Research Article

BIOMEDICAL Journal of Scientific & Technical Research

ISSN: 2574 -1241

DOI: 10.26717/BJSTR.2021.34.005524

The Usefulness of Prognostic Nutritional Index in Predicting Infection in Patients with Newly Diagnosed Pancreatic Cancer

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ARTICLE INFO

Received: February 17, 2021

Published: March 01, 2021

Citation: Branka Roganović, Nebojša Manojlović, Saša Perić, Sanja Tripković, Ana Roganović Sarić. The Usefulness of Prognostic Nutritional Index in Predicting Infection in Patients with Newly Diagnosed Pancreatic Cancer. Biomed J Sci & Tech Res 34(2)-2021. BJSTR. MS.ID.005524.

Abbreviations: PC: Pancreatic Carcinoma; CEA: Carcinoembryonic Antigen; PNI: Prognostic Nutritional Index; BMI: Body Mass Index; IQR: Interquartile Range; ROC: Receiver Operating Characteristic

ABSTRACT

Background/Aims: Data on the usefulness of prognostic nutritional index (PNI) in predicting infection in patients with pancreatic cancer before oncological treatment are limited. The aim of this study was to investigate the usefulness of PNI in predicting infection in patients with newly diagnosed pancreatic cancer.

Methods: The retrospective study included 59 adult patients. We recorded clinicopathological characteristics and laboratory analysis on admission and infectious complications that occurred during hospitalization. PNI was calculated using albumin and lymphocyte count. Association with infective complication was tested for the age, sex, body mass index, albumin levels, lymphocyte count, PNI, PNI<40.5, serum carbohydrate and carcinoembryonic antigen, tumour location, the existence of metastases and hospitalization length.

Results: In the analysed series, there were 36 (61%) male and 23 (39%) female patients; mean age was 62.5 years. Infectious complications were detected in 25 (42,4%) patients. Three factors were found to be associated with infectious complications (Binary logistic regression): serum albumin level (P=0.019), PNI (P=0.030) and PNI below 40.5 (P=0.026). ROC curve analysis determined PNI=39.5 as a new cut-off value for the occurrence of complications, but with relatively low sensitivity (40%) and specificity (38.2%).

Conclusion: Low serum albumin concentration and PNI could represent risk factors for infection in patients with newly diagnosed pancreatic cancer.

Introduction

Pancreatic Carcinoma (PC) is one of the most aggressive malignant tumours. It accounts for 458,918 new cancer cases and 432,242 cancer deaths a year worldwide [1]. Previous studies have shown that aggressive carcinomas lead to systemic inflammation and injury of the patient's immune system [2,3]. Based on this fact, several proinflammatory markers and proinflammatory scoring systems for predicting the prognosis of various malignant tumours have been defined [4-6]. Prognostic value of these scores has also been evaluated in patients with pancreatic carcinoma, especially in those with resectable tumour [7-11]. The results of several studies pointed out that the prognostic nutritional index (PNI) is an effective predictor for survival in pancreatic cancer patients after surgery and chemotherapy [12-15]. However, in the current literature there is a lack of data on the usefulness of PNI in predicting infection in patients with pancreatic cancer before starting the treatment.

This is of particular interest for the patients with newly diagnosed cancer, who might be candidates for surgical treatment or HT. Infectious complications deteriorate immune-nutritional

status and physical function of the patients and adversely affect the onset of treatment and the course of the disease. The aim of this study was to investigate the usefulness of PNI in predicting infection in patients with newly diagnosed pancreatic cancer.

Methods

Study Design and Patient Population: The retrospective study enrolled 59 adult patients with newly diagnosed pancreatic cancer, who were treated in our clinic during a two-year period. Patients included in the study had no cancer other than pancreatic, lymphoproliferative disease and active infection on admission. They also didn't take medication that may affect lymphocyte count. The study protocol was approved by the local Ethics Committee.

Clinicopathological Characteristics: Data on clinicopathological characteristics were obtained from medical records and included age, sex, Body Mass Index (BMI), laboratory findings, tumour location (head, body, or tail of the pancreas), the existence of distant metastases (lung, liver and peritoneum) and infectious complications that occurred during hospitalization. Infectious complications included pneumonia and urinary tract infection. Blood samples for analysis were collected from each patient within 24h from hospital admission and included serum albumin levels, lymphocyte counts, tumour markers: carbohydrate antigen (CA-19-9) and Carcinoembryonic Antigen (CEA). Prognostic Nutritional Index (PNI) was calculated as 10 x albumin (g/dL) + 0.005 × total lymphocyte count (per mm^3) [16]. The lower limit for PNI was defined as 40.5. Evaluation of risk factors. The influence on the occurrence of infectious complications was tested for the age, sex, BMI, albumin levels, lymphocyte counts, PNI, PNI <40.5, CA-19-9 and CEA levels, tumour location, the existence of metastases and hospitalization length.

