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***Retrospective Study***

**Prognostic value of inflammation-based markers in patients with pancreatic cancer administered gemcitabine and erlotinib**

Lee JM *et al.* Prognostic factors in pancreatic cancer

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**Abstract**

**AIM:** To evaluate the value of systemic inflammation-based markers as prognostic factors for advanced pancreatic cancer (PC).

**METHODS:** Data from 82 patients who underwent combination chemotherapy with gemcitabine and erlotinib for PC from 2011 to 2014 were collected retrospectively. Data that included the neutrophil-to-lymphocyte ratio (NLR), the platelet-to-lymphocyte ratio (PLR), and the C-reactive protein (CRP)-to-albumin (CRP/Alb) ratio were analyzed. Kaplan-Meier curves, and univariate and multivariate Cox proportional hazards regression analyses were used to identify the prognostic factors associated with progression-free survival (PFS) and overall survival (OS).

**RESULTS:** The univariate analysis demonstrated the prognostic value of the NLR (*P* = 0.049) and the CRP/Alb ratio (*P* = 0.047) in relation to PFS, and a positive relationship between an increase in inflammation-based markers and a poor prognosis in relation to OS. The multivariate analysis determined that an increased NLR [hazard ratio (HR) = 2.76, 95%CI: 1.33-5.75, *P* = 0.007] is an independent prognostic factor for poor OS. There was no association between the PLR and the patients’ prognoses in those who had received chemotherapy that comprised gemcitabine and erlotinib in combination. The Kaplan-Meier method and the log-rank test determined significantly worse outcomes in relation to PFS and OS in patients with an NLR > 5 or a CRP/Alb ratio > 5.

**CONCLUSION:** Systemic inflammation-based markers, including increases in the NLR and the CRP/Alb ratio, may be useful for predicting PC prognoses.

**Key words:** Pancreatic cancer; Neutrophil-to-lymphocyte ratio; C-reactive protein; Albumin; Prognostic factor

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**Core tip:** This retrospective study validates the value of systemic inflammation-based markers as prognostic factors for pancreatic cancer (PC). The neutrophil-to-lymphocyte ratio and the C-reactive protein-to-albumin ratio, which can be determined from routine blood tests before chemotherapy, can be used as useful biomarkers in PC to predict a patient’s response to chemotherapy.

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**INTRODUCTION**

Pancreatic cancer (PC) is a devastating malignant tumor that has a poor prognosis[1]. Although surgical resection offers a good prognosis and prolongs survival, only 10%-20% of patients are eligible for a curative resection at the time of diagnosis[2,3]. Systemic chemotherapy is a major treatment modality for unresectable PC, and the National Comprehensive Cancer Network recommends gemcitabine-based chemotherapy as standard therapy for advanced or metastatic PC. The findings from recent studies have demonstrated that gemcitabine and erlotinib (Tarceva®) administered in combination improve therapeutic response rates and overall survival (OS)[4-6]. However, the PC prognosis remains extremely poor, and it is difficult to predict in advanced PC before chemotherapy. Hence, to administer effective treatment, better prognostic predictors are required than those that are currently available.

Evidence is accumulating that supports the relationship between the inflammatory response and cancer development[7,8]. Bhatti *et al*[9] proposed that hematologic inflammation-based markers could be used as prognostic markers in resectable PC. C-reactive protein (CRP) levels, and leukocyte, neutrophil, lymphocyte, and platelet counts, as well as the neutrophil-to-lymphocyte ratio (NLR) and the platelet-to-lymphocyte ratio (PLR), could be prognostic markers for patients with PC[10,11]. Recently, an increase in the CRP/albumin (CRP/Alb) ratio has been reported to correlate with poor prognoses in patients with malignant tumors[12-14]. However, the relationship between the CRP/Alb ratio and the PC prognosis has not been studied. Since cancer progression depends on the systemic inflammatory response[15], we hypothesized that the status of the peripheral blood at the time of diagnosis reflects the inflammatory response and the disease activity associated with PC.

This study aimed to evaluate the prognostic value of systemic inflammation-based markers within the peripheral blood of patients with advanced or metastatic PC, and to determine their usefulness in predicting patients’ responses to chemotherapy.

**MATERIALS AND METHODS**

***Patients and study design***

We retrospectively collected data from patients with PC who were admitted to two tertiary hospitals, namely, Anam Hospital and Ansan Hospital in South Korea, between January 2011 and December 2014. Only consecutive patients with primary PC were included in the study. All of the patients met the following criteria: (1) the presence of a pathologically confirmed pancreatic adenocarcinoma; (2) receipt of first-line chemotherapy comprising gemcitabine and erlotinib administered in combination; and (3) the presence of locally advanced or metastatic PC. Gemcitabine was administered at 1000 mg/m2 three times per week, which was followed by rest for 1 wk. Erlotinib was administered as a single oral 150 mg dose during chemotherapy. Patients who had undergone previous curative resections of their primary pancreatic tumors, or who had undergone first-line chemotherapy that involved other chemotherapeutic agents, including 5-fluorouracil, were excluded from this study.

