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Complex interplay between type 2 diabetes mellitus and pancreatic cancer: insights from observational and mendelian randomization analyses

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Abstract

Background To investigate the causal relationship between type 2 diabetes mellitus (T2DM), pancreatic cancer (PC) risk and identify the mediating effects of various risk factors on that relationship.

Methods 581 PC patients and 582 healthy controls who visited our center from January 2013 to December 2023 were included in this retrospective study. Multivariable logistic regression was performed to evaluate the association between T2DM and PC through odds ratios (ORs) and 95% confidence intervals (CIs). Mendelian randomization (MR) studies were then conducted to explore the causal relationship between T2DM and PC, and causal mediation analysis (CMA) to examine the mediating role of common risk factors.

Results After adjusting for confounding factors, retrospective analysis revealed significant association between new-onset diabetes mellitus (NODM) and PC risk, with insulin treatment also linked to increased PC development. The standard inverse-variance weighted (IVW) method indicated that genetic susceptibility to T2DM was associated with an increased risk of developing PC (OR = 1.11; 95% CI = 1.034–1.193). Furthermore, MR showed T2DM, insulin treatment, FGF-4, and sulfhydryl oxidase 2 may be independently associated with the prevalence of PC. Specially, CMA demonstrated that insulin treatment, FGF4, and sulfhydryl oxidase 2 mediate the pathway from T2DM to PC, contributing 56.8%, 55.8%, and 5.9% of the total effect, respectively.

Conclusion This study supports the association between T2DM, specifically NODM, and increased PC risk, with insulin therapy, FGF4, and sulfhydryl oxidase 2 mediating this pathway. Further research is required to elucidate the mechanisms underlying these mediating effects.

Clinical trial number not applicable.

Keywords Pancreatic cancer, Type 2 diabetes mellitus, Mendelian randomization, Causal mediation analysis, Risk factors

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Background

Pancreatic cancer (PC) is a malignant tumor associated with low survival, with a median survival period of only 5–8 months and an outlier 5-year survival rate lower than 10% [1], causing a substantial global health burden [2]. Risk factors of PC primarily include personal attributes, lifestyle habits, metabolic disorders, and pancreatic disease status [3]. Notably, among these, type 2 diabetes mellitus (T2DM), a prevalent chronic noncommunicable disease, has shown complex bidirectional associations with PC [4].

Based on the time since onset, T2DM can be categorized as new-onset diabetes mellitus (NODM) or long-standing diabetes mellitus (LSDM) [5]. NODM, defined as a diagnosis within 24–36 months before PC surgery, is considered an early metabolic marker for PC [6], with numerous studies identifying a strong risk association between NODM and PC. In contrast, the relationship between LSDM and PC remains less consistent and varies both clinically and genetically [7, 8]. Glucose and lipid metabolism, especially glucose metabolism, and pancreatic disease status, could partially explain the connection between T2DM and PC [9]. Hyperinsulinemia and insulin resistance play key roles in PC progression, underscoring the influence of insulin in PC development [10, 11]. However, there is currently no direct research on the impact of T2DM therapies aimed at managing high blood glucose on PC risk. Although few studies suggest a higher risk of PC with insulin use, these findings are often confounded by bias [12]. Thus, T2DM therapy may be a pivotal mediator between T2DM and PC, which deserves further investigation.

Typical therapeutic strategies for T2DM include dietary management, oral medication, and insulin treatment. Recent research suggests that fibroblast growth factors (FGFs) may be involved in modulating various metabolic functions. Sun et al. reported that single intracerebroventricular administration of recombinant FGF4 can induce sustained T2DM remission in leptin receptor-deficient (*db/db*) mice [13]. Moreover, unlike FGF1 (a pan-FGFR ligand), FGF4 has no apparent effect on food intake. The potent anti-hyperglycemic and anti-inflammatory properties of FGF4 testify to its promising potential for use in the treatment of T2DM and related metabolic disorders [14, 15]. Some molecules involved in the FGF4 pathway, such as CSF-1, alpha-crystallin in B2, and gamma-crystallin in D, are known to be involved in cell proliferation, signaling, and differentiation, which may lead to the development of cancer [16–19]. However, FGF4 pathway has yet to be investigated for its mediating role between T2DM and PC.

Hence, in this article, we aimed to analyze the risk trends between T2DM and PC and assess their causal relationship through Mendelian randomization (MR) analysis. Additionally, we explored the mediating variables in the causal pathway to better understand the effects of T2DM on PC and the underlying mechanisms.

Methods

Statistical analysis of a single-center retrospective study

In this study, we included 581 adult patients (aged ≥ 18 years) who visited our center between January 2013 and December 2023 and were histopathologically confirmed with pancreatic cancer (PC) following surgery. Patients with other malignant tumors were excluded. Additionally, the Control Group comprised 582 participants, matched 1:1 with the patients by sex and age from the same hospital. All participants provided retrospective informed consent. The study was approved by the Ethics Committee of Hangzhou First People's Hospital (Approval No. KY-20201114-0178-01), and all procedures followed ethical guidelines.

The study participants were divided into the pancreatic cancer group and the control group and were further classified into the T2DM group and the non-T2DM group based on the presence of type 2 diabetes mellitus (T2DM). For participants with T2DM, we collected data on the age at diagnosis (< 55 years, 55–65 years, ≥ 65 years), disease duration (≤ 1 year, 1–2 years, 2–5 years, 5–10 years, 10–20 years, ≥ 20 years), diabetes status [new-onset diabetes mellitus (NODM, disease duration ≤ 2 years) and long-standing diabetes mellitus (LSDM, disease duration > 2 years)], and treatment methods (diet control, oral medication, insulin therapy).

