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ORIGINAL ARTICLE

Impact of diabetes mellitus on treatment efficacy in patients with advanced pancreatic cancer: the Italian, multicenter, observational PANCAKE study

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Available online 15 December 2025

Background: Diabetes mellitus (DM) is a known risk factor for pancreatic ductal adenocarcinoma (PDAC). Preclinical evidence suggests higher glucose levels may enhance chemotherapy injury to PDAC cells. Clinical evidence of DM's impact in patients with PDAC receiving palliative treatment remains conflicting, however.

Materials and methods: PANCAKE, an Italian multicenter observational study, assessed the impact of DM and blood glucose levels on progression-free survival during first-line treatment and overall survival (OS) in patients with advanced PDAC.

Results: Among 663 patients with available baseline and on-treatment glycemic values, DM was confirmed in 193 patients (29.1%). Pre-existing DM was associated with a modest but significant OS benefit [median OS 11.6 versus 10.3 months, adjusted hazard ratio (HR) 0.82, 95% confidence interval (CI) 0.67-0.99; $P = 0.036$]. This benefit was significantly associated with the chemotherapy regimen: it was observed only in patients treated with first-line gemcitabine—nab-paclitaxel, but not with FOLFIRINOX. A longitudinal, Bayesian joint modelling approach accounting for the concomitant use of glucose-lowering medications confirmed a statistically significant, but clinically modest prognostic effect of glycemic trends, as a 10 mg/dl-point increase from baseline blood glucose values resulted associated with a 4% reduction in the risk of death (HR for OS 0.9967, 95% CI 0.9939-0.9995).

Conclusions: DM and higher blood glucose levels show a statistically significant, though clinically modest, impact on the OS of patients affected by advanced PDAC, which may be differential according to the chemotherapy regimen. This evidence lays the foundations to guide future studies on pharmacological and dietary approaches targeting tumor metabolism in this setting.

Key words: pancreatic cancer, diabetes, glycemia, chemotherapy, Bayesian joint modelling

INTRODUCTION

Pancreatic ductal adenocarcinoma (PDAC) is among the deadliest cancers, with a 5-year survival rate of 5%-10%.[1,2] Most cases are diagnosed at an inoperable stage, where chemotherapy, typically FOLFIRINOX (FFX) or gemcitabine—nab-paclitaxel (Gem-NabP), remains the standard first-line treatment, yielding a median overall survival (OS) of <12 months. Apart from *BRCA1/2* and *PALB2* mutations, no biomarkers guide regimen selection.[3] To date, no biomarkers have been implemented in clinical practice to select the optimal regimen, with the exception of germline *BRCA1/2* and *PALB2* mutations, which may result in higher benefit from platinum-based regimens.[4,5] Given these modest results, research efforts to implement new treatment strategies and reliable biomarkers are constantly increasing.

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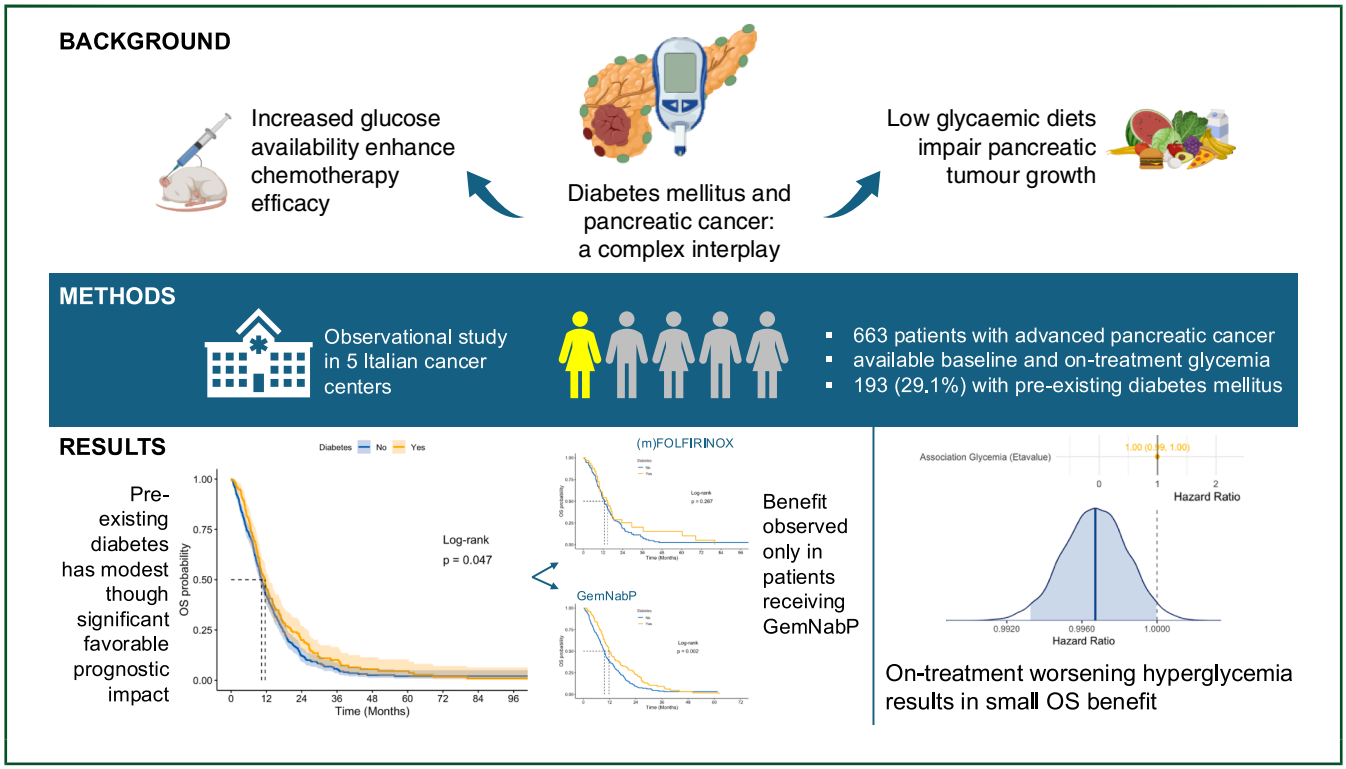
GRAPHICAL ABSTRACT



