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Glucagon-Like Peptide-1 Analogues and the Risk of Recurrent Pancreatitis in Diabetic Patients With History of Pancreatitis or Elevated Lipase: Retrospective Cohort Analysis

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ABSTRACT

Aims: The use of glucagon-like peptide-1 (GLP1) analogues has increased due to benefits in glycaemic control, weight loss, and cardiorenal protection. However, concerns persist regarding their potential link to pancreatitis. We assessed this link in high-risk patients with a history of pancreatitis or elevated lipase enzyme.

Methods: Retrospective data from a large health maintenance organisation (> 4.5 million insured members) were extracted using the MDClone data-sharing platform, with complete de-identification. We included adults with diabetes who experienced pancreatitis or had elevated lipase (> 1.5 times the upper reference limit), defining an index date for start of follow-up. GLP1 analogues were initiated in a portion of the cohort during the follow-up period. Patients who had used GLP1 analogues prior to or within 1 month of the index date were excluded. The primary outcome was recurrent pancreatitis. Survival and multivariate analyses, including time-varying models, were performed to assess the impact of GLP1 analogues on recurrent pancreatitis risk.

Results: The cohort included 46,186 patients (10,933 for pancreatitis, and 35,253 for elevated lipase, 55% men, median age 70.9 years). GLP1 analogue use was an independent risk factor for recurrent pancreatitis in a time-varying analysis (HR 1.252, 95% CI 1.178–1.332). This remained significant after adjusting for factors like gender, alcohol use, and medications associated with pancreatitis.

Conclusions: An increased risk of recurrent pancreatitis was observed in high-risk patients receiving GLP1 analogue therapy. These findings align with pharmacovigilance data and support caution when prescribing GLP1 analogues in this population. Prospective studies are warranted to further evaluate this association.

1 | Introduction

The global use of glucagon-like peptide 1 (GLP1) analogues for treatment of diabetes and obesity is increasing due to their profound effects on glycaemic control, promotion of weight loss, and cardiovascular and kidney protection [1–3]. However, gastrointestinal side effects are common and may lead to drug discontinuation [4].

Acute pancreatitis has an annual incidence of 13–45 per 100,000 people in the U.S. and mortality rate of about 1% [5, 6]. Major risk factors are cholelithiasis, alcohol abuse, hypertriglyceridemia,

diabetes mellitus, obesity and certain medications. It has been contemplated that GLP1 analogues might increase pancreatitis risk, as indicated by drug leaflet warnings for patients with a history of the condition. This is mostly based on pharmacovigilance and retrospective studies that have suggested a possible link between GLP1 analogues and pancreatitis [7–11]. Conversely, randomised controlled trials and meta-analyses of GLP1 analogues utilisation in patients with diabetes mellitus or obesity generally do not show a significant increase in pancreatitis risk [12–14]. Also, some trials have reported an increase in pancreatic enzyme levels under treatment with GLP1 analogues [15–18], but with unclear clinical relevance. Notably, most of the prospective studies excluded patients with a history of pancreatitis; thus, most of the evidence on these drugs was tested in a population at low risk for pancreatitis.

Given the insufficient evidence, we aimed to investigate whether GLP1 analogues are associated with a greater risk of pancreatitis in high-risk patients, namely those with a history of pancreatitis or a history of elevated lipase enzyme.

2 | Methods

We conducted a retrospective cohort study using the database of the largest Health Maintenance Organisation in Israel, Clalit Health Services (5,400,282 insured patients in November 2024). The study protocol received approval from the local Institutional Review Board. The data were extracted using the data-sharing platform powered by MDClone (https://www.mdclone.com). Data collection ensured anonymity, with patient information excluded from database analysis.

The study included adult (> 18 years) patients with diabetes mellitus who experienced an event of pancreatitis or had blood test results of elevated lipase values between January 1, 2012 and March 3, 2024, with a minimum observation period of 3 months. Of note, patients were included based on either International Statistical Classification of Diseases 10 (ICD-10) coding for pancreatitis or laboratory evidence of elevated serum lipase (> 1.5 × upper reference limit), even if a clinical diagnosis of pancreatitis was not documented. This deliberate inclusion criterion reflects a real-world scenario frequently encountered in practice, where clinicians must decide whether to initiate GLP1 receptor agonists in patients with a history of unexplained or asymptomatic lipase elevation. Imaging data were not uniformly available in the anonymised dataset; therefore, pancreatitis could not be systematically confirmed in these cases.