We documented each participant's demographic information (e.g., age, sex), social determinants (e.g., marital status, education level), lifestyle factors (e.g., smoking and alcohol consumption), and health status (e.g., body mass index [BMI], history of coronary heart disease [CHD], and hypertension). Marital status was categorized as "married/remarried," "unmarried/divorced," and "widowed." Education level was divided into three categories: primary school or below, junior high school, and high school or above. Smoking was defined as consuming more than one cigarette per day for more than six consecutive months, with smoking history classified as never smoked, former smoker, or current smoker. For current alcohol consumers, we inquired about specific details of alcohol use, including the type of beverage (spirits/beer/wine), drinking frequency (times per week), and quantity consumed per occasion. Excessive alcohol consumption was defined as a weekly intake of more than 210 g for men and more than 140 g for women. Moderate drinking was defined as consuming alcohol more than once per week for more than six consecutive months. Alcohol consumption was categorized as never consumed, former consumer, moderate drinker, or heavy drinker. We used

a BMI threshold of > 24 to define an individual as overweight/obesity [20].

Baseline data were organized and analyzed using SPSS 26.0 statistical software. For normally distributed continuous data, results are expressed as $\bar{x} \pm s$, and comparisons between two groups were performed using independent samples t-test. Categorical data are presented as frequency (percentage), and comparisons between groups were conducted using chi-square test.

Multivariable logistic regression was performed to assess the association between T2DM and PC via odds ratios (ORs) and 95% confidence intervals (CIs). This study used disease status as the dependent variable (coded as 1 for presence and 0 for absence), and included the following as independent variables in the regression model: diabetes status, diabetes by age at diagnosis (years), diabetes by time since diagnosis (years), diabetes status by subtypes, diet, use of oral medication, and use of insulin. Three models were used for analysis. Model 1: Includes basic demographic information (age, sex) as covariates. Model 2: Adds clinical information (smoking, alcohol use, hypertension, obesity, coronary heart disease) as covariates to Model 1 Model 3: Further includes socioeconomic information (marital status, education level) as covariates to Model 2 All three models underwent Hosmer-Lemeshow testing, with P-values > 0.05, indicating good model fit. Additionally, collinearity diagnostics showed that all models met the criteria of tolerance > 0.01, VIF < 10, CI < 30, and eigenvalues > 0.01, suggesting that there were no collinearity issues among the covariates. Subsequently, mediating effects were assessed by incorporating an interaction term into the model and comparing it to a noninteractive model through likelihood ratio tests and subsequently validated through stratified analysis of these variables.

GWAS data sources for T2DM

T2DM-associated GWAS data are accessible from FinnGen (https://www.finngen.fi/en). As of January 2022, the project had amassed 309,154 samples, 16,962,023 variables, and 180,756 control participants. The T2DMGWAS included 215,654 participants and 16,380,440 single-nucleotide polymorphisms (SNPs) (Supplementary Table S1).

GWAS data sources for PC

The relevant GWASs for PC included 476,245 participants and 24,195,229 SNPs. The aggregated dataset is accessible for free via the IEU OpenGWAS (Supplementary Table S1).

GWAS data sources for the mediating factors

Mediating factors included lipid metabolism (Body Mass Index (BMI), total cholesterol, high density lipoprotein (HDL) cholesterol, triglycerides, low density lipoprotein (LDL) cholesterol), glucose metabolism (two-hour glucose challenge, fasting blood insulin, peak insulin response, insulin secretion rate, insulin levels, fasting glucose, insulin treatment), pancreatic function (pancreatic volume, acute pancreatitis (AP), chronic pancreatitis, liver, biliary or pancreas problem, other disorders of glucose regulation and pancreatic internal secretion), and the FGF4 pathway (FGF4, CSF-1, alpha-crystallin in B2, gamma-crystallin in D, PGC cross-disorder traits, sulfhydryl oxidase 2) [16–19]. The SNPs aggregated dataset is accessible for free via the IEU OpenGWAS (https://gwas.mrcieu.ac.uk/) (Supplementary Table S1). This study utilized deidentified data from ethically approved trials, exempting the need for individual ethical approval.

IV selection

The conventional Bonferroni-corrected threshold of $p < 5 \times 10^{-8}$ was adopted as significant threshold, and the commonly used threshold of $p < 1 \times 10^{-5}$ as a suggestive evidence level. When none SNPs reaches significant threshold, suggestive evidence level was applied to find more SNPs [21]. SNPs were evaluated utilizing rigorous criteria (10,000 kb, $r^2 \leq 0.001$). Outlier SNPs were identified using the MR-PRESSO test and subsequently deleted. We exclude SNPs with a minor allele frequency (MAF) less than 0.01, which indicates that enough individuals in the sample carry the allele, increasing the likelihood of detecting an association with the phenotype [22–24]. The F statistic was calculated as $F = (R^2 / (1 - R^2)) * ((N - K - 1) / K)$, where $R^2 = 2 * MAF * (1 - MAF) * (\beta / SD)^2$ [25, 26], which is used to assess the strength of the SNPs. SNPs with F statistic < 10 were identified as weak IVs (Supplementary Table S2).

Mendelian randomization

Three fundamental assumptions must be upheld for MR: (1) correlation: the SNP demonstrates a significant association with the exposure factor; (2) independence: the SNP operates independently of any confounders; and (3) exclusion: the outcome is influenced by the SNP via only the exposure factor. After excluding SNPs with LD and those that were associated with other traits, a total of 306 SNPs were retained for genetic analysis. The inverse-variance weighted (IVW) method was applied to determine the causal effect of T2DM on PC, which combines the Wald ratio estimates of each SNP into 1 causal estimate for each exposure using the random-effects meta-analysis approach [27, 28]. In addition, sensitivity analyses were performed. Heterogeneity was assessed through Cochrane's Q test, where a *P*-value < 0.05 would be considered an indication of heterogeneity. When significant heterogeneity was detected, a random-effects model was used; otherwise, a fixed-effects model was used. The MR

Egger regression intercept analysis was conducted to examine horizontal pleiotropy, with a P-value < 0.05 considered as evidence of horizontal pleiotropy [25].

