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Systemic Inflammatory Response in Pancreatic Ductal Adenocarcinoma

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<http://dx.doi.org/10.5772/intechopen.78954>

Abstract

Pancreatic ductal adenocarcinoma induces systemic inflammatory response (SIR), which can be assessed either by ratios between blood cell counts (neutrophil to lymphocyte ratio, NLR; platelet to lymphocyte ratio, PLR) or concentrations of acute phase proteins, clotting factors and albumins. These tests are biologically justified by multiple events including bone marrow activation, development of immune-suppressing immature myeloid cells, generation of pre-metastatic niches and neutrophil extracellular trap formation from externalised DNA network in bidirectional association with platelet activation. Despite biological complexity, clinical assessment of SIR is widely available, patient-friendly and economically feasible. In this chapter, we present a review on NLR, PLR, Glasgow prognostic score and fibrinogen, recently reported to have a prognostic role regarding overall survival, cancer/progression free and cancer-specific survival in early and advanced pancreatic ductal adenocarcinoma. Practical consequences abound, including preference for surgical or combined, active or sparing treatment, as well as prediction of non-resectability or chemotherapy response. In this chapter, we also scrutinise the main controversies including different cut-off levels, hypothetic correlation with tumour burden and morphology, negative findings and discussions on the best marker. Future developments should include elaboration of complex scores as will be described here.

Keywords: pancreatic ductal adenocarcinoma, systemic inflammatory response, neutrophil to lymphocyte ratio, NLR, platelet to lymphocyte ratio, PLR, Glasgow prognostic score, fibrinogen

1. Introduction

Pancreatic ductal adenocarcinoma (PDAC) is known for notoriously difficult early diagnostics, almost complete lack of well-defined risk groups for targeted surveillance and poor response to treatment in advanced stages. Thus, PDAC remains among the most challenging cancers for medical professionals today. By incidence, pancreatic cancer was estimated to be the 12th most frequent malignant tumour worldwide in the year 2012. However, it ranked seventh in the global estimates of oncological mortality for the same year. The dismal prognosis is reflected in the high mortality-to-incidence ratio reaching 0.98 [1]. Pancreatic cancer encompasses 2.4% of global cancer incidence and 4.0% of cancer-attributable death cases in the world. Even more, it was predicted to be the fourth leading cause of oncological mortality in Europe, comprising 6% of cancer-induced death events in 2017 [2]. Considering the growing incidence, that might be attributable to the epidemic of obesity and metabolic syndrome, and low 5-year survival rate (6%), USA research teams have generated prognosis that pancreatic cancer might become the second most common cause of oncological mortality by the year 2030 [3].

PDAC is responsible for the bulk of pancreatic cancer burden as it is the most common and aggressive pancreatic tumour [4]. The overall survival and long-term survival rates of patients diagnosed with PDAC generally have not improved in last 30 years, despite multiple innovations in the surgery, including resection of multiple organs; anaesthesia; patient referral for surgery in accordance to surgeon's experience and the excellence of medical team/centre; molecular studies and trends towards personalised treatment as well as appearance of new drugs [3–5].

Currently, pTNM is the mainstay for pancreatic cancer staging [4]. Molecular portrait is important to select targets for personalised treatment. It can have a prognostic role as well. However, the current situation forces to look for additional prognostic factors in PDAC, aiming to stratify patient groups by the predicted treatment response or to adjust the necessary treatment intensity in order to improve the survival or life quality.

Recently, systemic inflammatory response (SIR) has been highlighted in different cancers, including PDAC [6–8]. The network of SIR involves cancer microenvironment, bone marrow and metastatic sites, manifesting as the changes of blood cell counts and ratios as well as blood levels of acute phase proteins. SIR encompasses complex interactions between at least three players: the tumour, the innate and adaptive immunity of the host and the distant tissues.

In SIR, the altered functions of bone marrow lead to switches in production and release of inflammatory cells, including neutrophils. Consequently, blood counts of neutrophils increase and immature myeloid derived suppressor cells (MDSC) appear in the peripheral blood.

Neutrophils develop in bone marrow, and 90% of the mature cells remain there until activating stimulus ensures rapid release in appropriate situations. In cancer-induced SIR, neutrophils are ejected from bone marrow in response to colony-stimulating factors that are produced by the malignant cells. In addition, neutrophil response is incited by tissue damage caused by cancer invasion and/ or by tumour necrosis due to hypoxia and insufficient blood supply in the core of growing mass. The colony-stimulating factors influence also the CXCR2/CXCR4 chemokine axis that is responsible for the circulation of neutrophils in

Class	Summary activity	Features and mechanisms	References
N1 neutrophils	Anti-tumour	Cytotoxic, capable to kill cancer cells: high levels of ROS immunostimulatory: <ul style="list-style-type: none"> high levels of Fas, TNF alpha, CCL3, ICAM1; low activity of arginase lead to activation of T cells 	[9]
N2 neutrophils	Pro-tumour	Lack significant cytotoxic activity Immunosuppressive: high activity of arginase Angiogenic: vascular endothelial growth factor (VEGF) Facilitate invasion: matrix metalloproteinases (MMP) 8, MMP9	[3, 9]
M1 macrophages	Pro-inflammatory	Restrict cancer growth Produce pro-inflammatory cytokines TNF alpha, IL-1, IL-6, IL-12, IL-23 Express MHC Produce NO synthase Enhance antigen presentation to T lymphocytes	[3] [10]
M2 macrophages	Anti-inflammatory	Promote cancer growth Immunosuppressive: secret IL-10, arginase, transforming growth factor beta Down-regulate MHC class II Facilitate angiogenesis Promote cancer cell migration	[3] [10]

Table 1. The subtypes of neutrophils and macrophages.

accordance to cellular maturity and life cycle: retention of immature myeloid cells in the bone marrow, release of mature cells upon necessity and return of ageing neutrophils that must be destroyed. Consequently, the neutrophil counts in blood of cancer patients increase, and there can be a shift to immature cell release.

In tumour microenvironment, neutrophils can differentiate towards either anti-cancerous N1 or pro-cancerous N2 phenotype (**Table 1**). These subtypes are considered to represent the end points of the activity spectrum, but any neutrophil can exhibit combined traits of both subtypes. Transforming growth factor beta is known as a potent mediator of N2 differentiation [9].

