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Neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio, and systemic immune-inflammation index as clinical predictive and prognostic markers in patients with advanced pancreatic cancer receiving gemcitabine monotherapy

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Abstract

Introduction. Pancreatic cancer is characterized by an increasing incidence and still poor prognosis despite the availability of various therapeutic options, currently including single- and multi-drug chemotherapy as well as molecularly targeted therapy. Therefore, appropriate qualification for particular therapies, based mainly on clinical and histological factors, is extremely important. Inflammatory status, associated with cancer development, justifies the search for prognostic markers related to the immune system, which could be additional factors facilitating selection of appropriate therapy.

This study aimed at assessing the prognostic value of the neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and systemic immune-inflammation index (SII) in patients with advanced pancreatic cancer undergoing gemcitabine monotherapy.

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Material and methods. A retrospective analysis of blood morphological parameters was performed in 167 patients with advanced pancreatic cancer treated with gemcitabine monotherapy in the first line in five oncology centers in Poland in the years 2017–2022. The NLR, PLR, and SII were calculated, and cut-off points between high and low values were defined. Clinical parameters and their distribution were assessed depending on the overall survival (OS) value equal to or greater than or less than median OS. The distribution of patients within OS intervals in relation to the categories of inflammatory markers was assessed.

Results. The median age of patients was 71 years, the majority were women (58%), with clinical stage IV (57%), and with dominant location of metastases in the liver (42.5%). The median NLR was 2.69 (range 0.5–36.65), PLR 146.54 (range 18.53–1118.57), and SII 784.75 (range 79.86–10622.67). The cut-off points were defined as 4.5625 for the NLR [125 patients (75.8%) with a value less than and 40 patients (24.3%) with a value equal to or greater], 150 for the PLR [87 (52.7%)/ 78 (47.3%)], and 897.619 for the SII [96 (58.2%)/69 (41.8%)]. Comparing the groups with OS longer than or equal to the median and OS shorter than the median, statistically significant differences were found in relation to body mass index (BMI) ($p = 0.02$), baseline stage ($p < 0.001$), and location of metastases ($p < 0.001$). There were statistically significantly more NLR and SII values below the cut-off points in patients with survival at least equal to median OS. Concerning the PLR, no statistically significant differences were found between groups determined by OS value.

Conclusions. We demonstrated the relationship between indicators calculated on the basis of blood count parameters and treatment results. It may indicate the predictive and prognostic importance of indices reflecting immune system status, which can be a valuable addition to the clinical criteria included in prognostic models.

Keywords: advanced pancreatic cancer, gemcitabine, overall survival, progression-free survival

Introduction

Pancreatic cancer is one of the most aggressive malignant tumors associated with poor prognosis. The non-specific clinical manifestation and lack of characteristic symptoms at an early stage of disease limit the possibility of early diagnosis [1, 2].

Fewer than 20% of cases are diagnosed at the resection stage; 30–40% of cases are diagnosed at the locally advanced stage, and more than half at the dissemination stage [3]. Diagnosing the disease at a highly advanced stage and limited treatment options result in an unfavorable prognosis. The 5-year survival rates in the general population of pancreatic cancer patients do not exceed 10% [4, 5]. In Poland, only 8% of patients survive 5 years after diagnosis [6].

In the majority of patients, chemotherapy is the only treatment affecting the prognosis. Since the end of the 20th century, standard care for patients with advanced, inoperable pancreatic cancer has been gemcitabine monotherapy. Multidrug regimens introduced into treatment in the last decade — FOLFIRINOX and gemcitabine in combination with paclitaxel in the form of a nanoparticle complex with albumin (nab-P, nab-paclitaxel) in the first line and a regimen combining nanoliposomal irinotecan (nal-IRI) with fluoropyridines in the second line — allowed for extension of median overall survival (OS). However, it still does not exceed one year [7, 8]. Guidelines of the European Society for Medical Oncology (ESMO) and the National Network of Multispecialty Centers (NCCN) recommend adapting the chemotherapy regimen to the patient's performance status — for patients with good performance status, multidrug regimens are recommended, and for patients with worse performance status, gemcitabine (or capecitabine or fluorouracil) as monotherapy.

In recent years, there has been a lot of data on the relationship between inflammation, carcinogenesis, and progression of malignancies, including pancreatic cancer [9]. Immunocompetent cells and inflammatory mediators are present in the microenvironment of most, if not all, tumors, regardless of the triggering factor. They may reflect the state of the anti-cancer immune response. This justifies the search for prognostic markers related to inflammatory indices. The usefulness of such markers and indices based on them in establishing prognosis in various patient cohorts and clinical settings has been assessed for many years.

In the population of pancreatic cancer patients, the prognostic and/or predictive significance of the modified Glasgow Prognostic Score (GPS) [10, 11], neutrophil-to-lymphocyte ratio (NLR) [12–17],

platelet-to-lymphocyte ratio (PLR) [18, 19], C-reactive-protein-to-albumin ratio (CRP/Alb) [20, 21], and prognostic nutritional index (PNI) [22] has already been assessed. However, these studies mainly included patients qualified for surgery or postoperative chemotherapy.

The systemic immune-inflammation index (SII), calculated on the basis of the number of platelets, neutrophils, and lymphocytes, is a relatively new tool. It was first used to assess the prognosis in hepatocellular carcinoma (HCC) patients [23]. A standardized cut-off value has not been established and varies for different cancer types, but a high negative predictive value of the SII has been observed in many tumors [24, 25]. The predictive value of the SII in cancer patients undergoing various systemic treatment methods was also described [26–28].

