Pulmonary outcomes of incretin-based therapies in COPD patients receiving single-inhaler triple therapy

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Shareable abstract (@ERSpublications)
This study showed that GLP-1 analogues were associated with reduced respiratory risks in patients with COPD and T2DM on single-inhaler triple therapy, with no significant gastrointestinal safety concerns https://bit.ly/4f0ytsm

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Abstract

Background Patients with COPD on triple therapy often face exacerbations and comorbidities. Emerging evidence suggests that glucagon-like peptide-1 (GLP-1) analogues may reduce the risk of exacerbation in patients with COPD and type 2 diabetes mellitus (T2DM). This study investigates the impact of GLP-1 analogues on pulmonary outcomes in patients with COPD on single-inhaler triple therapy (SITT) and T2DM.

Methods We conducted a retrospective cohort study using the TriNetX database and analysed adult patients with COPD and T2DM who received SITT between April 2005 and July 2023. Patients were categorised into GLP-1 analogue and dipeptidyl peptidase-4 inhibitor (DPP4i) cohorts. The primary efficacy outcome was COPD exacerbation, and the secondary efficacy outcomes were pneumonia, acute respiratory distress syndrome, intubation, oxygen dependence and all-cause mortality. The secondary outcomes were serious gastrointestinal adverse events.

Results We included 6898 patients, with 4184 receiving GLP-1 analogues and 2714 receiving DPP4i. After matching, 1751 GLP-1 analogue users were matched with 1751 DPP4i users. GLP-1 analogue users had an 18% lower risk of COPD exacerbation (hazard ratio (HR) 0.82 (95% CI 0.71–0.94)), a 28% reduced risk of pneumonia (HR 0.72 (95% CI 0.61–0.85)), a 34% reduced risk of oxygen dependence (HR 0.66 (95% CI 0.47–0.91)) and a 40% decreased risk of all-cause mortality (HR 0.60 (95% CI 0.47–0.77)). No significant serious gastrointestinal adverse events were observed.

Conclusion GLP-1 analogues may be associated with reduced COPD exacerbations, pulmonary comorbidities and mortality in patients with COPD receiving SITT and T2DM, with no significant serious gastrointestinal safety concerns.

Introduction

COPD is one of the leading causes of death worldwide and poses a significant healthcare burden due to exacerbations, mortality and associated pulmonary comorbidities [1]. Patients with COPD who have a high risk of acute exacerbations, elevated blood eosinophil counts or significant symptom burden while on fewer regimens are often prescribed triple therapy, comprising a combination of long-acting β_2-agonist (LABA), long-acting muscarinic antagonist (LAMA) and inhaled corticosteroid (ICS) [2]. Among the various forms of triple therapy, single-inhaler triple therapy (SITT) has shown better adherence compared to multiple-inhaler triple therapy (MITT) due to the convenience of using a single inhaler rather than

multiple inhalers or complex regimens [3, 4]. Mounting evidence also suggests that SITT may reduce mortality in patients with COPD [5]. Despite these options, there remains a need to further improve the survival and pulmonary outcomes of patients with COPD.

Emerging evidence indicates that glucagon-like peptide-1 receptor agonists (GLP-1RA) may reduce the risk of acute exacerbations in patients with COPD and lower the risk of mortality in patients with type 2 diabetes mellitus (T2DM) [6, 7]. GLP-1RA are a class of incretin-based glucose-lowering agents initially used for the treatment of T2DM, and their use has subsequently been extended for the management of obesity due to their weight loss effects [8]. Experimental studies have demonstrated that GLP-1RA modulate airway inflammation and mucus secretion, which may benefit COPD patients [6, 9–12]. However, limited data exist regarding their respiratory effects in patients with COPD on triple therapy, a group facing a heightened risk of exacerbation and pulmonary comorbidities.

We hypothesised that GLP-1 analogues, including GLP-1RA and glucose-dependent insulinotropic polypeptide (GIP)/GLP-1 co-agonists, may reduce the risk of COPD exacerbation and other pulmonary comorbidities, such as pneumonia and respiratory failure, in COPD patients receiving SITT. Therefore, we leveraged a large population-based cohort to investigate the effect of GLP-1 analogues on pulmonary outcomes in this high-risk population.

