Original Article

Systemic immune-inflammation index: a prognostic tiebreaker among all in advanced pancreatic cancer

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Background: Pancreatic ductal adenocarcinoma (PDAC) detains a dismal prognosis and has a limited number of prognostic factors. Inflammation has been demonstrated to play a key role both in PDAC initiation and progression and several inflammation-based prognostic scores have been investigated in a wide range of malignancies. We compared the most analyzed inflammation-based prognostic scores in order to establish their potential impact on prediction of the outcome in advanced PDAC patients.

Methods: A total of 234 advanced PDAC patients undergoing first-line chemotherapy in our institute were retrospectively analyzed. Baseline clinicopathological and pre-treatment laboratory data were collected. Survival was estimated using Kaplan-Meier method and survival differences were evaluated using the log-rank test. Level of statistical significance P was set at 0.05. Only those variables that proved to be associated with statistically significant differences in outcome were compared in multivariate analysis using multiple Cox regression, as to identify their independent role and their relative power against each other.

Results: In the whole cohort, median overall survival (OS) was 8.7 months (95% CI: 7.8–9.4 months), median progression-free survival (PFS) was 3.8 months (95% CI: 3.1–4.2 months). At univariate analysis high systemic immune-inflammation index (SII) was related to shorter OS [hazard ratio (HR) =2.04, 95% CI: 1.59–4.19, P=0.0001] and PFS (HR =1.52, 95% CI: 1.11–2.20, P=0.01). This was maintained at multivariate analysis both for OS (HR =2.11, 95% CI: 1.29–3.46, P=0.003) and PFS (HR =1.64, 95% CI: 1.14–2.37, P=0.008), whereas other inflammation-based scores lost their independent role. Elevated SII (≥1,200) was associated with low albumin levels (P=0.03) and with elevated lactate dehydrogenase (LDH) (P=0.01).

Conclusions: Elevated SII represents an independent negative prognostic factor above all others for both OS and PFS in advanced PDAC patients treated with first-line chemotherapy, thus confirming a pivotal role of systemic inflammation on PDAC progression and on patient outcome.

Keywords: Inflammation; pancreatic cancer; prognosis; systemic immune-inflammation index (SII)

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Introduction

Pancreatic ductal adenocarcinoma (PDAC) is characterized by poor prognosis. On top of that, its incidence is increasing worldwide in both men and women (1). PDAC is mostly diagnosed at advanced stage and surgery, which is the only potentially curative approach, is feasible only in 15–20% of patients (2). Chemotherapy regimens based on fluorouracil, irinotecan and oxaliplatin (FOLFIRINOX) or gemcitabine plus nab-paclitaxel showed antitumor activity with an improvement in survival (3,4). More recently, poly (ADP-ribose) polymerases (PARPs) inhibitor olaparib was demonstrated to be effective as maintenance treatment option in germline BRCA1/2 mutated metastatic PDAC patients who had not progressed during first-line platinum-based chemotherapy (5). Nevertheless, mortality rate is high, and the 5-year survival rate still stands at 9% (6). To note, neither prognostic nor predictive factors able to foresee tumor behavior are available. Translational research on this topic is still ongoing. carbohydrate antigen 19-9 (CA19-9) is often increased in advanced PDAC stages and its changes during treatment may be useful in predicting response and progression to current treatment (7-9). Other concomitant factors, such as biliary diseases, chronic renal failure or thyroid diseases, increase CA19-9 levels, thus reducing CA19-9 levels usefulness and precision (10). Inflammation has been documented to play a key role in PDAC initiation (11). Indeed, both immune cells and cytokines are involved in early pancreatic carcinogenesis and, furthermore, in cancer cells invasion, migration and metastasis (12). During the last few years, the role of inflammation-based prognostic scores has been deeply investigated, both in early and in advanced tumor stages in many cancer types, including PDAC. These scores, combining different circulating immune cells, such as neutrophils, lymphocytes, monocytes and platelets, are able to represent patient systemic inflammatory and immune status and show a significant prognostic role in patient outcome. Inflammation-based prognostic scores mostly studied in PDAC are neutrophil-to-lymphocyte ratio (NLR) (13), platelet-to-lymphocyte ratio (PLR) (14) and recently also the systemic immune-inflammation index (SII), composed by the combination of neutrophils, platelets and lymphocytes (15). Similarly, in other malignancies the systemic inflammation response index (SIRI), the advanced lung cancer inflammation index (ALI) (16) and the prognostic nutritional index (PNI) were documented to play a significant role in predicting patient outcome (17,18). In our retrospective study, we evaluated at the same time the role of the most investigated inflammation-based prognostic scores and their correlation with clinical characteristics and outcome in a setting of patients affected by advanced PDAC treated with first-line chemotherapy, in order to establish their potential prognostic impact in clinical practice.