This study aimed to assess the prognostic significance of the NLR, PLR, and SII in patients with advanced pancreatic cancer treated with gemcitabine in monotherapy. For this purpose, a retrospective analysis of laboratory parameters was performed.

Material and methods

The study included 167 patients with advanced pancreatic cancer treated with gemcitabine in monotherapy between 2017 and 2022 in five oncology centers in Poland (Opole Oncology Center in Opole, Oncology Clinic of the Jagiellonian University in Kraków, Białystok Oncology Center in Białystok, West Pomeranian Oncology Center in Szczecin, Department of Oncology and Radiotherapy, Medical University of Gdańsk). All patient data were anonymized after being extracted from individual files before analysis. The approval of the Bioethics Committee of the District Medical Chamber in Opole was obtained (resolution no. 347).

Gemcitabine was used as first-line treatment in all patients. In each of the centers involved in the study, it is possible to use nab-P in combination with gemcitabine as part of the drug program. In the majority of patients (80%) gemcitabine was used due to their failure to meet the drug program inclusion criteria [primarily due to the inability to confirm the presence of metastases and/or worse Eastern Cooperative Oncology Group (ECOG) performance status (PS)] (> 1). Gemcitabine was used as monotherapy at a starting dose of 1000 mg/m^2 of body surface (b.s.) every week, 7 times in an 8-week cycle, then 3 times in a 4-week cycle.

Several variables related to the patient's profile, biology, and disease stage were analyzed. Blood morphological parameters were analyzed in detail at the time of gemcitabine initiation, and the assessed parameters were calculated according to the following formulas [25]:

$$\text{NLR} = \frac{\text{number of neutrophils in peripheral blood per liter}}{\text{number of lymphocytes in peripheral blood per liter}}$$

$$\text{PLR} = \frac{\text{number of platelets in peripheral blood per liter}}{\text{liczba limfocytów we krwi obwodowej na liter}}$$

$$\text{SII} = \frac{\text{number of platelets in peripheral blood per liter} \times \\ \times \text{ number of neutrophils in peripheral blood per liter}}{\text{number of lymphocytes in peripheral blood per liter}}$$

Follow-up was completed on December 1, 2022. Due to the retrospective nature of the analysis, the cause of death was not determined. Overall survival was defined as the time from the treatment initiation to death, and progression-free survival as the time from treatment initiation to disease progression or death. Response to treatment was defined as no clinical and/or radiological evidence of disease progression.

Statistical methods

Mann-Whitney-Wilcoxon tests were used for continuous data and Fisher's and $\chi 2$ tests for categorical data. The Shapiro-Wilk test was used to test the normality hypotheses. The Kaplan-Meier estimator and the nonparametric Cox model were used in the survival analysis. Due to the relationships between the variables, only models with each variable analyzed individually were considered.

The optimal cut-off points for the NLR, PLR, and SII were 4.56, 150, and 897, respectively. They were determined based on receiver operating characteristic (ROC) curves and Youden's criterion. The analysis results showed that the area under the ROC curves (AUC) — AUROC for the NLR, PLR, and SII were 0.598 [95% confidence interval (CI) 0.509–0.688], 0.508 (95% CI 0.418–0.599), and 0.574 (95% CI 0.484–0.664), respectively, as shown in Figure 1.

Results

Clinical characteristics

The median age was 71 years (Tab. 1). Women predominated (almost 60%). More than half of the patients had a normal BMI, and one-third were overweight or obese. In the majority of patients (> 65%), the PS was assessed according to the ECOG score as good or very good. More than half were patients with clinical stage IV, and the liver was the most common location of metastases (42.5% of the study group).

Morphology parameters allowed for the assessment of white blood cell fraction disorders and the calculation of the NLR, PLR, and SII. The median NLR was 2.69 (range 0.5 — 36.65), PLR — 146.54 (range 18.53–1118.57), SII 784.75 (range 79.86–10622.67).