Type 2 and 3c (secondary to pancreatic diseases) diabetes mellitus (DM) affects up to ∼20%-30% of patients at the time of PDAC diagnosis. The complex interplay existing between DM and cancer has long been under investigation.[6-8] While DM is both a risk factor and potential consequence of PDAC, its impact on survival remains unclear due to conflicting studies.[9-15] Recently, a translational study provided a rationale to support a positive impact of DM on PDAC prognosis. The study demonstrated that tumor exposure to high glucose levels may have a chemosensitizer effect in preclinical PDAC models, by negatively regulating glutathione synthesis and in turn augmenting oxidative anti-tumor damage by chemotherapy.[15] This evidence was supported by a limited clinical validation, however, which showed that presence of at least one blood glucose value ≥200 mg/dl after the initiation of chemotherapy was associated with longer OS in a small, single-institution cohort of PDAC patients. Conversely, no difference based on glucose levels was observed in an independent cohort of PDAC patients who did not receive chemotherapy. Although intriguing, these data could be affected by an immortal time bias and by the dichotomization of continuous glucose values, potentially overestimating the prognostic impact of DM; a more robust assessment is therefore needed to verify the magnitude of the clinical impact of DM on the outcome of PDAC patients.

In this study, we analyzed a large multicenter cohort of patients affected by advanced PDAC treated with first-line chemotherapy to evaluate whether concomitant DM diagnosis, as well as baseline and early on-treatment glycemia, might be associated with clinical outcomes.

MATERIALS AND METHODS

Patient population and data collection

This was an observational, retrospective, multicenter study conducted in five Italian Cancer Centers [Fondazione IRCCS Istituto Nazionale dei Tumori di Milano (coordinating center); Azienda Ospedaliero-Universitaria Pisana, Pisa; Academic Hospital of Udine ASUFC, Udine; University Hospital and University of Cagliari, Cagliari; Fondazione Policlinico Universitario Agostino Gemelli IRCCS, Rome]. Data were collected from study initiation until data lock for all eligible patients, through an electronic database.

The main inclusion criteria consisted of: (i) age ≥18 years; (ii) histologically or cytologically confirmed diagnosis of pancreatic cancer (including PDAC or pancreatic carcinoma not otherwise specified, excluding neuroendocrine tumors and rare subtypes); (iii) locally advanced or metastatic disease stage; (iv) candidate to receive first-line treatment; (v) known medical history regarding presence or absence of DM diagnosis; (vi) available measurements of fasting plasma glucose concentration among three different timepoints: (1) within the 30 days before first-line treatment start, (2) at baseline (−3 to 0 days before first-line treatment start) and (3) after 30 ± 3 days from treatment start [referred to as T2, i.e. concomitant with second cycle treatment administration for every-month

regimens (e.g. Gem-NabP) or for third cycle treatment administration for bi-weekly regimens (e.g. FFX)]. Glycemia values at first radiological disease re-evaluation and at disease progression were also collected whenever available. Cases with no blood glucose measurements or that did not receive at least one cycle of systemic treatment were excluded from the analysis.

Periodic tumor assessment was carried out at the discretion of treating clinicians with frequency ranging from 8 to 16 weeks, as per clinical practice, and investigators were asked to provide disease status information according to RECIST (V. 1.1) criteria.[16] All patients were followed up until death, loss of contact, or the time of data lock (1 December 2023).

Written informed consent was obtained from all patients who were alive at the time of study conduction, while it was waived for deceased patients. The study was conducted in compliance with the principles outlined in the Declaration of Helsinki and received approval from the Institutional Review Board of the coordinating center (INT 231-21), and notified to each participating site.

Study objectives and statistical plan

The primary objective of the study was to investigate the association between pre-existing DM and the outcomes of patients with advanced PDAC treated with first-line chemotherapy. The primary endpoint of interest was progression-free survival (PFS), defined as the time between first-line chemotherapy initiation and disease progression or patient death, whichever occurred first. Overall survival, defined as the time between first-line chemotherapy initiation and patient death from any cause, was also explored. The presence of DM was defined according to the American Diabetes Association criteria,[17] by evaluating patients' medical history in electronic records documenting a confirmed DM diagnosis, previous and/or ongoing consultations with a diabetologist, and ongoing treatment with glucose-lowering medications (GLMs). Considered GLMs started at any time before and taken until first-line chemotherapy initiation were metformin, other oral GLMs (including sulfonylureas, meglitinides, thiazolidinediones, α-glucosidase inhibitors, DPP-4 inhibitors, SGLT2 inhibitors), and insulin therapy. GLM treatment duration was annotated, including the date of GLM treatment start and end, to assess the impact of GLM exposure on glucose levels and on patient outcomes.

For sample size calculation, based on previous studies,[14,15] we assumed that 20% of patients had DM at the time of first-line treatment start, and that non-diabetic patients had a median PFS on first-line chemotherapy of 6 months.[3] With these assumptions, ∼630 patients were needed to detect a hazard ratio (HR) for PFS of 0.75 in diabetic versus non-diabetic patients, with 90% power and two-sided α error of 0.05, accounting for ∼20% censoring.

The secondary objectives of the study were to explore the association between PFS and OS with (i) baseline glycemia, (ii) delta glycemia, defined as the absolute difference between T2 glycemia and baseline, alongside with their interaction, (iii) baseline use of GLMs and body mass index (BMI), (iv) the interaction between the metabolic parameters with the type of chemotherapy regimen (FFX versus Gem-NabP). For secondary analyses, glycemia continuous values were considered to carry out a more accurate inference. To minimize random fluctuations, the baseline glycemia value was calculated as the mean of the first two measurements within 30 days of treatment initiation.