We present the following article in accordance with the REMARK reporting checklist (available at http://dx.doi.org/10.21037/atm-20-3499).

Methods

Ethics statement

The study was approved by the Ethics Committee in our hospital (University Hospital-Marche Polytechnic University, Ancona, Italy, prot. 214341). All procedures were performed by the ethics standards of our institutional research committee and with those of the 1964 Helsinki Declaration and its later amendments or comparable ethical standards and individual consent for this retrospective analysis was waived. All patients' personal data have been secured.

Patients characteristics

In our study, we analyzed retrospectively data from 234 patients affected by advanced PDAC and treated with first-line chemotherapy in our Institution from 2010 to 2019.

The inclusion criteria consisted of:

(I) Age >18 years old;
(II) Eastern Cooperative Oncology Group (ECOG) performance status (PS) ≤3;
(III) Histologically or cytologically confirmed diagnosis of PDAC;
(IV) Locally advanced not resectable or metastatic PDAC according to the 8th edition of the American Joint Committee on Cancer (Chicago, IL, USA) (19);
(V) No hematological disorders before treatment start;
(VI) Written informed consent of the patient for each line of chemotherapy treatment.

The exclusion criteria consisted of:

(I) Lack of data about tumor diagnosis or follow-up;
(II) Patients undergoing second or subsequent lines of chemotherapy;
(III) Pre-existing diseases that contraindicated

chemotherapy.

Clinical variables

Collected pre-treatment data included demographic characteristics (gender, age), ECOG PS, measured by ECOG/WHO score, weight, tumor location, staging, grading, histological features, previous surgery on primary tumor, previous radiotherapy, previous adjuvant or neoadjuvant chemotherapy, complete blood cells counts, liver function parameters [including albumin, bilirubin and lactate dehydrogenase (LDH)], type of chemotherapy (mono-chemotherapy *vs.* chemotherapy combination), carcinoembryonic antigen (CEA) and CA19-9 levels. Data about overall survival (OS) and progression-free survival (PFS), clinical benefit, response to treatment, last time of follow-up, current status (alive/dead) were also collected.

Inflammation indexes

We considered laboratory data closest to time of chemotherapy starting. Inflammation was measured by SII, based on the platelet (P), neutrophil (N), and lymphocyte (L) counts and calculated using the formula: SII = P × N/L. Optimal cut-off for OS [1,200] and PFS [700] were calculated with receiver operating characteristic (ROC) analysis; SIRI, based on peripheral neutrophil, monocyte, and lymphocyte counts, calculated as (N × M)/L, considering 2,000 as cut-off; ALI, based on body mass index (BMI), serum albumin (A), peripheral neutrophil and lymphocyte counts, calculated as (BMI × A)/NLR. In addition, we considered NLR, PLR and lymphocyte-to-monocyte ratio (LMR). We also assessed nutritional status, measured by BMI, corresponding to weight (kg)/height $(m)^2$, and PNI, obtained by calculating 10 × serum albumin (g/dL) + 0.005 × total lymphocyte count, considering 18.5 and 43 as cut-off respectively.

