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Original article

Clinical implications of systemic inflammatory response markers as independent prognostic factors for advanced pancreatic cancer

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ABSTRACT

Background: Cancer-associated inflammation is a key molecular feature of pancreatic ductal adenocarcinoma. In this study, we systematically evaluated the prognostic relevance of systemic inflammatory response (SIR) markers in patients with advanced pancreatic cancer.
Methods: A total of 321 consecutive patients with pathologically-confirmed locally advanced or metastatic pancreatic adenocarcinoma were retrospectively recruited. The patients were divided into a test set (n = 110) and a validation set (n = 211). The associations between overall survival (OS) and clinically available SIR markers including white blood cell (WBC) count, absolute neutrophil count, absolute lymphocyte count, absolute monocyte count, platelet count, neutrophil-lymphocyte ratio (NLR), platelet/lymphocyte ratio (PLR) and lymphocyte/monocyte ratio (LMR) were analyzed using Kaplan–Meier curves and multivariate Cox proportional models.
Results: High WBC count, neutrophil count, monocyte count, NLR, PLR and low LMR were significantly associated with decreased OS in the test set. Using the validation set for confirmation, we found also in multivariate analysis an independent value of WBC count (hazard ratio (HR): 2.176, 95% confidence interval (CI): 1.560–3.035, $P < 0.001$), neutrophil count (HR: 2.807, 95% CI: 2.000–3.940, $P < 0.001$), monocyte count (HR: 1.848, 95% CI: 1.315–2.598, $P < 0.001$), NLR (HR: 2.204, 95% CI: 1.590–3.055, $P < 0.001$), PLR (HR: 1.537, 95% CI: 1.114–2.122, $P = 0.009$) and LMR (HR: 0.569, 95% CI: 0.412–0.784, $P = 0.001$) for OS in patients with advanced pancreatic cancer.
Conclusions: Our study confirmed that SIR markers can be used to determine optimal therapeutic strategies for individual patients and to predict pancreatic cancer prognosis.

Introduction

Pancreatic cancer (PC) ranks fourth in cancer-related mortality worldwide [1]. Surgical resection represents the only curative option. Nevertheless, more than 80% of patients are diagnosed at inoperable late stages [2], and despite advances in clinical management, the median survival of patients with advanced disease is approximately five to six months [3]. However, survival rates vary considerably among patients with advanced pancreatic cancer [4]. Therefore, identifying a molecular marker that could be used to determine the optimal therapeutic strategies for individual patients, and to predict pancreatic cancer prognosis remains important.

Traditional prognostic factors, such as tumor size, histologic grade, vascular invasion, perineural invasion, lymph node metastases, distant metastases and serum CA199 have been used routinely to predict outcome for pancreatic cancer patients [4,5]. These parameters are generally useful, however they are often insufficient to optimally predict individual patient prognoses. Therefore, current approaches have focused on the identification and characterization of novel biomarkers, which should ideally be easily accessible, reproducible, cost-effective and most importantly identify patients at high risk for disease progression and death. Clinically, there have been efforts to demonstrate a correlation

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between prognosis and systemic inflammatory response, which is characterized by elevated biochemical or hematologic markers, including CRP, white blood cells, neutrophils, and platelets [6–10]. Some biomarkers representing the degree of systemic inflammatory response, such as the Glasgow prognostic score, neutrophil lymphocyte ratio (NLR), and platelet lymphocyte ratio (PLR), have been shown to have prognostic value in certain types of cancer patients [6–10].

Recently the roles of inflammatory pathways in the initiation and progression of pancreatic cancer have been well-described [11]. Inflammatory processes have emerged as key mediators of pancreatic cancer progression and metastasis [12]. However, very few studies that have reported on the prognostic values of systemic inflammatory response markers in pancreatic cancer [6,13], and their widespread routine application has not yet been established, as some have failed independent external validation [14]. Therefore, in this study we systematically evaluate the independent prognostic relevance of these cost-effective and easily measured parameters on cancer-specific survival in a large cohort of patients with advanced pancreatic cancer.

Materials and methods

Patient

This study was approved by the Ethics Committee of the Fudan University Shanghai Cancer Center, Shanghai, China, and written informed consent was obtained from each participant in accordance with institutional guidelines.

