



Prognostic factors in advanced pancreatic ductal adenocarcinoma patients-receiving second-line treatment: a single institution experience

L. Gutierrez-Sainz¹ · D. Viñal¹ · J. Villamayor¹ · D. Martinez-Perez¹ · J. A. Garcia-Cuesta¹ · I. Ghanem¹ · A. Custodio^{1,2,3} · J. Feliu^{1,2,3}

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Abstract

Background Second-line (2L) treatments for advanced pancreatic ductal adenocarcinoma (PDAC) achieve a modest benefit at the expense of potential toxicity. In the absence of predictive factors of response, the identification of prognostic factors could help in the therapeutic decisions-making. The purpose of this study was to assess the prognostic factors associated with shorter survival in patients with advanced PDAC who received 2L treatment.

Methods We conducted a single institution retrospective study, which included all patients with advanced PDAC who received 2L treatment between September 2006 and February 2020 at La Paz University Hospital, Madrid (Spain). Significant variables in the logistic regression model were used to create a prognostic score.

Results We included 108 patients. The median overall survival (OS) was 5.10 months (95%CI 4.02–6.17). In the multivariate analysis, time to progression (TTP) shorter than 4 months after first-line treatment (OR 4.53 [95%CI 1.28–16.00] $p=0.01$), neutrophil-to-lymphocyte ratio (NLR) greater than 3 at the beginning of 2L (OR 9.07 [95%CI 1.82–45.16] $p=0.01$) and CA-19.9 level higher than the upper limit of normal at the beginning of 2L (OR 7.83 [95%CI 1.30–49.97] $p=0.02$) were independently associated with OS shorter than 3 months. The prognostic score classified patients into three prognostic groups (good, intermediate and poor) with significant differences in OS ($p < 0.001$).

Conclusions TTP shorter than 4 months after first-line treatment, NLR greater than 3 and CA-19.9 level higher than the upper limit of normal at the beginning of 2L were associated with shorter overall survival. We developed a prognostic score that classifies patients with advanced PDAC into three prognostic groups after progression to the first-line. This score could help in the decision-making for 2L treatment.

Keywords Advanced pancreatic ductal adenocarcinoma · Second-line treatment · Prognostic factors

Introduction

Pancreatic ductal adenocarcinoma (PDAC) is the fourth leading cause of cancer-related death worldwide [1], and the third one in Spain [2]. The 5-year survival rate is 2–9%

[3]. It is estimated that PDAC will become the second most common cause of cancer death by 2030 [4].

Unfortunately, more than 80% of PDAC patients are diagnosed in a metastatic or locally advanced stage [5]. In this scenery, palliative systemic chemotherapy can improve disease-related symptoms and prolong the overall survival. Until 2010, gemcitabine chemotherapy has been the only standard of care treatment available for these patients. Over the past 10 years, there have been major progresses in the management of these patients with the approval of two first-line chemotherapy combinations: the FOLFIRINOX (5-fluorouracil, irinotecan and oxaliplatin) and the gemcitabine plus nab-paclitaxel regimens. These chemotherapy schedules have shown to be superior to gemcitabine as first-line chemotherapy, achieving a median overall survival (OS)

✉ L. Gutierrez-Sainz
laura.gutierrezsainz@gmail.com

¹ Medical Oncology Department, Hospital Universitario La Paz, IdiPAZ, Paseo de la Castellana 261, 28046 Madrid, Spain

² Cátedra UAM-AMGEN, Madrid, Spain

³ CIBERONC, Madrid, Spain

of 11.1 months (95%CI 9–13.1) and 8.5 months (95%CI 7.89–9.53), respectively [6, 7].

In the second-line (2L) setting, chemotherapy regimens such as OFF (5-fluorouracil and oxaliplatin), FOLFIRI (5-fluorouracil and irinotecan), XELOX (oxaliplatin and capecitabine), GEMOX (gemcitabine and oxaliplatin) and combinations of 5-fluorouracil and nanoliposomal irinotecan (nal-IRI) have shown some activity after failure of gemcitabine [8–14]. Other chemotherapy regimens studied in 2L have been paclitaxel, docetaxel, nab-paclitaxel and capecitabine monotherapy [15–19]. Targeted therapies had also been examined with disappointing results [20–22].

