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Research Article

The Systemic Inflammation Response Index as a Prognostic Marker in Advanced Pancreatic Cancer

Deniz Tataroglu Ozyukseler,[1] Seval Ay,[2] Merve Turan,[1] Gulin Alkan,[3] Murat Ayhan,[1] Heves Surmeli,[1] Nedim Turan,[1] Hatice Odabas,[1] Mahmut Emre Yildirim[1]

[1]Department of Medical Oncology, Istanbul Kartal Dr. Lutfi Kirdar Training and Research Hospital, Istanbul, Türkiye
[2]Department of Medical Oncology, Istanbul Medeniyet University, Goztepe Training and Research Hospital, Istanbul, Türkiye
[3]Department of Medical Oncology, Istanbul University, Cerrahpasa Faculty of Medicine, Istanbul, Türkiye

Abstract

Objectives: Although pancreatic cancer is comparatively rare, it's the seventh cause of cancer-related mortality in the world. Surgery is the sole curative treatment option but approximately 85% of patients are diagnosed at inoperable stages. The standard treatment options for the advanced staged disease are 5-Fluorouracil, leucovorin, irinotecan, and oxaliplatin (FOLFIRINOX) or gemcitabine-based chemotherapy. In spite of those treatments, the 5-year survival rate is less than 5%. In this study, we aimed to evaluate the prognostic value of the systemic inflammation response index (SIRI).

Methods: A retrospective, single-center study consisting of 103 patients from December 2015 to December 2019, was performed. The cut-off SIRI values were determined as 1.8×10^9. We determine whether the SIRI was an independent prognostic parameter.

Results: We observed that the median OS for metastatic pancreatic cancer patients with SIRI values $<1.8\times10^9$ was better than the patients with SIRI values$\geq1.8\times10^9$ independent of the treatment choices (17.3 months vs 11.9 months).

Conclusion: SIRI seems to be an accessible, and cost-effective parameter as a strong prognostic determiner for advanced pancreatic cancer. Its value is independent of the treatment choice.

Keywords: Pancreatic adenocarcinoma, systemic inflammation response index, prognostic factor

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Despite its comparatively low incidence, pancreatic cancer (PC) is still the seventh dominant cause of cancer-related mortality in the world.[1] PC is commonly diagnosed in developed countries compared to developing countries.[2] %90 of diagnosed patients are older than 55 years old, especially in their seventies and eighties; also, it is rarely diagnosed before the age of 30.[3,4] PC is more frequently seen in males than females.[1] Surgery is the sole curative treatment option, although nearly 85% of patients are diagnosed at inoperable stages.[5] The standard chemotherapy protocols for the advanced staged disease are 5-Fluorouracil, leucovorin, irinotecan, and oxaliplatin (FOLFIRINOX) or gemcitabine-based chemotherapy.[6-8] Despite those effective treatment strategies, the one-year relative survival rate is 24%, and the five-year rate is 6%.[9] This poor prognosis of PC necessitates useful prognostic and predictive markers to optimize treatment strategies. In this context, systemic inflammation was one of the top topics studied. Cancer-related inflammation is suggested to be the seventh hallmark of cancer.[10] The interaction between systemic in-

Address for correspondence: Deniz Tataroglu Ozyukseler, MD. Tibbi Onkoloji Anabilim Dali, Istanbul Kartal Dr. Lutfi Kirdar Egitim ve Arastirma Hastanesi, Istanbul, Türkiye
Phone: +90 538 638 69 42 **E-mail:** drdeniztataroglu@gmail.com

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flammation and immune response plays a crucial role in cancer progression and survival.[11] Systemic inflammation consists of immune cells, cytokines, and inflammatory proteins, which can be detected in systemic circulation.[12] The regular marks of the systemic inflammatory response are circulating white cells such as lymphocyte, neutrophil, and monocyte counts and acute-phase proteins like C-reactive protein. These parameters can be easily measured as standardized assays in clinical practice. Systemic inflammatory indexes such as the neutrophil/lymphocyte ratio, the platelet/lymphocyte ratio, and the Glasgow prognostic score have shown their prognostic value in various cancers.[13-17] According to the results of the studies, elevated neutrophil/lymphocyte ratio and C-reactive protein are poor prognostic markers independent of the stage of PC.[14,18,19] Systemic inflammation seems to affect the patient's response to treatment as well. The study of PC in a mouse model exposed that systemic inflammation reduced the efficacy of gemcitabine treatment.[20] Tumor-associated macrophages also cause gemcitabine resistance in PC cells.[21] A retrospective study enrolling 574 patients put forth the systemic inflammation response index's (SIRI) ability to predict the survival of PC patients that received gemcitabine chemotherapy in 3 independent cohorts.[22] In this present study, we aimed to evaluate the prognostic value of SIRI and predict the survival of patients treated with gemcitabine-based chemotherapy, gemcitabine-cisplatin doublet regimen, or FOLFIRINOX triplet regimen as a first-line treatment for metastatic pancreatic cancer.

