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Research Article

Does the Prognostic Nutrition Index Predict the Development of Complications and Survival Following Pancreatoduodenectomy for Periampullary Carcinomas?

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Abstract

Introduction: It has been suggested that pre-operative nutritional scores may be useful in predicting post-operative outcome. The aim of this study was to evaluate the Onodera prognostic nutrition index (PNI) in a Western population in relation to outcomes following resection of periampullary carcinomas including its relation to mortality, pancreatic leak and tumour recurrence.

Methods: All patients undergoing resection between 2000 - 2010 were identified from a prospectively maintained database. The pre-operative Onodera PNI was calculated using the formula: 10 x albumin (g/dl) + 0.005 x total lymphocyte count (mm-3). PNI < 45 is regarded indicative of moderate-to-severe malnutrition. Pancreatic leak was defined according to ISGPF criteria.

Results: Of 251 patients undergoing resection, complete data was available for 206 patients. During the follow-up period there were 47 (22.3%) pancreatic leaks, 112 (54.4%) recurrences, and 116 (56.3%) deaths. Comparing patients with PNI < 45 to those with PNI > 45 there was a significant difference in relation to mortality [< 45 = 37 (71.2%); > 45 = 79 (51.2%); Chi-squared = 5.448, p = 0.020)] but not leak [< 45 = 10 (19.2%); > 45 = 37 (24.0%); Chi-squared = 0.272, p = 0.602)], or recurrence [< 45 = 30 (57.7%); > 45 = 82 (53.2%); Chi-squared = 0.156, p = 0.692].

Conclusions: This study demonstrates that PNI calculated pre-operatively was predictive of long-term outcome in terms of mortality but not development of post-operative complications or tumour recurrence.

Keywords: *Nutrition Index; Albumin; Periampullary Cancer; Morbidity; Mortality*

Introduction

Pancreatoduodenectomy (PD) is considered a highly invasive and technically challenging procedure with serious post-operative complications and poor long-term outcomes [1-3]. With advances in peri-operative care, the mortality of PD has fallen nationally in the USA to 3% and as low as 1% in high volume centres [4,5] although morbidity remains at 30 - 50% [2,4]. There is therefore an on-going research need to determine the prognostic value of pre-operative factors, which may facilitate risk stratification, and the development of targeted strategies to reduce post-operative morbidity and mortality, thereby improving surgical outcomes.

Cachexia and nutritional depletion are common in patients with malignant disease [6]. This is attributed to several factors including in relation to pancreatic cancer: tumour progression; deranged catabolic mechanisms; reduced oral intake associated with nausea; emotional response to physical disease; dysphagia; mechanical obstruction of the gastrointestinal or biliary tracts; concurrent pancreatitis; and malabsorption, all of which are exacerbated by cancer-related pain [1,7]. Impaired immuno-nutritional status is a key factor in many

regards. Pre-operative nutritional status plays an important role in immune system dysfunction including: susceptibility to infection; impaired protein synthesis - adversely affecting wound healing (leading to fistulas); coagulation; and vascular wall integrity, as well as leading to impaired suppression of tumour immunity [1,8,9]. Furthermore, deteriorating nutritional status is reported to be directly related to an increased incidence of post-operative complications in pancreatic, gastric and colorectal cancer [1,8,9] and it has been suggested that pre-operative nutritional scores may be of benefit in predicting outcome following surgical resection of upper gastrointestinal cancers.

Cachexia and nutritional depletion are common in patients with malignant disease [6]. This is attributed to several factors including in relation to pancreatic cancer: tumour progression; deranged catabolic mechanisms; reduced oral intake associated with nausea; emotional response to physical disease; dysphagia; mechanical obstruction of the gastrointestinal or biliary tracts; concurrent pancreatitis; and malabsorption, all of which are exacerbated by cancer-related pain [1,7]. Impaired immuno-nutritional status is a key factor in many regards. Pre-operative nutritional status plays an important role in immune system dysfunction including: susceptibility to infection; impaired protein synthesis - adversely affecting wound healing (leading to fistulas); coagulation; and vascular wall integrity, as well as leading to impaired suppression of tumour immunity [1,8,9]. Furthermore, deteriorating nutritional status is reported to be directly related to an increased incidence of post-operative complications in pancreatic, gastric and colorectal cancer [1,8,9] and it has been suggested that pre-operative nutritional scores may be of benefit in predicting outcome following surgical resection of upper gastrointestinal cancers.

Recent studies of patients undergoing PD have highlighted the importance of nutritional assessment and management in reducing post-operative morbidity, including fistula formation, and in recovering quality of life [10,11]. In 1981, Smale and colleagues highlighted the clinical relevance of pre-operative nutritional management and the need for a reliable, objective and readily available measurement of pre-operative nutritional status in rationalising the use of pre-operative nutritional support [6]. They used a previously developed and validated linear predictive nutritional assessment model, calculated using the equation:
Prognostic Nutritional Index (%) = 158 - 16.6 (serum albumin level) - 0.78 (triceps skinfold) - 0.20 (serum transferrin level) - 5.8 (grade of cutaneous delayed hyposensitivity reactivity to any of the three common recall antigens, mumps, SKSO, candida).