Statistical analysis

OS was defined as the range of time between chemotherapy initiation and death; for patients who had not died at last follow-up, OS was censored to last follow-up. PFS was defined as the range of time between chemotherapy initiation and disease progression or death; for patients who had not progressed or died at last follow-up, PFS was censored to last follow-up. The association between the categorical variables was estimated using the Chi-square test. Survival distribution was estimated using Kaplan-Meier curves and survival differences were evaluated using the log-rank test. Variables that achieved statistical significance ($P<0.05$) at univariate analysis were included in multivariate analysis using multiple Cox regression with stepwise method to identify independent prognostic factors. The hazard ratio (HR) was also calculated. Statistical analysis was conducted using MedCalc software version 19.1 for Windows and the cut-offs to consider high ratios were calculated using the ROC curve analysis. As the analyses presented are mainly comprised of scores deriving from different variables, correction for multiple testing was used (to reduce risk of family wise error) by Holm-Sidak procedure (20).

Results

Patients characteristics

A total of 234 patients affected by advanced PDAC were included in the study. Median age was 67 years (range, 31–85 years). Most of the patients presented with metastatic disease (83%) while 40 patients had locally advanced unresectable disease. Patients received different first-line chemotherapy regimens:

(I) FOLFIRINOX (fluorouracil 2,400 mg/m^2, leucovorin 400 mg/m^2, irinotecan 180 mg/m^2 and oxaliplatin 85 mg/m^2 doses every 2 weeks) (n=46);
(II) Gemcitabine plus nab-paclitaxel (gemcitabine 1,000 mg/m^2 plus nab-paclitaxel 200 mg/m^2 weekly on days 1, 8 and 15 every 4 weeks) (n=52);
(III) Gemcitabine (gemcitabine 1,000 mg/m^2 weekly on days 1, 8 and 15 every 4 weeks) (n=65);
(IV) GEMOX (gemcitabine 1,000 mg/m^2 on day 1 plus oxaliplatin 100 mg/mq on day 2 every 2 weeks) or cisplatin plus gemcitabine (cisplatin 50 mg/mq plus gemcitabine 1,200 mg/mq every 2 weeks) (n=41).

The remaining 30 patients received different treatment such as irinotecan, capecitabine or FOLFOX (fluorouracil 2,400 mg/m^2, leucovorin 400 mg/m^2 and oxaliplatin 85 mg/m^2 doses every 2 weeks). About one third of patients (n=85) had a biliary stent (*Table 1*). Median OS for whole study population was 8.7 months (95% CI: 7.8–9.4 months) while median PFS was 3.8 months (95% CI: 3.1–4.2 months). The median duration of follow-up was 29.2 months. A total of 41 patients (19.2%) had partial response (PR) while 47 (22.1%) had stable disease (SD) as best response to treatment. No complete response was observed. Progressive disease (PD) was observed in 71 (30%) patients while response could not

Table 1 Patient characteristics

Patient characteristics	N [%]
Age, years	
≥65	138 [59]
<65	96 [41]
Gender	
Male	131 [56]
Female	103 [44]
ECOG PS	
0–1	203 [87]
2–3	31 [13]
Chemotherapy regimen	
Folfirinox	46 [20]
Gemcitabine plus nab-paclitaxel	52 [22]
Gemcitabine	65 [28]
Gemcitabine plus cisplatin or oxaliplatin	41 [18]
Other (irinotecan, capecitabine, folfox)	30 [13]
Previous surgery	
Yes	41 [18]
No	193 [82]
Site of metastasis	
Liver	144 [62]
Peritoneum	42 [18]
Lung	65 [28]
Site of primary	
Head	149 [64]
Body/tail	85 [36]
Biliary stent	
Yes	85 [36]
No	149 [64]

ECOG, Eastern Cooperative Oncology Group; PS, performance status.

be evaluated in the remaining 21 patients.