The patients’ demographic, clinical, and laboratory data, including the WBC and differential counts, the platelet count, and information about tumor markers, were collected and analyzed. All of the laboratory data were obtained on the day of or on the day that followed hospital admission. The NLR was calculated by dividing the neutrophil count by the lymphocyte count, and the PLR was calculated by dividing the platelet count by the lymphocyte count. The CRP/Alb ratio was determined as the CRP level divided by the serum albumin level. The follow-up duration was defined as the period from the first day of treatment to the day of death or August 2015.

***Statistical analysis***

An increased NLR was defined as > 5, and an increased PLR was defined as > 150[14]. The CRP/Alb ratio cutoff value was 0.5, which was based on a previous study[13]. Progression was defined as a 25% or more increase in total tumor size and/or the appearance of new lesions at any site. Progression-free survival (PFS) was defined as the time from treatment to the first observation of progression. OS was defined as the date of the first treatment to the date of death. The Kaplan-Meier method and the log-rank test were used to compare the PFS and OS rates, and the 95%CI were calculated. The univariate and multivariate analyses were carried out using the Cox proportional hazards model, and student’s *t*-test was used to analyze the response and survival time results. A *P* value < 0.05 was considered statistically significant. The statistical analyses were conducted using IBM®SPSS® software version 20.0 (IBM Corporation, Armonk, NY, United States).

**RESULTS**

***Patient characteristics***

Table 1 presents the characteristics of the 82 patients who met all of the study’s eligibility criteria. The mean age of the patients when they were diagnosed with PC was 63.5 ± 10.7 years, and 60% of the patients were men. Most of the patients (85%) had favorable performance statuses with Eastern Cooperative Oncology Group (ECOG) scores of 0 or 1. The median values for the inflammatory markers were as follows: NLR: 3.1 (range, 1-48); PLR: 141 (range, 44-921); and CRP/Alb ratio: 0.5 (range, 0-38). All of the patients were finally diagnosed with pancreatic adenocarcinoma based on pathologic examinations. Fourteen patients (17%) had locally advanced PC and 68 patients (83%) had metastatic lesions when they were diagnosed with PC.

***Prognostic value of the factors associated with PC***

Univariate analyses were performed using sex, age, the tumor stage, the ECOG performance status score, the tumor markers, and the inflammatory markers as possible variables for PFS (Table 2), and it determined that an NLR > 5 (*P* = 0.049) and a CRP/Alb ratio > 0.5 (*P* = 0.047) were significant predictors of a poor prognosis. Univariate and multivariate analyses were also performed in relation to OS (Table 3). The univariate analysis revealed that the presence of distant metastasis (*P* = 0.017), an ECOG performance status score of 2 (*P* = 0.002), an NLR > 5 (*P* = 0.008), and a CRP/Alb ratio > 0.5 (*P* = 0.011) were significantly associated with poor OS. The multivariate analysis showed that an ECOG performance status score of 2 [hazard ratio (HR) = 2.94, 95%CI: 1.42-6.08, *P* = 0.004) and an NLR > 5 (HR = 2.76, 95%CI: 1.33-5.75, *P* = 0.007) were independent factors associated with the prognosis of PC.

***Inflammation-based factors and PC outcomes***

By the time this study was completed, 57 patients had died because of disease progression. The patients were categorized according to the NLR and the CRP/Alb ratio and subgroup analyses were performed. The groups were compared with respect to the duration of chemotherapy and the time until death (Table 4). Patients with initial NLRs ≤ 5 continued chemotherapy with gemcitabine and erlotinib for longer. The time to disease progression was significantly longer when the patients’ NLRs did not increase. The mean time until death was longer in patients who had NLRs ≤ 5 compared with patients who had NLRs > 5. The mean time until death was shorter in patients with CRP/Alb ratios > 0.5 compared with patients with CRP/Alb ratios ≤ 0.5.