Methods

Database

We conducted a retrospective cohort study using the TriNetX Analytics Network database, which contains anonymised electronic health records from over 101 million patients across more than 70 participating healthcare organisations (HCOs) globally, mainly in the Americas and Europe [13, 14]. These HCOs in the TriNetX network provide de-identified data for research under strict adherence to data privacy regulations such as the US Health Insurance Portability and Accountability Act and the European Union General Data Protection Regulation [14]. In return, the HCOs incur no cost and receive data query, analytic capabilities and hardware from TriNetX. The database offers comprehensive information on demographics, encounters, diagnoses, medications, procedures and laboratory results, all of which are harmonised into codes using common standards such as the International Classification of Diseases (ICD) for diagnoses [14].

Study design

We identified adult patients (aged ⩾18 years) diagnosed with COPD and T2DM who received SITT between April 2005 and July 2023 using ICD-10 and TriNetX codes (supplementary table S1). We selected patients with T2DM as it is currently the main indication for GLP-1 analogue use. April 2005 was chosen as the starting date since the first GLP-1 analogue was approved by the US Food and Drug Administration at that time and July 2023 was chosen as the end date to allow at least 1 year of follow-up. SITT was defined as a combined inhaler regimen of one of the following: fluticasone/umeclidinium/vilanterol, budesonide/glycopyrrolate/formoterol fumarate or beclomethasone dipropionate/formoterol/glycopyrronium [1].

The GLP-1 analogue (exposed) cohort was identified as patients who had a prescription for GLP-1 analogues, including GLP-1RA or GIP/GLP-1 co-agonists, within 1 year prior to the SITT start date and at least one prescription for GLP-1 analogues after SITT initiation. The dipeptidyl peptidase-4 inhibitor (DPP4i) (non-exposed) cohort consisted of patients with a prescription for DPP4i within 1 year before starting SITT and at least one prescription for GLP-1 analogues after SITT initiation. DPP4i were chosen as the control cohort because they share a similar glucose-lowering pathway with GLP-1RA, both being incretin-based therapies. Patients in the GLP-1 analogue cohort who received DPP4i during the data collection period were excluded, and similarly, patients in the DPP4i cohort who received GLP-1 analogues were also excluded.

We defined the index date as the start date of SITT following the diagnosis of COPD. Data collection began 1 year before the index date, and included age, sex, race, body mass index (BMI), haemoglobin A1c (HbA1c), absolute eosinophil count, forced expiratory volume in 1 s (FEV_1), long-term use of steroids, oxygen dependence, pre-existing comorbidities, as well as medication use for cardiovascular, diabetic and pulmonary diseases. The SITT, GLP-1 analogues and DPP4i used in the study and their related codes are summarised in supplementary table S1. All the data were identified using ICD-10 and TriNetX codes, which are also provided in supplementary table S1.

Outcome definition

The primary efficacy outcome was COPD exacerbation. The secondary efficacy outcomes were pneumonia, acute respiratory distress syndrome (ARDS), intubation, oxygen dependence and all-cause mortality. We

excluded patients with a prior diagnosis of oxygen dependence to focus on the role of GLP-1 analogues in primary prevention. Safety outcomes included serious gastrointestinal adverse events associated with the use of GLP-1 analogues, such as gastroparesis, biliary disease, pancreatitis and bowel obstruction [15]. All outcomes were defined as events occurring between 1 day and 1 year after the index date, and were identified using ICD-10 or TriNetX codes (supplementary table S1).

Statistical analysis

We performed propensity score matching in a 1:1 ratio, and included variables such as age, sex, race, tobacco use, BMI, HbA1c, absolute eosinophil count, FEV_1, long-term use of steroids, oxygen dependence, pre-existing comorbidities, as well as medication use for cardiovascular, diabetic and pulmonary diseases. These variables were chosen as they serve as potential confounding factors and are summarised in supplementary table S2. Propensity score matching was performed using the built-in function of the TriNetX platform [14]. The differences in baseline characteristics between the GLP-1 analogue and DPP4i cohorts were compared using standardised mean differences (SMDs), with SMD <0.1 indicating a balanced distribution of covariates between the two cohorts. The association between the GLP-1 analogue cohort and each outcome was accessed by using the Cox proportional hazards model. We used the log-rank test to compare survival distributions of the outcomes between both cohorts. Statistical significance was determined as p-value <0.05. All analyses were performed within the TriNetX platform.