Statistical analyses

Survival analysis. We first estimated the Kaplan—Meier curves for PFS and OS, overall and by DM status. The among group differences were tested using the log-rank test. Univariable analyses were conducted for DM, baseline glycemia, use of GLMs, and BMI (i.e. variables central to primary or secondary aims). Multivariable models were carried out by including a priori selected confounders on the basis of (i) their established prognostic relevance in advanced PDAC and/or (ii) their role as potential confounders of the association between DM or metabolic factors and outcomes, to avoid biases of 'univariable screening' (instability, inflated type-I error, and attenuation of exposure effects), namely age, sex, primary tumor site, stage at diagnosis, previous surgery, number of metastatic sites, Eastern Cooperative Oncology Group Performance Status at baseline, logarithm of CA19-9 at baseline, BMI, and type of chemotherapy regimen, and delta glycemia as covariates.

Since repeated measurements of glycemia over time were considered, a Bayesian joint modelling (JM) approach was adopted, which allows for modelling of the longitudinal trend of glycemia and including it in the survival model directly. This approach estimates jointly a longitudinal model for glycemia and a Cox model for the survival outcome through an association structure which takes into account the individual heterogeneity. Details concerning the JM methodology are provided in Supplementary Methods, available at https://doi.org/10.1016/j.esmogo.2025.100276.

Analyses were carried out using the R software [R version 4.3.3 (2023-10-31), Posit open-source data science company].

Ethics

The study was conducted in compliance with the principles outlined in the Declaration of Helsinki and received approval from the Institutional Review Board of the coordinating center (INT 231-21) and notified to each participating site.

RESULTS

Patients' characteristics

A total of 898 consecutive patients (May 2010 to July 2023) were considered, with 663 included in the final analysis

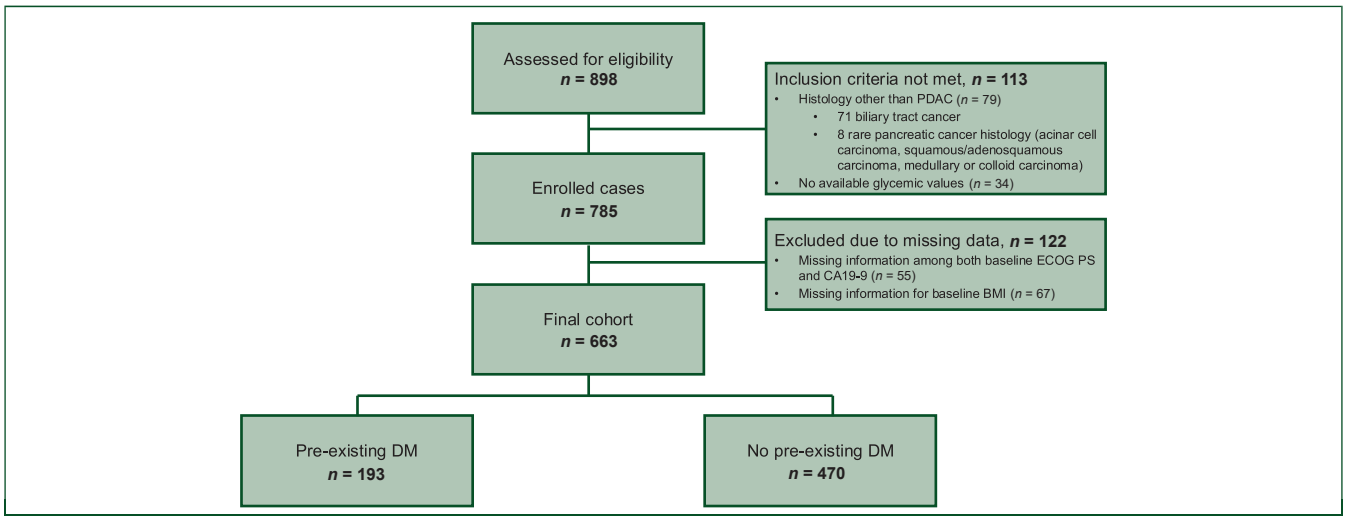


Figure 1. Study flow-chart. From initial 898 patients considered, 663 were included in the analysis, of whom 193 with pre-existing DM.
BMI, body mass index; DM, diabetes mellitus; ECOG PS, Eastern Cooperative Oncology Group Performance Status; PDAC, pancreatic ductal adenocarcinoma.

(Figure 1). Most had *de novo* metastatic disease (71.3%), and received Gem-NabP (60.8%) as first-line therapy. Other regimens included FFX (27.4%), gemcitabine (6.9%), FOLFOX (2.6%), and others (2.3%). DM was present in 193 patients (29.1%), who were generally older, more often male, had previously undergone surgery for resectable PDAC, and were more frequently treated with Gem-NabP over FFX. Notably, 14 patients (3%) were on GLMs without a confirmed DM diagnosis (Table 1).

The glycemia pattern and the use of GLMs over time are reported in Supplementary Table S1, available at https://doi.org/10.1016/j.esmogo.2025.100276, highlighting a statistically significant difference with a decreasing trend in glycemia values from baseline to the first disease re-evaluation. Of note, absolute differences were small, with median values varying from 111.5 mg/dl to 105 mg/dl.

At the time of data cut-off, after median follow-up time of 43.3 months [interquartile range (IQR) 22.2-109.1 months], 599 (90.3%) patients experienced disease progression to first-line treatment and 560 (84.5%) died, resulting in a median PFS (mPFS) of 6.5 months (IQR 3.1-10.4 months) and median OS (mOS) of 10.6 months (IQR 6.1-18.3 months).

