FIB-4 Trajectories and Predictors of Fibrosis Response in Type 2 Diabetes Treated with SGLT2 Inhibitors: A Propensity-Matched 12-Month Study

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Abstract

Aim: Sodium-glucose co-transporter 2 (SGLT2) inhibitors have demonstrated favorable effects on metabolic parameters, yet their impact on liver fibrosis indices such as the Fibrosis-4 (FIB-4) score remains underexplored. Understanding the comparative efficacy of empagliflozin and dapagliflozin in modulating hepatic and metabolic markers could guide therapeutic strategies in patients with type 2 diabetes mellitus (T2DM).

Methods: This study included patients with T2DM who were initiated on empagliflozin or dapagliflozin and followed for 12 months. Clinical and laboratory parameters were assessed at baseline and 12 months, including weight, HbA1c, lipid profile, ALT, AST, and FIB-4 score. Propensity score matching was employed to identify responders (≥20% reduction in FIB-4) and non-responders. Receiver operating characteristic (ROC) analysis was performed to evaluate predictive markers for FIB-4 improvement.

Results: A total of 200 patients were analyzed. Both empagliflozin and dapagliflozin groups demonstrated significant reductions in BMI, FBG, HbA1c, and FIB-4 scores ($p < 0.001$ for all). Between-group comparisons revealed no statistically significant differences in ΔBMI, ΔHbA1c, ΔAST, or ΔFIB-4. Among responders, the baseline FIB-4 score was significantly lower (1.48±0.52 vs. 1.80±0.42; $p = 0.0445$). ROC analysis identified ΔAST ≥7 U/L as the strongest predictor of FIB-4 response (AUC = 0.875, sensitivity = 83%, specificity = 83%).

Conclusions: Both SGLT2 inhibitors significantly improved metabolic and hepatic parameters in patients with T2DM. The magnitude of AST reduction emerged as a robust predictor of FIB-4 improvement, underscoring its potential role in monitoring hepatic response to treatment.

Keywords: *SGLT2 inhibitors; empagliflozin; dapagliflozin; FIB-4 score; liver fibrosis; diabetes mellitus*

1. Introduction

Type 2 diabetes mellitus (T2DM) is a major public health challenge associated with increasing global prevalence and substantial mortality. It accounts for approximately 1.5 million deaths annually and is a well-established risk factor for cardiovascular disease (CVD), including atherosclerosis, hypertension, and heart failure.[1,2]

Metabolic dysfunction-associated steatotic liver disease (MASLD) has recently been redefined as the leading cause of chronic liver disease worldwide. The diagnosis of MASLD requires imaging or histologic evidence of hepatic steatosis in addition to at least one of the following cardiometabolic risk factors: overweight or obesity, impaired glucose regulation or T2DM, hypertension, elevated plasma triglycerides, or reduced high-density lipoprotein (HDL).[3] Among these, T2DM is both highly prevalent and pathophysiologically linked to MASLD, with hepatic steatosis observed in up to 60% of patients with diabetes.[4] Although MASLD may be asymptomatic, disease progression can lead to hepatic inflammation, fibrosis, cirrhosis, and even hepatocellular carcinoma.[5]

Liver biopsy remains the gold standard for assessing hepatic fibrosis. However, its invasiveness, associated risks, sampling variability, and cost limit its widespread use in clinical practice.[6] In this context, the Fibrosis-4 (FIB-4) score has gained prominence as a reliable, non-invasive biomarker for detecting advanced fibrosis in patients with metabolic liver disease.[5]

Sodium-glucose co-transporter 2 (SGLT2) inhibitors have emerged as key therapeutic agents in the management of T2DM due to their cardiovascular and renal protective effects. Recent evidence also suggests potential hepatoprotective properties, including reductions in serum transaminases and improvements in hepatic fat content.[7] However, data on their influence on hepatic fibrosis remains scarce and inconclusive.

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This study aimed to evaluate the impact of SGLT2 inhibitor therapy—specifically empagliflozin and dapagliflozin—on liver fibrosis risk in patients with T2DM using serial assessment of the FIB-4 score over a 12-month follow-up period.

2. Materials and Methods

2.1. Ethical Considerations

The study was approved by the Institutional Review Board of the participating center (Approval Date: August 21, 2024; Decision No: 2024-13/2) and conducted in accordance with the ethical principles outlined in the Declaration of Helsinki. Written informed consent was obtained from all participants prior to enrollment.

2.2. Study Design and Setting

This study conducted at a tertiary care center specializing in the management of diabetes and liver disease. The objective was to evaluate the effects of sodium-glucose co-transporter 2 (SGLT2) inhibitors—empagliflozin (10 mg) and dapagliflozin (10 mg)—on liver fibrosis risk and associated metabolic parameters over a 12-month period.

2.3. Study Population

Patients aged ≥18 years with a confirmed diagnosis of type 2 diabetes mellitus (T2DM) according to the American Diabetes Association (ADA) criteria and baseline HbA1c ≥6.5% were eligible for inclusion.