Prognostic value of SII

Univariate analysis showed that high SII was significantly associated with a shorter OS (HR =2.04, 95% CI: 1.59–4.19, P=0.0001). In particular, median OS was 4.8 *vs.* 10.1 months in patients with SII ≥1,200 and SII <1,200 respectively (*Figure 1*). ECOG PS, PNI, hemoglobin, NLR, CEA, CA19-9, ALI, SIRI, albumin, LDH and chemotherapy regimen (monotherapy *vs.* combination) also had a statistically significant association with OS (*Table 2*). After correction for multiple testing, 8 variables (SII, CA19-9, CEA, ALI, ECOG PS, NLR, chemotherapy regimen and haemoglobin) were included in multivariate Cox-regression model. Multivariate analysis confirmed the independent prognostic value of SII (HR =2.11, 95% CI: 1.29–3.46, P=0.003), CA19-9 and chemotherapy regimen in terms of OS. Regarding PFS, SII was confirmed to be prognostic and significantly associated with disease progression (HR =1.52, 95% CI: 1.11–2.20, P=0.01) with a median PFS of 3.4 months for patients with high SII (≥700) and 6.9 for patients with low SII (*Figure 2*). ECOG PS, NLR, LDH, SIRI and ALI also had a statistically significant correlation with PFS.

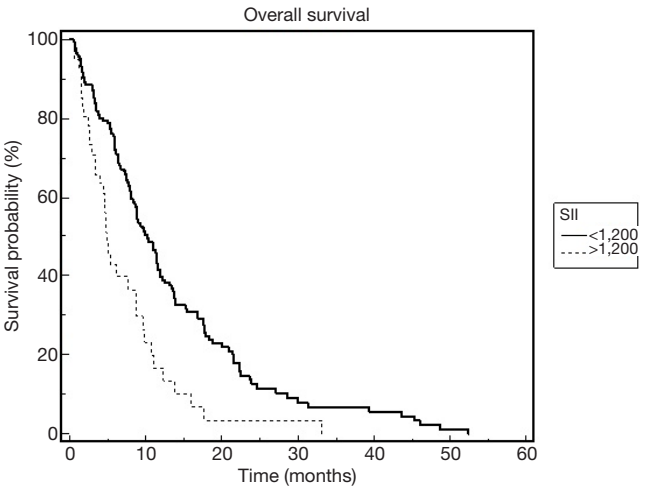

Figure 1 Kaplan-Meier curves for overall survival (OS) according to systemic immune-inflammation index (SII) value in whole patient cohort.

Among factors selected for multivariate analysis (NLR and SII) for PFS, SII (HR =1.64 95% CI: 1.14–2.37, P=0.008) was independently associated with PFS. We assessed the prognostic value of SII and other inflammatory markers also in the 52 patients who received treatment with gemcitabine and nab-paclitaxel and in the 46 patients treated with FOLFIRINOX regimen. In the group of patients treated with gemcitabine and nab-paclitaxel, 10 patients presented high SII value (≥1,200) and these

Table 2 Univariate and multivariate analysis for median overall survival (mOS)

Patients' characteristics	Subcategories	Univariate analysis		mOS (months)	Multivariate analysis	
		HR (95% CI)	P value		HR (95% CI)	P value
Age, years	≥65	0.96 (0.72–1.29)	0.81	–	–	–
	<65					
Gender	Male	1.06 (0.79–1.42)	0.68	–	–	–
	Female					
ECOG PS	0–1	0.44 (0.13–0.65)	0.002	8.81	–	NS
	2–3			4.32		
BMI, kg/m^2	≥18.5	0.75 (0.36–1.39)	0.33	–	–	–
	<18.5					
PNI	≥43	0.73 (0.51–0.98)	0.042	10.85	–	–
	<43			7.73		
Previous surgery	Yes	0.82 (0.59–1.13)	0.23	–	–	–
	No					
Hb, g/dL	≥12	0.70 (0.50–0.93)	0.015	9.44	–	NS
	<12			7.73		
NLR	≥4	1.57 (1.15–2.47)	0.007	5.82	–	NS
	<4			10.78		
CEA, ng/mL	>5	1.56 (1.16–2.28)	0.005	6.35	–	NS
	<5			9.57		
CA19-9, U/mL	>5,000	1.97 (1.57–3.86)	0.0001	5.82	1.89 (1.13–3.15)	0.015
	<5,000			9.57		
SII	≥1,200	2.04 (1.59–4.19)	0.0001	4.8	2.11 (1.29–3.46)	0.003
	<1,200			10.1		
PLR	>130	1.29 (0.96–1.81)	0.09	–	–	–
	<130					
ALI	≥25	0.59 (0.38–0.79)	0.001	11.51	–	NS
	<25			7.73		
LMR	≥2.9	0.80 (0.58–1.10)	0.17	–	–	–
	<2.9					
Albumin, g/dL	≥3.8	0.69 (0.47–0.93)	0.039	11.28	–	–
	<3.8			8.81		
Chemotherapy regimen	Monotherapy	1.48 (1.15–2.12)	0.008	6.02	1.47 (1.01–2.15)	0.046
	Combination			9.71		
LDH	≥ ULN	1.35 (1.01–1.91)	0.04	5.75	–	–
	< ULN			9.8		