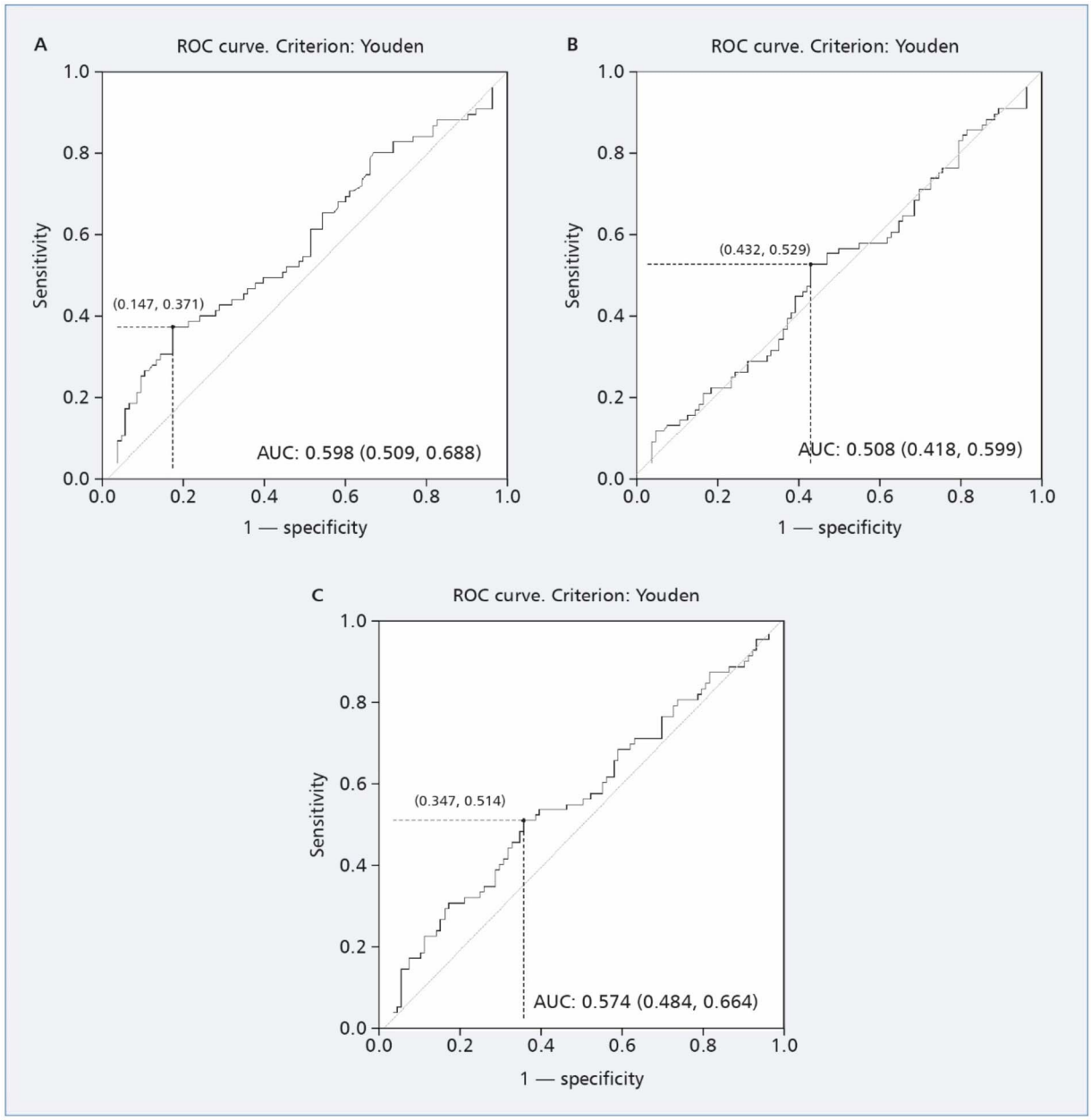

Figure 1. Receiver operating characteristic (ROC) curves; **A.** Neutrophil-to-lymphocyte ratio (PLR); **B.** Platelet-to-lymphocyte ratio (PLR); **C.** Systemic immune-inflammation index (SII); AUC — area under curve

In two patients, complete data on the percentage distribution of the white blood cell fraction were not obtained, and these patients were excluded from this part of the analysis.

Median overall survival was 6.48 months (range 5.75–8.45 months; Fig. 2), and the 6-, 12-, 18- and 24-month survival rates were 56%, 26%, 13%, and 8%, respectively.

The distribution of selected variables was assessed in patient subgroups defined based on median OS — in the group of patients with OS longer or equal to the median (OS ≥ median) and in the group with OS shorter than the median (OS < median; Tab. 2). There were no significant differences between the groups except for median BMI, clinical stage at baseline, and location of metastases ($p = 0.02$, $p < 0.001$ and $p < 0.001$, respectively).

Using predefined cut-off points for the NLR, PLR, and SII, patients were assigned to two groups according to each indicator: 125 patients (75.8%) presented the NLR < 4.5625 (hereinafter referred to as low), and 40 patients (24.3%) ≥ 4.5625 (referred to as high); 87 patients (52.7%) presented the PLR < 150 (low), and 78 patients (47.3%) ≥ 150 (high); 96 patients

Table 1. Patient characteristics

Feature	Number of patients n = 167 (%)
Age in years at diagnosis	
Median	71.24
Range	(47.44–85.87)
Sex	
Female	97 (58.08%)
Male	70 (41.92%)
BMI at initiation of gemcitabine treatment	
Median	22.84
Range	(14.88–34.11)
Underweight	22 (13.17%)
Standard	92 (55.09%)
Overweight and obesity	53 (31.74%)
ECOG PS at gemcitabine treatment initiation	
0	7 (4.19%)
1	102 (61.08%)
2	50 (29.94%)
3	7 (4.19%)
No data	1 (0.60%)
Clinical stage at baseline	
III	59 (35.33%)
IV	95 (56.89%)
No data	13 (7.78%)
Location of metastases at gemcitabine treatment initiation	
No metastases	60 (35.93%)
Liver and possibly other organs	71 (42.51%)
Other organs excluding the liver	36 (21.56%)
NLR at gemcitabine treatment initiation	
Median	2.69
Range	(0.5–36.65)
PLR at gemcitabine treatment initiation	
Median	146.54
Range	(18.53–1118.57)
SII at gemcitabine treatment initiation	
Median	784.75
Range	(79.86–10622.67)

BMI — body mass index; ECOG — Eastern Cooperative Oncology Group; NLR — neutrophil-to-lymphocyte ratio; PLR — platelet-to-lymphocyte ratio; PS — performance status; SII — systemic immune-inflammation index

(58.2%) presented the SII < 897.619 (low), and 69 patients (41.8%) ≥ 897.619 (high).

The numerical distribution of patients with OS ≥ median and OS < median was assessed in relation to the categories of the above indicators, and it was found that patients with survival at least equal to the median significantly more often had NLR and SII values below the cut-off points (Tab. 3). With regard to the PLR, no significant differences were found between the groups determined by the OS value.