Methods

A retrospective, single-center study consisting of one hundred and three patients from December 2015 to December 2019, was performed. The study was conducted in accordance with the ethical principles of the Helsinki Declaration (2013). The local ethics committee approved the protocol. Patients had pathologically confirmed metastatic staged pancreatic adenocarcinoma at the time of the diagnosis or upstaged during treatments or follow-ups. Patients with validated immunodeficiency or using medication for chronic diseases or having another primary malignant were excluded from all of the analyses. Data on clinical variables, including demographic data, complete blood counts, and treatment choices, were collected through patients' files, and missing data were obtained from the electronic medical record system. All patients had performed at least one of the standard radiologic studies such as computed tomography, magnetic resonance imaging, or positron emission tomography/computed tomography. Every three months, response assessments were made according to the Response Evaluation Criteria[23] and evaluated as complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD). Our primary outcome was progression-free survival (PFS); the secondary outcome was overall survival (OS) and SIRI's effect on these survival parameters. PFS was defined as the time from initiation of treatment to progression or death; OS was defined as the interval between the diagnosis and death or the last follow-up. SIRI was defined as peripheral neutrophil × monocyte/lymphocyte counts.[22] The cut-off SIRI value for the first-line treatment responses was determined with a ROC analysis as 1.8×10^9/L in the present study.

Patients received different chemotherapy regimens as gemcitabine-based regimens such as gemcitabine monotherapy (gemcitabine 1000 mg/m^2 weekly, on days 1, 8, and 15 every four weeks), and gemcitabine-cisplatin doublet regimen (gemcitabine 1000 mg/m^2 plus cisplatin 25 mg/m^2 on days 1, 8, and 15 every four weeks) or FOLFIRINOX triplet regimen (oxaliplatin, 85 mg/m^2; irinotecan, 180 mg/m^2; leucovorin, 400 mg/m^2; and fluorouracil, 400 mg/m^2 bolus followed by 2,400 mg/m^2 46-hour continuous infusion, once every two weeks).

Analyses were conducted with Statistical Package for the Social Sciences, version 27.0, and a two-tailed $p<0.05$ was thought-out statistically significant. Mean, standard deviation, median, minimum, maximum value frequency, and percentage were used for descriptive statistics. The distribution of variables was checked with a kolmogorov-simirnov test. Independent Samples t-test was used for the comparison of quantitative data. The Chi-Square test was used for the comparison of qualitative data. Kaplan-Meier was used in the survival analysis.

Results

The clinical characteristics of one hundred and three patients are listed in Table 1. The median age of patients was sixty-one. Forty-five patients (43.7%) were female, and fifty-eight patients (56.3%) were male. Fifty-one patients (49.5%) SIRI value was $\leq1.8\times10^9$/L fifty-two patients' (50.5%) was $>1.8\times10^9$/L. Twenty patients (19.4%) with The Eastern Cooperative Oncology Group performance status (ECOG-PS) 0 and 83 (80.6%) with ECOG-PS ≥1. Forty-seven patients' (45.6%) primary tumor was located in the head and fifty-six patients' (54.4%) were in the body or tail. Seventy-two patients (69.9%) were de novo metastatic. Forty-one patients (39.8%) received gemcitabine monotherapy; thirty patients (29.1%) received gemcitabine cisplatin doublet regimen; while thirty-two (%31.1) received FOLFIRINOX triplet regimen. Fifty-seven patients (55.3%) had one treatment line, thirty-seven patients (35.9%) had two treatment