However, there is considerable heterogeneity in the survival of patients with advanced PDAC receiving 2L, and we do not have predictive factors of response. Furthermore, after the first line, half of the patients present a clinical deterioration that limits the possibility of receiving 2L treatment [23]. In addition, the benefit of 2L chemotherapy is modest at the expense of potential toxicity. Therefore, treatment decision should be individualized in each patient [24, 25].

In the absence of predictive response factors, the identification of prognostic factors could help in therapeutic decisions-making. Some authors have developed several nomograms to predict survival of patients with advanced PDAC receiving 2L treatment; however, its application in clinical practice is complex [35–37]. On the other hand, Sin et al. have developed a prognostic score for survival that included patients up to 2012, so they did not incorporate information on patients treated with FOLFIRINOX and gemcitabine plus nab-paclitaxel [29]. The purpose of this study was to assess the prognostic factors associated with shorter survival in patients with advanced PDAC treated with 2L chemotherapy.

Methods

Patients

We conducted a single institution retrospective study, including all cancer patients with advanced PDAC, who received 2L treatment between September 2006 and February 2020 at La Paz University Hospital, Madrid (Spain). The diagnosis of PDAC was confirmed cytologically and/or histologically. Patients were aged 18 years or older and received at least one cycle of the planned 2L chemotherapy. This study was approved by the Ethics Committee of the La Paz University Hospital (code HULP: PI-2043), and was conducted in accordance with ethical standards of the Helsinki Declaration of the World Medical Association.

Data regarding clinical and demographic characteristics, tumor extension, as well as analytical parameters were collected from the medical record of each patient. The

following clinical variables were collected: age, gender, smoking history, pre-existing diabetes, history of previous chronic pancreatitis, presence of biliary stent, location of pancreatic tumor, stage at diagnosis, thrombosis occurrence at diagnosis and at the beginning of 2L treatment, first-line chemotherapy regimen, best response to first-line therapy according to RECIST criteria, time to progression (TTP) after first-line, type of progression to first-line, 2L chemotherapy regimen, number and location of metastatic sites at the beginning of 2L (liver, lung, peritoneal and others location), performance status at the beginning of 2L, history of pain at the beginning of 2L, history of ascites at the beginning of 2L date of progression to 2L and date of exitus. The following analytical parameters were collected before 2L chemotherapy treatment: haemoglobin, white blood cell count, platelets, bilirubin, albumin and CA-19.9 level.

Statistical analysis

Median value (interquartile range) and frequency (percentage) were provided for the description of continuous and categorical variables, respectively. TTP after first-line was calculated from the date of first administration of first-line treatment to the date of first progression. Progression-free survival (PFS) after 2L was calculated from the date of first administration of 2L treatment to the date of progression or death from any cause. OS was calculated from the date of first administration of 2L treatment to the date of death from any cause. Survival data were censored at the last follow-up. OS was estimated using the Kaplan–Meier method and described using median with 95% confidence intervals.

The primary objective of the study was the identification of prognostic factors associated with OS shorter than 3 months after the beginning of 2L treatment. Logistic regression model was performed to estimate Odds ratios (ORs) and 95% confident intervals for prognostic factors associated with OS shorter than 3 months. The association of prognostic factors with OS was first assessed using univariate logistic regression analyses, and then parameters with *p* values of less than 0.1 were entered into a final multivariable model. *p* value less than 0.05 was considered statistically significant and prognostic factors that yielded statistical significant were included in the prognostic score. The optimal cut-off point for NLR was determined using the Youden index and for CA-19.9 level was the upper limit of normal.

For the development of the score, each prognostic factor was assigned a particular score based on its β coefficient. The β coefficient for each prognostic factor was divided by the lowest β coefficient and rounded to the nearest whole number [26, 27]. The prognostic score was then applied to each patient. The sample was divided into three prognostic groups (good, intermediate, and poor prognosis). Survival

by prognostic group was represented by Kaplan–Meier curves and *p* values were calculated using the log-rank test. Model calibration and discrimination were assessed by the area under the receiver operating characteristic (ROC) curve [28]. All statistical analyses were carried out using SPSS v.25.

Results

Patient characteristics

A total of 108 patients were included. Baseline characteristics of the patients with OS shorter than 3 months and longer than or equal to 3 months are summarized in Table 1.

