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Triglyceride-glucose index and glycemic dynamics in pancreatic ductal adenocarcinoma: implications for disease progression and prognosis

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Abstract

Background To elucidate the relationship between the triglyceride-glycemic index (TyG) and clinical characteristics of pancreatic ductal adenocarcinoma (PDAC).

Methods A total of 1,594 individuals diagnosed with pancreatic and periampullary neoplasms were categorized into four groups: PDAC-early ($n=403$), locally advanced PDAC (LAPC, $n=315$), PDAC-late with distant metastasis ($n=371$), and other tumor types ($n=505$). TyG-high was defined as a TyG index greater than 8.81 in males and 8.73 in females.

Results The prevalence of TyG-high status was highest in PDAC-early (68.48%), followed by LAPC (53.33%), and lowest in PDAC-late (44.47%). TyG-high status significantly predicted worse PDAC prognosis ($P=0.0166$), particularly in PDAC-late ($P=0.0420$). Despite similar blood glucose levels across PDAC groups ($P=0.897$), PDAC-early patients showed significantly higher rates of glycemic disturbances (56.33% vs. 32.28%) and TyG-high status (68.48% vs. 47.13%) compared to those with other tumors. Progressive increases in glycemic disturbances and TyG-high status were observed from benign to pre-malignant lesions and PDAC-early. PDAC-early patients at the pancreatic head exhibited higher rates of glycemic disturbances (58.12% vs. 33.33%, $P<0.0001$), larger pancreatic duct diameters (0.4056 cm vs. 0.3398 cm, $P=0.0043$), and poorer prognosis compared to periampullary cancers, although the TyG-high rate and body mass index were similar.

Conclusion The TyG index exhibits a complex association with PDAC stages, profoundly shaping glycemic profiles. At the initial stages of PDAC, a notable elevation in TyG-high status and glycemic disturbances is observed. However, in advanced PDAC, while the TyG-high rate diminishes, abnormal glucose levels persist.

Keywords Glycemic status, Pancreatic cancer, Triglyceride-glucose index, Insulin resistance, Prognosis

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Introduction

Approximately 70% of individuals diagnosed with pancreatic ductal adenocarcinoma (PDAC) exhibit aberrant glycemic profiles [1]. The nexus between pancreatic malignancy and glucose regulation disorders is multifaceted and complex. Long-standing diabetes mellitus is acknowledged as a contributory risk factor for the onset of PDAC [2]. Conversely, PDAC itself can precipitate pancreatogenic diabetes, alternatively known as type 3c diabetes mellitus, delineating a bidirectional relationship [3, 4]. It is widely posited that diabetes manifesting within a two-year period antecedent to PDAC diagnosis is predominantly attributable to the malignancy, thereby termed pancreatic cancer-related new-onset diabetes (PCNOD) [5].

The pathophysiology of type 2 diabetes mellitus encompasses a spectrum of dysregulations, including impaired insulin secretion and heightened insulin resistance [6]. The etiological underpinnings of PCNOD, however, remain a subject of academic debate. A fraction of the scholarly discourse suggests an etiology rooted in compromised β-cell functionality within the islets of Langerhans [7], while an alternative hypothesis implicates insulin resistance as the primary mechanism [8]. The paucity of large-scale epidemiological studies significantly hampers the elucidation of PCNOD's pathogenesis. Moreover, the clinical implications of insulin resistance in the context of pancreatic carcinoma have yet to be definitively established, signaling an imperative for further investigative scrutiny.

Several methodologies are employed to evaluate insulin resistance, among which the hyperinsulinaemic–euglycaemic clamp test stands as the criterion standard [9]. Despite its accuracy, the clamp method is seldom applied in routine clinical settings due to its complexity. Alternative assessment tools include the Homeostatic Model Assessment of Insulin Resistance (HOMA-IR) [10] and the Oral Glucose Tolerance Test (OGTT)-related Insulin Sensitivity Index (ISI) [11]. However, these methods depend heavily on the measurement of insulin levels, where a lack of standardized procedures contributes to considerable measurement variability [12]. This inconsistency poses significant challenges in the clinical assessment of insulin resistance, potentially explaining the scarcity of large-scale studies investigating its impact on PDAC. Recently, the triglyceride-glucose index (TyG) has emerged as a robust proxy for insulin resistance, validated across multiple research studies [13–16]. The TyG index, calculated using two routinely measured clinical parameters—triglycerides (TG) and blood glucose (GLU)—offers a straightforward and reliable approach for assessing insulin resistance in large-scale clinical investigations. This methodology presents an opportunity to enhance our understanding of the interplay between insulin resistance and PDAC, underscoring the need for broader application in research settings.

In previous studies, the focus has predominantly centered on the association between glycemic status and the risk of PDAC incidence [16, 17]. Comparative research on the glycemic status of advanced PDAC, as well as other periampullary and pancreatic tumors, remains sparse. This group includes entities such as serous cystic neoplasm (SCN) and solid pseudopapillary neoplasm (SPN), which seldom evolve into PDAC [18, 19]; and intraductal papillary mucinous neoplasms (IPMN) and mucinous cystic neoplasm (MCN), which are considered precancerous lesions of PDAC [18]. Similarly, cancers of the ampullary region and the lower common bile duct, anatomically proximate to the PDAC at the head of the pancreas, are seldom examined. The assessment of glycemic status and TyG index in these neoplasms is rarely reported. However, delineating the differences in glycemic and TyG status among these tumors compared to PDAC could elucidate the broader impacts of metabolic dysregulation on pancreatic malignancies.

In this single-center retrospective analysis, we evaluated 1,594 patients encompassing 1,089 cases of PDAC, 105 cases of periampullary carcinoma, and 400 cases of other pancreatic neoplasms. This study aims to elucidate several pivotal aspects: the glycemic profiles and TyG index across these tumors; their correlation with the staging and prognosis of PDAC; and the influence of other biochemical markers on TyG status. Our objective is to provide robust clinical evidence to augment understanding of how TyG status and glycemic dysregulation influence the pathophysiology of PDAC. This inquiry into the metabolic aberrations associated with pancreatic tumors seeks to delineate their impact on disease progression and outcome, potentially offering novel insights into early diagnostic markers and therapeutic targets.

Materials and methods

Study population

This study received ethical approval from the Ethics Committee of Sun Yat-Sen University Cancer Center (SYSUCC). The cohort comprised individuals diagnosed with pancreatic or periampullary tumors and admitted to SYSUCC between May 2008 and July 2022. Eligibility criteria included absence of prior anti-tumor treatment, a confirmed pathological diagnosis, and comprehensive pre-treatment assessments. Upon admission, trained medical staff accurately recorded each patient's height and weight, while medical histories focusing on diabetes were meticulously obtained by attending physicians. Additionally, all participants underwent baseline evaluations that included comprehensive fasting blood biochemistry and lipid profiling prior to initiating any therapeutic interventions.

