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Pancreatic adenocarcinoma nutritional-clinical index (PANCIN): A novel prognostic tool in advanced pancreatic cancer ☆

Catia Carconi[a,b], Gabriele Capurso[b,c], Martina Abati[d], Monica Maria Vincenzi[e], Alice Burini[d], Sara Cardellini[d], Maddalena Pavarini[e], Maria Giulia Ubeira-Gabellini[e], Diego Palumbo[b,f], Nicolò Pecorelli[b,g], Marina Macchini[a], Nicole Liscia[a], Antonino Campisi[f], Giovanni Guarneri[g,h], Giuseppe Vanella[c], Claudio Fiorino[e], Massimo Falconi[b,g], Michele Reni[a,b,*], Giulia Orsi[a]

[a] Department of Medical Oncology, Pancreas Translational and Clinical Research Center, IRCCS San Raffaele Scientific Institute, Milan, Italy
[b] Vita-Salute San Raffaele University, Milan, Italy
[c] Pancreato-Biliary Endoscopy and Endosonography Division, Pancreas Translational & Clinical Research Center, IRCCS San Raffaele Scientific Institute, Milan, Italy
[d] Nutrition Service, Pancreas Translational & Clinical Research Center, IRCCS San Raffaele Scientific Institute, Milan, Italy
[e] Medical Physics, IRCCS San Raffaele Scientific Institute, Milan, Italy
[f] Department of Radiology, Pancreas Translational and Clinical Research Center, IRCCS San Raffaele Scientific Institute, Milan, Italy
[g] Pancreatic and Transplant Surgery Unit, Pancreas Translational and Clinical Research Center, IRCCS San Raffaele Scientific Institute, Milan, Italy
[h] Health Innovative Products and Technologies (HIP-TECH) PhD Program, Department of Life Sciences, University of Modena and Reggio Emilia, Modena, Italy

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ABSTRACT

Background & Aims: Nutritional status alterations are common in pancreatic ductal adenocarcinoma (PDAC), but their prognostic role in patients undergoing chemotherapy remains unclear. We assessed the impact of clinical-nutritional variables on treatment outcomes in advanced PDAC patients.

Methods: Clinical, anthropometric, and radiological data of locally advanced/metastatic PDAC patients treated with polychemotherapy (2019–2021), prospectively collected within the observational PAC-MAIN study (NCT04112836) were analyzed. Key predictors of progression-free (PFS) and overall survival (OS) were identified through a multistep feature selection process, developing the Pancreatic Adenocarcinoma Nutritional-Clinical Index (PANCIN). Associations with CA19.9, radiological response, chemotherapy dose intensity and toxicity were explored.

Results: Among 74 patients, Vitamin B12 levels, Mid-Upper Arm Circumference, and Visceral Fat-to-Muscle area Ratio were included in the PANCIN, emerging as strongest PFS/OS predictors. According to PANCIN stratification, median PFS was 6.2 (95% CI 3.5–9.7) vs 14.1 (8.8–20.3) months, and median OS was 10.4 (7.5–15.1) vs 19.8 (11.3–31.1) months, for high- vs low-risk patients, respectively ($p < 0.001$). PANCIN significantly correlated with CA19.9 and radiological response, infections and grade ≥3 hematologic toxicities.

Conclusions: PANCIN is a novel prognostic tool combining clinical-nutritional and radiological features, potentially aiding risk stratification and early nutritional support in advanced PDAC patients.

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1. Introduction

Pancreatic cancer (PDAC) represents one of the most lethal malignancies worldwide and the third leading cause of cancer-related mortality in high-income countries [1]. Despite therapeutic advances, median survival for metastatic PDAC patients remains below one year [2]. Moreover, approximately 80 % of patients are

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* Corresponding author at: Department of Medical Oncology IRCCS Ospedale San Raffaele, Vita e Salute University, Via Olgettina 60, 20132, Milan Italy.
E-mail address: reni.michele@hsr.it (M. Reni).

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diagnosed at an advanced stage, precluding surgical resection and limiting treatment options to systemic therapy [3].

Around 34–70 % of PDAC patients are malnourished at diagnosis [4–9]. Malnutrition in PDAC patients is multifactorial and negatively affects quality of life, treatment tolerance, and survival outcomes [10,11], often leading to chemotherapy delays, dose reductions, and early discontinuation due to treatment-related toxicities [12–14,15]. Conversely, stabilizing weight and skeletal muscle mass can improve both outcomes and quality of life in PDAC patients [14,16]. Malnutrition and sarcopenia remain underrecognized in clinical practice, mostly due to the methodological limitations of available screening tools, that focus on a narrow range of parameters, often lacking standardized measures and prospective validation in oncologic patients [17–19].

Given the clinical need to improve the early identification of nutritional status alterations in PDAC patients and the lack of evidence deriving from prospective and homogenous studies, we assessed the impact of a broad range of clinical, nutritional, and body composition variables on disease response and survival outcomes in a prospectively enrolled cohort of advanced PDAC patients.