Exclusion criteria included:

- Age <18 years
- Severe renal impairment (eGFR <30 mL/min/1.73 m^2)
- Active malignancy
- Pregnancy or lactation
- Introduction of new antidiabetic or antihyperlipidemic agents during the follow-up period
- Chronic viral hepatitis
- History of liver transplantation
- Low or normal BMI
- Hematologic disorders requiring transfusion (e.g., transfusion-dependent beta thalassemia)
- Patients who consume alcohol
- Patients who stop taking medication

2.4. Intervention and Treatment

All patients received either empagliflozin or dapagliflozin as part of their ongoing antidiabetic treatment. No modifications were made to their baseline antidiabetic, antihypertensive, or lipid-lowering regimens during the study period. Patients who required any therapeutic changes were excluded to isolate the effect of SGLT2 inhibitors.

2.5. Data Collection and Measurements

Baseline data were collected at the initiation of SGLT2 inhibitor therapy (0th month), and follow-up data were obtained at 12 months. Recorded variables included:

- Anthropometric parameters (weight, height, BMI)
- Glycemic markers (fasting blood glucose [FBG], HbA1c)
- Lipid profile (triglycerides, LDL, HDL)
- Liver enzymes (ALT, AST)
- Renal markers (creatinine, urea)
- Platelet counts

The FIB-4 score was calculated at baseline and at 12 months using the following equation:

$$\text{Fib4 score} = \frac{Age(years) \times AST(U/L)}{Plt\left(\frac{10^9}{L}\right) \times \sqrt{ALT\left(\frac{U}{L}\right)}}$$

The FIB-4 categories were defined as follows:

- Low risk: FIB-4 < 1.30
- Intermediate risk: 1.30 ≤ FIB-4 < 2.67
- High risk: FIB-4 ≥ 2.67

2.6. Outcomes

The primary outcome was the change in FIB-4 score from baseline to 12 months. Secondary outcomes included changes in anthropometric data, glycemic control (FBG, HbA1c), lipid profile, liver enzymes, and renal parameters. A favorable FIB-4 response was defined as a ≥20% reduction from baseline.

2.7. Statistical Analysis

Data normality was assessed using the Shapiro–Wilk test. Continuous variables were reported as mean ± standard deviation (SD) if normally distributed, or as median (minimum–maximum) if not. Categorical variables were summarized as counts and percentages. Within-group comparisons were performed using the Wilcoxon signed-rank test, while between-group comparisons were assessed using the Mann–Whitney U test or chi-square test, as appropriate. Associations between continuous variables were evaluated using Spearman's rank correlation.

Univariate analyses were conducted initially, followed by multivariate analyses to adjust for potential confounding factors. A two-sided p-value <0.05 was considered statistically significant.

To reduce confounding by indication, 1:1 nearest-neighbor propensity score matching (PSM) without replacement was performed using the MatchIt package in R version 4.5.0 (R Foundation for Statistical Computing, Vienna, Austria). Covariate balance between matched groups was assessed using standardized mean differences (SMD), with values <0.1 indicating acceptable balance. SMD plots were generated using the cobalt package.

Receiver operating characteristic (ROC) curve analysis was used to assess the discriminatory ability of ΔAST, ΔALT, ΔHbA1c, ΔTG, and ΔBMI for predicting FIB-4 response (defined as a ≥20% reduction at 12 months). The optimal cut-off points were determined using the Youden index. ROC analyses were performed in SPSS version 26.0 (IBM Corp., Armonk, NY, USA).

3. Results

Clinical and Laboratory Changes from Baseline to 12 Months in All Patients and Treatment Groups (Table 1, Figure 1)

At 12-month follow-up, patients receiving SGLT2 inhibitors exhibited significant improvements in multiple metabolic and hepatic parameters. In the overall cohort, body weight significantly decreased from 85.8±11.1 kg to 82.5±9.4 kg (p<0.001), with parallel reductions observed in both the empagliflozin group (85.2±11.5 to 81.7±9.7 kg, p<0.001) and the dapagliflozin group (86.7±10.6 to 83.5±8.9 kg, p<0.001). BMI decreased from 31.2±4.3 to 30.0±4.0 kg/m^2 in the entire cohort (p<0.001), with comparable reductions in empagliflozin (31.3±4.4 to 29.9±4.0 kg/m^2, p<0.001) and dapagliflozin (31.9±4.5 to 30.7±4.0 kg/m^2, p<0.001) subgroups.

Glycemic control improved markedly over the study period. Mean fasting blood glucose (FBG) levels decreased from 214.6±72.8 mg/dL to 162.9±36.2 mg/dL (p<0.001), and HbA1c levels declined from 9.1±1.6% to 7.8±1.0% (p<0.001). Both empagliflozin and dapagliflozin groups demonstrated statistically significant within-group improvements in FBG and HbA1c values (all p<0.001).