The date of the first occurrence of pancreatitis or detection of elevated lipase since 2012 was defined as the index date for start of study follow-up. Accordingly, the inclusion for pancreatitis by ICD code was defined as 'pancreatitis on index', and inclusion for elevated lipase enzyme was defined as 'elevated lipase on index'. The index date was assessed starting 2012 since GLP1 analogues were available in Israel starting that year. Patients who had received treatment with GLP1 analogues prior to or up to 1 month after the index date were excluded. The primary outcome was a new event of pancreatitis over the study follow-up (defined as 'recurrent pancreatitis'). The recurrent episode of pancreatitis was defined if it occurred at least 2 months after the index date to assure recurrence rather than persistence of the baseline episode. The duration of follow-up extended until the occurrence of recurrent pancreatitis, death or the end of the study.

The GLP1 analogues included in our dataset were exenatide, lixisenatide, liraglutide, dulaglutide, and semaglutide. All were prescribed at doses approved for the treatment of type 2 diabetes and not for obesity. In our country, GLP1 analogues approved for obesity are marketed under different brand names and are subject to strict purchase limitations that preclude use beyond the approved dose for a given indication. However, we cannot exclude the possibility that some patients received submaximal diabetes-approved doses, as individual-level dosing records were not available.

Data on patient characteristics and variables that are associated with risk of pancreatitis were collected at baseline (the index date). The date of a new prescription of GLP1 analogues was extracted. This is the only parameter that occurred during the study follow-up and not on the index date.

Information was extracted based on demographic parameters, ICD codes, laboratory values and the Anatomical Therapeutic Chemical (ATC) drug classification system. These included gender, age, socioeconomic status, smoking status, alcohol abuse, body mass index (BMI), duration of diabetes mellitus and haemoglobin A1c, triglyceride levels and estimated glomerular filtration rate (eGFR). The use of medications known to increase the risk of pancreatitis (Supporting Information S1: Table 1) was extracted and incorporated as a binary variable (use of ≥ 1 drug vs. none). This parameter was included in all multivariable and time-varying models. Information on the exact number or cumulative duration of such drugs was not available due to dataset anonymisation.

2.1 | Statistical Analysis

The statistical analysis for this paper was generated using SAS Software, Version 9.4.

Continuous variables are presented by mean ± std or median and interquartile range (IQR). Categorical variables are presented by number (N) and percentage (%).

We first assessed differences between patients who were started on GLP1 analogues during the study compared with patients who did not. Cox proportional hazard models were used to calculate univariate hazard ratios (HR) of baseline variables for GLP1 use. As the use of GLP1 occurred after the index date, death with no GLP1 use was treated as a competing risk.

Next, we assessed predictors of recurrent pancreatitis. In the univariate and multivariate analyses of the effect of GLP1 use on recurrent pancreatitis, GLP1 use was treated as a time-varying

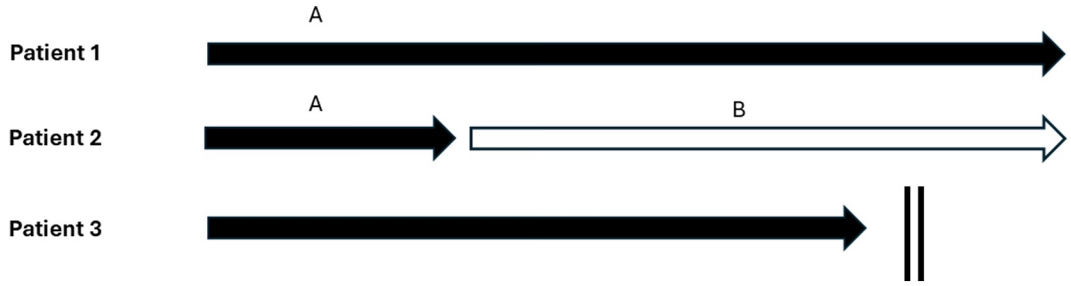

FIGURE 1 | A = 'no GLP'. B = 'GLP'. Patient 1—did not receive GLP1 analogues throughout the study. The patient was included in group A, 'no GLP'. Patient 2—did not receive GLP1 analogues during period of time A, and the data over that time was included in the 'no GLP' group. The patient then started GLP1 analogue therapy and switched to group B; the data over that time period was included in the 'GLP' group. Patient 3—died during the follow-up and did not receive GLP1 therapy until the time of death. The data for this patient was included in a competing risk analysis.

covariate, and death with no recurrent pancreatitis was treated as a competing risk.

