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CLINICAL STUDY

Prognostic and predictive significance of inflammatory markers in patients with locally advanced unresectable and metastatic pancreatic cancer treated with first-line chemotherapy FOLFIRINOX or Gemcitabine/Nabpaclitaxel

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ABSTRACT

BACKGROUND: Advanced pancreatic ductal adenocarcinoma (PDAC) remains a disease with a dismal prognosis, significantly limited therapeutic options, and few innovative drugs. Inflammation plays a significant role in the development and progression of PDAC. Systemic inflammatory indexes reflect the anti-tumor inflammatory capacity of and are of prognostic and predictive value in the treatment of patients with PDAC.

METHODS: In our retrospective study, we investigated the prognostic and predictive significance of inflammatory markers in chemonaive patients with locally advanced unresectable pancreatic cancer (LAPC) and metastatic pancreatic cancer (mPDAC), in relation to progression-free survival (PFS) and overall survival (OS). Survival analysis was conducted using the Kaplan–Meier method with log-rank tests in univariate analysis. We used multivariate Cox regression analysis to determine the impact of inflammatory markers on survival time.

RESULTS: The present clinical study included 46 patients with LAPC and mPDAC treated with FOLFIRINOX (folinic acid, fluorouracil, irinotecan, oxaliplatin) or GEM/Nab-P (gemcitabine/nab-paclitaxel) as first-line chemotherapy regimens. Performance status (PS) ECOG 0–1, neutrophil-to-lymphocyte ratio (NLR)≤2.09 and the prognostic nutritional index (PNI)≥49.09 were associated with significantly longer OS in the analyzed patient cohort, Multivariate analysis confirmed PS, NLR and PNI as independent prognostic factors for OS.

CONCLUSION: In our cohort of patients with advanced PDAC, PS, NLR and PNI were confirmed as independent prognostic factors for OS *(Tab. 9, Fig. 2, Ref. 82)*. Text in PDF www.elis.sk

KEY WORDS: pancreatic cancer, inflammatory markers, tumor microenvironment, chemotherapy.

Introduction

Pancreatic cancer (PC) is currently the fourth most common cause of cancer-related death (1).

According to the GLOBOCAN data from 2020, Slovakia has the fourth highest incidence of PC in the world, with projections indicating an increasing trend until 2040 (2). PDAC represents the most common form of exocrine pancreatic cancer, accounting for more than 85% of all pancreatic malignancies (3). The majority of patients with PDAC (80–85%) are diagnosed at advanced stages, presenting with locally advanced or metastatic disease (4). Despite extensive research over the past 40 years, there has been no significant therapeutic progress in the treatment of this disease (5, 6). The current standard of care for pancreatic cancer focuses on chemotherapeutic regimens and surgery (7).

The poor prognosis of PDAC is determined by its genetic profile and is related to the immunosuppressive tumor microenvironment (TME) of PDAC (8–10). The most commonly mutated PDAC genes (*KRAS, TP53, SMAD4*, and *CDKN2A)* play a role in altering TME, particularly in the regulation of local immunity (11, 12, 13). The TME PDAC assists tumor cells in signal transduction, invasion, and distant metastasis, contributing to tumor progression through multiple pathways (14). The stroma-rich TME limits the access of systemic therapies to tumor cells and contributes to the poor clinical outcomes of current treatment strategies (15, 16).

Inflammation is a hallmark of PDAC (17). Numerous chemokines as well as pro-inflammatory cytokines secreted by cancer-associated fibroblasts (CAFs) and infiltrating immune

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cells are present in the TME of PDAC (9). The infiltrate of inflammatory cells is skewed towards an immunosuppressive phenotype with a prevalence of myeloid-derived suppressor cells (MDSCs), M2 macrophages, and regulatory T cells (Tregs) over M1 macrophages, dendritic cells, and effector CD4+ and CD8+ T lymphocytes (18).

Based on the results of the PRODIGE and MPACT clinical trials, FOLFIRINOX and GEM/Nab-P have become the two current standard first-line treatment regimens for advanced pancreatic cancer (19, 20). In the PRODIGE trial, which compared FOLFIRINOX with gemcitabine in patients with advanced PC, FOLFIRINOX increased median OS by 4.3 months (11.1 vs 6.8 months) (19). The MPACT study compared GEM/Nab-P and gemcitabine alone, showing a median overall survival of 8.5 months with GEM/Nab-P compared to 6.7 months with gemcitabine (20). Despite the scientific advances in cytotoxic therapy, median OS for mPDAC patients has not surpassed approximately 1 year over the past decade (19). The few attempts to improve long-term survival outcomes with targeted therapy, alone or in combination, have not demonstrated benefits beyond those of cytotoxic chemotherapy (21–23).

Based on recent evidence, neoadjuvant chemotherapy with FOLFIRINOX and GEM/Nab-P regimens alters the immune microenvironment of PDAC, and different chemotherapy regimens appear to have varying effects (24).

Systemic inflammatory indexes reflect the anti-tumor inflammatory capacity of the host and are of prognostic or even predictive value in the treatment of patients with PDAC. Several reports confirm their prognostic and predictive significance in both localized and advanced stages of PDAC (25–29).

The neutrophil-to-lymphocyte ratio (NLR), also known as Zahorec index, was established by Roman Zahorec (30). It is calculated as a simple ratio between the number of neutrophils and lymphocytes measured in peripheral blood from a complete blood count. NLR serves as a biomarker that connects two components of the immune system: the innate immune response, primarily due to neutrophils, and adaptive immunity, supported by lymphocytes (31, 32). Twenty years of global research have confirmed the utility of NLR across clinical medicine (33, 34). NLR may serve as a reliable parameter of cancer-induced inflammation (30, 34). High NLR value has been associated with unfavorable OS in many solid tumors (33–35). Several studies have been conducted to investigate the prognostic role of NLR in pancreatic cancer (25, 33, 34, 36–39).