Statistical Analyses

Statistical analysis was performed using the standard software package SPSS, version 19.0 (SPSS Inc., version 19.0, Chicago, IL). All continuous variables were described in the form of the median [interquartile range (IQR): range between 25^{th} and 75^{th} per centile], or mean ± standard deviation, according to the data distribution. The normality distribution of data was tested with the Kolmogorov-Smirnov test. The categorical variables were expressed as absolute number (percentages) and examined using the chi-square test. Inter-group comparisons of continuous variables were performed by the non-parametric Mann-Whitney test, or the parametric Independent samples test, according to the data distribution. Binary logistic regression was used to examine demographic and clinical factors associated with the complications in the patients with pancreatic cancer. The critical value of PNI for the occurrence of infectious complications was calculated on the basis of the area under a Receiver Operating Characteristic (ROC) curve. All the analyses were evaluated at the level of statistical significance of $P<0.05$.

Results

Characteristics of the Patients: We retrospectively reviewed the data of 72 patients with newly diagnosed pancreatic cancer over the two years period. Thirteen patients were excluded from the study: 6 patients did not meet inclusion criteria, 3 patients died, and 4 patients didn't have completed laboratory analysis. The data were analysed for 59 patients: 36 (61%) male and 23 (39%) females; mean age was 62.5 years. Infectious complications were detected in 25 (42.4%) patients: 13 (22.1%) patients had urinary tract infection; 12 (20.3%) patients had pneumonia. Other characteristics of the series are presented in Table 1.

Table 1: Demographic and clinical characteristics of the patients.

Characteristics	With complications	Without complications	P value
Number of patients	25 (42,4)	34 (57,6)	
Gender: Male / Female	14(56,0)/11(44,0)	22(64,7)/12(35,3)	0,684**
Age (years)	62,48±12,14	62,50±12,74	0,995*
Age: <60 / ≥60	11(44,0)/14(56,0)	14(41,2)/20(58,8)	1,000**
Body Mass Index	25,39±4,33	23,97±3,53	0,170*
Albumin g/l	30,08±5,96	33,85±5,37	0,014*
Lymphocyte count $x10^3$/mm	1,30 (0,90-1,70)	1,30 (1,08-1,85)	0,381***
PNI	37,04±8,91	41,77±6,77	0,024*
PNI: <40,5/ ≥40,5	17(68,0)/8(32,0)	13(38,2)/21(61,8)	0,046**
CA19/9	231,30 (73,15-900,50)	143,55 (50,38-338,75)	0,111***
CEA	3,20 (1,85-11,20)	3,00 (2,10-7,12)	0,848***
Localization: head / body / tail	18(72,0)/5(20,0)/2(8,0)	16(47,1)/10(29,4)/8(23,5)	0,128**
Metastasis: yes/no	17(68,0)/8(32,0)	26(76,5)/8(23,5)	0,470**
Hospitalization length (days)	16,00 (12,50-19,00)	11,50 (9,00-15,00)	0,007***

Note: Values are presented as an absolute number (%), or as the mean value ± standard deviation, or as median (interquartile range) values for the lymphocyte count, CA19/9, CEA and hospitalization lenght. *Independent Samples Test; **Chi-square test; *** Mann-Whitney test.

Evaluation of Risk Factors: Clinicopathological characteristics of the patients were compared between two groups: the group with infection and the group without infection (Table 1). There was no statistically significant difference between the analysed groups for the age, sex, BMI, lymphocyte counts, CA-19-9, CEA, tumour location and existence of metastases. A significant difference was found for albumin, PNI, PNI<40.5 and length of hospitalization. The group of patients with infection had significantly lower serum albumin (P= 0.014) and significantly longer hospitalization (P=0.007) than the group without infection (Table 1). PNI was significantly lower (P=0.024) and the prevalence of PNI < 40.5 was significantly higher (68% vs. 38.2%; P 0.046) in the group with infection (Table 1 & Figures 1&2).

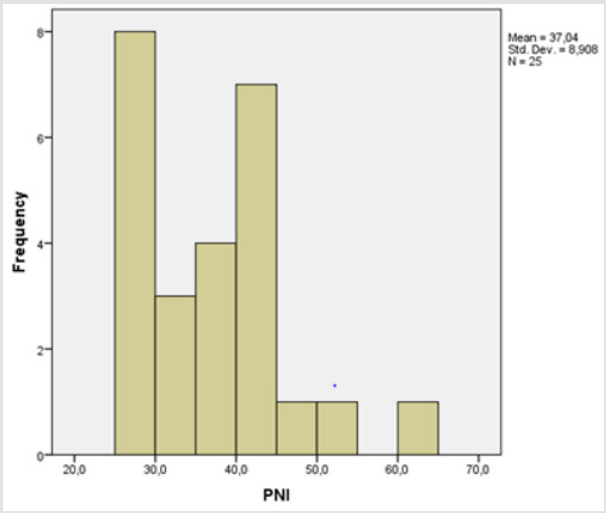

Figure 1: Distribution of PNI in a patient with complications.

