Controlling Nutritional Status score is superior to Prognostic Nutritional Index score in predicting survival and complications in pancreatic ductal adenocarcinoma: a Chinese propensity score matching study

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(Submitted 3 March 2020 – Final revision received 17 May 2020 – Accepted 20 June 2020 – First published online 29 June 2020)

Abstract
Preoperative nutritional status plays an important role in predicting postoperative outcomes. Prognostic Nutritional Index (PNI) and Controlling Nutritional Status (CONUT) are good tools to assess patients’ nutritional status. They have been used in predicting outcomes in various malignancies, but few studies have focused on pancreatic adenocarcinoma (PDAC) patients. Totally, 306 PDAC patients were enrolled. The propensity score matching (PSM) method was introduced to eliminate the baseline inequivalence. Patients with different PNI (or CONUT) scores showed inequivalence baseline characteristics, and patients with compromised nutritional status were related with a more advanced tumour stage. After PSM, the baseline characteristics were well balanced. Both low PNI (≤ 45) and high CONUT (≥ 3) were independent risk factors for poor overall survival (P < 0.05), and the result remained the same after PSM. Survival analysis demonstrated both patients with low PNI and high CONUT score were associated with poorer survival, and the result remained the same after PSM. The results of AUC indicated that CONUT might have a higher sensitivity and specificity in predicting complications and survival. Preoperative low PNI (≤ 45) and high CONUT (≥ 3) scores might be reliable predictors of prognosis and surgical complications in PDAC patients. Compared with PNI, CONUT might be more effective.

Key words: Prognostic Nutritional Index; Controlling Nutritional Status; Pancreatic ductal adenocarcinoma; Nutritional status; Propensity score matching

Pancreatic ductal adenocarcinoma (PDAC) is the most common malignant tumour of the pancreas, with a 5-year survival rate <6% (1). Currently, surgery remains the only potential curative therapy for PDAC, though <20% of patients are eligible for a radical resection when diagnosed. Nevertheless, some patients with resectable PDAC could not tolerate surgery due to compromised nutritional status; thus, they might lose the chance for radical resection.

In Western countries, obesity is associated with cancer development and progression (2), especially in PDAC patients (3). However, malnutrition is common in diagnosis (hypalbuminaemia, low BMI, weight loss, etc.) (4), especially in China (5, 6). The status of malnutrition could be attributed to pancreatic exocrine insufficiency, gastrointestinal obstruction and cancerous pain (7). Recently, many researches, especially in east Asia (8–9), have focused on the importance of patient’s nutritional status in treating PDAC. Inferior nutritional status can increase the morbidity and mortality in patients followed by pancreateoduodenectomy (10, 11). Malnutrition is always accompanied by immunological deterioration, which may contribute to tumour recurrence and metastasis by suppressing tumour-specific immunity, and it had been reported to predict adverse oncological outcomes (12, 13).

Low preoperative Prognostic Nutritional Index (PNI) value was found to be an independent risk factor for poor survival in many malignancies (14–16), including PDAC (7). Controlling Nutritional Status (CONUT) is another newly purposed index for objectively assessing patients’ nutritional status (17). Compared with PNI, CONUT also took serum cholesterol, which was an important biochemical parameter in most pancreas diseases, into account when assessing patients’ immunonutritional status. The prognostic significance of preoperative CONUT score has been noticed in many malignancies (18, 19), but few researches evaluated the efficiency in PDAC.

The significant baseline characteristics difference could be found between the two groups, which had been well-known

Abbreviations: ALB, albumin; CA, carbohydrate antigen; CONUT, Controlling Nutritional Status; OS, overall survival; PDAC, pancreatic adenocarcinoma; PNI, Prognostic Nutritional Index; POPF, postoperative pancreatic fistula; PSM, propensity score matching.

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indicators for poor prognosis, thus may produce great bias. Given this dilemma, propensity score matching (PSM), a widely used statistical approach to obtain highly selected patients with similar baseline characteristics and significantly improve the quality of further statistical analysis, is a suitable method to avoid potential bias.