Table 1. Demographics, tumor, and clinical characteristics of patients

	Min-Max	Median	Mean±SD/n-%	
Age	34.0-82.0	61.0	60.6±8.7	
Gender				
Female			45	43.7
Male			58	56.3
SIRI	0.08-19.58	1.83	2.95±3.35	
SIRI ≤ 1.8×10^9/L			51	49.5
SIRI > 1.8×10^9/L			52	50.5
ECOG				
0			20	19.4
≥1			83	80.6
Tumor localization				
Head			47	45.6
Body or Tail			56	54.4
De novo metastasic				
(-)			31	30.1
(+)			72	69.9
First-line chemotherapy Regimen				
Gemcitabine			41	39.8
Gemcitabine+Nab-paclitaxel			30	29.1
FOLFIRINOX			32	31.1
Number of chemotherapy lines				
I			57	55.3
II			37	35.9
III			4	3.9
IV			5	4.9
Response to treatment				
PD			38	36.9
SD			20	19.4
PR			45	43.7
Progression				
(-)			9	8.7
(+)			94	91.3
Mortality				
(-)			20	19.4
(+)			83	80.6

ECOG: Eastern Cooperative Oncology Group; SIRI: systemic inflammation response index; Nab-paclitaxel: 130-nanometer albumin-bound paclitaxel; FOLFIRINOX: 5-Fluorouracil, leucovorin, irinotecan, and oxaliplatin; PD: progressive disease; SD: stable disease; PR: partial response.

lines, 4 patients (3.9%) had three, and 5 patients (4.9%) had four. Sixty patients (56.7%) received one line, while forty-six patients (43.3%) received two lines or more cytotoxic treatments. After first-line treatment thirty-eight patients (36.9%) had PD, twenty patients (19.4%) had SD and forty-five patients (43.7%) experienced PR. At the last follow-up, 94 patients (91.3%) had confirmed disease progression after treatment, and 83 of those (80.6%) had passed away.

The cut-off value of SIRI was determined as 1.8×10^9 according to ROC analysis in our study, patients were distributed according to their SIRI values. In those two groups, patients were similar according to their age, gender, ECOG-PS, tumor localization, de novo metastases ratio, first-line chemotherapy choices, number of chemotherapy lines, responses to first-line treatment, and progression rates. Mortality rates were statistically different between the two groups (p=0.011) (Table 2).

There was no significant difference in PFS of the first-line treatment between patients who have lower or higher SIRI scores (12.5 months vs 15.7 months, p=0.672). According to log-rank analyses, median PFS was not statistically different according to treatment choices (p=0.928) (Table 3). Median OS for patients with SIRI values ≥1.8×10^9 was 11.9 months and 17.3 months for the ones with SIRI values <1.8×10^9 and this was statistically significant (p=0.003) (Fig. 1). Median OS does not differ according to treatment choices as well (p=0.627) (Table 4).

Discussion

Systemic inflammation is a highly important promoter of the proliferation, invasion, and metastasis of tumor cells.[22,24,25] Higher neutrophil counts have been associated with a worse prognosis in different various cancer types. Neutrophils in the tumor microenvironment produce pro-angiogenic factors that cause stimulation in tumor development and progression.[26] Also, lymphocytopenia has been connected with weaker anti-cancer defenses, which results in a poorer prognosis.[27] Also, higher monocyte counts are linked with a worse prognosis in various cancer types.[28–30] Besides, the immune system plays a critical role in cancer surveillance and elimination.[31]

Previous studies have confirmed that neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio, monocyte-to-lymphocyte ratio, and other inflammatory response markers can be used to predict tumor prognosis.[16,32,33] In recent years, many studies have been conducted on inflammation parameters, and cancer prognosis; SIRI is one of these parameters.[30,34,35]

There are many studies conducted to show SIRI's prognostic value on different types of cancer. In a study that enrolled 455 patients, the results showed that the preoperative SIRI can be used to predict the survival of patients with gastric adenocarcinoma after curative resection.[36] Chen et al., found that SIRI can predict postoperative survival, and especially, a high SIRI is an independent prognostic factor for esophagogastric junction patients.[37] Xu et al. evaluated the ability of the SIRI as a prognostic marker in patients with HCC after local treatment. Their results showed that SIRI levels were correlated with AFP levels and stage, which