2. Materials and methods

2.1. Study design

The present study is a post-hoc, not preplanned analysis, conducted on a subset of advanced PDAC patients enrolled at San Raffaele Hospital in the multicenter prospective observational cohort study PAC-MAIN (PAncreatic Cancer MAlnutrition and pancreatic exocrine INsufficiency), NCT04112836 [20]. The aim of our investigation was to assess the prognostic impact of prospectively collected clinical, nutritional and radiological variables in patients with locally advanced or metastatic PDAC receiving first-line polychemotherapy.

2.2. Patients

Patients aged ≥18 years, with a histological and imaging diagnosis of locally advanced or metastatic PDAC, treated with nab-paclitaxel- and gemcitabine-(AG) based poly-chemotherapy (AG or PAXG: cisplatin, nab-paclitaxel, capecitabine and gemcitabine [21]) at San Raffaele Hospital within the PAC-MAIN study were eligible for the analysis. Previous anticancer treatment, poor performance status (PS) (ECOG PS ≥3 [22]), treatment with mono-chemotherapy and disease recurrence after a previous surgical resection were the main exclusion criteria.

2.3. Study evaluation and variables

Within the PAC-MAIN study, patients underwent nutritional and radiological assessments before starting chemotherapy (baseline) and 8–12 weeks after treatment initiation. For the present analysis, only baseline assessments were considered. Complete blood tests were performed within 7 days prior to chemotherapy initiation. Serum tumor markers, including Carbohydrate Antigen 19–9 (CA 19–9) and Carcino-Embryonic Antigen (CEA) were measured at baseline and before each chemotherapy cycle. All clinical, nutritional, and radiological variables were prospectively recorded in an electronic database.

Clinical variables considered for the analysis included patients' general characteristics (gender, age, ECOG performance status), disease characteristics (stage [23], site of primary tumor, presence of liver metastases, CA19.9 levels), and biochemical measurements (neutrophil-to-lymphocyte ratio [NLR], total bilirubin, and C-reactive protein [CRP] levels).

Nutritional variables included, among others, biohumoral parameters, results from the Functional Assessment of Anorexia/Cachexia Treatment (FAACT) questionnaire, anthropometric measurements and body composition data derived from bioimpedance vector analysis (BIVA), as detailed in Supplementary Table 1. All anthropometric and BIVA measurements were carried out by a trained nutritionist.

Radiological variables consisted of Computed Tomography (CT)-derived body composition data and included visceral fat area (VFA), total abdominal muscle area (TAMA), and subcutaneous fat area (SFA), assessed as previously reported [24]. Sarcopenia was defined using predetermined sex- and BMI-specific TAMA cutoff values [25]. Sarcopenic obesity was defined as a high VFA/TAMA ratio (VFA/TAMA > 3.2), in line with previous studies [26,27]. Two senior radiologists independently reviewed the scans, assessing body composition at the level of the third lumbar vertebra (L3), as shown in Supplementary Figure 1. Image processing was done using sliceOmatic 5.0 software (Tomovision®, Montreal, QC, Canada) [24,28].

2.4. Outcomes

Primary outcome measures were Overall (OS) and Progression-free Survival (PFS). OS was defined as the time between the date of treatment start to death from any cause or last follow-up. PFS was defined as the time between the date of treatment start and the date of documented radiological disease progression or death, whichever occurred first; patients without an event (disease progression or death) were censored on the last follow-up date.

Secondary endpoints included objective response rate (ORR) and serum carbohydrate antigen 19.9 (CA19.9) response rate. ORR was defined as the incidence of either complete or partial responses on CT scans according to RECIST criteria version 1.1 [29]. CA19.9 response rate was defined as CA19.9 percentage variation at nadir (minor value assessed while on treatment) with respect to basal value, only in patients with elevated (namely over superior limit of laboratory normal level) CA19.9 level before chemotherapy start and in absence of relevant bilirubin elevation. With regards to CA19.9 variation, patients were classified as non-responders (<50 %) or responders (≥50 %) [30].

Moreover, exploratory analyses were conducted to investigate the potential correlation between the nutritional variables and chemotherapy-related toxicities and dose modifications. Toxicities were assessed according to National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) v5.0 [31], and evaluated in terms of presence versus absence of specific toxicity and of severity of the event (≥ versus < grade 3). The following toxicities were considered for the analysis: hematological toxicities (including neutropenia, anemia and thrombocytopenia); nausea and vomiting; fever; infections and sepsis; neuropathy; fatigue.

2.5. Statistical analysis

The following procedure was performed in parallel for the two outcomes (PFS and OS). Due to the small sample size, the entire dataset was used for training and no scaling was applied. Based on p-value in univariate logistic regression, candidate predictors were retained using a liberal threshold (global p-value<0.3) to avoid premature exclusion of potentially relevant variables[32] . Next, pairwise Spearman correlation was calculated among the remaining features. When two features had a correlation coefficient ($|\rho|$) > 0.8, the variable with the lower p-value was retained.

To minimize the risk of overfitting, a fixed number of three features was selected for the multivariate model. This choice was confirmed using the backward elimination technique [33], which showed that model performance improved when moving from two

to three variables and remained stable when adding a fourth variable.