Bidirectional two-sample Mendelian randomization

We used the R software package (4.0.2), including two-sample MR and Mendelian Randomization. The causal impact of PC on T2DM was probed using identical procedures. SNPs with LD and those correlated with other traits were eliminated, yielding 37 significant SNPs for analysis (Supplementary Table S2).

Causal mediation analysis

If a causal relationship between T2DM and PC is established, two-step MR should subsequently be used to investigate the mediating effects of common risk factors for PC. Prevalent risk factors for PC were regarded as mediators, including glucose metabolism, lipid metabolism, pancreatic function and relevant phenotypes of the FGF4 pathway, with comprehensive data shown in the Supplementary Table S1. First, we estimated the causal effect of T2DM on these factors through two-sample MR to identify those factors significantly impacted by T2DM. Second, we identified causal risk factors for PC through two-sample MR. The overlapping traits of the first and second steps were identified as substantial mediating factors. The PhenoScanner V2 tool was used to detect SNPs pertaining to T2DM among the IVs. This ensures independence of the two sets of SNPs: T2DM (exposure) and risk factors (mediating factors). Using the product coefficient method, the indirect effect of T2DM on the mediating factors was measured by multiplying the influence of mediating factors on PC. The 95% CI for this indirect effect was estimated using the delta method.

Results

Baseline characteristics

Table 1 presents the baseline characteristics of the patients in the PC group and control group. Among the 1,163 participants, the patient group had a greater proportion of older individuals and was predominantly male (mean [standard deviation] age, 67.34 [55.32–79.36] years; male, 60.07%). Among the social determinants, a significantly higher percentage of individuals in the control group had junior high and higher education levels (41.92%), compared to the PC group (32.88%). The proportion of smokers/ex-smokers in the PC group was notably greater, while alcohol consumption was not significantly different between the two groups. Furthermore, there were fewer individuals with hypertension in the control group than in the PC group, yet there were more overweight individuals in the control group (182, 31.27%).

Effects of T2DM on PC

The associations between T2DM and PC risk are presented in Table 2. Across all models, patients with T2DM had a notably greater risk of developing PC than non-T2DM individuals. There was a downward trend in PC risk as T2DM duration increased. The risk of PC for NODM patients was greater than that for LSDM patients. Furthermore, the results suggested a trend toward increased cancer risk with age at T2DM diagnosis, peaking at > 65 years. Compared with T2DM patients managed through diet and oral medication, T2DM patients treated with insulin had a greater risk of PC.

Bidirectional two-sample MR analysis

Bidirectional two-sample MR was conducted to explore the relationship between T2DM and PC risk. A total of 306 SNPs were carefully selected to represent the genetic predisposition to T2DM (Supplementary Table S2). Using the standard IVW method, we found that genetic susceptibility to T2DM was associated with an increased risk of developing PC (OR = 1.11; 95% CI = 1.034–1.193; P = 0.0039) (Supplementary Table S3). The results of the MR analysis for T2DM and PC are illustrated in Fig. 1. In contrast, the analysis did not find a statistically significant causal relationship between PC and T2DM (Supplementary Table S3). Additionally, the MR-Egger intercepts indicated no evidence of directional pleiotropy (P > 0.05), and the analysis showed no significant heterogeneity (Supplementary Table S4).

Causal mediation analysis

We performed CMA to assess the proportion of patients with T2DM influencing PC risk through modifiable risk factors. Figure 2 elucidates the causal impact of T2DM on prevalent risk factors, establishing a causal link with HDL, total cholesterol, decreased peak insulin response, diminished insulin levels, fasting glucose, T2DM, insulin treatment, other glucose regulations and pancreatic internal secretory disorders, FGF-4, and sulfhydryl oxidase2 (Supplementary Table S3, S5-6).

Based on CMA, T2DM, insulin treatment, FGF-4, and sulfhydryl oxidase 2 may be independently associated with the prevalence of PC, which is unrelated to other risk factors (Fig. 3). We quantified the mediating effects of T2DM, insulin treatment, FGF-4, and sulfhydryl oxidase 2, as shown in Fig. 4. The mediating role of insulin treatment in the causal pathway from T2DM to PC was 0.061 (95% CI = 0.043–0.076), accounting for 56.8% of the total effect. The mediating role of FGF4 was 0.058 (95% CI = 0.023–0.095), contributing to 55.80% of the total effect. Sulfhydryl oxidase 2 mediated a causal pathway from T2DM to PC with an effect size of 0.006 (95% CI = 0.002–0.009), accounting for 5.90% of the total effect.

Table 1 Baseline data of the study population

	Control group		Patients			
	N = 582		*N* = 581		T	*P* value
	n	%	*n*	%		
Age	62.47 ± 16.91		67.34 ± 12.02			
Sex					3.73	**0.05**
Male	317	54.47	349	60.07		
Female	265	45.53	232	39.93		
Education					15.97	**< 0.001**
Primary school and below	338	58.08	390	67.13		
Junior	123	21.13	74	12.74		
High school or above	121	20.79	117	20.14		
Marriage status					8.06	**0.02**
Married/remarried	476	81.79	507	87.26		
Unmarried/divorce	106	18.21	73	12.56		
Widowed	0	0.00	1	0.17		
Alcohol [a]					3.71	0.29
Never	481	82.65	469	80.72		
Ever	21	3.61	34	5.85		
Moderate	66	11.34	61	10.50		
Heavy	14	2.41	17	2.93		
Smoking status [b]					6.16	**0.05**
Never	475	81.62	448	77.11		
Ever	26	4.47	45	7.75		
Current	81	13.92	88	15.15		
Overweight/obesity status [c]					5.11	**0.02**
Yes	182	31.27	147	25.30		
No	400	68.73	434	74.70		
Hypertension status					1.62	0.20
Yes	231	39.69	252	43.37		
No	351	60.31	329	56.63		
CHD status					2.77	0.10
Yes	129	22.16	106	18.24		
No	453	77.84	475	81.76		

Note: Data are presented as the number (%) or mean ± standard deviation

CHD, coronary heart disease

[a] Moderate alcohol consumption was defined as alcohol intake > 1 occasion/week that was sustained for more than six continuous months. Heavy alcohol consumption was defined as 210 g of weekly alcohol for males and 140 g for females

[b] Smoking was defined as smoking > 1 cigarette/day for more than six consecutive months

[c] Overweight/obesitywas defined as a BMI (body mass index) > 24 kg/m^2

Discussion

In this retrospective study and bidirectional two-sample MR, we identified associations between T2DM subtypes and PC and revealed cancer risk among individuals with T2DM with diverse characteristics. This study is the first analysis identifying three mediating factors, including insulin treatment, FGF4 and sulfhydryl oxidase 2 between T2DM and PC via two-step MR.

