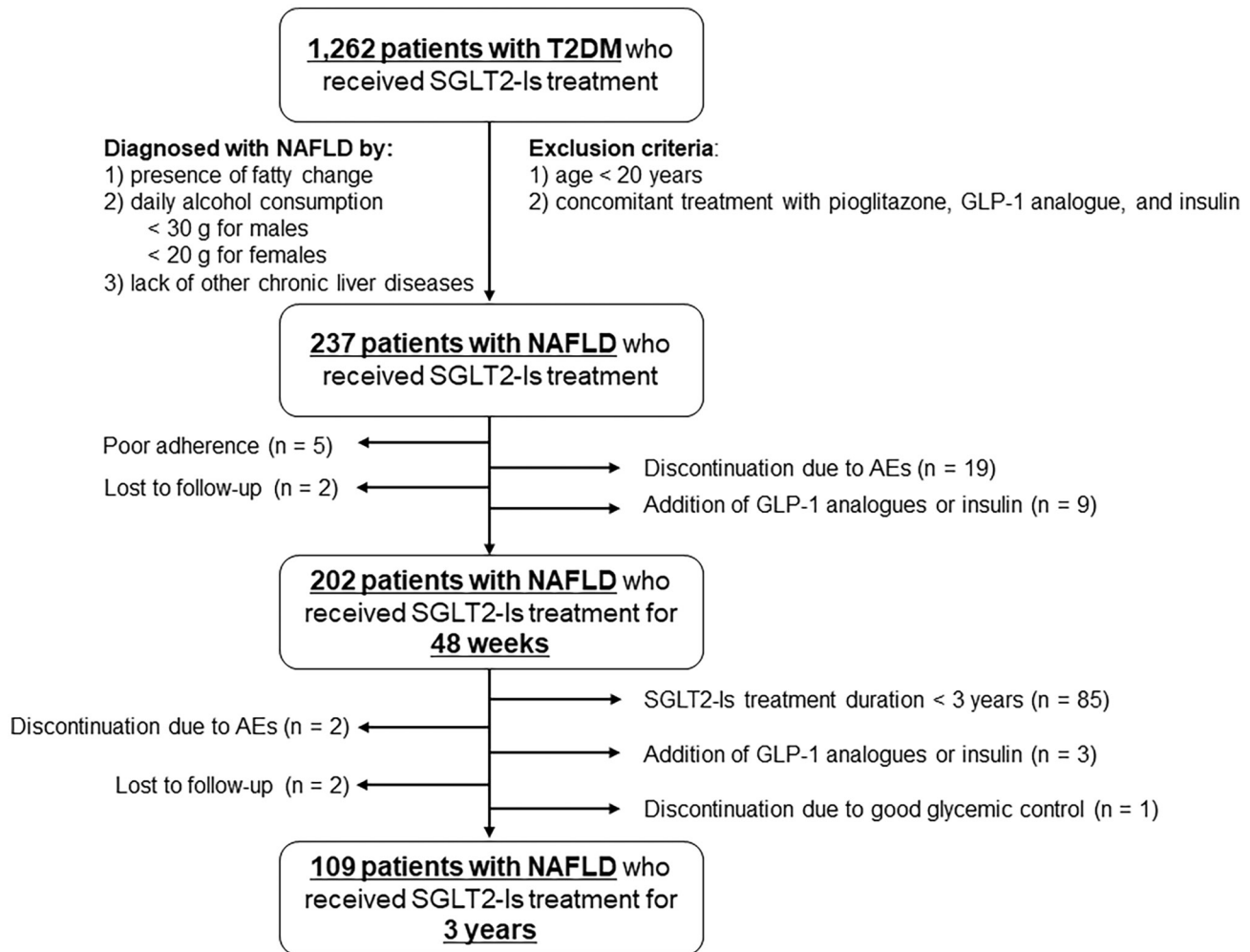


FIGURE 1 Flow chart of the study. Abbreviations: AEs, adverse events; GLP-1, glucagon-like peptide-1; NAFLD, nonalcoholic fatty liver disease; SGLT2-Is; SGLT2 inhibitors; T2DM, type 2 diabetes mellitus.