Neutrophils are capable to facilitate the metastatic spread of PDAC. Clusters formed by neutrophils and circulating cells of pancreatic ductal adenocarcinoma have been observed in peritumoural blood vessels. Further, significant relationship was found between neutrophil-characterising blood indices (neutrophil to lymphocyte ratio) and distant metastasis after curative surgery [11]. These clinical observations are explained by a complex network of pathogenetic events. Neutrophils can promote tumour cell proliferation and invasion (see **Figure 1**), as well as enhance angiogenesis and increase vascular permeability. Neutrophils also represent the main cell population involved in the formation of pre-metastatic niche

before malignant cells arrive to the site of metastasis. In the pre-metastatic niches, neutrophils and immature bone marrow-derived cells gather in clusters that ensure tumour cell homing. When circulating tumour cells reach the ‘prepared’ metastatic site, neutrophils anchor cancer cells to the endothelium, facilitating trans-endothelial migration and invasion. Indeed, malignant cells entrapped in distant organs produce cytokines to attract neutrophils. The classic inflammation-related adhesion molecules, including integrins, can promote cancer cell adhesion [9]. Thus, interleukin-induced expression of ICAM1 has been shown to support the extravasation of malignant cells and pathogenesis of the PDAC metastasis [12]. Leukotrienes, secreted by neutrophils, further promote tumour cell proliferation and growth of the metastasis [9]. To enhance carcinogenesis, neutrophils act in concert with macrophages, similarly to the parallel effects of MDSCs and M2 macrophages. For instance, bone marrow-derived macrophages are involved in the generation of premetastatic niches by pancreatic cancer exosomes [13].

Within the framework of SIR, neutrophils derive unique structures—neutrophil extracellular traps (NETs). NETs represent a mesh of chromatin and nuclear proteins [9]. These structures possibly have evolutionary developed as a mechanism of antimicrobial response. In cancer patient, NETs can wrap a circulating tumour cell, resulting in either reactive oxygen species (ROS)-mediated destruction or facilitated adhesion in a pre-metastatic niche. NETosis evolves in different stressful conditions, including pre-eclampsia, major surgery or surgical infection. Consequently, surgery is not only a mechanical tool to withdraw the tumour from the body, but it can also become a major immunologic switch. Prolonged or complicated surgical intervention might threaten patient’s life directly but also through SIR-associated pathways. Indeed, surgical stress or postsurgical infection is shown to facilitate metastatic spread, and NETosis is demonstrated in these conditions [9]. SIR-based molecular events highlight the association between infection or surgery-induced inflammation [14, 15] and recurrence or metastatic spread of the cancer.

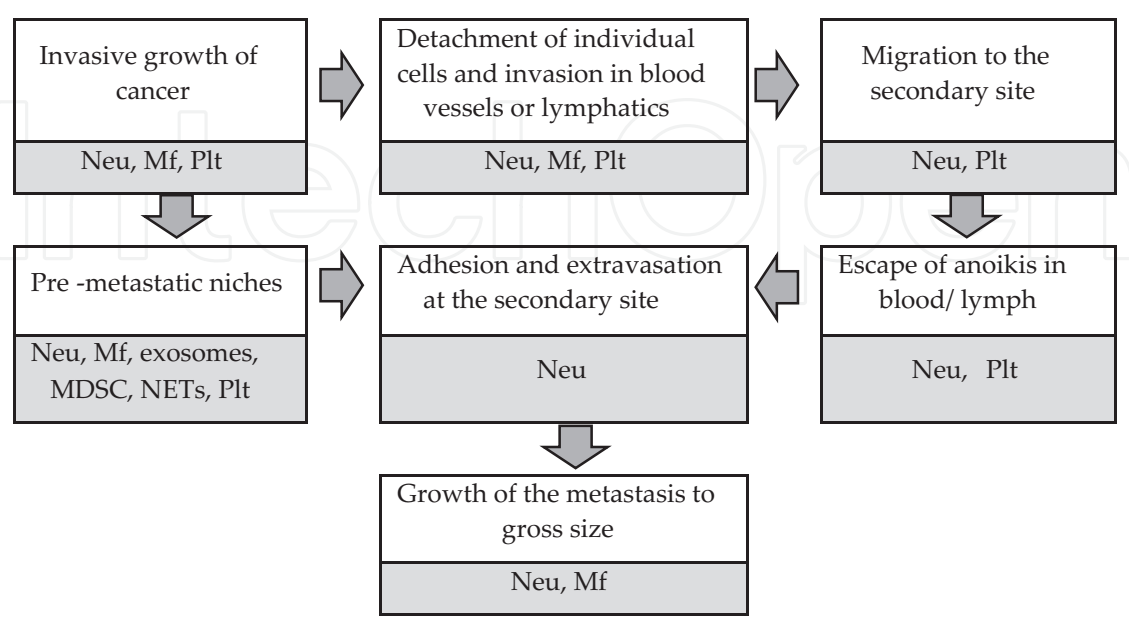


Figure 1. The main pathogenetic events in metastatic dissemination of cancer. Abbreviations: Neu, neutrophils; Mf, macrophages; Plt, platelets; MDSC, myeloid derived suppressor cells; NETs, neutrophil extracellular traps.

Neutrophils along with macrophages and other innate immunity cells are considered to have predominantly pro-tumourous activity, contrasting with adaptive immunity (lymphocytes) having protective role. However, this assumption is not straightforward—N1 neutrophils exhibit contra-cancer activity. Type I interferons can convert neutrophils into anti-tumourous fighters with rich armoury: enhanced production of ROS, suppressed ability to form pre-metastatic niches, upregulated ROS-mediated killing of NET-trapped cancer cells, active direct cytotoxicity (via ROS or antibody-dependent cell-mediated cytotoxicity) and improved capacity to stimulate adaptive immunity [9].

MDSCs represent heterogeneous population of immature cells (namely, the precursors of granulocytes, macrophages, monocytes and dendritic cells) sharing immunosuppressive function and myeloid origin. These cells express wide spectrum of enzymes, inflammatory mediators as well as reactive oxygen species and/or reactive nitrogen intermediates [3]. MDSCs travel via blood from their site of origin in bone marrow to the tumour and to peripheral tissues. In the cancer microenvironment, MDSCs along with M2 macrophages (see **Table 1**) exert immunosuppressive effect [16]. Within the complex immunosuppressive network of events in tumours stroma, MDSCs suppress the activity of CD8-positive T lymphocytes; induce T-cell apoptosis by ROS and nitric oxide derivatives; promote T-cell anergy via regulatory T lymphocytes; inhibit T cell migration via nitration of chemokines and T-cell receptors; block interferon (IFN) gamma pathway and cleave arginine and cysteine via upregulated arginase. The IFN gamma, arginine and cysteine are essential for T lymphocyte activity. In addition to the anti-T cell activities, MDSCs block the M1 phenotype of tumour-infiltrating macrophages. Production of pro-inflammatory interleukin (IL) 6 by MDSCs promote JAK/STAT mediated pathways stimulating cancer cell proliferation, survival and evasion from antigen presentation to dendritic cells [3]. In distant tissues, immature myeloid cells participate in the generation of pre-metastatic niches [14, 17].