The Onodera PNI is commonly used in Japan [1] and comprises a simple formula requiring knowledge of peripheral blood albumin concentration and total lymphocyte count. A PNI score of less than 45 is regarded indicative of moderate-to-severe malnutrition. Advantages of the Onodera PNI above other nutritional indices include its convenience, simplicity and ease of use. Values for albumin concentration and lymphocyte count are obtained as part of the routine pre-operative assessment, therefore clinicians and researchers at all institutions should be able to calculate this index.

Multiple published studies have successfully used the Onodera index to consider the prognostic value of nutritional status, including gastrointestinal cancer surgery [12], abdominal surgery in those over 60 years old [13], oesophagectomy for oesophageal carcinoma [14], and risk of tuberculosis post-gastrectomy [15]. The Onodera PNI has been reported as a better predictor of clinical outcomes in infants' post-cardiac surgery, when compared with height-age-weight measures [16], and it is also arguably a better marker of nutritional status when compared with body mass index (BMI). A patient's BMI, which can remain relatively high despite underlying cachectic processes [1,17], is no longer regarded an independent risk factor for morbidity or mortality after major abdominal surgery when an enhanced recovery program is used [18], and average BMI values may vary between different populations [1,17].

In a recently published retrospective study of post-operative outcomes in patients who underwent resection for adenocarcinoma of the pancreas, Kanda and colleagues used the Onodera PNI, with a cut-off value for clinically significant malnutrition of less than 45 [1]. The authors reported significant associations between low PNI and poor survival, increased occurrence of post-operative complications and a higher prevalence of pancreatic fistulas [1].

The aim of the present study was to evaluate the Onodera PNI score in a Western population in relation to outcomes following resection of periampullary carcinomas, including its relation to pancreatic leak, tumour recurrence and mortality.

Methods

Patients with periampullary carcinomas (head of pancreas, distal bile duct and ampulla) undergoing resection at the Pancreatic Unit, St. James's University Hospital (SJUH), Leeds, United Kingdom, during the period from January 2000 through December 2010 were identified from a prospectively maintained database.

The pre-operative Onodera PNI was calculated for each patient using the equation: 10 x albumin (g/dl) + 0.005 × total lymphocyte count (mm^{-3}). A PNI of less than 45 was taken as the cut-off for moderate-to-severe malnutrition. Post-operative outcomes were recorded, including mortality, tumour recurrence, and pancreatic leak as defined according to the International Study Group for Pancreatic Fistula (ISGPF) criteria [19].

Statistical analysis

Categorical data was presented as frequency and proportions (%), and was analysed using the Pearson's chi-squared test with Yates' correction. Logistic regression analysis was used to assess the impact of pre-operative PNI on outcome. Receiver operating characteristic (ROC) curve analysis was performed to identify the sensitivity and specificity of PNI as a predictor of statistically significant outcomes. Fisher's exact test was used to explore associations between PNI, other variables and mortality. Statistical analyses were performed using SPSS for Windows™ version 18.0 (SPSS Inc, Chicago, Ill, USA), and statistical significance was taken at the 5% level.

Results

Of 251 patients undergoing resection during the period of the study, complete data was available for 206 individuals. Patient demographics and clinical characteristics are summarised in table 1.

	Number of patients
Mean (range) age (years)	65 (33 - 83)
Gender ratio (M:F)	108:98
Pre-operative measurements	
Albumin (g/L) [Mean ± SD]	39.5 ± 5.63
Lymphocyte count (10^9/L) [Mean ± SD]	1.93 ± 0.78
PNI [Mean ± SD]	49.1 ± 7.33
Surgery	
Pylorus preserving pancreatoduodenectomy	182
Whipple procedure	24

Table 1: *Demographics and clinical characteristics of 206 patients.*

During the post-operative period there were 47 (22.3%) pancreatic leaks and in long-term follow-up there were 112 (54.4%) recurrences, and 116 (56.3%) deaths. The relationships between PNI and outcome measures are shown in table 2 and figure 1. Comparing patients with pre-operative PNIs less than 45 to those greater than 45 there was a significant difference in relation to mortality (Chi-squared, p = 0.020) but no significant difference in relation to pancreatic leak or development of recurrence.