Additionally, we conducted a study involving patients who underwent pancreaticoduodenectomy [20], selecting a cohort for the comparative assessment of pancreatic duct diameters. This analysis focused on intraoperative measurements of the pancreatic section under direct visualization in patients with pancreatic head cancer versus those with periampullary carcinoma.

Data collection

The initial phase of data collection involved querying the medical record system for entries containing "pancreas" or "pancreatic" within the pathology reports. Subsequent manual review isolated cases of pancreatic and other periampullary tumors. Comprehensive patient data were extracted from the pathology reports, admission records, nursing logs, blood tests, and imaging results. Key variables included sex, age, pathological diagnosis, height at admission, weight at admission, history of diabetes, pretreatment fasting triglyceride and glucose levels, tumor stage, and subsequent treatments. Data extraction was independently conducted by two of the study's authors, Song and Zhang. The cohort ultimately consisted of 1,594 patients. Additionally, baseline liver function data were collated for these patients, including prothrombin time (PT), albumin (ALB), globulin (GLOB), total protein (TP), alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), total bilirubin (TBIL), direct bilirubin (DBIL), and indirect bilirubin (IBIL). These data were independently compiled and verified by Jiang and Li. Survival status was monitored through outpatient follow-ups or telephone interviews, with the final follow-up in March 2024. Overall survival was defined from the time of pathological diagnosis to either the last follow-up or the patient's death.

Additionally, lipid and blood glucose data were sourced from the National Health and Nutrition Examination Survey (NHANES, https://www.cdc.gov/nchs/nhanes/index.htm) spanning from 1999 to 2018. Selection criteria for the NHANES dataset included the availability of sex, age, glycosylated hemoglobin, glucose, C-peptide, insulin, triglyceride, and HDL-C data. A total of 30,337 cases were analyzed to assess the relationship between insulin resistance and blood insulin levels.

Assessment of insulin resistance

Insulin resistance was evaluated using the TyG index, a robust marker for this metabolic condition. The TyG index is calculated using the formula: $TyG = Ln(TG \times GLU \times 0.5)$, where TG and GLU are expressed in mg/dL. TyG-high was classified as a TyG index exceeding 8.81 in males and 8.73 in females, indicating a state of insulin resistance [21].

In addition, for the data derived from the NHANES database, we assessed insulin resistance using HOMA-IR. The calculation formula for HOMA-IR is: GLU (mg/dL)×insulin (μU/mL)/405 [22]. This approach allows for a standardized evaluation of insulin resistance across the studied cohort.

Classification of glycemic status

Glycemic status was determined in accordance with the diagnostic guidelines established by the American Diabetes Association [23]. Patients reporting a prior diagnosis of diabetes were categorized as diabetic. Those without a previous diagnosis were classified as diabetic if fasting blood glucose (FBG) levels exceeded 7 mmol/L. Among the remaining participants, those with FBG levels ranging from 6.1 mmol/L to 7.0 mmol/L were identified as prediabetic. Individuals with FBG levels of 6.1 mmol/L or below were considered to have normal glucose metabolism. Diabetes diagnosed during hospital admission or within two years was categorized as new-onset diabetes. Thus, patients were stratified into four groups: long-term diabetes (long DM), newly diagnosed diabetes (new-onset DM), prediabetes (pre-DM), and normal glucose metabolism (normal). "Glycemic status alteration" or "glycemic disturbances" include long-term DM, new-onset DM, and pre-DM.

Classification of PDAC

For patients with PDAC, staging was classified as follows: "PDAC-early" for patients with no distant metastasis undergoing successful radical surgery; "Locally advanced PDAC (LAPC)" was designated for those exhibiting vascular invasion without distant metastasis; "PDAC-late" was applied to patients presenting with distant metastases, including those detected during intraoperative exploration. Patients diagnosed with periampullary carcinoma and other pancreatic tumor types were grouped into an "other" category.

Serum insulin measurement

Blood samples were collected after an overnight fast from patients at SYSUCC and subsequently stored at -80 °C. The fasting serum insulin levels were determined using an enzyme-linked immunosorbent assay (ELISA) with the ALPCO Insulin ELISA Kit (cat. no. 80-INSHU-E01.1).

Statistical analyses

For continuous variables adhering to a normal distribution, means and standard deviations were calculated to describe the data's central tendency and dispersion. For variables not exhibiting normal distribution, medians and interquartile ranges (IQR) were used to summarize the central tendency and variability. Categorical variables were examined using contingency tables, analyzed with the chi-square test and Fisher's exact test to determine significant associations between categories. Statistical

significance was established at a P-value of less than 0.05 ($P<0.05$). Analyses were performed using IBM SPSS Statistics version 23.0, R software version 4.0.2, and Python version 3.6.1.

Results

Study population

Of the 1,594 patients included in the study, 403 were classified into the PDAC-early group, 315 into the LAPC group, 371 into the PDAC-late group, and 505 into the other group. Significant differences in glycemic status were observed between PDAC patients and those with other tumor types ($P<0.001$, Fig. 1A), with a higher prevalence of diabetes or prediabetes noted among the PDAC cohort. However, no significant differences in glycemic status were found among the PDAC-early, LAPC, and PDAC-late groups ($P=0.897$, Fig. 1A). FBG levels were higher in PDAC patients compared to those with other tumors (median glucose levels: 6.08 mmol/L vs. 5.34 mmol/L, $P<0.001$, Fig. 1B). TyG-high rates were 68.48%, 53.33%, 44.47%, and 47.12% in the PDAC-early, LAPC, PDAC-late, and other groups, respectively ($P<0.001$, Fig. 1C). Median TyG values were 9.06 in the PDAC-early group, 8.86 in the LAPC group, 8.68 in the PDAC-late group, and 8.71 in the other group (Table 1). Additional baseline characteristics are displayed in Table 1.

Glycemic status and TyG index across PDAC stages

In an evaluation of glycemic status among PDAC patients across different stages, no significant differences were observed in median FBG levels among PDAC-early, LAPC, and PDAC-late groups (6.05 mmol/L, 6.14 mmol/L, and 6.07 mmol/L respectively; $P=0.642$, Fig. 1B). However, the rates of TyG-high status was highest in PDAC-early (68.48%), followed by LAPC (53.33%), and lowest in PDAC-late (44.47%) (Fig. 1C). Multivariate logistic regression analysis including tumor stage, sex, age, and body mass index (BMI) identified sex, BMI and PDAC stage as independent risk factors for TyG-high status among PDAC patients, while age was not significant (Supplementary Table 1). Notably, BMI values were lower in LAPC and PDAC-late patients compared to those in the PDAC-early group (Fig. 1D). Further analysis demonstrated that TyG-high status was associated with increased BMI across all stages, independently of tumor stage or tumor type (Fig. 1E). Moreover, no significant differences in BMI were noted among PDAC stages when controlling for TyG status (Fig. 1F and G), suggesting that the relationship of BMI and TyG status is independent of cancer stages.