A time-varying model considers a change in risk factors over time. To elaborate, the study participants were classified by GLP1 therapy or no therapy in each time period over the study follow-up and not by dichotomous allocation for GLP1 therapy. In other words, all patients were considered as 'no GLP' starting the index date. If a patient started GLP1 analogue therapy, his follow-up would switch to a group of 'GLP'. Patients who died during the study (with no GLP therapy initiation) were included in a competing risk analysis. Figure 1 illustrates patient categories for better clarification.

Prior to modelling, triglycerides and lipase were log-transformed to eliminate skewness.

The decision of which variables to include in the multivariate analysis of GLP1 use on recurrent pancreatitis was guided by prior articles on this subject and clinical and statistical considerations.

Two-sided p values less than 0.05 were considered statistically significant.

3 | Results

3.1 | Study Design and Cohort Overview

The study design is illustrated in Figure 2. The cohort included 46,186 adults (55% men, median age 70.9 years, IQR 69.6–79.4) who had either a documented episode of pancreatitis (n = 10,933) or elevated serum lipase ≥ 1.5 × the upper limit of normal (n = 35,253) at the index date. All patients were GLP1-naive at baseline. During follow-up, 6133 patients initiated GLP1 therapy, whereas 40,053 remained unexposed until the end of the study (among them, 17,138 patients died before treatment initiation and were considered a competing risk group). Outcomes included recurrent pancreatitis (n = 15,649), absence of recurrence (n = 19,301), and death as a competing event (n = 11,236). Each participant could contribute person-years to both exposure periods ('no GLP1' and 'GLP1 therapy'), consistent with the time-updated Cox model applied in this analysis.

3.2 | Patients Who Received GLP1 Analogues Compared to Non-Users

We first assessed differences between patients who started GLP1 analogue treatment during the study compared to patients who did not receive GLP1 analogues until the end of follow-up (regardless of the primary outcome of recurrent pancreatitis). GLP1 analogues were prescribed for 6133 patients (exenatide, n = 85; lixisenatide, n = 151; liraglutide, n = 1875; dulaglutide, n = 2240; semaglutide, n = 1612; all drugs in diabetes-approved doses) compared to 22,915 patients who did not receive GLP1 analogues (Table 1). GLP1 analogue users were younger compared to non-users (63.3 years, IQR 55.5–70.3, vs. 68.4 years, IQR 59.2–76.4). GLP1 users had a longer duration of diabetes mellitus prior to the index date (median 13.4 years, IQR 7.9–18.9 vs. 11.3 years, IQR 5.6–17.2 years) and poorer glycaemic control (HbA1c 7.3%, IQR 6.5%–8.6% vs. 6.4%, IQR 5.9%–7.3%). Additionally, GLP1 analogue users had higher BMI and triglyceride levels compared with non-users.

There were 17,138 patients who died during the follow-up without GLP1 therapy (data not shown). Their data was used as a competing risk in the survival model. These patients were significantly older compared to the other study groups (median age 77.5 years, IQR 69.0–84.0), had lower kidney function (eGFR 53 mL/min/1.73 m^2 compared to 79 and 85 mL/min/1.73 m^2 in the other study groups) and higher rates of a history of pancreatitis before the index date (21% vs. 13% and 10% in other study groups). The metabolic parameters of haemoglobin A1c, BMI and triglyceride levels were comparable with patients who did not receive GLP1 analogue treatment until the end of the study. The percentage of male participants, SES and duration of diabetes mellitus were similar in all study groups.

3.3 | Characterisation of Patients by Occurrence of the Primary Outcome—Recurrent Pancreatitis

The primary outcome of recurrent pancreatitis occurred in 15,649 patients compared with 19,301 patients who did not develop recurrent pancreatitis. Table 2 presents the characteristics of these study groups as extracted from the index date. Patients who developed recurrent pancreatitis and those who