Table 2. Quantitative and qualitative data analyses

	SIRI ≤ 1.8 Mean±sd/n-%		SIRI > 1.8 Mean±sd/n-%		p
Age	60.24±9.07		60.98±8.41		0.660[t]
Gender					
Female	27	52.9	18	34.6	0.061[X²]
Male	24	47.1	34	65.4	
ECOG-PS					
0	11	21.6	9	17.3	0.585[X²]
1	40	78.4	43	82.7	
Tumor localization					
Head	24	47.1	23	44.2	0.773[X²]
Body or Tail	27	52.9	29	55.8	
Metastasis					
(-)	15	29.4	16	30.8	0.881[X²]
(+)	36	70.6	36	69.2	
First-line chemotherapy					
Gemcitabine	19	37.3	22	42.3	0.846[X²]
Gemcitabine+Nab-paclitaxel	15	29.4	15	28.8	
FOLFIRINOX	17	33.3	15	28.8	
Number of chemotherapy lines					
I	24	47.1	33	63.5	0.059[X²]
II	19	37.3	18	34.6	
III	3	5.9	1	1.9	
IV	5	9.8	0	0.0	
Response to the first-line treatment					
PD	20	39.2	18	34.6	0.371[X²]
SD	12	23.5	8	15.4	
PR	19	37.3	26	50.0	
Progression					
(-)	3	5.9	6	11.5	0.309[X²]
(+)	48	94.1	46	88.5	
Mortality					
(-)	15	29.4	5	9.6	0.011[X²]
(+)	36	70.6	47	90.4	

[t]t test / X^2 Chi-square test; ECOG-PS, Eastern Cooperative Oncology Group Performance Score; SIRI, systemic inflammation response index; Nab-paclitaxel, 130-nanometer albumin-bound paclitaxel; FOLFIRINOX, 5-Fluorouracil, leucovorin, irinotecan, and oxaliplatin; PD, progressive disease; SD, stable disease; PR, partial response.

also predict prognosis.[38] Hua et al. studied preoperative SIRI levels to predict survival in postmenopausal breast cancer patients and defined SIRI as a reliable predictor of survival for that patients.[39]

A study conducted in a mouse model with PC showed that systemic inflammation weakens the response to gemcitabine treatment.[20] Also, tumor-associated macrophages exposed gemcitabine resistance in PC cells.[21] A retrospective study enrolling 574 patients put forth SIRI's capability to predict the survival of PC patients that received gemcitabine-based chemotherapy.[22] Kamposioras et al. enrolled twenty-six locally advanced or metastatic PC patients who were treated with the FOLFIRINOX regimen in the study. Even if their study is small-scaled, they showed SIRI's prognostic value for the patients treated with FOLFOXIRI as a first-line treatment.[40]

In our study, we constructed a SIRI based on peripheral neutrophil, monocyte, and lymphocyte counts. The cut-off SIRI value used in our study was 1.8×10^9 L. Our results display that, the patients with SIRI scores equal to or higher than 1.8×10^9 L would have worse overall survival after first-line chemotherapy compared with those with SIRI scores lower than 1.8×10^9 L in both patients who received gemcitabine-based chemotherapy

Table 3. Progression-free survival according to SIRI levels and chemotherapy choices

	Progression-Free Survival (Month)				p
	Mean	% 95 CI	Median	% 95 CI	
SIRI ≤ 1.8×10⁹/L	15.7	10.9-20.4	9.1	6.4-11.8	0.672
SIRI > 1.8×10⁹/L	12.5	9.9-15.0	9.4	7.6-11.2	
First-line chemotherapy regimen					
Gemcitabine	15.1	9.7-20.4	8.2	5.4-11.0	0.928
Gemcitabine+ Nab-paclitaxel	12.1	9.4-14.8	9.6	5.3-13.9	
FOLFIRINOX	15.2	10.0-20.4	9.4	5.9-12.9	

Kaplan-Meier (Log-Rank); SIRI, systemic inflammation response index; Nab-paclitaxel, 130-nanometer albumin-bound paclitaxel; FOLFIRINOX, 5-Fluorouracil, leucovorin, irinotecan, and oxaliplatin.

