



Prognostic modeling of overall survival in metastatic pancreatic cancer: an inflammation-based tool validated in PANTHEIA-SEOM cohort

Vilma Pacheco-Barcia¹ · Axel Mariño-Mendez² · María Ángeles Vicente Conesa³ · María de Toro Carmena⁴ · Paula Cerdà Serdà⁵ · Carmen Guillen-Ponce⁶ · Mónica Benavente Lucas⁷ · Raquel Hernández San Gil⁸ · Ángela Lamarca⁹ · Javier Gallego¹⁰ · María Luisa Soriano Tabares de Nava¹¹ · Jorge Hernando¹² · Elena Brozos-Vazquez¹³ · Ana López-Alfonso¹⁴ · Jorge Adeva¹⁵ · Ismael Ghanem¹⁶ · Sandra Soriano¹⁷ · Javier Soto-Alsar⁷ · Andrés Muñoz⁷ · Paula Jimenez-Fonseca² · Alberto Carmona-Bayonas³

Received: 9 June 2026 / Accepted: 12 August 2026
© The Author(s) 2026

Abstract

Purpose To develop and internally validate the PANTHEIA-SIRI prognostic model, which integrates log-transformed systemic inflammation response index (SIRI) with clinical predictors, to estimate overall survival (OS) in metastatic pancreatic ductal adenocarcinoma (mPDAC) treated with first-line chemotherapy.

Methods We used data from the multicenter PANTHEIA-SEOM registry. OS was defined from chemotherapy start. The model was fitted as a Weibull accelerated failure time model in the survival-analysis population with multiple imputation. Predictors were log-transformed baseline SIRI, modeled with restricted cubic splines, ECOG, tumor burden, chemotherapy regimen, and anorexia-cachexia syndrome. Internal validation used a separate, non-overlapping cohort from the same registry; the centers contributing to each cohort are listed in a supplementary annex. TRIPOD was followed. Discrimination was assessed with Harrell's C-index and calibration with IPCW Brier scores and IPA.

Results The derivation cohort comprised 672 patients with SIRI data (593 analyzed for survival) across 22 Spanish hospitals (2015–2025); 80.1% had died after a median OS of 9.9 months. The imputation-pooled derivation C-index was 0.654 (95% CI, 0.627–0.681); optimism-corrected, 0.629. Internal validation used 62 separate patients from the same registry; 96.8% had died after a median OS of 9.2 months. The validation C-index was 0.603 (95% CI, 0.518–0.687). Calibration was adequate at 6 and 12 months.

Conclusions The PANTHEIA-SIRI model provides individualized OS estimates in mPDAC with routine clinical predictors. Its open-access calculator (<https://pantheia-siri.shinyapps.io/calc/>) may support prognostic communication, treatment-intensity selection, and supportive-care planning. Routine clinical implementation will require further validation in larger, fully independent cohorts.

Keywords Cachexia · Chemotherapy · ECOG · Internal validation · Systemic inflammation · Survival

Introduction

Pancreatic ductal adenocarcinoma (PDAC) is projected to become the second leading cause of cancer-related death in the United States by 2040 [1]. Most patients present with metastatic disease. Despite current first-line regimens,

such as gemcitabine plus nab-paclitaxel or FOLFIRINOX, median overall survival (OS) remains below 12 months, and the 5-year OS rate is approximately 3% [2, 3]. However, survival varies between patients, from a few weeks to more than 2 years. This variability supports the need for prognostic models that can guide treatment intensity, supportive care, and prognostic communication.

Most prognostic models in PDAC have been developed in resectable disease and have not been validated in metastatic disease [4]. A systematic review of 49 models reported that few achieved a C-index above 0.70 in independent

Vilma Pacheco-Barcia, Axel Mariño-Mendez These authors have contributed equally to this work.

Extended author information available on the last page of the article

validation, and that validation in routine clinical practice was uncommon [4]. In metastatic PDAC, validated models are limited. One example is the MPACT trial nomogram, with a C-index of 0.67 [5]. Therefore, there is a need for prognostic tools based on variables available in clinical practice.

Systemic inflammation is associated with poor outcomes in PDAC through tumor-related cytokine release, metabolic alterations, and immune dysfunction [6, 7]. The systemic inflammation response index (SIRI), calculated from neutrophil, monocyte, and lymphocyte counts, is available from routine blood tests and has been associated with outcomes in solid tumors [8, 9]. Our group previously showed, in a multicenter cohort of 672 patients, that SIRI was independently associated with OS, progression-free survival, and objective response when modeled as a continuous log-transformed variable [10].

That previous work assessed the prognostic association between SIRI and outcomes in metastatic PDAC after adjustment for confounders [10]. The present study assessed whether SIRI, included in a multivariable model, can estimate individualized OS. We developed the PANTHEIA-SIRI model, a Weibull accelerated failure time model that combines log-transformed SIRI, modeled with restricted cubic splines, with ECOG performance status, tumor burden (sum of RECIST target-lesion diameters), first-line chemotherapy regimen, and cancer anorexia-cachexia syndrome. The model was implemented in an open-access calculator. In contrast to most existing tools, which were developed in resectable disease or rely on pathological or post-treatment variables, the present model is designed for the metastatic, first-line setting, uses only pretreatment variables available in routine practice, and models inflammation as a continuous predictor rather than as a dichotomized cut-off. As internal performance may overestimate predictive accuracy, validation in an independent cohort is required before clinical use [11]. We aimed to describe the structure and coefficients of the PANTHEIA-SIRI model and to evaluate its discrimination and calibration in an extended multicenter cohort, according to the TRIPOD framework.

Methods

Study design and cohorts

PANTHEIA-SEOM is a multicenter observational cohort study promoted by the Spanish Society of Medical Oncology. It enrolled consecutive adults with histologically or cytologically confirmed metastatic PDAC who started first-line systemic chemotherapy at 22 Spanish hospitals between 2015 and 2025. Data were prospectively recorded in a centralized electronic case-report form. The protocol was approved by the ethics committee of each participating

center. Written informed consent was obtained from all living patients. For deceased or lost-to-follow-up patients, a waiver was granted under strict pseudonymization and in compliance with the European Union General Data Protection Regulation. The study was conducted in accordance with the Declaration of Helsinki, ICH Good Clinical Practice guidelines, and STROBE and REMARK reporting standards [12, 13]. This manuscript follows the TRIPOD recommendations for prediction-model development and validation [11].