Results

Composition of the cohorts

A total of 6898 patients diagnosed with COPD on SITT and T2DM were included in the study, with 4184 patients receiving GLP-1 analogues and 2714 receiving DPP4i (supplementary figure S1). Before propensity score matching, patients receiving GLP-1 analogues had younger age (64.5 *versus* 71.1 years), higher BMI (37.7 *versus* 31.1 $kg \cdot m^{-2}$) and greater HbA1c (7.8% *versus* 7.5%) compared to those receiving DPP4i (table 1). There were also more female (51% *versus* 44.4%) and White (68.3% *versus* 65.8%) patients in the GLP-1 analogue cohort compared to the DPP4i cohort. After matching, a total of 1751 GLP-1 analogue users were matched with 1751 DPP4i users. The baseline characteristics between the two cohorts were adequately balanced, with SMDs ranging from 0.00 to 0.05, except for mean BMI (34.5±7.9 *versus* 33.4±7.9 $kg \cdot m^{-2}$; SMD 0.14) (table 1). Nevertheless, the BMI subgroups between both cohorts were adequately balanced. Mean ages in the GLP-1 analogue and DPP4i cohorts were similar (68.2±8.7 *versus* 68.3±9.7 years), as were mean HbA1c (7.7±1.7% *versus* 7.7±1.7%), female sex (47.3% *versus* 47.6%) and White race (70.4% *versus* 69.4%). Pre-existing comorbidities such as asthma (19.1% *versus* 18.7%) and sleep apnoea (36.4% *versus* 36.0%) were comparable. Additionally, the use of COPD-associated medications such as azithromycin (28.8% *versus* 28.6%), prednisone (40.7% *versus* 40.9%) and montelukast (19.6% *versus* 18.6%) was similar between both cohorts.

Outcomes

Over the median follow-up period of 1 year, 382 GLP-1 analogue users and 459 DPP4i users experienced COPD exacerbations (table 2). Cox proportional hazard analyses revealed that GLP-1 analogues were associated with an 18% lower risk of acute exacerbation (hazard ratio (HR) 0.82 (95% CI 0.71–0.94); p=0.003) compared to DPP4i. For secondary efficacy outcomes, the GLP-1 cohort had a reduced risk of pneumonia (HR 0.72 (95% CI 0.61–0.85); p<0.001) and oxygen dependence (HR 0.66 (95% CI 0.47–0.91); p=0.010). There were no significant differences in the risk of ARDS and intubation. Additionally, patients on GLP-1 analogues had a 40% decreased risk of all-cause mortality (HR 0.60 (95% CI 0.47–0.77); p<0.001) compared to those on DPP4i. There were no significant differences observed in the risk of gastroparesis, biliary disease, pancreatitis or bowel obstruction between the cohorts.

Discussion

In this propensity score-matched cohort study, we compared the pulmonary and safety outcomes of COPD patients treated with SITT who received concomitant GLP-1 analogues (GLP-1RA or GIP/GLP co-agonists) *versus* DPP4i. We reported three novel findings. First, patients receiving GLP-1 analogues had a lower risk of COPD exacerbations, pneumonia and oxygen dependence than those receiving DPP4i. Second, GLP-1 analogues did not appear to increase the risk of serious gastrointestinal adverse events. Third, there seemed to be a mortality benefit among patients on GLP-1 analogues compared to those on DPP4i. To the best of our knowledge, this is the first study describing the association between GLP-1 analogues and improved pulmonary and mortality outcomes among COPD patients treated with SITT. These findings are clinically important considering the increased risk of respiratory complications and associated mortality in patients requiring triple therapy for COPD [1, 2].

TABLE 1 Patient baseline characteristics before and after propensity score matching