A Cox proportional hazards model with 1000 bootstrap repetitions was run for each possible feature combination and ranked based on C-index performance calculated on the training set. Models were then filtered to include only those with a bootstrap frequency above the 80th percentile of the distribution and a good C-index performance (C-index > 0.65) for both outcomes. These models were then fitted to the original training dataset. The prognostic index for each patient was derived, with the median value used to discriminate between low- and high-risk populations for both outcomes independently. Kaplan-Meier survival curves and log-rank tests were subsequently generated.

Due to the small population size, which precluded external validation, model robustness was assessed through bootstrap resampling, and performance indicators were corrected for optimism, according to Steyerberg et al. [34]. Among the models considered, the one with the best Kaplan-Meier separation was selected.

The preprocessing and modeling analysis were carried out using Python 3.7.9 with in-house code: specifically, the medicalAI library in mAItre (Medical Artificial Intelligence Toolkit for REsearch), following a similar approach to that described by Ubeira-Gabellini et al. [35].

2.6. Patient consent

All patients provided written informed consent, which was reviewed and approved by San Raffaele Hospital ethics committee on April 11st 2019, allowing for data collection, analysis, and processing. Data was irreversibly anonymized before being entered into the electronic database.

3. Results

3.1. Study population

A total of 74 PDAC patients were enrolled in the study between April 2019 and July 2021. Of these, 12 patients (16.0 %) had stage II or III locally advanced disease, while 62 (84 %) were metastatic at diagnosis. Among the metastatic cohort, 43 patients (69 %) presented with liver metastases. All 74 patients received at least one cycle of AG-based polychemotherapy, with 24 patients (32 %) receiving doublet chemotherapy (AG), and 50 patients (68 %) receiving quadruplet chemotherapy (PAXG). The median number of chemotherapy cycles was 5.5 [IQR 4–6] both for the entire cohort of patients and for each chemotherapy subgroup [IQR for AG: 4.4 −6.0; IQR for PAXG: 3.6–6.0]. At baseline, 32 (52 %) patients had low serum albumin levels (<3.5 g/dL), and 34 (55 %) had elevated Vitamin B12 levels, defined as above our laboratory's upper limit of normal (ULN) (>711 pg/mL). Baseline demographic and clinical characteristics are summarized in Table 1.

Data from the initial nutritional assessment were available for all patients, while baseline CT images were available and analyzed for 70 (94.6 %) patients. According to BMI classification [36], 7 (9.5 %) patients were underweight and 25 (33.8 %) were overweight or obese at the time of the first nutritional evaluation. Waist-to-Hip ratio (WHR) values were above the normal range in 8 (20 %) male patients (≥1.0) and 17 (50 %) female patients (≥0.85). Overall, the entire population experienced weight loss, which was observed across all BMI categories. Of note, 59/74 (80 %) patients met GLIM criteria for malnutrition, 26/59 (44 %) having stage 1 (moderate) and 33/59 (56 %) having stage 2 (severe) malnutrition, respectively [37]. Table 2 and Table 3 summarize patients' nutritional and radiological baseline assessments, respectively.

Table 1
Patients' clinical characteristics at diagnosis.

Clinical variable	Patients (n = 74) n (%)
Age (years), median (range)	62.8 (40–79)
Sex	
Female	34 (46)
Male	40 (54)
ECOG Performance Status	
0	12 (16)
1	57 (77)
2	5 (7)
Stage [20]	
II	1 (1)
III	11 (15)
IV	62 (84)
Primary tumor site	
Head/Uncinate	41 (55)
Body/Tail	33 (45)
Biliary stent	
Yes	31 (42)
No	43 (58)
Liver metastases	
Yes	43 (69)
No	19 (31)
NA	12
CA19.9 (U/mL)	
Median (IQR)	462 (40.8 - 5154)
0–37 U/ml	17 (23)
> 37 U/ml	57 (77)
Regimen of first chemotherapy	
AG	24 (32)
PAXG	50 (68)
NLR	
Median (IQR)	3.2 (2.3 – 5.5)
Serum albumin (g/L)	
Median (IQR)	39.2 (36.2 – 42.5)
CRP (mg/L)	
Median (IQR)	8.2 (2.5 – 27.2)
Vitamin B12 (pg/mL) [a]	
Median (IQR)	843 (526 – 1309)
197–711	27 (44.2)
>711	34 (55–8)
NA	13

[a] Ranges were defined using the upper and lower normal limits established by the San Raffaele Hospital laboratory.
CA19.9: Carbohydrate Antigen 19.9; IQR: interquartile range; AG: Nab-paclitaxel, Gemcitabine; PAXG: Cisplatin, Nab-Paclitaxel, Capecitabine, Gemcitabine; NLR: neutrophil-to-lymphocyte ratio; CRP: C-reactive protein.

3.2. Prognostic index and primary outcomes

At a median follow-up of 42.1 (38.1 – 53.7) months, the median PFS and OS for the entire cohort were 9.0 months (IC95 %: 6.1 – 12.0 months) and 13.0 months (CI 95 %: 10.1 – 15.9 months), respectively.