Two nested derivation populations were defined: the SIRI-evaluable cohort (672 patients with blood counts sufficient to compute SIRI, used for baseline description) and the survival-analysis population (593 patients with valid OS), in which the prognostic model was developed. The internal validation cohort comprised a separate, non-overlapping set of patients enrolled later in the same registry, with no patient overlap with the derivation cohort and mostly from the same centers plus one additional center; the institutions contributing to each cohort are listed in Supplementary Table S1. Both cohorts had the same eligibility criteria, treatment patterns, and OS definition.

Outcome and predictors

The primary outcome was OS, defined as the time from first-line chemotherapy start to death from any cause. Patients alive at last contact were censored at that date.

Five predictors were prespecified on biological and clinical grounds: (1) SIRI, calculated as neutrophils $\times$ monocytes/lymphocytes from complete blood counts obtained within 14 days before first-line chemotherapy initiation; (2) ECOG performance status (0, 1, or ≥ 2); (3) baseline tumor burden, defined as the sum of RECIST target-lesion diameters and modeled as three levels (> 5 cm, ≤ 5 cm, or non-measurable disease); (4) first-line chemotherapy regimen (FOLFIRINOX, gemcitabine plus nab-paclitaxel, gemcitabine monotherapy, or other); and (5) cancer anorexia-cachexia syndrome, operationalized as a baseline symptom composite (presence of anorexia, cachexia, asthenia, or weight loss $> 5\%$) consistent with international consensus criteria [14]; alternative operational definitions are examined in Supplementary Table S2.

SIRI was selected as the inflammation marker after a comparative evaluation of candidate blood-count indices. Among log-transformed indices including the neutrophil-to-lymphocyte, monocyte-to-lymphocyte, derived neutrophil-to-lymphocyte and platelet-to-lymphocyte ratios, the systemic immune-inflammation index, the pan-immune-inflammation value, and others, log-transformed SIRI provided the best fit for OS (lowest Akaike information criterion) while remaining statistically indistinguishable from the top-ranked indices for progression-free survival and

objective response (Supplementary Table S3). SIRI was log-transformed after Box–Cox analysis identified the natural logarithm as the most appropriate transformation and was modeled as a three-knot restricted cubic spline with knots at the 10th (−0.32), 50th (0.74), and 90th (2.03) percentiles of the registry distribution. Regimen-specific interaction terms with log (SIRI) were prespecified to assess whether the association between SIRI and OS differed by first-line chemotherapy regimen.

Statistical analysis

The PANTHEIA-SIRI model was fitted as a Weibull accelerated failure time model. Results are reported as time ratios (TR), which estimate the relative change in expected survival time associated with each predictor. $TR > 1$ indicates longer expected survival, whereas $TR < 1$ indicates shorter expected survival. Hazard ratios can be derived as $HR = TR^{(-1/\sigma)}$, where σ is the Weibull scale parameter.

The PANTHEIA-SIRI model was developed within a multiple-imputation framework. Missing baseline predictor values were imputed by predictive mean matching, generating ten imputed datasets, with the per-predictor missing-data pattern summarized in Supplementary Table S4 [15]. Model coefficients were estimated in each imputed dataset of the full derivation registry and pooled using Rubin's rules, so that coefficient estimation used all available information under a missing-at-random assumption. Tumor burden was modeled as a three-level variable (> 5 cm, ≤ 5 cm, or non-measurable disease): the non-measurable level was taken directly from the RECIST assessment and was not imputed, whereas the $\leq 5/> 5$ cm split was imputed only among patients with measurable or unknown-status disease. Predictor collinearity was assessed with generalized variance inflation factors, redundancy analysis, and variable clustering (Supplementary Tables S5 and S6, Supplementary Figure S1).

Model performance was evaluated through discrimination, calibration, and risk stratification [11, 16]. In the derivation registry, discrimination was summarized as the Harrell's C-index pooled across the ten imputed datasets (Rubin's rules), and internal validity was assessed by enhanced bootstrap with optimism correction of the C-index and the calibration slope (1000 replicates; Supplementary Table S7). As a sensitivity analysis, we additionally performed internal–external cross-validation across geographic regions (leave-one-region-out): the model was refitted with each of six regions omitted in turn and validated on the held-out region, with all metrics averaged across the imputed datasets (Supplementary Table S8, Supplementary Figure S2). As a consistency check, discrimination and calibration were additionally computed on directly observed predictor values, which yielded concordant estimates; reporting

was based on the imputation framework to avoid summarizing performance solely on imputed values. Calibration was assessed at 6 and 12 months using inverse probability of censoring weighted (IPCW) Brier scores and the index of prediction accuracy (IPA). IPA was calculated as $1 - (BS/BS_{\text{null}})$, where BS_{null} is the Brier score of the null Kaplan–Meier model [17]. Positive IPA values indicate better prediction than the null model.

Calibration was also assessed graphically by plotting model-predicted survival probabilities against Kaplan–Meier estimates across risk groups defined by tertiles of the linear predictor. Risk stratification was evaluated with Kaplan–Meier curves according to the median and tertiles of the linear predictor. Between-group comparisons used the log-rank test.

All analyses were two-sided, with a significance threshold of $p < 0.05$. Analyses were performed with R version 4.3 using the rms, Hmisc, and mice packages [18, 19]. Analytical code and model coefficients are available at https://github.com/albertocarm/pantheia_model and archived on Zenodo: <https://doi.org/10.5281/zenodo.18444522>.

Results

Cohort characteristics

The derivation cohort comprised 672 patients with metastatic PDAC and blood counts sufficient to compute SIRI, treated at 22 Spanish hospitals between 2015 and 2025; their baseline characteristics are shown in Table 1. Survival analyses were performed in the 593 patients with complete overall-survival data. The median age was 65.8 years (range, 25.8 to 90.1), and 53% were men. ECOG performance status was 0 or 1 in 84% of patients. Liver metastases were present in 66%, and weight loss $> 5\%$ at diagnosis in 68%. The cancer anorexia-cachexia syndrome symptom composite (anorexia, cachexia, asthenia, or weight loss $> 5\%$; the variable used in the model) was present in 75% of patients. First-line chemotherapy was gemcitabine plus nab-paclitaxel in 58% and FOLFIRINOX in 24%. Missing baseline data in the derivation registry were limited (chemotherapy regimen 0%, tumor burden 21.9%, cancer anorexia-cachexia syndrome 0.3%, log-SIRI 0%, ECOG 0.8%; Supplementary Table S4).