Table 2 *(continued)*

Table 2 *(continued)*

Patients' characteristics	Subcategories	Univariate analysis		mOS (months)	Multivariate analysis	
		HR (95% CI)	P value		HR (95% CI)	P value
Stage	LAPC	0.88 (0.55–1.39)	0.58	–	–	–
	IV					
Site of primary	Head	1.29 (0.70–2.41)	0.41	–	–	–
	Body/tail					
Liver metastasis	Present	1.19 (0.85–1.69)	0.29	–	–	–
	Absent					
Peritoneal carcinomatosis	Present	0.97 (0.64–1.47)	0.88	–	–	–
	Absent					
SIRI	≥2,000	1.63 (1.99–2.51)	0.0035	5.82	–	–
	<2,000			11.28		

ALI, advanced lung cancer inflammation index; BMI, body mass index; CA19-9, carbohydrate antigen 19-9; CEA, carcinoembryonic antigen; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; Hb, haemoglobin; HR, hazard Ratio; LAPC, locally advanced pancreatic cancer; LDH, lactate dehydrogenase; LMR, lymphocyte-to-monocyte ratio; NLR, neutrophil-to-lymphocyte ratio; NS, not significative; PLR, platelet-to-lymphocyte ratio; PNI, prognostic nutritional index; PS, performance status; SII, systemic immune-inflammation index; SIRI, systemic inflammation response index; ULN, upper limit normal.

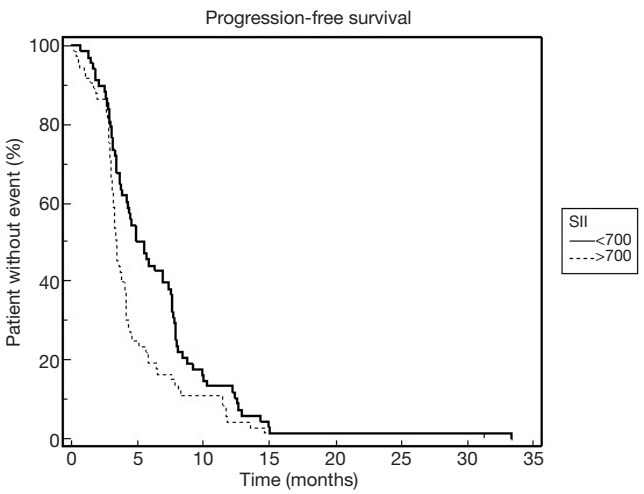

Figure 2 Kaplan-Meier curves for progression-free survival (PFS) according to systemic immune-inflammation index (SII) value in whole patient cohort.

patients had a significantly shorter OS compared to patients with low SII with a median OS of 4.8 *vs.* 11.9 months, respectively (HR =3.97 95% CI: 3.29–78.6, P=0.0006). The prognostic value of SII was confirmed also in the subgroup of patients treated with FOLFIRINOX with a median OS of 5.2 *vs.* 11.6 months for patients with high SII *vs.* low SII (HR =2.30, 95% CI: 1.16–9.39, P=0.031).

SII and clinicopathological characteristics

A high SII (≥1,200), detected in 53 patients (22.6%), was associated with low albumin levels (P=0.03) and with elevated LDH (P=0.01). There was also a trend for association between high SII and low BMI but it was not statistically significant (P=0.06).