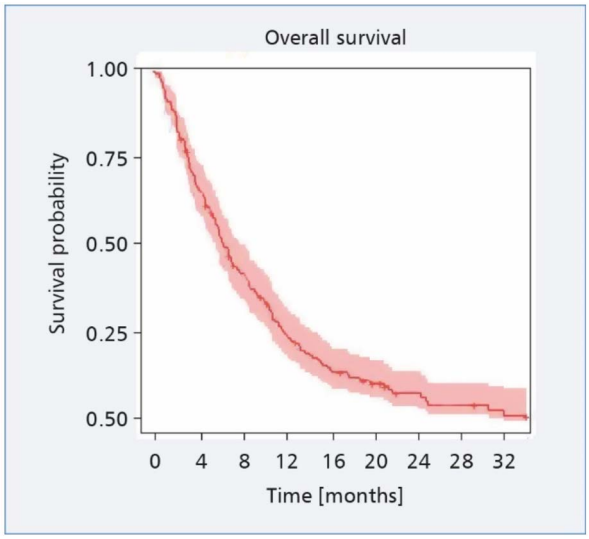

Figure 2. Overall survival in all patients

Table 2. Selected clinical and laboratory features in the subgroups with overall survival (OS) equal to or longer than the median and shorter than the median

Feature	OS ≥ median	OS < median	p value
Age at diagnosis [yrs.]			0.22
Median	71.9	70.5	
Range	(55.8–85.5)	(47.4–85.9)	
Sex			0.63
Female	48	48	
Male	31	38	
BMI at gemcitabine treatment initiation			**0.02**
Median	23.8	22.1	
Range	(15.4–34.1)	(14.9–33.6)	
ECOG PS at gemcitabine treatment initiation			0.96
0	3	4	
1	50	51	
2	23	27	
3	3	4	
Clinical stage at baseline			< **0.001**
III	38	21	
IV	33	61	
No data	8	4	
Location of metastases at gemcitabine treatment initiation			< **0.001**
No metastases	39	20	
Liver and possibly other organs	20	50	
Other organs excluding the liver	20	16	

BMI — body mass index; ECOG — Eastern Cooperative Oncology Group; PS — performance status

Table 3. Neutrophil-to-lymphocyte ratio (NLR), platelet-to--lymphocyte ratio (PLR), and systemic immune-inflammation index (SII) in the subgroups with overall survival (OS) equal to or longer than the median and shorter than the median

Feature	OS ≥ median	OS < median	p value
NLR value at gemcitabine treatment initiation			< **0.001**
< 4.5625	69	56	
≥ 4.5625	10	30	
PLR value at gemcitabine treatment initiation			0.21
< 150	46	41	
≥ 150	33	45	
SII value at gemcitabine treatment initiation			**0.01**
< 897.619	54	42	
≥ 897.619	25	44	

A significant relationship was demonstrated between the NLR, SII, and OS at the adopted cut-off points (Fig. 3, Tab. 4). Survival analysis using the Kaplan-Meier curve for all patients showed that a low SII (p = 0.0019) and NLR (p < 0.0001) were significantly associated with longer OS. Concerning the PLR index, no significance was demonstrated, although patients with a PLR value < 150 achieved longer survival than patients with a value ≥ 150.

Cox regression analysis was also performed to assess whether and how the category of each indicator affects the risk of death. It was shown that in patients with a high NLR, the risk of death was 2.5382 times higher than in patients with a low NLR. Similarly, in patients with a high SII, the risk of death was 1.6738 times higher than in patients with a low SII (Tab. 5). Similar to previous analyses regarding the PLR, the Cox regression model with this variable also turned out to be insignificant.