The model was developed within a multiple-imputation framework in this survival-analysis population (Methods); 80.1% had died after a median OS of 9.9 months. The internal validation cohort comprised 65 consecutive, separate patients enrolled later in the same registry (no patient overlap with the derivation cohort); of these, 62 had complete covariate data and constituted the analytical validation set. Baseline characteristics of the derivation and validation cohorts are compared in Supplementary Table S9, and the

Table 1 Baseline characteristics of the PANTHEIA-SEOM derivation cohort

Characteristic	<i>n</i> = 672 [<i>N</i> (%)]
Age, median (range), year	65.8 (25.8 to 90.1)
Male sex	349 (53.2)
ECOG-PS	
0	159 (23.9)
1	400 (60.2)
2	96 (14.4)
≥ 3	10 (1.5)
Cancer anorexia-cachexia syndrome (composite)	506 (75.3)
Anorexia	297 (44.2)
Cachexia	78 (11.6)
Asthenia	330 (49.1)
Weight loss > 5% at diagnosis	458 (68.2)
Metastatic site	
Liver metastases	445 (66.2)
Peritoneal metastases	204 (30.4)
Pulmonary metastases	158 (23.5)
Tumor burden (RECIST target-lesion sum)	
> 5 cm	179 (26.6)
≤ 5 cm	114 (17.0)
Non-measurable disease	228 (33.9)
Not recorded	151 (22.5)
Elevated SIRI (> 2.3)	307 (45.7)
First-line chemotherapy regimen	
FOLFIRINOX	160 (23.8)
Gemcitabine plus nab-paclitaxel	392 (58.3)
Gemcitabine monotherapy	75 (11.2)
Other	45 (6.7)

Data are presented as No. (%) unless otherwise indicated. The derivation cohort comprised the 672 patients with blood counts sufficient to compute SIRI; survival analyses were restricted to the 593 with complete overall-survival data. “Cancer anorexia-cachexia syndrome” is the baseline symptom composite used in the model (presence of anorexia, cachexia, asthenia, or weight loss > 5%); its individual components are listed beneath it and may overlap. Tumor burden refers to the baseline sum of RECIST target-lesion diameters; non-measurable disease denotes the absence of measurable target lesions, and “Not recorded” denotes patients with measurable or unknown-status disease whose target-lesion sum was not documented. Percentages may not sum to 100% because of rounding or missing data.

ECOG-PS, Eastern Cooperative Oncology Group performance status
SIRI, Systemic Inflammation Response Index *N*, number.

centers contributing to each cohort are listed in Supplementary Table S1. In this cohort, 97% had died after a median OS of 9.2 months.

Model specification and derivation performance

Coefficients of the final Weibull accelerated failure time model, pooled across the ten imputed datasets, are reported in Table 2. The two restricted cubic spline terms for

log(SIRI) were associated with shorter expected survival time: $TR = 0.12$ for spline term 1 ($p = 0.001$) and $TR = 0.20$ for spline term 2 ($p < 0.001$). ECOG performance status was associated with shorter expected survival in a graded pattern: $TR = 0.68$ for ECOG 1 and $TR = 0.46$ for ECOG ≥ 2 , both versus ECOG 0; both $p \leq 0.002$. Cancer anorexia-cachexia syndrome was also associated with shorter expected survival ($TR = 0.66$; $p < 0.001$). Among first-line regimens, gemcitabine monotherapy was associated with shorter expected OS than FOLFIRINOX ($TR = 0.68$; $p = 0.05$).

Interaction terms between log (SIRI) and treatment regimen were significant for FOLFIRINOX ($TR = 2.01$; $p = 0.006$), gemcitabine plus nab-paclitaxel ($TR = 2.08$; $p = 0.002$), and gemcitabine monotherapy ($TR = 1.91$; $p = 0.02$), indicating that the association between SIRI and expected survival varied according to first-line chemotherapy regimen. The Weibull scale parameter (σ) was 0.874, and the shape parameter (γ) was 1.144.

In the derivation registry, the PANTHEIA-SIRI model showed an imputation-pooled Harrell’s C-index of 0.654 (95% CI, 0.627–0.681); the bootstrap optimism-corrected C-index was 0.629, and discrimination computed on directly observed predictor values was concordant (Table 3). No relevant collinearity was detected among predictors (all $GVI\hat{F}^{(1/2df)} < 1.06$; Supplementary Table S5). The integrated Brier score was 0.174, and IPA was positive at the clinically relevant horizons (0.085 at 6 months and 0.132 at 12 months; Supplementary Table S10).

Internal validation

In the validation cohort, the C-index was 0.603 (95% CI, 0.518–0.687), with an absolute decrease of 0.051 compared with derivation (Table 3). The validation cohort had a high event rate, with 60 deaths (96.8%) and only 2 censored patients. As a sensitivity analysis, internal–external cross-validation across geographic regions yielded region-specific C-indices between 0.60 and 0.69 (event-weighted pooled, 0.636), with calibration slopes from 0.53 to 1.50, indicating discrimination that remained stable across geographic origins (Supplementary Table S8, Supplementary Figure S2).

Calibration was assessed at 6 and 12 months. IPA values were 0.088 at 6 months and 0.042 at 12 months, indicating better prediction than the null model at both time points (Table 3). Estimation beyond 12 months was limited by the small number of patients still at risk, which renders Kaplan–Meier and IPCW estimates unstable; interpretation was therefore restricted to the 6- and 12-month horizons.

