# Glucagon-Like Peptide-1 Receptor Agonists vs Dipeptidyl Peptidase-4 Inhibitors on Major Liver Outcomes in Patients with Type 2 Diabetes and Nonalcoholic Fatty Liver Disease

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## BACKGROUND

- Nonalcoholic fatty liver disease (NAFLD), also known as metabolic dysfunction-associated fatty liver disease (MASLD), elevates the risk of cirrhosis and liver cancer.[1] Current treatments are limited.[2]
- Glucagon-like peptide-1 receptor agonists (GLP-1RA), a type of diabetes medication, have shown potential benefits for biochemical and histological markers of NAFLD, reducing liver damage and aiding weight loss.[3]
- The long-term effects of GLP-1RAs on major liver outcomes, such as cirrhosis and hepatocellular carcinoma (HCC), have not been studied.

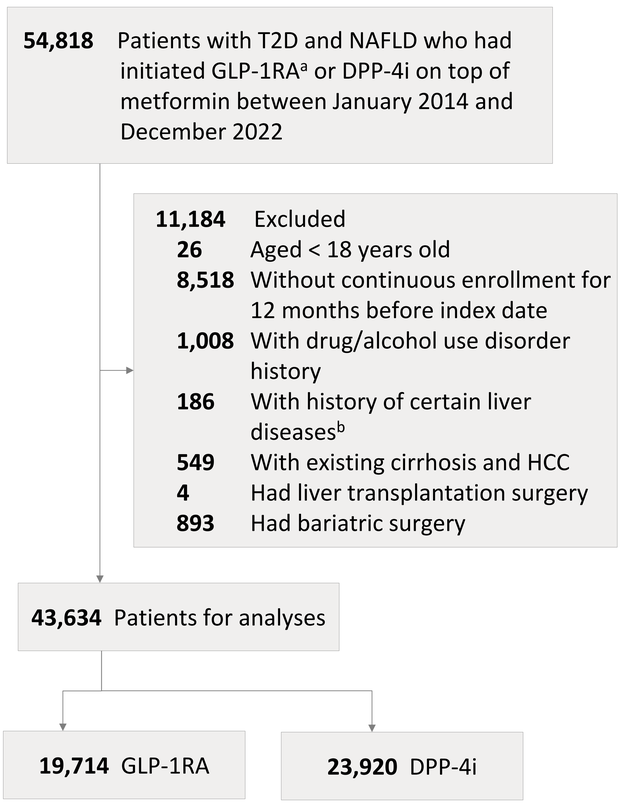
## OBJECTIVE

To determine the effectiveness of GLP-1RA in reducing major liver outcomes among patients with type 2 diabetes (T2D) and NAFLD.

## METHODS

- Study design: Retrospective cohort study with **comparative effectiveness** design.
- Study period: January 2014 to December 2022.
- Data source: **IBM MarketScan** Commercial Claims.
- Study population (see **Figure 1**).
- Active comparator: Dipeptidyl peptidase-4 inhibitor (DPP-4i).
- Outcomes:
  - Primary: Composite of cirrhosis and HCC.
  - Secondary: cirrhosis (compensated and decompensated), and HCC.
- Statistical analyses:
  - Kaplan-Meier, Cox-proportional hazard model with **overlap weighting**.
  - Bootstrap iteration was used for generating confidence interval.
- Subgroup analyses (see **Table 3**).

### Figure 1. Study Participants Inclusion Flow Chart




a. Oral semaglutide (Rybelsus) was not included in our study.
b. Alcohol related liver disease, autoimmune liver disease, hemochromatosis, Wilson, alpha-1-antitrypsin deficiency, Budd-Chiari, unspecified chronic hepatitis, secondary or unspecified biliary cirrhosis.