The activities of neutrophils and MDSC in tumour stroma are carried out in cooperation with tumour-infiltrating macrophages. Macrophages are recruited by cancer-produced signal molecules, including cytokines and growth factors, as well as by tumour necrosis. In cancer microenvironment, macrophages acquire M2 differentiation and can enhance tumour progression, angiogenesis and metastatic spread [10]. M2 macrophages along with MDSC are immune suppressors in the cancer stroma [16]. In distant tissues, macrophages assist in the creation of premetastatic niches. As noted, this mechanism has been demonstrated in PDAC: bone marrow-derived macrophages are involved in the generation of premetastatic niches by pancreatic cancer exosomes [13].

In turn, lymphocytes mostly play a defensive role against cancer in the whole body and in tumour microenvironment [10].

The pathogenetic association between PDAC and activated blood clotting is acknowledged for centuries, reflected by the historic descriptions of migratory thrombophlebitis, also known as Trousseau syndrome. The related clinical events include thromboembolism and nonbacterial thrombotic endocarditis in cancer patients, occasionally manifesting as the first sign of malignant disease [18]. In peripheral blood, platelet counts increase in response to local cancer invasion causing endothelial damage. The platelet response is also generated by the pro-inflammatory cytokines (IL-1, IL-3 and IL-6) that are produced by the cancer and promote megakaryocyte development [8]. Thrombocytosis has been observed in 15.2% of PDAC patients [19].

Parameter/score	Definition
NLR	Ratio between the absolute counts of neutrophils and lymphocytes in the peripheral blood
PLR	Ratio between the absolute counts of platelets and lymphocytes in the peripheral blood
Glasgow prognostic score	
0	CRP < 10 mg/L AND albumin \geq 35 g/L
1	One high-risk finding: CRP \geq 10 mg/L OR albumin <35 g/L
2	Both high-risk findings: CRP \geq 10 mg/L AND albumin <35 g/L
Modified Glasgow prognostic score	
0	CRP \leq 10 mg/L irrespective of albumin level
1	Increased CRP on the background of normal albumin level: CRP > 10 mg/L AND albumin \geq 35 g/L
2	Increased CRP and hypoalbuminemia: CRP > 10 mg/L AND albumin <35 g/L

Abbreviation: CRP, C-reactive protein.

Table 2. Parameters of systemic inflammatory reaction.

Locally, platelets promote angiogenesis, invasion, production of growth factors and adhesion molecules [8]. Platelets facilitate metastatic spread by creating clusters with circulating tumour cells and protecting them from immune surveillance, promoting the development of pre-metastatic niches and tumour cell attachment to distant tissues. Along with the metastatic spread, platelets are suggested to have a major role in epithelial-mesenchymal transition—process during which epithelial malignant cells change the phenotype to mesenchymal-like, plastic cells with enhanced capability for invasion into connective tissues, blood and lymphatic vessels as well as metastatic spread [8].

Considering pathogenetic and prognostic role of the interaction between tumour and host inflammatory response, systemic inflammatory response has recently become a hot topic in medical research. Several indices are elaborated to evaluate SIR (**Table 2**). Neutrophil to lymphocyte ratio (NLR), platelet to lymphocyte ratio (PLR) and Glasgow prognostic score (GPS) represent the best-known examples.

Although almost all immune and inflammatory cells can have dual effects in cancer, neutrophils mainly act as tumour promoters while lymphocytes represent the protective innate immunity. Thus, NLR represents the balance between pro- and contra-tumourous immune and inflammatory processes of the host. Similarly, activation of blood clotting is associated with burden of invasive tumour, that damages endothelium like ‘dozen of sharp knives’, and platelets also facilitate the further development and spread of the cancer while lymphocytes exhibit protective action. Hence, PLR is another measure of equilibrium between pro- and contra-tumourous events within SIR. GPS reflects the upregulation of acute phase protein (measured by the prototypic C-reactive protein) and degree of catabolism by hypoalbuminemia. In addition, combined inflammation-based scores have been proposed, derived from combinations of SIR-related factors in order to reach higher prognostic value.

Considering high mortality and poor treatment results of pancreatic ductal adenocarcinoma and the need for prognostic and predictive novelties, this chapter scrutinises the assessment of SIR in PDAC, potential practical implementations and restrictions of those parameters.

2. NLR in pancreatic ductal adenocarcinoma

Neutrophil to lymphocyte ratio is calculated as the ratio between the count of neutrophilic leukocytes and lymphocytes in peripheral blood, using the values detected in a routine full blood count. Hence, the parameter is easily available, especially in carefully examined cancer patients, and economically nondemanding. In fact, sufficient awareness and algorithm for interpretation are the only prerequisites to obtain an additional piece of information from routine blood tests. At present, the association between NLR and different aspects of survival, for example, overall, recurrence free or cancer-specific survival, remains one of the best substantiated aspects in the SIR research in cancer.

2.1. NLR and survival

The prognostic importance of NLR is shown over the whole course of PDAC and is applicable to wide treatment spectrum—from surgically resectable early cases to advanced or metastatic tumours eligible only for non-surgical treatment. Several research teams have demonstrated independent prognostic value of NLR, confirmed by multivariate analysis. In few studies, the association with survival is confirmed by univariate but not multivariate analysis. Some of the reports are on better scores, for example, Glasgow prognostic score had higher informativity in the study performed by Yamada et al. [20].

Although only a minor fraction (around 20%) of pancreatic cancers are amenable to surgery, surgical removal of tumour is highly advisable, if feasible because surgery provides the only definitive cure [5]. Pre-treatment NLR has been evaluated as a prognostic factor for surgically treated PDAC patients, mostly with positive findings. Thus, in a large cohort of 442 patients subjected to pancreatic resection for PDAC, high NLR was associated with significantly lower median survival. The difference was also biologically important: only 12.6 months in those presenting with high NLR (defined in this study by receiver operating characteristics (ROC) curve analysis as ≥ 5) patients versus 25.7 months in patients having low NLR. Cox proportional hazards analysis confirmed NLR as an independent prognostic factor, associated with hazard ratio (HR) 1.66; 95% confidence interval (CI): 1.12–2.46; $p = 0.012$ [21]. In a small group of 46 patients subjected to pancreaticoduodenectomy, high NLR (≥ 2.5) was associated with lower overall survival rate. In addition, it predicted surgical complications worse than Clavien-Dindo grade 3 [22]. Among 381 patients treated by curative resection of PDAC, high NLR (≥ 2) was significantly and independently associated with overall survival [23]. The prognostic value was especially clear in stage I/II [24]. In 110 surgically treated pancreatic cancer patients, high NLR (≥ 5) was an independent prognostic factor for worse cancer-specific survival, as confirmed by $p < 0.039$ [25].

Standard preoperative assessment of NLR is recommended in cases of borderline resectable pancreatic cancer by consensus statement by the International Study Group of Pancreatic Surgery [26].