The results from a bidirectional two-sample MR of individuals of European descent indicate that an increased OR for T2DM enhances susceptibility to PC, as based on the fixed-effects model. Inverse MR findings suggest the lack of a causal relationship between PC and T2DM, and similar outcomes were also observed in other research [29].The studies lacked evidence of a causal impact of T2DM on PC risk [30]. The discrepancy in results could be due to our use of recent T2DM and PC GWASs. Simultaneously, we employed multivariable regression to correct for confounding factors, and the retrospective study findings aligned with previous findings. A meta-analysis encompassing 88 retrospective studies revealed that the risk of PC increases in the initial years after the diagnosis of T2DM [31]. Consistently, the risk posed by T2DM persisting for less than two years is greater for NODM than for LSDM, suggesting the "diabetesizing" role of PC. As time progresses, the risk decreases and maintains an enduring association with PC. There is a temporal dependence between T2DM and

Table 2 Association between T2DM-related variables and PC risk (581 patients and 582 control participants)

	Control group		Patients			Model 1		Model 2		Model 3	
	N = 582		*N* = 581								
	n	%	*n*	%	*P* value*	OR	95% CI	OR	95% CI	OR	95% CI
T2DM status					< 0.001						
No T2DM	475	81.62	387	66.61		Ref		Ref		Ref	
YES	107	18.38	194	33.39		2.06	1.56–2.71	2.10	1.58–2.77	2.14	1.62–2.84
T2DM by age at diagnosis (years)					< 0.001						
No T2DM	475	81.62	387	66.61		Ref		Ref		Ref	
≤ 55	45	7.73	49	8.43		1.38	0.89–2.12	1.37	0.88–2.12	1.36	0.87–2.11
55 to ≤ 65	40	6.87	73	12.56		2.12	1.41–3.20	2.18	1.44–3.30	2.25	1.48–3.42
> 65	22	3.78	72	12.39		3.27	1.97–5.42	3.38	2.03–5.63	3.59	2.14–6.04
T2DM by time since diagnosis (years)					< 0.001						
No T2DM	475	81.62	387	66.61		Ref		Ref		Ref	
≤ 1	8	1.37	26	4.48		3.81	1.69–8.56	3.97	1.75–8.98	4.16	1.82–9.49
1 to ≤ 2	12	2.06	32	5.51		3.38	1.70–6.69	3.46	1.74–6.91	3.65	1.80–7.40
2 to ≤ 5	13	2.23	29	4.99		2.44	1.25–4.80	2.72	1.37–5.37	2.58	1.29–5.13
5 to ≤ 10	41	7.04	64	11.02		1.74	1.14–2.65	1.69	1.11–2.5	1.75	1.14–2.70
10 to ≤ 20	11	1.89	24	4.13		2.38	1.14–4.96	2.44	1.16–5.10	2.59	1.23–5.50
> 20	22	3.78	19	3.27		0.93	0.49–1.76	0.93	0.49–1.77	0.94	0.49–1.80
T2DM status by subtypes					< 0.001						
No T2DM	475	81.62	387	66.61		Ref		Ref		Ref	
Yes, ≤2years (NODM)	73	12.54	145	24.96		2.21	1.61–3.04	2.25	1.63–3.10	2.32	1.68–3.21
Yes, >2years (LSDM)	34	5.84	49	8.43		1.72	1.08–2.72	1.76	1.10–2.80	1.77	1.10–2.84
T2DM control measures					< 0.001						
Diet											
No T2DM	475	81.62	387	66.61		Ref		Ref		Ref	
YES	8	1.37	18	3.10		2.54	1.08–5.93	2.40	1.02–5.67	2.43	1.02–5.78
No use	99	17.01	176	30.29		2.02	1.52–2.68	2.07	1.55–2.76	2.12	1.58–2.84
Use of oral medication					< 0.001						
No T2DM	475	81.62	387	66.61		Ref		Ref		Ref	
YES	83	14.26	135	23.24		1.86	1.36–2.53	1.91	1.40–2.61	1.93	1.41–2.65
No use	24	4.12	59	10.15		2.74	1.67–4.51	2.72	1.65–4.49	2.88	1.73–4.80
Use of insulin					< 0.001						
No T2DM	475	81.62	387	66.61		Ref		Ref		Ref	
YES	16	2.75	41	7.06		2.84	1.5–5.17	2.88	1.58–5.26	3.11	1.68–5.76
No use	91	15.64	153	26.33		1.92	1.43–2.58	1.95	1.45–2.64	1.98	1.46–2.68

Model 1: Adjusted for age and sex

Model 2: adjusted for Model 1 and alcohol consumption status (never, ever, moderate, heavy), smoking status (never, ever, smoking), overweight status, hypertension status, and CHD status

Model 3: adjusted for Model 2 and education level (primary school and below, junior high school or above) and marital status (married/remarried, sedentary/divorced, bereft of one's spouse)

*Differences between groups were evaluated using the χ^2 test

LSDM, long-standing type 2 diabetes mellitus; NODM, new-onset type 2 diabetes mellitus; PC, pancreatic cancer

PC. Our findings support the implementation of regular cancer screening in elderly patients who develop hyperglycemia within 2 years, providing guidance for glycemic control in elderly LSDM patients.