***Prognostic comparisons based on the NLR and the CRP-to-albumin ratio***

The NLR has been identified as a prognostic indicator in patients with PC who are undergoing gemcitabine-based chemotherapy; therefore, we compared the cancer prognosis in a group of patients with NLR ≤ 5 with that in a group of patients with NLR > 5. Kaplan-Meier analyses determined that PFS was significantly better in patients with NLRs ≤ 5 (4.9 ± 0.5 mo) compared with those with NLRs > 5 (3.1 ± 0.7 mo) (*P* = 0.043) (Figure 1A), and that OS was significantly better in patients with NLRs ≤ 5 (11.1 ± 1.2 mo) compared with those with NLRs > 5 (5.8 ± 0.9 mo) (*P* = 0.005) (Figure 1B). PFS for patients with CRP/Alb ratios > 0.5 (3.2 ± 0.4 mo) was significantly worse compared with those with CRP/Alb ratios ≤ 5 (5.3 ± 0.7 mo) (*P* = 0.034) (Figure 2A), and OS for patients with CRP/Alb ratios > 0.5 (7.9 ± 1.2 mo) was significantly worse compared with those with CRP/Alb ratios ≤ 5 (12.7 ± 1.2 mo) (*P =* 0.007) (Figure 2B).

**DISCUSSION**

Systemic chemotherapy is recommended as palliative therapy for PC[16], but only a limited number of patients benefit from chemotherapy. Gemcitabine-based combination therapy is considered an effective first-line treatment for advanced PC[4,17-19]. While the tumor stage and the carbohydrate antigen 19-9 levels have been used to predict patients’ prognoses[20-22], predicting the therapeutic effect of or a patient’s response to chemotherapy is difficult.

Findings from recent studies of different malignant tumors have suggested that increases in the levels of systemic inflammation are indicative of poor survival[23,24]. Inflammatory cells within the tumor microenvironment play important roles in tumor development and in the survival of malignant cells[25,26]. Therefore, systemic inflammation-based markers may be indicators of cancer prognosis and of patients’ responses to therapy. Since these markers can be readily measured in peripheral blood samples, its usefulness would be greatly expectable in practice. Indeed, some investigators have described the prognostic value of these systemic inflammatory response markers in advanced PC[11,27-29].

The current investigation scrutinized the value of a number of clinical parameters, including the NLR, PLR, and the CRP/Alb ratio, as prognostic predictors in patients with PC who received combination chemotherapy that comprised gemcitabine and erlotinib. The univariate and multivariate analyses determined that a higher ECOG performance status score, metastatic disease, a higher NLR, and a higher CRP/Alb ratio were associated with poor outcomes. A multivariate analysis of the significant inflammation-related factors determined that the NLR was independently associated with OS. In the patients with PC, a higher NLR was associated with significantly worse OS (2.6 mo) compared with a lower NLR (8.5 mo), but the PLR was not determined to be an independent prognostic factor. A higher CRP/Alb ratio was associated with a poor prognosis according to the univariate analysis, but the multivariate analysis did not show that it was an independent prognostic factor.

The mechanism that underlies the association between inflammation-based markers and poor PC outcomes has not been clarified. Systemic inflammatory changes would be reflected in increases in the neutrophil levels, and these could be induced by tumor invasion and disease progression, despite the administration of chemotherapy. Inflammatory responses can inhibit the immune system by suppressing the cytolytic activity of the immune cells, including that associated with the lymphocytes, activated T cells, and natural killer cells[30]. Furthermore, inflammatory responses can promote tumor angiogenesis, invasion, and metastasis by recruiting regulatory T lymphocytes and activating cytokine production[31,32]. Since an increase in the neutrophil count or a decrease in the lymphocyte count within the WBC count will present as a higher NLR, the NLR will be strongly associated with the prognosis for a patient with a malignant tumor. Moreover, cancer progression against chemotherapy activates inflammatory processes within the tumor microenvironment[33], and the WBC ratios may change under these conditions.

The prognostic value of the preoperative NLR has been described in patients with resectable PC[34-36], but the response of the NLR to chemotherapy and its value as a prognostic marker have not been established. We observed that the mean times until disease progression or death were significantly shorter in patients with NLRs > 5 compared with those whose NLRs were not elevated. Elevated neutrophil counts may aid cancer progression by providing a favorable environment for tumor growth. Furthermore, lymphocytopenia, which can be induced by many of the inhibitory immunologic mediators that are released by tumor cells, results in a weakened immune system that would contribute to poor patient outcomes during systemic chemotherapy.

To the best of our knowledge, this is the first study to evaluate the value of the CRP/Alb ratio in advanced PC. Another strength of our study is that the data were only collected from patients who were receiving a unified chemotherapy regimen that comprised gemcitabine and erlotinib. While other studies of PC have included both resectable and unresectable tumors[9,37], we excluded patients with PC who had undergone surgery from the analysis. However, there are several limitations to our study. First, this was a retrospective study that involved a relatively small number of patients. While an elevated NLR was related to the PC prognosis, we could not validate the prognostic value of the PLR in this study. More data obtained from larger numbers of patients will be required to determine the true value of the PLR for predicting PC prognoses. Second, while we excluded those patients who had been diagnosed with acute pancreatitis or other infections, patients with early infections may have been included during the selection process. Since pancreatic duct obstruction and biliary tract invasion are relatively frequent in PC, patients with potentially aggressive disease may have been allocated to the group containing patients with higher NLRs. Finally, this study only evaluated patients who received combination chemotherapy with gemcitabine and erlotinib; hence, it is difficult to extrapolate the data to all patients with PC. The therapeutic strategy for PC may differ considerably in relation to a patient’s socioeconomic status, comorbidities, and other factors. However, since gemcitabine-based chemotherapy is widely recommended as first-line palliative chemotherapy for PC throughout the world, the NLR, which is easily calculated, would assist clinicians to predict patients’ therapeutic responses and PC prognoses.