The majority ($n=63$, 58.3%) were females with a median age of 65 years (37–86 years). Approximately half of the patients ($n=55$, 50.9%) had smoking history and one-third ($n=36$, 33.3%) had pre-existing diabetes. Most of the pancreatic tumors were localized to the head of the pancreas ($n=62$, 57.4%) and about half of the patients ($n=52$, 48.1%) had metastatic disease at diagnosis. 23 patients (21.3%) had biliary stent.

The most frequently first-line chemotherapy received was FOLFIRINOX ($n=45$, 41.7%), and gemcitabine plus nab-paclitaxel with or without an experimental drug ($n=29$, 26.8%), followed by gemcitabine with or without an experimental drug ($n=17$, 15.7%), gemcitabine plus erlotinib ($n=15$, 13.9%) and XELOX ($n=2$, 1.9%). Most of the patients ($n=47$, 43.5%) achieved stabilization of the disease, 20 patients (18.5%) partial response, one patient (0.9%) complete response and around one-third of the patients ($n=40$, 37%) had disease progression as best response to first-line chemotherapy. TTP after first-line was longer than or equal to 4 months in 56.5% of the patients. The most frequent type of progression to first-line chemotherapy was the appearance of new lesions ($n=60$, 55.6%), followed by an increase in size of previously existing metastases ($n=35$, 32.4%) and local progression ($n=13$, 12%).

The most frequently used 2L chemotherapy was gemcitabine plus capecitabine ($n=24$, 22.2%), followed by XELOX/OFF ($n=18$, 16.6%) and gemcitabine plus nab-paclitaxel ($n=16$, 14.8%). Approximately half of the patients ($n=60$, 55.6%) had two or more metastatic site at the beginning of 2L and 40.7% of the patients had one metastatic site. The most frequent site of metastasis was the liver ($n=77$, 71.3%), followed by the lung ($n=39$, 36.1%) and the peritoneum ($n=33$, 30.6%).

Prognostic factors of OS in patients receiving 2L

With a median follow-up of 6.74 months, a total of 105 patients (97.2%) had confirmed progressive disease to 2L

and 102 patients (94.4%) had died. The median PFS after 2L was 2.60 months (95%CI 2.14–3.05) and the median OS was 5.10 months (95%CI 4.02–6.17).

In the univariate analysis, we identified eight prognostic factors associated with OS shorter than 3 months (Table 2). In the multivariate model, only three independent variables were directly associated with OS shorter than 3 months: TTP shorter than 4 months after first-line treatment (OR 4.53 [95%CI 1.28–16.00] $p=0.01$), NLR greater than 3 at the beginning of 2L (OR 9.07 [95%CI 1.82–45.16] $p=0.01$) and CA-19.9 level higher than the upper limit of normal at the beginning of 2L (OR 7.83 [95%CI 1.30–49.97] $p=0.02$) (Table 3).

Development a prognostic score

The prognostic score was calculated by assigning one point to each of the variables identified as independent prognostic factors in the multivariate analysis.

The sum of all points resulted in an individual score that ranged from 0 to 3. Patients were classified into three prognostic groups: good (0–1 points), intermediate (2 points) and poor prognosis (3 points). The proportion of patients classified as good, intermediate and poor prognosis were 37%, 38% and 25%, respectively. There was a significant difference in OS among the three prognostic groups: good prognosis, median OS of 9.43 months (95%CI 5.55–13.31); intermediate prognosis, median OS of 6.63 months (95%CI 4.33–8.93) and poor prognosis, median OS 1.93 months (95%CI 1.65–2.21) ($p < 0.001$) (Fig. 1). The number of patients with OS shorter than 3 months in each group was 2.5%, 26.8% and 70.4%, respectively.

The area under the ROC curve for the prognostic score was 0.84 (95%CI 0.76–0.91), suggesting that the model is accurate.

Validation of the prognostic score of Sinn et al

We validated the prognostic score developed by Sinn et al. [29] in our cohort. This prognostic score included the following variables: Karnofsky performance status at start of 2L treatment (90–100% assigned 1 point, 80% or less 2 points), CA-19.9 level at the beginning of 2L (less than 37 U/MI assigned 1 point, 37–1000 U/MI 2 points, greater than 1000 U/MI 3 points) and TTP after first-line therapy (4 months or longer assigned 1 point, less than 4 months 2 points).