In the present study, we balanced the baseline characteristics using PSM to evaluate the significance of preoperative PNI or CONUT score as a predictor of postoperative complications and overall survival (OS) in resectable PDAC patients.

Methods

Ethics statement

This study was approved and was taken in accordance with the Declaration of Helsinki and the Clinical Research Ethics Committee of Huashan Hospital. All patients agreed to voluntarily donate their clinical data and follow-up data for research-related purposes only and signed an informed consent form on admission.

Patients

Patients included in this study have to fulfill the following criteria: (1) aged from 18 to 80 years; (2) resectable primary tumour and confirmed by postoperative histopathological examination and (3) Eastern Cooperative Oncology Group score ranged from 0 to 2. Patients with the following criteria were excluded from our study: (1) patients received any preoperative neoadjuvant chemotherapy, chemoradiation therapy or other anti-tumour immunotherapy were excluded from this study and (2) patients with any distant metastasis or arterial involvement, which was confirmed pre- or intra-operatively. From 2012 to 2014, totally, 566 patients were eligible enrolled in this study. After further excluding those with incomplete follow-up data (survival data, postoperative metastasis data, etc.) (n 96), not willing to take part in this study (n 39), patients with perioperative immunotherapy (n 125) and eventually a total of 306 participants were enrolled in the final analyses of the present study. Pathological tumour stage was assessed according to the tumour, node, metastasis (TNM) staging system (AJCC, 8th edition).

Perioperative evaluation and follow-up

Serum samples of all patients were obtained and analysed within 1 week before surgery. Parameters included a complete blood cell count, serum albumin (ALB), alanine transaminase, total bilirubin, total cholesterol, carbohydrate antigen (CA) 125 and CA 19-9. CT and/or MRI was performed to evaluate primary tumour extension and rule out distant metastasis. Positron emission tomography-computed tomography (PET-CT), endoscopic ultrasonography or endoscopic retrograde cholangiopancreatography was also performed to help diagnosis when it was necessary.

All patients were followed every month in the first postoperative 6 months and every 3–6 months since after. Blood tests and CT scans were performed at every visit. OS was the primary outcome of our study. Postoperative pancreatic fistula (POPF), delayed gastric empty, post-pancreatectomy haemorrhage and chylous fistula were defined according to the consensus proposed by the International Study Group of Pancreatic Surgery. Surgical site infection and pleural effusion were based on the clinical manifestations, laboratory results and imaging findings.

Results

High or low Prognostic Nutritional Index scores in pancreatic adenocarcinoma patients

Together, seventy-five patients were divided into the low PNI group, while the other 231 patients were in the high PNI group. We found that patients in the low PNI group tended to have more advanced tumour stages, higher CA 125 and 19-9 levels, more advanced tumour stages, males, lower BMI, lower leucocyte count, lower total cholesterol, and total lymphocyte count and total cholesterol (online Supplementary Fig. S1(b)). In our study, we defined CONUT score <3 as low CONUT and CONUT score ≥3 as high CONUT.

Propensity score matching

A logistic regression model was used to estimate PSM based on patient’s sex, age, BMI, alanine transaminase, total bilirubin, PNI score (or CONUT score), CA 125, CA 19-9, tumour stage, tumour size, presence of R1 resection and lymph node metastasis. After one-to-one PSM matching without replacement conducted by a 0.1 caliper matching on the estimated propensity score, seventy-two pairs of matched cases were identified when patients were classified by PNI, and seventy-nine pairs were identified when patients were classified by CONUT.

Statistical analysis

All statistical analyses were performed with SPSS 23.0 (IBM). Normally distributed data were expressed as mean values and standard deviations, and asymmetrically distributed data were expressed as medians and ranges. The difference of baseline characteristics was assessed by t-test for continuous variables and χ2 test for categorical variables. The Cox regression model was performed to investigate the correlation between patient’s survival and risk factors. The Kaplan–Meier method and log-rank test were used for survival analysis. Outcomes were presented using hazard ratios and associated 95% CI. P < 0.05 was considered statistically significant.
score was significantly worse than those with high PNI score (online Supplementary Table S2 and Fig. S2).