Lipid profile changes were modest. Triglyceride levels decreased from 173.7±57.3 to 149.9±39.9 mg/dL (p<0.001), with similar reductions observed in both treatment groups. LDL cholesterol levels improved from 125.8±28.1 to 114.5±22.3 mg/dL overall (p<0.001), with consistent changes in both subgroups. No significant changes were observed in HDL cholesterol levels (all p>0.05).

Table 1

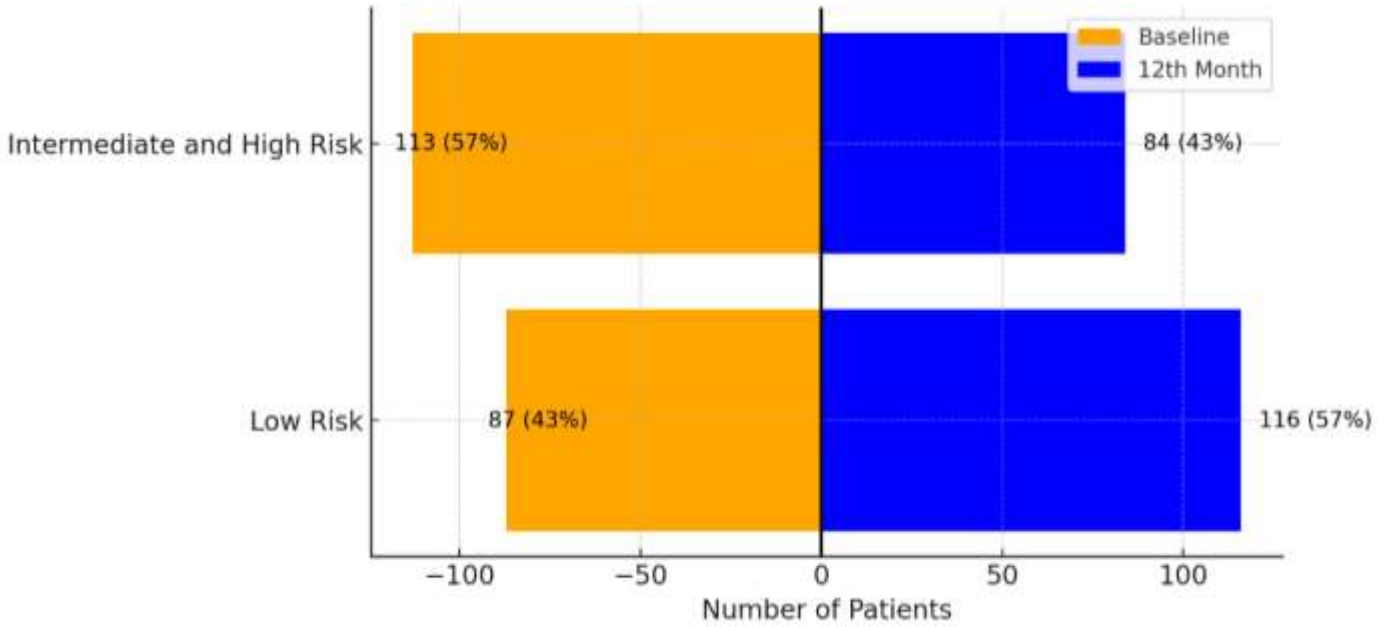
Baseline and 12-month clinical and laboratory parameters of all patients, and those treated with empagliflozin or dapagliflozin