The platelet-to-lymphocyte ratio (PLR) is defined as the ratio of platelets to lymphocytes. PLR has emerged in recent years as an effective indicator reflecting the severity of the systemic inflammatory response (40, 41). Elevated PLR is closely related to poor prognosis in various cancers (42, 43) and is associated with unfavorable overall survival in patients with pancreatic cancer (41).

The lymphocyte-to -monocyte ratio (LMR) is a ratio calculated by dividing the absolute lymphocyte count by the absolute monocyte count from a blood test. Lymphocytes are involved in cytotoxic cell death and are associated with the inhibition of tumor cell proliferation and migration (44–46). Lymphopenia typically indicates disease severity and can enable tumor cells to evade the immunity of tumor-infiltrating lymphocytes (TILs) (47). Two meta-analyses have shown that elevated LMR value before treatment can predict a good prognosis in patients with solid tumors (48, 49).

The systemic immune inflammation index (SII) calculated as: P (platelets) x N (neutrophils) / L (lymphocytes), provides a relatively comprehensive view of the balance between host inflammation and immune status (50, 51). This marker was first proposed by Hu et al. and has shown a higher predictive value for cancer prognosis than other inflammatory factors such as NLR and PLR (51–53). However, the prognostic value of SII in PC patients remains controversial. Li et al. conducted a study evaluating the prognostic impact of SII in PC patients through a meta-analysis (28), finding that high SII value was associated with poor OS in these patients (28).

The prognostic nutritional index (PNI) is calculated based on serum albumin concentration and peripheral blood lymphocyte count (10 × serum albumin (g/dl) + 0.005 × total lymphocyte count (/mm3)), serving as an indicator of the nutritional and immune status of cancer patients (54, 55). Many studies have recognized PNI as an independent prognostic indicator of various malignancies (55–57). Geng et al identified PNI as an independent prognostic factor for OS in patients with advanced PDAC (58).

Currently, no predictive biomarkers are available in routine clinical practice to identify patients with advanced PDAC who are more likely to benefit from FOLFIRINOX or GEM/Nab-P.

Based on the above, the focus of our study was to investigate the prognostic and predictive significance of inflammatory markers in chemonaive patients with advanced PDAC (LAPC and mPDAC), treated with first-line chemotherapy regimens FOLFIRINOX or GEM/Nab-P.

Materials and methods

In this retrospective study, we reviewed data of chemonaive patients with LAPC or mPDAC, treated with FOLFIRINOX or GEM/Nab-P as first-line chemotherapy. The study included patients treated between January 2010 and December 2021 at the National Cancer Institute in Bratislava at the Department of Clinical Oncology, University Hospital of Merciful Brothers in Bratislava. All patients had histologically confirmed PDAC and were clinically examined with complete medical history, physical examination, and laboratory and imaging tests to determine the extent of the disease.

Inflammatory indexes were calculated using established formulas based on the absolute number of individual blood elements in peripheral blood and serum albumin levels assessed prior to the administration of the first cycle of the first-line cytostatic treatment.

Statistical evaluation of the dataset was conducted using the computer program IBM SPSS Statistics, Version 29.0.0.0 (241). Overall survival was calculated from the date of diagnosis to the date of patient death in months and progression-free survival was calculated from the date of diagnosis to the date of diagnosed disease progression during or after first-line cytostatic therapy.

Receiver-operating characteristic (ROC) analysis was used to find the optimal cut-off values of the inflammatory markers, balancing marker sensitivity and specificity. The Younden index (J) was employed to determine the cut-off value that maximizes marker efficiency (59, 60). Descriptive statistical analysis using crosstabs was used to determine the positive and negative predictive values of each marker. Cut-off values for the inflammatory indexes were assessed based on their ability to predict OS of≥18 months as identified through ROC analysis and the Younden index.

In our patient cohort, we evaluated the prognostic and predictive significance of the individual inflammatory markers in relation to PFS and OS across various categories, including both chemotherapy regimens collectively and separately for LAPC or mPDAC, as well as according to performance status (PS) categorized by Eastern Cooperative Oncology Group (ECOG), ECOG 0–1 and ECOG 2.

Survival analysis was performed using the Kaplan–Meier method with log-rank tests in univariate analysis. Multivariate Cox regression analysis was performed to determine the impact of clinicopathological variables, including the marker CA 19-9, and inflammatory markers, on survival time. The level of statistical significance was set at $p<0.05$.

Results

Patient characteristics

A total of 46 patients met the entry criteria and were included in the analysis with complete admission data. The median age of patients was 58 years (range 37–76 years), with 31 patients (67%) younger than 65 years, 14 patients (30%) younger than 50 years and 7 patients (15%) younger than 45 years. The median OS of patients was 15 months (range 4–66 months), and the median PFS was 9 months (range 2–43 months).

A summary of the characteristics of the analyzed patient cohort is presented in Table 1.

Tab. 1. Patient characteristics.

Variable		No (%)
Age		
	≥65 years old	15 (33%)
	< 65 years old	31 (67%)
Gender		
	male	23 (50%)
	female	23 (50%)
Status of disease		
	LAPC	14 (30%)
	mPDAC	32 (70%)
ECOG PS		
	ECOG 0–1	39 (85%)
	LAPC	14 (30%)
	mPDAC	25 (55%)
	ECOG 2	7 (15%)
	LAPC	0 (0%)
	mPDAC	7 (15%)
1st line chemotherapy		
	FOLFIRINOX	33 (72%)
	LAPC	12 (26%)
	mPDAC	21 (46%)
	GEM/Nab-P	13 (28%)
	LAPC	2 (4%)
	mPDAC	11 (24%)

ECOG PS – performance status according to Easter Cooperative Oncology Group; LAPC – locally advanced pancreatic cancer; mPDAC – metastatic pancreatic adenocarcinoma; FOLFIRINOX – 5-fluorouracil-folinic acid-irinotecan-oxaliplatin; GEM/Nab-P – gemcitabin/nab-paclitaxel

Statistical analysis

Patients were stratified according to the clinicopathological categories and markers CA 19-9, NLR, PLR, LMR, PNI, SII in terms of OS and PFS.

