

Retrospective Study

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

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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, 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 = 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.

Table 1 Patient demographics and laboratory findings

Characteristic	
No. of patients, <i>n</i>	82
Age, mean \pm SD, yr	63.5 \pm 10.7
Male, <i>n</i> (%)	49 (60)
Laboratory findings	
WBC count, mean \pm SD	6259 \pm 2667
Platelet count, mean \pm SD, \times 1000	225 \pm 94
Neutrophil count, mean \pm SD	4175 \pm 2139
Lymphocyte count, mean \pm SD	1462 \pm 729
CRP, mean \pm SD, mg/dL	12.5 \pm 23.8
Albumin, mean \pm SD, g/dL	3.5 \pm 0.6
CA19-9, median, IU/mL	503.8
CEA, median, ng/mL	2.8
ECOG performance status score, <i>n</i> (%)	
0	22 (27)
1	48 (58)
2	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, <i>n</i> (%)	14 (17)
Metastatic, <i>n</i> (%)	68 (83)

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.

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

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

Parameter	<i>n</i>	Univariate analysis	
		HR (95%CI)	<i>P</i> 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.

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,

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 (yr)					
≥ 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)	0.24		
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.

$P = 0.007$) 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

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 \pm SD, mo	3.0 \pm 1.7	1.9 \pm 1.2	0.016	3.0 \pm 1.8	2.3 \pm 1.4	0.08
Time until death, mean \pm SD, mo	9.3 \pm 5.9	4.7 \pm 3.5	0.014	10.0 \pm 5.4	6.0 \pm 5.5	0.01

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

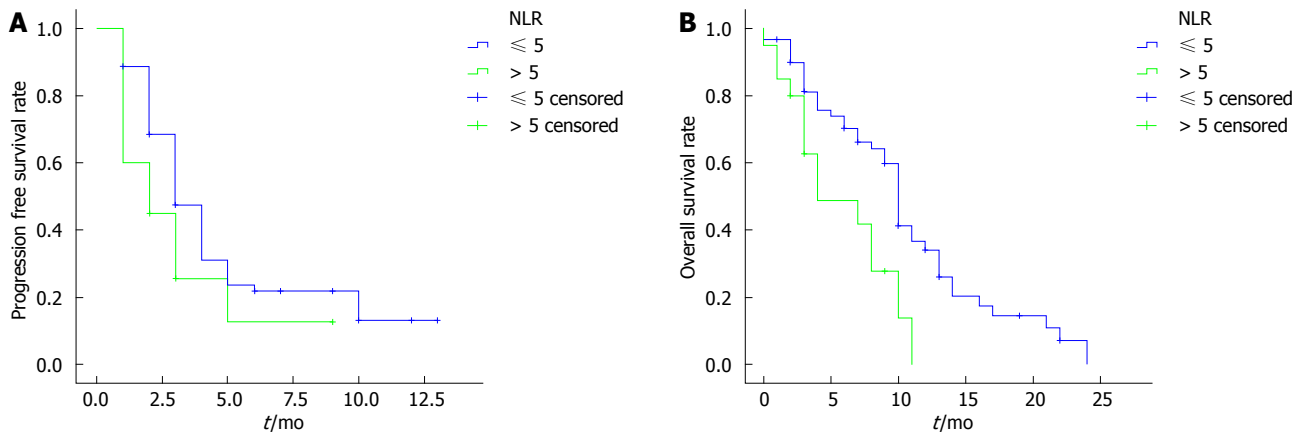


Figure 1 Kaplan-Meier curves for progression-free survival and overall survival according to the neutrophil-lymphocyte ratio. A: PFS stratified according to the NLR; B: Overall survival stratified according to the NLR. NLR: Neutrophil-to-lymphocyte ratio; PFS: Progression-free survival.

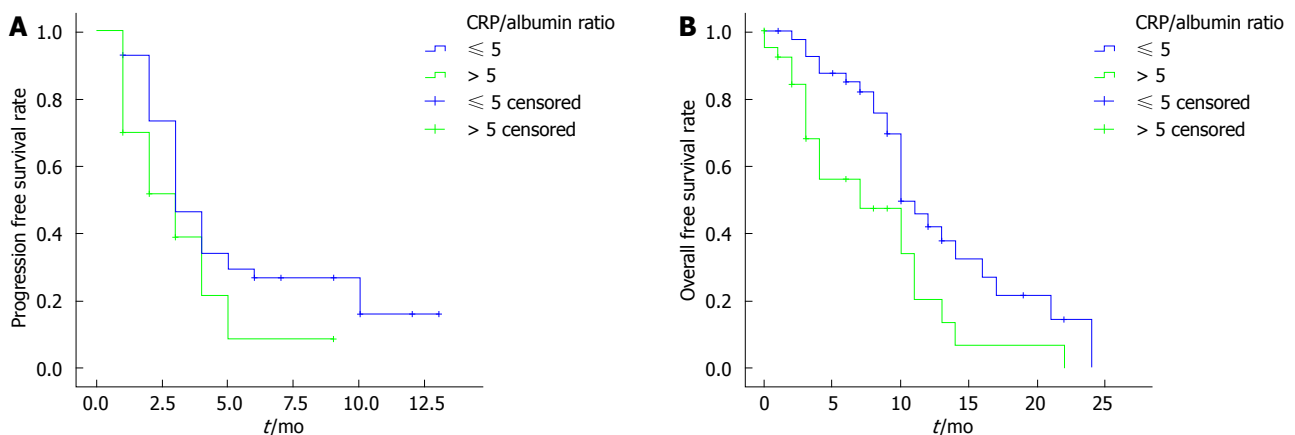


Figure 2 Kaplan-Meier curves for progression-free survival and overall survival according to the C-reactive protein /albumin ratio. A: Progression-free survival stratified according to the CRP/albumin ratio; B: Overall survival stratified according to the CRP/albumin ratio. CRP: C-reactive protein.

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 (hazard ratio = 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.

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