Out of all the recorded variables, only 19 features evaluated at baseline were selected for statistical analysis, as the remaining were highly correlated with one another.

The clinical, nutritional, and radiological variables included in the analysis were: sarcopenia, VFA, TAMA, VFA/TAMA ratio, NLR, total bilirubin, serum albumin, CRP, vitamin B12, body cell mass (BCM), BCM index (BCMi), BCM percentage (BCMp), fat mass (FM), FM index (FMi), mid-upper arm circumference (MUAC), waist-to-hip ratio (WHR), FAACT total score, anorexia/cachexia (AC) subscale score, and modified Glasgow Prognostic Score (mGPS).

Correlation and variance filtering excluded several variables from the analysis, resulting in a reduced feature set for model development. Following pairwise Spearman correlation analysis, the final multivariable models retained three independent predictors (see Supplementary Figure 2a and 2b).

From the analysis conducted, several models emerged with different performances in predicting the two primary outcomes,

Table 2
Baseline nutritional assessment.

Nutritional variable	Patients (n = 74) N (%)
BMI (kg/m²)[a]	
Median (IQR)	23.7 (20.9 - 26.5)
<18.5	7 (9.5)
18.5–24.9	42 (56.7)
25–29.9	18 (24.3)
>30	7 (9.5)
Unintentional body weight loss[b]	
Yes	65 (88)
No	9 (12)
≤ 5 %	23 (31)
>5 %	51 (69)
MUAC (cm)[c]	
Median (IQR)	27.0 (25.0 - 29.0)
≤24	13 (17.6)
>24	61 (82.4)
WHR[a]	
Median (IQR)	0.9 (0.8 - 1.0)
Female (n = 34)	
Median (range)	0.8 (0.7 - 1.0)
≤0.85	17 (50.0)
>0.85	17 (50.0)
Male (n = 40)	
Median (range)	0.9 (0.8 - 1.1)
≤1	32 (80.0)
>1	8 (20.0)
25-OH Vitamin D (ng/mL)[d]	
Median (IQR)	21.0 (15.9 - 29.2)
<20	27 (44.2)
20–68	33 (54.0)
>68	1 (2.0)
NA	13
mGPS	
0	35 (56.4)
1	17 (27.4)
2	10 (16.2)
NA	12 (16.2)
BCM (%)	
Median (IQR)	48.8 (46.0 - 51.4)
BCM index (kg/m²)	
Median (IQR)	8.8 (7.7 - 10.4)
FM index (kg/m²)	
Median (IQR)	5.4 (3.6 - 7.1)
FFM index (kg/m²)	
Median (IQR)	18.1 (15.1 – 21.1)
Phase angle (°)	
Median (IQR)	5.1 (4.2 - 6.0)

[a] Cut-offs were chosen according to WHO Report [32];
[b] Unintentional body weight loss calculated over the six months before diagnosis of PDAC;
[c] Cut-off was selected according to the value proposed by Tang et al. [34];
[d] Ranges were defined using the upper and lower normal limits established by the San Raffaele Hospital laboratory. BMI: Body Mass Index; IQR: interquartile range; MUAC: mid-upper arm circumference; WHR: Waist-Hip Ratio; 25-OH: 25-hydroxyvitamin D; mGPS: Modified Glasgow Prognostic Score; NA: Not Available; BCM: Body Cell Mass; FM: Fat Mass; FFM: Fat Free Mass.

Table 3
Baseline radiological assessment.

Radiological variable	Patients (n = 74) N (%)
CT scan	
Yes	70 (94.6)
No	4 (5.4)
Sarcopenia	
All patients	56 (75.7)
Male	30 (53.6)
Female	26 (35.1)
VFA (cm²)	
Median (IQR)	65.7 (35.4 - 129.7)
SFA (cm²)	
Median (IQR)	122.1 (67.9 - 185.2)
TAMA (cm² / m²)	
Median (IQR)	36.9 (31.7 - 42.1)
VFA/TAMA	
Median (IQR)	2.0 (1.0 - 3.3)
Sarcopenic obesity	
All patients	19 (25.7)
Male	15 (20.3)
Female	4 (5.4)

CT: Computed Tomography; NA: Not Applicable; VFA: Visceral Fat Area; IQR: interquartile range; SFA: Subcutaneous Fat Area; TAMA: Total Abdominal Muscle Area.