In most studies, preoperative NLR has been assessed. However, the patient's immune status after the surgery might be as important. Indeed, postoperative NLR, evaluated 1 month after the surgery, was shown to have a prognostic value for overall and recurrence-free survival. Comparing the patients with $\text{NLR} \geq 3$ versus $\text{NLR} < 3.0$, the 1-year survival rate was 42.6 versus 81.9% and 3-year survival rate: 7.3 versus 33.9% ($p < 0.001$). Notably, the differences were confirmed to be statistically significant despite relatively small study group comprising 86 patients [27].

However, negative observations have also been reported. In a reliably large study group of 217 surgically treated PDAC patients, overall survival was significantly associated with age, adjuvant treatment, cancer invasion in blood vessels and lymphatics, R1 and pTN while NLR was not predictive of OS [28]. Assessing 379 consecutive patients who underwent curative resection for pancreatic cancer, no significant differences in overall survival were found in patients showing high versus low NLR although another SIR marker, the Glasgow prognostic score was confirmed as a significant predictor of survival [20].

A meta-analysis of eight studies including 1519 patients with resectable pancreatic cancer has been recently carried out by Mowbray et al. [29]. The pooled data confirm association between high NLR and low overall survival: $\text{HR} = 1.77$; 95% CI: 1.45–2.15; $p < 0.01$ [29]. In a systematic review of resectable pancreatic cancer, 10 studies were eligible and 8 had reported NLR. Significant association with survival was found in three of them [5].

The prognostic value of NLR has also been investigated in advanced and metastatic PDAC cases. In a large cohort of patients (497) diagnosed with locally advanced pancreatic cancer and treated by neoadjuvant or definitive chemoradiotherapy, elevated NLR was significantly associated with worse 1-year overall survival and 1-year progression free survival rates. In this study, the median value was selected as the cut-off threshold. Patients presenting with low NLR (< 1.89), had 1-year survival rate of 73.2% and 1-year progression free survival rate of 43.9%, contrasting with those having high NLR (≥ 1.89): 60.8% survived at least 1-year and 31.3% were free of progression at least for 1-year (both $p < 0.001$) as reported by Lee et al., [30]. In advanced pancreatic cancer, high NLR was a significant independent prognostic marker for shorter survival. The median survival was 2.6 versus 8.5 months in patients having $\text{NLR} \geq 5$ versus $\text{NLR} < 5$ [31]. In 132 patients who underwent chemotherapy for advanced pancreatic cancer, high baseline NLR (> 2.78 , based on ROC) and high value after two cycles of chemotherapy were associated with lower overall survival. In addition, even worse prognosis was identified in patients who had both these factors. The overall survival was 15.2 months in patients who had low baseline NLR and did not experience the increase of NLR after two cycles of chemotherapy, but only 3.8 months in those having both undesirable factors: high NLR and increase during treatment. If only baseline NLR was high, the survival was 7.6 months. If only NLR increase was observed, the survival was 6.8 months [32]. High NLR retained a prognostic value in elderly (at least 75 years of age) patients who underwent chemotherapy for unresectable PDAC [33].

Interesting findings have been reported on NLR in patients who underwent preoperative chemoradiotherapy followed by complete surgical resection. Such research design allows

morphological evaluation of the response to preoperative treatment. Poor response was associated with higher pre-treatment NLR [34]. To predict efficacy of chemotherapy, both pre-treatment NLR and its dynamics are considered important. Thus, low baseline NLR and low NLR after first-line chemotherapy were associated with higher efficacy of chemotherapy [8] in parallel to the abovementioned study [32].

In patients receiving stereotactic radiotherapy for advanced PDAC, high NLR (>5) was associated with significantly shorter median survival: 6.9 versus 8.5 months; $p = 0.0057$ [35].

Again, the prognostic role of NLR in advanced pancreatic cancer has not always been confirmed. In 122 patients, undergoing chemotherapy for inoperable pancreatic cancer, both high and low NLR was associated with the same median survival of 10 months. In the same study, the dynamics of NLR still predicted outcomes although the biological difference was tiny: the median overall was 10 versus 11 months; $p < 0.001$. The dynamics was assessed as the ratio of pre-treatment NLR versus NLR after first-line chemotherapy. Changes in NLR predicted the efficacy of chemotherapy and the outcome [8].

The prognostic value of NLR is retained in metastatic PDAC. In treatment-naïve patients diagnosed with metastatic PDAC, NLR was significantly associated with survival, and multivariate analysis identified NLR as an independent prognostic factor. In addition, NLR also predicted the efficacy of oxaliplatin treatment [36]. In 39 patients with locally advanced unresectable and metastatic PDAC treated with gemcitabine and paclitaxel, higher NLR was associated with lower overall survival [37]. In similar but larger study group comprising 261 patients with inoperable pancreatic cancer (both metastatic and locally advanced cases), high NLR (≥ 5) was an independent prognostic factor for worse cancer specific survival, as confirmed by $p < 0.001$ [25]. High NLR was associated with worse overall survival in the general group of PDAC patients, in metastatic cases and in those who had distant metastasis but also received chemotherapy [38]. Radiofrequency ablation (combined with systemic chemotherapy) for hepatic oligometastatic pancreatic cancer was associated with worse survival in patients having elevated NLR (≥ 2.5). In this clinical situation, NLR was confirmed as an independent predictive factor, along with cancer location in pancreatic head and diameter of the metastasis [39].

In 306 patients receiving palliative chemotherapy, NLR ≥ 5 was associated with shorter overall survival. In addition, multivariate analysis identified the independent predictive value of NLR [40]. Similarly, prognostic value of NLR in patients receiving palliative chemotherapy was reported by Xue et al., [41]. In patients undergoing gastroenterostomy for advanced pancreatic cancer, high NLR (≥ 4) was associated with shorter survival: 3.4 versus 9.4 months; $p < 0.001$ [42]. Thus, low NLR might be useful to identify those who have higher benefit from palliative surgery.

Several meta-analyses have been devoted to NLR in pancreatic cancer. Zhou et al. [43] carried out a meta-analysis of 43 cohort studies containing 8252 patients and concluded that high NLR was significantly associated with worse overall survival (hazard ratio (HR) = 1.81; 95% confidence interval (CI): 1.59–2.05; $p < 0.001$) and cancer-free survival: HR = 1.66; 95% CI: 1.17–2.35; $p = 0.005$ [43]. Similar findings were reported by Cheng et al. [44].

2.2. NLR and cancer burden

2.2.1. NLR and local tumour features: pT and other traits

If NLR in particular and SIR in general are mostly dictated by the events in cancer stroma, NLR should correlate with cancer burden, reflected by pT or cancer size. However, the data are controversial. Thus, in a study of 442 patients undergoing surgical treatment for pancreatic cancer, there was no association between NLR and tumour size or pT. No correlation was found with perineural invasion, involvement of resection margins, and invasion into blood or lymphatic vessels [21]. In contrast, high NLR (≥ 2) was significantly associated with pT and grade among 381 patients treated by curative resection [23]. In a recent meta-analysis of 8252 cases, lower NLR was observed in patients having smaller ($p = 0.0007$), better differentiated ($p = 0.003$) tumours at earlier ($p = 0.02$) stage [43].