We also observed significant differences in OS among the three prognostic groups: good prognosis (median OS of 7.16 months [95%CI 3.63–10.69]), intermediate prognosis (median OS of 4.86 months [95%CI 1.20–8.53]) and poor prognosis (median OS 3.03 months [95%CI 0.66–5.40]),

Table 1 Baseline characteristics of the patients with OS shorter than 3 months and OS longer than or equal to 3 months

Characteristics	Total (N= 108)	Patients with OS < 3 months (N= 31)	Patients with OS ≥ 3 months (N= 77)
Age at the beginning of 2L–n° (%)			
< 70 years	70 (64.8)	22 (71)	48 (62.3)
≥ 70 years	38 (35.2)	9 (29)	29 (37.3)
Sex–n° (%)			
Male	45 (41.7)	12 (38.7)	33 (42.9)
Female	63 (58.3)	19 (61.3)	44 (57.1)
Smoking history–n° (%)			
Smoker	27 (25)	5 (16.1)	22 (28.6)
Former smoker	28 (25.9)	5 (16.1)	23 (29.9)
Never smoker	53 (49.1)	21 (67.7)	32 (41.6)
Tumor stage at diagnosis–n° (%)			
Localized/borderline disease	28 (25.9)	7 (22.6)	21 (27.3)
Locally advanced disease	28 (25.9)	8 (25.8)	20 (26)
Advanced PDAC	52 (48.1)	16 (51.6)	36 (46.8)
Thrombosis at diagnosis–n° (%)	16 (14.8)	4 (12.9)	12 (15.6)
First-line chemotherapy regimen–n° (%)			
FOLFIRINOX	45 (41.7)	13 (41.9)	32 (41.6)
Gemcitabine + nab-paclitaxel ± experimental drug	29 (26.8)	4 (12.9)	25 (32.5)
Gemcitabine ± experimental drug	17 (15.7)	7 (22.6)	10 (13)
Gemcitabine + erlotinib	15 (13.9)	6 (19.4)	9 (11.7)
XELOX	2 (1.9)	1 (3.2)	1 (1.3)
RECIST best response to first-line–n° (%)			
Complete response	1 (0.9)	0 (0)	1 (1.3)
Partial response	20 (18.5)	5 (16.1)	15 (19.5)
Stable disease	47 (43.5)	10 (32.3)	37 (48.1)
Progressive disease	40 (37)	16 (51.6)	24 (31.2)
TTP after first-line– n° (%)			
< 4 months	47 (43.5)	22 (71)	25 (32.5)
≥ 4 months	61 (56.5)	9 (29)	52 (67.5)
Second-line chemotherapy regimen–n° (%)			
Gemcitabine + capecitabine	24 (22.2)	5 (16.1)	19 (24.7)
XELOX/OFF	18 (16.6)	4 (12.9)	14 (18.2)
Gemcitabine + nab-paclitaxel	16 (14.8)	3 (9.7)	13 (16.9)
Gemcitabine	15 (13.9)	6 (19.4)	9 (11.7)
FOLFIRI/ nal-IRI	10 (9.3)	1 (3.2)	9 (11.7)
Capecitabine	8 (7.4)	6 (19.4)	2 (2.6)
FOLFIRINOX	5 (4.6)	2 (6.5)	3 (3.9)
Gemcitabine + erlotinib	3 (2.8)	2 (6.5)	1 (1.3)
GEMOX	2 (1.9)	1 (3.2)	1 (1.3)
Experimental drugs	7 (6.5)	1 (3.2)	6 (7.8)
Performance status at the beginning of 2L–n° (%)			
0	23 (21.3)	3 (9.6)	20 (26)
1	59 (54.6)	14 (45.2)	45 (58.4)
2	26 (24.1)	14 (45.2)	12 (15.6)
Pain at the beginning of 2L–n° (%)	51 (47.2)	21 (67.7)	30 (39)
Ascites at the beginning of 2L–n° (%)	15 (13.9)	6 (19.4)	9 (11.7)
Thrombosis at the beginning of 2L–n° (%)	26 (24.1)	8 (25.8)	18 (23.4)
Anemia at the beginning of 2L (gr/dl)–n° (%)	50 (46.3)	20 (4.5)	30 (39)