**High or low Controlling Nutritional Status scores in pancreatic adenocarcinoma patients**

After stratified by CONUT score, 217 patients had a low CONUT score, and the remaining eighty-nine patients had a high CONUT score. Patients in the high CONUT group had significantly lower BMI, lower leucocyte count, ALB, total cholesterol, higher CA 125 and CA 19-9 levels, more advanced tumour stage, higher incidence of lymph node metastasis and larger tumour size (all \( P < 0.05 \); Table 2).

High CONUT score was proved as an independent prognostic risk factor for poor OS (hazard ratio 3.93, \( P < 0.001 \)) (online Supplementary Table S3). Furthermore, patients in the high CONUT group had significantly worse survival than patients in the low CONUT group (online Supplementary Table S4 and Fig. S2).

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**Table 1. Baseline characteristics of patients with high or low Prognostic Nutritional Index (PNI) score (Numbers and percentages; mean values and standard deviations; medians and ranges)**

<table>
<thead>
<tr>
<th>Index</th>
<th>Before PSM</th>
<th></th>
<th>After PSM</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Low PNI score ( n = 75 )</td>
<td>High PNI score ( n = 231 )</td>
<td>Low PNI score ( n = 72 )</td>
<td>High PNI score ( n = 72 )</td>
</tr>
<tr>
<td>Male</td>
<td>36</td>
<td>48.0</td>
<td>150</td>
<td>64.9</td>
</tr>
<tr>
<td>Age (years)</td>
<td>62.07</td>
<td>61.85</td>
<td>0.661</td>
<td>62.83</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>9.25</td>
<td>9.19</td>
<td>0.080</td>
<td>10.91</td>
</tr>
<tr>
<td>Leucocytes (10⁹/l)</td>
<td>21.38</td>
<td>22.15</td>
<td>0.039</td>
<td>21.52</td>
</tr>
<tr>
<td>Albumin (g/l)</td>
<td>4.35</td>
<td>5.98</td>
<td>&lt;0.001</td>
<td>4.36</td>
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<tr>
<td>Alamine transaminase (U/l)</td>
<td>1.27</td>
<td>1.61</td>
<td>0.128</td>
<td>1.79</td>
</tr>
<tr>
<td>Total bilirubin (µmol/l)</td>
<td>47.00</td>
<td>41.00</td>
<td>0.733</td>
<td>49.00</td>
</tr>
<tr>
<td>Albumin (g/l)</td>
<td>38.45</td>
<td>39.49</td>
<td>0.064</td>
<td>38.40</td>
</tr>
<tr>
<td>Total cholesterol (mg/dl)*</td>
<td>180.68</td>
<td>202.06</td>
<td>&lt;0.001</td>
<td>180.69</td>
</tr>
<tr>
<td>CA 125 (U/ml)</td>
<td>34.29</td>
<td>27.02</td>
<td>0.637</td>
<td>35.00</td>
</tr>
<tr>
<td>CA 19-9 (U/ml)</td>
<td>22.00</td>
<td>17.00</td>
<td>0.001</td>
<td>22.00</td>
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<td>Tumour stage</td>
<td>220.00</td>
<td>90.00</td>
<td>0.002</td>
<td>215.00</td>
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<tr>
<td>Stage I</td>
<td>47.00–846.00</td>
<td>34.00–306.00</td>
<td>48.75–837.50</td>
<td>60.50–440.50</td>
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<td>Stage II</td>
<td>12</td>
<td>16.0</td>
<td>75</td>
<td>32.5</td>
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<td>Stage III</td>
<td>47</td>
<td>62.7</td>
<td>146</td>
<td>63.2</td>
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<tr>
<td>Stage IV</td>
<td>16</td>
<td>21.3</td>
<td>10</td>
<td>43</td>
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<tr>
<td>R1 resection</td>
<td>53</td>
<td>70.7</td>
<td>89</td>
<td>38.5</td>
</tr>
<tr>
<td>Lymph node metastasis</td>
<td>4.01</td>
<td>3.67</td>
<td>0.061</td>
<td>4.00</td>
</tr>
<tr>
<td>Tumour size (cm)</td>
<td>1.33</td>
<td>1.39</td>
<td>1.34</td>
<td>1.19</td>
</tr>
</tbody>
</table>

PSM, propensity score matching; CA, carbohydrate antigen.
* To convert cholesterol in mg/dl to mmol/l, multiply by 0.0259.