Variable	All Patients (n=200)		Empagliflozin (n=111)		Dapagliflozin (n=89)		p1	p2	p3
	0th month	12th month	0th month	12th month	0th month	12th month			
Female, n (%)	99 (49.5%)		56 (50.5%)		43 (48.3%)		N/A	N/A	N/A
Smoker, n (%)	70 (35.0%)		36 (32.4%)		34 (38.2%)		N/A	N/A	N/A
Weight (kg)	85.8 ± 11.1	82.5 ± 9.4	85.2 ± 11.5	81.7 ± 9.7	86.7 ± 10.6	83.5 ± 8.9	<0.001	<0.001	<0.001
	85.0 (78.0–94.0)	83.0 (75.0–89.0)	83.0 (77.0–93.5)	82.0 (74.0–89.0)	86.0 (80.0–95.0)	85.0 (78.0–90.0)			
Height (cm)	166.2 ± 9.2		166.9 ± 9.7		165.3 ± 8.5		N/A	N/A	N/A
	165.0 (158.0–174.0)		165.0 (159.0–175.0)		165.0 (158.0–171.0)				
BMI (kg/m²)	31.2 ± 4.3	30.0 ± 4.0	31.3 ± 4.4	29.9 ± 4.0	31.9 ± 4.5	30.7 ± 4.0	<0.001	<0.001	<0.001
	31.2 (28.0–33.7)	29.7 (27.3–32.4)	31.2 (27.9–33.9)	29.6 (26.8–32.0)	31.2 (29.1–34.0)	30.1 (27.9–33.1)			
FBG (mg/dL)	214.6 ± 72.8	162.9 ± 36.2	213.4 ± 70.4	160.0 ± 29.3	216.1 ± 76.0	166.4 ± 43.3	<0.001	<0.001	<0.001
	192.5 (165.0–265.0)	155.0 (143.0–174.0)	190.0 (168.0–257.0)	155.0 (145.0–174.0)	201.0 (153.0–267.0)	155.0 (140.0–174.0)			
HbA1c (%)	9.1 ± 1.6	7.8 ± 1.0	9.1 ± 1.5	7.8 ± 0.9	9.0 ± 1.7	7.7 ± 1.2	<0.001	<0.001	<0.001
	9.0 (7.5–10.1)	7.7 (7.0–8.3)	9.1 (7.7–10.2)	7.8 (7.0–8.3)	8.8 (7.4–10.1)	7.5 (7.0–8.5)			
HDL (mg/dL)	43.9 ± 9.0	44.5 ± 7.9	43.3 ± 9.6	44.0 ± 8.1	44.7 ± 8.2	45.1 ± 7.6	0.1986	0.1841	0.6621
	42.0 (38.0–49.0)	42.0 (40.0–47.0)	42.0 (37.0–47.5)	42.0 (39.5–46.0)	43.0 (40.0–50.0)	43.0 (40.0–47.0)			
LDL (mg/dL)	125.8 ± 28.1	114.5 ± 22.3	125.0 ± 27.9	115.4 ± 21.8	126.9 ± 28.5	113.4 ± 23.0	<0.001	<0.001	<0.001
	128.5 (108.0–145.0)	113.5 (99.0–132.2)	129.0 (104.5–145.0)	114.0 (101.0–132.5)	128.0 (108.0–148.0)	113.0 (98.0–132.0)			
TG (mg/dL)	173.7 ± 57.3	149.9 ± 39.9	176.5 ± 59.5	150.7 ± 41.3	170.1 ± 54.5	148.9 ± 38.3	<0.001	<0.001	<0.001
	165.5 (147.0–198.2)	144.0 (132.8–161.0)	166.0 (153.0–200.5)	144.0 (129.0–161.0)	165.0 (134.0–192.0)	144.0 (137.0–161.0)			
ALT (U/L)	33.6 ± 6.9	34.8 ± 5.5	33.6 ± 7.0	34.8 ± 5.7	33.6 ± 6.8	34.7 ± 5.4	<0.001	0.0027	0.0062
	34.0 (30.0–39.0)	35.0 (33.0–39.0)	34.0 (30.0–40.0)	35.0 (33.0–39.0)	34.0 (30.0–39.0)	35.0 (33.0–38.0)			
AST (U/L)	35.1 ± 9.5	32.3 ± 6.6	34.8 ± 9.7	32.2 ± 6.7	35.5 ± 9.2	32.4 ± 6.5	<0.001	<0.001	<0.001
	35.0 (31.0–42.0)	33.0 (29.0–36.2)	34.0 (31.0–41.0)	33.0 (29.0–36.0)	35.0 (30.0–43.0)	33.0 (29.0–37.0)			
Creatinine	0.9 ± 0.1	1.0 ± 0.2	0.9 ± 0.1	1.0 ± 0.2	0.9 ± 0.1	0.9 ± 0.2	<0.001	<0.001	0.0431
(mg/dL)	0.9 (0.8–1.0)	1.0 (0.8–1.1)	0.9 (0.8–1.0)	1.0 (0.8–1.1)	0.9 (0.8–1.0)	0.9 (0.8–1.0)			
Urea (mg/dL)	34.1 ± 7.6	34.4 ± 7.8	34.8 ± 8.2	35.4 ± 8.0	33.1 ± 6.8	33.1 ± 7.5	0.5785	0.4583	0.9751
	34.0 (30.0–39.0)	34.0 (30.0–39.2)	35.0 (30.0–40.0)	35.0 (31.0–40.5)	33.0 (30.0–38.0)	33.0 (28.0–37.0)			
FIB-4 score	1.4 ± 0.5	1.2 ± 0.3	1.5 ± 0.6	1.2 ± 0.3	1.4 ± 0.5	1.2 ± 0.4	<0.001	<0.001	<0.001
	1.4 (1.1–1.7)	1.2 (1.0–1.5)	1.4 (1.1–1.7)	1.2 (1.0–1.4)	1.4 (1.0–1.8)	1.3 (1.0–1.5)			

BMI: body mass index, FBG: fasting blood glucose, HDL: high-density lipoprotein, LDL: low-density lipoprotein, TG: triglyceride, ALT: alanine aminotransferase, AST: aspartate aminotransferase
Continuous variables are presented as mean ± standard deviation/median (interquartile range), and categorical variables as n (%).
p1: Within-group comparison between baseline and 12-month values in the overall cohort.
p2: Within-group comparison for patients treated with empagliflozin.
p3: Within-group comparison for patients treated with dapagliflozin.
Changes from baseline were assessed using the Wilcoxon signed-rank test for continuous variables.
Categorical variables were not analyzed longitudinally.