	Before propensity score matching			After propensity score matching		
	GLP-1 analogues (n=4184)	DPP4i (n=2714)	SMD	GLP-1 analogues (n=1751)	DPP4i (n=1751)	SMD
Basic demographics						
Age (years)	64.5±9.3	71.1±9.9	0.69	68.2±8.7	68.3±9.7	0.01
Female	2132 (51.0)	1206 (44.4)	0.13	828 (47.3)	834 (47.6)	0.01
Race						
White	2858 (68.3)	1786 (65.8)	0.05	1233 (70.4)	1215 (69.4)	0.02
Black or African American	618 (14.8)	276 (10.2)	0.14	199 (11.4)	201 (11.5)	0.00
Asian	47 (1.1)	148 (5.5)	0.24	34 (1.9)	35 (2.0)	0.00
BMI ($kg \cdot m^{-2}$)	37.7±8.4	31.1±7.8	0.82	34.5±7.9	33.4±7.9	0.14
25–29.99 $kg \cdot m^{-2}$	602 (14.4)	672 (24.8)	0.26	366 (20.9)	366 (20.9)	0.00
30–34.99 $kg \cdot m^{-2}$	1074 (25.7)	617 (22.7)	0.07	469 (26.8)	449 (25.6)	0.03
35–39.99 $kg \cdot m^{-2}$	1105 (26.4)	368 (13.6)	0.33	343 (19.6)	325 (18.6)	0.03
⩾40 $kg \cdot m^{-2}$	1222 (29.2)	287 (10.6)	0.48	267 (15.2)	269 (15.4)	0.00
Pertinent laboratory data						
Haemoglobin A1c (%)	7.8±1.9	7.5±1.6	0.15	7.7±1.7	7.7±1.7	0.00
6.5–8%	1809 (43.2)	988 (36.4)	0.14	715 (40.8)	703 (40.1)	0.01
8–10%	1147 (27.4)	540 (19.9)	0.18	438 (25.0)	433 (24.7)	0.01
>10%	624 (14.9)	193 (7.1)	0.25	174 (9.9)	170 (9.7)	0.01
Absolute eosinophil count ($\times 10^3\ \mu L^{-1}$)	0.4±3.7	0.6±5.1	0.04	0.4±3.5	0.4±3.1	0.00
0.10–0.30$\times 10^3\ \mu L^{-1}$	1950 (46.6)	1164 (42.9)	0.07	810 (46.3)	800 (45.7)	0.01
>0.30$\times 10^3\ \mu L^{-1}$	1037 (24.8)	666 (24.5)	0.01	443 (25.3)	446 (25.5)	0.00
FEV_1 (% pred)	62.6±20.0	64.0±21.3	0.06	61.9±17.2	61.7±19.7	0.01
Hospitalisation data						
Emergency department	1704 (40.7)	1003 (37.0)	0.08	691 (39.5)	702 (40.1)	0.01
Inpatient hospitalisation	1232 (29.4)	904 (33.3)	0.08	592 (33.8)	577 (33.0)	0.02
ICU hospitalisation	380 (9.1)	334 (12.3)	0.10	204 (11.6)	197 (11.3)	0.01
Underlying comorbidities/conditions						
Hypertension	3335 (79.7)	2020 (74.4)	0.13	1347 (76.9)	1347 (76.9)	0.00
Hyperlipidaemia	3163 (75.6)	1762 (64.9)	0.24	1255 (71.7)	1243 (71.0)	0.02
Ischaemic heart diseases	1723 (41.2)	1218 (44.9)	0.07	793 (45.3)	774 (44.2)	0.02
Gastro-oesophageal reflux	1823 (43.6)	948 (34.9)	0.18	696 (39.7)	683 (39.0)	0.02
Chronic kidney disease	1061 (25.4)	980 (36.1)	0.23	559 (31.9)	544 (31.1)	0.02
Asthma	1028 (24.6)	458 (16.9)	0.19	334 (19.1)	327 (18.7)	0.01
Chronic sinusitis	217 (5.2)	86 (3.2)	0.10	65 (3.7)	68 (3.9)	0.01
Sleep apnoea	2070 (49.5)	773 (28.5)	0.44	638 (36.4)	630 (36.0)	0.01
Nicotine dependence, cigarettes	990 (23.7)	477 (17.6)	0.15	367 (21.0)	359 (20.5)	0.01
Former smoker	1663 (39.7)	884 (32.6)	0.15	614 (35.1)	631 (36.0)	0.02
Long-term use of systemic steroids	266 (6.4)	211 (7.8)	0.06	137 (7.8)	142 (8.1)	0.01
Oxygen dependence	664 (15.9)	488 (18.0)	0.06	319 (18.2)	320 (18.3)	0.00
Psychosocial problems	17 (0.4)	11 (0.4)	0.00	10 (0.6)	10 (0.6)	0.00
Use of diabetes medications						
Biguanides	1925 (46.0)	1264 (46.6)	0.01	822 (46.9)	823 (47.0)	0.00
Sulfonylureas	642 (15.3)	713 (26.3)	0.27	381 (21.8)	382 (21.8)	0.00
Thiazolidinediones	105 (2.5)	96 (3.5)	0.06	65 (3.7)	60 (3.4)	0.02
α-glucosidase inhibitors	10 (0.2)	10 (0.4)	0.02	10 (0.6)	10 (0.6)	0.00
SGLT2 inhibitors	779 (18.6)	303 (11.2)	0.21	254 (14.5)	254 (14.5)	0.00
Insulin	2212 (52.9)	1577 (58.1)	0.11	981 (56.0)	980 (56.0)	0.00
Use of cardiovascular medications						
ACE inhibitors	1209 (28.9)	811 (29.9)	0.02	578 (33.0)	537 (30.7)	0.05
Angiotensin II receptor blockers	1240 (29.6)	758 (27.9)	0.04	487 (27.8)	505 (28.8)	0.02
Aspirin	1497 (35.8)	1134 (41.8)	0.12	694 (39.6)	699 (39.9)	0.01
β-blockers	2098 (50.1)	1527 (56.3)	0.12	968 (55.3)	955 (54.5)	0.01
Calcium channel blockers	1371 (32.8)	1161 (42.8)	0.21	693 (39.6)	679 (38.8)	0.02
Loop diuretics	1817 (43.4)	1400 (51.6)	0.16	869 (49.6)	831 (47.5)	0.04
Thiazides	1030 (24.6)	534 (19.7)	0.12	370 (21.1)	382 (21.8)	0.02
Statins	2839 (67.9)	1905 (70.2)	0.05	1226 (70.0)	1223 (69.8)	0.00
Use of COPD medications						
Azithromycin	1191 (28.5)	764 (28.2)	0.01	504 (28.8)	500 (28.6)	0.01
Prednisone	1776 (42.4)	1042 (38.4)	0.08	713 (40.7)	716 (40.9)	0.00