PFS and OS. The best-performing model, based on the p-values of the individual variables, the overall model, and the C-index, included vitamin B12, MUAC, and VFA/TAMA ratio. The proportional hazards assumption for this final Cox-model was formally tested using Schoenfeld residuals. No violations were observed (all $p > 0.05$), indicating that the proportional hazards assumption holds for our model. The p-values from the Log-Rank test were both below the 0.05 threshold (p-value = 0.000685 for PFS; p-value = 0.00025 for OS), as shown in Table 4. The final Pancreatic Adenocarcinoma Nutritional-Clinical INdex (PANCIN) represented a linear combination of the three selected variables with their respective coefficients obtained from the model (PANCIN index = $\beta_1{}^*x_1 + \beta_2{}^*x_2 + \beta_3{}^*x_3$). Vitamin B12 and VFA/TAMA had positive coefficients, while MUAC coefficient was negative, indicating that they were directly and inversely correlated with the PANCIN value, respectively. Patients classified as high-risk according to the PANCIN index had a median PFS of 6.2 months (95 %CI: 3.5–9.7) and a median OS of 10.4 months (95 %CI: 7.5–15.1). In contrast, low-risk patients had a median PFS of 14.1 months (95 % CI: 8.8–20.3) and a median OS of 19.8 months (95 %CI: 11.3–31.1). Survival curves for primary outcomes in high- and low-risk patients, according to PANCIN index, are shown in Fig. 1.

3.3. Secondary outcomes

An analysis was conducted to evaluate how the derived prognostic index correlated with secondary endpoints, ORR and CA19.9 response rate. As shown in Fig. 2a and Fig. 2b, PANCIN index was predictive of both radiological and biohumoral response.

3.4. Exploratory analyses

An exploratory analysis assessing the correlation between PANCIN and chemotherapy-related toxicities was performed separately for PFS and OS.

With regards to PFS, the PANCIN index showed a clear ability to discriminate patients who developed treatment-related infections (p-value=0.01) and those who tended to experience grade ≥3 hematological toxicities (p-value=0.05). Other toxicities, such as fatigue, nausea/vomiting, and neuropathy, showed a trend towards significance, particularly when comparing the presence versus the absence of toxicity.

Similar trends were observed for OS: the PANCIN index could indeed discriminate patients with higher risk of infections (p-value=0.001), while a trend towards significance emerged for grade ≥3 hematological toxicities (p-value=0.17). For some toxicities, such as fatigue and neuropathy, the comparison was not feasible due to the limited number of patients in one of the subgroups.

Further exploratory analyses assessing the correlation with chemotherapy dose intensity did not show significant differences according to PANCIN risk groups (Supplementary Figure 3).

4. Discussion

By assessing the impact of different baseline variables on survival outcomes in a cohort of advanced PDAC patients, we identified a novel prognostic index, PANCIN, integrating radiological