Isolating tumor stage, no direct correlation with glycemic status was evident (Fig. 1A). However, when incorporating BMI, age, sex, insulin resistance and tumor stage into a comprehensive multivariate analysis, a significant impact of tumor stage on glycemic status was revealed (Supplementary Table 2). In a cohort of PDAC patients with TyG-high status, those in the PDAC-early stage exhibited a higher proportion of normal glycemic status compared to their counterparts in the LAPC and PDAC-late stages (31.52%, 29.76%, and 24.24%, respectively). This trend was also observed among PDAC patients without TyG-high status, where 70.08% of PDAC-early, 61.22% of LAPC, and 60.68% of PDAC-late patients maintained normal glycemic levels. These findings emphasize the distinct influence of PDAC stage and TyG index as independent risk factors for glycemic alterations.

Speculatively, the influence of tumor stage on glycemic status, independent of insulin resistance indicator TyG, might be attributed to diminished insulin secretion in PDAC-late patients. Initial analyses of the NHANES database indicated a positive correlation between TyG and blood insulin levels (Supplementary Table 3), a finding echoed in the literature [24]. Although the dietary patterns of the population in the NHANES database differ from those of patients at SYSUCC, the relationship between TyG and blood insulin in the NHANES database still provides valuable insights for our study. Thus, an increase in TyG not only signifies insulin resistance but also an elevation in serum insulin levels. In PDAC-late patients, a notable down-regulation of the TyG index was observed (Table 1), indicative of reduced blood insulin levels. To further investigate, we analyzed blood insulin levels in two groups: 10 patients newly diagnosed with diabetes in the early stage of PDAC and 10 in the late stage, prior to any treatment intervention. Notably, TyG levels were elevated in the PDAC-early group compared to the PDAC-late group, while GLU levels were comparable between the cohorts (Supplementary Fig. 1). Results demonstrated a significant reduction in insulin levels among PDAC-late patients ($P=0.0443$, Fig. 1H), supporting the hypothesis that relative to patients with early-stage PDAC, those with advanced PDAC demonstrate attenuated levels of insulin resistance and blood insulin, highlighting a progression-associated alteration in glucose metabolism.

Previous data have shown that insulin can exacerbate PDAC progression [25, 26], and prolonged insulin resistance may deteriorate prognosis [27]. Our findings indicate that while glycemic status alone does not significantly impact prognosis, TyG-high status serves as a poor prognostic marker, particularly in PDAC-late patients (Fig. 2 and Supplementary Fig. 2).

Glycemic alterations and TyG index across pancreatic tumor types

In our analysis, PDAC-early patients demonstrated significantly higher rates of glycemic status alterations

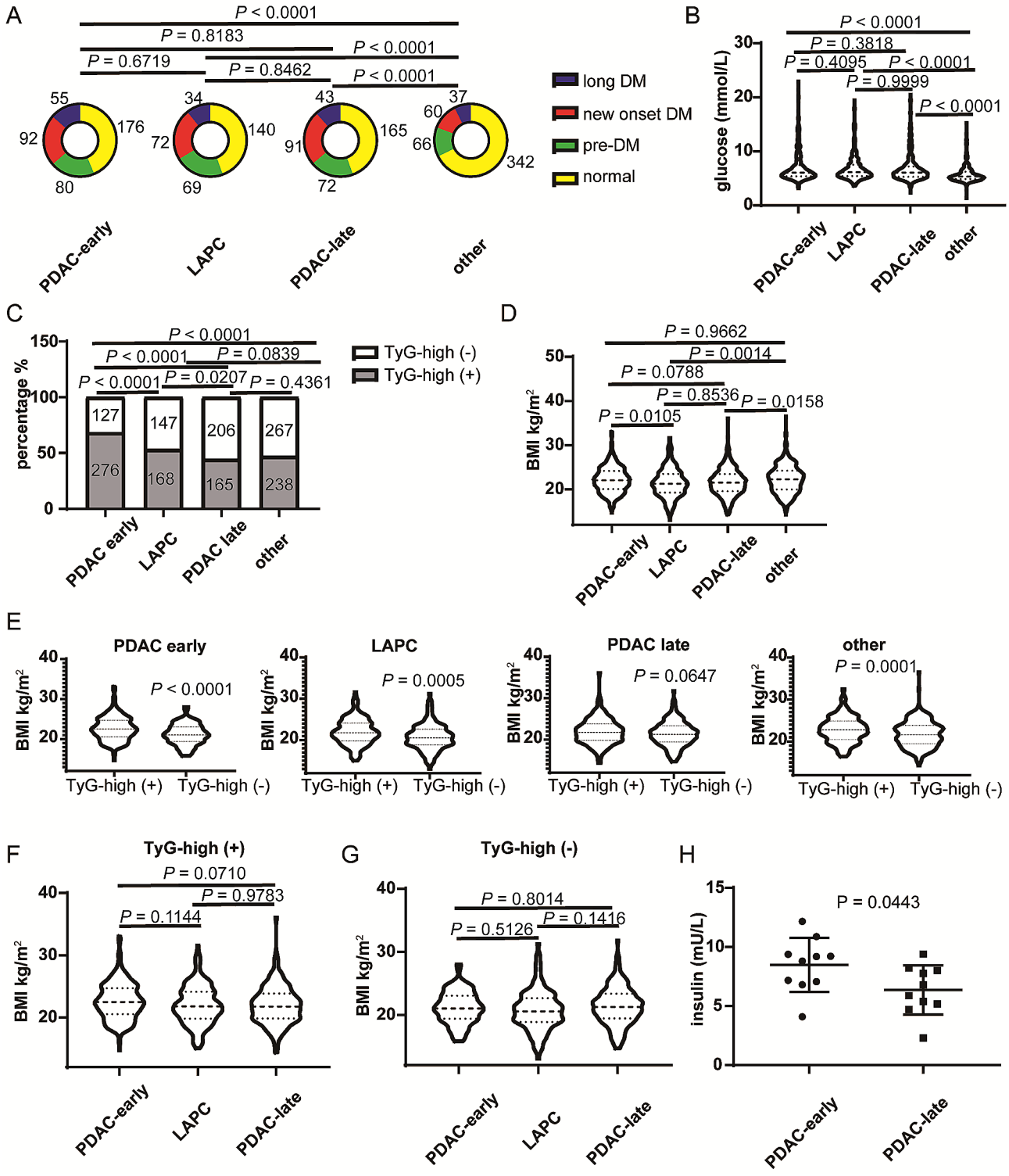

Fig. 1 Interrelations of Glycemic Status, TyG index, and BMI Across Patient Groups. (**A**) Distribution of glycemic status across four patient groups: early-stage PDAC (PDAC-early), locally advanced pancreatic cancer (LAPC), late-stage PDAC (PDAC-late), and other tumor. (**B**) Levels of fasting blood glucose in the aforementioned patient groups. (**C**) TyG status measurements in the same cohorts. (**D**) Comparison of BMI among the four groups. (**E**) Correlation between BMI and TyG status across all patients. (**F**-**G**) BMI comparisons in PDAC patients, categorized by the presence (**F**) or absence (**G**) of TyG-high status. (**H**) Comparative analysis of serum insulin levels among patients newly diagnosed with diabetes in the early and late stages of PDAC, consisting of two groups of 10 patients each