The following cut-off values for consecutive markers were used in the analysis:

Tab. 2. Characteristics of cut-off value of markers CA 19-9 and inflammatory indexes.

Variable	Cut-off value OS≥18 M	Sensitivity	Specificity	Positive predictive value	Negative predictive value	Pearson Chi square	p	AUC	Younden index
CA 19 -9 U/ml	≤361.95	82.4%	55.2%	81.3%	82.4%	3.490	0.062	0.546	0.272
NLR	≤2.09	64.7%	17.2%	80%	64.7%	10.644	0.001	0.710	0.475
PLR	≤200.39	82.4%	65.5%	76.9%	82.4%	1.681	0.195	0.552	0.168
LMR	≥2.48	47.1%	24.1%	50%	58.8%	1.470	0.225	0.521	0.229
PNI	≥49.09	70.6%	48.3%	75%	70.6%	2.171	0.141	0.575	0.223
SII	≤396.52	41.2%	10.3%	72.2%	41.2%	5.988	0.014	0.629	0.308

	Minimum	Maximum	Median	Average	SD	Standard error
CA 19 -9 U/ml	0.8	707953.4	166.75	16285	104260.6	15372.4
NLR	0.89	11.51	2.4	2.99	2.005	0.296
PLR	71.61	325.86	151.76	165.94	62.447	9.207
LMR	0.82	8.13	2.76	2.99	1.261	0.189
PNI	34.0	56.09	49.75	48.60	4.888	0.721
SII	198.98	2829.12	671.89	879.25	645.82	95.221

CA 19-9 – cancer antigen 19-9; NLR – neutrophil-to-lymphocyte ratio; PLR – platelet-to-lymphocyte ratio; LMR – lymphocyte-to-monocyte ratio; PNI – prognostic nutritional index; SII – systemic immune-inflammation index; AUC – area under curve

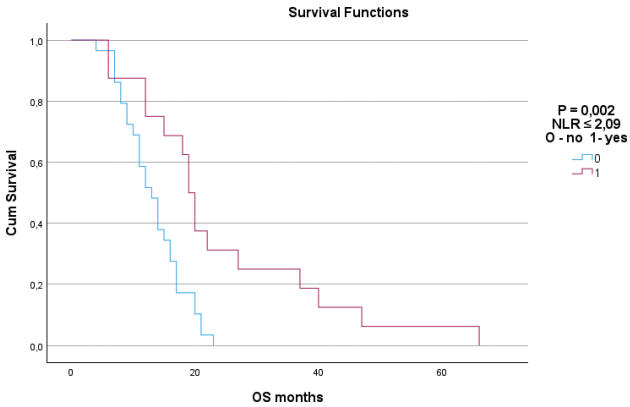

Fig. 1. Kaplan–Meier analysis of overall survival according to NLR. OS – overall survival; P – P-value; Cum Survival – cumulative survival; NLR – neutrophil to lymphocyte ratio

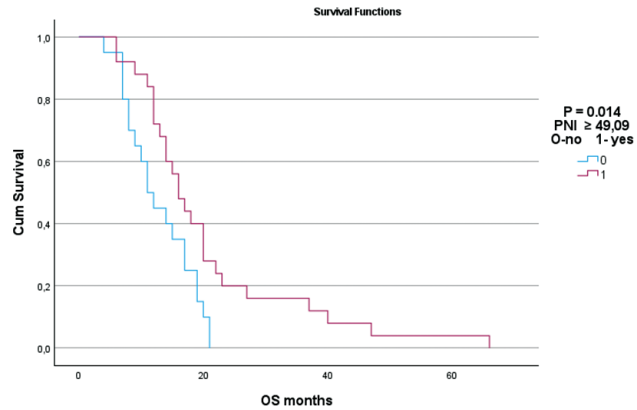

Fig. 2. Kaplan–Meier analysis of overall survival according to PNI. OS – overall survival; P – P-value; Cum Survival – cumulative survival; NLR – neutrophil-to-lymphocyte ratio

CA 19-9≤361.95 U/ml; NLR≤2.09; PLR≤200.39; LMR≥2.48; PNI≥49.09; SII≤396.52.

Characteristics of markers CA 19-9 and inflammatory indexes are presented in Table 2.

Univariate analysis of OS showed that PS ECOG 0–1 vs ECOG 2 (P=0.010), NLR≤2.09 vs NLR>2.09 (p=0.002), and PNI≥49.09 vs PNI<49.09 (p=0.014), were significantly associated with longer OS (Figs 1 and 2).

The impact of age (p=0.754), cancer stage (p=0.557), type of chemotherapy (p=0.622), CA 19-9 level (p=0.472), PLR (p=0.471), LMR (p=0.560), and SII (p=0.080) was shown to be statistically insignificant. Longer OS was observed in patients aged≥65 years and those with mPDAC as well as in association with FOLFIRINOX treatment, CA 19-9≤361.95 U/ml, PLR>200.39, LMR<2.48, and SII≤396.52.

In multivariate analysis, PS ECOG (HR 2.85, 95% CI (1.21–6.69), p=0.016), NLR (HR 0.34, 95% CI (0.17–0.71), p=0.004) and PNI (HR 0.47, 95% CI (0.25–0.89), p=0.021) were confirmed as independent prognostic factors for OS.

Kaplan–Meier analysis of PFS did not yield statistically significant results for the investigated variables, except for the borderline statistical significance in median PFS differences for PNI≥49.09 vs PNI<49.09 (p=0.051), with longer PFS associated with PNI≥49.09. The effects of other analyzed variables on PFS were as follows: longer PFS was associated with age<65 years (p=0.891), mPDAC (p=0.720), PS ECOG 0–1 (p=0.071), CA 19-9≤361.95 U/ml (p=0.321); NLR≤2.09 (p=0.334); PLR>200.39 (p=0.635); LMR<2.48 (p=0.385) and SII≤396.52 (p=0.254). The chemotherapy regimens based on FOLFIRINOX or GEM/Nab-P had a similar impact on PFS, with a median PFS of 9 months (p=0.941).