Continued

TABLE 1 Continued

	Before propensity score matching			After propensity score matching		
	GLP-1 analogues (n=4184)	DPP4i (n=2714)	SMD	GLP-1 analogues (n=1751)	DPP4i (n=1751)	SMD
Methylprednisolone	1253 (29.9)	877 (32.3)	0.05	555 (31.7)	565 (32.3)	0.01
Betamethasone	277 (6.6)	149 (5.5)	0.05	99 (5.7)	98 (5.6)	0.00
Montelukast	839 (20.1)	470 (17.3)	0.07	344 (19.6)	325 (18.6)	0.03
Roflumilast	107 (2.6)	89 (3.3)	0.04	57 (3.3)	62 (3.5)	0.02
Beclomethasone	66 (1.6)	202 (7.4)	0.29	55 (3.1)	49 (2.8)	0.02
Budesonide	1261 (30.1)	806 (29.7)	0.01	550 (31.4)	523 (29.9)	0.03
Flunisolide	10 (0.2)	10 (0.4)	0.02	10 (0.6)	10 (0.6)	0.00
Fluticasone	2880 (68.8)	1933 (71.2)	0.05	1253 (71.6)	1251 (71.4)	0.00
Mometasone	216 (5.2)	167 (6.2)	0.04	102 (5.8)	99 (5.7)	0.01
Albuterol	3112 (74.4)	2051 (75.6)	0.03	1323 (75.6)	1313 (75.0)	0.01
Arformoterol	113 (2.7)	96 (3.5)	0.05	70 (4.0)	67 (3.8)	0.01
Salmeterol	617 (14.7)	423 (15.6)	0.02	289 (16.5)	276 (15.8)	0.02
Indacaterol	10 (0.2)	10 (0.4)	0.02	10 (0.6)	10 (0.6)	0.00
Olodaterol	133 (3.2)	79 (2.9)	0.02	54 (3.1)	46 (2.6)	0.03
Aclidinium	12 (0.3)	30 (1.1)	0.10	10 (0.6)	10 (0.6)	0.00
Glycopyrronium	496 (11.9)	440 (16.2)	0.13	226 (12.9)	225 (12.8)	0.00
Tiotropium	847 (20.2)	631 (23.2)	0.07	413 (23.6)	378 (21.6)	0.05
Umeclidinium	2466 (58.9)	1714 (63.2)	0.09	1103 (63.0)	1102 (62.9)	0.00

Data are presented as mean±SD or n (%), unless otherwise stated. GLP-1: glucagon-like peptide-1; DPP4i: dipeptidyl peptidase-4 inhibitors; SMD: standardised mean difference; BMI: body mass index; FEV_1: forced expiratory volume in 1 s; ICU: intensive care unit; SGLT2: sodium-glucose cotransporter-2; ACE: angiotensin-converting enzyme.