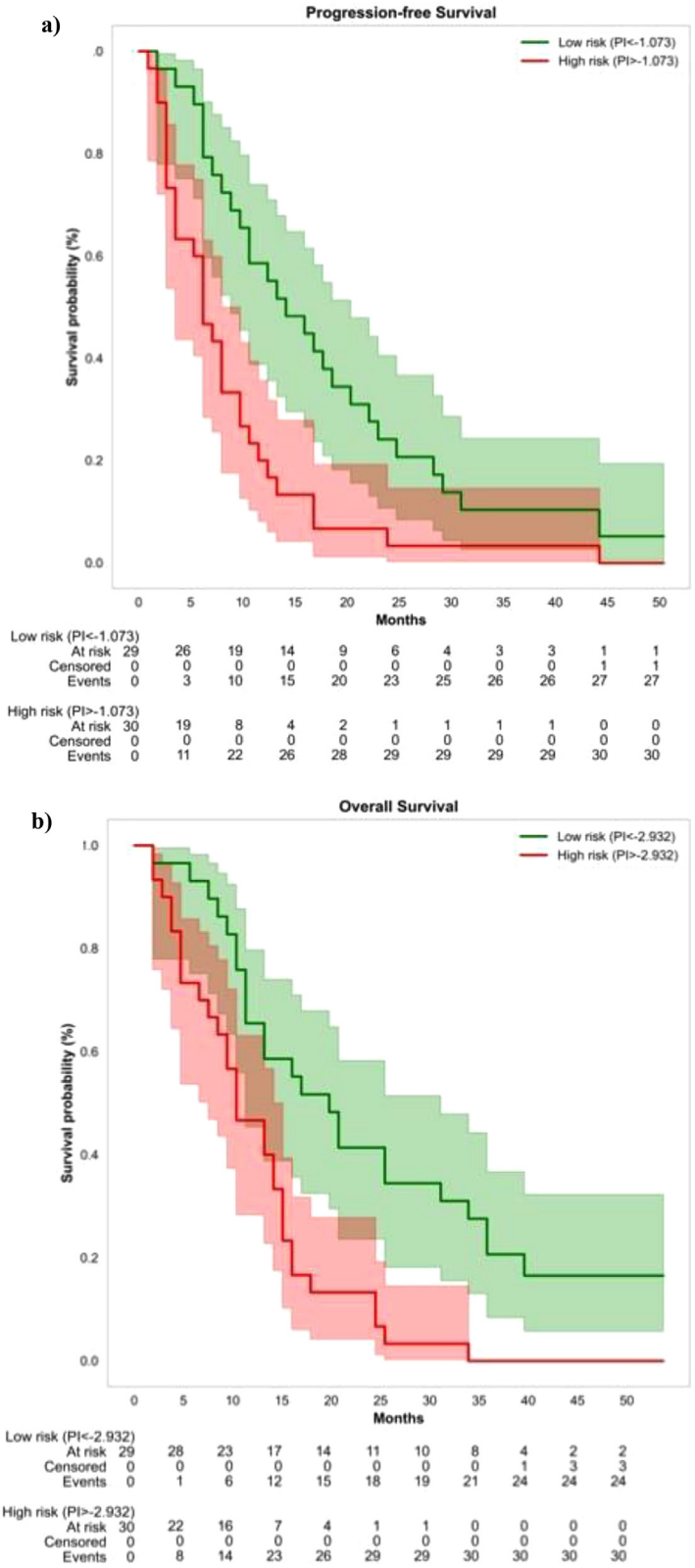

Fig. 1. Survival curves for primary outcomes. Kaplan–Meier survival curves for (a) PFS and (b) OS. The red curve represents high-risk patients, whereas the green curve represents low-risk patients. The median value of the index was used as the cut-off to stratify the two groups. Below each graph, the number of patients at risk (with and without the event) is reported at each time point (in months).

Table 4
Model variables for primary outcomes. The best model identified for the two outcomes, PFS and OS, included the model variables with their respective p-values and hazard ratios. Overall p-value of the model, frequency across the 1000 bootstrap populations, C-index obtained from MedicalAI, and optimism-corrected C-index are reported for both endpoints.

Outcome	Variable	Coefficient	p-value	HR	Model p-value	Frequency	C-index	CorrectedC-index[a]
PFS	Vitamin B12	0.00117	0.00001	1.00064	0.00016	453	0.70692	0.69042
	MUAC	−0.09095	0.01536	0.84832				
	VFA/TAMA	0.18949	0.03511	1.01332				
OS	Vitamin B12	0.00082	0.00145	1.00082	0.00025	641	0.67001	0.64957
	MUAC	−0.15122	0.00121	0.85966				
	VFA/TAMA	0.24948	0.00682	1.28336				

[a] Optimism-corrected C-index; HR: hazard ratio; PFS: Progression Free Survival; MUAC: mid-upper arm circumference; VFA/TAMA: Visceral Fat Area/ Total Abdominal Muscle Area; OS: overall survival.

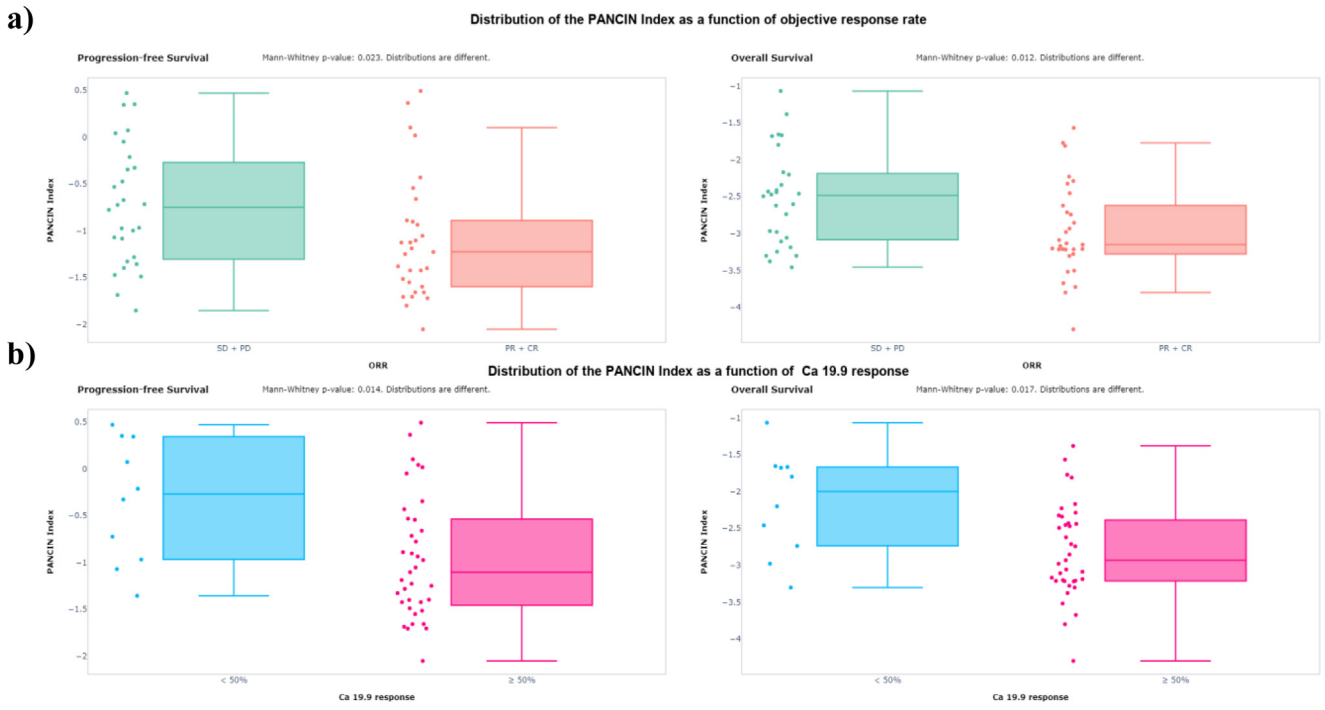

Fig. 2. Box plots of secondary outcomes. Box plots illustrate the distribution of the PANCIN index according to objective response rate (a) and CA19–9 response rate (b), stratified by the two clinical outcomes. For both panels, PFS is shown on the left and OS on the right. In each panel, individual data points are displayed alongside the corresponding box plot, representing the underlying value distribution.