Discussion

There is a deep link between PDAC and inflammation: both hereditary and sporadic chronic pancreatitis increase by 10 times the risk of developing PDAC (21,22). Indeed, inflammation, mediated by immune cells and cytokines, both locally and systemically, triggers pro-inflammatory pathways and may play a key role in the early development of PDAC (23). In this study we compared several immune and nutritional scores (NLR, PLR, LMR, ALI, SIRI, SII, PNI), extensively investigated in other cancers, including PDAC (24-27) and we documented the value of SII in prediction of patient outcome. In particular, patients with high SII showed a shorter OS (median OS 4.5 *vs.*

10.1 months) and PFS (median PFS 3.4 *vs.* 6.9 months). SII maintained its value in multivariate analysis both for OS and PFS, suggesting a strong impact of inflammatory systemic status on cancer natural history and, therefore, on patient outcome. In addition, we confirmed the prognostic role of high baseline concentration of tumor marker CA19-9 (28,29). Also, mono-chemotherapy regimen was correlated with worse OS. To note, PDAC patients candidate to first-line mono-chemotherapy are generally characterized by worse PS at diagnosis, more comorbidities and therefore a lower likelihood of response to treatment. The SII includes three significant blood cell components linked to cancer initiation and progression, in particular neutrophils, platelets and lymphocytes and its close relationship with survival and in PDAC patients emphasizes even more the role of those inflammatory mediators in cancer. It has been amply demonstrated that chronic inflammation generates an immunosuppressive and tumor-promoting microenvironment by the accumulation of pro-inflammatory cytokines and immune suppressor cells infiltration, promoting tumour initiation, progression and metastasis (30). Moreover, many studies have underlined that thrombocytosis and neutrophilia are related to cancer evolution and worse clinical outcome, also in PDAC (31-34). Increasing evidences have shown the crosstalk between cancer cells and platelets, and the concept of tumour cell-induced platelet aggregation has been developed since late 19th century (35). Cancer cells, by secreting thrombopoietic cytokine such as interleukin-1 (IL-1), interleukin-3 (IL-3) and interleukin-6 (IL-6) are the main cause of hepatic thrombopoietin secretion and thrombocytosis (36). Recent studies have also demonstrated how platelets impact positively on cancer cells proliferation, stimulating mitogenic pathways (37). It has been observed in experimental models that decreasing plasmatic platelets concentration the tumor burden decrease and cancer cells chemo-sensibility increase (38). Platelets also increase cancer cell migration and invasion, showing involvement in circulating tumour cells (CTCs) adherence to endothelium and transmigration into tissues (39). Platelet-tumour cells aggregates exhibit ligands of endothelium cells receptors [P-selectin, intercellular cell adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule-1 (VCAM-1)], improving endothelial activation, cancer cells extravasation (40) and, therefore, leading to the formation of early metastatic niches (41). Platelets may adhere at the surface of CTCs, protecting them from immune cells surveillance and promoting cancer cell survival (42).

It has been widely demonstrated that increased concentration of circulating neutrophils is a predictor of worse outcome in advance cancer patients (43,44). It seems that cancer cells are able to produce cytokines such as granulocyte colony-stimulating factor (G-CSF) and IL-6, leading to an increased neutrophil count in patient blood (45). At the same time, it has been shown that neutrophils may produce growth factors, which stimulate cancer cell tumorigenicity. Likewise, neutrophils bound to CTCs surround and protect them from immune circulating cells. In addition, neutrophils promote CTCs endothelium adhesion and extravasation, and therefore, metastasis initiation (46). On the other side, lymphocytes own an essential anti-cancer cell role. It has been demonstrated that lymphopenia is related to shorter survival and lower response to treatment in several malignancies, including pancreatic cancer, representing the immune system inability of contrasting tumor progression (47). SII, including platelets, neutrophils and lymphocytes, may represent a valid surrogate of inflammatory and immune status of patients affected by advanced PDAC. Zhang *et al.* (15) evaluated the prognostic role of SII in a cohort of advanced PDAC patients. They demonstrated in univariate and multivariate analysis, that SII was significantly correlated with OS, in both normal and elevated CA19-9 patients' subgroups, with a median OS of 5.7 and 7.9 months for patients with higher and lower SII respectively. Jomrich *et al.* (48) analyzed the prognostic role of NRL, PLR and SII in a cohort of patients affected by PDAC who underwent surgical resection. They found that SII, but not NLR and PLR was an independent prognostic factor in PDAC patients undergoing surgery with a median OS of 14.2 *vs.* 20.5 months for patients with high or low SII respectively. In our study, we assessed some of the most investigated inflammation indexes in cancer (ALI, SIRI, NRL, PLR, and SII) and demonstrated SII superiority in predicting OS and PFS. Interestingly, SII maintained its strong prognostic value both in subgroup treated with gemcitabine and nab-paclitaxel and subgroup treated with FOLFIRINOX, two commonly used chemotherapy regimens in advanced PDAC. In addition, we found that high SII was related to low plasmatic albumin and elevated plasmatic LDH concentration. The association between high serum LDH levels and low albumin with worse outcome in PDAC has been suggested by several studies. Focusing on LDH, an interesting work by Yu *et al.* (49) investigated the link between serum level of LDH and systemic inflammation markers such as NRL, PLR and LRM in advanced