The results of univariate and multivariate analyses for OS, and PFS are summarized in Tables 3 and 4.

The analysis also showed some noteworthy results, although they were not statistically significant. PLR≤200.39 was associated with lower OS and PFS median values compared to PLR>200.39, contrary to our anticipation of longer OS and PFS in the subgroup with PLR≤200.39. Similarly, LMR≥2.48 was associated with lower OS and PFS median values compared to LMR<2.48 despite our expectation of longer OS and PFS in the subgroup with LMR≥2.48. The patient with the shortest PFS (2 months) and OS (4 months) had the highest NLR and the lowest LMR values in the analyzed cohort (11.51 and 0.82, respectively). In contrast, the patient with the lowest NLR value in the cohort (NLR=0.89) had an LMR value of 4.85, which exceeded the calculated cut-off value for LMR. This patient experienced PFS and OS durations of 23 and 41 months, respectively, both exceeding their respective median values in this dataset.

The patient with the longest OS in the cohort (66 months) had all inflammatory index values within the prognostically favorable range: NLR 1.49 (NLR≤2.09), PLR 134.68 (PLR≤200.39), LMR 3.04 (LMR≥2.48), PNI 52.75 (PNI≥49.09), and SII 346.13 (SII≤396.52). All three mentioned patients had mPDAC and were treated with the FOLFIRINOX cytostatic regimen.

We also conducted a combined analysis of the prognostic and predictive significance of inflammatory markers in relation to PDAC stage, PS according to ECOG, first-line chemotherapy regimen, and their impact on OS and PFS of PDAC patients in our patient cohort. The results are presented in Tables 5–9.

In both LAPC and mPDAC subgroups, the patients with NLR≤2.09 exhibited a significantly higher median OS compared to those with NLR>2.09 (p=0.003). Among subgroups stratified by chemotherapy regimen (FOLFIRINOX and GEM/Nab-P) (p=0.004) and PS ECOG 0–1 (p=0.006), only the PS ECOG 2 subgroup exhibited a lower median OS value. By multivariate analysis, NLR was confirmed as an independent prognostic/predictive factor for OS in the LAPC and mPDAC subgroups (HR 0.30, 95% CI (0.14–0.68), p=0.004); PS ECOG 0–1 (HR 0.38, 95% CI (0.18–0.81), p=0.012), and in the CHET FOLFIRINOX and GEM/Nab-P subgroups (HR 0.30, 95% CI (0.14–0.64), p=0.002). Regarding PFS assessment, there were no statistically significant results in the individual subcategories.

In the LAPC and mPDAC subgroups, patients with PNI≥49.09 exhibited a higher OS median value compared to those with

PNI<49.09; the difference was statistically significant (p=0.025). For both the FOLFIRINOX and the GEM/Nab-P regimens, the difference resulted in higher OS median value (p=0.030). Patients with PNI≥49.09 yielded higher median PFS value compared to those with PNI<49.09 in the LAPC and mPDAC subgroups (p=0.039).

Multivariate analysis confirmed PNI as an independent prognostic factor for OS for LAPC and mPDAC subgroups (HR 0.47, 95% CI (0.24–0.91), p=0.026) and for both FOLFIRINOX and GEM/Nab-P regimens (HR 0.47, 95% CI (0.28–0.90), p=0.022). PNI was not validated as an independent prognostic factor for PFS in the LAPC and mPDAC subgroups (HR 0.56, 95% CI (0.28–1.00), Pp0.050)**.**

PLR, LMR, and SII did not exhibit a significant statistical impact on OS or PFS in any individual subcategories.

Discussion

The size of the analyzed set and the imbalance of the compared arms in some analyses had an impact on the statistical results in some cases. One reason for not including a sufficient number of patients was the gradual introduction of cytostatic regimens, FOLFIRINOX and GEM/Nab-P, for the treatment of advanced PDAC, based on the results of clinical trials. Specifically, the FOLFIRINOX regimen has been in use since 2011, and Gem/Nab-P since 2013. Additionally, the GEM/Nab-P regimen was primarily limited to first-line treatment in patients with poorer performance status, such as those with Karnofsky score (KS) of 70–80%, or PS ECOG of 1–2 (19, 20, 61).

There was an apparent shift in age at diagnosis to younger age categories in the analyzed set.

Tab. 3. Univariate and multivariate analysis for independent OS prognostic factors.

Variable	Number of Patients	OS Average	OS Median	Univariate analysis		Multivariate analysis		
				p	Chi-square	HR	(95% CI)	p
Age				0.754	0.098			
≥65 years	14	15.86	17.00					
<65 years	31	17.68	14.00					
Status of disease				0.557	0.344			
LAPC	13	19.00	14.00					
mPDAC	32	16.34	15.00					
ECOG PS				**0.010**	6.687	2.85	1.21–6.69	0.016
				0.010	6.687			
ECOG 0-1	38	18.37	15.00					
ECOG 2	7	10.29	9.00					
1st line chemotherapy				0.622	0.243			
GEM/Nab-P	12	15.58	12.00					
FOLFIRINOX	33	17.67	15.00					
CA 19-9 U/ml				0.472	0.516			
≤361.95	29	17.48	17.00					
>361.95	16	16.49	14.00					
NLR				**0.002**	9.812	0.34	0.17–0.71	**0.004**
≤2.09	16	24.16	19.00					
>2.09	29	13.24	13.00					
PLR				0.471	0.519			
≤.200.39	32	17.84	14.00					
>200.39	13	15.31	15.00					
LMR				0.560	0.340			
≥2.48	31	17.19	14.00					
< 2.48	14	16.93	16.00					
PNI				**0.014**	6.009	0.47	0.27–0.89	**0.021**
≥49.09	25	20.52	16.00					
< 49.09	20	12.85	11.00					
SII				0.080	3.060			
≤396.52	10	23.70	19.00					
>396.52	35	15.23	14.00					

OS – overall survival; ECOG PS – performance status according Easter Cooperative Oncology Group; FOLFIRINOX – 5-fluorouracil-folinic acid-irinotecan-oxaliplatin; GEM/Nab-P; gemcitabin/nab-paclitaxel; CA 19-9 – cancer antigen 19-9; NLR – neutrophil to lymphocyte ratio; PLR – platelet to lymphocyte ratio; LMR – lymphocyte to monocyte ratio; PNI – prognostic nutritional index; SII – systemic immune-inflammation index

Tab. 4. Univariate and multivariate analysis for independent PFS prognostic factors.