2.2.2. NLR and regional lymph node involvement: pN

The association between NLR and regional lymph node status also is controversial. While some research teams have observed higher NLR values in patients affected by tumour metastases in regional lymph nodes, other studies have not confirmed these findings. NLR was associated with lymph node metastasis in the study of 159 surgically treated PDAC patients [45]. Similarly, high NLR (≥ 2) was significantly associated with pN among 381 patients treated by curative resection [23]. In contrast, no correlation was found between NLR and cancer spread to regional lymph nodes reflected by pN or with invasion into lymphatic vessels by Sierzega et al. [21], evaluating 442 surgically treated patients. In Austrian cohort of 110 surgically treated pancreatic cancer patients, NLR lacked correlation with stage [25].

2.2.3. NLR and presence of distant metastasis: pM

In contrast to the previous aspects of tumour burden, namely, pT, size or pN, there is almost general agreement that pM1 is associated with higher NLR.

In patients diagnosed with unresectable pancreatic cancer, high pre-treatment NLR significantly correlated with presence of liver metastases [8]. Distant metastases were significantly more frequently identified in patients presenting with high NLR (> 5): 61.6 versus 30.1%; $p < 0.0001$ [38]. In advanced pancreatic cancer (including both metastatic and locally advanced cases), high NLR (≥ 5) correlated with the presence of metastatic disease [25]. The association between NLR and presence of distant metastases has also been confirmed by a meta-analysis by Yang et al., showing the HR = 1.69; 95% CI: 1.10–2.59; $p = 0.016$ [46].

2.3. Diagnostic role of NLR in pancreatic tumours

The diagnostics of PDAC is frequently a difficult issue. However, the close association between chronic pancreatitis and PDAC significantly limits the applicability of SIR for early diagnostics.

Baseline NLR in unresectable pancreatic cancer has been found to be significantly higher than in healthy controls: 3.81 versus 1.80; $p < 0.001$ [8]. Although the biological difference in the detected levels is remarkable, the comparison between advanced cancer and healthy

persons is not the model to make conclusions on the feasibility of NLR for early diagnostics. Currently, NLR has no role in the primary diagnostic algorithms for PDAC. However, it can assist to solve specific diagnostic questions.

SIR parameters have been proposed as markers of malignancy in pancreatic cystic neoplasms. Thus, in 245 patients with mucinous cystic pancreatic neoplasms, $\text{NLR} \geq 1.96$ was significantly ($p < 0.001$) associated with invasive carcinoma [47]. In 318 surgically treated patients with pancreatic cystic neoplasms, high NLR was significantly associated with malignant tumour by univariate analysis. However, PLR was found to be superior by multivariate analysis [48].

Regarding intraductal papillary mucinous neoplasms (IPMNs), a trend to higher median NLR was observed in malignant cases: 2.23 versus 2.04 in benign cases. However, because of the rarity of IPMNs, only 60 patients were enrolled in the study, and the difference in medians did not reach statistical significance, reflected by $p = 0.14$. By the cut-off at 3.6, the prediction of malignant behaviour became significant. Still, the sensitivity was only 40% while the specificity reached 93%. By multivariate analysis, enhancement in a solid nodule was found to be superior in comparison with $\text{NLR} \geq 3.6$ or height of mural nodule ≥ 11 mm [49]. Assessing 76 patients, higher NLR was reported in malignant than in benign IPMNs: 2.51 versus 2.01 [50]. In a large group of 272 surgically resected IPMNs, NLR exceeding 4.0 was an independent factor (by multivariate analysis), associated with invasive carcinoma. To enhance the predictive value, a nomogram was created incorporating NLR (>4.0) along with cyst size (>3 cm), identification of enhanced solid component, dilation of pancreatic duct (>5 mm) and the presence of jaundice [51]. In PDAC patients, significantly higher NLR has been reported than in case of pancreatic neuroendocrine neoplasms or pancreatic IPMNs [52].

2.4. Confounding factors in NLR assessment

Smoking and a wide spectrum of non-oncological diseases are known to influence NLR. In patients affected by unresectable pancreatic cancer, smoking history significantly ($p = 0.001$) correlated with higher NLR [8].

3. PLR in pancreatic ductal adenocarcinoma

3.1. PLR and survival

PLR is the second best known cellular parameter characterising SIR. Similarly to NLR, most studies have concentrated on the prognostic value of PLR regarding the survival. Two meta-analyses have been published recently (2018), and both teams have reached very similar conclusions on the association between elevated PLR and worse overall survival. In a meta-analysis of 17 studies on PLR in pancreatic cancer, the negative prognostic role of high PLR was confirmed by hazard ratio for worse overall survival $\text{HR} = 1.28$; 95% CI: 1.17–1.40; $p < 0.001$ and worse progression-free survival $\text{HR} = 1.27$; 95% CI = 1.03–1.57; $p = 0.03$ [53]. In another meta-analysis of 17 studies (including 16 reports on association between PLR and overall survival in 3028 patients), high PLR also was found to be associated with worse overall survival $\text{HR} = 1.22$; 95% CI: 1.09–1.36; $p < 0.001$. Interestingly, the prognostic role was confirmed in the subgroup of Asians ($\text{HR} = 1.22$; 95% CI: 1.11–1.34; $p < 0.001$) but not

Caucasians characterised by HR = 1.20; 95% CI: 0.90–1.62; $p = 0.22$ [54]. The same conclusion, pointing to significant role of PLR in Asia-based studies but not in those carried out in Europe, was reported earlier by Song et al., [55].

Regarding surgically treated PDAC, prognostic role has been ascribed to PLR. In 131 surgically treated PDAC patients, PLR was an independent factor predicting overall and cancer free survival [56]. In a small group of 46 patients treated with pancreaticoduodenectomy for pancreatic cancer, high PLR ≥ 200 was associated with lower overall survival and was the only independent prognostic indicator contrasting with NLR [22]. In borderline resectable PDAC, high PLR (>225) was an independent factor predicting worse survival. The median survival was 10.2 versus 24.7 months in high versus low PLR groups; $p = 0.003$ [57].

However, these findings have been challenged by a lot of contrary reports. PLR did not predict survival in 217 patients treated for resectable pancreatic cancer [28]. In even larger cohort of 442 pancreatic resections for cancer, there was no association between PLR and survival although NLR was an independent predictor of poor prognosis [21]. In 159 surgically treated patients, PLR lacked prognostic value in regard to overall survival; $p = 0.463$ although PLR was associated with lymph node metastasis that in turn was independent prognostic factor for overall survival [45]. In 379 consecutive patients who underwent curative resection for pancreatic cancer, PLR was not associated with survival [20]. In 110 surgically treated pancreatic cancer patients, high PLR (≥ 150) was not associated with cancer-specific survival, as confirmed by $p < 0.458$ [25].