Risk stratification by the predicted linear score showed ordered survival curves in both binary, low risk and high risk (Fig. 1A) and tertile, low-, intermediate-, and high-risk (Fig. 1B) classifications. The binary classification separated

Table 2 PANTHEIA-SIRI Weibull accelerated failure time model coefficients for overall survival

Variable	Coefficient	SE	TR	p value
Intercept	3.805	0.191	NA	< 0.001
Tumor burden: ≤ 5 cm vs > 5 cm	0.063	0.140	1.07	0.65
Tumor burden: non-measurable vs > 5 cm	-0.006	0.104	0.99	0.96
log(SIRI), spline term 1	-2.116	0.644	0.12	0.001
log(SIRI), spline term 2	-1.596	0.442	0.20	< 0.001
Gem/nab-P vs FOLFIRINOX	-0.154	0.134	0.86	0.25
Gemcitabine vs FOLFIRINOX	-0.392	0.200	0.68	0.05
Other regimen vs FOLFIRINOX	0.434	0.303	1.54	0.15
ECOG-PS 1 vs 0	-0.382	0.118	0.68	0.001
ECOG-PS ≥ 2 vs 0	-0.779	0.153	0.46	< 0.001
Cancer anorexia-cachexia syndrome (yes vs no)	-0.417	0.103	0.66	< 0.001
FOLFIRINOX $\times$ log(SIRI)	0.698	0.253	2.01	0.006
Gem/nab-P $\times$ log(SIRI)	0.734	0.243	2.08	0.002
Gemcitabine $\times$ log(SIRI)	0.649	0.268	1.91	0.02
Weibull scale parameter (σ)	0.874			

TR > 1 indicates longer expected survival time; TR < 1 indicates shorter expected survival time. $HR = TR^{(-1/\sigma)}$, where σ is the Weibull scale parameter. Tumor burden was modeled as a 3-level variable (> 5 cm [reference], ≤ 5 cm, and non-measurable disease); the non-measurable level was taken from the measurable-disease assessment and the $\leq 5/ > 5$ split was multiply imputed only among patients with measurable or unknown-status disease. log (SIRI) was modeled with a 3-knot restricted cubic spline (knots at the 10th, 50th, and 90th percentiles). Coefficients were estimated across ten multiply imputed datasets generated by predictive mean matching and pooled using Rubin's rules. Weibull scale parameter $\sigma = 0.874$; Weibull shape parameter $\gamma = 1.144$. The spline and interaction terms jointly describe a non-linear, regimen-dependent association between SIRI and expected survival; no manual calculation is required because the open-access calculator performs all computations.

ECOG-PS, Eastern Cooperative Oncology Group performance status FOLFIRINOX, fluorouracil, leucovorin, irinotecan, and oxaliplatin; Gem/nab-P, gemcitabine plus nab-paclitaxel NA, not applicable SE, standard error SIRI, Systemic Inflammation Response Index TR, time ratio.

Table 3 PANTHEIA-SIRI model performance in derivation and internal validation cohorts

Performance metric	Derivation ($n = 593$)	Internal validation ($n = 62$)
Median overall survival, months	9.9	9.2
Deaths, No. (%)	475 (80.1)	60 (96.8)
Discrimination		
Harrell C-index (95% CI)	0.654 (0.627–0.681)	0.603 (0.518–0.687)
Calibration (IPCW Brier/IPA)		
6-month prediction horizon	0.191/0.085	0.183/0.088
12-month prediction horizon	0.207/0.132	0.227/0.042
Integrated Brier score	0.174	0.184

Model coefficients were estimated within a multiple-imputation framework (ten imputed datasets generated by predictive mean matching and pooled with Rubin's rules) using the full derivation registry. Derivation discrimination is the imputation-pooled Harrell C-index; the bootstrap optimism-corrected C-index was 0.629, and discrimination computed on directly observed predictor values was concordant. Confidence intervals were estimated with 1000 bootstrap replicates. IPA was calculated as $1 - (\text{Brier score}/\text{null Brier score})$; positive values indicate better prediction than the null model. Calibration was evaluated at the 6- and 12-month horizons; estimation beyond 12 months was unstable because of the small number of patients still at risk.

CI, confidence interval IPA, index of prediction accuracy IPCW, inverse probability of censoring weighted.

low- and high-risk groups with a trend toward statistical significance (log-rank $p = 0.057$), whereas the tertile classification did not ($p = 0.43$). Risk stratification is therefore

presented as exploratory. Calibration plots at 6 and 12 months showed agreement between predicted and observed survival across risk groups (Fig. 1C and 1D).