Variable	Number of Patients	OS Average	OS Median	Univariate analysis p	Univariate analysis Chi-square	Multivariate analysis HR	Multivariate analysis (95% CI)	Multivariate analysis p
Age				0.891	0.019			
≥65 years	15	9.67	8.00					
<65 years	31	9.81	10.00					
Status of disease				0.720	0.129			
LAPC	14	8.86	5.00					
mPDAC	32	10.16	9.00					
ECOG PS				0.071	3.269			
ECOG 0-1	39	10.41	10.00					
ECOG 2	7	6.14	4.00					
1st line chemotherapy				0.941	0.005			
GEM/Nab-P	13	9.54	9.00					
FOLFIRINOX	33	9.85	9.00					
CA 19-9				0.321	0.985			
≤361.95	30	9.97	10.00					
>361.95	16	9.38	7.00					
NLR				0.334	0.932			
≤2.09	16	11.50	9.00					
>2.09	30	8.83	7.00					
PLR				0.635	0.225			
≤200.39	32	9.67	9.00					
>200.39	13	10.00	11.00					
LMR				0.385	0.755			
≥2.48	32	9.38	7.00					
< 2.48	14	10.64	10.00					
PNI				**0.051**	3.820	0.58	0.32–1.06	0.076
≥49.09	26	11.54	10.00					
<49.09	20	7.45	5.00					
SII				0.254	1.302			
≤396.52	10	13.00	9.00					
> 396.52	36	8.86	7.00					

PFS – progression-free survival; ECOG PS – performance status according Easter Cooperative Oncology Group; FOLFIRINOX – 5-fluorouracil-folinic acid-irinotecan-oxaliplatin; GEM/Nab-P – gemcitabin/nab-paclitaxel; CA 19-9 – cancer antigen 19-9; NLR – neutrophil to lymphocyte ratio; PLR – platelet to lymphocyte ratio; LMR – lymphocyte to monocyte ratio; PNI –. prognostic nutritional index; SII – systemic immune-inflammation index

In the Slovak Republic, as well as globally, this may be related to both the fundamental lack of screening for PDAC, and the prevalence of other non-cancerous diseases that increase the risk of cancer, including PDAC. The incidence of these conditions is associated with lifestyle habits and the presence of risk factors, particularly obesity and smoking which elevate the risk of PDAC (62, 63, 64, 65). Typically, the incidence of PDAC before the age of 45 years is rare, with an obvious exception of cases with a known increased risk of developing PDAC (65). In our patient cohort, the median OS across all variables was 15 months. By cytostatic regimen, the median OS was 15 months in the FOLFIRINOX subgroup and 12 months in the GEM/Nab-P 12 subgroup. These survival rates were longer than those reported in clinical trials, setting the standard for first-line treatment of advanced PDAC (19, 20, 66).

The determination of the cut-off value itself was essential to the subsequent statistical analyses. Finding the optimal cut-off point for some indexes based on ROC analysis, Younden's index, the positive predictive value of the marker proved challenging. This difficulty stemmed from both the size of the cohort (fewer patients) and the wide range of values observed across the inflammatory indexes assessed. However, the cut-off values that reflected strong marker characteristics tended to yield statistically significant results in subsequent analyses, particularly for NLR.

The baseline values of inflammatory indexes at the time of diagnosis, before the first cycle of chemotherapy in treatment-naive patients, seem to predict the prognosis of patients with advanced PDAC. It appears that a comprehensive assessment of multiple inflammatory indexes could provide a more accurate reflection of the immune system status, individual immune components, overall inflammatory capacity, and potentially the TME of PDAC, compared to assessing single inflammatory indexes in isolation.

The combined assessment of inflammatory indexes, along with a thorough evaluation of clinicopathological categories, including OM CA 19-9, could enhance the accuracy of prognosis determination in patients with advanced PDAC and facilitate treatment decision-making.

In their review article, Firment and Hulin demonstrate the utility of inflammation-based scores (such as cancer inflammation prognostic score (CIPS), hemoglobin x albumin/lymphocyte x platelets score (HALP) and SII) as well as ratios (such as C-reactive protein-to-albumin ratio (CAR), C-reactive protein-to-lymphocyte ratio (CLR), fibrinogen-to-albumin ratio (FAR) and NLR) for monitoring inflammation throughout the course of cancer development, including stratification, diagnosis, and prognosis (30, 33, 34, 67–70).

Turner et al demonstrated in their study that a combination of local inflammatory cell analysis and systemic inflammatory response can significantly aid in estimating prognosis and tailoring treatment plans for patients with colorectal cancer (71).

Yang et al, in their study, showed that a nomogram model based on the prognostic immune-inflammatory-nutrient score (PIIN), derived from fibrinogen, NLR, SII, PNI, and albumin-bilirubin (ALBI) scores, can serve as a valuable method for prognostic stratification and postoperative follow-up in customizing individualized treatment for pancreatic cancer (72). Neumann et

Tab. 5. Univariate and multivariate analysis for NLR in categories OS and PFS.