Figure 1

Change in FIB-4 Risk Distribution at Baseline and 12th Month



This mirrored horizontal bar chart illustrates the distribution of patients categorized as "Low Risk" and "Intermediate and High Risk" according to their FIB-4 scores at baseline and after 12 months of treatment. Orange bars represent the baseline distribution, while blue bars show the distribution at the 12th month. Labels within the bars indicate the absolute number of patients and their corresponding proportions. The chart demonstrates a net shift from higher-risk to lower-risk categories, highlighting the potential treatment-associated improvement in liver fibrosis risk stratification.

Table 2

Comparison of 12-month changes in anthropometric and laboratory parameters between treatment groups

	Dapagliflozin (n=89)		Empagliflozin (n=111)		p
	Mean ± SD	Median (Min-Max)	Mean ± SD	Median (Min-Max)	
Δ Weight, kg	3.20 ± 2.95	3.0(-3.0-12)	3.53 ± 3.11	3.0(-2.0-13)	0.489
Δ BMI, kg/m^2	1.15 ± 1.0	0.97(-1.23-4.63)	1.24 ± 1.0	1.14(-0.63-4.66)	0.500
Δ FBG, mg/dl	49.6±53.8	46(-56-185)	53.3±60.2	40.0(-113-258)	0.816
Δ Hba1c %	1.22 ± 1.0	1.0(-0.90-3.90)	1.37 ± 0.99	1.20(-0.30-3.90)	0.211
Δ ALT (U/L)	-2.14±5.6	-2.0(-23-13)	-1.65±5.24	-1.0(-25-7)	0.514
Δ AST (U/L)	3.14±5.22	4.0(-11-18)	2.60±5.4	2.0(-11-16)	0.281
Δ Creatinine mg/dL	-0.001±0.12	0.00(-0.30-0.39)	-0.031±0.12	0.00(-0.40-0.39)	0.206
Δ FIB-4	0.26±0.56	0.21(-0.89-2.20)	0.25±0.47	0.20(-0.63-1.71)	0.993

Continuous variables are expressed as mean ± standard deviation and median (minimum–maximum). Statistical comparisons between dapagliflozin and empagliflozin groups were performed using the Mann–Whitney U test.
Δ: Change from baseline to 12 months.
Abbreviations: BMI, body mass index; FBG, fasting blood glucose; ALT, alanine aminotransferase; AST, aspartate aminotransferase.

Liver enzyme levels showed favorable trends. ALT remained stable overall but demonstrated a small yet significant increase (33.6±6.9 to 34.8±5.5 U/L, p<0.001), while AST levels decreased from 35.1±9.5 to 32.3±6.6 U/L (p<0.001).

Importantly, the FIB-4 score decreased significantly from 1.4±0.5 to 1.2±0.3 in the overall population (p<0.001), with similar declines observed in the empagliflozin (1.5±0.6 to 1.2±0.3, p<0.001) and dapagliflozin (1.4±0.5 to 1.2±0.4, p<0.001) groups. These changes translated into a notable shift in FIB-4 risk categories over the 12-month period (Figure 1), with an increase in the proportion of patients categorized as low risk and a decrease in those classified as intermediate or high risk.

Serum creatinine levels increased slightly but significantly in the overall cohort (0.9±0.1 to 1.0±0.2 mg/dL, p<0.001), with a less pronounced change in the dapagliflozin group (0.9±0.1 to 0.9±0.2 mg/dL, p=0.0431). Urea levels remained stable in all groups (all p>0.05).

Comparison of 12-Month Changes Between Dapagliflozin and Empagliflozin Groups (Table 2)

Between-group analysis revealed no statistically significant differences in the magnitude of change across key clinical variables, suggesting that both empagliflozin and dapagliflozin exerted

comparable effects.

Mean weight reduction was similar between the dapagliflozin and empagliflozin groups (3.20±2.95 kg vs. 3.53±3.11 kg, p=0.489), as was BMI reduction (1.15±1.00 vs. 1.24±1.00 kg/m^2, p=0.500). HbA1c declined by 1.22±1.00% in the dapagliflozin group and by 1.37±0.99% in the empagliflozin group (p=0.211), and FBG reductions were also similar (49.6±53.8 vs. 53.3±60.2 mg/dL, p=0.816).