In summary, our results strongly support the idea that systemic inflammation-based parameters may be useful prognostic markers for patients with advanced PC. The NLR when determined at the time of a diagnosis of PC could be a valuable marker for predicting a patient’s response to chemotherapy with gemcitabine and erlotinib. Furthermore, the CRP/Alb ratio may be valuable as a prognostic factor in PC. More prospective studies are needed to verify the usefulness of these inflammation-based markers in patients with PC.

**COMMENTS**

***Background***

Inflammation based markers have been known to have a prognostic value predicting the outcome of various cancers. Since the status of the peripheral blood reflects the inflammatory response at the time of diagnosis, it could be used the systemic inflammation based markers [neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio, C-reactive protein (CRP)-to-albumin ratio, *etc*.] as a prognostic biomarker in advanced pancreatic cancer (PC).

***Research frontiers***

It is important to be able to predict the outcome and response to chemotherapy in advanced PC. This study assessed the prognostic value of systemic inflammation based markers in patients with palliative chemotherapy due to inoperable PC.

***Innovations and breakthroughs***

Although prior investigators had studied about the prognostic value of NLR in malignancy, there was no study about the CRP-to-albumin ratio in PC. The present study showed that both NLR and CRP-to-albumin ratio can be useful and easy biomarkers to predict the response and outcome of PC.

***Applications***

It can be easily calculated NLR or CRP-to-albumin ratio from routine blood tests. The systemic inflammation-based markers can be useful tool to predict the outcome in patients with PC.

***Terminology***

The NLR was calculated by dividing the neutrophil count by the lymphocyte count, and the PLR was calculated by dividing the platelet count by the lymphocyte count. The CRP/Alb ratio was determined as the CRP level divided by the serum albumin level.

***Peer-review***

The manuscript by Lee *et al* aims to identify inflammation-based markers in patients with pancreatic cancer treated with gemcitabine and erlotinib. Eighty-two pancreatic cancer patients were enrolled in this retrospective study. Patients received combination chemotherapy with gemcitabine and erlotinib. Multivariate analysis demonstrated that an increased neutrophil-to-lymphocyte ratio (HR 2.76, 95%CI: 1.33-5.75, *P* = 0.007) was an independent prognostic factor for poor overall survival. CRP/albumin ratio was related to progression free survival. The manuscript is in general well written and the topic is of interest.

**REFERENCES**

1 **Siegel RL**, Miller KD, Jemal A. Cancer statistics, 2015. *CA Cancer J Clin* 2015; **65**: 5-29 [PMID: 25559415 DOI: 10.3322/caac.21254]

2 **Ferrone CR**, Pieretti-Vanmarcke R, Bloom JP, Zheng H, Szymonifka J, Wargo JA, Thayer SP, Lauwers GY, Deshpande V, Mino-Kenudson M, Fernández-del Castillo C, Lillemoe KD, Warshaw AL. Pancreatic ductal adenocarcinoma: long-term survival does not equal cure. *Surgery* 2012; **152**: S43-S49 [PMID: 22763261 DOI: 10.1016/j.surg.2012.05.020]

3 **Stathis A**, Moore MJ. Advanced pancreatic carcinoma: current treatment and future challenges. *Nat Rev Clin Oncol* 2010; **7**: 163-172 [PMID: 20101258 DOI: 10.1038/nrclinonc.2009.236]

4 **Moore MJ**, Goldstein D, Hamm J, Figer A, Hecht JR, Gallinger S, Au HJ, Murawa P, Walde D, Wolff RA, Campos D, Lim R, Ding K, Clark G, Voskoglou-Nomikos T, Ptasynski M, Parulekar W. Erlotinib plus gemcitabine compared with gemcitabine alone in patients with advanced pancreatic cancer: a phase III trial of the National Cancer Institute of Canada Clinical Trials Group. *J Clin Oncol* 2007; **25**: 1960-1966 [PMID: 17452677 DOI: 10.1200/JCO.2006.07.9525]

5 **Yang ZY**, Yuan JQ, Di MY, Zheng DY, Chen JZ, Ding H, Wu XY, Huang YF, Mao C, Tang JL. Gemcitabine plus erlotinib for advanced pancreatic cancer: a systematic review with meta-analysis. *PLoS One* 2013; **8**: e57528 [PMID: 23472089 DOI: 10.1371/journal.pone.0057528]