Clinical and laboratory data

Clinical and laboratory data were collected every 3 months during the study period. Body mass index (BMI) was calculated as weight (kg) divided by height squared (m^2). Laboratory evaluation included complete blood count, routine liver biochemistry (aspartate aminotransferase [AST], alanine aminotransferase [ALT], albumin, and gamma-glutamyl transpeptidase [GGT]), kidney biochemistry (urea nitrogen, creatinine, and estimated glomerular filtration rate), fasting lipids (triglyceride, high-density lipoprotein cholesterol, and low-density lipoprotein cholesterol), fasting plasma glucose, hemoglobin A1c (HbA1c), and uric acid. The FIB-4 index was calculated to estimate the degree of liver fibrosis, as reported previously.^[21] FIB-4 index values of <1.30, between 1.30 and 2.67, and ≥ 2.67 corresponded to low, intermediate, and high risk of advanced fibrosis, respectively, as proposed previously.^[23] The change in platelet counts was also examined in patients with platelet counts $< 180 \times 10^3/\mu l$, which corresponds to

patients with advanced fibrosis according to previous reports.^[25,26]

Statistical analyses

Continuous variables are presented as medians and interquartile ranges (IQRs) in parentheses, whereas categorical variables are presented as numbers and percentages in parentheses. The kinetics of the aforementioned factors were examined using the Wilcoxon signed-rank test. The McNemar–Bowker test was used to analyze the changes in the proportion of the FIB-4 index–based fibrosis risk groups from baseline to week 48. Changes in the FIB-4 index during the 3-year SGLT2-I treatment period were evaluated using the Friedman test, followed by *post hoc* pairwise comparisons with the Bonferroni test. All statistical analyses were performed using IBM SPSS version 17.0 (IBM Japan). The level of statistical significance was set at $p < 0.05$.

RESULTS

Patient characteristics

The baseline characteristics of the 202 patients with NAFLD complicated by T2DM who received SGLT2-I treatment for 48 weeks are given in [Table 1](#). There were 120 males and 82 females, with a median age of 56 years (IQR, 48–66 years) and a median HbA1c level of 7.7% (IQR, 7.0%–8.6%). Before SGLT2-I initiation, 59 patients (29.2%) received dietary and/or exercise therapies without oral hypoglycemic agents (OHAs), whereas the remaining 143 (70.8%) received other OHAs, including biguanides (n = 102), dipeptidyl peptidase-4 inhibitors (n = 127), and others (n = 59). The following SGLT2-Is were administered: canagliflozin (n = 43), ipragliflozin (n = 42), tofogliflozin (n = 9), dapagliflozin (n = 29), luseogliflozin (n = 38), and empagliflozin (n = 41). The median FIB-4 index was 1.42 (IQR, 0.92–2.14). Among the FIB-4-based fibrosis risk groups, 44.5% (n = 90) were in the low-risk group, 42.1% (n = 85) were in the intermediate-risk group, and 13.4% (n = 27) were in the high-risk group.

Changes in clinical characteristics of 48-week SGLT2-I treatment

Significant decreases in body weight, BMI, AST, ALT, GGT, uric acid, plasma glucose, HbA1c, and FIB-4 index were found at week 48 ([Table 2](#)). Significant reductions in these parameters were observed regardless of gender ([Table S1](#)) and menopausal status ([Table S2](#)). No significant changes in overall platelet counts were observed, whereas they significantly increased in patients with levels $<180 \times 10^3/\mu\text{l}$ ($146 \times 10^3/\mu\text{l}$ to $158 \times 10^3/\mu\text{l}$; $p < 0.05$) ([Table 2](#)). Overall, the median value of FIB-4 index decreased from 1.42 at baseline to 1.25 at week 48 ($p < 0.001$; [Figure 2A](#)). In the low-risk group, the median level decreased from 0.88 at baseline to 0.81 at week 48, although the difference was not statistically significant ($p = 0.25$; [Figure 2B](#)). In the intermediate-risk and high-risk groups, the median levels significantly decreased from 1.77 and 3.33 at baseline to 1.58 and 2.75 at week 48, respectively ($p < 0.001$ for both; [Figure 2C,D](#)).

The changes in the proportion of fibrosis risk groups from baseline to week 48 are shown in [Figure 3](#). Overall, the proportion of patients in the low-risk group increased from 44.5% (90 of 202) to 52.5% (106 of 202) at week 48, whereas that of the high-risk group decreased from 13.4% (27 of 202) to 8.4% (17 of 202) ($p < 0.001$; [Figure 3A](#)). Among 90 patients in the low-risk group, 83 (92.2%) remained at low risk, and 7 (7.8%) changed to intermediate risk at week 48 ([Figure 3B](#)). Among the 85 patients in the intermediate-risk group, 23 (27.1%) improved to low risk; 59 (69.4%) remained at intermediate risk; and 3 (3.5%) changed to high risk at week 48 ([Figure 3C](#)).