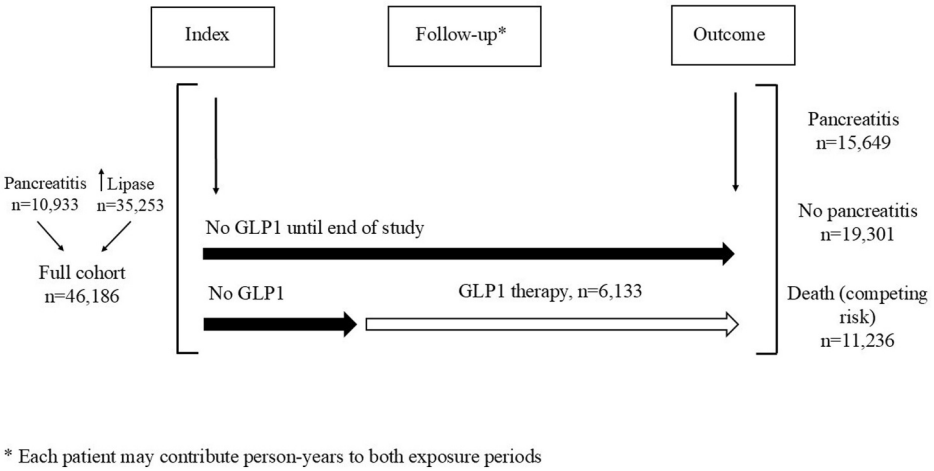

FIGURE 2 | Study design and time-varying exposure to GLP1 therapy. The figure depicts the study cohort ($n = 46,186$), consisting of patients with prior pancreatitis ($n = 10,933$) or elevated lipase ($n = 35,253$) at the index date. All were GLP1-naive at baseline. During follow-up, 6133 patients initiated GLP1 therapy, while others remained unexposed until the end of the study. Outcomes were recurrent pancreatitis ($n = 15,649$), no recurrence ($n = 19,301$), and death as a competing risk ($n = 11,236$). The schematic illustrates that each patient could contribute person-time to both exposure periods ('no GLP1' and 'GLP1 therapy'), consistent with the time-varying analytical approach used to avoid immortal-time bias.

TABLE 1 | Patients who received GLP1 analogues compared to non-users.

	No GLP1 agonists ($n = 22,915$)	**GLP1 agonists ($n = 6133$)**	**Hazard ratio (95% confidence interval)**
Age at first pancreatitis, years	68.4 (59.2–76.4)	63.3 (55.5–70.3)	0.961 (0.960–0.963)
Gender, male, *n* (%)	12,565 (55%)	3476 (57%)	1.085 (1.032–1.141)
SES, *n* (%)			
High	3424 (15%)	816 (13%)	Reference
Medium	13,431 (59%)	3524 (57%)	1.052 (0.975–1.134)
Low	4513 (20%)	1369 (22%)	1.258 (1.154–1.372)
Time from diabetes onset to first pancreatitis, yrs	11.3 (5.6–17.2)	13.4 (7.9–18.9)	1.015 (1.013–1.017)
BMI, mg/kg^2	27.5 (24.5–31.2)	30.8 (27.7–34.5)	1.069 (1.064–1.073)
Haemoglobin A1c, %	6.4 (5.9–7.3)	7.3 (6.5–8.6)	1.227 (1.214–1.241)
Triglycerides, mg/dL	132 (96–187)	157 (112–223)	1.720 (1.656–1.786)
eGFR, mL/min/1.73 m^2	79 (56–95)	85 (59–99)	1.014 (1.013–1.015)
Smoking, *n* (%)	8947 (39%)	2630 (43%)	1.325 (1.260–1.393)
Alcohol, *n* (%)	1209 (5%)	310 (5%)	0.810 (0.722–0.908)
Lipase, U/L	126 (102–186)	126 (103–178)	0.901 (0.845–0.961)
Lipase grade, *n* (%)			
1	3171 (14%)	1157 (19%)	Reference
2	3202 (14%)	1159 (19%)	1.006 (0.928–0.1091)
3	786 (3%)	229 (4%)	0.815 (0.708–0.938)
Pancreatitis on index (by ICD code), *n* (%)	6126 (27%)	1302 (21%)	0.878 (0.826–0.933)
History of > 1 pancreatic event[a], *n* (%)	2955 (13%)	635 (10%)	0.571 (0.527–0.620)
Drugs associated with risk of pancreatitis, *n* (%)	20,603 (90%)	5786 (94%)	1.254 (1.124–1.399)

Abbreviations: BMI, body mass index; CI, confidence interval; eGFR, estimated glomerular filtration rate; GLP1, glucagon-like peptide 1; SES, socioeconomic status.
[a]History of pancreatitis before the index date.

TABLE 2 | Baseline characteristics by occurrence of pancreatitis.