6 **Diaz Beveridge R**, Alcolea V, Aparicio J, Segura Á, García J, Corbellas M, Fonfría M, Giménez A, Montalar J. Management of advanced pancreatic cancer with gemcitabine plus erlotinib: efficacy and safety results in clinical practice. *JOP* 2014; **15**: 19-24 [PMID: 24413779 DOI: 10.6092/1590-8577/1570]

7 **Grivennikov SI**, Greten FR, Karin M. Immunity, inflammation, and cancer. *Cell* 2010; **140**: 883-899 [PMID: 20303878 DOI: 10.1016/j.cell.2010.01.025]

8 **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**: 759-771 [PMID: 24154716 DOI: 10.1038/nrc3611]

9 **Bhatti I**, Peacock O, Lloyd G, Larvin M, Hall RI. Preoperative hematologic markers as independent predictors of prognosis in resected pancreatic ductal adenocarcinoma: neutrophil-lymphocyte versus platelet-lymphocyte ratio. *Am J Surg* 2010; **200**: 197-203 [PMID: 20122680 DOI: 10.1016/j.amjsurg.2009.08.041]

10 **Bilici A**. Prognostic factors related with survival in patients with pancreatic adenocarcinoma. *World J Gastroenterol* 2014; **20**: 10802-10812 [PMID: 25152583 DOI: 10.3748/wjg.v20.i31.10802]

11 **Martin HL**, Ohara K, Kiberu A, Van Hagen T, Davidson A, Khattak MA. Prognostic value of systemic inflammation-based markers in advanced pancreatic cancer. *Intern Med J* 2014; **44**: 676-682 [PMID: 24750233 DOI: 10.1111/imj.12453]

12 **Kinoshita A**, Onoda H, Imai N, Iwaku A, Oishi M, Tanaka K, Fushiya N, Koike K, Nishino H, Matsushima M. The C-reactive protein/albumin ratio, a novel inflammation-based prognostic score, predicts outcomes in patients with hepatocellular carcinoma. *Ann Surg Oncol* 2015; **22**: 803-810 [PMID: 25190127 DOI: 10.1245/s10434-014-4048-0]

13 **Xu XL**, Yu HQ, Hu W, Song Q, Mao WM. A Novel Inflammation-Based Prognostic Score, the C-Reactive Protein/Albumin Ratio Predicts the Prognosis of Patients with Operable Esophageal Squamous Cell Carcinoma. *PLoS One* 2015; **10**: e0138657 [PMID: 26390126 DOI: 10.1371/journal.pone.0138657]

14 **Xue P**, Kanai M, Mori Y, Nishimura T, Uza N, Kodama Y, Kawaguchi Y, Takaori K, Matsumoto S, Uemoto S, Chiba T. Neutrophil-to-lymphocyte ratio for predicting palliative chemotherapy outcomes in advanced pancreatic cancer patients. *Cancer Med* 2014; **3**: 406-415 [PMID: 24519894 DOI: 10.1002/cam4.204]

15 **Borsig L**, Wolf MJ, Roblek M, Lorentzen A, Heikenwalder M. Inflammatory chemokines and metastasis--tracing the accessory. *Oncogene* 2014; **33**: 3217-3224 [PMID: 23851506 DOI: 10.1038/onc.2013.272]

16 **Sultana A**, Tudur Smith C, Cunningham D, Starling N, Tait D, Neoptolemos JP, Ghaneh P. Systematic review, including meta-analyses, on the management of locally advanced pancreatic cancer using radiation/combined modality therapy. *Br J Cancer* 2007; **96**: 1183-1190 [PMID: 17406358 DOI: 10.1038/sj.bjc.6603719]

17 **Burris HA**, Moore MJ, Andersen J, Green MR, Rothenberg ML, Modiano MR, Cripps MC, Portenoy RK, Storniolo AM, Tarassoff P, Nelson R, Dorr FA, Stephens CD, Von Hoff DD. 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**: 2403-2413 [PMID: 9196156]

18 **Heinemann V**, Boeck S, Hinke A, Labianca R, Louvet C. Meta-analysis of randomized trials: evaluation of benefit from gemcitabine-based combination chemotherapy applied in advanced pancreatic cancer. *BMC Cancer* 2008; **8**: 82 [PMID: 18373843 DOI: 10.1186/1471-2407-8-82]

19 **Von Hoff DD**, Ervin T, Arena FP, Chiorean EG, Infante J, Moore M, Seay T, Tjulandin SA, Ma WW, Saleh MN, Harris M, Reni M, Dowden S, Laheru D, Bahary N, Ramanathan RK, Tabernero J, Hidalgo M, Goldstein D, Van Cutsem E, Wei X, Iglesias J, Renschler MF. Increased survival in pancreatic cancer with nab-paclitaxel plus gemcitabine. *N Engl J Med* 2013; **369**: 1691-1703 [PMID: 24131140 DOI: 10.1056/NEJMoa1304369]