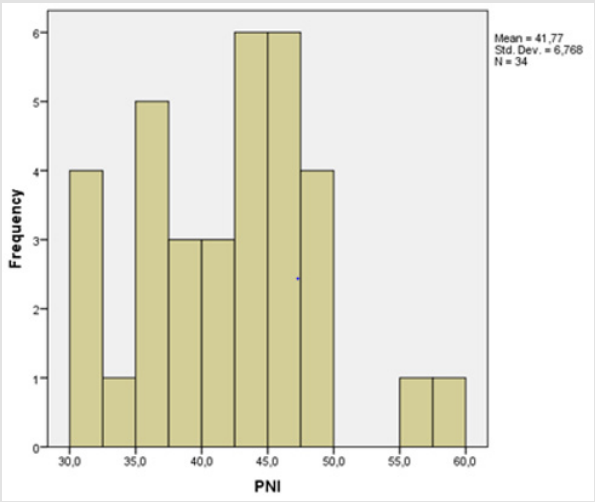

Figure 2: Distribution of PNI in a patient without complications.

Predictors of Infectious Complications: The results of binary logistic regression indicated three variables that significantly influenced the occurrence of infectious complications: serum albumin (OR:1.130, 95%CI:1.020-1.250; P=0.019), PNI (OR:1.086, 95% CI: 1.008-1.169; P=0.030) and PNI below 40.5 (OR:3.136, 95%CI:1.156-10.204; P=0.026). Patients who have lower albumin, lower PNI, and a PNI index value below 40.5 are more likely to develop infection (Table 2). The most important predictor is PNI below 40.5: patients with a PNI below 40.5 are 3.5 times more likely to get an infection, than the patients with a PNI 40.5 and greater. When ROC analysis was performed to calculate the sensitivity and specificity of the PNI, it was shown that PNI is a good indirect indicator of the occurrence of infectious complications in patients with pancreatic cancer. ROC curve analysis also determined PNI=39.5 as a new cut-off value for the occurrence of complications, but with relatively low sensitivity (40%) and specificity (38.2%) (Figure 3).

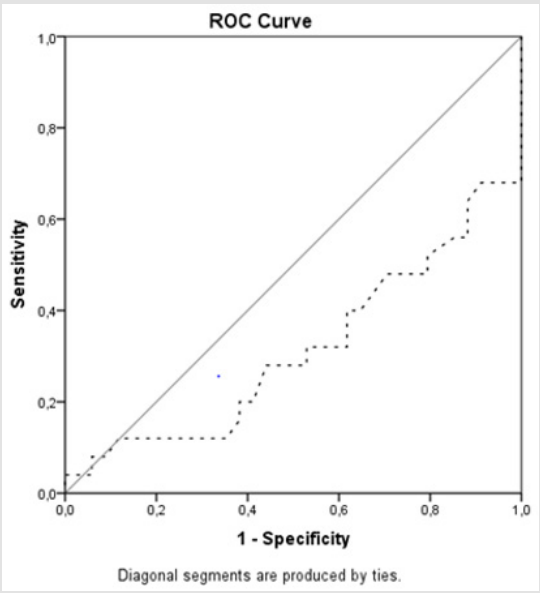

Figure 3: Receiver operating characteristic curves for predicting complications with prognostic nutritional index < 39.5.

Table 2: Predictors of infectious complications in patients with diagnosed pancreatic cancer.

Binary logistic regression		
Characteristics	**OR (95%CI)**	**P value**
Gender: Male / Female	1,440 (0,500-4,147)	0,499
Age (years)	1,000 (0,959-1,043)	0,995
Age: <60 / ≥60	0,891 (0,314-2,531)	0,828
Body Mass Index	1,103 (0,958-1,270)	0,173
Albumin g/l	1,130 (1,020-1,250)	0,019
Lymphocyte count x10^3/mm	0,837 (0,454-1,544)	0,570

PNI	1,086 (1,008-1,169)	0,030
PNI: <40.5/ ≥40.5	3,436 (1,156-10,204)	0,026
CA19/9	1,000 (0,999-1,001)	0,853
CEA	0,998 (0,978-1,019)	0,862
Localization: head / body / tail	0,444 (0,125-1,578)	0,210
head	2,893 (0,960-8,713)	0,059
body	0,600 (0,176-2,046)	0,414
tail	0,283 (0,054-1,468)	0,133
Metastasis: yes/no	1,529 (0,482-4,855)	0,471
Hospitalization length (days)	1,088 (0,995-1,190)	0,063

Note: OR -Odss ratio, CI-Confidence interval. Significant values (P<0.05) are presented in bold.