Table 1 Characteristics of patients

	PDAC early	PDAC LAPC	PDAC late	other	*P* values
N	403	315	371	505	-
Age	60.49 (53.88–67.46)	59.77 (53.10–66.20)	58.48 (51.85–65.17)	51.93 (41.95–61.25)	< 0.001
Sex					< 0.001
Male	243	174	240	222	
Female	160	141	131	283	
Height cm	164 (157–170)	162 (157–168)	163.5 (158–170)	162 (156–168)	0.011
Weight kg	59.3 (52.0–65.0)	56.0 (48.9–64.0)	57.7 (51.0–65.0)	57.7 (52.0–65.0)	0.017
BMI	22.06 (20.05–24.17)	21.26 (19.26–23.53)	21.51 (19.58–23.48)	22.67 (20.00-24.25)	< 0.001
Glycemic status					< 0.001
Long DM	55	34	43	37	
New onse DM	92	72	91	60	
Normal	176	140	165	342	
Pre-DM	80	69	72	66	
GLU mmol/L	6.05 (5.37–7.46)	6.14 (5.41–7.52)	6.07 (5.27–7.22)	5.34 (4.86–6.22)	< 0.001
TG mmol/L	1.69 (1.15–2.66)	1.35 (0.99–2.13)	1.19 (0.87–1.73)	1.39 (0.92–1.98)	< 0.001
TyG	9.06 (8.64–9.62)	8.86 (8.45–9.32)	8.68 (8.45–9.32)	8.71 (8.27–9.17)	< 0.001
TyG-high					< 0.001
No	127	147	206	267	
Yes	276	168	165	238	

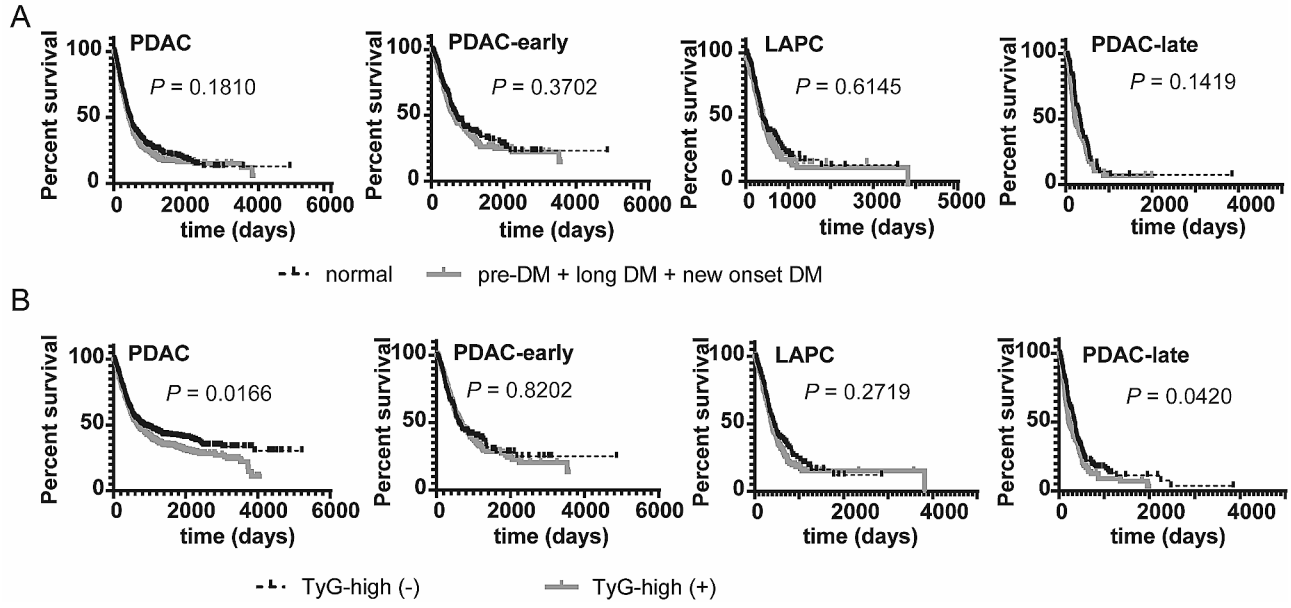

Fig. 2 Impact of Glycemic Variables on Prognosis in Pancreatic Cancer. (**A**) Prognostic significance of glycemic status in pancreatic cancer patients. (**B**) Impact of TyG status on survival outcomes in the same cohort

(68.73% vs. 32.28%, $P<0.0001$, Fig. 1A) and TyG-high status (68.49% vs. 47.14%, $P<0.0001$, Fig. 1C) compared to those with other tumor types. These differences occurred despite no significant disparities in BMI across the groups (Fig. 1D). This pattern suggests a unique link between the pathophysiology of PDAC and both the development of insulin resistance and alterations in glycemic control. Further investigation involving a multifactorial logistic regression analysis confirmed the type of tumor as an independent risk factor for TyG-high status (Supplementary Table 4). Both TyG-high status and the tumor type independently contributed to glycemic alterations (Supplementary Table 5). These results support the hypothesis that PDAC-early potentially triggers alterations in glycemic status through mechanisms both dependent on and independent of insulin resistance.

We selected four representative tumor groups to explore the metabolic implications associated with pancreatic neoplasms: SPN and SCN, which are less likely to progress to PDAC [18, 19]; and MCN and IPMN,

regarded as precancerous lesions predisposing to PDAC [18]. Stratified analysis demonstrated varying rates of normal glycemic status among these groups: 84.85% (112/132) in patients with SPN and SCN, 57.81% (37/64) in those with MCN and IPMN, and 43.67% (176/403) in patients with early-stage PDAC ($P<0.001$, Fig. 3A). Correspondingly, the prevalence of TyG-high status was 28.79% (38/132) in the SPN+SCN group, 45.31% (29/64) in the MCN+IPMN cohort, and 68.48% (276/403) in the early PDAC group ($P<0.001$, Fig. 3B). These findings occurred irrespective of BMI among the groups (Fig. 3C), suggesting a potential intrinsic connection between pancreatic neoplastic tumorigenesis and metabolic dysregulation.