20 **Eloubeidi MA**, Desmond RA, Wilcox CM, Wilson RJ, Manchikalapati P, Fouad MM, Eltoum I, Vickers SM. Prognostic factors for survival in pancreatic cancer: a population-based study. *Am J Surg* 2006; **192**: 322-329 [PMID: 16920426 DOI: 10.1016/j.amjsurg.2006.02.017]

21 **Humphris JL**, Chang DK, Johns AL, Scarlett CJ, Pajic M, Jones MD, Colvin EK, Nagrial A, Chin VT, Chantrill LA, Samra JS, Gill AJ, Kench JG, Merrett ND, Das A, Musgrove EA, Sutherland RL, Biankin AV. The prognostic and predictive value of serum CA19.9 in pancreatic cancer. *Ann Oncol* 2012; **23**: 1713-1722 [PMID: 22241899 DOI: 10.1093/annonc/mdr561]

22 **Ballehaninna UK**, Chamberlain RS. The clinical utility of serum CA 19-9 in the diagnosis, prognosis and management of pancreatic adenocarcinoma: An evidence based appraisal. *J Gastrointest Oncol* 2012; **3**: 105-119 [PMID: 22811878 DOI: 10.3978/j.issn.2078-6891.2011.021]

23 **Zhou X**, Du Y, Huang Z, Xu J, Qiu T, Wang J, Wang T, Zhu W, Liu P. Prognostic value of PLR in various cancers: a meta-analysis. *PLoS One* 2014; **9**: e101119 [PMID: 24968121 DOI: [10.1371/journal.pone.0101119](http://dx.doi.org/10.1371/journal.pone.0101119" \t "_blank)]

24 **Diakos CI**, Charles KA, McMillan DC, Clarke SJ. Cancer-related inflammation and treatment effectiveness. *Lancet Oncol* 2014; **15**: e493-e503 [PMID: 25281468 DOI: 10.1016/S1470-2045(14)70263-3]

25 **Whiteside TL**. The tumor microenvironment and its role in promoting tumor growth. *Oncogene* 2008; **27**: 5904-5912 [PMID: 18836471 DOI: 10.1038/onc.2008.271]

26 **Colotta F**, Allavena P, Sica A, Garlanda C, Mantovani A. Cancer-related inflammation, the seventh hallmark of cancer: links to genetic instability. *Carcinogenesis* 2009; **30**: 1073-1081 [PMID: 19468060 DOI: 10.1093/carcin/bgp127]

27 **An X**, Ding PR, Li YH, Wang FH, Shi YX, Wang ZQ, He YJ, Xu RH, Jiang WQ. Elevated neutrophil to lymphocyte ratio predicts survival in advanced pancreatic cancer. *Biomarkers* 2010; **15**: 516-522 [PMID: 20602543 DOI: 10.3109/1354750X.2010.491557]

28 **Teo M**, Mohd Sharial MS, McDonnell F, Conlon KC, Ridgway PF, McDermott RS. Prognostic role of neutrophil-to-lymphocyte ratio in advanced pancreatic ductal adenocarcinoma: impact of baseline fluctuation and changes during chemotherapy. *Tumori* 2013; **99**: 516-522 [PMID: 24326841 DOI: 10.1700/1361.15104]

29 **Luo G**, Guo M, Liu Z, Xiao Z, Jin K, Long J, Liu L, Liu C, Xu J, Ni Q, Yu X. Blood neutrophil-lymphocyte ratio predicts survival in patients with advanced pancreatic cancer treated with chemotherapy. *Ann Surg Oncol* 2015; **22**: 670-676 [PMID: 25155401 DOI: 10.1245/s10434-014-4021-y]

30 **el-Hag A**, Clark RA. Immunosuppression by activated human neutrophils. Dependence on the myeloperoxidase system. *J Immunol* 1987; **139**: 2406-2413 [PMID: 2821114]

31 **Germano G**, Allavena P, Mantovani A. Cytokines as a key component of cancer-related inflammation. *Cytokine* 2008; **43**: 374-379 [PMID: 18701317 DOI: 10.1016/j.cyto.2008.07.014]

32 **Mantovani A**, Allavena P, Sica A, Balkwill F. Cancer-related inflammation. *Nature* 2008; **454**: 436-444 [PMID: 18650914 DOI: 10.1038/nature07205]

33 **Quail DF**, Joyce JA. Microenvironmental regulation of tumor progression and metastasis. *Nat Med* 2013; **19**: 1423-1437 [PMID: 24202395 DOI: 10.1038/nm.3394]