Discussion

In the patients with malignant tumours, systemic inflammatory response plays a crucial role in the development and progression of tumours [7-20]. On the other hand, nutritional status has a significant role in the prognosis of these patients [21-23]. In 1984. Onodera and colleagues defined PNI as a simple index, based on the values of serum albumin and lymphocytes, which reflects both: the patient's nutritional and inflammatory status [16]. PNI was originally established to estimate the operative risk in patients with malignant gastrointestinal tumours. Onodera's results indicated that gastrointestinal surgery can be safely performed when the PNI is over 45.16 Studies carried out on the following years reported that low preoperative PNI is a poor prognostic factor for overall survival in patients with different types of human malignant tumours [24-34]. Considering pancreatic cancer, many authors have identified low PNI as a prognostic factor for shorter survival in patients with resectable disease and in those who underwent chemotherapy, or chemoradiotherapy for unresectable cancer [15,35-39].

Furthermore, Kim NH demonstrated that PNI below 45 is significantly associated with early recurrence after curative surgical resection [40]. We investigated the significance of PNI in predicting infection in patients with pancreatic carcinoma before starting the therapy – chemotherapy or/and surgery. According to our results, low PNI, especially PNI below 40.5 on hospital admission was significantly associated with the occurrence of infectious complications during hospitalization. The calculated critical value of PNI for the occurrence of infectious complications was 39.5. These results are partly consistent with the results of other authors, although an adequate comparison is not possible, due to the different design of the studies. Namely, studies on the prognostic significance of PNI for the occurrence of complications in patients with various carcinomas were mainly conducted in the patients who underwent surgery. In general, most authors agree that low preoperative PNI can predict postoperative complications, such as pneumonia, urinary and wound infection, anastomotic leakage, bleeding [41-47].

Some studies have shown that pancreatic cancer patients with a low preoperative PNI, or with PNI reduction postoperatively, have a higher risk of complications after pancreaticoduodenectomy [48,49]. Narongsak et college demonstrated that early postoperative PNI below 40.5 is a significant predictive factor for postoperative infective complications such as intra-abdominal abscess, surgical site infection, pneumonia, septicaemia and urinary tract infection [50]. In the study of Watanabe PNI below 40 was significantly associated with postoperative pneumonia, while Kanda et al pointed to PNI cut-off value 45 as the prognostic factor for the complications after pancreaticoduodenectomy11,48 Our PNI cut-off value of 39.5 is lower than the cut off values in previous studies, possibly due to the fact that this study included patients before surgery or chemotherapy. It should also be mentioned that some studies have not confirmed the predictive usefulness of PNI for the occurrence of postoperative complications, especially intraabdominal infections and pancreatic fistula [51-53].

The results of the present study indicate that, beside PNI, low serum albumin is a predictor of infectious complications in patients with newly diagnosed pancreatic carcinoma. This result is not surprising, since albumin does not only reflect nutritional, but also inflammatory and immunological status [54,55]. In malignant diseases, hypoalbuminemia is a consequence of the increased demand for amino acids, and increased microvascular permeability, due to the action of inflammatory cytokines and, on the other hand, shortened albumin half-life [54-56]. Several studies have indicated that in patients with gastrointestinal malignancies, hypoalbuminemia is a good predictor for postoperative complications [48,50,57-59]. Narongsak et al. reported that low preoperative serum albumin is a significant predictive factor for serious infective complications after pancreaticoduodenoctomy [50].

In the Augustine study, preoperative hypoalbuminemia was pointed as an independent risk factor for Clavien-Dindo grade IV complication and mortality after pancreatic surgery [60]. Furthermore, there is evidence that postoperative decrease of serum albumin is a risk factor for the occurrence of complications after abdominal surgery [60,61]. According to the cited studies, it is clear that hypoalbuminemia is a good predictor for infection in patients with pancreatic carcinoma, especially after pancreatic resection. Our result pointed hypoalbuminemia as a risk factor for infection in these patients even before surgery, or chemotherapy.

Limitation of the Study

This study has some limitations. First: Due to the retrospective design of the study, there may have been a certain degree of selection bias. Second: A small number of patients were included in the study. Third: With respect of relatively low sensitivity and specificity for PNI cut off value of 39.5, this result should be accepted with

caution. Further investigations are needed to test its significance in clinical practice.

Conclusion

This study showed that serum albumin concentration and PNI are significant factors associated with infection in patients with pancreatic carcinoma. Infectious complications can postpone the onset of treatment and adversely affect the course of the disease. Therefore, patients with low serum albumin and PNI on hospital admission should be closely followed up during hospitalization and early intervention with immuno-nutrition should be considered.

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ISSN: 2574-1241

DOI: 10.26717/BJSTR.2021.34.005524

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