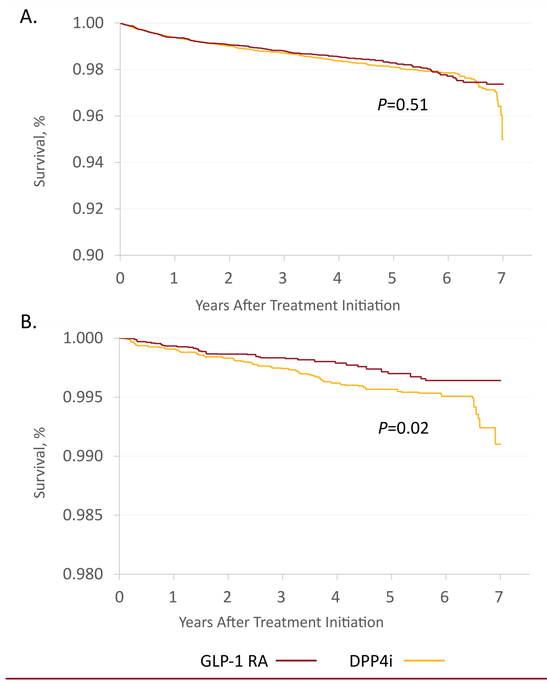
## RESULTS

- The GLP-1RA group had a higher obesity rate (**Table 1**). However, all covariates were balanced between two groups after weighting.
- GLP-1RA did not significantly reduce the risk of cirrhosis/HCC compared to DPP-4i (**Figure 2A** and **Table 2**).
- However, GLP-1 RA initiators had a lower risk of HCC compared to DPP-4i (**Figure 2B** and **Table 2**).
- Subgroup analyses showed consistent nonsignificant results (**Table 3**).

### Table 1. Unadjusted Baseline Characteristics

| Characteristics | DPP-4i | GLP-1RA |
|---|---|---|
| Age, y, median (IQR) | 55.0 (11.0) | 54.0 (11.0) |
| Male, n (%) | 11,286 (58.4) | 8,055 (41.7) |
| **Obesity, n (%)** | **8,191 (34.2)** | **10,137 (51.4)** |
| Statin, n (%) | 10,632 (44.4) | 8,622 (43.7) |
| Insulin, n (%) | 2,525 (10.6) | 5,352 (27.1) |

### Figure 2. Weighted Kaplan-Meier Curve of the Primary Outcome (A) and HCC (B)

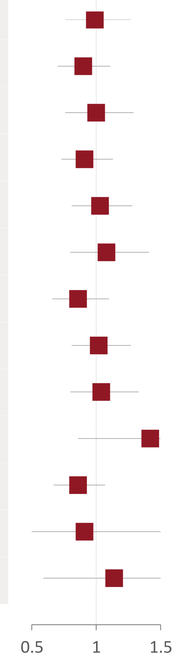



### Table 2. Adjusted Hazard Ratios for All Outcomes after Overlap Weighting

| Outcomes | aHR (95%CI) |
|---|---|
| **Composite of cirrhosis & HCC** | **0.94 (0.77-1.11)** |
| Overall cirrhosis | 0.97 (0.79-1.15) |
| Compensated cirrhosis | 0.82 (0.53-1.16) |
| Decompensated cirrhosis | 0.97 (0.78-1.17) |
| **HCC** | **0.62 (0.37-0.93)** |

### Table 3. Subgroup Analyses for Primary Outcome

| Variables | Subgroups | aHR (95%CI) |
|---|---|---|
| Age | >55 | 0.99 (0.76-1.27) |
| | ≤55 | 0.90 (0.70-1.11) |
| Gender | Male | 1.00 (0.76-1.29) |
| | Female | 0.91 (0.73-1.13) |
| Index year | <2016 | 1.03 (0.81-1.28) |
| | ≥2016 | 1.08 (0.80-1.41) |
| Obesity | Yes | 0.86 (0.66-1.10) |
| | No | 1.02 (0.81-1.27) |
| GLP-1 RA type | Dulaglutide | 1.04 (0.80-1.33) |
| | Exenatide | 1.42 (0.86-2.10) |
| | Liraglutide | 0.86 (0.67-1.07) |
| | Lixisenatide | 0.91 (0.00-2.68) |
| | Semaglutide | 0.36 (0.59-1.94) |




## STRENGTHS & LIMITATIONS

- Major strength: Head-to-head comparison between GLP-1 RA and DPP-4i, reducing confounding bias and preventing overestimation.
- Major limitation: The study design and using MarketScan database may not capture all possible outcomes required longer follow-up.

## CONCLUSIONS

GLP-1 RA does not significantly reduce the risk of cirrhosis compared to DPP-4i. However, our study suggests a slightly lower risk of HCC in GLP-1 RA. Further research with longer follow-up periods should be considered.

## REFERENCES

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