Pre-existing DM is associated with a small, significant survival benefit

Kaplan—Meier curves stratified by DM status are reported both for OS and for PFS in Figure 2A and B. Patients with a confirmed diagnosis of pre-existing DM at the time of first-line treatment start had non-statistically significantly different PFS when compared with non-diabetic patients [mPFS 6.6 versus 6.5 months, respectively; log-rank $P = 0.308$, unadjusted HR 0.91, 95% confidence interval (CI) 0.77-1.08; $P = 0.311$; Figure 2A]. Conversely, a modest though significant difference between diabetic and non-diabetic patients was observed for OS (mOS 11.6 versus 10.3 months, respectively; log-rank $P = 0.047$, unadjusted HR 0.83, 95% CI 0.69-0.99; $P = 0.047$; Figure 2B). No significant differences, in terms of both PFS and OS, were observed according to baseline BMI and baseline use of GLMs. These results were confirmed at multivariable analysis, with a significantly lower risk for death for the DM group (HR 0.82, 95% CI 0.67-0.99, $P = 0.036$), while no significant difference was highlighted in terms of PFS (HR 0.88, 95% CI 0.73-1.06, $P = 0.188$, Supplementary Table S2, available at https://doi.org/10.1016/j.esmogo.2025.100276).

Next, after exclusion of cases treated with chemotherapy other than FFX or Gem-NabP, we tested the impact of DM according to the chosen chemotherapy regimen. At univariable analyses, FFX was associated with favorable mPFS and mOS, but a trend toward an opposite effect was observed when the interaction with DM was tested for PFS (unadjusted HR 0.65 in favor of diabetic patients treated with Gem-NabP, 95% CI 0.41-1.01, $P = 0.056$). Conversely, a significant interaction was observed at multivariable analysis: in patients affected by DM, Gem-NabP was associated with better PFS (HR 0.55, 95% CI 0.35-0.88, $P = 0.012$) and OS (HR 0.62, 95% CI 0.38-1.01, $P = 0.055$), while no difference was observed in patients treated with FFX (Supplementary Table S3, Figure S1A-D, available at https://doi.org/10.1016/j.esmogo.2025.100276).

Baseline and early on-treatment glycemia do not affect clinical outcomes

Then, we investigated the impact of early fasting glycemia, as evaluated as a continuous variable, on patient outcomes. As depicted in Table 2, the univariable analyses indicate no statistically significant association between baseline glycemia values and the outcomes, with a HR of 1.00 in both cases (95% CI 0.997-1.002, $P = 0.526$ for PFS and 95% CI 0.997-1.002, $P = 0.719$ for OS, respectively).

Upon evaluation in a multivariable analysis, the results confirmed the absence of a statistically significant association with PFS and OS both baseline values (HR 1.00, 95% CI 0.996-1.003, $P = 0.654$ for PFS and 95% CI 0.996-1.002,

Table 1. Patients' characteristics in the overall cohort and according to pre-existing DM

Variable	Total cohort $N = 663$	No DM $n = 470$	DM $n = 193$	*P* value
Age, years	66.5 (59.2-73.4)	65.7 (57.9-72.7)	68.0 (62.9-74.5)	<0.001
Sex				
Female	340 (51.3)	254 (54.0)	86 (44.6)	0.026
Male	323 (48.7)	216 (46.0)	107 (55.4)	
Primary tumor site				0.204
Body	183.0 (27.6)	136 (28.9)	47 (24.4)	
Head	372.0 (56.1)	253 (53.8)	119 (61.7)	
Tail	108.0 (16.3)	81 (17.2)	27 (14.0)	
Stage at initial diagnosis[a]				
Resectable	74 (11.2)	39 (8.30)	35 (18.1)	0.004
Borderline	12 (1.8)	8 (1.70)	4 (2.07)	
Locally advanced	104 (15.7)	74 (15.7)	30 (15.5)	
Metastatic	473 (71.3)	349 (74.3)	124 (64.2)	
Prior surgery	125 (18.9)	69 (14.7)	56 (29.0)	<0.001
Number of metastatic sites				
0-1	376 (56.7)	263 (56.0)	113 (58.5)	0.198
2	193 (29.1)	133 (28.3)	60 (31.1)	
≥3	94 (14.2)	74 (15.7)	20 (10.4)	
Use of GLMs	189 (28.5)	14 (3.0)	175 (90.7)	<0.001
BMI (baseline)	22.8 (20.9-25.1)	22.7 (20.9-24.8)	23.0 (20.9-25.8)	0.202
ECOG PS (baseline)				0.491
0	326 (49.2)	235 (50.0)	91 (47.2)	
1	297 (44.8)	210 (44.7)	87 (45.1)	
2-3	40 (6.0)	25 (5.32)	15 (7.77)	
log_{10} CA19-9 (baseline)	2.8 (1.9-3.6)	2.8 (1.9-3.6)	2.7 (1.9-3.6)	0.801
Chemotherapy regimen				<0.001
FOLFIRINOX	182 (27.5)	149 (31.7)	33 (17.1)	
Gem-NabP	403 (60.8)	273 (58.1)	130 (67.4)	
Other	78 (11.8)	48 (10.2)	30.0 (15.5)	

Continuous variables are reported as median (interquartile range, IQR), categorical variables as *n* (%); *P* values are reported according to the Wilcoxon rank sum test, Pearson Chi-squared test, or Fisher's exact test, as appropriate. Baseline is referred to as the date of start of first-line treatment.
BMI, body mass index; DM, diabetes mellitus; ECOG PS, Eastern Cooperative Oncology Group Performance Status; Gem-NabP, gemcitabine and albumin-bound (nab) paclitaxel; GLMs, glucose lowering medications.
[a]For the purposes of this work, only patients who had locally advanced or metastatic disease in their disease history were included, regardless of their stage at the time of first diagnosis.