(VFA/TAMA ratio) and clinical-nutritional parameters (Vitamin B12 and MUAC).

An elevated VFA/TAMA ratio is an indicator of sarcopenic obesity, a condition characterized by low muscle mass and excessive adiposity, which has been associated with poor OS in PDAC patients [24,38,39]. From a clinical perspective, since chemotherapy dosing is conventionally based on body surface area (BSA) or weight, sarcopenic obese patients often receive disproportionately high drug doses, being potentially exposed to increased risk of chemotherapy toxicity [40,41]. Furthermore, sarcopenia compromises immune response, making patients more susceptible to infections and reducing their ability to cope with treatment- and disease-related stress [25,42]. Notably, while most patients in our cohort were classified as normal weight based on BMI, two out of three had occult pre-existing low skeletal muscle mass, underscoring the limitations of BMI-based measurements and highlighting the need for a radiological assessment of body composition for a more accurate nutritional evaluation [43–45].

Vitamin B12 is essential for DNA methylation and fatty acid metabolism [46]. While its deficiency is well known in conditions such as pernicious anemia and neurological disorders [47], the implications of elevated B12 levels in cancer remain less understood. B12 hypervitaminosis is increasingly recognized as a negative prognostic marker in oncology, with studies linking it to poor performance status [48] and increased short-term mortality [43,49]. High B12 levels have been associated with worse clinical conditions, low prealbumin levels, and advanced cancer stages, potentially reflecting increased tumor burden [48]. A proposed mechanism for this association involves the production of vitamin B12-binding proteins by inflammatory cells, that could contribute to elevated circulating B12 levels in aggressive cancer types with a pronounced inflammatory response [49]. Our analysis confirmed a strong association between high B12 levels and worse survival outcomes in PDAC patients, supporting its role as a surrogate marker of aggressive disease.

Although traditionally used in malnourished populations, the anthropometric parameter MUAC is gaining attention in oncology for its ability to reflect both muscle mass and subcutaneous fat [50]. Several studies have reported that MUAC is predictive of performance status in cancer patients and serves as an independent prognostic factor for short-term survival [51,52]. A recent meta-analysis proposed a MUAC cut-off of 24 cm as an indicator of un-

derweight status [53]. However, in our cohort, the median MUAC was 27 cm, with over 80 % of patients exceeding the 24 cm cut-off. Interestingly, while BIVA is widely used for body composition assessment in oncology, its derived measurements did not significantly correlate with survival outcomes in our cohort [45]. This may be caused by fluid imbalances, which can distort BIVA-derived measurements of fat-free mass and that are common in advanced PDAC patients due to dehydration or malignant ascites [54,55].

A key advantage of PANCIN is its ability to combine different anthropometric, biochemical, and radiological parameters, significantly predicting both survival outcomes and tumor response. Indeed, when analyzed individually, each parameter has its own limitations. Vitamin B12 levels may be influenced by other inflammatory conditions and supplementation. Although no patient declared regular vitamin B12 parenteral/oral intake, that was explicitly contraindicated at first oncological consultation, occasional use of multivitamin oral supplements including vitamin B12 could not be completely ruled out. Additionally, MUAC is an operator-dependent measure and VFA/TAMA ratio is only a quantitative and not a qualitative measure of patient body composition, which may fail to identify patients with preserved muscle mass but significant functional impairment [56]. Moreover, a single parameter may not be sensitive enough to detect all high-risk patients, highlighting the need for complementary measures. By integrating these three factors, PANCIN represents a more robust tool for patient stratification. Furthermore, PANCIN may help identifying patients at higher risk of infectious complications and severe hematological events, which have a significant impact on patient morbidity and mortality and add substantial costs to the healthcare system [57]. In this perspective, PANCIN may serve as a useful tool for closer toxicity monitoring during chemotherapy.

From a clinical perspective, early risk-stratification of PDAC patients may help guide tailored nutritional interventions, aiming at reducing cancer related-inflammation and cachexia, enhancing immune response and restoring body composition, with a possible positive impact on treatment outcome and tolerance. Immunonutrition, which combines liquid nutritional supplements with specific nutrients [58] to modulate inflammatory and immune responses, has shown promising results in surgical oncology and perioperative care [59]. Similarly, increasing evidence is supporting the beneficial role of tailored multimodal pre-habilitation approaches, entailing nutritional and physical interventions, in improving surgical and oncological outcomes in early-stage PDAC [60]. These findings suggest potential efficacy of analogous interventions in advanced PDAC patients receiving chemotherapy. Lastly, prompt management of pancreatic exocrine insufficiency, which is common in advanced PDAC patients, has a well- established role in maintaining or restoring body weight, promoting optimal nutritional status and muscle mass, possibly improving outcomes [61].