Table 1 (continued)

Characteristics	Total (N= 108)	Patients with OS <3 months (N=31)	Patients with OS ≥ 3 months (N=77)
NLR at the beginning of 2L–n° (%)			
≤ 3	38 (35.2)	2 (6.5)	36 (46.8)
> 3	70 (64.8)	29 (93.5)	41 (53.2)
Thrombopenia at the beginning of 2L–n° (%)	19 (17.6)	9 (29)	10 (13)
Hyperbilirrubinemia at the beginning of 2L–n° (%)	9 (8.3)	3 (9.7)	6 (7.8)
Hypoalbuminemia at the beginning of 2L–n° (%)	31 (28.7)	13 (41.9)	18 (23.4)
CA-19.9 elevation at the beginning of 2L–n° (%)	79 (73.1)	29 (93.5)	50 (64.9)

PDAC advanced pancreatic ductal adenocarcinoma, FOLFIRINOX 5-fluorouracil, irinotecan and oxaliplatin, XELOX oxaliplatin and capecitabine, TTP time to progression, OFF 5-fluorouracil and oxaliplatin, FOLFIRI 5-fluorouracil and irinotecan, nal-IRI 5-fluorouracil and nanoliposomal irinotecan, GEMOX gemcitabine and oxaliplatin, NLR neutrophil-to-lymphocyte ratio

Table 2 Univariate binary logistic regression analysis of potential prognostic factor for OS shorter than 3 months

Prognostic factors	OR	95%CI	p =
Age (≥ 70 years)	1.47	0.59–3.64	0.39
Sex (male)	1.18	0.50–2.78	0.69
Smoking history (smoker)	2.08	0.70–6.10	0.18
Pre-existing diabetes (yes)	2.07	0.79–5.40	0.13
History of previous chronic pancreatitis (yes)	1.75	0.45–6.69	0.41
Presence of biliary stent (yes)	1.18	0.41–3.34	0.75
Tumor localization (body and tail)	1.03	0.44–2.41	0.93
Tumor stage at diagnosis (advanced PDAC)	1.21	0.52–2.79	0.64
Thrombosis at diagnosis (yes)	1.24	0.36–4.21	0.72
RECIST best response to first-line (PD/SD)	1.36	0.45–4.11	0.58
TTP after first-line (<4 months)	5.08	2.04–12.63	0.00
Type of progression to first-line (increased in the number/size of metastasis)	2.41	0.50–11.60	0.27
Number of metastatic sites at the beginning of 2L (≥ 2)	1.68	0.71–3.97	0.23
Liver metastasis at the beginning of 2L (yes)	1.02	0.40–2.56	0.96
Lung metastasis at the beginning of 2L (yes)	1.26	0.52–3.06	0.59
Peritoneal metastasis at the beginning of 2L (yes)	1.37	0.56–3.33	0.48
Other locations of metastasis at the beginning of 2L (yes)	1.46	0.57–3.72	0.42
Performance status at the beginning of 2L (2)	4.46	1.74–11.39	0.00
Pain at the beginning of 2L (yes)	3.29	1.36–7.94	0.00
Ascites at the beginning of 2L (yes)	1.81	0.58–5.61	0.30
Thrombosis at the beginning of 2L (yes)	1.14	0.43–2.98	0.78
Anemia at the beginning of 2L (< 11.8 gr/dl)	2.84	1.19–6.77	0.01
NLR at the beginning of 2L (> 3)	12.73	2.83–57.12	0.00
Thrombopenia at the beginning of 2L (< 150 × 10 ⁹ /l)	2.74	0.98–7.61	0.05
Hyperbilirrubinemia at the beginning of 2L (> 1.2 mg/dl)	1.26	0.29–5.42	0.74
Hypoalbuminemia at the beginning of 2L (< 3.5 gr/dl)	2.36	0.97–5.75	0.05
High CA-19.9 at the beginning of 2L (≥ 37 UI/ml)	7.83	1.73–35.35	0.00