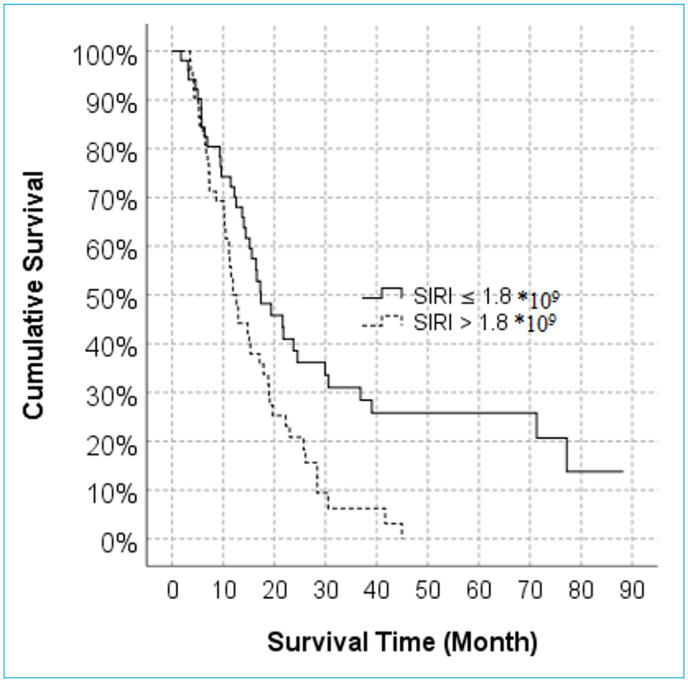

Figure 1. Overall survival of metastatic pancreatic cancer patients according to their systemic inflammation response index (SIRI) levels.

and FOLFIRINOX. We couldn't show its value in the PFS results. As a result, our study showed that SIRI could be used as a prognostic factor for PC and its significance is independent of the chemotherapy choice. There are also limitations in our study, especially in the design, which contained retrospective data collection. Secondly, again because of its retrospective nature, the treatment regimens in our study were not uniform. Furthermore, the small patient sample size might have generated biases in the analysis. A better-designed, prospective study with larger sample size is therefore needed to validate the relationship identified in the study between SIRI and PC prognosis.

Conclusion

Despite the widely recognized limitations, our data suggest that the SIRI seems to be an accessible, and cost-effective method for predicting the survival of patients with advanced PC after first-line chemotherapy independent of their treatment choices. Also, it seems to be valuable as a strong prognostic determinant.

Table 4. Overall survival according to SIRI levels and chemotherapy choices

	Survival Time (Month)				p
	Mean	% 95 CI	Median	% 95 CI	
SIRI ≤ 1.8×10⁹/L	32.7	23.7-41.8	17.3	11.0-23.7	0.003
SIRI > 1.8×10⁹/L	15.7	12.7-18.7	11.9	10.0-13.8	
First-line chemotherapy regimen					
Gemcitabine	23.1	15.0-31.1	13.7	9.7-17.6	0.627
Gemcitabine+Nab-paclitaxel	24.0	16.8-31.2	19.4	12.3-26.5	
FOLFIRINOX	24.5	15.2-33.7	15.3	9.4-21.2	

Kaplan-Meier (Log-Rank); SIRI, systemic inflammation response index; Nab-paclitaxel, 130-nanometer albumin-bound paclitaxel; FOLFIRINOX, 5-Fluorouracil, leucovorin, irinotecan, and oxaliplatin.

Disclosures

Ethics Committee Approval: The study was approved by the Ethics Committee of Kartal Dr. Lutfi Kirdar City Hospital (Approval No: 2020/514/177/42. Date:13.05.2020).