Variable	NLR	Number of Patients	OS Average months	OS Median months	Univariate analysis OS		Multivariate analysis OS		
					Chi-square	p	HR	(95% CI)	p
M stage					9.127	**0.003**	0.30	0.14–0.68	**0.004**
LAPC	NLR>2.09	6	11.50	11.00					
	NLR≤2.09	7	25.43	20.00					
mPDAC	NLR>2.09	23	13.70	14.00					
	NLR≤2.09	9	23.11	19.00					
PS ECOG									
ECOG 0-1	NLR>2.09	23	13.83	14.00	7.445	**0.006**	0.38	0.18–0.81	**0.012**
	NLR≤2.09	15	25.33	20.00					
ECOG 2	NLR>2.09	6	11.00	9.00					
	NLR≤2.09	1	6.00	6.00					
CHET					8.422	**0.004**	0.30	0.14–0.64	**0.002**
FOLFIRINOX	NLR>2.09	22	14.0	14.00					
	NLR≤2.09	11	25.0	19.00					
GEM/Nab-P	NLR>2.09	7	10.86	11.00					
	NLR≤2.09	5	22.20	22.00					
Variable	NLR	Number of Patients	PFS Average months	PFS Median months	Univariate analysis PFS		Multivariate analysis PFS		
					Chi-square	p	HR	(95% CI)	p
M stage					0.622	0.430			
LAPC	NLR>2.09	7	8.14	5.00					
	NLR≤2.09	7	9.57	11.00					
mPDAC	NLR>2.09	23	9.04	10.00					
	NLR≤2.09	9	13.00	9.00					
PS ECOG					2.602	0.107			
ECOG 0-1	NLR>2.09	24	9.42	9.00					
	NLR≤2.09	15	12.00	10.00					
ECOG 2	NLR>2.09	6	6.50	3.00					
	NLR≤2.09	1	4.00	4.00					
CHET					0.857	0.355			
FOLFIRINOX	NLR>2.09	22	9.09	9.00					
	NLR≤2.09	11	11.36	8.00					
GEM/Nab-P Gem/Nab-P	NLR>2.09	8	8.16	5.00					
	NLR≤2.09	5	11.80	10.00					

OS – overall survival; PFS – progression – free survival; ECOG PS – performance status according Easter Cooperative Oncology Group; FOLFIRINOX – 5-fluorouracil-folinic acid.irinotecan. oxaliplatin; GEM/Nab-P; gemcitabin/nab-paclitaxel; LAPC – locally advanced pancreatic cancer; mPDAC – metastatic pancreatic adenocarcinoma; NLR – neutrophil to lymphocyte ratio

Tab. 6. Univariate and multivariate analysis for PLR in categories OS and PFS.

Variable	PLR	Number of Patients	Univariate analysis OS: OS Average	OS Median	Chi-square	p	Multivariate analysis OS: HR	(95% CI)	p
M stage					0.178	0.673			
LAPC	PLR>200.39	1	8.00	8.00					
	PLR≤200.39	12	19.92	14.00					
mPDAC	PLR>200.39	12	15.92	15.00					
	PLR≤200.39	20	16.60	13.00					
PS ECOG					0.050	0.823			
ECOG 0-1	PLR>200.39	8	17.75	15.00					
	PLR≤200.39	30	18.53	15.00					
ECOG 2	PLR>200.39	5	11.40	12.00					
	PLR≤200.39	2	7.50	6.00					
CHET					0.103	0.748			
FOLFIRINOX	**PLR>200.39**	8	14.38	15.00					
	PLR≤200.39	25	18.72	15.00					
GEM/Nab-P P	**PLR>200.39**	5	16.80	12.00					
	PLR≤200.39	7	14.71	13.00					
	PLR≤200.39	10	24.00	19.00					

Variable	PLR	Number of Patients	OS Average	OS Median	Univariate analysis PFS: Chi-square	p	Multivariate analysis PFS: HR	(95% CI)	p
M stage					0.135	0.713			
LAPC	PLR>200.39	1	5.00	5.00					
	PLR≤200.39	13	9.15	9.00					
mPDAC	PLR>200.39	12	10.42	11.00					
	PLR≤200.39	20	10.00	8.00					
PS ECOG					1.255	0.263			
ECOG 0-1	**PLR>200.39**	8	11.75	11.00					
	PLR≤200.39	31	10.07	9.00					
ECOG 2	**PLR>200.39**	5	7.20	5.00					
	PLR≤200.39	2	3.50	3.00					
CHET					0.414	0.520			
FOLFIRINOX	**PLR>200.39**	8	10.38	11.00					
	PLR≤200.39	25	9.68	8.00					
GEM/Nab-P	**PLR>200.39**	5	9.40	5.00					
	PLR≤200.39	8	9.63	9.00					

OS – overall survival; PFS – progression-free survival; ECOG PS – performance status according Easter Cooperative Oncology Group; FOLFIRINOX – 5-fluorouracil. folinic acid. irinotecan. oxaliplatin; GEM/Nab-P; gemcitabin/nab-paclitaxel; LAPC – locally advanced pancreatic cancer; mPDAC – metastatic pancreatic adenocarcinoma; PLR – platelet to lymphocyte ratio

al further underscored the prognostic significance and relevance of inflammatory markers as stratification parameters in studies focused on inflammation or patient immune response. In their research, they evaluated inflammatory markers, namely NRL, PLR, LMR and CRP-to-albumin ratio (CAR) and identified a new composite score, referred to as the inflammatory reference index (IBI) (73).

Recently, Dekker et al published a study where they qualitatively assessed the prognostic value of combined ABC factors in localized PDAC. The ABC factors include tumor anatomy (A: resectable, borderline resectable, or locally advanced), biologic factor (B: CA 19-9), and condition factor (C: performance status). They found that these ABC factors, as assessed at the time of diagnosis, were independent prognostic factors for OS in patients with localized PDAC who initially received FOLFIRINOX treatment (74).