Despite similar histological characteristics and proximate anatomical locations [28], a comparative analysis between early PDAC at the head of the pancreas (PDAC-early-head, $n=308$) and periampullary carcinomas (including duodenal papillary and lower common bile duct carcinomas, $n=105$) demonstrated significant

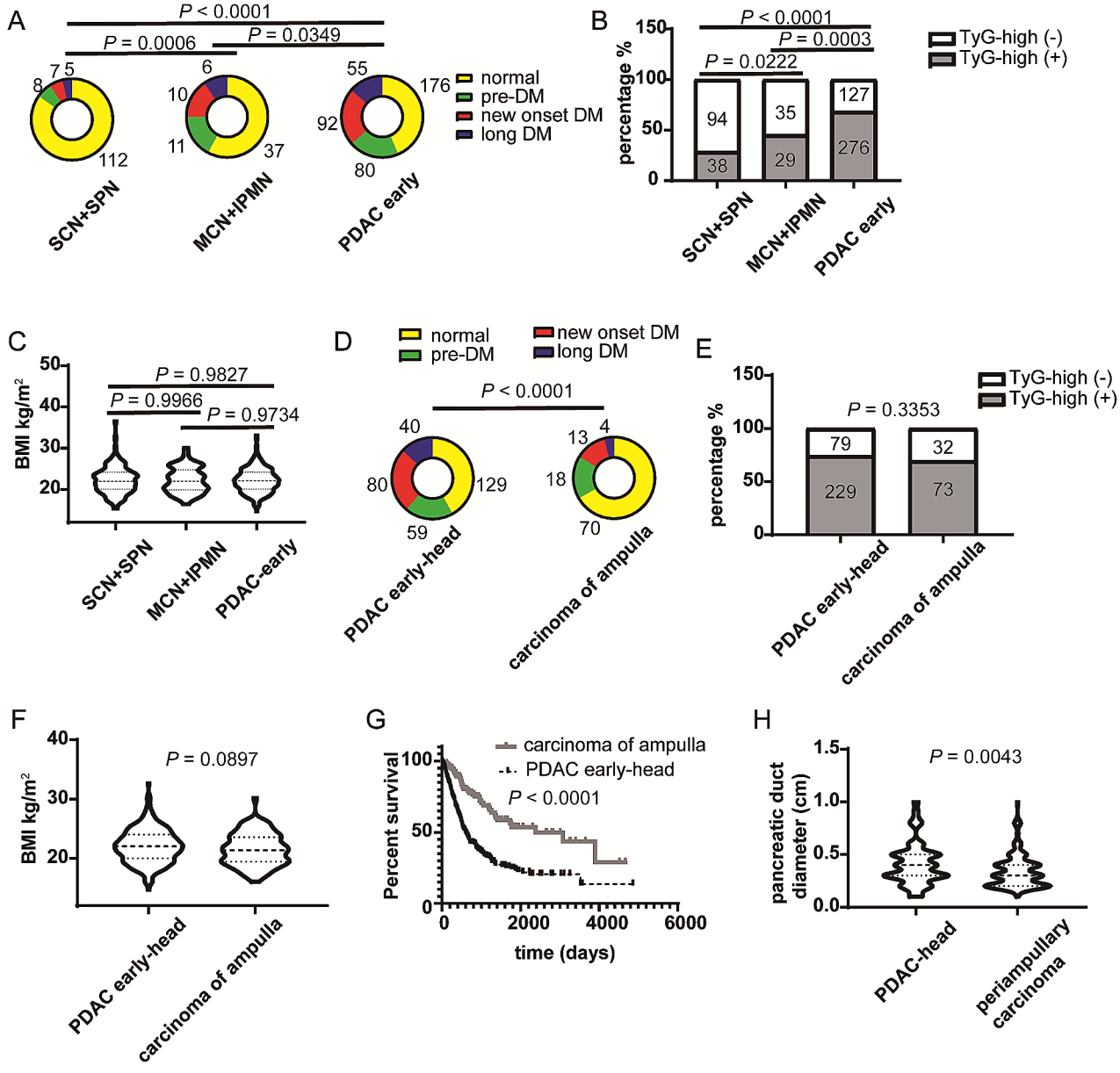

Fig. 3 Metabolic Profiles and Survival in Different Pancreatic Disorders. (**A**-**C**) Comparative analysis of glycemic status, TyG status, and BMI among patients with serous cystic neoplasms (SCN), solid pseudopapillary neoplasms (SPN), mucinous cystic neoplasms (MCN), intraductal papillary mucinous neoplasms (IPMN), and early-stage PDAC. (**D**-**G**) Examination of glycemic status, TyG status, BMI, and survival rates in patients with periampullary tumors compared to early-stage PDAC patients. (**H**) Comparative evaluation of pancreatic duct diameters in patients with periampullary tumors versus early-stage PDAC

differences in glycemic alterations. PDAC-early-head was associated with a notably higher rate of glycemic status alteration (58.12% vs. 33.33%, $P<0.001$, Fig. 3D), despite similar rates of TyG-high status ($P=0.3353$, Fig. 3E) and no significant differences in BMI ($P=0.0897$, Fig. 3F) between the groups. Periampullary carcinomas, often diagnosed earlier due to symptomatic obstructive jaundice, not only showed a better prognosis ($P<0.001$, Fig. 3G) but also exhibited a paradoxically high rate of TyG-high status (Fig. 3E) alongside a lower rate of glycemic alteration (Fig. 3D). Furthermore, during pancreaticoduodenectomy, larger pancreatic duct diameters were observed in patients with PDAC-early-head compared to those with periampullary carcinomas (mean diameter: 0.41 cm versus 0.34 cm, $P=0.0043$, Fig. 3H), suggesting a shorter duration of pancreatic duct obstruction in the latter group. This dilation in PDAC-early-head patients may indicate chronic pancreatitis, beta-cell destruction, and reduced insulin secretion, thus underscoring the significance of insulin resistance-independent pathways in the modulation of glycemic status.