Beyond the identification of causality, potential mediators are also an area of research focus. The CMA suggested that insulin's method of controlling blood glucose mediates the causal effect of T2DM on PC. The type of treatment for type 2 diabetes mellitus (T2DM) may depend on the severity of the condition. Severe T2DM is associated with an increased risk of pancreatic cancer, and this relationship may be influenced by the treatments administered for managing severe T2DM. It is important to consider how the severity of T2DM and its treatment could potentially mediate this risk. Previous research has indicated that physiological insulin levels facilitate pancreatic cell secretion of digestive enzymes for fat breakdown, yet high insulin levels can induce pancreatic inflammation and precancerous cell growth [32]. In the treatment of pancreatic cancer, researchers are committed to blocking the insulin /IGF signaling pathway in order to achieve cancer targeted therapy [33]. Therefore,

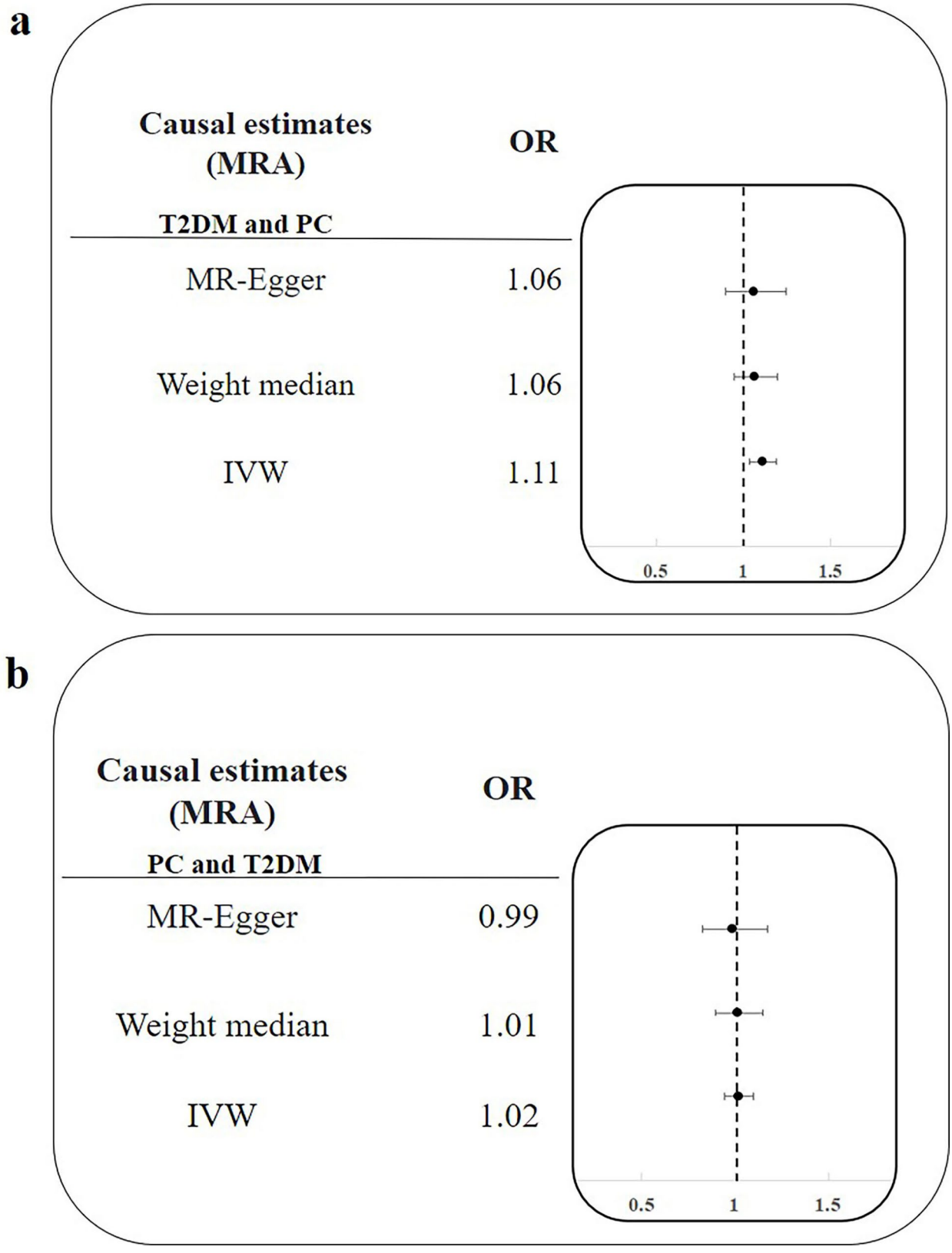

Fig. 1 Forest plot of the estimated results (ORs and 95% CIs) from the MR analysis. The point estimates are represented by a bullet along with the 95%CIs. (**a**) The directional association between T2DM and PC risk. (**b**) The directional association between PC and T2DM risk. IVW, inverse-variance weighted; MR ANALYSIS, MR analysis; PC, pancreatic cancer; T2DM, type 2 diabetes mellitus