TABLE 1 Baseline characteristics of the 202 patients with NAFLD complicated by T2DM who received SGLT2-Is for 48 weeks

Factors	n = 202
Age (years)	56 (48–66)
Gender (male/female)	120/82
Premenopausal/postmenopausal	18/64
Body weight (kg)	76.1 (67.2–89.0)
BMI (kg/m ²)	28.1 (24.9–31.7)
Platelets ($\times 10^3/\mu\text{l}$)	214 (174–256)
AST (U/L)	37 (25–54)
ALT (U/L)	52 (33–82)
GGT (U/L)	56 (36–88)
Uric acid (mg/dl)	5.3 (4.4–6.1)
Plasma glucose (mg/dl)	158 (137–199)
HbA1c (%)	7.7 (7.0–8.6)
Diabetes treatment prior to SGLT2-Is	
Diet/exercise only (without OHAs)	59 (29.2%)
OHAs	
Biguanides	102 (50.5%)
DPP4 inhibitors	127 (62.9%)
α -glucosidase inhibitors	31 (15.3%)
Sulfonylureas	23 (11.4%)
Glinides	5 (2.5%)
SGLT2-Is	
Canagliflozin	43 (21.3%)
Ipragliflozin	42 (20.8%)
Tofogliflozin	9 (4.5%)
Dapagliflozin	29 (14.4%)
Luseogliflozin	38 (18.8%)
Empagliflozin	41 (20.3%)
FIB-4	1.42 (0.92–2.14)
FIB-4-based risk groups	
Low risk (<1.3)	90 (44.5%)
Intermediate risk ($1.3 \leq$ and <2.67)	85 (42.1%)
High risk (≥ 2.67)	27 (13.4%)

Note: Data are presented as numbers (percentages) or medians (interquartile ranges).

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; DPP4, dipeptidyl peptidase-4; GGT, gamma-glutamyl transpeptidase; HbA1c, hemoglobin A1c; OHAs, oral hypoglycemic agents.

Among the 27 patients in the high-risk group, 13 (48.1%) improved to intermediate risk, and 14 (51.9%) remained at high risk at week 48 ([Figure 3D](#)).

Long-term outcomes of SGLT2-I treatment

Of the 202 patients analyzed earlier, 109 had available data to evaluate the long-term outcomes of SGLT-I treatment ([Figure 1](#)). Significant decreases in body

TABLE 2 Changes in clinical characteristics in the 202 patients who received SGLT2-is for 48 weeks

	SGLT2-Is therapy		p-Value
	Baseline	48 weeks	
Body weight (kg)	76.1 (67.2–89.0)	74.0 (64.0–85.9)	<0.001
BMI (kg/m ²)	28.1 (24.9–31.7)	27.4 (24.1–30.6)	<0.001
Platelets ($\times 10^3/\mu\text{l}$)	214 (174–256)	213 (174–254)	0.36
<80 $\times 10^3/\mu\text{l}$	146 (134–164)	158 (128–169)	<0.05
AST (U/L)	37 (25–54)	24 (19–39)	<0.001
ALT (U/L)	52 (33–82)	30 (21–51)	<0.001
GGT (U/L)	56 (36–88)	37 (24–63)	<0.001
Uric acid (mg/dl)	5.3 (4.4–6.1)	4.8 (4.0–5.6)	<0.001
Plasma glucose (mg/dl)	158 (137–199)	134 (116–158)	<0.001
HbA1c (%)	7.7 (7.0–8.6)	6.9 (6.4–7.5)	<0.001
FIB-4	1.42 (0.92–2.14)	1.25 (0.82–1.93)	<0.001

Note: Data are expressed as medians (interquartile ranges).