	No pancreatitis (n = 19,301)	Pancreatitis (n = 15,649)	Hazard ratio (95% confidence interval)
Age at first pancreatitis, years	67.6 (58.4–75.3)	69.7 (60.8–78.1)	0.994 (0.993–0.995)
Gender, male, n (%)	10,384 (54%)	9051 (58%)	1.150 (1.114–1.187)
SES, n (%)			
High	2917 (15%)	2097 (13%)	Reference
Medium	11,135 (58%)	9425 (60%)	1.106 (1.055–1.160)
Low	3920 (20%)	3164 (20%)	1.126 (1.066–1.190)
Time from diabetes onset to first pancreatitis, years	11.7 (5.8–17.7)	12.2 (6.7–17.4)	1.002 (1.001–1.004)
BMI, mg/kg^2	28.2 (25.0–32.0)	27.8 (24.7–31.6)	0.996 (0.994–0.999)
Haemoglobin A1c, %	6.5 (6.0–7.5)	6.6 (6.0–7.7)	1.014 (1.004–1.024)
Triglycerides, mg/dL	134 (97–191)	138 (99–197)	1.146 (1.114–1.179)
eGFR, mL/min/1.73 m^2	81 (58–96)	68 (40–90)	0.996 (0.996–0.997)
Smoking, n (%)	7418 (38%)	6288 (40%)	1.160 (1.123–1.197)
Alcohol, n (%)	852 (4%)	1257 (8%)	1.437 (1.357–1.522)
Lipase, U/L	125 (102–182)	129 (104–189)	1.030 (0.986–1.077)
Lipase grade, n (%)			
1	3136 (16%)	1838 (12%)	Reference
2	3073 (16%)	1988 (13%)	1.095 (1.028–1.166)
3	686 (4%)	501 (3%)	1.156 (1.047–1.276)
Pancreatitis on index (by ICD code), n (%)	4457 (23%)	4211 (27%)	1.225 (1.181–1.270)
History of > 1 pancreatic event[a], n (%)	1703 (9%)	3737 (24%)	1.820 (1.755–1.888)
Drugs associated with risk of pancreatitis, n (%)	17,050 (88%)	15,000 (95%)	1.859 (1.716–2.014)

Abbreviations: BMI, body mass index; CI, confidence interval; eGFR, estimated glomerular filtration rate; GLP1, glucagon-like peptide 1; SES, socioeconomic status.
[a]History of pancreatitis before the index date.

did not develop recurrent pancreatitis had comparable age, rate of male participants, socioeconomic status, smoking rates and metabolic indices, encompassing BMI, glycaemic control and triglycerides. The rate of alcohol use was higher (8% vs. 4%) and the eGFR was lower (67 vs. 80 mL/min/1.73 m^2) among those who developed recurrent pancreatitis during the study versus those who did not. Patients who developed recurrent pancreatitis also used more medications that are associated with the disease. Patients who developed recurrent pancreatitis had a significantly higher rate of a history of multiple pancreatic events, i.e. at least one episode of ICD10-coded pancreatitis before the index date (24% vs. 9%).

A total of 11,236 patients died before the end of the study with no recurrent pancreatitis until the time of death. Their data was used as a competing risk in the survival model. These patients were significantly older compared to the other study groups (median age 78.2 years, IQR 70.0–84.7) and had lower kidney function (eGFR 55 mL/min/1.73 m^2 compared to 81 and 68 mL/min/1.73 m^2 in the other study groups). The duration of diabetes and SES were comparable to the other study groups. The rate of inclusion of patients for ICD10 diagnosis of pancreatitis on the index date was comparable between all study groups.

3.4 | Predictors for Recurrent Pancreatitis

The most significant independent predictors of recurrent pancreatitis in this study were male gender, alcohol abuse, inclusion for pancreatitis by ICD coding on the index date, a history of > 1 pancreatic event, and the use of medications that are associated with pancreatitis (Table 3). The use of GLP1 analogue therapy was an independent risk factor for recurrent pancreatitis in a univariate time varying analysis (HR 1.249, 95% CI 1.178–1.324) and after adjustment for these independent predictors in two models (HR 1.252, 95% CI 1.178–1.332 or HR 1.291, CI 1.211–1.376, Table 3).

Patients who developed recurrent pancreatitis initiated GLP1 therapy significantly earlier after the index date than those who did not (median 11.9 vs. 24.2 months, HR 0.989, 95% CI 0.987–0.991, $p < 0.001$), indicating temporal proximity between treatment initiation and recurrence.