Furthermore, a detailed investigation of cases with advanced PDAC revealed differences in the behavior of inflammatory indexes between the LAPC and mPDAC subgroups.

In mPDAC patients, particularly those with PS ECOG2, the activation of inflammatory changes (manifesting as higher NLR and lower LMR) was associated with a worse prognosis. Conversely, in patients with LAPC, the activation of inflammatory changes did not worsen the prognosis. Also, based on SII results, it seems that inflammation activation at some stage of the disease actually led to improved treatment outcomes, especially in terms of prolonged OS.

In patients with PS ECOG 2, the performance status itself appears to be a stronger predictor for OS and PFS than inflammatory indexes. However, it is important to note that there were only 7 patients in the VS ECOG 2subgroup, resulting in marked imbalance between the evaluated arms.

Subgroup analysis of inflammatory indexes in the FOLFIRINOX and GEM/Nab-P regimen subgroups demonstrated that patients with well-controlled inflammation survived longer with the FOLFIRINOX regimen (lower NLR and higher LMR) whereas patients with active inflammation survived longer with the GEM/Nab-P regimen (higher NLR, lower LMR). This finding supports the notion that cytostatic treatment can modulate the immune environment of TME PDAC.

An increasing number of studies demonstrate that TME PDAC can be remodeled by chemotherapy. This remodeling is due to immunogenic cell death, selection and/or upbringing of predominant tumor clones, adaptive gene mutations, and cytokine/chemokine induction (24, 75–78).

Evaluating inflammatory indexes at the beginning of treatment, while using consistent blood count parameters, could influence our decision on selecting the most suitable cytostatic regimen as the first line of treatment, to achieve the best possible results. This suggests that inflammatory indexes, in addition to their prognostic significance, may also have predictive significance in patients with advanced PDAC.

The majority of patients who receive first-line therapy ultimately experience disease progression, with 1-year failure rates of 60% to 80% (19, 20). In addition, many patients respond poorly to treatment due to refractory primary disease, making the management of such cases challenging (79).

Tab. 7. Univariate and multivariate analysis for LMR in categories OS and PFS.

			Univariate analysis OS				Multivariate analysis OS		
Variable	LMR	Number of Patients	OS Average	OS Median	Chi-square	p	HR	(95% CI)	p
M stage					0.926	0.336			
LAPC	LMR<2.48	2	15.00	8.00					
	LMR≥2.48	11	19.73	14.00					
mPDAC	LMR<2.48	12	17.25	16.00					
	LMR≥2.48	20	15.80	13.00					
PS ECOG					0.018	0.892			
ECOG 0-1	LMR<2.48	13	17.92	20.00					
	LMR≥2.48	25	18.60	15.00					
ECOG 2	LMR<2.48	1	4.00	4.00					
	LMR≥2.48	6	11.33	9.00					
CHET					0.633	0.426			
FOLFIRINOX	LMR<2.48	11	13.73	14.00					
	LMR≥2.48	22	19.64	15.00					
GEM/Nab-P	LMR<2.48	3	28.67	27.00					
	LMR≥2.48	9	11.22	11.00					
			Univariate analysis PFS				**Multivariate analysis PFS**		
Variable	LMR	Number of Patients	OS Average	OS Median	Chi-square	p	HR	(95% CI)	p
M stage					0.524	0.469			
LAPC	LMR<2.48	2	9.50	5.00					
	LMR≥2.48	12	8.75	5.00					
mPDAC	LMR<2.48	12	10.83	10.00					
	LMR≥2.48	20	9.75	7.00					
PS ECOG					2.255	0.133			
ECOG 0-1	LMR<2.48	13	11.31	10.00					
	LMR≥2.48	26	9.96	8.00					
ECOG 2	LMR<2.48	1	2.00	2.00					
	LMR≥2.48	6	6.83	4.00					
CHET					0.804	0.370			
FOLFIRINOX	LMR<2.48	11	9.36	10.00					
	LMR≥2.48	22	10.09	8.00					
GEM/Nab-P Gem/Nab-P	LMR<2.48	3	15.33	14.00					
	LMR≥2.48	10	7.80	5.00					

OS – overall survival; PFS – progression-free survival; ECOG PS – performance status according Easter Cooperative Oncology Group; FOLFIRINOX – 5-fluorouracil-folinic acid-irinotecan-oxaliplatin; GEM/Nab-P; gemcitabin/nab-paclitaxel; LAPC – locally advanced pancreatic cancer; mPDAC – metastatic pancreatic adenocarcinoma; LMR – lymphocyte to monocyte ratio

Emerging evidence suggests that chemotherapy administered in the second-line chemotherapy can prolong OS and provide symptom relief (80, 81). OS may be longer in patients who maintain performance status that allows for the administration of second-line chemotherapy. In the AGEO trial, patients receiving FOLFIRINOX and GEM/nab-P regimens achieved a median OS of 18 months (82).

Second-line treatment was not included in our analysis; therefore, we cannot assess whether the longest survival was achieved in patients receiving both investigated regimens in the first- and second-line treatments. A pretreatment analysis of inflammatory indexes could be beneficial in determining the optimal therapeutic sequence to achieve the maximum survival benefit, considering the currently limited therapeutic options for PDAC.

Conclusion

Despite extensive worldwide research, advanced PDAC remains a disease with a poor prognosis, significantly limited therapeutic options, and few innovative drugs. The main research focus is on the TME of PDAC, which determines the nature of the disease and contributes to therapy failures. Inflammation plays an essential role in PDAC development and progression. Global research efforts are centered on identifying prognostic and predictive markers, crucial for early diagnosis and management of both localized and advanced stages of the disease.

Inflammatory indexes are cost-effective markers that can be derived from routine differential blood counts examined in

Tab. 8. Univariate and multivariate analysis for PNI in categories OS and PFS.