From a practical standpoint, the inclusion of CT-derived body composition parameters may raise concerns regarding feasibility in routine clinical settings. In the present study, VFA and TAMA were assessed at the level of the third lumbar vertebra using a standardized semi-automated approach (SliceOmatic®). L3-based body composition assessment has demonstrated high robustness and reproducibility across oncologic populations and is increasingly recognized as a reliable surrogate of whole-body muscle and adipose tissue distribution [58,59]. While the need for dedicated post-processing tools and trained operators may represent a potential limitation, it should be noted that baseline contrast-enhanced CT imaging is already part of standard care in advanced PDAC. In addition, recent semi-automated and artificial intelligence–based solutions have shown good agreement with reference methods, substantially reducing analysis time and operator dependency, thereby supporting clinical scalability [60].

In the present cohort, stratified analyses according to chemotherapy regimen were not feasible due to the limited sample size. However, available evidence suggests that the overall toxicity burden of AG and PAXG regimens is comparable [21]. The applicability of the PANCIN index in patients treated with other standard chemotherapy regimens, such as mFOLFIRINOX, has not been addressed in the present study and warrants dedicated validation. In a randomized trial, mFOLFIRINOX has been associated with a higher incidence of hepatotoxicity compared with PAXG [62], which may further affect nutritional and metabolic status, potentially reinforcing the clinical relevance of baseline nutritional and body composition assessment in this setting.

Other limitations of the study include the small sample size, the lack of an external population for validation and the unavailability of a second assessment for most patients, which did not allow for a longitudinal evaluation of PANCIN modifications over time in correlation with chemotherapy administration and nutritional interventions. Nevertheless, sample size limitation is mitigated by several strengths. First, the analyzed cohort derived from a prospective study, ensuring systematic data collection. Second, the study population was clinically homogeneous, with all patients presenting advanced-stage disease and receiving AG-based polychemotherapy, thereby reducing potential disease heterogeneity or treatment variability. Finally, the extended follow-up period allowed for the evaluation of mature survival outcomes, strengthening the robustness of our findings.

An additional limitation relates to the internal validation strategy. While bootstrap resampling is appropriate for small datasets and provides optimism-corrected performance metrics, thresholds derived through this procedure may be partially optimized for the study population. In this context, the median value was deliberately adopted as a robust, assumption-free cut-off suitable for an exploratory prognostic study, minimizing the risk of overfitting. Although alternative clinically meaningful thresholds may enhance interpretability, their reliable identification requires larger datasets and external validation. Moreover, because PANCIN is based on a simple linear combination of routinely available variables, it can be readily implemented as a continuous risk score or straightforward calculator, supporting its potential clinical applicability.

Although formal calibration metrics were not computed due to the limited sample size, observed outcomes were consistent with PANCIN-based risk stratification, supporting its qualitative reliability for both primary and secondary endpoints. In this context, PANCIN represents a prognostic index with potential clinical relevance, whose applicability warrants external validation.

5. Conclusion

Our study highlights the prognostic significance of combined clinical-nutritional and radiological parameters in predicting survival and response outcomes in advanced PDAC patients undergoing chemotherapy, underscoring the importance of early multidisciplinary nutritional assessment. The integration of nutritional and body composition evaluations into routine clinical settings may help identifying high-risk patients, promoting early nutritional interventions and therapeutic adjustments with the aim to improve quality of life and, ultimately, clinical outcomes.

Author contributions

Carconi Catia: Data curation; Investigation; Methodology; Formal analysis; Validation; Roles/Writing - original draft. Capurso Gabriele: Conceptualization; Data curation; Funding acquisition; Investigation; Methodology; Project administration; Resources; Supervision; Validation; Writing - review & editing. Abati Martina,

Burini Alice, Cardellini Sara: Data curation; Investigation; Writing - review & editing. Vincenzi Monica Maria, Pavarini Maddalena, Ubeira-Gabellini Maria Giulia, Fiorino Claudio: Formal analysis; Methodology; Validation; Writing - review & editing. Palumbo Diego, Campisi Antonino: Data curation; Investigation; Writing - review & editing. Pecorelli Nicolò, Guarneri Giovanni: Methodology; Validation; Writing - review & editing. Macchini Marina, Liscia Nicole: Data curation; Investigation; Writing - review & editing. Vanella Giuseppe, Falconi Massimo: Validation; Writing - review & editing. Reni Michele, Orsi Giulia: Conceptualization; Data curation; Investigation; Methodology; Project administration; Supervision; Validation; Writing - review & editing.

Declaration of competing interest

The authors declare the following financial interests/personal relationships. **Michele Reni:** Personal honoraria for consulting and advisory role from LeoPharma, Viatris, BMS; research funding to institution from AstraZeneca; travel expenses from Daiichi Sankyo. All other authors declare no competing interests.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.dld.2026.02.015.

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