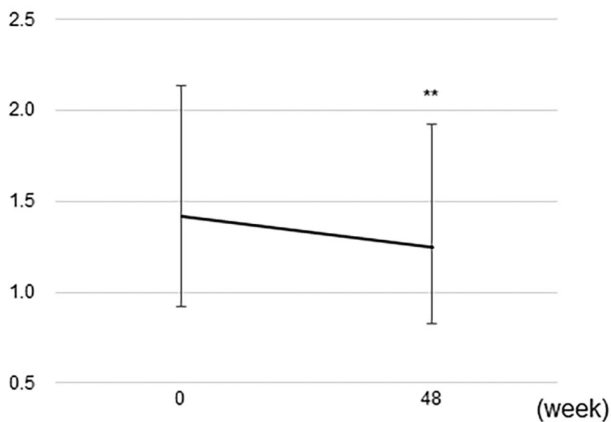
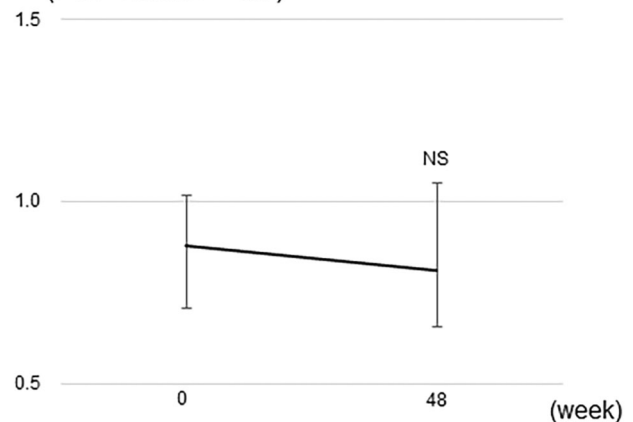
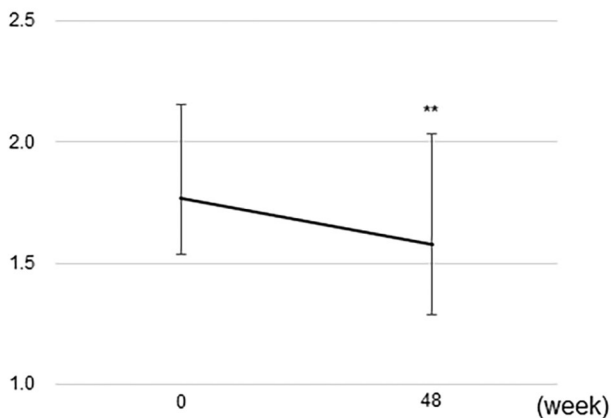
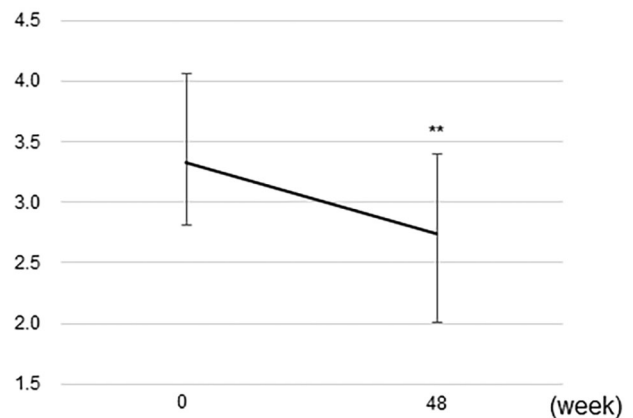
(A) Whole (n = 202)**(B) Low-risk group (n = 90)
(FIB-4 index < 1.3)****(C) Intermediate-risk group (n = 85)
(FIB-4 index between 1.3 and 2.67)****(D) High-risk group (n = 27)
(2.67 ≤ FIB-4 index)**

FIGURE 2 Changes in Fibrosis-4 index (FIB-4) from baseline to 48 weeks after administration of SGLT2-Is: all patients (A), low-risk group (FIB-4 index < 1.3) (B), intermediate-risk group (1.3 ≤ FIB-4 index < 2.67) (C), and high-risk group (2.67 ≤ FIB-4 index) (D). Error bars show the interquartile ranges. ***p* < 0.001 versus baseline. Abbreviation: N.S., not significant.