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**High or low Prognostic Nutritional Index scores in pancreatic adenocarcinoma patients after propensity score matching**

After one to one case matching, PSM identified seventy-two pairs of patients. After PSM, low PNI score was still associated with lower leucocyte count and lower total cholesterol in the blood, while other baseline characteristics were not significantly different between the two groups (Table 1). After PSM, the mean survival time in patients with low PNI score was still significantly lower than patients with high PNI score (\( P < 0.001 \)) (online Supplementary Table S2, Fig. 1).

**High or low Controlling Nutritional Status scores in pancreatic adenocarcinoma patients after propensity score matching**

After matching, PSM identified seventy-nine pairs of patients with similar propensity score from the low and high CONUT group. After PSM, patients in the low and high CONUT score
group only showed difference in leucocyte count, ALB and total cholesterol level (Table 2). In fact, these three parameters were just what the CONUT score was calculated from. Preoperative high CONUT score remained an independent prognostic risk factor of poor OS (hazard ratio 3.25, P < 0.001) (online Supplementary Table S3). After PSM, patients in the high CONUT score group had worse mean survival time than patients in the low CONUT score group (online Supplementary Table S4, Fig. 2).

**Correlation of Prognostic Nutritional Index/Controlling Nutritional Status score with postoperative complications**

The overall postoperative complications in patients with high CONUT score or patients with low PNI score were significantly higher. When patients were stratified by CONUT score, the high CONUT score group tended to have a higher incidence of POPF, DGE, pleural effusion and abdominal infection. Meanwhile, patients with low PNI score were related with the prevalence and severity of POPF, chylos fistula, DGE and postoperative bleeding (all P < 0.05) (Table 3).

**Comparison between Prognostic Nutritional Index and Controlling Nutritional Status scores in predicting outcomes**

Receiver operating curves were generated for both PNI and CONUT to predict postoperative complications and survival (online Supplementary Fig. S3), and the effectiveness of preoperative PNI or CONUT as a predictor was compared by AUC of each receiver operating curves. According to the result, CONUT tended to have both higher sensitivity and specificity in predicting postoperative complications (0.826 v. 0.740), 1-year survivals (0.783 v. 0.754) and 3-year survivals (0.563 v. 0.540) than PNI.
Discussion

There was increasing evidence suggesting that poor preoperative nutritional status might be a potentially powerful predictor of poor outcomes in cancer patients. PNI and CONUT scores were two objective and easy-use tools to assess patient’s nutritional status in clinical practice and were capable of predicting outcomes in cancer patients. In our study, we demonstrated that both preoperative PNI and CONUT might be reliable predictors...
of surgical and oncological outcomes in PDAC patients who were eligible for tumour resection. Preoperative low PNI (≤45) or high CONUT score (≥5) was an independent prognostic risk factor for poor OS and higher incidence of postoperative complications.

There were many different clinical scores that had been developed to assess the patient’s nutritional status, including Nutritional Risk Screening Score 2002 (30), Subjective Global Assessment (31) and Malnutrition Screening Tool (32). Nevertheless, these scores were largely based on some subjective parameters reported by the patients, which might easily cause errors because patient did not usually recall these clearly enough. This kind of error would trigger huge bias, which may contribute because patient did not usually recall these clearly enough.

In previous studies focusing on the prognostic value of PNI or CONUT in various cancers, patients with different PNI (or CONUT) scores showed the significant difference in several baseline clinicopathological features (19,21,34). Likewise, we also found that patients with compromised nutritional status seemed to suffer more advanced disease. To avoid these potential biases, we utilised PSM method. After PSM, three distinct parameters still showed significant difference between the two groups (ALB, leucocytes and total cholesterol), just because all three factors were what CONUT was calculated from. What is more important, after PSM, patients in the two groups with different PNI or CONUT scores showed no significant difference in all other well-known risk factors (CA 19-9, TMN stage, etc.) for poor prognosis before surgery.