Significant results are in bold

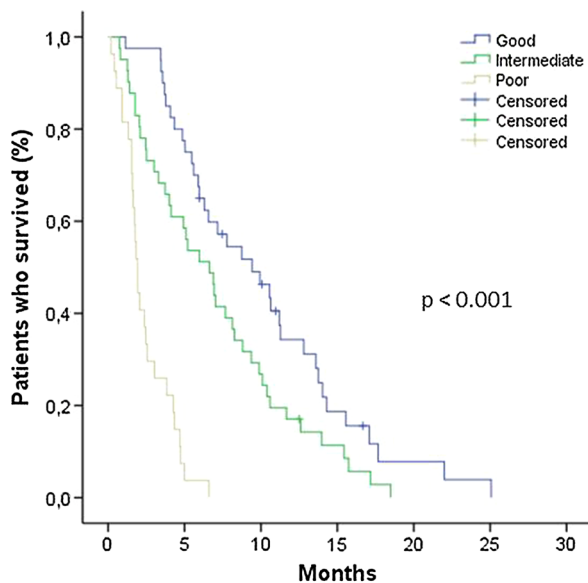
PDAC advanced pancreatic ductal adenocarcinoma, PD progressive disease, SD stable disease, TTP time to progression, NLR neutrophil-to-lymphocyte ratio

Table 3 Multivariate binary logistic regression analysis of potential prognostic factor for OS shorter than 3 months

Prognostic factors	β	OR	95%CI	<i>p</i>	Score
TTP after first-line (< 4 months)	1.511	4.53	1.28–16.00	0.01	1
Performance status at the beginning of 2L (2)	0.634	1.88	0.41–8.47	0.4	
Pain at the beginning of 2L (yes)	0.306	1.35	0.38–4.75	0.63	
Anemia at the beginning of 2L (< 11.8 gr/dl)	1.084	2.95	0.90–9.65	0.07	
NLR at the beginning of 2L (> 3)	2.205	9.07	1.82–45.16	0.01	1
Thrombopenia at the beginning of 2L (< 150 × 10 ⁹ /l)	1.326	3.76	0.87–16.31	0.07	
Hypoalbuminemia at the beginning of 2L (< 3.5 gr/dl)	-0.444	0.64	0.17–2.40	0.51	
High CA-19.9 at the beginning of 2L (≥ 37 UI/ml)	2.059	7.83	1.30–49.97	0.02	1

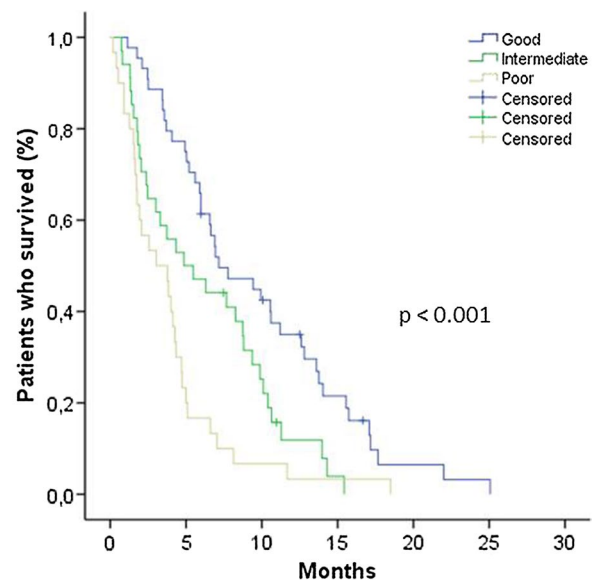
Significant results are in bold

TTP time to progression, NLR neutrophil-to-lymphocyte ratio



Good	40	31	17	6	2	1	0
Intermediate	41	24	11	4	0	0	0
Poor	27	2	0	0	0	0	0

Fig. 1 Kaplan–Meier curves for overall survival among the three prognostic groups (good, intermediate and poor prognosis)



Good	44	33	18	8	2	1	0
Intermediate	34	17	8	1	0	0	0
Poor	30	7	2	1	0	0	0

Fig. 2 Kaplan–Meier curves for the validation of the prognostic score of Sinn et al

($p < 0.001$) (Fig. 2). The area under the ROC curve for the prognostic score of Sinn et al., was 0.71 (95%CI 0.61–0.81).

Discussion

The benefit of 2L treatment in advanced PDAC is marginal, so there is some uncertainty about its use [25]. In addition, the standard of care treatment in second and subsequent lines is not well-defined. Therefore, accurate estimation of life expectancy is critical to plan the treatment strategy. The median OS usually ranges from 4 to 7 months [5], which resembles our cohort. Other series have also reported similar results in OS [8–10, 12, 14].