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References

1. International Agency for Research on Cancer, WHO. Global Cancer Observatory 2018.
2. Wong MCS, Jiang JY, Liang M, Fang Y, Yeung MS, Sung JJY. Global temporal patterns of pancreatic cancer and association with socioeconomic development. Sci Rep 2017;7:3165.
3. Midha S, Chawla S, Garg PK. Modifiable and non-modifiable risk factors for pancreatic cancer: A review. Cancer Lett 2016;381:269–77. [CrossRef]
4. Wood HE, Gupta S, Kang JY, Quinn MJ, Maxwell JD, Mudan S, et al. Pancreatic cancer in England and Wales 1975-2000: patterns and trends in incidence, survival and mortality. Aliment Pharmacol Ther 2006;23:1205–14. [CrossRef]
5. Kamisawa T, Wood LD, Itoi T, Takaori K. Pancreatic cancer. Lancet 2016;388:73–85. [CrossRef]
6. Burris HA 3rd, Moore MJ, Andersen J, Green MR, Rothenberg ML, Modiano MR, 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;15:2403–13 [CrossRef]
7. Conroy T, Desseigne F, Ychou M, Bouché O, Guimbaud R, Bécouarn Y, et al; Groupe Tumeurs Digestives of Unicancer; PRODIGE Intergroup. FOLFIRINOX versus gemcitabine for metastatic pancreatic cancer. N Engl J Med 2011;364:1817–25.
8. Von Hoff DD, Ervin T, Arena FP, Chiorean EG, Infante J, Moore M, et al. Increased survival in pancreatic cancer with nab-paclitaxel plus gemcitabine. N Engl J Med 2013;369:1691–703.
9. Siegel RL, Miller KD, Jemal A. Cancer Statistics, 2017. CA Cancer J Clin 2017;67:7–30. [CrossRef]
10. Mantovani A. Cancer: Inflaming metastasis. Nature 2009;457:36–7. [CrossRef]
11. Diakos CI, Charles KA, McMillan DC, Clarke SJ. Cancer-related inflammation and treatment effectiveness. Lancet Oncol 2014;15:e493–e503. [CrossRef]
12. Miller KD, Siegel RL, Lin CC, Mariotto AB, Kramer JL, Rowland JH, et al. Cancer treatment and survivorship statistics, 2016. CA Cancer J Clin 2016;66:271–89.
13. Szkandera J, Gerger A, Liegl-Atzwanger B, Absenger G, Stotz M, Samonigg H, et al. Validation of the prognostic relevance of plasma C-reactive protein levels in soft-tissue sarcoma patients. Br J Cancer 2013;109:2316–22. [CrossRef]
14. Stotz M, Gerger A, Eisner F, Szkandera J, Loibner H, Ress AL, et al. Increased neutrophil-lymphocyte ratio is a poor prognostic factor in patients with primary operable and inoperable pancreatic cancer. Br J Cancer 2013;109:416–21.
15. Szkandera J, Absenger G, Liegl-Atzwanger B, Pichler M, Stotz M, Samonigg H, et al. Elevated preoperative neutrophil/lymphocyte ratio is associated with poor prognosis in soft-tissue sarcoma patients. Br J Cancer 2013;108:1677–83.
16. Szkandera J, Gerger A, Liegl-Atzwanger B, Absenger G, Stotz M, Friesenbichler J, et al. The lymphocyte/monocyte ratio predicts poor clinical outcome and improves the predictive accuracy in patients with soft tissue sarcomas. Int J Cancer 2014;135:362–70. [CrossRef]
17. Forrest LM, McMillan DC, McArdle CS, Angerson WJ, Dunlop DJ. Comparison of an inflammation-based prognostic score (GPS) with performance status (ECOG) in patients receiving platinum-based chemotherapy for inoperable non-small-cell lung cancer. Br J Cancer 2004;90:1704–6. [CrossRef]
18. Cheng H, Long F, Jaiswar M, Yang L, Wang C, Zhou Z. Prognostic role of the neutrophil-to-lymphocyte ratio in pancreatic cancer: a meta-analysis. Sci Rep 2015;5:11026. [CrossRef]
19. Stevens L, Pathak S, Nunes QM, Pandanaboyana S, Macutkiewicz C, Smart N, et al. Prognostic significance of pre-operative C-reactive protein and the neutrophil-lymphocyte ratio in resectable pancreatic cancer: a systematic review. HPB (Oxford) 2015;17:285–91. [CrossRef]
20. Knoop RF, Sparn M, Waldmann J, Plassmeier L, Bartsch DK, Lauth M, et al. Chronic pancreatitis and systemic inflammatory response syndrome prevent impact of chemotherapy with gemcitabine in a genetically engineered mouse model of pancreatic cancer. Neoplasia 2014;16:463–70. [CrossRef]
21. Weizman N, Krelin Y, Shabtay-Orbach A, Amit M, Binenbaum Y, Wong RJ, et al. Macrophages mediate gemcitabine resistance of pancreatic adenocarcinoma by upregulating cytidine deaminase. Oncogene 2014;33:3812–9. [CrossRef]
22. Qi Q, Zhuang L, Shen Y, Geng Y, Yu S, Chen H, et al. A novel systemic inflammation response index (SIRI) for predicting the survival of patients with pancreatic cancer after chemotherapy. Cancer 2016;122:2158–67.
23. Schwartz LH, Litière S, de Vries E, Ford R, Gwyther S, Mandrekar S, et al. RECIST 1.1-Update and clarification: From the RECIST committee. Eur J Cancer 2016;62:132–7.
24. Candido J, Hagemann T. Cancer-related inflammation. J Clin Immunol 2013;33:S79–S84. [CrossRef]
25. Coussens LM, Werb Z. Inflammation and cancer. Nature