Surgical outcome	**Number of patients (percentage)**		**Chi-squared**	***p***
	Onodera PNI			
	< 45	**> 45**		
Pancreatic leak	10 (19.2%)	37 (24.0%)	0.272	0.602
Recurrence	30 (57.7%)	82 (53.2%)	0.156	0.692
Mortality	37 (71.2%)	79 (51.2%)	5.448	0.020

Table 2: *Chi-squared test results for Onodera PNI and surgical outcomes in 206 patients with pancreatic cancer.*

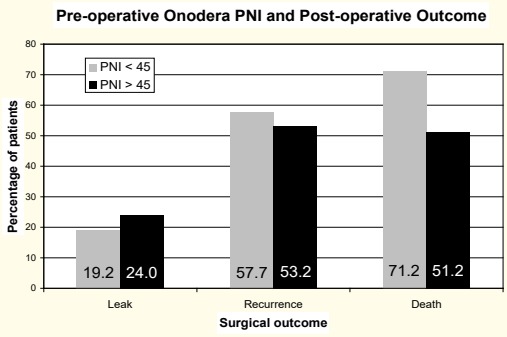

Figure 1: *Chi-squared test results for Onodera PNI as a predictor of surgical outcome.*

**p = 0.020*

The results of the logistic regression analysis of PNI as a prognostic factor for mortality are summarised in table 3. Logistic regression analysis identified a PNI at a cut-off value < 50 as the strongest predictor of mortality. The mortality rate of patients with a PNI score < 50 was just over twice that of patients with a PNI > 50 (OR 2.103; 95% CI 1.201 - 3.682; p = 0.009).

PNI	Odds ratio, OR (95% CI)	SE	*p*
< 55	1.645 (0.846 - 3.197)	0.339	0.142
< 50	2.103 (1.201 - 3.682)	0.286	0.009
< 45	1.855 (0.959 - 3.590)	0.337	0.066
< 40	4.307 (1.207 - 15.372)	0.649	0.024
< 35	7.486 (0.931 - 60.233)	1.064	0.058

Table 3: *Logistic regression analysis of Onodera PNI for mortality in 206 patients with pancreatic cancer.*

The ROC curve analysis of Onodera PNI as a predictor of mortality is shown in figure 2. A PNI of 45 as a predictor of mortality was found to have a sensitivity of 0.811 and a specificity of 0.310. In comparison, PNI of 50 was found to have a lower sensitivity of 0.578 but higher specificity of 0.603.

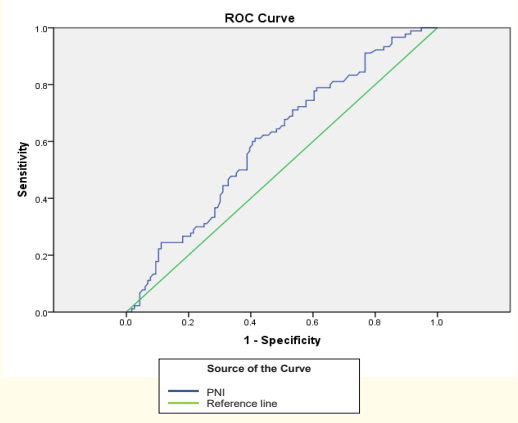

Figure 2: *ROC curve analysis of Onodera PNI as a predictor of mortality.*

Fisher's exact test identified a significant association between tumour origin and post-operative mortality ($p < 0.001$) with ampullary tumours having a better prognosis compared with tumours originating in the head of the pancreas or distal bile duct.

The significance of a PNI < 50 as a prognostic factor for mortality decreased slightly when logistic regression analysis was performed adjusting for tumour origin (OR 2.093, 95% CI 1.159 - 3.779; $p = 0.014$). The results of the logistic regression analysis of PNI and tumour origin as prognostic factors for mortality are summarised in table 4. Amongst the patients with a PNI < 50 the mortality of those with ampullary tumours was less than patients with carcinoma of the head of the pancreas (OR 0.345; 95% CI 0.170 - 0.701; $p = 0.003$).

Variables	Odds ratio, OR (95% CI)	SE	*p*
Tumour origin			
Head of pancreas	REF	REF	REF
Ampullary	0.363 (0.180 - 0.731)	0.357	0.005
Distal bile duct	1.843 (0.900 - 3.775)	0.366	0.095
PNI < 55	1.679 (0.831 - 3.394)	0.359	0.149
Tumour origin			
Head of pancreas	REF	REF	REF
Ampullary	0.345 (0.170 - 0.701)	0.362	0.003
Distal bile duct	1.707 (0.829 - 3.516)	0.369	0.147
PNI <5 0	2.093 (1.159 - 3.779)	0.302	0.014
Tumour origin			
Head of pancreas	REF	REF	REF
Ampullary	0.337 (0.166 - 0.684)	0.362	0.003
Distal bile duct	1.774 (0.865 - 3.637)	0.366	0.118
PNI < 45	2.074 (1.027 - 4.189)	0.359	0.042
Tumour origin			
Head of pancreas	REF	REF	REF
Ampullary	0.344 (0.168 - 0.703)	0.365	0.003
Distal bile duct	1.879 (0.914 - 3.865)	0.368	0.086
PNI < 40	5.266 (1.401 - 19.798)	0.676	0.014
Tumour origin			
Head of pancreas	REF	REF	REF
Ampullary	0.370 (0.183 - 0.750)	0.361	0.006
Distal bile duct	1.880 (0.915 - 3.860)	0.367	0.086
PNI < 35	7.629 (0.910 - 63.940)	1.085	0.061