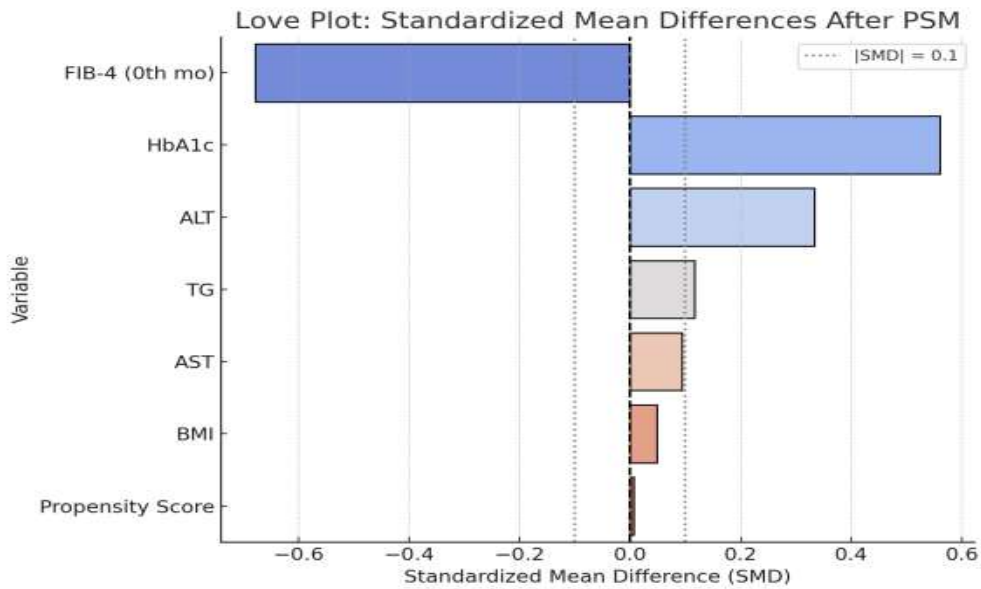
Changes in hepatic markers such as ALT (−2.14±5.6 vs. −1.65±5.24 U/L, p=0.514) and AST (3.14±5.22 vs. 2.60±5.40 U/L, p=0.281) were comparable. FIB-4 score changes did not differ significantly (0.26±0.56 vs. 0.25±0.47, p=0.993). These findings support a class effect of SGLT2 inhibitors on hepatic and metabolic outcomes.

Predictors of FIB-4 Response: Matched Analysis and ROC Evaluation (Table 3, Figure 2, Figure 3)

To assess predictors of favorable hepatic response, patients were categorized as responders (≥20% reduction in FIB-4 at 12 months) and non-responders. Propensity score matching (PSM) yielded two well-balanced groups (n=27 per group), with all baseline covariates demonstrating standardized mean differences <0.1, confirming adequate matching (Figure 2).

Figure 2

Standardized mean differences (SMDs) of baseline covariates between responder and non-responder groups following 1:1 propensity score matching.



Each bar represents the SMD for a specific covariate, comparing the matched responder and non-responder groups. The vertical dashed lines at ±0.1 denote the threshold for acceptable covariate balance. All covariates demonstrated satisfactory balance after matching (SMD < 0.1), indicating successful adjustment of baseline differences between groups.

Table 3

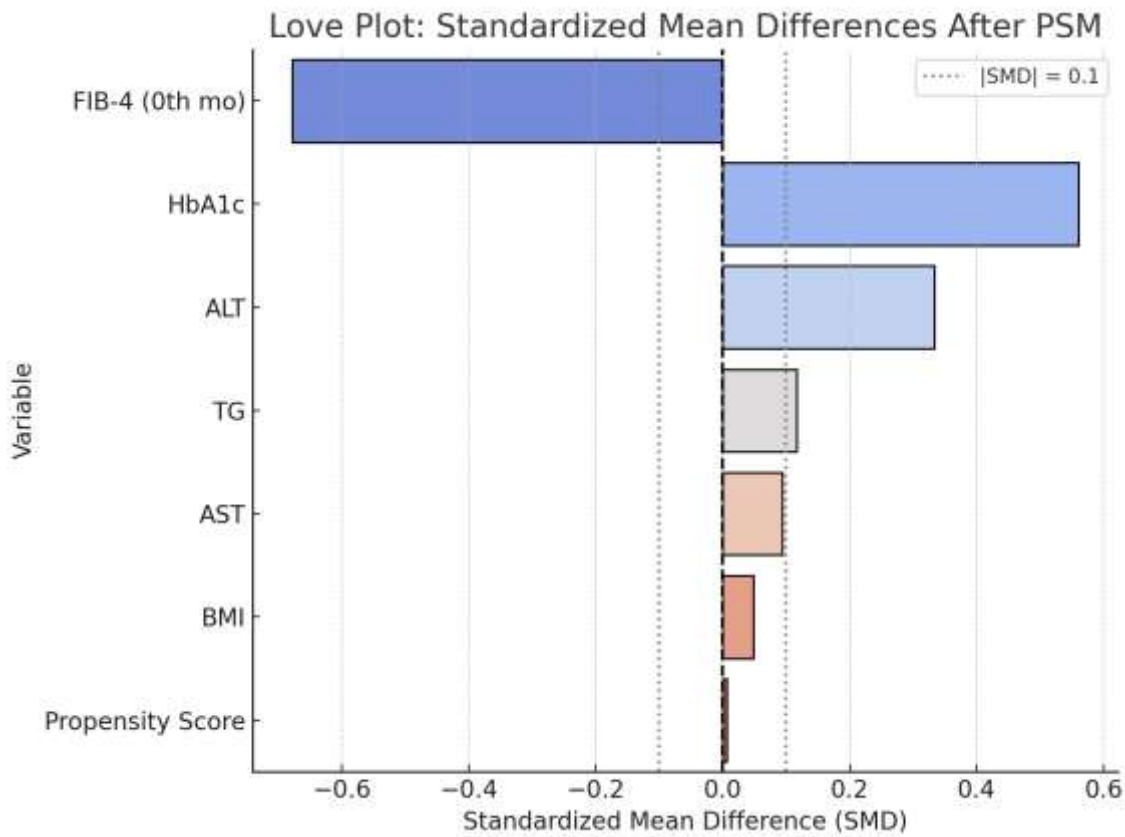
Baseline Characteristics of Propensity Score-Matched Responders and Non-Responders