Exposure		Outcome	Method	N of SNPs	β	SE	P	OR(95%CI)	Low_CI	Up_CI
T2DM	Lipid Metabolism	BMI	IVW	243	0.00	0.00	0.78	0.98	0.97	1.00
		Total cholesterol	IVW	85	0.02	0.01	0.01	1.02	1.01	1.03
		HDL cholesterol	IVW	240	-0.02	0.00	0.00	1.05	1.03	1.07
		triglycerides	IVW	232	0.02	0.00	0.00	1.02	0.99	1.04
		LDL cholesterol	IVW	103	0.01	0.01	0.34	1.02	1.00	1.04
	Glycometabolism	two-hour glucose challenge	IVW	83	0.07	0.05	0.15	1.07	0.97	1.13
		Fasting blood insulin	IVW	299	-0.03	0.01	0.03	1.01	0.99	1.03
		Peak insulin response	IVW	277	-0.10	0.03	0.00	0.90	0.86	0.95
		Insulin secretion rate	IVW	215	-0.09	0.06	0.10	0.91	0.81	1.02
		Insulin levels	IVW	90	-0.13	0.05	0.01	0.88	0.80	0.96
		Fasting glucose	IVW	290	0.03	0.01	0.00	1.04	1.02	1.05
		Diabetes, insuline treatment	IVW	110	0.76	0.02	0.00	2.15	2.06	2.24
		Pancreas volume	IVW	288	0.00	0.01	0.78	1.00	0.98	1.02
	Pancreatic function	AP	IVW	198	0.09	0.06	0.14	1.10	0.97	1.24
		Chronic pancreatitis	IVW	198	-0.02	0.08	0.85	0.99	0.84	1.16
		Liver, biliary or pancreas problem	IVW	291	0.00	0.00	0.00	1.00	1.00	1.00
		Other disorders of glucose regulation and pancreatic internal secretion	IVW	305	0.26	0.04	0.00	1.30	1.20	1.41
	Fibroblast growth factor 4	FGF-4	IVW	35	0.32	0.10	0.00	1.38	1.13	1.69
		CSF-1	IVW	35	0.11	0.10	0.30	1.11	0.91	1.37
		Alpha-crystallin A chain	IVW	296	0.01	0.03	0.64	1.01	0.96	1.06
		Beta-crystallin B2	IVW	296	-0.04	0.03	0.13	0.96	0.92	1.01
		Gamma-crystallin D	IVW	296	0.03	0.03	0.27	1.03	0.98	1.08
		PGC cross-disorder traits	IVW	70	0.00	0.03	0.87	1.00	0.96	1.06
		Sulfhydryl oxidase 2	IVW	295	0.06	0.03	0.01	1.06	1.01	1.17

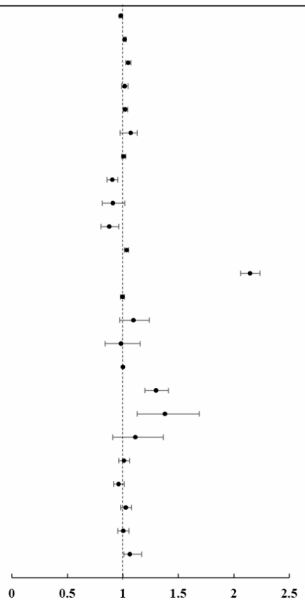

Fig. 2 Separate MR associations between genetically predicted T2DM and each risk factor. IVW, inverse-variance weighted; PC, pancreatic cancer; T2DM, type 2 diabetes mellitus; AP, acute pancreatitis; LDL, low-density lipoprotein; HDL, high density lipoprotein; CSF, colony-stimulating factor; FGF, fibroblast growth factor

Exposure		Outcome	Method	N of SNPs	β	SE	P	OR	Low_CI	Up_CI
Lipid Metabolism	BMI	PC	IVW	1936	0.08	0.07	0.26	1.13	0.93	1.37
	Total cholesterol		IVW	198	0.00	0.08	0.96	0.97	0.80	1.16
	HDL cholesterol		IVW	1314	-0.12	0.06	0.06	1.07	0.96	1.19
	Triglycerides		IVW	1128	-0.07	0.07	0.33	1.13	0.89	1.43
	LDL cholesterol		IVW	606	-0.04	0.08	0.67	0.92	0.80	1.06
Glycometabolism	Two-hour glucose challenge		IVW	11	-0.01	0.11	0.92	0.99	0.79	1.23
	Fasting blood insulin		IVW	46	0.05	0.10	0.59	1.01	0.42	2.41
	Peak insulin response		IVW	34	-0.07	0.05	0.12	0.93	0.85	1.02
	Insulin secretion rate		IVW	17	0.00	0.05	0.95	1.00	0.91	1.10
	Insulin levels		IVW	6	0.04	0.11	0.71	1.04	0.83	1.31
	Fasting glucose		IVW	62	0.00	0.09	0.97	1.00	0.84	1.20
	Diabetes, insuline treatment		IVW	229	0.08	0.04	0.04	1.08	1.00	1.16
	Pancreas volume		IVW	66	-0.08	0.15	0.60	0.92	0.69	1.24
	AP		IVW	11	0.03	0.03	0.31	1.03	0.98	1.08
Pancreatic function	Chronic pancreatitis		IVW	7	0.04	0.04	0.39	1.04	0.95	1.13
	Liver, biliary or pancreas problem		IVW	63	-0.87	2.47	0.72	0.42	0.00	2.90
	Other disorders of glucose regulation and pancreatic internal secretion		IVW	26	0.02	0.03	0.43	1.02	0.97	1.08
	FGF-4		IVW	5	0.18	0.08	0.02	1.20	1.03	1.39
	Alpha-crystallin A chain		IVW	22	0.07	0.08	0.39	1.07	0.91	1.26
	Beta-crystallin B2		IVW	32	0.05	0.06	0.38	1.05	0.94	1.18
Fibroblast growth factor 4	Gamma-crystallin D		IVW	26	-0.03	0.06	0.64	0.97	0.86	1.10
	PGC cross-disorder traits		IVW	42	0.02	0.12	0.88	1.02	0.80	1.30
	PGCB		IVW	6	0.01	0.08	0.90	1.01	0.86	1.18
	Sulfhydryl oxidase 2		IVW	29	0.10	0.03	0.00	1.11	1.04	1.18