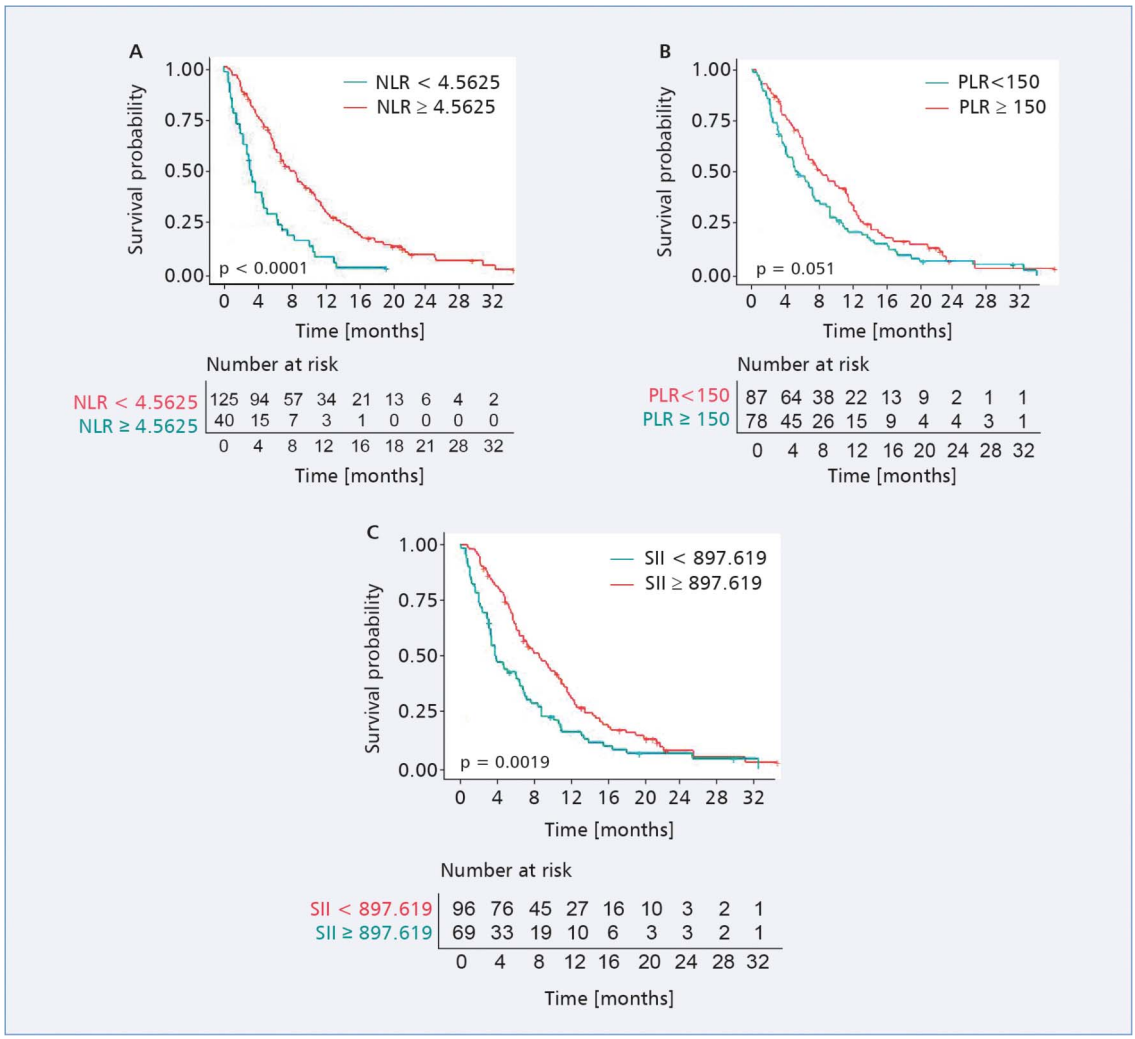

Figure 3. Overall survival according to the neutrophil-to-lymphocyte ratio (NLR) (**A**), platelet-to-lymphocyte ratio (PLR) (**B**), and systemic immune-inflammation index (SII) (**C**)

Table 4. Median overall survival (OS) for all patients and by the neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and systemic immune-inflammation index (SII)

Index	Category	Median OS (95% CI) [months]	p value
NLR Cut-off point: 4.5625	< 4.5625 ≥ 4.5625	7.99 (6.84–10.32) 3.19 (2.43–5.19)	< **0.0001**
PLR Cut-off point: 150	< 150 ≥ 150	7.86 (6.12–11.01) 5.19 (3.85–7.20)	0.051
SII Cut-off point: 897.619	< 897.619 ≥ 897.619	8.68 (6.90–11.01) 3.94 (3.32–6.84)	**0.0019**
Total		6.48 (5.75–8.45)	

CI — confidence interval

Table 5. Univariate nonparametric Cox regression models

Index	HR	95% CI	p value
NLR Cut-off point: 4.5625	2.538	1.732–3.719	< **0.00001**
PLR Cut-off point: 150	1.38	0.9965–1.912	0.05
SII Cut-off point: 897.619	1.674	1.205–2.326	**0.003**

CI — confidence interval; HR — hazard ratio; NLR — neutrophil-to-lymphocyte ratio; PLR — platelet-to-lymphocyte ratio; SII — systemic immune-inflammation index

Discussion

Despite the introduction of new therapeutic methods in the last decade, advanced pancreatic adenocarcinoma is still associated with a poor prognosis [4–6]. The current treatment algorithm for advanced pancreatic cancer in patients with good or very good performance status includes multidrug chemotherapy regimens (FOLOFIRINOX, nab-P with gemcitabine), and in selected cohorts — olaparib (in patients with a BRCA1/2 mutation) or pembrolizumab [in patients with mismatch repair deficiency (dMMR) and high microsatellite instability (MSI-H)] [7, 8, 29]. In patients with poorer performance status, single-drug chemotherapy with gemcitabine is possible, and such treatment is still used in daily clinical practice [30].

In pancreatic adenocarcinoma, as in many other cancers, more and more data indicate a close relationship between inflammation and carcinogenesis, tumor progression, and metastasizing [31, 32]. The main prognostic impact of inflammatory markers can be attributed to the cytokine-driven immunogenic tumor microenvironment [31, 33]. In recent years, inflammatory markers and indices based on them have been frequently used to assess prognosis and predict treatment outcomes in daily clinical practice. One of the recently evaluated prognostic indicators is the SII, which is a combination of NLR and PLR, whose importance has been evaluated in many cancers [34–38].

This study aimed to assess the prognostic value of the NLR, PLR, and SII in patients with advanced pancreatic cancer treated with gemcitabine in monotherapy. For this purpose, a retrospective analysis of laboratory parameters was performed.

It was shown that low SII and NLR values are significantly associated with prolonged OS ($p = 0.0019$ and $p < 0.0001$, respectively). No such relationship was found in the case of the PLR; however, patients with PLR values < 150 had numerically longer survival than patients with values ≥ 150.

The majority of the study cohort were women (58%), patients with clinical stage IV (57%) and distant metastases predominantly in the liver (42.5%). Taking into account the clinically based model for assessing long response (LR) probability in patients treated with gemcitabine in monotherapy, which was proposed in a previous study, the majority of patients in the current cohort belonged to the group with a lower probability of LR (women, with the presence of liver metastases and with an NLR value > 8) [30].

The median OS rate in the study group was 6.48 months (range 5.75–8.45 months), and the 6-, 12-, 18-, and 24-month survival rates were 56%, 26%, 13%, and 8%, respectively. Despite the presence of the worse predictive factors defined in the above-mentioned model [30], these results were better than those obtained in the study by Burris et al. [39], comparing gemcitabine monotherapy and 5-fluorouracil, in which a median OS rate of 5.65 months and 12-month survival rate of 18% were achieved in the gemcitabine arm. It should be emphasized that the summary of these data is only indicative and does not meet the formal requirements for comparison.