	Responder (n=27)		Non-responder (n=27)		p-value
Variable	Mean ± SD	Median (IQR)	Mean ± SD	Median (IQR)	
BMI	31.25 ± 3.82	30.72 (29.47–33.14)	31.05 ± 4.44	32.11 (27.97–33.85)	0.9369
HbA1c	9.54 ± 1.87	10.10 (7.75–11.10)	8.59 ± 1.52	8.20 (7.30–10.10)	0.1936
ALT	36.06 ± 6.14	36.00 (30.00–41.00)	33.94 ± 6.53	32.50 (30.00–40.50)	0.3723
AST	41.17 ± 5.07	41.00 (38.25–44.75)	40.56 ± 7.72	37.50 (34.25–44.00)	0.3659
TG	167.67 ± 43.01	165.00 (152.75–178.00)	163.28 ± 31.50	163.50 (155.75–176.75)	1.0
FIB-4 (baseline)	1.48 ± 0.52	1.37 (1.00–1.72)	1.80 ± 0.42	1.87 (1.50–2.08)	0.0445
Propensity Score	0.22 ± 0.13	0.19 (0.12–0.30)	0.22 ± 0.13	0.19 (0.13–0.28)	1.0

BMI: body mass index; HbA1c: hemoglobin A1c; ALT: alanine aminotransferase; AST: aspartate aminotransferase; TG: triglycerides; FIB-4: fibrosis-4 score.Data are presented as mean ± standard deviation and median (interquartile range). Comparisons were made using the Mann–Whitney U test for continuous variables. This table summarizes the clinical and laboratory parameters after 1:1 nearest neighbor propensity score matching based on baseline covariates. All covariates showed satisfactory post-matching balance (SMD < 0.1), supporting the effectiveness of the propensity score matching procedure.

Figure 3

Standardized mean differences (SMDs) of baseline covariates between responder and non-responder groups following 1:1 propensity score matching.



Each bar represents the SMD for a specific covariate, comparing the matched responder and non-responder groups. The vertical dashed lines at ±0.1 denote the threshold for acceptable covariate balance. All covariates demonstrated satisfactory balance after matching (SMD < 0.1), indicating successful adjustment of baseline differences between groups.

Baseline characteristics were mostly similar between groups. BMI (31.25±3.82 vs. 31.05±4.44 kg/m^2, p=0.9369), HbA1c (9.54±1.87% vs. 8.59±1.52%, p=0.1936), ALT, AST, and triglycerides were all comparable (all p>0.05). However, baseline FIB-4 was significantly lower in responders (1.48±0.52 vs. 1.80±0.42, p=0.0445), suggesting a more modifiable fibrotic burden in this subgroup.

Receiver operating characteristic (ROC) analysis was performed to identify biochemical predictors of FIB-4 response (Figure 3). Among all evaluated variables, ΔAST emerged as the most accurate predictor, with an AUC of 0.875 (95% CI: 0.779–0.971), and an optimal cut-off of ≥7 U/L, yielding 83% sensitivity and 83% specificity per the Youden index. Other variables, including ΔALT, ΔHbA1c, ΔTG, and ΔBMI, showed weaker discriminative performance.

4. Discussion

In this prospective study, 12-month therapy with SGLT2 inhibitors—empagliflozin or dapagliflozin—led to significant improvements in metabolic parameters and liver fibrosis risk, as assessed by FIB-4 score, in overweight and obese patients with T2DM. Both agents resulted in reductions in BMI, fasting blood glucose, HbA1c, triglycerides, and LDL cholesterol. Importantly, FIB-4 score values declined significantly in both groups. The magnitude of AST reduction (ΔAST ≥7 U/L) emerged as a strong independent predictor of fibrosis regression, highlighting its potential as a simple clinical marker for monitoring hepatic improvement.