$P = 0.467$ for OS, respectively) and delta glycemia (HR 1.00, 95% 0.997-1.003, $P = 0.866$ for PFS and 95% CI 0.997-1.001, $P = 0.116$ for OS, respectively). Supplementary Figure S2, available at https://doi.org/10.1016/j.esmogo.2025.100276, illustrates the interaction between baseline and delta glycemia on 1-year PFS. Most patients had stable glycemia (<200 mg/dl), with minimal impact on PFS. Those with baseline glycemia <200 mg/dl and a >50 mg/dl increase at T2 showed reduced PFS, however, as did patients with high initial glycemia (>200 mg/dl) followed by a sharp decline. In contrast, those with initially high glycemia and a further increase at T2 had better PFS, though such extreme glycemic patterns were only anticipated by the model but were not observed. Similar trends were seen for 6-month PFS (Supplementary Figure S3, available at https://doi.org/10.1016/j.esmogo.2025.100276).

Longitudinal glycemic trends reveal a clinically modest impact on survival

Next, to further evaluate the impact of longitudinal glycemic trends on time-to-event outcomes, Bayesian JMs were adopted both for PFS and OS including longitudinal predictors of fasting blood glucose levels. The elpd criterion indicated that the optimal association structure for JMs was one that incorporated the current glycemia value for OS and the area under the curve of the linear predictor extracted by the longitudinal component of the model for PFS.

Figure 3 presents the forest plots, which depict the posterior mean of the coefficients for the longitudinal component and the posterior estimates of the HRs for the survival component, for each of the estimated joint models. For PFS, the HR of the model's association parameter (ETA area under the curve) yielded a posterior mean of ∼1.0000 (95% CI 0.9996-1.0004), indicating no significant association between glycemia initial values or its trend over time and PFS. When assessing the relationship between OS and glycemia, the HR of the glycemia association parameter in the model is ∼0.9967 (95% CI 0.9939-0.9995).

Supplementary Figure S4A and B, available at https://doi.org/10.1016/j.esmogo.2025.100276, depicts the longitudinal and survival components of the joint model for PFS and for OS for four exemplar patients. In particular, Supplementary Figure S4A, available at https://doi.org/10.1016/j.esmogo.2025.100276, illustrates the predicted model components for patients 195 and 657, who exhibited a comparable PFS, ∼5 months, but markedly disparate glycemic levels. This suggests that the initial glycemic level

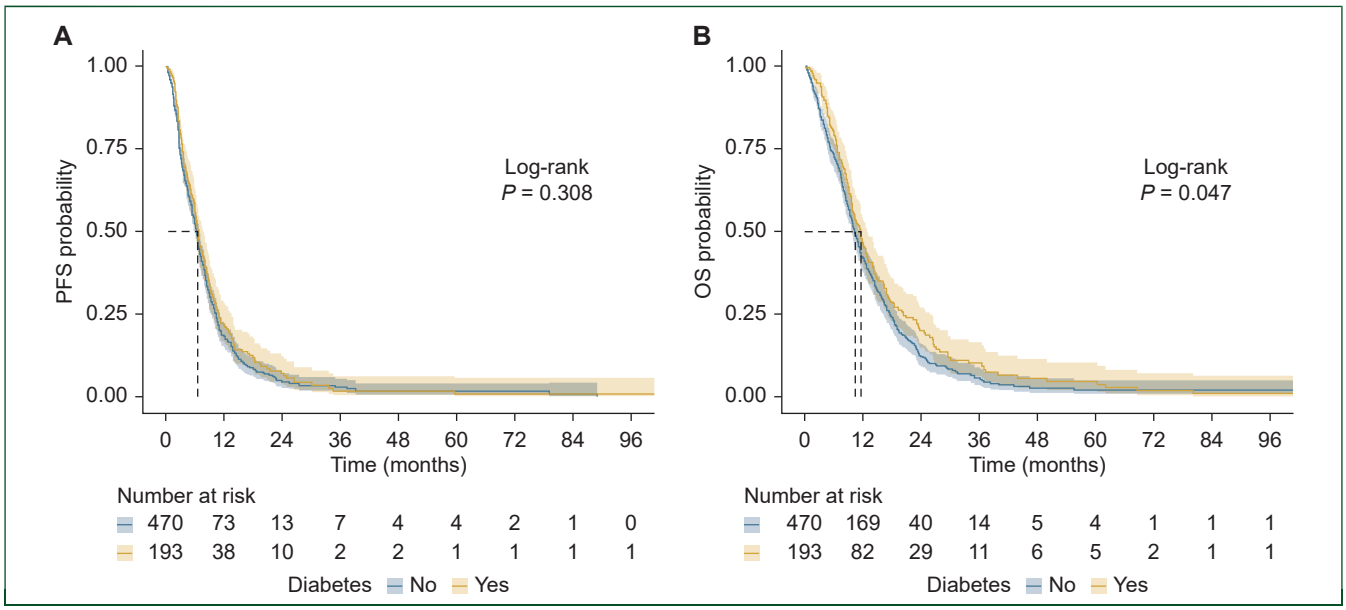


Figure 2. Survival outcomes according to pre-existing DM. Progression-free survival (PFS) (A) and overall survival (OS) (B) stratified by pre-existing diabetes. The dashed vertical lines represent the median PFS or OS time.
DM, diabetes mellitus.

has a negligible impact on PFS. A similar outcome is evident in the case of patients 264 and 549, who exhibited a longer PFS (∼25 months), and a similar outcome is observed when OS is considered (Supplementary Figure S4B, available at https://doi.org/10.1016/j.esmogo.2025.100276).