Selected clinical variables were analyzed depending on the OS value (≤ or > median). In such subgroups, statistically significant differences were found in terms of the median BMI ($p = 0.02$), clinical stage at gemcitabine treatment initiation ($p < 0.001$), and location of metastases ($p < 0.001$). This means that in the analyzed group, OS equal to or longer than the median was achieved mainly by patients with a higher BMI, with lower clinical stage, and without liver metastases. It could be assumed that these features contributed to a slightly better general condition of the patients, but this was not reflected in the assessment of ECOG performance status ($p = 0.96$).

The medians of the NLR, PLR, and SII calculated on the basis of blood counts were 2.69 (range 0.5–36.65), 146.54 (range 18.53–1118.57), and 784.75 (range 79.86–10622.67), respectively.

Two patients were excluded from the analysis due to a lack of data on white blood cell percentage distribution. Additionally, based on appropriate statistical methods, cut-off values for each indicator were determined, which were 4.5625, 150, and 897.619 for the NLR, PLR, and SII, respectively. These values are similar to those adopted in the meta-analysis by Oh D et al. [40], in which high NLR and PLR values were considered to be 2.0–5.0 and 150–200, respectively. In turn, in the work of Jomrich et al. [41], the optimal cut-off values for the SII, PLR, and NLR were set at 873, 179, and 225, respectively.

Comparing subgroups of patients defined in terms of median OS and taking into account the cut-off points of individual indicators, it was shown that in the group with OS $\geq$ median, the NLR and SII values below the cut-off points were found significantly more often ($p < 0.001$ and $p = 0.01$, respectively). With regard to the PLR, this difference was only numerical and without statistical significance ($p = 0.21$). The data we obtained are consistent with other studies. The meta-analysis by Yang et al. [42] showed that a higher NLR value is associated with worse survival in pancreatic cancer patients. Subgroup analysis showed that the worsening of OS occurred mainly in patients with metastases, poor tumor differentiation, poorer performance status, high CA-19.9 and CRP levels, and low albumin levels. The meta-analysis by Oh et al. [40] confirmed the above observations regarding the NLR and demonstrated the prognostic significance of the PLR. Significant correlations have been reported between high NLR and PLR values and worsened survival [40]. Jomrich et al. [41] showed that the preoperative SII value is an independent and stronger prognostic factor for OS in patients with resected pancreatic cancer than the NLR and PLR. The authors additionally concluded that SII measurement is easy to use and cheap, and patients with elevated SIIs before surgery may benefit from anti-inflammatory treatment [41].

Conclusions

The results of our analysis show the relationship between indicators calculated on the basis of blood count parameters and treatment outcomes, which may indicate their predictive and prognostic importance. They can be a valuable addition to the clinical criteria included in prognostic models. Further research is necessary to confirm the prognostic values of the analyzed indicators to determine their possible relationships with the clinical and biological tumor characteristics and develop more comprehensive prognostic and predictive criteria for individual therapies.

Article Information and Declarations

Data availability statement

All analyzed data are included in this work. Further inquiries may be directed to the corresponding author.

Ethics

The approval of the Bioethics Committee of the District Medical Chamber in Opole was obtained (resolution no. 347/2023).

Author contributions

I.R.: should be considered the primary author; concept, methods, research, data analysis, literature review, preparation of the original manuscript, data collection, final acceptance of manuscript; A.S.: statistical analysis, final acceptance of manuscript; J.S., B.Cz.-A., A.Ch.-B., M.T., K.W., W.R., M.J.: data collection, final acceptance of manuscript; P.Z.: data collection, statistical analysis, final acceptance of manuscript; B.R.: should be considered the primary author; concept, methods, research, data analysis, literature review, preparation of the original manuscript, data collection, final acceptance of manuscript.

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Conflict of interest

All authors declare no conflict of interest in connection with this work.

Supplementary material

None.

References

1. Luo W, Tao J, Zheng L, et al. Current epidemiology of pancreatic cancer: Challenges and opportunities. Chin J Cancer Res. 2020; 32(6): 705–719, doi: 10.21147/j.issn.1000-9604.2020.06.04, indexed in Pubmed: 33446994.
2. Jagadeesan B, Haran P, Praveen D, et al. A comprehensive review on pancreatic cancer. Res J Pharm Technol. 2021; 14(1): 552–554, doi: 10.5958/0974-360x.2021.00100.1.
3. McGuigan A, Kelly P, Turkington RC, et al. Pancreatic cancer: A review of clinical diagnosis, epidemiology, treatment and outcomes. World J Gastroenterol. 2018; 24(43): 4846–4861, doi: 10.3748/wjg.v24.i43.4846, indexed in Pubmed: 30487695.
4. Tuveson DA, Neoptolemos JP. Understanding metastasis in pancreatic cancer: a call for new clinical approaches. Cell. 2012; 148(1-2): 21–23, doi: 10.1016/j.cell.2011.12.021, indexed in Pubmed: 22265397.
5. Ilic I, Ilic M, Ilic I, et al. Epidemiology of pancreatic cancer. World J Gastroenterol. 2016; 22(44): 9694–9705, doi: 10.3748/wjg.v22.i44.9694, indexed in Pubmed: 27956793.
6. Raczyński I, Didkowska J, Radecka B. Advanced pancreatic cancer: diagnosis and systemic treatment evolution over the last decades. Oncol Clin Pract. 2022; 18(5): 326–334, doi: 10.5603/ocp.2022.0030.
7. Conroy T, Desseigne F, Ychou M, et al. Groupe Tumeurs Digestives of Unicancer, PRODIGE Intergroup. FOLFIRINOX versus gemcitabine for metastatic pancreatic cancer. N Engl J Med. 2011; 364(19): 1817–1825, doi: 10.1056/NEJMoa1011923, indexed in Pubmed: 21561347.