3.5 | Subgroups Analysis

We sought to assess whether the use of GLP1 analogues in patients who were included for increased lipase levels is associated

TABLE 3 | Independent predictors of pancreatitis, multivariate time varying analyses.

Risk factor	Model A (n = 43,410, p < 0.001)	Model B (n = 40,833, p < 0.001)
Gender		
Male	1.104 (1.067–1.143)	1.082 (1.044–1.121)
Female	Reference	Reference
Smoking		
Yes	1.064 (1.027–1.102)	1.062 (1.024–1.101)
No	Reference	Reference
Alcohol		
Yes	1.303 (1.227–1.383)	1.325 (1.246–1.410)
No	Reference	Reference
Pancreatitis on index date		
Yes	1.189 (1.145–1.234)	1.298 (1.247–1.350)
No	Reference	Reference
History of > 1 pancreatic event[a]		
Yes	1.781 (1.714–1.850)	1.713 (1.646–1.781)
No	Reference	Reference
Medications		
Yes	1.782 (1.640–1.936)	1.756 (1.606–1.920)
No	Reference	Reference
Age	0.995 (0.994–0.996)	0.989 (0.987–0.990)
Body mass index		0.991 (0.987–0.994)
Duration of diabetes[b]		1.001 (0.999–1.002)
Triglycerides		1.057 (1.025–1.090)
Glomerular filtration rate		0.994 (0.993–0.994)
GLP1 analogues		
Yes	1.252 (1.178–1.332)	1.291 (1.211–1.376)
No	Reference	Reference

Note: Results are presented as hazard ratio (95% CI).
Abbreviations: CI, confidence interval; GLP1, glucagon-like peptide 1.
[a]History of pancreatitis before the index date.
[b]Time from diagnosis of diabetes mellitus to index date.

with a higher risk for recurrent pancreatitis (n = 29,949). Alcohol abuse and medications associated with pancreatitis were found to strongly predict the development of recurrent pancreatitis (Table 4). GLP1 analogue therapy was also an independent risk factor for recurrent pancreatitis in this subgroup of patients (HR 1.412, 95% CI 1.274–1.566).

We further assessed a subgroup of patients who had a history of > 1 pancreatic event (Table 4). Similar predictors for recurrent pancreatitis, specifically alcohol abuse and medications that associate with pancreatitis, were detected in these patients. GLP1 analogue therapy was an independent risk factor for recurrent pancreatitis in this subgroup of patients (HR 1.358, 95% CI 1.174–1.572).

TABLE 4 | Independent predictors of pancreatitis, multivariate time varying analyses.

Risk factor	Lipase only (n = 29,949, p < 0.001)	More than one episode of pancreatitis (n = 6,775, p < 0.001)
Gender		
Male	0.976 (0.908–1.050)	1.044 (0.973–1.121)
Female	Reference	Reference
Smoking		
Yes	1.110 (1.031–1.196)	0.987 (0.918–1.062)
No	Reference	Reference
Alcohol		
Yes	1.488 (1.315–1.684)	1.214 (1.091–1.351)
No	Reference	Reference
Medications		
Yes	1.924 (1.613–2.294)	1.832 (1.497–2.242)
No	Reference	Reference
Age	0.998 (0.996–1.001)	0.991 (0.989–0.994)
Lipase grade	1.098 (1.043–1.156)	
GLP1 analogues		
Yes	1.412 (1.274–1.566)	1.358 (1.174–1.572)
No	Reference	Reference

Note: Results are presented as hazard ratio (95% CI).
Abbreviations: CI, confidence interval; GLP1, glucagon-like peptide 1.

4 | Discussion

This study demonstrates that treatment with GLP1 analogues in patients who live with diabetes and are at high risk for developing pancreatitis, specifically those with a history of pancreatitis or elevated pancreatic enzyme levels, is linked to a higher incidence of subsequent pancreatitis episodes.

An important methodological consideration of our study is that a substantial proportion of participants were included on the basis of elevated lipase levels without confirmed clinical pancreatitis. We chose this approach intentionally, as it represents a frequent and clinically relevant dilemma: whether isolated or unexplained pancreatic enzyme elevations should influence decisions regarding GLP1 analogue therapy. While this design broadens the external validity of our findings, it also introduces potential diagnostic heterogeneity, since not all biochemical elevations necessarily represent true pancreatic inflammation.