In a recent meta-analysis, published in 2018, the association between PLR and overall survival was not significant in surgically treated patients (HR = 1.45; 95% CI: 0.84–2.50; $p = 0.19$) although it was confirmed in the general group of 3028 patients (HR = 1.22; 95% CI: 1.09–1.36; $p < 0.001$) as well as in subgroups subjected to chemotherapy (HR = 1.18; 95% CI: 1.04–1.35; $p = 0.01$) or combined treatment (HR = 1.29; 95% CI: 1.07–1.57; $p = 0.009$). The difference might be attributable to the patient number, constituting only 228 surgically treated cases in contrast to 1313 patients who underwent chemotherapy and 1214—combined treatment [54]. However, another meta-analysis including eight studies, 1904 patients and 823 surgically treated cases, noted the same lack of association with overall survival shown by HR = 1.24; 95% CI: 0.95–1.62; $p = 0.11$ [55].

In 497 patients with locally advanced pancreatic cancer treated by chemoradiotherapy, elevated pre-treatment PLR (defined by the median as ≥ 149) was associated with worse 1-year survival rate and 1-year progression-free survival rate: 61.3 and 32.5% in contrast to those presenting with low PLR: 68.1% ($p = 0.029$) and 37.9% ($p = 0.027$), respectively [30]. Although in this study, both NLR and PLR were significantly associated with survival, greater biological differences were observed between NLR-defined groups (**Table 3**).

Gao et al. also noted that NLR is more sensitive than PLR in predicting treatment efficacy in unresectable pancreatic cancer [8]. In 88 pancreatic cancer patients treated by combination chemotherapy with gemcitabine and erlotinib, neither progression free survival nor overall survival was predicted by PLR while NLR had a prognostic role [58]. In 56 patients subjected to preoperative chemoradiotherapy and subsequent surgical treatment allowing to evaluate

SIR parameter	1-Year overall survival rate			1-Year progression free survival rate		
	High SIR	Low SIR	p	High SIR	Low SIR	p
NLR	73.2	60.8	<0.001	43.9	31.3	<0.001
PLR	68.1	61.3	0.029	37.9	32.5	0.027

Abbreviations: SIR, systemic inflammatory reaction; NLR, neutrophil to lymphocyte ratio; PLR, platelet to lymphocyte ratio.

Table 3. Prognostic estimated by PLR versus NLR in advanced pancreatic cancer [30].

the pathologic response, higher mean PLR was observed in poor versus good response group: 172.9 versus 147.3; however, the difference did not reach statistical significance. NLR was superior in this study [34]. In 261 patients with inoperable pancreatic cancer (including both metastatic and locally advanced cases), high PLR (≥ 150) was not associated with cancer-specific survival, as confirmed by $p < 0.612$ [25].

In contrast, in a small cohort of 66 patients diagnosed with advanced pancreatic cancer, only PLR (not NLR or other SIR parameters) was associated with survival [59]. In advanced pancreatic cancer, high PLR was a significant independent prognostic marker for shorter survival. The median survival was 4.0 versus 9.1 months in patients having $PLR \geq 200$ versus $PLR < 200$ [31].

3.2. PLR and metastatic spread

Several reports indicate an important role of platelet activation in the metastatic cancer spread. PLR was significantly associated with lymph node metastasis; $p < 0.001$ [45]. Anti-platelet treatment, for example, by Clopidogrel, can inhibit the development of metastases [60].

3.3. Diagnostic role of PLR in pancreatic tumours

Differential diagnosis between chronic pancreatitis, presenting with tumour-like mass, and pancreatic ductal adenocarcinoma, can be difficult. Although inflammation is involved in both diseases, thrombocytosis and lymphopenia are more likely to occur in patients harbouring a malignant tumour. Comparing PLR in PDAC and inflammatory masses of pancreatic head, difference was revealed: PLR was 91 (interquartile range (IQR): 77.2–106.6) in patients diagnosed with pseudo-tumorous inflammation and 161.9 (IQR: 117.5–205.6) in PDAC. By ROC analysis, PLR reached area under curve (AUC) value of 88.8%, and the sensitivity and specificity were 79.4 and 92.6%, using cut-off at 113.5 [61]. Another study assessed the diagnostic value of PLR in the distinction between inflammatory pancreatic mass and PDAC in surgically treated patients. The sensitivity and specificity of PLR was comparable to CA 19-9, and combination of both improved the predictive value [62].

In mucinous cystic neoplasms, elevated PLR was shown to be significantly associated with presence of invasive carcinoma in 245 patients from Shanghai [47] and 318 patients from Singapore [48].

4. Classic and modified Glasgow prognostic score in pancreatic ductal adenocarcinoma

Glasgow prognostic score is based on the evaluation of the prototypic acute phase protein, C-reactive protein; and albumin levels in blood serum. CRP is a nonspecific, but sensitive marker of systemic inflammatory reaction, produced in response to pro-inflammatory cytokines (IL-1, IL-6, TNF alpha). Hypoalbuminemia is induced by malnutrition, cancer cachexia or SIR. GPS represents a summary estimate of two crucial pathogenetic processes: the humoral SIR and cancer cachexia therefore it benefits from considerable sensitivity [14].

Two alterations of Glasgow prognostic score are known: the modified GPS and the high sensitivity GPS. In the modified GPS, albumin level influences the score only if CRP is increased. High sensitivity GPS differs from the original GPS by lower cut-off level for CRP [14].

Imaoka et al. evaluated the prognostic value of mGPS across all stages of pancreatic cancer. After adjustment, both mGPS values 1 and 2 showed prognostic significance reflected in the hazard ratios: mGPS of 1 was associated with HR = 1.772; 95% CI: 1.417–2.215, but mGPS of 2 yielded HR = 2.033; 95% CI: 1.284–3.219. However, the biological significance was remarkable between mGPS of 0 and elevated values: the median survival was 15.8 months versus 5.8 versus 4.8 months in those presenting with mGPS 0, 1 or 2, respectively. In this study, the prognostic value of mGPS was not demonstrated in patients who had localised tumours and underwent surgical resection. Instead, mGPS was important in advanced pancreatic cancer [63]. Similarly, in advanced pancreatic cancer, high mGPS was a significant independent prognostic marker for shorter survival. The median survival by mGPS (2 versus 1 versus 0) was 1.8 months versus 9.6 versus 8.3 months [31]. As will be discussed further, most scientists agree on prognostic role of mGPS in advanced pancreatic cancer. The findings in resectable cases are more controversial.

