EVALUATION OF LIVER OUTCOMES RELATIVE TO USE OF GLP-1 RECEPTOR AGONISTS (GLP1A) AND/OR SGLT-2 INHIBITORS (SGLT2I) IN REAL-WORLD POPULATIONS DIAGNOSED WITH TYPE II DIABETES (T2DM) AND NASH/NAFLD OR AT RISK OF NASH

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1. BACKGROUND AND AIM

Currently, no drugs are FDA approved for the treatment of NASH/NAFLD. However, some success has been observed with GLP1a in histological resolution of NASH without worsening of fibrosis and with SGLT2i in reduction of body weight, ALT, and FIB4 compared with baseline values. Here, we examined development of advanced liver disease in T2DM patients with NASH/NAFLD or at risk of NASH with regard to use of SGLT2i and GLP1a.

2. METHODS

Data collected from a proprietary US EMR database were limited to adult T2DM (ICD10 E11. 9) patients diagnosed with NASH/NAFLD (ICD10 K76, 75.81) or with a risk profile of Age >50 + ALT >30 U/L + [BMI >30 or T2DM] and without viral hepatitis or evidence of alcohol abuse. Index date was the first calculable FIB4 between Jul 2015 to Jun 2017 with >1y history and >2y follow-up or to death. Advanced liver disease was defined as cirrhosis (compensated or decompensated), hepatocellular carcinoma, or liver transplant. All-cause death was not considered. Propensity scores (PS) using age, obesity, race/ethnicity, gender, NASH/NAFLD v RISK, statin use, major cardiovascular events (MACE), and FIB4 at index were used to match treated and non-treated groups. Cumulative Incidence curves were computed for 4 patient characteristics of interest: treatment, FIB4 group, Age group, and prior MACE. Cox proportional models were used to determine hazard ratios (HR) between groups. All multiple regression models used complete-case analysis and included treatment, MACE, FIB4, gender, age, race/ethnicity, and all covariates with p <0.200 by individual models.

3. RESULTS

Of 30MM adult patients, 31323 met all study criteria and either received SGLT2i and/or GLP1a at index (treated, 10%, 3208) or never received these therapies prior to or during follow up from index (not-treated, 90%, 28115) [Table 1].

Mean follow up was 36.5 months. Significant differences were observed between treated and not-treated groups for age, gender, race, BMI, and comorbidities at index. Advanced liver disease at index was significantly lower for the treated group (16%, 516/3208 v 29%, 8169/28115 not-treated, p<0.001). PS-matching of patients without advanced liver disease at index yielded 1720 pairs, which remained different for hyperlipidemia (89% treated, 84% not-treated, p<0.001) [Table 2].

Patients treated with GLP-1 or SGLT2 were found to have significantly lower incidence during follow-up vs those with no treatment. FIB4 and age groups and were found to have a positive association with incidence of ALD during follow-up, though the magnitude of this effect appeared to be smaller in within matched cohort. Prior MACE was found to be associated with increased incidence of ADL during follow-up as well [Figure 1].

Cox hazard ratios for developing advanced liver disease were favorable for treatment (0.74 [0.63-0.87] p<0.001) and unfavorable for FIB4 >2.67 (2.17 [1.59-2.96] p<0.001), MACE (2.32 [1.91-2.82], p<0.001), Age ≥75 (1.84 [1.91-2.82] p=0.005), and CVD (1.27 [1.07-1.52] p=0.007) at index [Figure 2].

TABLE 1: PATIENT DISPOSITION

SGLT2i or GLP1a N (% by row)	NASH / NAFLD	Risk	w/o Advanced Liver Disease at Index	Advanced Liver Disease at Index	Total
Never treated	5,700 (20)	22,415 (80)	19,946 (71)	8,169 (29)	28115
Treated at Index	862 (27)	2,346 (77)	2,692 (84)	516 (16)	3208
Total	6562 (21)	24761 (79)	22,638 (72)	8,685 (28)	31323