Our findings align with previous retrospective pharmacovigilance studies. For instance, a real-world study utilising the FDA's Post Marketing Adverse Event Reporting System (FAERS) database [7] found that users of GLP1 analogues had an increased risk of pancreatitis (ROR = 9.65, CI = 9.17–10.16). Another FDA pharmacovigilance report [10] indicated that exenatide was significantly associated with a disproportionality signal for pancreatitis (ROR = 1.76, CI = 1.61–1.92, p < 0.001). Additionally, a study based on the French Pharmacovigilance

Database demonstrated a strong association between the use of exenatide (ROR = 28.29, CI = 12.84–62.34, $p < 0.0001$) and liraglutide (ROR = 30.36, CI = 15.36–60.01, $p < 0.0001$) and pancreatitis [11]. However, it is important to note that pharmacovigilance studies have inherent limitations, such as selection bias and recall bias. Thus, there is a need for additional retrospective studies that extend beyond pharmacovigilance methods.

In contrast, large randomised controlled trials (RCTs) of GLP1 analogues have not established a significant association between their use and an increased risk of pancreatitis. These trials primarily focused on efficacy outcomes such as glycaemic control and cardiovascular impacts, rather than pancreatitis as a primary outcome. Cardiovascular outcome trials (CVOTs) involving GLP1 analogues did not show elevated rates of clinical pancreatitis compared with placebo. However, a correlation between GLP1 analogues and increased blood pancreatic enzyme levels was noted, albeit without clear clinical significance [15–18].

Consistent with the RCTs, a meta-analysis did not show an increased risk of pancreatitis among users of GLP1 analogues (OR 0.93, CI 0.65–1.34) [19]. Another meta-analysis that examined the benefit-harm balance of GLP1 analogues used for weight loss did not show a clinically significant difference in the risk of pancreatitis between the treatment and the placebo groups (RR 1.87, CI 0.52–6.67) [14]. Comparisons among different medications in this class did not reveal a clinically significant risk of pancreatitis for any of the drugs.

The discrepancies between RCT results and those from pharmacovigilance studies, including ours, may stem from differences in study populations. Previous RCTs concentrated primarily on cardiovascular, renal, and weight loss outcomes, with inclusion and randomisation criteria aligned with these objectives. Pancreatitis was not a primary endpoint, resulting in unmatched baseline risk factors. Furthermore, these trials generally excluded patients with a history of pancreatitis or elevated pancreatic enzyme levels, whereas our study specifically targeted individuals with these risk factors.

Our findings indicate that the overall risk of recurrent pancreatitis associated with GLP1 analogues is increased by up to 29%. Population studies suggest that the annual incidence of acute pancreatitis ranges from 13 to 45 cases per 100,000 individuals, whereas the incidence of chronic pancreatitis is between 5 and 12 cases per 100,000. Approximately 20%–30% of individuals with pancreatitis will experience a recurrence. These estimates can vary significantly due to underlying risk factors, the causes of pancreatitis, and demographic characteristics. In situations where the absolute risk of recurrent pancreatitis is low, the clinical significance of a 29% increase in incidence may be uncertain. However, given that GLP1 analogues are often prescribed to patients who already have a higher baseline risk for pancreatitis due to conditions such as obesity and diabetes, the increased risk associated with GLP1 therapy could become clinically relevant.

The temporal proximity between GLP1 analogue initiation and recurrence observed in our cohort may suggest a time-linked effect, although causality cannot be inferred from observational data. Despite multivariable adjustment for major confounders, including alcohol use and pancreatitis-associated medications, residual confounding and confounding by indication remain possible.

Our multivariable analysis identified several independent predictors of recurrent pancreatitis; the additive effect of these factors suggests that individuals with multiple risk factors may have substantially higher susceptibility to recurrence. Although our dataset was not powered to formally test interaction terms, prior literature has suggested that combinations of risk factors may have multiplicative effects on pancreatitis risk. For example, large cohort studies have shown that the combination of alcohol abuse and smoking results in a markedly higher cumulative risk of chronic pancreatitis than either factor alone, suggesting a synergistic effect [20]. Similarly, the presence of multiple metabolic syndrome components (obesity, hyperlipidaemia, hypertension, diabetes) has been shown to synergistically worsen the severity and outcomes of acute pancreatitis, rather than acting independently or additively [21]. These observations underscore the need to move beyond single-variable appraisal towards composite risk stratification tools that incorporate both additive and multiplicative interactions, thereby informing safer prescribing of GLP1 analogues in high-risk individuals.