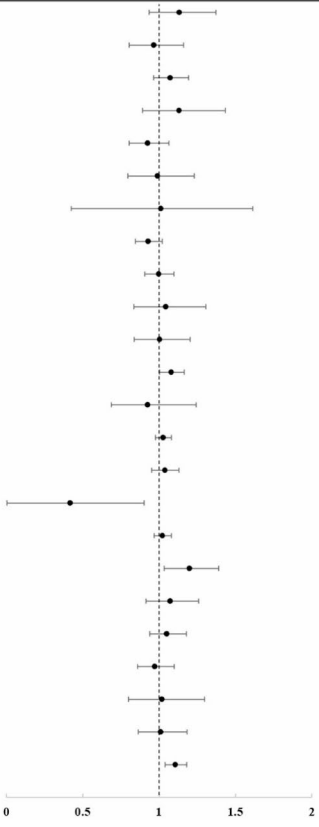

Fig. 3 MR associations of each genetically predicted risk factor with PC. IVW, inverse-variance weighted; PC, pancreatic cancer; T2DM, type 2 diabetes mellitus; AP, acute pancreatitis; LDL, low-density lipoprotein; HDL, high-density lipoprotein; CSF, colony-stimulating factor; FGF, fibroblast growth factor

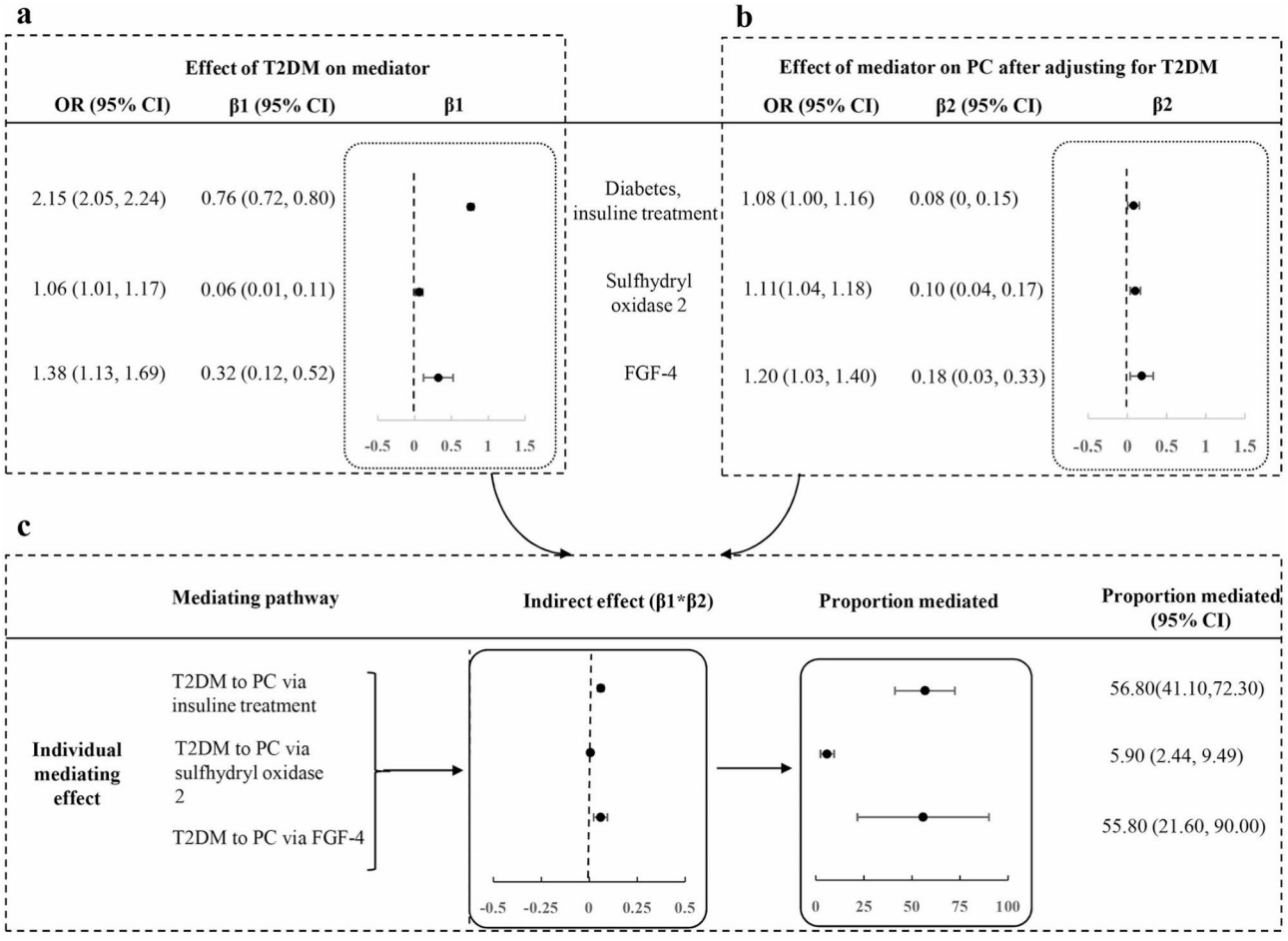

Fig. 4 MR-estimated effects of mediators. (**a**) MR-estimated effects of T2DM on each mediator, presented as β/ORs with 95% CIs. (**b**) MR-estimated effects of each mediator on PC, presented as β/ORs with 95% CIs. (**c**) MR-estimated effects of indirect effects of each mediator by the product of coefficients method with delta method-estimated 95%CIs. MR-estimated proportions (%) are presented with 95% CIs. T2DM, type 2 diabetes mellitus; PC, pancreatic cancer

from a public health perspective, patients with T2DM should utilize diet, exercise, and oral medication for optimal control. Careful consideration is required when initiating insulin therapy for T2DM to maintain insulin levels within the normal range.