Subgroup analysis: TBIL

The TyG index is calculated based on GLU and TG. Since obstructive jaundice affects both glucose and lipid metabolism [29, 30], it may influence TyG levels by altering GLU and TG. In the PDAC-early subgroup, TyG-high patients showed significant elevations in ALT, AST, ALP, TBIL, DBIL, and IBIL (Supplementary Table 6). These patterns were consistent across the LAPC, PDAC-late, and other tumor groups (Supplementary Table 6). For patients with TBIL≥34.2 umol/L, there were no significant differences in the proportion of glycemic alteration among the PDAC-early, LAPC, and PDAC-late groups ($P=0.783$); the PDAC-early group exhibited the highest proportion of TyG-high (86.6%), followed by the LAPC group (81.7%), and the PDAC-late group with the lowest (74.7%). Similar trends in glycemic alteration and TyG-high status were observed for patients with TBIL<34.2 umol/L (Supplementary Table 7). Additionally, among patients with TBIL<34.2 umol/L, the SCN+SPN group had the lowest rates of glycemic alteration and TyG-high status, with higher rates in the MCN+IPMN group and the highest in the PDAC-early group (Supplementary Table 8), maintaining a consistent trend. For patients with TBIL≥34.2 μmol/L, statistical evaluation was not performed for the SCN+SPN and MCN+IPMN groups due to the small sample size ($n=4$ for each group). These findings indicate that while TBIL is significantly correlated with TyG status, the relationship between tumor presence and TyG is independent of TBIL levels. Previous research on TyG and insulin resistance has predominantly focused on patients with normal TBIL levels. Utilizing data from the NHANES database for patients with TBIL≥34.2 umol/L (1999–2018, $n=177$), we observed that the HOMA-IR value remains higher in the TyG-high status group in the case of elevated TBIL (mean HOMA-IR: 1.892 versus 4.180, $P<0.001$, Supplementary Fig. 3), confirming that TyG remains associated with insulin resistance even in the context of elevated TBIL.

Subgroup analysis: sex

In our prior analysis, we identified sex differences as an independent risk factor for TyG-high (Supplementary Table 1). Among female PDAC patients, glycemic status did not vary significantly across PDAC-early, LAPC, and PDAC-late stages; however, the incidence of abnormal glycemic status was consistently higher in the PDAC group compared to the other group (Supplementary Fig. 4). Similarly, the incidence of TyG-high followed a trend of being highest in the PDAC-early group, followed by the LAPC group, and lowest in the PDAC-late group (Supplementary Table 9). This trend was also observed among male PDAC patients (Supplementary Table 9), suggesting that the relationships between tumor, TyG-high, and glycemic status are independent of sex.

IPMN was predominantly found among males, while MCN, SPN, and SCN were more common among females (Supplementary Table 10). Among female patients, the lowest incidence of TyG-high was observed in the SCN+SPN group, it increased in the MCN+IPMN group, and was highest in the PDAC-early group (Supplementary Table 11). Conversely, the proportion of patients with normal glycemic status was highest in the SCN+SPN group, lower in the MCN+IPMN group, and lowest in the PDAC-early group (Supplementary Table 11). Similar trends were observed for glycemic status and TyG status among male patients (Supplementary Table 11).

Intriguingly, the proportion of female PDAC patients with TyG-high was higher than that of male PDAC patients (Supplementary Table 9). However, the incidence of TyG-high was lower among female patients in the SCN+SPN and MCN+IPMN groups compared to male patients (Supplementary Table 11). Notably, there is no statistical difference between the incidence of TyG-high in women and men in the NHANES database, which comprises data mainly from healthy individuals (female versus male: 31.9% versus 33.2%, $P=0.8215$). This suggests that the relationship between sex and TyG status differs in PDAC patients compared to other populations.

Subgroup analysis: age

Our previous analysis revealed that age is associated with both TyG status and glycemic alterations (Supplementary Table 2, Supplementary Table 4, Supplementary Table 5). Analysis of the NHANES database data showed that the

incidence of TyG-high and FBG levels increased until 70 years of age, entering a plateau phase in the 50-59-year age group (Supplementary Fig. 5A and 5B). In terms of blood insulin levels, compared with the reference group of 20–29 years, there were no significant differences in the 30-39-year and 40-49-year groups, but the insulin levels in the 50-59-year group were significantly higher (Supplementary Fig. 5C). Given that TyG-high incidence, FBG, and blood insulin levels all underwent significant changes at 50 years, we set the cutoff value for age in our subgroup analysis at 50 years.

Among PDAC patients younger than 50 years, the incidence of TyG-high was highest in the PDAC-early group (63.9%), followed by the LAPC group (48.1%), and lowest in the PDAC-late group (42.9%). In contrast, the proportion of patients with normal glycemic status was comparable among the three groups, approximately 60% (Supplementary Table 12). Similar patterns were observed in PDAC patients aged 50 years or older (Supplementary Table 12). In the other group, regardless of age, the proportion of patients with normal glycemic status was higher than that in PDAC patients (Supplementary Table 12). Regarding TyG status in the other group, the proportion of TyG-high was as high as 58.8% in individuals aged 50 years or older, second only to the PDAC-early group, higher than both the LAPC and PDAC-late groups (Supplementary Table 12). However, in patients younger than 50 years, the incidence of TyG-high was the lowest in the other group, likely due to the predominance of SPN (with a low TyG-high proportion) in younger patients and the higher incidence of periampullary carcinomas (with a high TyG-high proportion) in patients aged 50 years or older (Supplementary Table 13).

In comparing the SCN+SPN, MCN+IPMN, and PDAC-early groups, the proportion of patients with normal glycemic status was highest in the SCN+SPN group, followed by the MCN+IPMN group, and lowest in the PDAC-early group, both in patients younger than 50 years and those aged 50 years or older (Supplementary Table 14). Regarding the incidence of TyG-high, in patients aged 50 years or older, it was lowest in the SCN+SPN group, higher in the MCN+IPMN group, and highest in the PDAC-early group (Supplementary Table 14). However, in patients younger than 50 years, the PDAC-early group had the highest incidence of TyG-high, while the SCN+SPN and MCN+IPMN groups had comparable rates (Supplementary Table 14), likely due to sampling error given the small sample size of 24 cases in the MCN+IPMN group within this age range.

Multivariate logistic regression identifies independent risk factors for TyG-high

We included liver function indicators (ALT, AST, TBIL, DBIL, IBIL, ALP, ALB), inflammation markers (white blood cell [WBC], C-reactive protein [CRP], neutrophil [NE], lymphocyte [LY]), sex, age, BMI, and PDAC stage in a multivariate analysis and found that tumor stage remains an independent risk factor for TyG-high status (Supplementary Table 15). This indicates that the relationship between the tumor and TyG is independent and stable.

Discussion

This study analyzed glycemic alterations and TyG status among patients with various stages and types of pancreatic and periampullary tumors. Patients were stratified into groups by disease stage: PDAC-early, LAPC, PDAC-late and other tumor types. Notably, patients with PDAC exhibited significant glycemic alterations, which appeared to be independent of the tumor stage. The incidence of TyG-high status was highest in the PDAC-early group, decreased in LAPC patients, and was lowest among those with PDAC-late, suggesting a nuanced relationship between tumor progression and metabolic dysfunction (Fig. 4). Our findings indicate that both the tumorigenesis and the progression of pancreatic tumors are intricately linked with metabolic changes, shedding light on potential mechanisms of disease progression.