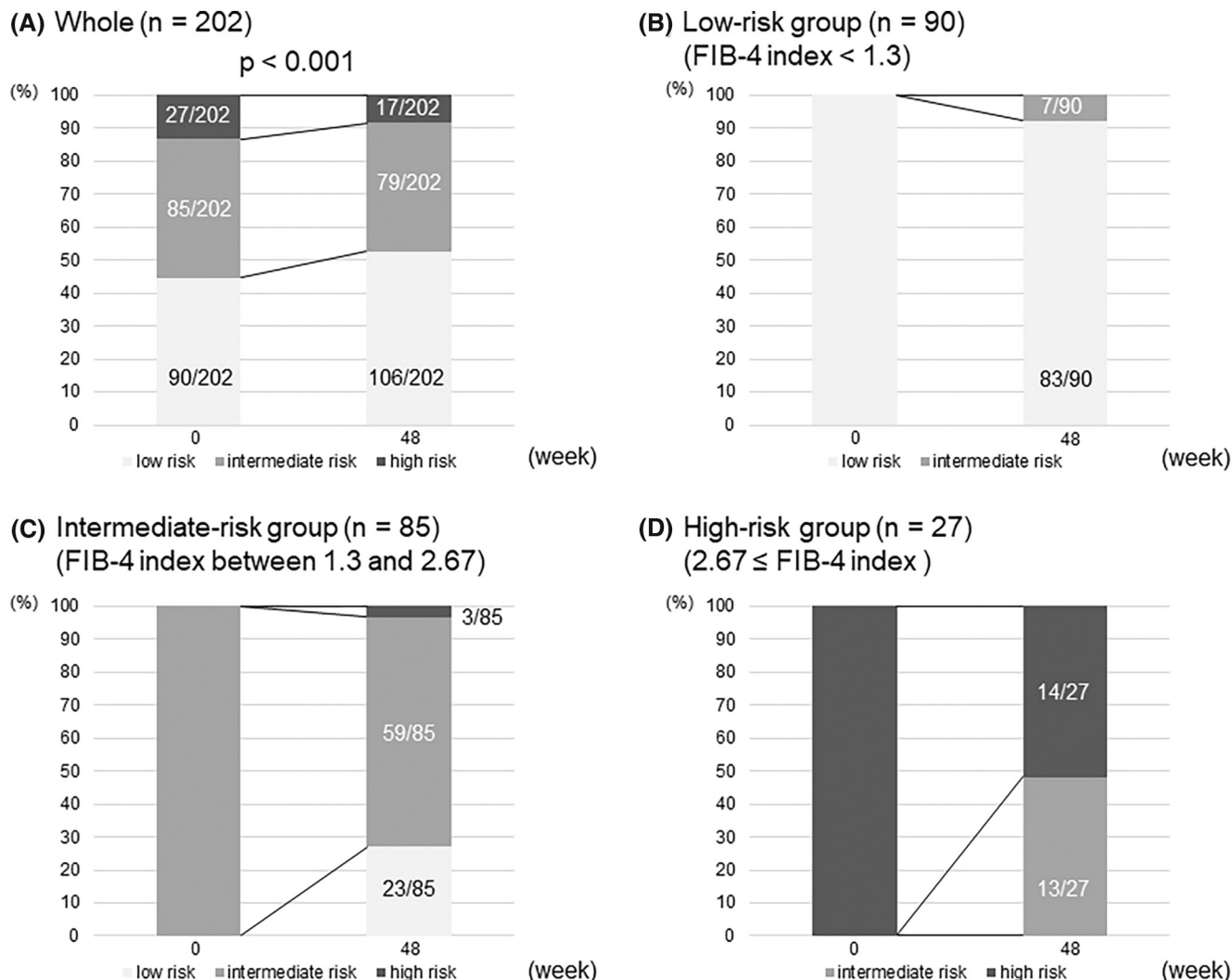


FIGURE 3 Changes in the proportion of fibrosis risk groups from baseline to week 48 in all patients (A), low-risk group (FIB-4 index < 1.3) (B), intermediate-risk group (1.3 ≤ FIB-4 index < 2.67) (C), and high-risk group (2.67 ≤ FIB-4 index) (D).

weight, BMI, AST, ALT, GGT, uric acid, plasma glucose, HbA1c, and FIB-4 index were found at 3 years of SGLT-1 treatment (Table 3). Overall, the FIB-4 index maintained a significant reduction from baseline throughout the 3 years of treatment (Figure 4A). In the low-risk group, there was no significant change in the FIB-4 index over the 3 years (Figure 4B). Meanwhile, in the intermediate-risk and high-risk group (1.3 ≤ FIB-4 index), the FIB-4 index significantly decreased from baseline throughout the 3 years (Figure 4C).