Table 4: *Logistic regression analysis of Onodera PNI and tumour origin for mortality in 206 patients with pancreatic cancer.*

Univariate analysis did not identify significant associations between other pre-operative factors and mortality, including Fisher's exact test for patient gender ($p = 0.889$) and ROC curve analysis for age ($p = 0.147$) therefore these were not built into multivariate analysis.

Discussion

This study has demonstrated that a PNI of < 45, as advocated by Kanda., *et al*. [1], was predictive of long-term outcome in terms of patient mortality although it was unable to predict the development of post-operative complications or the development of tumour re-

currence. However, whilst Kanda and colleagues reported an OR of 2.06 ($p < 0.001$) [1] for a PNI of < 45, the current study showed that although there was an odds ratio of 1.86 ($p = 0.066$), the selection of a PNI of 50 based on ROC analysis lead to improved statistical performance with an OR of 2.10 ($p = 0.009$). It is unclear as to whether this difference between Japanese and English populations is related to a difference in patient or tumour characteristics.

The Onodera PNI is a very practicable pre-operative assessment tool in patients with pancreatic cancer, and may provide a marker of optimisation of nutritional status ahead of surgery. Furthermore, as it becomes more widely used in research settings, it may help to advance our understanding of the complex relationship between immuno-nutritional status and outcomes in periampullary cancers. Further studies are required to establish the accuracy of the Onodera PNI as a prognostic marker for specific post-operative complications and to validate the usefulness of different cut-off values as optimum predictors in different populations. As per the work of Kanda and colleagues, we similarly found the accuracy of the Onodera PNI cut-off at less than 45 limits its usefulness [1]. Additional studies in this area may lead to the development of a more sensitive and specific prognostic formula, perhaps additionally taking into account other pathophysiological predictive factors beyond the scope of immuno-nutritional measures.

There are a number of limitations worth noting in the present study. Firstly, although the components of the PNI (serum albumin concentration and total lymphocyte count) have been shown to correlate with increased post-operative morbidity and mortality [1,12-17], previous use of this index has raised some debate as to whether these serological markers accurately reflect nutritional status [17]. Serum albumin levels are not only influenced by impaired nutrition in advanced pancreatic cancer but albumin is also a negative acute-phase serum protein [1,17,20]. Similarly, lymphocyte count is affected by the acute-phase response and stage of disease [1,17,21]. Despite its aforementioned advantages compared with other nutritional indices, the Onodera PNI is certainly affected by inflammatory disorders and these must be taken into account [1,17]. That said, it is standard practice not to operate on patient with cholangitis or other acute infections and so the strength of this argument against PNI is unclear.

Secondly, in terms of data analysis, the present study does not consider other nutritional indices, for comparison against the predictive value of the Onodera PNI. However, standard anthropometric measures, when assessed alone, are believed to be of limited value in patients presenting with cancer [22]. There are several scoring systems that have been used to assess patients in this setting including: subjective global assessment [23]; nutritional risk screening [24]; and nutritional risk index [25], although none have been applied specifically to, and validated for, periampullary cancers. They are also more complex than the PNI and depend on subjective information in relation to weight loss, whereas the PNI is purely objective based on data from 2 routine blood tests.

Finally, the complex relationship between average immuno-nutritional status and population differences may account in part for some of the differences in our findings in a Western population, compared to the findings of Kanda and colleagues whose study involved a Japanese population.

As evidence emerges that immune-nutritional status may be of importance in predicting outcome of periampullary cancers, and that peri-operative nutritional supplementation may reduce complications and improve outcome [11,26], it is clear that an optimal index needs to be developed that is simple, reproducible, and uniformly applicable thus allowing comparison of global populations. Until there is consensus, as per current European guidelines for patients undergoing major surgery, comprehensive and thorough nutritional assessment and management are recommended [1,27].

Conclusions

This study has demonstrated that in keeping with existing data that a PNI of < 45 prior to resection was predictive of long-term outcome in terms of patient mortality, however, unlike the prior study it was unable to predict the development of post-operative complications or the development of tumour recurrence. ROC analysis indicated that a PNI < 50 was superior to a PNI of < 45 in the current population with an improved OR. However, the sensitivity and specificity of the PNI score currently limit its use, and further developments are required to improve its statistical profile to allow its use in the clinical setting.

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