DISCUSSION

Metabolic reprogramming is a hallmark of cancer,[8,9] allowing tumor cells to exploit alternative energy sources for rapid growth and spread. Pharmacological and dietary interventions targeting tumor metabolic vulnerabilities have been studied.[18] Different compounds have been tested or are under evaluation in the preclinical and clinical setting specifically in PDAC, including inhibitors of oxidative phosphorylation (like metformin or devimistat), LDH-, IDH1-, or GSK3-inhibitors, with modest results in clinical trials so far.[10,19,20] As far as dietary approaches are concerned, low-glycemic, ketogenic and fasting-mimicking diets (FMD) are being tested in clinical trials, alone and in combination with standard therapies. The phase Ib NCT03340935 trial tested the safety of cyclic FMD in combination with standard anticancer therapies in patients with advanced solid tumors. Within this study, a subset of patients achieved complete and long-lasting tumor remissions, including one patient with metastatic PDAC receiving Gem-NabP with FMD cycles.[21,22] A clinical trial investigating the combination of cisplatin, gemcitabine, and nab-paclitaxel with a ketogenic diet is also currently ongoing.[23] In PDAC, these approaches have a strong rationale, as pancreatic tumors thrive in a nutrient-poor, hypoxic microenvironment by up-regulating aerobic glycolysis (the so-called Warburg effect), autophagy, macropinocytosis, and metabolic crosstalk with stromal cells.[24,25] Syndecan 1 (SDC1) has been shown to support macropinocytosis in *KRAS*-driven PDAC cells, while its depletion reduced albumin-dependent tumor growth.[26] Moreover, PDAC cells are able to counter low glucose and lipids levels in the tumor microenvironment by producing monounsaturated fatty acids by up-regulating the stearoyl-CoA desaturase enzyme, exploiting this as an alternative source of energy.[18] In this scenario, caloric restriction may impair stearoyl-CoA desaturase activity, enhance SDC1-mediated albumin uptake, including nab-paclitaxel, thereby boosting chemotherapy efficacy and altering tumor growth.[27] By contrast, patients with PDAC often experience cancer-related cachexia, weight loss, and hyperglycemia, making caloric restriction and antimetabolic therapies challenging. Recent evidence suggests hyperglycemia may enhance chemotherapy efficacy by increasing oxidative damage. If clinically significant, this could challenge the rationale for antimetabolic and nutrient restriction trials.[15]

In this scenario, our findings obtained in real-world setting confirm that DM and hyperglycemia demonstrate a statistically significant impact, though clinically modest, on patients' outcomes. To clarify the meaning of our findings, a 10 mg/dl-point increase in glycemia baseline values was associated with a 4% reduction in the hazard for OS. So, approximately, if fasting blood glucose increases steadily by 40 mg/dl (e.g. from 90 to 130 mg/dl, i.e. from normal to DM), the risk of death decreases by about 16% (HR = 0.84). While possible, spontaneous and significant blood glucose fluctuations are rare in most patients, and inducing hyperglycemia pharmacologically raises safety and ethical concerns.

Notably, in our work, diabetic patients showed a significant survival benefit over non-diabetic cases only when treated with Gem-NabP, whereas this was not observed among those receiving FFX. Biological hypotheses may underlie this finding: under conditions of enhanced

Table 2. Multivariable Cox model for PFS and OS including baseline glycemia, delta glycemia and confounders

Characteristics	Progression-free survival			Overall survival		
	HR	95% CI	*P* value	HR	95% CI	*P* value
Baseline glycemia	1.00	1.00-1.00	0.526	1.00	1.00-1.00	0.719
c-index	0.516			0.518		
Age	1.00	0.99-1.01	0.602	1.00	0.99-1.01	0.461
Sex						
Female	—	—		—	—	
Male	1.08	0.91-1.27	0.366	1.23	1.04-1.46	0.017
Primary tumor site						
Body	—	—		—	—	
Head	0.97	0.79-1.18	0.738	1.03	0.84-1.26	0.765
Tail	0.77	0.59-1.00	0.050	0.85	0.65-1.12	0.261
Stage at initial diagnosis						
Resectable	—	—		—	—	
Borderline	1.40	0.74-2.65	0.300	2.25	1.14-4.45	0.019
Locally advanced	1.16	0.77-1.74	0.478	1.14	0.75-1.74	0.538
Metastatic	1.60	1.07-2.37	0.021	1.49	0.98-2.27	0.063
Prior surgery						
No	—	—		—	—	
Yes	1.06	0.77-1.46	0.702	0.75	0.54-1.05	0.099
Number of metastatic sites						
0-1	—	—		—	—	
2	1.19	0.98-1.43	0.079	1.13	0.93-1.37	0.236
≥3	0.97	0.75-1.25	0.798	0.99	0.76-1.29	0.926
Use of GLMs						
No	—	—		—	—	
Yes	0.88	0.70-1.09	0.243	0.85	0.68-1.05	0.137
Chemotherapy regimen						
FOLFIRINOX	—	—		—	—	
Gem-NabP	1.01	0.82-1.25	0.925	1.13	0.91-1.39	0.273
Other	1.51	1.09-2.10	0.014	1.40	1.00-1.96	0.049
BMI (baseline)	1.01	0.98-1.04	0.454	0.99	0.96-1.01	0.281
ECOG PS (baseline)						
0	—	—		—	—	
1	1.47	1.23-1.75	<0.001	1.89	1.57-2.28	<0.001
2-3	2.58	1.77-3.76	<0.001	3.06	2.07-4.54	<0.001
log_{10} CA19-9 (baseline)	1.06	0.98-1.14	0.124	1.20	1.11-1.30	<0.001
Baseline glycemia	1.00	1.00-1.00	0.654	1.00	1.00-1.00	0.467
Delta glycemia (T2 − baseline)	1.00	1.00-1.00	0.866	1.00	0.99-1.00	0.116
c-index	0.628			0.678		

BMI, body mass index; CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group Performance Status; Gem-NabP, gemcitabine and albumin-bound (nab) paclitaxel; GLMs, glucose lowering medications; HR, hazard ratio.

phagocytosis and aerobic glycolysis, such as those observed in diabetic patients, nab-paclitaxel may be more effectively taken up by tumor cells (via SDC-1) and thus exert greater antitumor activity compared with FFX components, whose cellular uptake mechanisms are independent of these pathways. Intratumor metabolic heterogeneity may also play a role in this context: multiomic analyses have identified distinct metabolic subtypes of PDAC, defined by glucose and lipid/cholesterol metabolism gene expression, which partly overlap with known prognostic subtypes.[27,28] Among these, the glycolytic subtype, characterized by an enhanced Warburg effect and low expression of the mitochondrial pyruvate carriers MPC1 and MPC2, has been associated with worse prognosis and potentially limited sensitivity to agents targeting oxidative phosphorylation. Recently, the AVENGER 500 trial[20] failed to demonstrate a benefit from adding the Krebs cycle enzymes inhibitor devimistat to FFX. Based on the above rationale, both these mechanisms could have been partially overcome by Gem-NabP, suggesting that combining devimistat with this regimen rather than FOLFIRINOX might have yielded different results.