The predictive effect of PNI or CONUT could be attributed to several reasons. First of all, the elements of PNI and CONUT had been reported to have a close relation with the patient’s prognosis. ALB had long been regarded as an important marker of nutritional status, and low ALB was associated with advanced stages of cachexia and poor perioperative outcomes in cancer (35). In PDAC, hypoalbuminaemia had already been noticed being related to the outcome of patients receiving surgery or chemotherapy (36,37). Total lymphocyte count was an immunological indicator. The decrease of lymphocytes, primary T lymphocytes, indicated inadequate immune response against tumour. Total lymphocyte count alone might not be sensitive enough in predicting oncological outcomes, as current studies found controversial results on it (38,39). These results suggesting total lymphocyte count was related to the patient’s outcome, but it should be used with other parameters to enhance its predictive power (like PNI and CONUT). Total cholesterol level had been reported to correlate with survival in malignancies (40). Hypocholesterolaemia-induced compromised membrane integrity might defect the immune function of normal cells and finally lead to cancer progression (41). And hypocholesterolaemia may be the result of cancer growth, as cancer cells tended to overexpress LDL receptor and taken up all the LDL cholesterol into cancer cells (42). In PDAC, tumour cells overexpressed fatty acid synthase and tended to take up cholesterols from circulation as ingredients to build blocks for the cell membrane, which led to hypocholesterolaemia in patients (43). All the evidence showed that abnormal cholesterol levels played an important role in PDAC oncogenesis and cancer progression.

As expected, we demonstrated CONUT might be superior to PNI in predicting both survival and complications.
preoperatively, because CONUT also considered total cholesterol, which played an important role in cancer progression when compared with PNI score. Interestingly, in another study focused on preoperative CONUT score in colorectal cancer, it found that twenty-seven of a total of 204 patients were included in the high CONUT group but not in the low PNI group, while no patient in the low PNI group was excluded from the high CONUT group. This evidence suggested that CONUT might be more sensitive than PNI, which was consistent with our results that CONUT had higher AUC than PNI in predicting survival and complications. In our study, POPF was significantly related to both low PNI and high CONUT score. This result was consistent with several previous studies. We assumed that tissue fragility, impaired coagulation caused by compromised nutritional status together with the systematic inflammatory response induced by cancer might delay the healing of the anastomosis and result in POPF. Moreover, the high incidence of POPF would also give rise to a higher incidence of post-pancreatectomy haemorrhage, surgical site infection and chylous fistula. Furthermore, high incidence of DGE was probably attributed to increased intra-abdominal infection and chylous fistula. Noteworthy issue in PDAC patients who were eligible for curative tumour resection in China. And the early recognition and objective assessment of nutritional problems is the key point for PDAC management. Preoperative nutrition support could affect both short-term and long-term outcomes independent of other prognostic factors, and similar phenomena have been recognised by other researchers. However, few studies reported about the use and the effect of preoperative nutrition support in PDAC patients. Whether PDAC patients would benefit from nutrition support strategies and which patients would benefit from them is still ambiguous. In this study, we have discovered an effective and objective tool to recognise malnutrition PDAC patients. We hope preoperative nutrition supports would improve the survival and reduce postoperative complications of the identified PDAC patients using CONUT index. The results might help us to find an optimal way to manage nutritional status in PDAC patients.

This study had some limitations. The study was performed in a retrospective design, which may have some potential bias. However, we enlarged our sample size and used the PSM method to eliminate the selection bias.

Conclusion

In this study, both preoperative low PNI (≤15) and high CONUT (≥3) scores were reliable predictors of OS and surgical complications in PDAC patients. Compared with PNI, CONUT might be more effective in predicting surgical and oncological outcomes in PDAC.

Acknowledgements


The authors declare that there are no conflicts of interests.

Supplementary material

For supplementary materials referred to in this article, please visit https://doi.org/10.1017/S0007114520002299

References

Nutrition states in pancreatic cancer patients