Adverse events

Of the 237 patients with NAFLD complicated by T2DM who received SGLT2-I treatment, 21 (8.9%) discontinued treatment due to adverse events during the observation period (Figure 1). Of the 21 patients, 19 (90.5%) discontinued treatment within 48 weeks of treatment. Among the adverse events leading to treatment

discontinuation, genitourinary tract infection was the most frequently observed (23.8%) (Table S3).

DISCUSSION

This study revealed that SGLT2-I administration for 48 weeks not only improved glycemic control but also reduced body weight, uric acid and transaminase levels, and the FIB-4 index in 202 patients with NAFLD complicated by T2DM. Notably, these effects were sustained during the 3 years of SGLT2-I treatment. Recently, SGLT2-Is have been reported to improve the severity of NAFLD complicated by T2DM.^[14–20] The Japan Society of Hepatology guidelines suggest that SGLT2-Is are one of the effective treatments for NAFLD complicated by T2DM.^[27] However, previous studies had a small number of patients and/or a relatively short treatment study. The strength of this study is that it examined the effect of 48-week

TABLE 3 Changes in clinical characteristics in the 109 patients who received SGLT2-Is for 3 years

	SGLT2-I therapy		
	Baseline	3 years	p-Value
Body weight (kg)	75.0 (67.9–89.7)	71.8 (64.0–85.7)	<0.001
BMI (kg/m ²)	27.2 (24.8–31.8)	26.2 (24.4–30.6)	<0.001
Platelets (×10 ³ /μl)	214 (182–258)	211 (177–244)	0.10
AST (U/L)	38 (26–54)	28 (18–36)	<0.001
ALT (U/L)	55 (37–75)	35 (21–57)	<0.001
GGT (U/L)	56 (35–89)	33 (24–58)	<0.001
Uric acid (mg/dl)	5.2 (4.3–5.9)	4.9 (4.3–5.6)	<0.01
Plasma glucose (mg/dl)	162 (144–207)	146 (120–170)	<0.001
HbA1c (%)	7.9 (7.3–8.8)	7.2 (6.6–7.8)	<0.001
FIB-4 index	1.33 (0.93–2.06)	1.29 (0.85–1.86)	<0.05

Note: Data are expressed as medians (interquartile ranges).

SGLT-I treatment in more than 200 patients, as well as 3 years of treatment in more than 100 patients. In addition to improving glycemic control, the preventive effects of SGLT2-Is on cardiovascular disease and chronic kidney disease, well-known extrahepatic complications in patients with NAFLD,^[28,29] have been reported at high evidence level.^[30] Thus, when combined with their sustained lowering effects on liver enzymes and FIB-4 index, SGLT2-Is might be one of the promising options for patients with NAFLD with T2DM.

It is well known that gender and menopausal status influence the onset and progression of NAFLD.^[31,32] According to a systematic review and meta-analysis, although women have a lower risk of NAFLD, women with NAFLD have a higher risk of developing liver fibrosis compared with men, especially for patients over 50 years old.^[31] In this study, significant improvements in body weight, glycemic control, uric acid, liver enzymes, and FIB-4 index were found regardless of gender and menopausal status. Because of the small number of premenopausal women in this study, further validation is needed to determine whether there are differences in the influence of SGLT2-Is on the liver across gender and menopausal status.

As already established, ALT and GGT, routine clinical biochemical markers, reflect liver injury and inflammation.^[33] Furthermore, it has recently been reported that dynamic changes in ALT and GGT well reflect changes in histopathological severity of NAFLD.^[34] In particular, GGT is known to be a marker of insulin resistance,^[35] which plays a key role in the progression of NAFLD. Moreover, elevated GGT activity is associated with increased risk of cardiovascular disease, a common extrahepatic complication of NAFLD.^[36] Thus, the decrease in GGT with SGLT2-I treatment might lead to prevention of disease progression, improvement in histopathological severity of NAFLD, and a reduction in the risk of developing cardiovascular disease.

The degree of liver fibrosis is a histological index that accurately reflects the prognosis of patients with NAFLD.^[3,4] The important goal of NAFLD treatment is to improve liver fibrosis and prevent the disease progression. Two pilot studies (24-week canagliflozin for 5 patients^[14] and 24-week empagliflozin for 9 patients^[15]) demonstrated improvement of liver fibrosis by SGLT2-Is on liver biopsy specimens. Recently, a randomized controlled trial reported that liver fibrosis significantly improved in the ipragliflozin-treated group (n = 21) compared with that in the control group.^[16] Although liver biopsy is the gold standard for the assessment of liver fibrosis, it is invasive and carries a risk of complications; therefore, it is difficult to perform this procedure simply and repeatedly. The drawbacks of liver biopsy may have markedly restricted patient enrollment or study period in previous studies.