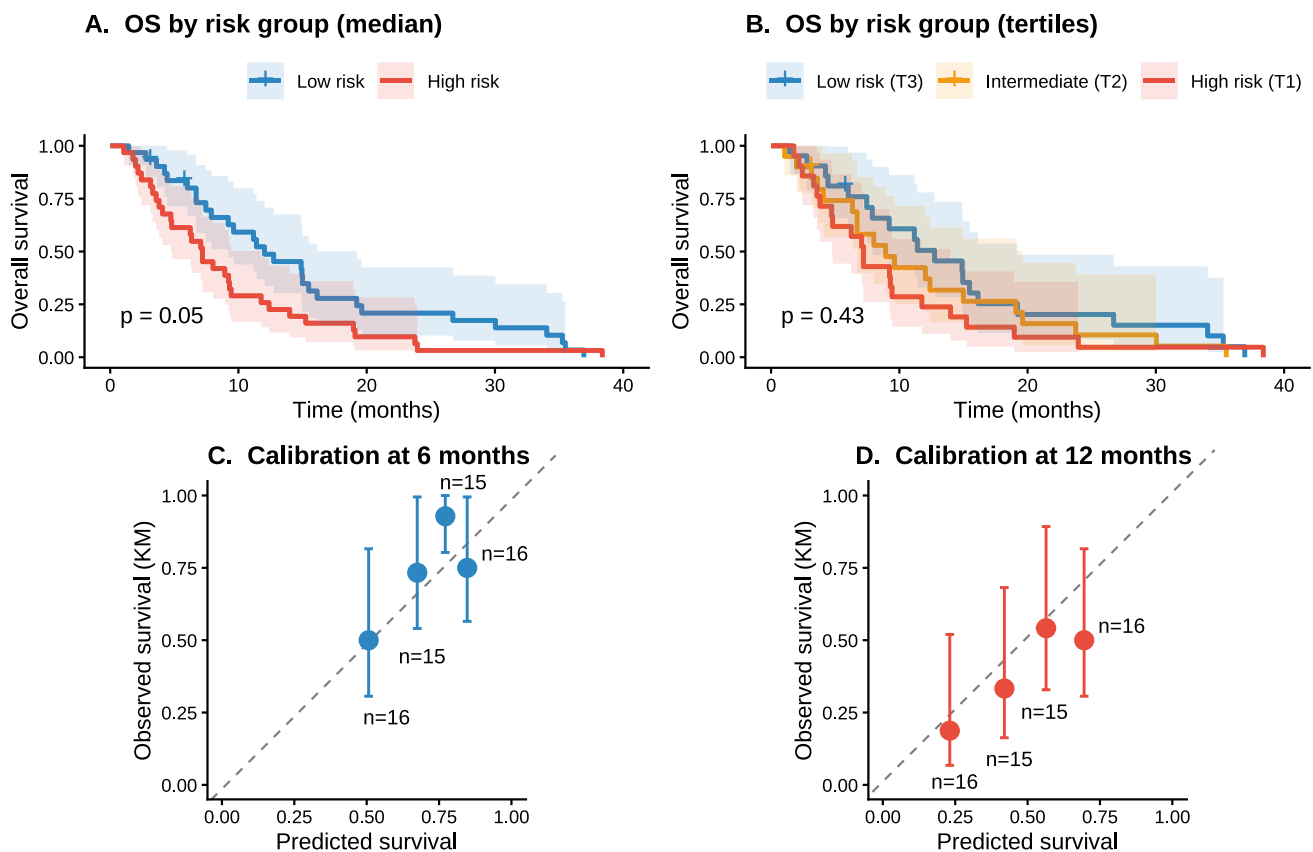


Fig. 1 Internal validation of the PANTHEIA-SIRI prognostic model in the validation cohort ($n = 62$). **A** Kaplan–Meier OS curves stratified by binary risk groups defined by the median predicted linear score: low risk versus high risk. **B** Kaplan–Meier OS curves stratified by tertiles of the predicted linear score: T1, high risk; T2, intermediate risk; T3, low risk. **C** Calibration plot at 6 months, showing model-predicted survival probability against Kaplan–Meier observed

survival within risk groups. **D** Calibration plot at 12 months, with the same structure. Error bars represent 95% confidence intervals, and group sample sizes are shown. The dashed diagonal line represents perfect calibration. p values correspond to log-rank tests for panels A and B. Per-group sample sizes are annotated within each panel and are small; subgroup estimates should be interpreted with caution *KM*, Kaplan–Meier OS, overall survival

Discussion

In this study, we developed and validated the PANTHEIA-SIRI prognostic model for OS in patients with metastatic PDAC treated with first-line chemotherapy. The model combines log-transformed SIRI with ECOG performance status, tumor burden, chemotherapy regimen, and cancer anorexia-cachexia syndrome. It showed a C-index of 0.654 in the derivation phase and 0.603 in the validation cohort, with calibration maintained at 6 and 12 months. These results support the transportability of the model within the PANTHEIA-SEOM framework and its potential use for individualized survival estimation.

The performance of the PANTHEIA-SIRI model should be interpreted in the context of available prognostic models in PDAC. In resectable disease, models such as the MSKCC nomogram and the international Amsterdam model include pathological variables, including margin status, lymph-node ratio, and tumor differentiation, and achieved validated

C-indices of 0.62 and 0.65, respectively [20–22]. In patients treated with neoadjuvant therapy, the MGH/MSKCC nomogram, which includes post-treatment variables such as residual tumor size, post-treatment CA 19-9, and ypN status, reported C-indices of 0.71 to 0.73 [23]. In metastatic PDAC, the MPACT trial nomogram, based on neutrophil-to-lymphocyte ratio, albumin, Karnofsky performance status, sum of target-lesion diameters, liver metastases, and prior Whipple resection, reported a C-index of 0.67 [5]. The validation C-index of 0.603 observed in our cohort is within the range reported for prognostic models based on routine variables in metastatic disease. This level of discrimination is expected in metastatic PDAC, where outcomes are uniformly poor and event times are tightly clustered. In the validation cohort, the central 50% of deaths occurred within a window of approximately 7.5 months (between 2.2 and 9.6 months) and the central 75% within a span of approximately 14 months, with a median time to death of 9.2 months (Supplementary Figure S3). This compression of event times reduces the number of

discordant patient pairs available for concordance estimation and constrains the achievable C-index, so that calibration and clinical applicability, rather than discrimination alone, become the more informative measures of model usefulness in this setting.

The PANTHEIA-SIRI model has several relevant features. First, SIRI was modeled as a continuous predictor with restricted cubic splines, avoiding dichotomization by a fixed cut-off. This approach preserves information and reduces the variability associated with threshold selection in inflammation biomarkers [8, 25]. Second, the model integrates inflammation with performance status, cachexia, tumor burden, and systemic treatment. These domains reflect patient condition, tumor extent, and treatment selection, which are central determinants of prognosis in metastatic PDAC. Third, the interaction terms between log (SIRI) and treatment regimen indicate that the association between SIRI and expected survival varied according to first-line chemotherapy regimen (Supplementary Figure S4). This finding is hypothesis-generating and may be consistent with reports that systemic therapy can modify the immune tumor microenvironment in PDAC [26].

The validation cohort had a high event rate, with 60 deaths (96.8%) and only 2 censored patients. This may reduce the number of informative patient pairs for concordance estimation and should be considered when comparing C-index values between derivation and validation cohorts. Calibration was better than the null model at the 6- and 12-month horizons. Beyond 12 months, a few patients remained at risk, which makes Kaplan–Meier and inverse-probability-of-censoring-weighted estimates unstable; performance was therefore not reported at later horizons. In pivotal metastatic PDAC trials, median OS was 11.1 months with FOLFIRINOX and 8.5 months with gemcitabine plus nab-paclitaxel, supporting the clinical relevance of 6- and 12-month prediction horizons in this setting [3, 24].

From a clinical perspective, the five predictors included in the PANTHEIA-SIRI model are available in routine practice and do not require additional testing. The open-access calculator (<https://pantheia-siri.shinyapps.io/calc/>), an experimental research tool, translates these variables into individualized OS estimates. The model and its calculator must not be used to withhold or deny standard systemic therapy from any patient; their intended role is to complement, not to replace, clinical judgment. Its potential role is to support prognostic communication, guide treatment-intensity discussions, identify patients who may benefit from early nutritional, functional, or palliative-care support, and standardize baseline risk description in clinical studies.