TABLE 2: PATIENT CHARACTERISTICS AT INDEX

Characteristics, n/N (%)	(A) Treated	(B) Not-Treated	(C) Matched Treated	(D) Matched Not-Treated
N	3208	28115	1720	1720
Age				
18-50	**373/3208 (12)**	**1792/28115 (6)**	157/1720 (9)	155/1720 (9)
51-64	**1938/3208 (60)**	**11774/28115 (42)**	1097/1720 (64)	1099/1720 (64)
65-74	**755/3208 (24)**	**9545/28115 (34)**	405/1720 (24)	405/1720 (24)
75+	**142/3208 (4)**	**5004/28115 (18)**	61/1720 (4)	61/1720 (4)
Gender				
Female	**1687/3208 (52.6)**	**14067/28109 (50.0)**	866/1720 (50.3)	875/1720 (50.9)
Male	**1521/3208 (47.4)**	**14042/28109 (50.0)**	854/1720 (49.7)	845/1720 (49.1)
Race/Ethnicity				
White	**2375/2969 (80.0)**	**19286/25916 (74.4)**	1357/1720 (78.9)	1359/1720 (79.0)
Black	**419/2969 (14.1)**	**4607/25916 (17.8)**	257/1720 (14.9)	259/1720 (15.1)
Hispanic	**112/2969 (3.8)**	**1322/25916 (5.1)**	64/1720 (3.7)	62/1720 (3.6)
Other	**63/2969 (2.1)**	**701/25916 (2.7)**	42/1720 (2.4)	40/1720 (2.3)
Obese (BMI ≥30)	**1630/2082 (78.3)**	**12753/20216 (63.1)**	1352/1720 (78.6)	1345/1720 (78.2)
Risk Group				
RISK	**2346 (73.1)**	**22415 (79.7)**	1287 (74.8)	1292 (75.1)
NAFLD	**817 (25.5)**	**5332 (19.0)**	416 (24.2)	413 (24.0)
NASH	**45 (1.4)**	**368 (1.3)**	17 (1.0)	15 (0.9)
FIB4 Category				
<1.3	**1973 (61.5)**	**12763 (45.4)**	1110 (64.5)	1120 (65.1)
≥1.3<2.67	**1025 (32.0)**	**11380 (40.5)**	533 (31.0)	530 (30.8)
≥2.67	**210 (6.5)**	**3972 (14.1)**	77 (4.5)	70 (4.1)
Comorbidities				
Compensated Cirrhosis	**512/3208 (16.0)**	**8089/28115 (28.8)**	0/1720 (0.0)	0/1720 (0.0)
Decompensated Cirrhosis	**478/3208 (14.9)**	**7818/28115 (27.8)**	0/1720 (0.0)	0/1720 (0.0)
Hepatocellular Carcinoma	**3/3208 (0.1)**	**104/28115 (0.4)**	0/1720 (0.0)	0/1720 (0.0)
Liver transplant	**5/3208 (0.2)**	**189/28115 (0.7)**	0/1720 (0.0)	0/1720 (0.0)
MACE	**523/3208 (16.3)**	**7040/28115 (25.0)**	194/1720 (11.3)	190/1720 (11.0)
Cardiovascular Disease	2254/3208 (70.3)	19466/28115 (69.2)	1104/1720 (64.2)	1092/1720 (63.5)
Cancer	**325/3208 (10.1)**	**4089/28115 (14.5)**	163/1720 (9.5)	178/1720 (10.3)
Hyperlipidemia	**2742/3208 (85.5)**	**22131/28115 (78.7)**	**1525/1720 (88.7)**	**1450/1720 (84.3)**
Hypertension	**2182/3208 (68.0)**	**18117/28115 (64.4)**	1091/1720 (63.4)	1035/1720 (60.2)
Drugs				
GLP1a	**2281/3208 (71.1)**	**0/28115 (0.0)**	1186/1720 (69.0)	0/1720 (0.0)
SGLT2i	**1326/3208 (41.3)**	**0/28115 (0.0)**	769/1720 (44.7)	0/1720 (0.0)
Statins	**2476/3208 (77.2)**	**17869/28115 (63.6)**	1395/1720 (81.1)	1395/1720 (81.1)

4. LIMITATIONS

While adjustments were made for most comorbidities and liver disease severity, the full spectrum of concomitant medications was not accounted for in these analyses. This remains a concern and limitation to these analyses.