Matsumoto et al reported significant prognostic value of mGPS in resectable pancreatic cancer. However, the role of mGPS in this study was to predict recurrence. According to their findings, mGPS (2 versus 0 or 1) was an independent predictive factor for tumour recurrence within 6 months, along with CA 19-9 (at least 300 U/mL) and tumour diameter (at least 30 mm). To detect survival, the number of these risk factors was significant, as it was associated with significantly ($p < 0.001$) different median survival: 35.5 versus 26.3 versus 15.9 months in those having 0, 1 or 2 or the identified factors, respectively [64].

mGPS (of 2) predicted postoperative pneumonia in 46 patients subjected to pancreaticoduodenectomy for pancreatic cancer. However, mGPS was not associated with overall survival contrasting with NLR and PLR [22].

Still, several researchers and teams have reported on the association between elevated mGPS and survival in surgical PDAC patients. In resectable PDAC, longer overall survival is observed in patients having mGPS of 0: 27–37 months contrasting with less than 18 months in patients with elevated mGPS [65]. In 101 patients treated by pancreatic resection for PDAC,

mGPS of 0, 1 and 2 classified the patients in three distinct groups by overall survival: 37.5 months, 11.5 months and 7.3 months [66].

Elevated classic GPS (0 versus 1 and 2), was not associated with cancer-specific survival in 110 surgically treated pancreatic cancer patients, as confirmed by $p < 0.585$ [25].

Despite the controversies, standard preoperative assessment of mGPS is recommended in cases of borderline resectable pancreatic cancer by consensus statement by the International Study Group of Pancreatic Surgery [26].

In 261 patients with inoperable pancreatic cancer (including both metastatic and locally advanced cases), elevated GPS (0 versus 1 and 2) was significantly associated with worse cancer-specific survival, as confirmed by $p < 0.029$. However, by multivariate analysis, GPS was not an independent prognostic factor in this cohort [25]. Nevertheless, the next level of evidence has been reached: mGPS was an independent prognostic factor in 187 patients with inoperable pancreatic cancer [67]. GPS is associated with survival in patients with unresectable pancreatic cancer treated with gemcitabine [68]. In 96 patients who underwent chemoradiotherapy for histologically confirmed, locally advanced PDAC, Glasgow prognostic score (of 2) was an independent predictor of worse overall survival and progression free survival [69]. In 40 patients undergoing adjuvant chemotherapy by gemcitabine after curative resection, elevated GPS (defined as 1 or 2 in contrast to 0) was associated both with worse disease-free survival ($p = 0.001$) and overall ($p = 0.035$) survival [70].

mGPS shows specific associations with response to treatment. Comparing the efficacy of JAK/STAT inhibitor ruxolitinib or placebo in combination with capecitabine (in both groups) for second-line treatment of metastatic pancreatic cancer, ruxolitinib showed trend to survival benefit only in those patients who had elevated mGPS (1 or 2) or CRP. Thus, in patients who had mGPS of 1–2, treatment by ruxolitinib resulted in hazard ratio $HR = 0.60$; 95% CI: 0.35–1.03; $p = 0.063$. In contrast, mGPS of 0 was associated with $HR = 0.91$; 95% CI = 0.46–1.74; $p = 0.77$. The trend reached statistical significance when the groups were compared by C-reactive protein level. Thus, the HR for overall survival in ruxolitinib group was $HR = 0.47$; 95% CI: 0.26–0.85; $p = 0.011$ in patients whose CRP was above the median value (>13 mg/L) contrasting with $HR = 0.89$; 95% CI: 0.47–1.65; $p = 0.70$ in those who had $CRP \leq 13$ mg/L. The biological differences were minor: the median survival was 2.7 months receiving ruxolitinib versus 1.8 months in controls. The overall survival rates at 3, 6 and 12 months were 48 versus 29%; 42 versus 11% and 11 versus 0% in the ruxolitinib versus placebo groups [71]. In contrast, high mGPS was associated with poor outcome in patients with gemcitabine-refractory advanced pancreatic cancer treated by salvage chemotherapy [72].

Modified Glasgow prognostic score was evaluated in 56 patients who underwent preoperative chemoradiotherapy followed by surgical resection of pancreatic cancer, thus ensuring the option to assess the treatment efficacy by morphology. By this design, mGPS did not predict the response to treatment. However, only five patients presented with mGPS of 1 or 2, while most of the cohort (51 cases) had mGPS of 0. All five patients exhibiting elevated mGPS responded poorly, but this was insufficient to reach statistical significance [34].

5. Fibrinogen and D-dimers in pancreatic ductal adenocarcinoma

Extensive alterations of blood clotting have been demonstrated in pancreatic cancer patients. Sun et al. characterised different coagulation parameters in 139 patients diagnosed with pancreatic cancer and compared the data to forty age- and gender-matched controls. Cancer patients had significantly higher level of fibrinogen ($p < 0.01$), D-dimers ($p < 0.01$), antithrombin III ($p = 0.015$), factor VIII ($p < 0.01$), as well as increased international normalised ratio ($p = 0.022$), longer prothrombin time ($p < 0.01$) and prolonged activated partial thromboplastin time; $p < 0.01$ [73].

Plasma fibrinogen levels are significantly higher in pancreatic cancer than in case of benign pancreatic tumours [74]. Hyperfibrinogenemia has been observed in 24.8% [19]–41.1% of pancreatic cancer patients [74]. In pancreatic cancer patients, levels of fibrinogen and D-dimers are higher before surgery, but significantly lower at the recurrence-free period after surgery; $p < 0.01$ [75]. Fibrinogen level in pancreatic cancer also correlates with NLR and PLR and shows negative correlation with lymphocyte to monocyte ratio [76]. Thus, in pancreatic tumours, hyperfibrinogenemia is associated with malignant course, depends on cancer presence in the body and correlates with SIR parameters. Therefore, elevated fibrinogen level can be considered a component of cancer-induced SIR. It is associated with patient's prognosis.

In 96 patients who underwent chemoradiotherapy for histologically confirmed, locally advanced PDAC, elevated fibrinogen level (≥ 400 mg/dL) was an independent predictor of worse overall and progression free survival [69]. Similarly, in 321 patients with locally advanced or metastatic pancreatic adenocarcinoma, high plasma fibrinogen was associated with shorter survival. It was confirmed an independent prognostic factor [76]. Wang et al. [19] also noted the association between higher levels of fibrinogen and worse prognosis. However, controversies remain. For instance, elevated preoperative concentrations of D-dimers but not fibrinogen were associated with shorter overall and progression-free survival in the study of Cao et al. [77].

In PDAC, plasma fibrinogen levels increase along with higher stage. In 125 PDAC patients, higher mean fibrinogen concentration was found in stage III/IV patients compared to those diagnosed at stage I/II. Higher levels of fibrinogen correlated with the presence of distant metastasis [19, 74].

D-dimers represent another blood clotting parameter that is widely studied in pancreatic cancer, including the prognostic role. Thus, elevated preoperative concentrations of D-dimers were associated with shorter overall and progression-free survival [77]. D-dimers also reflect tumour burden. Higher D-dimer levels in plasma were associated with higher stage and grade [73].