This study evaluated the antifibrotic effect of SGLT2-Is using the FIB-4 index, which is a noninvasive alternative to liver biopsy for assessing liver fibrosis,^[21–23] in a relatively large number of patients. Of note, SGLT2-Is significantly reduced this index in the intermediate-risk and high-risk groups with an FIB-4 index of ≥1.3, suggesting that SGLT2-Is may have a favorable effect on liver fibrosis in patients at risk for liver fibrosis progression. Meanwhile, no significant change in the FIB-4 index was found in the low-risk group with an FIB-4 index of <1.3. This finding may be interpreted as SGLT2-Is preventing the disease progression. However, it is unclear whether SGLT2-Is are beneficial or required for patients with a low FIB-4 index. Such ameliorating and preventive effects should be further investigated in a prospective, controlled study involving a large number of patients and a long study period.

Changes in the FIB-4 index should be interpreted with caution, as the decrease in the FIB-4 index is not only due to improvement in liver fibrosis, but also to normalization of AST and ALT (i.e., improvement in liver inflammation).

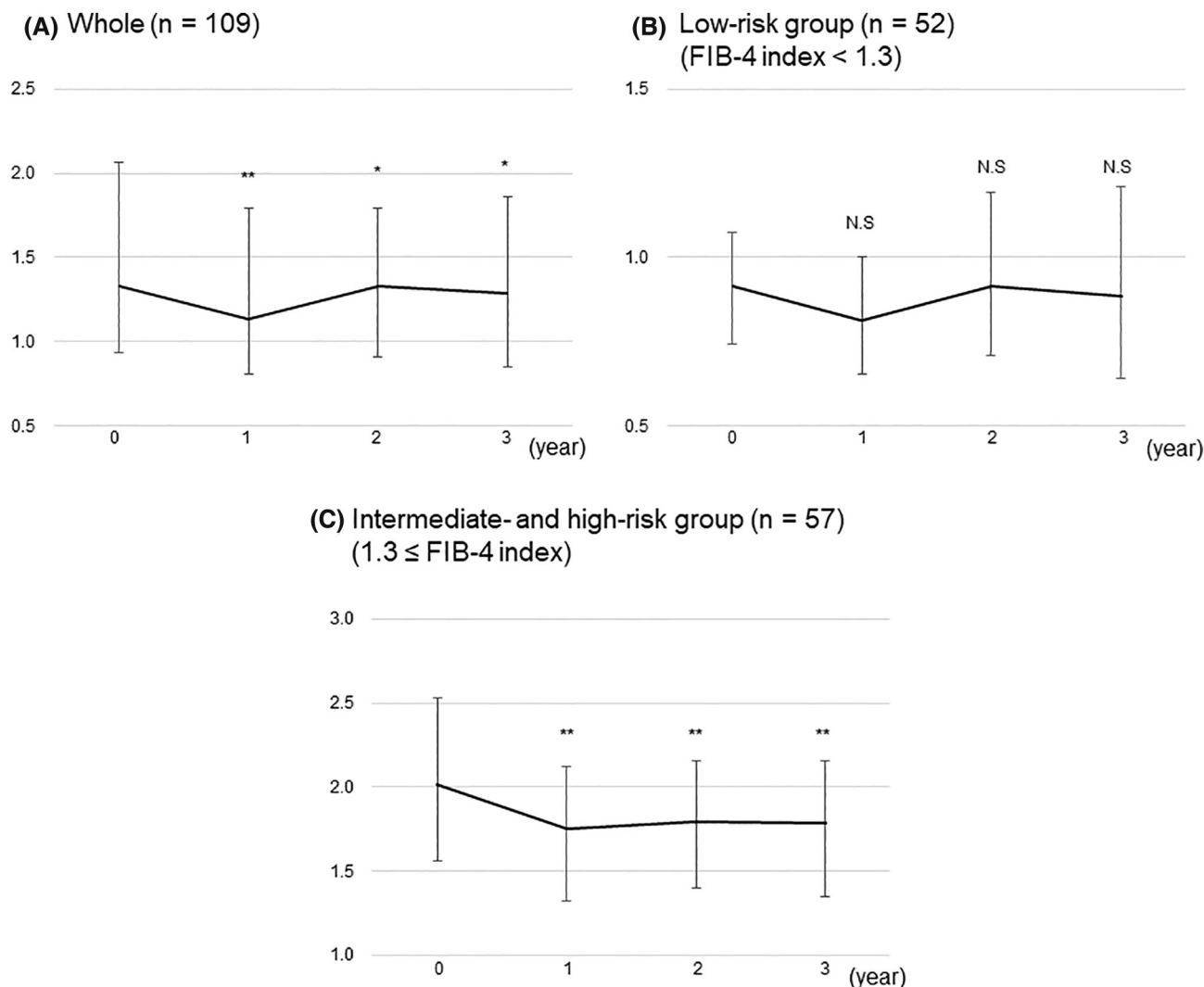


FIGURE 4 Changes in FIB-4 from baseline to 3 years after administration of SGLT2-Is in all patients (A), the low-risk group (FIB-4 index < 1.3) (B), and the intermediate-risk and high-risk group ($1.3 \leq$ FIB-4 index) (C). Error bars show the interquartile ranges. ** $p < 0.001$ versus baseline; * $p < 0.05$ versus baseline.

Patients with NAFLD had a slower decline in platelet counts with progressive fibrosis than patients with other chronic liver diseases,^[25,26] which may explain why there was no change in overall platelet counts in this study. On the other hand, the significant increase in platelet counts after SGLT2-I administration in patients with low platelet counts supported the possibility of improved liver fibrosis in patients with advanced fibrosis. Moreover, considering that liver fibrosis is caused by a protracted wound-healing process in response to repetitive injury induced by inflammation, it is assumed that improving this inflammation might lead to prevent subsequent fibrosis development and improve existing fibrosis.^[37]

The mechanism by which SGLT2-Is prevent/ameliorate liver fibrosis is complex and may involve various factors, not all of which are fully understood.^[38] It is conceivable that SGLT2-Is may have an indirect antifibrotic effect by lowering blood glucose and insulin levels, thereby improving insulin resistance,