8. Von Hoff DD, Ervin T, Arena FP, et al. Increased survival in pancreatic cancer with nab-paclitaxel plus gemcitabine. N Engl J Med. 2013; 369(18): 1691–1703, doi: 10.1056/NEJMoa1304369, indexed in Pubmed: 24131140.
9. Perusina Lanfranca M, Zhang Y, Girgis A, et al. Interleukin 22 Signaling Regulates Acinar Cell Plasticity to Promote Pancreatic Tumor Development in Mice. Gastroenterology. 2020; 158(5): 1417–1432.e11, doi: 10.1053/j.gastro.2019.12.010, indexed in Pubmed: 31843590.
10. Jamieson NB, Denley SM, Logue J, et al. A prospective comparison of the prognostic value of tumor- and patient-related factors in patients undergoing potentially curative surgery for pancreatic ductal adenocarcinoma. Ann Surg Oncol. 2011; 18(8): 2318–2328, doi: 10.1245/s10434-011-1560-3, indexed in Pubmed: 21267785.
11. La Torre M, Nigri G, Cavallini M, et al. The glasgow prognostic score as a predictor of survival in patients with potentially resectable pancreatic adenocarcinoma. Ann Surg Oncol. 2012; 19(9): 2917–2923, doi: 10.1245/s10434-012-2348-9, indexed in Pubmed: 22488099.
12. Stotz M, Gerger A, Eisner F, et al. Increased neutrophil-lymphocyte ratio is a poor prognostic factor in patients with primary operable and inoperable pancreatic cancer. Br J Cancer. 2013; 109(2): 416–421, doi: 10.1038/bjc.2013.332, indexed in Pubmed: 23799847.
13. An X, Ding PR, Li YH, et al. Elevated neutrophil to lymphocyte ratio predicts survival in advanced pancreatic cancer. Biomarkers. 2010; 15(6): 516–522, doi: 10.3109/1354750X.2010.491557, indexed in Pubmed: 20602543.
14. Hasegawa S, Eguchi H, Tomokuni A, et al. Pre-treatment neutrophil to lymphocyte ratio as a predictive marker for pathological response to preoperative chemoradiotherapy in pancreatic cancer. Oncol Lett. 2016; 11(2): 1560–1566, doi: 10.3892/ol.2015.4057, indexed in Pubmed: 26893780.
15. Chen Y, Yan H, Wang Y, et al. Significance of baseline and change in neutrophil-to-lymphocyte ratio in predicting prognosis: a retrospective analysis in advanced pancreatic ductal adenocarcinoma. Sci Rep. 2017; 7(1): 753, doi: 10.1038/s41598-017-00859-5, indexed in Pubmed: 28392554.
16. Bhatti I, Peacock O, Lloyd G, et al. Preoperative hematologic markers as independent predictors of prognosis in resected pancreatic ductal adenocarcinoma: neutrophil-lymphocyte versus platelet-lymphocyte ratio. Am J Surg. 2010; 200(2): 197–203, doi: 10.1016/j.amjsurg.2009.08.041, indexed in Pubmed: 20122680.
17. Guthrie GJK, Charles KA, Roxburgh CSD, et al. The systemic inflammation-based neutrophil-lymphocyte ratio: experience in patients with cancer. Crit Rev Oncol Hematol. 2013; 88(1): 218–230, doi: 10.1016/j.critrevonc.2013.03.010, indexed in Pubmed: 23602134.
18. Smith RA, Bosonnet L, Raraty M, et al. Preoperative platelet-lymphocyte ratio is an independent significant prognostic marker in resected pancreatic ductal adenocarcinoma. Am J Surg. 2009; 197(4): 466–472, doi: 10.1016/j.amjsurg.2007.12.057, indexed in Pubmed: 18639229.
19. Li Bo, Zhou P, Liu Y, et al. Platelet-to-lymphocyte ratio in advanced Cancer: Review and meta-analysis. Clin Chim Acta. 2018; 483: 48–56, doi: 10.1016/j.cca.2018.04.023, indexed in Pubmed: 29678631.
20. Haruki K, Shiba H, Shirai Y, et al. The C-reactive Protein to Albumin Ratio Predicts Long-Term Outcomes in Patients with Pancreatic Cancer After Pancreatic Resection. World J Surg. 2016; 40(9): 2254–2260, doi: 10.1007/s00268-016-3491-4, indexed in Pubmed: 26956901.
21. Wu M, Guo J, Guo L, et al. The C-reactive protein/albumin ratio predicts overall survival of patients with advanced pancreatic cancer. Tumour Biol. 2016; 37(9): 12525–12533, doi: 10.1007/s13277-016-5122-y, indexed in Pubmed: 27344157.
22. Ikeguchi M, Goto K, Watanabe J, et al. Clinical importance of preoperative and postoperative prognostic nutritional index in patients with pancreatic ductal adenocarcinoma. Ann Hepatobiliary Pancreat Surg. 2019; 23(4): 372–376, doi: 10.14701/ahbps.2019.23.4.372, indexed in Pubmed: 31825004.
23. Hu Bo, Yang XR, Xu Y, et al. Systemic immune-inflammation index predicts prognosis of patients after curative resection for hepatocellular carcinoma. Clin Cancer Res. 2014; 20(23): 6212–6222, doi: 10.1158/1078-0432.CCR-14-0442, indexed in Pubmed: 25271081.
24. Tang JN, Goyal H, Yu S, et al. Prognostic value of systemic immune-inflammation index (SII) in cancers: a systematic review and meta-analysis. J Lab Precis Med. 2018; 3: 29–29, doi: 10.21037/jlpm.2018.03.04.
25. Zhong JH, Huang DH, Chen ZY. Prognostic role of systemic immune-inflammation index in solid tumors: a systematic review and meta-analysis. Oncotarget. 2017; 8(43): 75381–75388, doi: 10.18632/oncotarget.18856, indexed in Pubmed: 29088873.
26. Casadei-Gardini A, Scarpi E, Ulivi P, et al. Inflammatory indexes as predictors of prognosis and bevacizumab efficacy in patients with metastatic colorectal cancer. Oncotarget. 2016; 7(22): 33210–33219, doi: 10.18632/oncotarget.8901, indexed in Pubmed: 27120807.
27. Lolli C, Basso U, Derosa L, et al. Systemic immune-inflammation index predicts the clinical outcome in patients with metastatic renal cell cancer treated with sunitinib. Oncotarget. 2016; 7(34): 54564–54571, doi: 10.18632/oncotarget.10515, indexed in Pubmed: 27409344.
28. Tian BW, Yang YF, Yang CC, et al. Systemic immune-inflammation index predicts prognosis of cancer immunotherapy: systemic review and meta-analysis. Immunotherapy. 2022; 14(18): 1481–1496, doi: 10.2217/imt-2022-0133, indexed in Pubmed: 36537255.
29. NCCN guidelines Version 1. Pancreatic Adenocarcinoma. www.nccn.org (01.10.2023).
30. Raczyński I, Zając P, Streb J, et al. Systemic treatment of patients with advanced pancreatic cancer — is there still a place for gemcitabine in the first-line setting? Experience of Polish oncology centers. Oncol Clin Pract. 2023, doi: 10.5603/ocp.97305.
31. Mantovani A, Allavena P, Sica A, et al. Cancer-related inflammation. Nature. 2008; 454(7203): 436–444, doi: 10.1038/nature07205, indexed in Pubmed: 18650914.
32. Proctor MJ, Morrison DS, Talwar D, et al. An inflammation-based prognostic score (mGPS) predicts cancer survival independent of tumour site: a Glasgow Inflammation Outcome Study. Br J Cancer. 2011; 104(4): 726–734, doi: 10.1038/sj.bjc.6606087, indexed in Pubmed: 21266974.
33. Jomrich G, Hollenstein M, John M, et al. The modified glasgow prognostic score is an independent prognostic indicator in neoadjuvantly treated adenocarcinoma of the esophagogastric junction. Oncotarget. 2018; 9(6): 6968–6976, doi: 10.18632/oncotarget.24087, indexed in Pubmed: 29467943.
34. Aziz MH, Sideras K, Aziz NA, et al. The Systemic-immune-inflammation Index Independently Predicts Survival and Recurrence in Resectable Pancreatic Cancer and its Prognostic Value Depends on Bilirubin Levels: A Retrospective Multicenter Cohort Study. Ann Surg. 2019; 270(1): 139–146, doi: 10.1097/SLA.0000000000002660, indexed in Pubmed: 29334554.
35. Feng JF, Chen S, Yang X. Systemic immune-inflammation index (SII) is a useful prognostic indicator for patients with squamous cell carcinoma of the esophagus. Medicine (Baltimore). 2017; 96(4): e5886, doi: 10.1097/MD.0000000000005886, indexed in Pubmed: 28121932.
36. Geng Y, Shao Y, Zhu D, et al. Systemic Immune-Inflammation Index Predicts Prognosis of Patients with Esophageal Squamous Cell Carcinoma: A Propensity Score-matched Analysis. Sci Rep. 2016; 6: 39482, doi: 10.1038/srep39482, indexed in Pubmed: 28000729.
37. Tong YS, Tan J, Zhou XL, et al. Systemic immune-inflammation index predicting chemoradiation resistance and poor outcome in patients with stage III non-small cell lung cancer. J Transl Med. 2017; 15(1): 221, doi: 10.1186/s12967-017-1326-1, indexed in Pubmed: 29089030.
38. Lolli C, Basso U, Derosa L, et al. Systemic immune-inflammation index predicts the clinical outcome in patients with metastatic