FIGURE 1: CUMULATIVE INCIDENCE OF ALD IN UNMATCHED & MATCHED COHORTS

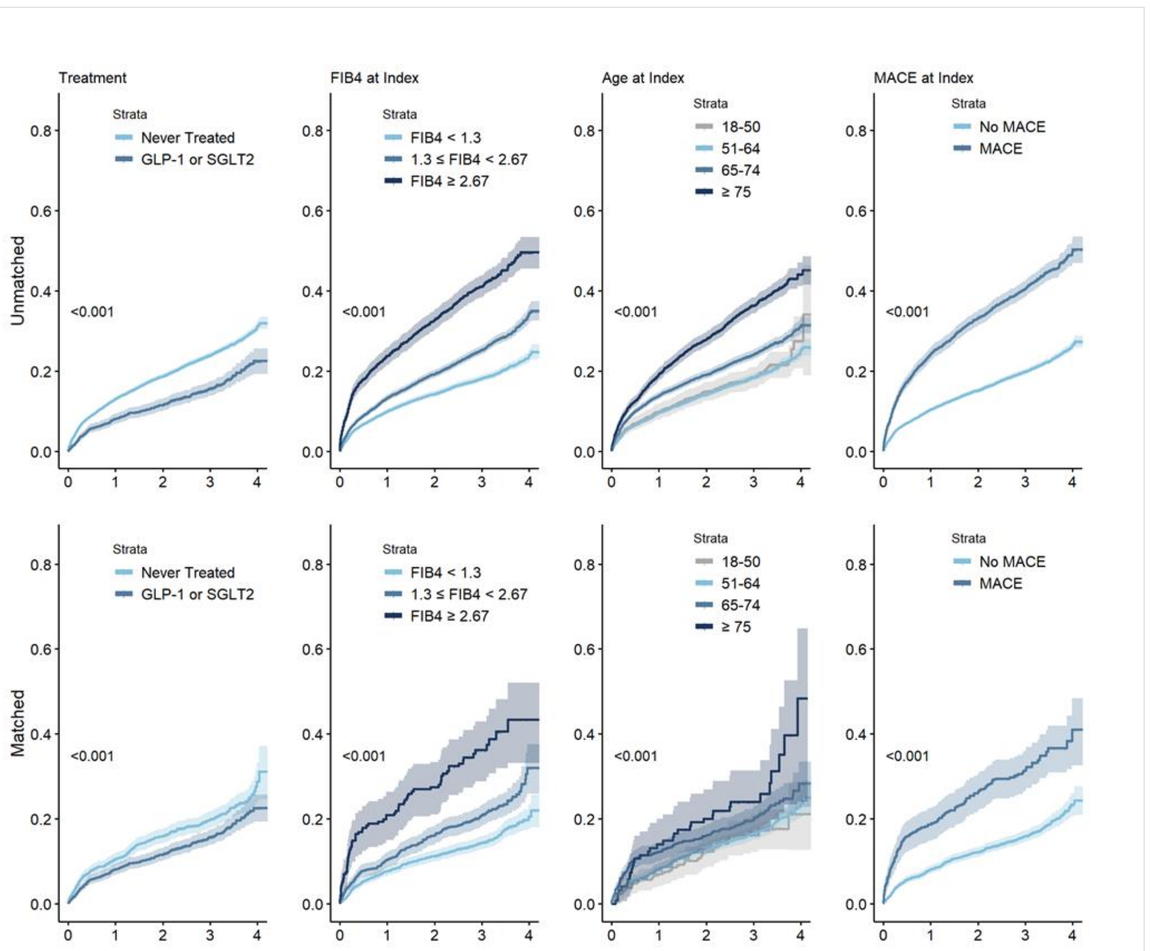
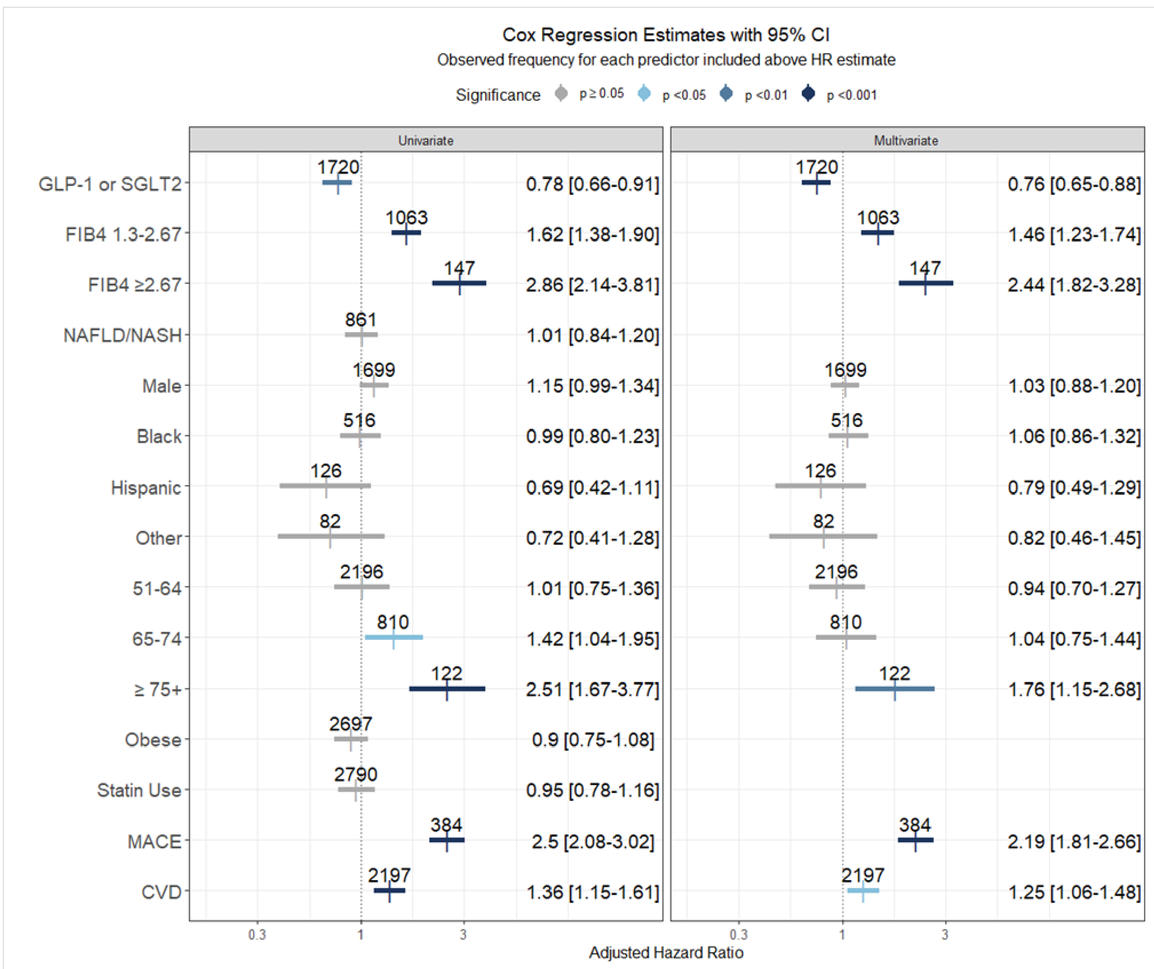


FIGURE 2: COX REGRESSION ESTIMATES WITH 95% CI



5. CONCLUSION

In T2DM patients with NASH/NAFLD or at risk of NASH, the risk of developing advanced liver disease was lower in patients treated with SGLT2i and/or GLP1a.

This study was supported by Gilead Sciences, Inc. One or more of the authors receive research support and/or serve as advisors for AbbVie, Ambys, Arbutus, Assembly Biosciences, Bristol-Myers Squibb, Co-Crystal, Conatus, Dova, Durect, Echosens, EdiGene, Eisai, Exact Sciences, Exelixis, Ferring, Gilead, GlaxoSmithKline, Intercept, Janssen, Ligand, Mallinckrodt, Merck, Roivant, Shionogi, Spark Therapeutics, Surrozen, Target (HCC, HCV, NASH), and Trio Health. S. Milligan, N. Afdhal, J. Broestl, and A. Frick are employed by Trio Health. K. Juneja is employed by Gilead Sciences. N. Afdhal owns stock in Spring Bank.