Owing to the absence of predictive response factors in second and subsequent lines, the identification of prognostic factors could help in therapeutic decisions-making. In our cohort, TTP shorter than 4 months after first-line treatment, NLR greater than 3 and CA-19.9 level higher than the upper limit of normal at the beginning of 2L were independent prognostic factors for OS shorter than 3 months. These three variables play a crucial role in the prognosis of patients with advanced PDAC. Short TTP after first-line is a strong negative prognostic factor for time to second progression and residual survival [30]. High NLR is an unfavorable predictor of OS in patients with advanced PDAC at the time of diagnosis and it could be a novel marker of survival evaluation [31, 32]. CA-19.9 level higher than the upper limit of normal is a reliable prognostic marker for survival in patients with

advanced PDAC during first-line [33] and 2L chemotherapy [34].

A simple prognostic score could be a useful tool for clinical management by predicting patient life expectancy. Following the procedure stated above, we were able to develop a new prognostic score that included these three significant prognostic factors (CA-19.9 level, NLR value and TTP after first-line). This score allows reliable differentiation into three prognosis groups (good, intermediate and poor) with significant differences in OS. Thus, the median OS was 1.93, 6.63 and 9.43 months for poor, intermediate and good prognostic groups, respectively. Sinn et al. [29] developed another prognostic score in patients with advanced PDAC receiving 2L treatment, which also included CA-19.9 level and TTP after first-line. In addition, this score included Karnofsky performance status. We validated this score in our cohort, obtaining significant differences in OS among the three prognostic groups. However, the area under the ROC curve was lower than with our prognostic score, suggesting that our model could be more accurate. Furthermore, Sinn et al., only included patients up to 2012; therefore, they did not include information of patients treated with FOLFIRINOX and gemcitabine plus nab-paclitaxel, regimens which are the current standard first-line treatment. Others authors have developed several prognostic nomograms for predicting survival of patients with advanced PDAC prior to the administration of 2L chemotherapy using clinical and analytical parameters [35–37]. The advantage of our score compared to these nomograms is that our score is easier to use in routine clinical practice. In addition, this score is able to identify poor prognosis patients regardless of the performance status. Knowing the prognosis of patients before starting 2L treatment could help us keep the patient and his family informed, make decision-making easier, optimize care results and classify patients in homogeneous groups for clinical trials. In addition, all patients should be given the opportunity to consult with a nutritionist, a social worker and palliative care health providers for assistance in terms of care, symptom management and end-of-life discussions, mainly those in the intermediate and poor prognostic groups.

There are several limitations to our study, including its retrospective nature, and the involvement of only one institution. In addition, we did not include information concerning the dose of the chemotherapy received as well as its tolerability. Despite these limitations, this study provides relevant information about prognostic factors for survival, which should be considered in advanced PDAC patients receiving 2L treatment. Furthermore, we have developed a prognostic score to help in decision-making for the initiation of 2L treatment. This prognostic score is accurate with an area under the ROC curve of 0.84. External validation will definitively confirm the relevance and the prognostic usefulness of our score in the future.

In conclusion, the survival of patients with advanced PDAC who received 2L treatment was poor. The identification of prognostic factors might be useful to decide which patients should receive 2L treatment. In our cohort, TTP shorter than 4 months after first-line treatment, NLR greater than 3 and CA-19.9 level higher than the upper limit of normal at the beginning of 2L were associated with shorter OS. Taking into consideration these variables, we developed a prognostic score to help in therapeutic decisions-making. Further prospective studies are needed to derive definitive conclusions.

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Author contributions Conceptualization: JF, LG-S; data collection: LG-S, DM, JAG-C; data analysis: JF, LG-S; writing—original draft preparation: JF, LG-S; writing—review and editing: JF, DV, JV, DM-P, JAGC, IG, AC.

Declarations

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval and compliance with ethical standards This study was approved by the Ethics Committee of the La Paz University Hospital (code HULP: PI-2043), and was conducted in accordance with ethical standards of the Helsinki Declaration of the World Medical Association.

Informed consent Local ethical committee approved the use of anonymized historic data for the study and waived informed consent from patients.

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