This study has several limitations. First, the validation cohort was drawn from the same registry as the derivation cohort, with partial overlap of participating centers (Supplementary Table S1). This analysis should therefore be

considered an internal–external (geographic) validation rather than a fully independent external validation. Second, the validation cohort was small ($n = 62$) and had a high event rate, with only two censored patients. This reduced the number of informative patient pairs for concordance estimation and may have limited the precision of the C-index. The sample size also limited stratum-specific calibration analyses and the assessment of model performance beyond 12 months. Third, missing baseline predictors were handled by multiple imputation, which assumes that data were missing at random conditional on the observed covariates and outcome; departures from this assumption could affect the pooled coefficient estimates.

Fourth, the model does not include molecular variables, such as circulating tumor DNA dynamics, tumor genomic alterations, or transcriptomic signatures. These variables could improve prognostic estimation in future model versions. Finally, the model may require recalibration as the treatment landscape of metastatic PDAC changes, particularly if therapies targeting cancer cachexia or systemic inflammation, such as the GDF-15 inhibitor ponesimab, become part of clinical practice [27].

In conclusion, the PANTHEIA-SIRI model provides individualized OS estimates for patients with metastatic PDAC treated with first-line chemotherapy. The model combines log-transformed SIRI with ECOG performance status, tumor burden, chemotherapy regimen, and cancer anorexia-cachexia syndrome, all variables available in routine practice. In geographic validation across centers, its performance was within the range reported for metastatic PDAC prognostic tools, with calibration maintained at 6 and 12 months. The open-access calculator (<https://pantheia-siri.shinyapps.io/calc/>) may help translate prognostic estimation into clinical practice within the PANTHEIA-SEOM framework, supporting prognostic communication, treatment planning, and early supportive-care interventions. Evaluation in larger independent prospective cohorts will be needed before routine implementation.

Supplementary Information The online version contains supplementary material available at <https://doi.org/10.1007/s12094-026-04554-8>.

Acknowledgements The authors thank the Spanish Society of Medical Oncology (SEOM) for promoting independent research through the SEOM-PANDORA platform, and IRICOM, Natalia Cateriano, and Miguel Vaquero for technical engineering support. None of these contributors received specific compensation for their role in this study beyond their institutional duties. Finally, we are grateful to all investigators participating in the PANTHEIA-SEOM project, in addition to the authors of this work: L. Cabezón, S. Custodio-Cabello, Hospital Universitario de Torrejón; A. Romano, Hospital de la Santa Creu i Sant Pau; A. García, J. Capdevila, Hospital Universitario Vall d'Hebron; C. Fabregat, Institut Català d'Oncologia; W. Parra, Hospital Universitario 12 de Octubre; P. Swizler, Hospital Universitario La Paz; S. Galvan, Hospital Universitario de Gran Canaria; D. Gutiérrez-Abad and E. Martínez-Moreno, Hospital Universitario de Fuenlabrada; L. Visa,

Hospital Universitario del Mar; I. Hernández, Complejo Hospitalario Universitario de Navarra; A. Martín-Carnicero, Hospital San Pedro; I. Macías, F. Castet and T. Macarulla, Hospital Clinic de Barcelona.

Author contributions Dr V. Pacheco-Barcia had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Concept and design: V. Pacheco-Barcia, A. Carmona-Bayonas, A. Mariño-Mendez, and P. Jimenez-Fonseca. Acquisition, analysis, or interpretation of data: all authors. Drafting of the manuscript: V. Pacheco-Barcia, A. Carmona-Bayonas, A. Mariño-Mendez, and P. Jimenez-Fonseca. Critical review of the manuscript for important intellectual content: all authors. Statistical analysis: A. Carmona-Bayonas and V. Pacheco-Barcia. Obtained funding: V. Pacheco-Barcia and P. Jimenez-Fonseca. Administrative, technical, or material support: V. Pacheco-Barcia, P. Jimenez-Fonseca, and A. Mariño-Mendez. Supervision: V. Pacheco-Barcia, P. Jimenez-Fonseca, and A. Mariño-Mendez.

Funding This research was supported by unrestricted grants from Nutricia Danone, Pfizer, Servier, LEO Pharma and received an SEOM grant 2024. The funders had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; or decision to submit the manuscript for publication.

Data availability The analytical code and model coefficients are publicly available at https://github.com/albertocarm/pantheia_model and archived on. Patient-level data are publicly available there. The validated prognostic calculator is freely accessible at <https://pantheia-siri.shinyapps.io/calcul/>.

Declarations

Conflict of interest V. Pacheco-Barcia has received research support from Nutricia, Pfizer, Servier and Leo Pharma for PANTHEIA-SEOM research; speaker honoraria from Pierre Fabre, Nutricia, Servier, Pfizer, AstraZeneca, Leo Pharma; consultancy or advisory board from Advanced Accelerator Applications, a Novartis company, Pfizer, Nutricia, Servier; travel support from Amgen, Servier, Pfizer, Nutricia, Merck. No other disclosures were reported. A. Mariño-Mendez reported receiving speaker honoraria from AstraZeneca and Recordati; educational support from Merck; travel support from Bristol Myers Squibb, Leo Pharma, Merck, MSD, Nutricia, Pierre Fabre, and Pfizer. No other disclosures were reported. P. Cerdà has received speaker honoraria from Eisai, Roche, AstraZeneca, BMS, and MSD; consultancy or advisory board from BMS and AstraZeneca; travel support from Roche, AstraZeneca, MSD, Eisai, Servier, Lilly, and Nutricia. No other disclosures were reported. A. Lamarca declares Travel and educational support from Ipsen, Pfizer, Bayer, AAA, SirtEx, Novartis, Mylan, Delcath Advanz Pharma, and Roche; Speaker honoraria from Merck, Pfizer, Ipsen, Incyte, AAA/Novartis, QED, Servier, AstraZeneca, EISAI, Roche, Advanz Pharma, Jazz Therapeutics, and MSD; Advisory and consultancy honoraria from EISAI, Nutricia, Ipsen, QED, Roche, Servier, Boston Scientific, Albireo Pharma, AstraZeneca, Boehringer Ingelheim, GENFIT, TransThera Biosciences, Taiho, MSD, JAZZ Therapeutics, and Viatris; Principal Investigator-associated Institutional Funding from QED, Merck, Boehringer Ingelheim, Servier, AstraZeneca, GenFit, Panbela Therapeutics, Novocure GmbH, Camurus AB, Albireo Pharma, Taiho, TransThera, Jazz Therapeutics, Roche, Novartis, Crinetics Pharmaceuticals, MSD, AbbVie, Revolution Medicines, and Incyte; Member of the Knowledge Network and NETConnect Initiatives funded by Ipsen. E. Brozos-Vazquez declares fee's speaking from LEO Pharma, Rovi, Roche, Kyowa Kirin, Merck, Bayer, Pierre Fabre, Sanofi, Amgen; and Advisory honoraria from Servier, Pfizer, and Bayer. J. Adeva reported financial interests from Incyte,