Overall, while our findings remain exploratory, our data may guide future research directions in this field: firstly, our findings suggest that antimetabolic strategies should be tested in combination with Gem-NabP rather than FFX; moreover, given the confirmed favorable prognostic impact of hyperglycemia, our study underscores the need for caution when testing low-carbohydrate or calorie-restricted diets in patients with PDAC. Overall, reconciling conflicting evidence on systemic metabolism in PDAC requires biomarkers to tailor antimetabolic strategies to specific patients and treatments. Hyperglycemia may therefore benefit some patients, while caloric restriction aids others. Finally, our work provides a methodological framework that can serve in future studies evaluating longitudinal biomarker

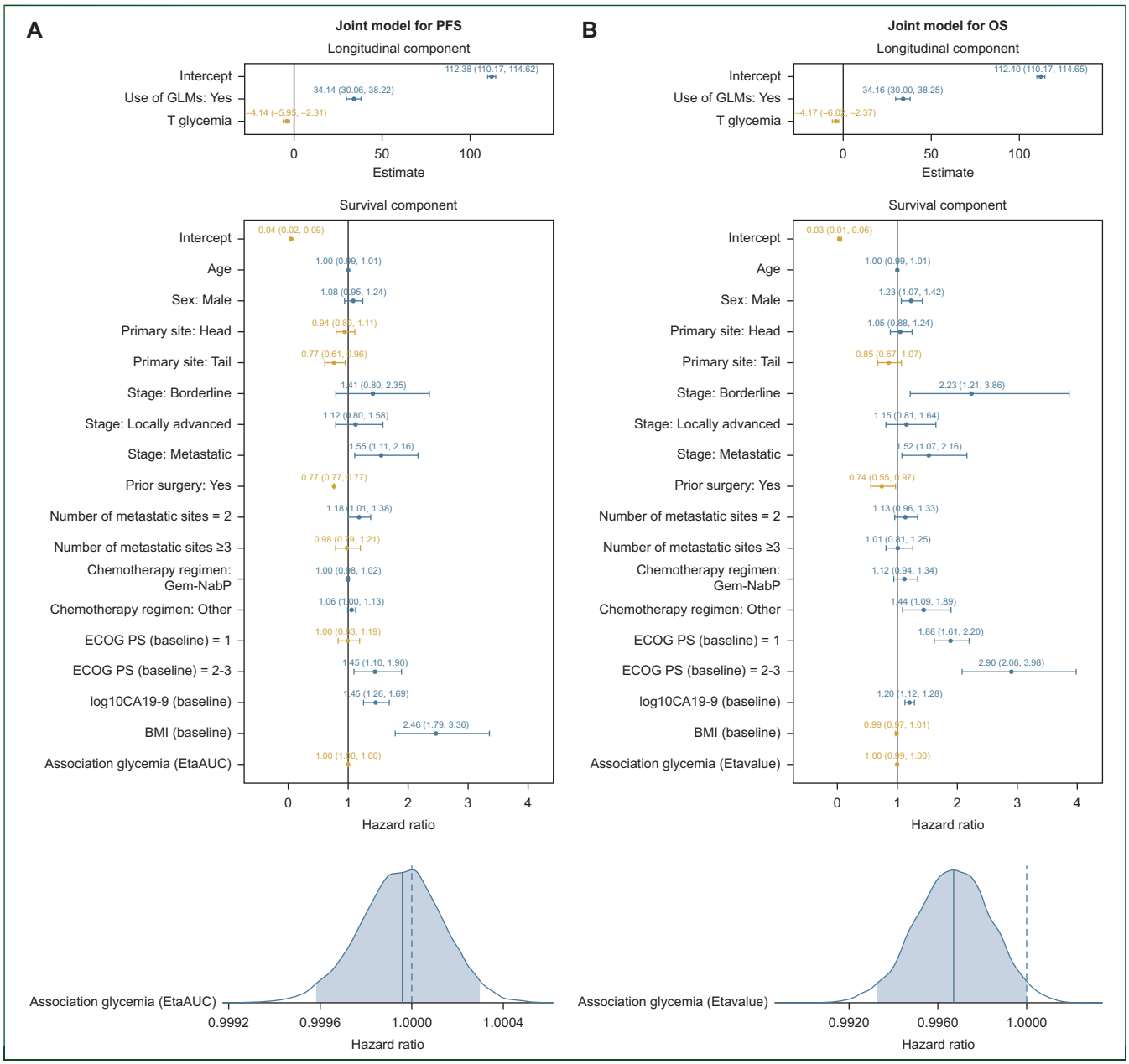


Figure 3. Forest plots for joint modelling survival outcomes. (A) Forest plot for joint modelling progression-free survival and posterior distribution density of glycemia's parameter (EtaAUC); (B) Forest plot for joint modelling overall survival and posterior distribution density of glycemia's parameter (Etavalue). The longitudinal component quantifies the extent to which the parameters under consideration resulted in a reduction in glycemic levels over time. The survival component reported the estimated hazard ratio (HR) of the covariates considered in the joint models. The risk factors are represented in blue, while the protective factors are represented in yellow. The posterior distribution of the HR for the optimal association parameter between the longitudinal glycemia values and the survival model (for the PFS), and of the HR for the optimal association parameter between the longitudinal glycemia values and the survival model (for the OS) are illustrated with a density plot. The blue solid line represents the mean posterior estimate, while the light-blue areas represent the 95% Credible Intervals. The HR of EtaAUC was not statistically significant for PFS, with a HR value of 0.99996 (95% CI 0.99964-1.00025). Conversely, a statistically significant difference was observed for Etavalue in the OS model, with a HR value of 0.9967 (95% CI 0.9939-0.9995).