Variable	PNI	Number of Patients	OS Average	OS Median	Univariate analysis OS		Multivariate analysis OS		
					Chi-square	p	HR	(95% CI)	p
M stage					5.003	**0.025**	0.47	0.24–0.91	**0.026**
LAPC	PNI<49.09	4	12.75	10.00					
	PNI≥49.09	9	21.78	18.00					
mPDAC	PNI<49.09	16	12.88	11.00					
	PNI≥49.09	16	19.81	16.00					
PS ECOG					3.126	0.077			
ECOG 0-1	PNI<49.09	14	13.64	11.00					
	PNI≥49.09	24	21.13	16.00					
ECOG 2	PNI<49.09	6	11.00	9.00					
	PNI≥49.09	1	6.00	6.00					
CHET					4.705	**0.030**	0.47	0.25–0.90	**0.022**
FOLFIRINOX	PNI<49.09	13	13.46	14.00					
	PNI≥49.09	20	20.40	16.00					
GEM/Nab-P	PNI<49.09	7	11.71	11.00					
	PNI≥49.09	5	21.00	22.00					
Variable	**PNI**	**Number of Patients**	**OS Average**	**OS Median**	**Univariate analysis PFS**		**Multivariate analysis PFS**		
					Chi-square	p	HR	(95% CI)	p
M stage					4.248	**0.039**	0.53	0.28–1.00	**0.050**
LAPC	PNI<49.09	4	5.50	5.00					
	PNI≥49.09	10	10.20	10.00					
mPDAC	PNI<49.09	16	7.94	6.00					
	PNI≥49.09	16	12.38	10.00					
PS ECOG					2.602	0.107			
ECOG 0-1	PNI<49.09	14	7.86	6.00					
	PNI≥49.09	25	11.84	10.00					
ECOG 2	PNI<49.09	6	6.50	3.00					
	PNI≥49.09	1	4.00	4.00					
CHET					3.094	0.079			
FOLFIRINOX	PNI<49.09	13	8.15	6.00					
	PNI≥49.09	20	10.95	10.00					
GEM/Nab-P Gem/Nab-P	PNI<49.09	7	6.14	5.00					
	PNI≥49.09	6	13.50	11.00					

OS – overall survival; PFS – progression-free survival; ECOG PS – performance status according Easter Cooperative Oncology Group; FOLFIRINOX – 5-fluorouracil-folinic acid-irinotecan-oxaliplatin; GEM/Nab-P; gemcitabin/nab-paclitaxel; LAPC – locally advanced pancreatic cancer; mPDAC – metastatic pancreatic adenocarcinoma; PNI – prognostic nutritional index

Tab. 9. Univariate and multivariate analysis for SII in categories OS and PFS.

Variable	SII	Number of Patients	OS Average	OS Median	Univariate analysis OS		Multivariate analysis OS		
					Chi-square	p	HR	(95% CI)	p
M stage					1.874	0.171			
LAPC	SII>396.52	8	16.00	12.00					
	SII≤396.56	5	23.80	**20.00**					
mPDAC	SII>396.52	27	15.00	15.00					
	SII≤396.56	5	23.60	15.00					
PS ECOG					3.792	**0.051**			
ECOG 0-1	SII>396.52	29	16.10	14.00					
	SII≤396.56	9	25.67	19.00					
ECOG 2	SII>396.52	6	11.00	9.00					
	SII≤396.56	1	6.00	6.00					
CHET					2.153	0.142			
FOLFIRINOX	SII>396.52	26	15.12	14.00					
	SII≤396.56	7	27.14	19.00					
GEM/Nab-P Gem/Nab-P	SII>396.52	9	15.56	12.00					
	SII≤396.56	3	15.67	19.00					
Variable	**SII**	**Number of Patients**	**OS Average**	**OS Median**	**Univariate analysis PFS**		**Multivariate analysis PFS**		
					Chi-square	p	HR	(95% CI)	p
M stage					1.041	0.308			
LAPC	SII>396.52	9	7.22	5.00					
	SII≤396.56	5	11.80	14.00					
mPDAC	SII>396.52	27	9.41	10.00					
	SII≤396.56	5	14.20	8.00					
PS ECOG					2.627	0.105			
ECOG 0-1	SII>396.52	30	9.33	9.00					
	SII≤396.56	9	14.00	11.00					
ECOG 2	SII>396.52	6	6.50	3.00					
	SII≤396.56	1	4.00	4.00					
CHET					1.249	0.264			
FOLFIRINOX	SII>396.52	26	8.54	7.00					
	SII≤396.56	7	14.71	11.00					
GEM/Nab-P Gem/Nab-P	SII>396.52	10	9.70	6.00					
	SII≤396.56	3	9.00	9.00					

OS – overall survival; PFS – progression-free survival; ECOG PS – performance status according Easter Cooperative Oncology Group; FOLFIRINOX – 5-fluorouracil-folinic acid-irinotecan-oxaliplatin; GEM/Nab-P; gemcitabin/nab-paclitaxel; LAPC – locally advanced pancreatic cancer; mPDAC – metastatic pancreatic adenocarcinoma; SII – systemic immune-inflammation index

clinical practice. The prognostic significance of these indexes has been demonstrated in numerous studies and meta-analyses.

In our cohort of advanced PDAC patients, PS ECOG, NLR, and PNI were confirmed as independent prognostic factors for overall patient survival in both univariate and multivariate analyses across LAPC, mPDAC, and FOLFIRINOX, and GEM/Nab cytostatic regimens. We further demonstrate that the combined assessment of clinicopathological categories and inflammatory indexes can provide comprehensive information about patient immune status and partially reflects the TME of PDAC. This combined approach serves as both a prognostic and predictive marker in selecting first-line cytostatic regimens for advanced PDAC treatment.

Our goal is to broaden therapeutic options for patients with PDAC. Through meticulous clinical and histopathological examination along with available imaging and laboratory tests, we already have in hand a spectrum of prognostic and predictive markers guiding our therapeutic decisions aimed at extending the lives of patients with advanced PDAC while maintaining an acceptable quality of life.

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