Several animal studies have indicated that GLP1 mimetic therapy can induce pancreatic acinar inflammation and pyknosis, as well as increased pancreatic ductal turnover and ductal metaplasia in rats [22, 23]. These effects could potentially contribute to the development of pancreatitis. However, other studies have disputed these findings, and the topic remains contentious [24, 25]. Nevertheless, our research suggests that initiation of GLP1 analogues soon after a pancreatic event is associated with a greater risk for recurrent event of pancreatitis. If GLP1 mimetic therapy does indeed trigger pancreatitis episodes or hinder the healing of an injured pancreas, it may be prudent to delay the initiation of this treatment in patients with a history of pancreatitis until a significant time has passed since the acute episode.

Our study has several limitations. As a retrospective analysis, it is inherently prone to biases typical of this type of research. One is selection bias, as the treating physicians determined which patients received GLP1 analogues and which did not. In this line, only GLP1 analogue use was modelled as a time-updated variable, whereas other covariates (e.g., BMI, HbA1c, triglycerides) were captured at baseline and may have changed over time. This could underestimate confounding by indication, as deterioration in these parameters may prompt GLP1 initiation and independently increase pancreatitis risk. While ideal, incorporating multiple time-varying covariates would have required more complex modelling and consistent longitudinal data, which were not available in this retrospective design. Additionally, the significant number of patient deaths during the study period raises questions about how these outcomes might have differed if those patients had been treated with GLP1 analogues; to address this, we employed a competing risk analysis to evaluate the effect of patient death on study outcomes. Another notable limitation is the inability

to distinguish between different types of pancreatitis, such as acute, chronic, and biliary pancreatitis. This limitation prevents us from determining whether certain cases were related to gallstones, which could have been managed surgically. However, this bias is likely to influence the study population as a whole, rather than being more pronounced in either the GLP1 analogue treatment group or the control group. Finally, because our database lacked access to individual imaging or clinical records, we could not confirm the diagnosis of pancreatitis in patients included solely for elevated lipase. This limitation may have led to the inclusion of cases with subclinical or non-pancreatic causes of enzyme elevation. Nonetheless, this reflects a real-world clinical context in which clinicians often encounter unexplained lipase elevations and must weigh the safety of GLP1 analogue therapy in such patients.

In summary, an increased risk of recurrent pancreatitis was observed in patients with a history of pancreatitis or elevated levels of lipase enzyme receiving GLP1 analogue therapy. Therefore, healthcare providers should proceed with caution when considering these medications for such patients. If GLP1 analogues are prescribed to high-risk individuals, it might be advisable to postpone the start of treatment for more than 1 year following a pancreatitis episode or the identification of elevated pancreatic enzyme levels.

Additional prospective research is necessary to further investigate these findings, especially in populations at higher risk for pancreatitis. This ongoing research is crucial to determine whether it is appropriate to avoid GLP1 analogue therapies in these high-risk groups.

Author Contributions

Design: Bronya Calvarysky and Talia Diker Cohen. Conduct/data collection: Bronya Calvarysky, Yaara Gal, Shiri Kushnir, Adi Turjeman and Talia Diker Cohen. Analysis: Bronya Calvarysky, Yaara Gal, Shiri Kushnir, Adi Turjeman, Tzippy Shochat, Idit Dotan and Talia Diker Cohen. Writing manuscript: Bronya Calvarysky, Yaara Gal, Shiri Kushnir, Adi Turjeman, Tzippy Shochat, Idit Dotan and Talia Diker Cohen.

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The authors have nothing to report.

Ethics Statement

The study protocol received approval from the local Institutional Review Board.

Consent

The authors have nothing to report.

Conflicts of Interest

ID has received fees from Astra Zeneca, Novonordisk, Abbott, Boeringham Ingleheimer, Elli Lilly and Sanofi for educational lectures, and participated in advisory boards of Elli Lilly, Novonordisk, Boeringham Ingleheimer, Sanofi and Novartis that are outside the scope of this work. Other authors have nothing to disclose.

Data Availability Statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

Peer Review

The peer review history for this article is available at https://www.webofscience.com/api/gateway/wos/peer-review/10.1002/dmrr.70116.

Code Availability

The authors have nothing to report.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.

Table S1: Drugs that are associated with pancreatitis.