Advisory Board, Personal; Servier, Advisory Board, Personal; MSD, Advisory Board, Personal; Taiho Oncology, Advisory Board, Personal; AstraZeneca, Advisory Board, Personal; Incyte, Invited Speaker, Personal; Servier, Invited Speaker, Personal; MSD, Invited Speaker, Personal; AstraZeneca, Invited Speaker, Personal; Taiho Oncology, Invited Speaker, Personal; and Non-Financial Interests from Servier, Principal Investigator Taiho Oncology, Principal Investigator; AstraZeneca, Principal Investigator. A. López-Alfonso reported financial interests speaker honoraria from AstraZeneca, Servier, AstraZeneca. S. Soriano reported receiving educational support from Merck, Novartis; travel support from Merck, MSD, Ipsen, Novartis, Takeda. J. Soto Al-sar reported receiving research support from Pierre Fabre and Amgen; and speaker or consultant honoraria from LEO Pharma, MSD, BMS, Takeda, Roche, Merck, Pfizer, Recordati, AstraZeneca, Nestlé, Abbott, Techdow. A. Muñoz reported consultant or advisory role for GSK, Pfizer, BMS-Celgene, Sanofi, Astra-Zeneca, MSD, Lilly, Servier, Roche, Taiho, Leo Pharma, Regeneron, Jazz Pharmaceuticals. Research funding from Leo Pharma. Speakers' bureau: Rovi, Menarini, Stada, Medscape, Incyte, Taiho. Patents, Royalties, Other Intellectual Property: Risk assessment model in venous thromboembolism in cancer patients (genomic risk score). Liquid biopsy developed with Laser technology. P. Jimenez-Fonseca reported receiving research support from Astellas, AstraZeneca, BMS, and MSD; and speaker or consultant honoraria from Amgen, Astellas, AstraZeneca, BeiGene, BMS, Esteve, Leo Pharma, MSD, Novartis, Nutricia, Pfizer, Pierre Fabre, Rovi, Servier, Takeda, and Viatris. A. Carmona-Bayonas reported receiving research support from Astellas, AstraZeneca, BMS, and MSD; speaker honoraria from Novartis and Astellas; consultant honoraria from Astellas; and travel support from Amgen, Astellas, and Servier. The remaining authors declare that this research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Open Access This article is licensed under a Creative Commons Attribution 4.0 International License, which permits use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if changes were made. The images or other third party material in this article are included in the article's Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article's Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit <http://creativecommons.org/licenses/by/4.0/>.

References

1. Rahib L, Wehner MR, Matrisian LM, Nead KT. Estimated Projection of US Cancer Incidence and Death to 2040. *JAMA Netw Open*. 2021;4(4):e214708.
2. Bray F, Laversanne M, Sung H, Ferlay J, Siegel RL, Soerjomataram I, et al. Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin*. 2022;74(3):229–63.
3. Von Hoff DD, Ervin T, Arena FP, Chiorean EG, Infante J, Moore M, et al. Increased survival in pancreatic cancer with nab-paclitaxel plus gemcitabine. *N Engl J Med*. 2013;369(18):1691–703.
4. Ioannou LJ, Maharaj AD, Zalberg JR, Loughnan JT, Croagh DG, Pilgrim CH, et al. Prognostic models to predict survival in patients with pancreatic cancer: a systematic review. *HPB (Oxford)*. 2022;24(8):1201–16.
5. Goldstein D, Von Hoff DD, Chiorean EG, Reni M, Tabernero J, Ramanathan RK, et al. Nomogram for estimating overall