which is a cause of steatosis and fibrosis progression in patients with NAFLD.^[39] SGLT2-Is may also contribute to the improvement of liver fibrosis by inhibiting inflammatory cytokines such as interleukin-6, tumor necrosis factor- α and monocyte chemoattractant protein 1, which are drivers of more advanced liver disease.^[40,41] Reportedly, SGLT2-Is reduce the activity of NLR family pyrin domain-containing 3 inflammasome,^[42] which plays an important role in liver fibrosis.^[43] Interestingly, anti-inflammatory and antifibrotic properties of SGLT2-Is have been suggested as a common mechanism for its protective effects on the heart^[44] and kidney,^[45] as well as the liver. In addition, the potential impact of SGLT2-Is on the development of HCC via the hepatoprotective effects described above and its direct anti-HCC activity have attracted attention.^[46–48] These findings are based on animal experiments, and further studies are needed to elucidate the inhibitory effect of SGLT2-Is on the

development and progression of NAFLD and HCC in clinical practice.

This study has several limitations. First, given that this study was retrospective and lacked a control group without SGLT2-Is, the results must be interpreted carefully. The criteria for treatment decision and discontinuation were not standardized and were left to each physician. Second, liver biopsy was not performed to diagnose NAFLD or assess liver fibrosis. In this study, the FIB-4 index was used as an evaluation of the degree of liver fibrosis as a substitute for the diagnosis of liver biopsy. However, it should be noted that the diagnostic performance of FIB-4 index is suggested to be relatively less accurate in patients with T2DM.^[49] According to the NAFLD practice guidelines in Japan and the United States,^[27,50] the FIB-4 index is a simple, accurate, and inexpensive method of assessing liver fibrosis, and its measurement is recommended.

CONCLUSIONS

This study suggested that SGLT2-I treatment offered a favorable effect on improvement in the FIB-4 index as a surrogate marker of liver fibrosis in patients with NAFLD complicated by T2DM, especially those with intermediate and high risks of advanced fibrosis and that the antifibrotic effect is sustained with long-term SGLT2-I treatment. Further studies are required to investigate whether long-term SGLT2-I treatment improves the prognosis and prevents liver-related and extrahepatic complications in patients with NAFLD complicated by T2DM.

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CONFLICT OF INTEREST

Nothing to report.

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SUPPORTING INFORMATION

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