SGLT2 inhibitors are widely used in T2DM due to their proven cardioprotective and renoprotective properties.[1] Given the high co-prevalence of MASLD in T2DM[4] and its established association with CVD[2,3], therapeutic agents that address both metabolic and hepatic risks are of increasing clinical interest. The severity of MASLD, particularly the fibrosis stage, has been shown to be a strong predictor of adverse cardiovascular outcomes.[3]

Several recent studies have explored the hepatic benefits of SGLT2 inhibitors. A meta-analysis by Mantovani et al.[7] confirmed that SGLT2 inhibitors significantly reduce hepatic fat accumulation and transaminase levels in patients with T2DM and NAFLD. Arai et al.[8] reported a significant decrease in FIB-4 scores and improvements in transaminases, glucose, body weight, and HbA1c after 48 weeks of SGLT2 inhibitor therapy. Similarly, Shinozaki et al.[9] observed reductions in FIB-4, fasting glucose, and liver enzymes after long-term empagliflozin treatment.

In our cohort, the proportion of patients in the intermediate and high-risk FIB-4 categories decreased from 50% and 6.5% at baseline to 40.5% and 1.5%, respectively, in 12 months. These results are consistent with the findings of Liu et al., who reported post-treatment improvement in fibrosis risk categories in diabetic patients receiving SGLT2 inhibitors.[10] The E-LIFT trial

demonstrated similar effect.[11] Likewise, Kahl et al.[12] showed reductions in hepatic fat content in empagliflozin-treated patients compared to placebo, while Lai et al.[13] provided histologic evidence of steatosis, ballooning, and fibrosis improvement.

Shibuya et al.[14] found that SGLT2 inhibitors outperformed metformin in reducing hepatic steatosis and HbA1c in patients with NAFLD. Takahashi et al.[15] further demonstrated that ipragliflozin prevented new-onset NASH and improved hepatic and metabolic outcomes over time.

4.1. Mechanistic Insights

The mechanistic basis for these effects includes reductions in hepatic inflammation, oxidative stress, and stellate cell activation. Empagliflozin has been shown to downregulate fibrogenic gene expression and inflammatory cytokines in animal models[16], while dapagliflozin reduces macrophage infiltration and fibrosis signaling pathways.[17] These pleiotropic effects, combined with improvements in weight, insulin sensitivity, and lipid metabolism, are likely to contribute to the observed fibrosis regression.

4.2. Clinical Implications

These findings reinforce the potential of SGLT2 inhibitors to offer multi-organ protection in patients with T2DM, extending beyond the cardiovascular and renal systems to the liver. The identification of ΔAST as a sensitive and accessible marker for fibrosis response may facilitate non-invasive risk stratification and treatment monitoring in MASLD. Given the high prevalence of MASLD among diabetic patients, clinicians may consider SGLT2 inhibitors, particularly in individuals with suspected or early-stage fibrosis. Given the accessibility of AST in routine panels, ΔAST could serve as a simple early indicator of hepatic improvement in daily practice.

4.3. Strengths and Limitations

This study's strengths include its real-world and the direct comparison of two SGLT2 inhibitors over a 12-month period. The use of the FIB-4 score, a validated and widely accepted non-invasive fibrosis marker, enhances clinical applicability. Moreover, propensity score matching in the responder analysis strengthens the internal validity of fibrosis-related outcomes.

However, several limitations should be acknowledged. The observational design precludes definitive causal inference despite statistical adjustment. The fact that the follow-up period of the patients is 1 year is limiting in terms of predicting the effects in the longer term. Liver fibrosis was assessed using a surrogate index rather than histological confirmation or elastography. The sample size of the matched cohort was relatively small, and the study was conducted at a single tertiary care center, which may limit generalizability.

5. Conclusion

In conclusion, empagliflozin and dapagliflozin were both associated with significant improvements in hepatic and metabolic outcomes in overweight and obese patients with T2DM. The reduction in FIB-4 scores and the predictive value of AST dynamics highlight the potential antifibrotic role of SGLT2 inhibitors. These findings support the integration of liver fibrosis assessment into routine diabetes care and warrant future randomized trials incorporating histologic and imaging-based fibrosis endpoints.

Statement of ethics

The study was approved by the Institutional Review Board (Approval Date: August 21, 2024; Decision No: 2024-13/2) and conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from all participants before enrollment.

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Conflict of interest statement

The authors declare that they have no conflict of interest.

Availability of data and materials

This Data and materials are available to the researchers.

Author contributions

Concept: NY, AE, Design: NY, AE, GZG, NK. Data Collection or Processing: NY, AE, GZG,. Analysis or Interpretation: NY, NK. Literature Search: NY, AE, GZG, NK. Writing: NY, NK.

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