34 **Stotz M**, Gerger A, Eisner F, Szkandera J, Loibner H, Ress AL, Kornprat P, AlZoughbi W, Seggewies FS, Lackner C, Stojakovic T, Samonigg H, Hoefler G, Pichler M. Increased neutrophil-lymphocyte ratio is a poor prognostic factor in patients with primary operable and inoperable pancreatic cancer. *Br J Cancer* 2013; **109**: 416-421 [PMID: 23799847 DOI: 10.1038/bjc.2013.332]

35 **Aliustaoglu M**, Bilici A, Seker M, Dane F, Gocun M, Konya V, Ustaalioglu BB, Gumus M. The association of pre-treatment peripheral blood markers with survival in patients with pancreatic cancer. *Hepatogastroenterology* 2010; **57**: 640-645 [PMID: 20698242]

36 **Smith RA**, Bosonnet L, Raraty M, Sutton R, Neoptolemos JP, Campbell F, Ghaneh P. Preoperative platelet-lymphocyte ratio is an independent significant prognostic marker in resected pancreatic ductal adenocarcinoma. *Am J Surg* 2009; **197**: 466-472 [PMID: 18639229 DOI: 10.1016/j.amjsurg.2007.12.057]

37 **Yang JJ**, Hu ZG, Shi WX, Deng T, He SQ, Yuan SG. Prognostic significance of neutrophil to lymphocyte ratio in pancreatic cancer: a meta-analysis. *World J Gastroenterol* 2015; **21**: 2807-2815 [PMID: 25759553 DOI: 10.3748/wjg.v21.i9.2807]

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**Figure 1 Kaplan-Meier curves for progression-free survival and overall survival according to the neutrophil-lymphocyte ratio**. A: PFS stratified according to the NLR; B: Overall survival stratified according to the NLR. NLR: Neutrophil-to-lymphocyte ratio.

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**Figure 2 Kaplan-Meier curves for progression-free survival and overall survival according to the C-reactive protein /albumin ratio**. A: Progression-free survival stratified according to the CRP/albumin ratio; B: Overall survival stratified according to the CRP/albumin ratio. CRP: C-reactive protein.

**Table 1 Patient demographics and laboratory findings**

|  |  |
| --- | --- |
| Characteristic |  |
| No. of patients, *n* | 82 |
| Age, mean ± SD, yr | 63.5 ± 10.7 |
| Male, *n* (%) | 49 (60) |
| Laboratory findings |  |
| WBC count, mean ± SD | 6259 ± 2667 |
| Platelet count, mean ± SD, × 1000 | 225 ± 94 |
| Neutrophil count, mean ± SD | 4175 ± 2139 |
| Lymphocyte count, mean ± SD | 1462 ± 729 |
| CRP, mean ± SD, mg/dL | 12.5 ± 23.8 |
| Albumin, mean ± SD, g/dL | 3.5 ± 0.6 |
| CA19-9, median, IU/mL | 503.8 |
| CEA, median, ng/mL | 2.8 |
| ECOG performance status score |  |
| 0, *n* (%) | 22 (27) |
| 1, *n* (%) | 48 (58) |
| 2, *n* (%) | 12 (15) |
| Inflammatory markers |  |
| NLR, median, range | 3.1 (1-48) |
| PLR, median, range | 141 (44-921) |
| CRP/albumin ratio, median, range | 0.5 (0-37.7) |
| Staging |  |
| Locally advanced, *n* (%) | 14 (17) |
| Metastatic, *n* (%) | 68 (83) |

SD: Standard deviation; WBC:White blood cell; CRP: C-reactive protein; NLR: Neutrophil-to-lymphocyte ratio;PLR: Platelet to lymphocyte ratio; CA19-9: Carbohydrate antigen 19-9; CEA: Carcinoembryonic antigen; ECOG: Eastern Cooperative Oncology Group.