FGF4 is a member of the fibroblast growth factor family, which plays a crucial role in various physiological and pathological processes. Previous studies have confirmed that FGF4 is important in regulating glucose homeostasis. For example, Sun et al. found that centrally administered FGF4 induced sustained remission in a T2DM mouse model, suggesting that FGF4 may regulate blood glucose levels by affecting glucose-sensing neurons in the brain [15]. Additionally, the role of FGF4 in promoting epithelial-mesenchymal transition (EMT), as well as the proliferation, migration/invasion, and colony formation of pancreatic cancer cells, highlighting the potential role of FGF4 in the progression of pancreatic cancer [34]. Qi et al. demonstrated that FGF4 increases intracellular calcium ion concentration by upregulating the expression of the calcium signaling-related protein Orai1, thereby promoting EMT [34]. Ying et al. found that FGF4 exerts a powerful antihyperglycemic effect by targeting skeletal muscle, where FGFR1c is highly expressed [14]. These findings suggest that FGF4 plays a critical role in both T2DM and PC. The dual role of FGF4 in T2DM and PC suggests that it may act as a bridge between the two diseases. On one hand, FGF4 may influence the progression of T2DM by regulating glucose homeostasis and insulin sensitivity; on the other hand, it may promote pancreatic cancer development by facilitating EMT and cellular proliferation. These findings help us better understand the biological link between T2DM and PC and provide clues for further exploration of potential therapeutic targets.

Based on the aforementioned studies, it can be speculated that FGF4 may play a role in the connection between T2DM and PC through the following mechanisms: In T2DM, FGF4 may influence disease progression by regulating glucose homeostasis and insulin sensitivity; in PC, FGF4 may promote tumor development by

facilitating EMT and cell proliferation; and FGF4 may affect the behavior of pancreatic cancer cells by modulating intracellular calcium ion concentrations, which offers potential avenues for the development of new therapeutic strategies.

While FGF4 provides valuable insights into the T2DM-PC connection, another important molecule, Quiescin sulfhydryl oxidase (QSOX), also warrants attention for its role in cancer progression. QSOX is a unique, multidomain disulphide catalyst that is localized primarily to the Golgi apparatus and secreted fluids and has attracted attention owing to its overproduction in tumors [35]. Sulfhydryl oxidase1 activity can be associated with metastasis or progression in several cancers, such as breast cancer and pancreatic ductal adenocarcinoma [36]. Mechanistically, QSOX1 post-translationally activates matrix metalloproteinases (MMPs) [37]. Although whether sulfhydryl oxidase 2 is involved in tumor growth has not been revealed yet, the regulatory role of sulfhydryl oxidase2 in PC development should not be ignored via its similar sequence and structure to sulfhydryl oxidase 1. But no studies explored its role in T2DM. Our study emphasized for the first time that sulfhydryl oxidase2 may plays a mediatory role in association between T2DM and PC. This finding suggests that sulfhydryl oxidase2 could also be a potential therapeutic target for PC invasion, providing a valuable direction for treatment.

Moreover, our retrospective study and MR results refute an association between excess body weight and PC risk, as participant-reported body weight measures might introduce common biases in retrospective studies, such as survival bias or overweight misclassification. Cancer is often characterized by symptoms of weight loss and reduced body mass prior to or early in diagnosis, a factor possibly accounting for previous MR findings [38].

There are still some limitations of our research. First, retrospective studies risk recall bias, selection bias, and information bias in data collection, thereby reducing the reliability of the study outcomes. Second, due to limited data on MR in individuals of east Asian descent, MR research was conducted solely among European populations, necessitating caution when applying its results to other groups. Larger-scale GWASs in individuals of East Asian descent are needed to reassess outcomes in the future. Due to the lack of relevant GWAS data for T2DM subtypes, the associations of NODM and LSDM with PC can only be deduced from retrospective studies. In addition, two-step MR analysis may not adequately control for potential interplay between exposure and mediators, causing bias. In summary, identifying FGF4 and sulfhydryl oxidase 2 as potential mediators in the relationship between T2DM and PC provides us with a new perspective, helping us to better understand the association between these two diseases and offering potential targets for future therapeutic strategies. These findings advance our understanding of disease processes and offer significant directions for further research.

Conclusions

Our study identified the high risk of developing PC in T2DM patients, suggesting that insulin therapy may play a mediating role in the causal pathway between T2DM and PC, which potentially offers a reliable reference for glycemic management protocols in T2DM patients. The results are limited by multiple factors and may need to be confirmed in later studies. Moreover, the findings regarding the mediatory role of FGF4 in the above association demonstrated its potential as a predictive biomarker of PC.

Abbreviations

AP	acute pancreatitis
BMI	body mass index
CHD	coronary heart disease
CSF-1	colony-stimulating factor
ECM	extracellular matrix proteins
FGF4	fibroblast growth factor 4
FGFR	fibroblast growth factor receptor
GSN	glucose-sensitive neuron
GWAS	genome-wide association study
HDL	high-density lipoprotein
IV	instrumental variable
IVW	inverse-variance weighted
LD	linkage disequilibrium
LDL	low-density lipoprotein
LSDM	long-standing diabetes mellitus
MMP	matrix metalloproteinase
MR	Mendelian randomization
CMA	causal mediation analysis
NODM	new-onset diabetes mellitus
OR	odds ratio
PC	pancreatic cancer
SNP	single-nucleotide polymorphism
T2DM	type 2 diabetes mellitus

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12885-025-13976-6.

Supplementary Material 1

Supplementary Material 2

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None.

Author contributions

WYX is first authors. LQ, and ZXF designed the study. XL, GY, JHB, and YJF collected the data. WYX analyzed the data. WYX drafted the manuscript. XL and GY contributed to the interpretation of the results and critical revision of the manuscript for important intellectual content and approved the final version of the manuscript. All authors have read and approved the final manuscript.

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Data availability
All data generated or analysed during this study are included in this published article.

Declarations

Ethics approval and consent to participate
All procedures were performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. The study was approved by the Ethics Committee of Hangzhou First People's Hospital (Approval No. KY-20201114-0178-01). All participants provided written informed consent. The study was carried out in accordance with the applicable guidelines and regulations.

Consent for publication
Not Applicable.

Competing interests
The authors declare no competing interests.

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