Between January 2011 and August 2013, 321 consecutive patients who had pathologically-confirmed locally advanced or metastatic pancreatic adenocarcinoma were retrospectively recruited from the Fudan University Shanghai Cancer Center, Shanghai, China. The criteria for locally advanced disease included tumor invasion of the celiac trunk or superior mesenteric artery or both, which corresponded with stage III pancreatic cancer according to the International Union Against Cancer (6th edition). Standard radiological studies included contrast-enhanced abdominal CT scans, magnetic resonance imaging (MRI), and/or MR-cholangiopancreaticography (MRCP). Patients suffering from acute infectious diseases were excluded from all analyses. The acute infectious diseases in this study mostly indicate acute pancreatitis and cholangitis. Given acute infection in other part of the body could also induce changes of blood cell count, patients with such acute infectious disease have also been excluded from our study. Totally, 24 patients were excluded from this study due to acute infectious diseases.

Laboratory measurements

Routine laboratory measurements, including white blood cell (WBC) count, neutrophil count, lymphocyte count, monocyte count, and platelet count, were performed prior to cancer diagnostic interventions or treatments. The neutrophil-lymphocyte ratio (NLR), platelet/lymphocyte ratio (PLR) and lymphocyte/monocyte ratio (LMR) were calculated.

Statistical analyses

All data are expressed as mean ± SD (standard deviation). Student's t-test was used to analyze the results, and chi-squared tests were used to identify significant associations. The overall survival (OS) was defined as the interval between the date of a definitive diagnosis and death. The Kaplan–Meier method was used to compare OS between patients in different groups, and the log-rank test was used to estimate differences in survival. Univariate and multivariate analyses were performed using the Cox proportional hazards regression model in Statistical Package for Social Sciences version 15.0 (SPSS, Inc). Hazard ratios (HRs) estimated from the Cox analysis were reported as relative risks with corresponding 95% confidence intervals (CIs). A P value <0.05 was considered statistically significant.

Results

Patient characteristics and clinical features

Among the 321 patients enrolled in the study, 210 (65.6%) were male. The tumors were located in the pancreatic head in 118 (36.9%) of the patients and in the pancreatic body-tail in 203 (63.1%) of the patients. According to AJCC staging, 110 (34.3%) were diagnosed with stage III pancreatic cancer; the remaining patients were diagnosed with stage IV pancreatic cancer, and 171 (53.3%) of the patients had CA 19-9 ≥1000 IU/ml. All patients received gemcitabine-based palliative chemotherapy. 110 patients were part of the test group and the remaining 211 patients were part of the validation group. Detailed clinicopathological characteristics are summarized in Table 1.

Identification of prognostic systemic inflammatory response (SIR) markers using a test set

The 321 patients were assigned to either a test set (n = 110) or a validation set (n = 211). Only the test dataset was used for identification of the prognostic SIR markers. Descriptive statistics for 8 SIR markers in patients in both the test and validation groups are shown in Table 1. For each SIR marker, the median level was used as the cut-off value to analyze its association with clinical outcome in patients with advanced pancreatic cancer. We applied a Kaplan–Meier survival analysis to each of the SIR markers to reveal markers that were correlated with overall survival. We identified six SIR markers that are significantly associated with patient survival, including WBC count (log rank = 8.904, P = 0.003), neutrophil count (log rank = 13.148, P < 0.001), monocyte count (log rank = 12.684, P < 0.001), NLR (log rank = 4.681, P = 0.031), PLR (log rank = 2.990, P = 0.098) and LMR (log rank = 7.325, P = 0.007) (Fig. 1).

Table 1
Clinical information for data sets.

Variables		Test set (N = 110, %)	Validation set (N = 211, %)	*P*-value
Age (years)	Mean ± SD	60.8 ± 9.2	61.2 ± 10.7	0.453[a]
Gender	Male	74 (67.3)	134 (63.5)	0.503
	Female	36 (32.7)	77 (36.5)	
Location	Head	40 (36.4)	78 (37.0)	0.915
	Body, tail	70 (63.6)	133 (63.0)	
Stage	III	33 (30.0)	77 (63.0)	0.245
	IV	77 (70.0)	134 (37.0)	
CA19-9	<1000 IU/ml	59 (53.6)	112 (53.1)	0.925
	≥1000 IU/ml	51 (46.4)	99 (46.9)	
WBC	Median (Range)	6.3 (2.5–19.2)	5.7 (1.7–20.3)	0.633[a]
Neutrophil	Median (Range)	4.2 (0.8–15.5)	3.7 (0.7–18.3)	0.714[a]
Lymphocyte	Median (Range)	1.4 (0.3–3.3)	1.3 (0.3–4.2)	0.981[a]
PLT	Median (Range)	185 (27–676)	170 (27–543)	0.257[a]
Monocyte	Median (Range)	0.4 (0.2–1.5)	0.4 (0.1–1.6)	0.843[a]

Abbreviations: SD, standard deviation; WBC, white blood cell; PLT, platelet.
[a] This comparison was performed using a Student's t-test. All other P-values were obtained using Pearson's χ^2 test.

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