**Table 2 Univariate analysis of the clinical parameters for the prediction of progression-free survival**

|  |  |  |  |
| --- | --- | --- | --- |
| Parameter | *n* | Univariate analysis | |
| HR (95%CI) | *P* value |
| Sex |  |  |  |
| Woman | 33 | 1 |  |
| Man | 49 | 1.37 (0.82-2.3) | 0.232 |
| Age (yr) |  |  |  |
| < 65 | 41 | 1 |  |
| ≥ 65 | 41 | 0.85 (0.52-1.41) | 0.536 |
| Staging |  |  |  |
| Locally advanced | 14 | 1 |  |
| Metastatic | 68 | 1.39 (0.68-2.82) | 0.367 |
| ECOG performance status score |  |  |  |
| 0-1 | 70 | 1 |  |
| 2 | 12 | 1.49 (0.77-2.87) | 0.234 |
| CA19-9 (IU/mL) |  |  |  |
| < 1000 | 48 | 1 |  |
| ≥ 1000 | 34 | 1.33 (0.81-2.21) | 0.264 |
| CEA (ng/mL) |  |  |  |
| < 5 | 46 | 1 |  |
| ≥ 5 | 29 | 1.24 (0.72-2.13) | 0.441 |
| NLR |  |  |  |
| ≤ 5 | 62 | 1 |  |
| > 5 | 20 | 1.80 (1.04-3.19) | 0.049 |
| PLR |  |  |  |
| ≤ 150 | 46 | 1 |  |
| > 150 | 36 | 1.22 (0.73-2.02) | 0.448 |
| CRP/albumin ratio |  |  |  |
| ≤ 0.5 | 42 | 1 |  |
| > 0.5 | 40 | 1.72 (1.07-2.80) | 0.047 |

ECOG: Eastern Cooperative Oncology Group; CA19-9: Carbohydrate antigen 19-9; CEA: Carcinoembryonic antigen; NLR: Neutrophil-to-lymphocyte ratio;PLR: Platelet-to-lymphocyte ratio; CRP: C-reactive protein; HR: Hazard ratio.

**Table 3 Univariate and multivariate analysis of the clinical parameters for the prediction of overall survival**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Parameter | *n* | Univariate analysis | |  | Multivariate analysis | |
| HR (95%CI) | *P* value | HR (95%CI) | *P* value |
| Sex |  |  |  |  |  |  |
| Woman | 33 | 1 |  |  |  |  |
| Man | 49 | 1.26 (0.73-2.17) | 0.418 |  |  |  |
| Age (years) |  |  |  |  |  |  |
| ≥ 65 | 41 | 1 |  |  |  |  |
| < 65 | 41 | 1.27 (0.75-2.17) | 0.379 |  |  |  |
| Staging |  |  |  |  |  |  |
| Locally advanced | 14 | 1 |  |  | 1 |  |
| Metastatic | 68 | 2.87 (1.20-6.83) | 0.017 |  | 2.10 (0.85**-**5.18) | 0.108 |
| ECOG performance status score |  |  |  |  |  |  |
| 0-1 | 70 | 1 |  |  | 1 |  |
| 2 | 12 | 2.96 (1.49**-**5.89) | 0.002 |  | 2.94 (1.42**-**6.08) | 0.004 |
| CA19-9 (IU/mL) |  |  |  |  |  |  |
| < 1000 | 48 | 1 |  |  |  |  |
| ≥ 1000 | 34 | 1.45 (0.79**-**2.66) | 0.224 |  |  |  |
| CEA (ng/mL) |  |  |  |  |  |  |
| < 5 | 46 | 1 |  |  |  |  |
| ≥ 5 | 29 | 1.67 (0.90**-**3.10) | 0.107 |  |  |  |
| NLR |  |  |  |  |  |  |
| ≤ 5 | 62 | 1 |  |  | 1 |  |
| > 5 | 20 | 2.61 (1.29**-**5.27) | 0.008 |  | 2.76 (1.33**-**5.75) | 0.007 |
| PLR |  |  |  |  |  |  |
| ≤ 150 | 46 | 1 |  |  |  |  |
| > 150 | 36 | 1.43 (0.79**-**2.60) | 0.240 |  |  |  |
| CRP/albumin |  |  |  |  |  |  |
| ≤ 0.5 | 42 | 1 |  |  | 1 |  |
| > 0.5 | 40 | 2.13 (1.19**-**3.81) | 0.011 |  | 1.60 (0.84**-**3.04) | 0.151 |

ECOG: Eastern Cooperative Oncology Group; CA19-9: Carbohydrate antigen 19-9; CEA: Carcinoembryonic antigen; NLR: Neutrophil-to-lymphocyte ratio;PLR: Platelet-to-lymphocyte ratio; CRP: C-reactive protein; HR: Hazard ratio.

**Table 4 Mean times to disease progression and death according to the neutrophil-to-lymphocyte ratio and the C-reactive protein/albumin ratio**

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| Variable | NLR ≤ 5 | NLR > 5 | *P* value |  | CRP/albumin ratio ≤ 0.5 | CRP/albumin ratio > 0.5 | *P* value |
| Time until disease progression, mean ± SD), mo | 3.0 ± 1.7 | 1.9 ± 1.2 | 0.016 | 3.0 ± 1.8 | 2.3 ± 1.4 | 0.080 |
| Time until death, mean ± SD,  mo | 9.3 ± 5.9 | 4.7 ± 3.5 | 0.014 | 10.0 ± 5.4 | 6.0 ± 5.5 | 0.010 |

NLR: Neutrophil-to-lymphocyte ratio; CRP: C-reactive protein.