Age and BMI were identified as contributing factors to the observed metabolic changes, underscoring the complexity of the interaction between tumor biology and systemic metabolic responses. The inclusion of other pancreatic and periampullary tumors, such as SCN and SPN as a control group, provided a comparative backdrop that highlighted the specific impact of pancreatic pathology on metabolic alterations.

The TyG index offers a streamlined method for assessing insulin resistance [13–16], often surpassing the predictive capability of the HOMA-IR [31]. In PDAC, the TyG index evaluates metabolic disruptions associated with tumor-induced changes in glucose metabolism [27]. The robustness of the TyG index as a reliable marker is further reinforced by its strong positive correlation with serum insulin levels, a finding corroborated by data from the NHANES (Supplementary Table 3) and mirrored in other scholarly research [24]. This convergence of evidence suggests that the TyG index reflects both insulin sensitivity and circulating insulin levels. The upregulation of the TyG index may thus serve as a significant indicator of both altered insulin action and PDAC pathology. Previous research highlights that glycemic alterations in PDAC result from reduced insulin secretion and enhanced insulin resistance. [32, 33]. Comparative analyses between diabetic patients with PDAC and those with conventional type 2 diabetes mellitus typically reveal similar insulin resistance profiles; however, PDAC is distinctly characterized by a reduction in insulin secretion [7]. Our findings confirm this, identifying both

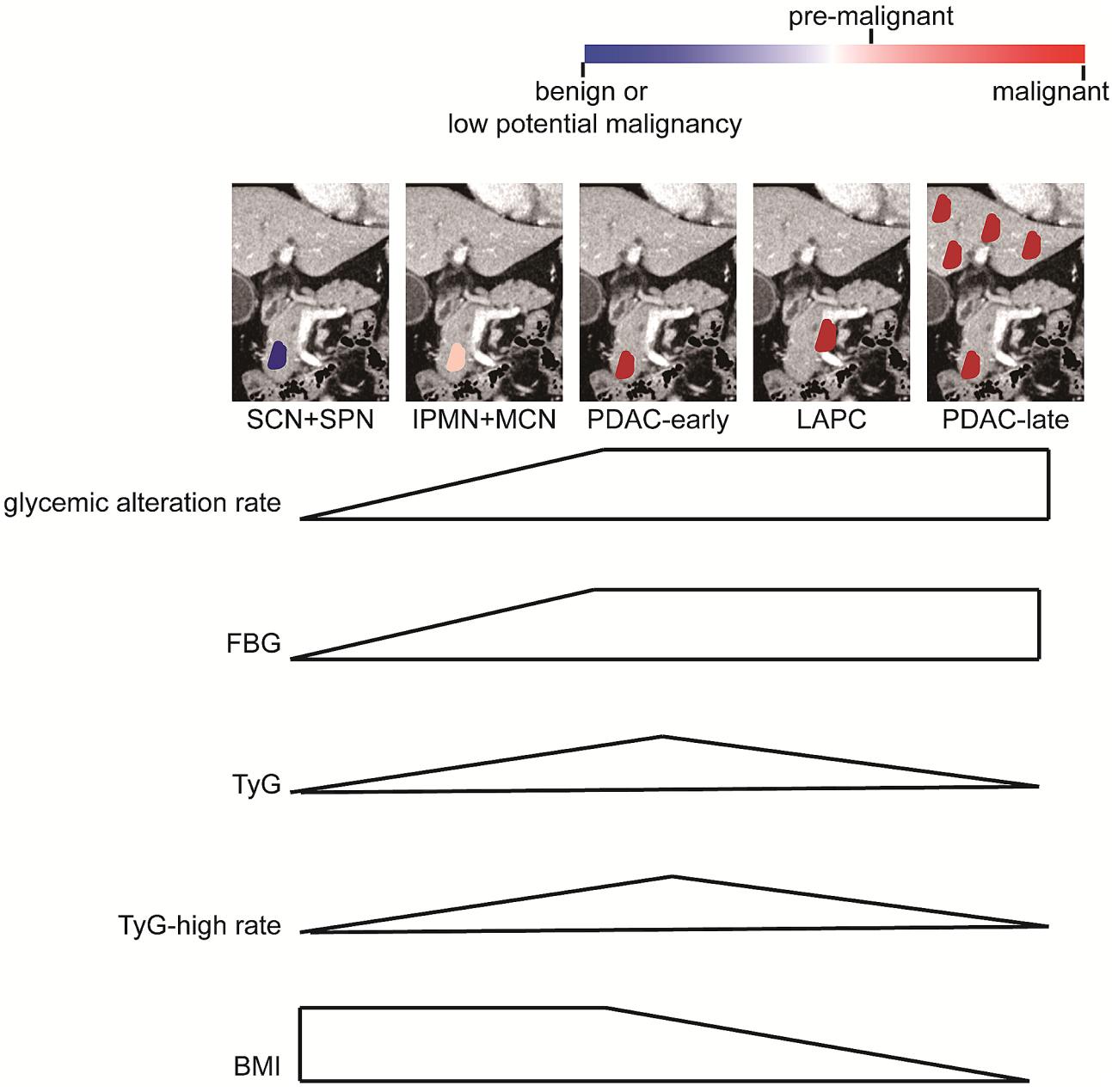

Fig. 4 Schematic diagram of our study

insulin resistance and tumor-related factors as pivotal contributors to the altered glycemic landscape in PDAC patients. Notably, the prevalence of TyG-high status peaks during the early stages of PDAC and declines in advanced PDAC, indicating compensatory mechanisms involving alternative metabolic or hormonal pathways. The TyG index, used as a proxy for insulin resistance, showed a positive correlation with serum insulin levels, affirming its robustness. Analysis of serum insulin in ten PDAC patients revealed that reduced insulin resistance in LAPC and late-stage PDAC coincided with lower insulin levels, paradoxically maintaining elevated glucose levels. This suggests that PDAC begins with high insulin resistance and compensatory hyperinsulinemia, transitioning in advanced stages to decreased insulin secretion and resistance, establishing a new metabolic homeostasis. The findings advocate for a nuanced understanding of the metabolic alterations at different tumor stages to better tailor therapeutic strategies that concurrently address oncological and metabolic challenges in PDAC.