Higher concentration of D-dimers predicts shorter survival and non-resectability [75]. The association between non-resectability and elevated D-dimer levels in peripheral blood was also confirmed by Durczynski et al. [78] who assessed 64 patients. The concentration of D-dimers was higher in those who had metastatic cancer in comparison with patients suffering from locally advanced disease [78]. Thus, if the pancreatic tumour seems resectable

by preoperative imaging, high preoperative level of D-dimers might suggest the presence of occult liver metastases or unresectability of other cause, and the surgery should be started with diagnostic laparoscopy in contrast to laparotomy that might turn out to become exploratory laparotomy only.

6. Complex SIR-based scores in pancreatic ductal adenocarcinoma: presence and future

Considering the complexity of carcinogenesis and inflammation, any single parameter has limitations and shortcomings, reflected in the controversial reports. To improve the efficacy of SIR parameters, combinations of those have been tested.

6.1. Combination of baseline and dynamic estimates of NLR

In advanced PDAC, several teams have explored the combination of baseline NLR and dynamics upon the influence of chemotherapy [32]. The baseline value is scored as high or low in regard to threshold level. The cut-offs in SIR studies frequently are identified by ROC analysis or by median value. The dynamics is scored as either increase or decrease in response to the treatment; ratio between NLR in a predefined time point during treatment versus pre-treatment NLR (ratio < 1 is analogous to decrease) or high versus low value (against the threshold) in a predefined time point during treatment. The score is based on the count of adverse prognostic factors: high baseline NLR or increase of NLR upon treatment.

6.2. NLR and other SIR parameters

Combined SIR scores have been generated, including NLR and other SIR parameters. The results might be assessed by the count of adverse prognostic factors, for example high NLR or another parameter that exceeds the cut-off level. Summary score including NLR and PLR is the most obvious option that has been already successfully tested in other cancers, for example, gastric carcinoma [14]. This approach has been fruitful also in PDAC. In patients with locally advanced pancreatic cancer treated by chemoradiotherapy, it was noted that the combination of both elevated NLR and PLR is associated with especially low 1-year survival rate and 1-year progression-free survival rate [30]. Other combinations have been evaluated as well, for example, NLR and blood counts of regulatory T lymphocytes in resectable PDAC [79]. Combined index based on hypoalbuminemia and NLR has been advocated to evaluate the prognosis of gastric cancer [80]. Analogously, in patients receiving stereotactic radiotherapy for advanced PDAC, high NLR (>5) and low albumin levels were associated with shorter median overall survival [35].

6.3. NLR and cancer burden

Currently, there are only few data suggesting dependence of NLR on the tumour burden. The correlations with pT or size have been reported with some authors while corroborated by others.

Survival studies frequently indicate the independent prognostic value of SIR. Hypothetically, SIR is a characteristic of patient's fight, and not a tumour trait. If so, higher informative value could be obtained through complex scores comprising both NLR and an estimate of tumour burden by cancer markers (such as CA 19-9 or CEA), positron emission tomography findings or clinical characteristics of the tumour, for example, the presence of distant metastases or unresectable tumour. All these approaches have been successfully tested in PDAC.

In metastatic pancreatic cancer, a combined score of pre-treatment NLR and CA 19-9 was found to be superior to either parameter alone [81]. In resectable pancreatic cancer, the 2-year overall survival rate was significantly lower in those presenting with high preoperative NLR in combination with high CA 19-9 versus the patients having both values in the low range: 37.5 versus 89.9%, respectively [82]. A complex score including NLR along with metabolic activity detected by positron emission tomography (PET) has been found informative [83]. To predict the overall survival of PDAC patients receiving palliative chemotherapy, $\text{NLR} \geq 5$ was incorporated in a complex score, designated the prognostic index. The other parameters within the framework of this score were performance status, presence of distant metastases or unresectable tumour, as well as high CEA or CA 19-9 [40].

6.4. Fibrinogen-based complex scores

Similarly to NLR, fibrinogen level has been successfully incorporated in complex scores along with other SIR parameters, for example, GPS, or tumour burden, reflected by stage and/or tumour markers, for example, CA19-9. In cancers of other organs, fibrinogen has also been assessed along with D-dimer levels or NLR [14].

In 96 patients who underwent chemoradiotherapy for histologically confirmed, locally advanced PDAC, Glasgow prognostic score (of 2) and fibrinogen (≥ 400 mg/dL) were independent predictors of worse overall survival and progression free survival. Complex score based on fibrinogen and GPS had prognostic value [69].

In a large cohort of patients (321 cases) with locally advanced or metastatic pancreatic adenocarcinoma, high plasma fibrinogen was shown to be an independent prognostic factor. It was incorporated in a predictive model along with tumour stage and CA 19-9 level, improving the predictive capability [76].

Prognostic model for overall survival was elaborated on the basis of independent prognostic factors, identified in 125 PDAC patients by the Cox proportional hazard model. These factors comprised plasma fibrinogen, cancer stage and the presence of distant metastasis [19].

6.5. SIR-based complex scores: Future developments in PDAC

Carcinomas of different organs differ markedly by their molecular pathogenesis, prognostic factors and involvement of the inflammation in various stages of carcinogenesis. In addition, even cancers of the same organ are heterogeneous, adding complexity to any cancer research. Nevertheless, the keynotes of SIR-based prognostic scores elaborated in cancers other than

PDAC might yield fruitful research data. Hypothetically, simultaneous assessment of NLR and platelet count, or NLR along with hyperfibrinogenemia might have prognostic value in PDAC, especially, considering the marked tendency to up-regulated blood clotting in pancreatic cancer patients. NLR can also be evaluated along with GPS or mGPS, or patient's somatic, metabolic and/or psychological status.

7. Conclusions

In conclusion, pancreatic ductal adenocarcinoma is associated with systemic inflammatory reaction. The complex pathogenesis of SIR includes ejection of platelets, neutrophils and myeloid-derived suppressor cells from bone marrow, development of neutrophil extracellular traps and pre-metastatic niches as well as upregulated levels of acute phase proteins and blood clotting factors. Despite the biological complexity, SIR can be easily evaluated by patient friendly and cheap blood tests. NLR and PLR are the most frequently used cellular SIR parameters reflecting the balance between pro-tumourous (neutrophils, platelets) and contra-tumourous (lymphocytes) activities. Glasgow prognostic score, levels of fibrinogen and D-dimers characterise proteins that are involved in SIR and thus—in blood clotting. Significant associations with survival have been demonstrated, mostly regarding NLR in surgically treated and advanced cases. PLR is beneficial to estimate prognosis in advanced cases. Both NLR and PLR can improve the preoperative diagnostics of malignancy in pancreatic cystic tumours, while PLR can be helpful to distinguish between pseudo-tumorous chronic pancreatitis and PDAC. Complex SIR-based scores are developing in order to increase the diagnostic accuracy.

Conflict of interest

Authors have no conflicts of interest to declare.

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