At present, the US Food and Drugs Administration and the European Medical Agency , while agreeing that the scienti c evidence in the literature does not clearly demonstrate the existence of a causal association between exposure to incretin-mimetics drugs and the risk of pancreatitis or pancreatic carcinoma, continue to consider that exposure to these drugs represents a potential risk factor for pancreatitis or pancreatic cancer until conclusive data are available and therefore will continue to closely monitor any reports [13]. Moreover, given the considerable discrepancy of the data available on the incidence of pancreatitis in relation to the incretin-mimetics use in di erent national territories [14-19], it is hypothesizable that the postulated negative e ect of this class of drugs, might be modulated by both genetic and environmental characteristics, related to the di erent populations evaluated.

erefore, the aim of our study was to investigate the association of the exposure to the incretino-mimetic drugs and elevation of pancreatic enzymes and the incidence of pancreatitis and pancreatic cancer in the Ferrara territory of Emilia Romagna Italian region.

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Methods

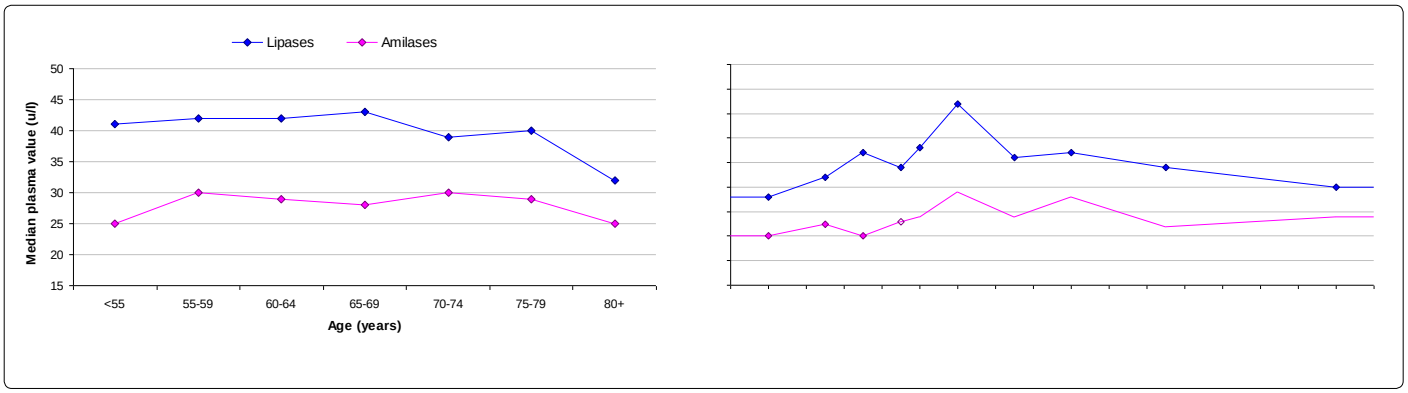
Study Design

We conducted a Retrospective study on patients diagnosed with type 2 diabetes mellitus (T2DM) referring to the Diabetologic outpatient services of the health service of the district of Ferrara (Italy),

Contents	Total (n=2058)	Controls (n=1102)	Incretins treated (n=956)	p-value
Age, mean ± SD	66.8 ± 11.6	67.9 ± 12.2	65.5 ± 10.8	<0.001
Men, n (%)	1185 (57.6)	619 (56.2)	566 (59.2)	0.165
Smoking status*, n (%)				
Current	277 (21.9)	152 (22.2)	125 (21.6)	0.302
Former	372 (29.5)	189 (27.7)	183 (31.6)	
Never	613 (48.6)	342 (50.1)	271 (46.8)	
Alcohol use**, n (%)	529 (46.0)	251 (41.8)	278 (50.5)	0.003
Diabetes duration	11 [6-18]	11 [5-18]	12 [7-17]	<0.001
median [IQ range]				
BMI, mean ± sd	30.5 ± 6.1	30.1 ± 6.1	31.0 ± 6.1	<0.001
BMI< 25 Kg/m^2	336 (16.3)	218 (19.8)	118 (12.3)	<0.001
BMI ≥25<30	746 (36.3)	390 (35.4)	356 (37.2)	
BMI≥30	976 (47.4)	494 (44.8)	482 (50.4)	
Total Cholesterol, mean ± sd	175.8 ± 45.0	176.6 ± 48.7	174.8 ± 40.4	0.345
HDL-C, mean ± sd	45.9 ± 13.4	45.5 ± 14.5	46.2 ± 11.9	0.22
LDL-C, mean ± sd	100.4 ± 35.5	101.5 ± 37.3	99.2 ± 33.3	0.131
Triglycerides, median [IQ range]	130 [95-177]	129 [96-176]	132 [95-179]	0.557
Creatinine, median [IQ range]	0.95 [0.77-1.29]	0.98 [0.78-1.38]	0.93 [0.76-1.20]	<0.001
Creatinine ≥ 1.2, n (%)	615 (29.9)	368 (33.4)	247 (25.8)	<0.001
Glucose, median [IQ range]	145 [119-185]	147 [116-195]	146 [123-177]	0.621
Hba1c, median [IQ range]	7.4 [6.7-8.4]	7.3 [6.5-8.4]	7.5 [6.9-8.3]	<0.001
Hba1c>7%, n (%)	1275 (62.0)	630 (57.2)	645 (67.5)	<0.001

Table 1: Selected clinical characteristics of general population and treatment groups

*Smoking status available for 1262 patients (38.0% controls and 39.4% incretins treated);**Alcohol consumption available for 1150 patients (45.5% controls and 42.5% incretins treated)



95% CI 1.06-1.67, respectively). Finally 19 patients (0.9%) experienced episodes of acute pancreatitis requiring hospitalization a er the baseline visit, with no signi cant di erences between the two treatment groups, whereas 59 patients (2.9%) had a new discharge diagnosis of pancreatic cancer, with patients treated with incretin-mimentics agents having a lower likelihood of disease (Table 2).

Discussion

Our study demonstrates that the elevation of pancreatic enzymes during the incretin-mimetics treatment is a common nding, con rming the data reported in the literature so far and suggests that the elevation of pancreatic enzymes during incretin-mimetics therapy is not associated with an increased risk of pancreatitis or pancreatic cancer [20,21], in a sample of Italian T2DM patients (district of Ferrara, Emilia Romagna Italian Region). ese ndings are based on an unselected sample of type II diabetes patients, enrolled without restrictive exclusion criteria and followed-up with routine clinical care assessment schedule, therefore enhancing the external validity of our results. A biological explanation for an asymptomatic increase of pancreatic enzymes has been suggested: GLP-1 acts on receptors that are also located on the exocrine pancreas, thus stimulating trophism and secretive function and causing growth-dependent release of pancreatic enzymes from the acinar cells [22]. is pharmacological e ect has raised the issue of a possible induction of latent pancreatic damage, potentially causing

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