- survival in patients with metastatic pancreatic cancer. *Pancreas*. 2020;49(6):744–50.
6. Hanahan D. Hallmarks of Cancer: New Dimensions. *Cancer Discov*. 2022;12(1):31–46.
 7. Diakos CI, Charles KA, McMillan DC, Clarke SJ. Cancer-related inflammation and treatment effectiveness. *Lancet Oncol*. 2014;15(11):e493–503.
 8. Qi Q, Zhuang L, Shen Y, Geng Y, Yu S, Chen H, et al. A novel systemic inflammation response index (SIRI) for predicting the survival of patients with pancreatic cancer after chemotherapy. *Cancer*. 2016;122(14):2158–67.
 9. Pacheco-Barcia V, Custodio-Cabello S, Carrasco-Valero F, Palka-Kotlowska M, Mariño-Mendez A, Carmona-Bayonas A, et al. Systemic Inflammation Response Index and weight loss as prognostic factors in metastatic pancreatic cancer: A concept study from the PANTHEIA-SEOM trial. *World J Gastrointest Oncol*. 2024;16(2):386–97.
 10. Carmona-Bayonas A, Mariño Méndez A, Vicente Conesa MA, Jimenez-Fonseca P, De Toro Carmena M, Guillén-Ponce C, et al. 2026 Systemic Inflammation Response Index integrates host inflammation to predict outcomes and treatment benefit in metastatic pancreatic cancer: a study by the PANTHEIA-SEOM Research Group. *Pancreatol*.
 11. Collins GS, Reitsma JB, Altman DG, Moons KG. Transparent reporting of a multivariable prediction model for individual prognosis or diagnosis (TRIPOD): the TRIPOD statement. *BMJ*. 2015;350:g7594.
 12. von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP, et al. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *Lancet*. 2007;370(9596):1453–7.
 13. McShane LM, Altman DG, Sauerbrei W, Taube SE, Gion M, Clark GM. Statistics Subcommittee of the NCI-EORTC Working Group on Cancer Diagnostics Reporting recommendations for tumor marker prognostic studies (REMARK). *J Natl Cancer Inst*. 2005;97(16):1180–4.
 14. Fearon K, Strasser F, Anker SD, Bosaeus I, Bruera E, Fainsinger RL, et al. Definition and classification of cancer cachexia: an international consensus. *Lancet Oncol*. 2011;12(5):489–95.
 15. van Buuren S, Groothuis-Oudshoorn K. mice: multivariate imputation by chained equations in R. *J Stat Softw*. 2011;45(3):1–67.
 16. Steyerberg EW, Vergouwe Y. Towards better clinical prediction models: seven steps for development and an ABCD for validation. *Eur Heart J*. 2014;35(29):1925–31.
 17. Graf E, Schmoor C, Sauerbrei W, Schumacher M. Assessment and comparison of prognostic classification schemes for survival data. *Stat Med*. 1999;18(17–18):2529–45.
 18. Harrell FE Jr. Regression modeling strategies: with applications to linear models, logistic and ordinal regression, and survival analysis. 2nd ed. Springer; 2015.
 19. R Core Team. R: A Language and Environment for Statistical Computing. R Foundation for Statistical Computing; 2023.
 20. Brennan MF, Kattan MW, Klimstra D, Conlon K. Prognostic nomogram for patients undergoing resection for adenocarcinoma of the pancreas. *Ann Surg*. 2004;240(2):293–8.
 21. Ferrone CR, Kattan MW, Tomlinson JS, Thayer SP, Brennan MF, Warshaw AL. Validation of a postresection pancreatic adenocarcinoma nomogram for disease-specific survival. *J Clin Oncol*. 2005;23(30):7529–35.
 22. van Roessel S, Strijker M, Steyerberg EW, Groen JV, Mieog JS, Groot VP, et al. International validation and update of the Amsterdam model for prediction of survival after pancreatoduodenectomy for pancreatic cancer. *Eur J Surg Oncol*. 2020;46(5):796–803.
 23. Qiao G, Ilagan CH, Fernandez-Del Castillo C, Ferrone CR, Janseen QP, Balachandran VP, et al. Development and validation of the Massachusetts General Hospital/Memorial Sloan Kettering nomogram to predict overall survival of resected patients with pancreatic ductal adenocarcinoma treated with neoadjuvant therapy. *Surgery*. 2022;172(4):1228–35.
 24. Conroy T, Desseigne F, Ychou M, Bouché O, Guimbaud R, Bécaouarn Y, et al. FOLFIRINOX versus gemcitabine for metastatic pancreatic cancer. *N Engl J Med*. 2011;364(19):1817–25.
 25. Royston P, Altman DG, Sauerbrei W. Dichotomizing continuous predictors in multiple regression: a bad idea. *Stat Med*. 2006;25(1):127–41.
 26. Michelakos T, Cai L, Villani V, Sabbatino F, Kontos F, Fernández-Del Castillo C, et al. Tumor microenvironment immune response in pancreatic ductal adenocarcinoma patients treated with neoadjuvant therapy. *J Natl Cancer Inst*. 2021;113(2):182–91.
 27. Groarke JD, Crawford J, Collins SM, Lubaczewski S, Roeland EJ, Naito T, et al. Ponesimab for the Treatment of Cancer Cachexia. *N Engl J Med*. 2024;391(24):2291–303.

Publisher's Note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Authors and Affiliations

Vilma Pacheco-Barcia¹  · Axel Mariño-Mendez²  · María Ángeles Vicente Conesa³  · María de Toro Carmena⁴  · Paula Cerdà Serdà⁵  · Carmen Guillén-Ponce⁶  · Mónica Benavente Lucas⁷ · Raquel Hernández San Gil⁸  · Ángela Lamarca⁹  · Javier Gallego¹⁰  · María Luisa Soriano Tabares de Nava¹¹  · Jorge Hernando¹²  · Elena Brozos-Vázquez¹³  · Ana López-Alfonso¹⁴  · Jorge Adeva¹⁵  · Ismael Ghanem¹⁶  · Sandra Soriano¹⁷  · Javier Soto-Alsar⁷  · Andrés Muñoz⁷  · Paula Jimenez-Fonseca² · Alberto Carmona-Bayonas³

✉ Vilma Pacheco-Barcia
vilmapbarcia@yahoo.es

¹ Medical Oncology Department, Hospital Universitario La Luz, Gastrointestinal Cancer Unit, One Oncology Madrid Quirónsalud, Universidad Francisco de Vitoria, Calle del Maestro Ángel Llorca 8, 28003 Madrid, Spain

² Medical Oncology Department, Hospital Universitario Central de Asturias, Universidad de Oviedo, ISPA, Oviedo, Spain

³ Medical Oncology Department, Hospital Universitario Morales Meseguer, Murcia, Spain

⁴ Medical Oncology Department, Hospital Universitario La Princesa, Madrid, Spain

- ⁵ Medical Oncology Department, Hospital de la Santa Creu i Sant Pau, Barcelona, Spain
- ⁶ Medical Oncology Department, Hospital Universitario Ramón y Cajal, Madrid, Spain
- ⁷ Medical Oncology Department, Hospital General Universitario Gregorio Marañón, Universidad Complutense, Madrid, Spain
- ⁸ Medical Oncology Department, Hospital Universitario de Canarias, San Cristóbal de La Laguna, Spain
- ⁹ Medical Oncology Department, Fundación Jiménez Díaz University Hospital – Health Research Institute Fundación Jiménez Díaz (IIS-FJD) –Universidad Autónoma de Madrid (UAM), Madrid, Spain
- ¹⁰ Medical Oncology Department, Hospital General Universitario de Elche, Elche, Spain
- ¹¹ Medical Oncology Department, Hospital Nuestra Señora de la Candelaria, Santa Cruz de Tenerife, Spain
- ¹² Medical Oncology Department, Hepatobiliary Pancreatic Cancer and Endocrine Tumors Unit, Vall d'Hebron University Hospital, Barcelona, Spain
- ¹³ Medical Oncology Department, Complejo Hospitalario Universitario de Santiago, Santiago de Compostela, Spain
- ¹⁴ Medical Oncology Department, Hospital Universitario Infanta Leonor, Madrid, Spain
- ¹⁵ Medical Oncology Department, Hospital Universitario, 12 de Octubre, Madrid, Spain
- ¹⁶ Medical Oncology Department, Hospital Universitario La Paz, Madrid, Spain
- ¹⁷ Medical Oncology Department, Hospital Parc Tauli, Barcelona, Spain