PDAC patients after gemcitabine-based treatment. They demonstrated that higher LDH serum levels predicted worse patients' outcome and were positively linked with NRL and PLR and negatively with LMR, underlining the deep correlation between systemic inflammation and hypoxia in advanced PDAC. Serum LDH is an indicator of tumor hypoxia and it is known that PDAC, marked by an abundant desmoplastic stroma and low blood supply, induce hypoxic stress in cancer cells, facilitating tumor progression and worse patients' outcome and response to chemotherapy (50). Cancer cells hypoxia adaptation is mediated by hypoxia-inducible factor 1 (HIF-1) and preclinical studies have demonstrated how HIF-1 may enhance systemic inflammation status (51). Our study confirmed this evidence showing a significant association between high SII and elevated serum LDH levels in advanced PDAC patients.

Conclusions

To conclude, our results demonstrated that evaluation of inflammatory status at diagnosis has clinical strong implications, regardless of therapeutic strategies adopted. Among the most analyzed inflammation-based prognostic scores in cancer patients, we demonstrated that SII detained the strongest negative prognostic value in advanced PDAC patients, taking into account several chemotherapeutic regimens, and may represent the most useful score in clinical practice for predicting patient outcome. Patients characterized by high SII may benefit from earlier supportive care concurrently with chemotherapy. Moreover, targeting inflammation pathways may become a novel weapon to place side by side to standard chemotherapy. Early trials have been already developed to test target therapies against inflammatory targets and immune tumor microenvironment (52). Therefore, advanced PDAC patients that show high SII before treatment start may be candidate to a drugs combination consisting of chemotherapy plus anti-inflammatory drugs in the near future. Clinical trials are needed to validate this therapeutic strategy in advanced PDAC patients and SII may be a useful parameter for better patient stratification. The limitations of the study are mainly related to the fact that this is a monocentric study conducted retrospectively and the non-uniformity of the treatment proposed in the first line. However, the prognostic ability of SII was further confirmed by separately evaluating patients receiving gemcitabine plus nab-paclitaxel and FOLFIRINOX, respectively. In addition, it is not possible to exclude a conditioning of the results by tumor-independent factors capable of inducing a pro-inflammatory state (infections in progress, chronic inflammatory diseases). In particular, we did not have information about concurrent infections and inflammatory conditions of our patients, such as cholangitis. Moreover, other inflammatory markers such as C-reactive protein (CRP) and procalcitonin are not assessed in our clinical practice routinely and were not available for our analysis. Beyond limitations we mentioned, our study confirms the independent prognostic value of SII and justifies its possible use in clinical practice. The balance of costs and benefits is an important element in planning an anti-tumor treatment program and the fact that SII can be determined in a simple and cost-effective way through routine laboratory investigations makes it a handy and accessible parameter for clinical management.

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Footnote

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/atm-20-3499). The authors have no conflicts of interest to declare

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Our project has been approved by the Ethics Committee in our hospital (University Hospital-Marche Polytechnic University, Ancona, Italy, prot. 214341). All procedures were performed

by the ethics standards of our institutional research committee and with those of the 1964 Helsinki Declaration and its later amendments or comparable ethical standards and individual consent for this retrospective analysis was waived.

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