measurements also with novel treatments that promise to revolutionize PDAC management like *RAS* inhibitors.[29]

Our study has limitations: the retrospective nature of this study prevents us from drawing firm conclusions as to why we observed a prognostic impact of DM but not of baseline glycemia: this latter, although calculated as the mean of two measurements taken before chemotherapy, may have been influenced by various confounding factors, including the time of measurement (early or late in the morning) and patients' dietary intake (formally fasting from the night before, but in practice not strictly controllable). By contrast, a standardized diagnosis of DM, even though retrospective, provides a more comprehensive and less instantaneous assessment, potentially serving as a surrogate for different lifestyle patterns and pharmacological treatments. HbA1c could represent a better biomarker for assessing the glycemic profile in a stable and consistent manner over time, but it was not routinely tested in our

cohort. We have therefore started a prospective validation study, PANCAKE-2, in which we aim to prospectively validate our results by including repeated measurements of HbA1c and blood insulin levels.

Similarly, given the observational and retrospective design of the study, while OS was unequivocal to assess, PFS could have been influenced by variability in both timing and methods of evaluation. This, together with an insufficiently large sample size, may explain the lack of statistical significance in PFS results, although the effect remained directionally consistent with that observed for OS.

In conclusion, DM and hyperglycemia have a statistically significant though clinically modest impact on OS in advanced PDAC. These results raise caution regarding future investigations of antimetabolic strategies aimed at lowering blood glucose as a potential anticancer approach in PDAC; contrarily, our findings could help inform future strategies designed to harness hyperglycemia to enhance chemotherapy efficacy, which will require the identification of novel biomarkers and achieving a greater magnitude of effect to be clinically meaningful.

FUNDING

None declared.

DISCLOSURE

FN received honoraria from AstraZeneca and Accademia della Medicina. GT reports funds from the Ministero della Salute (Ricerca Corrente 2022), the AIRC (Investigator Grant number IG26330), Ministero dell'Università e della Ricerca (PRIN 2022 PNRR Prot P2022LN3KS and PRIN 2022 Prot 2022P79F9N), and Agenzia Italiana del Farmaco, Ministero della Salute (J38D19000690001) FIMP, outside the submitted work; and consulting or advisory role for Bristol Myers Squibb, AstraZeneca, Merck Sharpe & Dohme, Merck, and Servier. LS is supported by the AIRC under My First Grant (MFAG27367), outside the submitted work, and reports consulting or advisory role for Pierre—Fabre, AstraZeneca, Bayer, SERVIER, Merck, Amgen, GlaxoSmithKline, Incyte, Leopharma, Merck Sharpe & Dohme, and Takeda. CV reports consulting or advisory role for Amgen, AstraZeneca, Bristol Myers Squibb, EISAI, Incyte, Merck Sharpe & Dohme, Roche, Servier, Taiho Oncology. MS reports serving for advisory board and speakers' bureau for Amgen, MERCK, Merck Sharpe & Dohme, EISAI, Servier, AstraZeneca, Sanofi, Daiichi Sankyo. FP reports receiving Research funding (to Institution) from Lilly, Bristol Myers Squibb, Incyte, AstraZeneca, Amgen, Agenus, Rottapharm. Personal honoraria as an invited speaker from BeiGene, Daiichi-Sankyo, Seagen, Astellas, Ipsen, AstraZeneca, Servier, Bayer, Takeda, Johnson & Johnson, Bristol Myers Squibb, Merck Sharpe & Dohme, Amgen, Merck—Serono, Pierre—Fabre. Advisory/Consultancy from BMS, MSD, Amgen, Pierre—Fabre, Johnson & Johnson, Servier, Bayer, Takeda, Astellas, GlaxoSmithKline, Daiichi Sankyo, Pfizer, BeiGene, Jazz Pharmaceuticals, Incyte, Rottapharm, Merck-Serono, Italfarmaco, Gilead, AstraZeneca, Agenus. FDB reported receiving personal fees from Bristol Myers Squibb, Roche, Merck, Bayer, Ignyta, Dephaforum, Biotechespert, Prime Oncology, Pfizer, Nadirex, Ambrosetti, Incyte, Motore Sanità, Fare Comunicazione, Itanet, European School of Oncology, Accmed, Idea-z, Dynamicom Education, Pierre Fabre, Mattioli 1885, MCCann Health, Merck Sharpe & Dohme, IQVIA, Celgene, Amgen, and Sanofi; grants from Novartis, Roche, Bristol Myers Squibb, Celgene, Incyte, Nerviano Medical Sciences, Merck, Darmstadt, Kymab, Pfizer, Tesaro, and Kenilworth; serving on advisory boards for Tiziana Life Sciences, Bristol Myers Squibb, Celgene, Novartis, Servier, Pharm Research Associated, Daiichi Sankyo, Ignyta, Amgen, Pfizer, Octimet Oncology, Incyte, Pierre—Fabre, Eli Lilly, Roche, AstraZeneca, Gentili, Dephaforum, Merck, Kenilworth, Bayer, Fondazione Menarini, Sanofi, Taiho; serving as principal investigator for studies by Novartis Farma, AstraZeneca, F. Hoffmann-La Roche, Bristol Myers Squibb, AnHeart Therapeutics, and Apollomics outside the submitted work. MN reported receiving personal fees from AstraZeneca, Incyte, Accademia della Medicina, Sandoz, Medpoint, Servier, EMD Serono, Basilea Pharmaceutica, Merck Sharpe & Dohme Italia, and Taiho outside the submitted work. All other authors have declared no conflicts of interest.

DATA SHARING

Authors confirm that data supporting this study are available within the article and its supplementary material. Anonymized individual patient data are available upon reasonable request to the corresponding author.

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