Based on the 2023 Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines, COPD patients were recommended to start triple therapy (LABA+LAMA+ICS) if they experience frequent exacerbations and have a blood absolute eosinophil count $\geqslant 0.3\times10^3\ \mu L^{-1}$. Additionally, it was recommended to escalate to triple therapy if patients have exacerbations while on monotherapy and have a blood absolute eosinophil count $\geqslant 0.3\times10^3\ \mu L^{-1}$ or if they have a blood absolute eosinophil count $\geqslant 0.1\times10^3\ \mu L^{-1}$ while on dual therapy with LABA and LAMA [2]. Among the available options, SITT combines three medications into a single inhaler, offering improved adherence and persistence compared to MITT [3, 4]. Triple therapy has shown to reduce future exacerbations, healthcare resource utilisation and mortality in patients with

TABLE 2 Cox proportional hazard analysis for the association between the use of incretin-based therapies (glucagon-like peptide-1 (GLP-1) analogues *versus* dipeptidyl peptidase-4 inhibitors (DPP4i)) and patient outcomes

	GLP-1 analogues		DPP4i		Hazard ratio[#] (95% CI)	p-value (log-rank)
	At-risk patients (n)	Cases (n)	At-risk patients (n)	Cases (n)		
Primary efficacy outcome						
COPD exacerbation	1751	382	1751	459	0.82 (0.71–0.94)	0.003
Secondary efficacy outcomes						
Pneumonia	1751	224	1751	310	0.72 (0.61–0.85)	<0.001
Acute respiratory distress syndrome	1751	10	1751	11	0.84 (0.35–2.02)	0.692
Intubation	1751	38	1751	55	0.71 (0.47–1.07)	0.096
Oxygen dependence[¶]	1272	59	1312	94	0.66 (0.47–0.91)	0.010
All-cause mortality	1751	105	1751	178	0.60 (0.47–0.77)	<0.001
Gastrointestinal safety outcomes						
Gastroparesis[¶]	1689	15	1686	13	1.18 (0.56–2.47)	0.667
Biliary disease[¶]	1698	10	1709	12	0.77 (0.33–1.83)	0.555
Pancreatitis[¶]	1700	10	1698	10	1.29 (0.51–3.26)	0.595
Bowel obstruction[¶]	1659	15	1645	27	0.56 (0.30–1.06)	0.072

[#]: after propensity score matching by incorporating variables: age, sex, race, body mass index, haemoglobin A1c, absolute eosinophil count, forced expiratory volume in 1 s, long-term use of steroids, oxygen dependence, underlying comorbidities, and medication use for cardiovascular disease, diabetes mellitus and pulmonary diseases; [¶]: patients were excluded from the results if they experienced the outcome prior to the time window.

COPD [16, 17]. Since COPD patients on triple therapy are typically a high-risk population experiencing COPD exacerbations and related pulmonary complications, efficacious treatments are crucial for improving their respiratory outcomes and reducing healthcare burdens.

Recent observational studies have found an association between GLP-1 analogues and a decreased risk of acute exacerbation in patients with COPD and T2DM [6, 9]. Furthermore, GLP-1 analogues have been linked to a lower incidence of respiratory disease in patients with T2DM or those who are overweight or obese [11]. Our study extends and corroborates these results with novel findings that GLP-1 analogues reduce the risk of COPD exacerbations and common respiratory comorbidities associated with COPD such as pneumonia and oxygen dependence in patients with COPD receiving SITT and T2DM.

The exact mechanisms underlying these associations are still unclear. GLP-1 and GIP are incretin hormones that stimulate insulin secretion in a glucose-dependent manner, suppress gastric emptying and reduce food intake [18, 19]. They are inactivated by DPP4 after being secreted into the bloodstream. GLP-1 analogues, including GLP-1RA and GIP/GLP-1 co-agonists, are new types of incretin-based glucose-lowering agents that target these mechanisms and are currently used in patients with diabetes or obesity [19]. The GLP-1 receptor is not only present in the pancreas, but also in other organs such as the heart, kidney and lung [18]. Pre-clinical studies have shown that GLP-1 analogues may inhibit inflammatory factors, decrease oxidative stress, and reduce the proliferation and migration of smooth muscle cells, potentially improving airway inflammation and airflow limitation in COPD patients [18]. Experimental studies have also suggested that GLP-1 analogues may decrease protease levels in lung tissues, reducing the area of dilated alveolar tissues and inhibiting emphysema formation in mice [18]. Although previous reports have indicated that GLP-1 analogues may increase the risk of biliary or gastrointestinal adverse events, our study found no significant differences in serious safety concerns between GLP-1 analogues and DPP4i in our cohort of patients with COPD receiving SITT and T2DM [15].

