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Prognostic nutritional index predicts survival and correlates with systemic inflammatory response in advanced pancreatic cancer

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Abstract

Background: Recent studies have implied a prognostic value of the prognostic nutritional index (PNI) in certain types of human cancers. However, the value of PNI for predicting survival in patients with pancreatic cancer remains unknown. The goal of this study was to investigate the predictive significance of PNI in patients with advanced pancreatic cancer.

Methods: A total of 321 consecutive patients with pathologically-confirmed locally advanced or metastatic pancreatic ductal adenocarcinoma (PDAC) were retrospectively recruited between January 2011 and August 2013. The patients were divided into a test set (n = 110) and a validation set (n = 211). We evaluated the association between PNI and overall survival (OS). The relationship between PNI and systemic inflammatory response markers, including the neutrophil/lymphocyte ratio (NLR), platelet/lymphocyte ratio (PLR), and lymphocyte/monocyte ratio (LMR) was also assessed. In addition, the associations between PNI and the TNF-α were analyzed.

Results: Kaplan–Meier analyses showed that a low PNI correlated significantly with a shorter OS in patients with advanced pancreatic cancer (190 days for patients with a low PNI vs. 290 days for patients with a high PNI, log-rank = 12.566, $P < 0.001$). Multivariate analysis identified PNI as an independent prognostic factor for OS (hazard ratio [HR]: 0.627, 95% confidence interval [CI]: 0.453–0.868, P = 0.003). PNI also correlated positively with NLR and PLR and negatively with LMR. Additionally, patients with a low PNI exhibited high levels of TNF-α.

Conclusions: Our results confirm that PNI is associated with the systemic inflammatory response and can be used to predict survival in advanced pancreatic cancer.

Keywords: Prognostic nutritional index; Prognosis; Systemic inflammatory response; Pancreatic cancer

Introduction

Pancreatic cancer is the fourth leading cause of cancer death worldwide, with an overall 5-year survival rate of less than 5%.[1] More than 80% of patients are diagnosed at late, inoperable 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

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pancreatic cancer.[4] Therefore, the identification of a molecular marker that could be used to determine the optimal therapeutic strategy for individual patients and to predict the prognosis of pancreatic cancer is important.

Nutritional status plays an important role in the overall survival of malignant tumors. A worsening nutritional status leads to increased susceptibility to infection, delayed wound healing, impaired blood clotting and vessel wall fragility, and it directly increases the occurrence of postoperative complications.[5–7] It can also contribute to tumor development through the suppression of tumor immunity.[8] Patients with pancreatic cancer suffer from an absence of appetite, feeling of satiety, abdominal pain, nausea, emesis and diarrhea, which cause involuntary weight loss to the point of anorexia, tissue wasting and malnutrition.[2,9] Approximately 80% of all pancreatic ductal adenocarcinoma patients suffer from a wasting syndrome referred to as "cancer anorexia–cachexia syndrome", characterized by anorexia, loss of weight, asthenia, and a poor prognosis.[9] Moreover, a systemic inflammatory response is clearly implicated in the progressive nutritional and functional decline in the cancer patients and their subsequent poor outcome.[10,11] Systemic inflammation has been associated with unsatisfactory clinical outcomes, affecting tumor proliferation and survival, angiogenesis, metastasis, and response to treatment.[12] However, to date, there have been few studies that have investigated the association between nutritional status and systemic inflammation in patients with advanced pancreatic cancer.

There is no gold standard for defining nutritional status, however, the concept of a prognostic nutrition index (PNI) was suggested by Smale and colleagues in 1981,[13] and various PNIs have subsequently been widely used to assess patients' nutritional status in patients with cancer.[14,15] The PNI, which is calculated based on the serum albumin concentration and peripheral blood lymphocyte count, was originally proposed as a preoperative risk factor and determinant of surgical indication in colorectal cancer, but it is now widely used as a parameter for nutritional assessment in cancer patients.[16]

To date, there have been few studies that have investigated the association between PNI and survival in pancreatic cancer patients. Therefore, the primary purpose of this study was to study the prognostic value of PNI and demonstrated the association between PNI and systemic inflammatory response in patients with advanced pancreatic cancer.

Materials and methods

Patients

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 the institutional guidelines. Between January 2011 and August 2013, 345 consecutive patients with 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 to 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 and 321 patients were enrolled in the study. Among the 321 patients enrolled in the study, we divided them into two groups via the period patients enrolled in the study, 110 patients were part of the test group, and the remaining 211 patients were part of the validation group.

Laboratory measurements

Routine laboratory measurements, including white blood cell (WBC) count, neutrophil count, lymphocyte count, monocyte count, platelet count and serum albumin were performed prior to conducting the cancer diagnostic interventions or treatments. The neutrophil/lymphocyte ratio (NLR), platelet/lymphocyte ratio (PLR) and lymphocyte/monocyte ratio (LMR) were calculated. The PNI was calculated according to the following formula: $10 \times$ serum albumin (g/dl) $+ 0.005 \times$ total lymphocyte count (per mm^3).[16] The median PNI level of all 110 samples was 47.3 and was selected as the cut-off between a high and a low PNI.

Enzyme-linked immunosorbent assay (ELISA)

The concentrations of serum TNF-α was measured by ELISA. Blood samples were stored at room temperature for 30 min, centrifuged (12,000 6 $\times$ g) for 15 min, and then cryopreserved at -80 °C. The concentration of TNF-α was measured using a sandwich ELISA kit (DuoSet; R&D Systems, Minneapolis, MN, USA).

Statistical analyses

All of the data are expressed as the mean $\pm$ SD (standard deviation). The Student's t-test was used to analyze the results, and chi-squared tests were used to identify significant associations. Overall survival (OS) was defined as the interval between the date of a definitive diagnosis and