renal cell cancer treated with sunitinib. Oncotarget. 2016; 7(34): 54564–54571, doi: 10.18632/oncotarget.10515, indexed in Pubmed: 27409344.
39. Burris HA, Moore MJ, Andersen J, et al. Improvements in survival and clinical benefit with gemcitabine as first-line therapy for patients with advanced pancreas cancer: a randomized trial. J Clin Oncol. 1997; 15(6): 2403–2413, doi: 10.1200/JCO.1997.15.6.2403, indexed in Pubmed: 9196156.
40. Oh D, Pyo JS, Son BK. Prognostic Roles of Inflammatory Markers in Pancreatic Cancer: Comparison between the Neutrophil-to-Lymphocyte Ratio and Platelet-to-Lymphocyte Ratio. Gastroenterol Res Pract. 2018; 2018: 9745601, doi: 10.1155/2018/9745601, indexed in Pubmed: 29977290.
41. Jomrich G, Gruber ES, Winkler D, et al. Systemic Immune-Inflammation Index (SII) Predicts Poor Survival in Pancreatic Cancer Patients Undergoing Resection. J Gastrointest Surg. 2020; 24(3): 610–618, doi: 10.1007/s11605-019-04187-z, indexed in Pubmed: 30923999.
42. Yang JJ, Hu ZG, Shi WX, et al. Prognostic significance of neutrophil to lymphocyte ratio in pancreatic cancer: a meta-analysis. World J Gastroenterol. 2015; 21(9): 2807–2815, doi: 10.3748/wjg.v21.i9.2807, indexed in Pubmed: 25759553.