Another key finding of this study was that GLP-1 analogues reduced all-cause mortality by 40% in COPD patients receiving SITT. The mechanism could be related to decreased COPD exacerbation and pulmonary outcomes, as described earlier. Additionally, it might be associated with the known weight loss effects of GLP-1 analogues [19, 20]. A previous meta-analysis has also reported the cardiovascular and renal benefits of GLP-1RA in the general population with T2DM, which may contribute to the mortality benefit [7]. The same meta-analysis also reported a 12% reduction in all-cause mortality. However, our study found a higher degree of reduction in mortality, which is unlikely to be explained solely by the cardiovascular and renal benefits. We hypothesise that GLP-1 analogues may provide a greater benefit to patients with high mortality and morbidity risk, such as those with COPD requiring triple therapy. Further prospective studies are needed to validate these findings.

Our study has several limitations. First, the observational nature of the study design introduces potential confounding factors and biases. To minimise this, we employed propensity score matching by incorporating key covariates such as demographics, BMI, important laboratory results (including HbA1c, eosinophil count and FEV_1), pre-existing comorbidities, long-term use of steroids, oxygen dependence, and medication use for cardiovascular, diabetic and pulmonary diseases. Second, we relied on ICD-10 and TriNetX codes for the data collection and as such the possibility of under-reporting or misclassification could not be excluded. Third, we were unable to assess the degree of BMI loss as these data were not available on the TriNetX platform. Since GLP-1 analogues are known for their weight loss effects, variations in weight loss could be related to pulmonary and mortality risk. Fourth, we did not have access to individual data due to the anonymous nature and limited access to the database. As a result, we were unable to determine the country of origin for the patients included, which may affect the generalisability of our results. However, we were able to obtain other demographic data such as age, sex and race. Fifth, the number of exacerbations in the previous year before the index date has been demonstrated as the best predictor of future exacerbation risk [21]. However, we were unable to include this data because this was not reported by the TriNetX database. Nevertheless, we did include covariates such as prior use of azithromycin, steroids, hospital admissions and intensive care unit admissions in the propensity score matching to minimise possible differences in baseline severity between the GLP-1 analogue and DPP4i cohorts. Sixth, we were unable to determine whether the reported blood eosinophil counts were taken during stable disease, at the time of exacerbation or while the patient was on corticosteroid treatment. Since blood eosinophil counts are influenced by these conditions, this may introduce a confounding factor. To mitigate this, we focused on COPD patients requiring SITTs to reduce heterogeneity. It is important to note that prior to 2019, the GOLD guidelines did not include blood eosinophil counts as a biomarker to predict the response to ICS therapy in COPD patients. Since our study also included patients before 2019, the recommendations for using triple therapy may not fully apply to the entire dataset. Seventh, we lacked

information on individual socioeconomic status for each cohort. A difference in socioeconomic status could potentially contribute to a biased risk estimate presented in this study. Although we used ICD code Z65 ("Problems related to other psychosocial circumstances") as a surrogate for socioeconomic status, the small number of patients in both cohorts may indicate under-coding. We also attempted to use HbA1c levels as a surrogate marker for socioeconomic status, as previous studies have indicated a strong association between glycaemic control and socioeconomic status [22]. However, this approach may still fail to fully capture the true socioeconomic status of the patients.

In conclusion, this study demonstrated that GLP-1 analogues may reduce pulmonary and mortality events in patients with coexisting COPD on SITT and T2DM, with no significant serious gastrointestinal safety signals. These results provide new perspectives regarding the potential use of these medications as a preferred diabetes medication in patients with coexisting COPD on SITT or as adjunctive treatments for COPD patients on SITT. Currently, GLP-1 analogues are not approved for the treatment of COPD, and further prospective studies are required to confirm the efficacy and safety of GLP-1 analogues in this population.

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