2002;420:860–7. [CrossRef]
26. Elinav E, Nowarski R, Thaiss CA, Hu B, Jin C, Flavell RA. Inflammation-induced cancer: crosstalk between tumours, immune cells and microorganisms. Nat Rev Cancer 2013;13:759–71.
27. Dings RP, Nesmelova I, Griffioen AW, Mayo KH. Discovery and development of anti-angiogenic peptides: A structural link. Angiogenesis 2003;6:83–91. [CrossRef]
28. Dunn GP, Old LJ, Schreiber RD. The immunobiology of cancer immunosurveillance and immunoediting. Immunity 2004;21:137–48. [CrossRef]
29. Kim BW, Jeon YE, Cho H, Nam EJ, Kim SW, Kim S, et al. Pretreatment diagnosis of endometrial cancer through a combination of CA125 and multiplication of neutrophil and monocyte. J Obstet Gynaecol Res 2012;38:48–56. [CrossRef]
30. Lee YY, Choi CH, Sung CO, Do IG, Huh S, Song T, et al. Prognostic value of pre-treatment circulating monocyte count in patients with cervical cancer: comparison with SCC-Ag level. Gynecol Oncol 2012;124:92–7. [CrossRef]
31. Sasaki A, Iwashita Y, Shibata K, Matsumoto T, Ohta M, Kitano S. Prognostic value of pre-operative peripheral blood monocyte count in patients with hepatocellular carcinoma. Surgery 2006;139:755–64. [CrossRef]
32. Ku JH, Kang M, Kim HS, Jeong CW, Kwak C, Kim HH. The prognostic value of pretreatment of systemic inflammatory responses in patients with urothelial carcinoma undergoing radical cystectomy. Br J Cancer 2015;112:461–7.
33. Shao Y, Ning Z, Chen J, Geng Y, Gu W, Huang J, et al. Prognostic nomogram integrated systemic inflammation score for patients with esophageal squamous cell carcinoma undergoing radical esophagectomy. Sci Rep 2015;5:18811.
34. Zou W. Immunosuppressive networks in the tumour environment and their therapeutic relevance. Nat Rev Cancer 2005;5:263–74. [CrossRef]
35. Atzpodien J, Reitz M. Peripheral blood neutrophils as independent immunologic predictor of response and long-term survival upon immunotherapy in metastatic renal-cell carcinoma. Cancer Biother Radiopharm 2008;23:129–34.
36. Li S, Lan X, Gao H, Li Z, Chen L, Wang W, et al. Systemic Inflammation Response Index (SIRI), cancer stem cells and survival of localised gastric adenocarcinoma after curative resection. J Cancer Res Clin Oncol 2017;143:2455–68. [CrossRef]
37. Chen Y, Jin M, Shao Y, Xu G. Prognostic value of the Systemic Inflammation Response Index in patients with adenocarcinoma of the oesophagogastric junction: a propensity score-matched analysis. Dis Markers 2019;2019:4659048.
38. Xu L, Yu S, Zhuang L, Wang P, Shen Y, Lin J, et al. Systemic inflammation response index (SIRI) predicts prognosis in hepatocellular carcinoma patients. Oncotarget 2017;8:34954–60.
39. Hua X, Long ZQ, Huang X, Deng JP, Wen W, He ZY, et al. The preoperative systemic inflammation response index (SIRI) independently predicts survival in postmenopausal women with breast cancer. Curr Probl Cancer 2020;44:100560.
40. Kamposioras K, Razzaq M, Ahmad U, Damyanova I, Papaxoinis G. Systemic inflammatory response index (SIRI) predicts poor survival in pancreatic cancer patients treated with FOLFIRINOX. Ann Oncol 2019;30:IV45. [CrossRef]