Periampullary carcinoma, histopathologically akin to PDAC at the pancreatic head, exhibits similar patterns of insulin resistance [28]. Our study indicates that glycemic alterations are less frequent in periampullary carcinoma

patients than in PDAC patients, possibly due to the earlier detection from obstructive jaundice in ampullary carcinoma [34, 35]. In our cohort undergoing pancreaticoduodenectomy, PDAC patients generally had a larger main pancreatic duct diameter compared to periampullary carcinoma patients, indicating prolonged duct obstruction often linked to chronic pancreatitis [36]. Consequently, prolonged pancreatic duct obstruction and dilation can lead to severe stromal fibrosis, acinar cell destruction, and islet atrophy, resulting in decreased endocrine and exocrine pancreatic functions, including reduced digestive enzymes and insulin secretion [37, 38]. The association between ductal obstruction and reduced insulin secretion may shed light on diabetes pathogenesis in PDAC [37], underscoring the intricate relationship between pancreatic changes and metabolic dysfunctions.

The influence of insulin in exacerbating PDAC is increasingly recognized [25, 26]. The TyG index has been implicated in forecasting poorer outcomes in PDAC, likely due to the synergistic effects of hyperglycemia and elevated insulin levels [27]. Our findings corroborate these observations, showing a positive correlation between the TyG index and serum insulin, with higher indices predicting worse prognoses in PDAC. Subgroup analysis reveals that TyG status impacts prognosis most in late-stage and least in early-stage PDAC. The gradient in insulin resistance—from high in early to lower in advanced stages—suggests persistent hyperinsulinemia in late-stage PDAC patients, contributing to their deteriorating condition. The consistent correlation between TyG-high and poor outcomes highlights the detrimental role of sustained insulin resistance and hyperinsulinemia. Future research should explore the mechanistic pathways linking insulin resistance and hyperinsulinemia with PDAC progression, such as the tumor-promoting effects of insulin-like growth factors I and II on PDAC [39], to refine therapeutic strategies.

Previous data indicate that 70–80% of PDAC patients experience cachexia, characterized by over 2% weight loss in 3–6 months or a BMI below 21 [40, 41]. Insulin resistance is a key factor in PDAC cachexia [42] and cachexia is more prevalent in late-stage PDAC [43], matching our findings: early-stage PDAC patients have higher BMI and TyG levels, while advanced PDAC patients (including LAPC and late-stage PDAC) have lower levels. Previous studies also show cancer-related cachexia reduces the insulin/glucagon ratio [44], consistent with our observation of lower serum insulin in late-stage PDAC. Intriguingly, cachexia is not associated with FBG levels [43], aligning with our finding of no significant glycemic status difference across PDAC stages. These suggest that the BMI decline in late-stage PDAC is tied to cachexia. Though cross-sectional, our study hypothesizes that insulin resistance drives BMI decline and cachexia in early-stage PDAC (high TyG and BMI), while BMI decline and cachexia may reduce insulin resistance in late-stage PDAC (low TyG and BMI). Studies have demonstrated that weight loss induced by exercise or dietary interventions ameliorates insulin resistance and lower TyG [45, 46], supporting our hypothesis.

The relationship between the TyG index and insulin resistance has primarily been studied in populations without jaundice [14, 15, 31]. Pancreatic head and ampullary tumors often cause obstructive jaundice, which affects pancreatic enzyme excretion and liver function, disrupting glucose and lipid metabolism [29, 30]. Our NHANES database analysis shows a positive correlation between the TyG index and HOMA-IR in individuals with elevated bilirubin, indicating the TyG index is relevant to insulin resistance even with jaundice. Subgroup analysis of 1,594 patients, categorized by elevated TBIL, revealed consistent relationships between tumors and glycemic status, as well as tumors and TyG index, irrespective of TBIL levels.

This study has several limitations. Firstly, there was no large-scale direct measurement of serum insulin levels; these were primarily estimated using the TyG index. Secondly, the assessment of diabetes status relied on patient medical history and FBG rather than on hemoglobin A1c (HbA1c) measurements. These limitations highlight the need for comprehensive metabolic profiling in future studies to better understand insulin resistance, glycemic status, and PDAC progression.

Conclusion

In PDAC, the prevalence of TyG-high status exhibits a notable trend: it is higher in the early stages of the disease and diminishes in advanced stages. This observation underscores a unique, intrinsic relationship between insulin resistance and PDAC pathophysiology. Furthermore, the rate of alterations in glycemic status in PDAC patients surpasses that observed in other tumors, attributable to both insulin resistance and insulin-independent effects mediated by the tumor. Our findings suggest that persistent insulin resistance is associated with poorer outcomes in PDAC patients, highlighting the prognostic significance of metabolic dysregulation in this malignancy. These insights advocate for a deeper investigation into the metabolic mechanisms at play in PDAC, potentially guiding more targeted therapeutic strategies and improving patient prognosis.

Abbreviations

PDAC	Pancreatic ductal adenocarcinoma
PCNOD	Pancreatic cancer-related new-onset diabetes
HOMA-IR	Homeostatic Model Assessment of Insulin Resistance
OGTT	Oral Glucose Tolerance Test
HOMA-IR	Homeostatic Model Assessment of Insulin Resistance
ISI	Insulin Sensitivity Index
TyG	Triglyceride-glucose index

TG	Triglycerides
GLU	Blood glucose
SCN	Serous cystic neoplasm
SPN	Solid pseudopapillary neoplasm
IPMN	Intraductal papillary mucinous neoplasms
MCN	Mucinous cystic neoplasm
SYSUCC	Sun Yat-Sen University Cancer Center
PT	Prothrombin time
ALB	Albumin
GLOB	Globulin
TP	Total protein
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
ALP	Alkaline phosphatase
TBIL	Total bilirubin
DBIL	Direct bilirubin
IBIL	Indirect bilirubin
NHANES	National Health and Nutrition Examination Survey
FBG	Fasting blood glucose
Long DM	long-term diabetes
New-onset DM	Newly diagnosed diabetes
Pre-DM	prediabetes
Normal	Normal glucose metabolism
LAPC	Locally advanced PDAC
ELISA	Enzyme-linked immunosorbent assay
IQR	Interquartile ranges
BMI	Body mass index
HbA1c	Hemoglobin A1c
WBC	White blood cell
CRP	C-reactive protein
NE	Neutrophil
LY	Lymphocyte

Supplementary Information

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Supplementary Material 1

Supplementary Material 2

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Author contributions

Yunda Song contributed to the conception, design, data analysis and revised the manuscript. Lingmin Jiang was involved in data collection and contributed to the revision of the paper. Yuanxia Han provided assistance in the revision and proofreading of the paper. Subo Zhang interpreted experimental results, drafted and revised the manuscript. Shengping Li participated in data collection, contributed to the conception, and was involved in the revision of the paper.

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Data availability

All data generated or analyzed during this study are included in this article and its supplementary material files. Further inquiries can be directed to the corresponding author.

Declarations

Ethical approval

This study protocol was reviewed and approved by the Ethics Committee of SYSUCC (SL-B2023-211-01). All the participants provided written informed consent.

Conflict of interest

No conflict of interest exists in the submission of this manuscript.

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