# A presurgical prognostic stratification based on nutritional assessment and CA19-9 in pancreatic carcinoma: an approach with non-anatomic biomarkers

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The authors declare no potential conflicts of interest.

**Article Summary**

This study aimed to stratify the probability of surviving PC, based on systematically chosen non-anatomic biomarkers. The importance of this study is the neutrophil-to-lymphocyte ratio and prognostic nutritional index were independent prognostic risk factors in PC, and integrating these indexes with CA19-9 levels could successfully stratify survival.

## Abstract

***Background:*** Nutritional status and tumor markers are important prognostic indicators for surgical decisions in pancreatic carcinoma (PC). This study aimed to stratify the probability of surviving PC, based on systematically chosen non-anatomic biomarkers.

***Methods:*** We included 187 consecutive patients that underwent surgical resections for PC. We performed multivariable analyses to evaluate prognostic indicators, including four blood-test indexes: the neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio, prognostic nutritional index (PNI), and the modified Glasgow prognostic score; and four body-composition indexes: the normalized total psoas muscle area, the normalized total elector spine muscle area, the psoas muscle computed tomography (CT) value, and the elector spine muscle CT value.

***Results:*** Poor survival was associated with two independent risk factors: NLR≥3.0 (hazard ratio [HR]: 1.54) and PNI <36 (HR: 1.60), and with high CA19-9 levels (≥37 IU/ml). The two indexes were not significantly associated with clinicopathological factors, including CA19-9. Patients with no risk factors had significantly better survival than those with one (*P*=0.007) or two risk factors (*P*=0.001), and survival was similar in the latter two groups (*P*=0.253). A presurgical non-anatomic scoring system (range: 0-2) was constructed: 0 points for no risk factors, 1 point for 1 or 2 nutritional risk factors, and 1 point for CA19-9≥37 IU/ml. Survival rate at 3 years decreased with increasing scores (76% for score 0, 42% for score 1, and 21% for score 2; all *P*<0.05).

***Conclusion:*** NLR and PNI were independent prognostic risk factors in PC, and integrating these indexes with CA19-9 levels could successfully stratify survival.

## Introduction

Surgical resection is the only curative treatment for patients with pancreatic carcinoma (PC); however, even after curative resection, the prognostic outcome remains dismal. In clinical situations, patients with PC are evaluated primarily based on the radiographic tumor stage. For patients with resectable cancers, perioperative therapy is currently an acceptable treatment strategy [1]; however, it remains unknown whether these therapeutic strategies are suitable for patients in poor general conditions, including malnutrition, frailty, sarcopenia, or elevated tumor markers. Realistically, surgeons have to consider these non-anatomic factors along with the anatomic tumor stage.

In this complex situation, preoperative nutritional status has been highlighted as a prognostic factor in PC [2-11]. Nutritional parameters are classified into two broad categories: the “blood test” index and “body composition” index. The blood test indicates systemic immuno-nutritional function, which is represented by the neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), prognostic nutritional index (PNI), and modified Glasgow prognostic score (mGPS) [2-6, 10, 11]. The body composition index is assessed by the volume and quality of skeletal muscle and fat tissue [7, 8]. Many previous studies [7, 8, 12-14] have assessed truncal skeletal muscle with computed tomography (CT), which is routinely performed in patients scheduled to undergo surgery for an abdominal malignancy. To date, several studies have reported prognostic factors for PC that focus on either the blood test or the body composition indexes. [2-11]. However, these two indexes have not been comprehensively compared.

This retrospective study aimed to determine the most reliable preoperative nutritional indexes for assessing prognosis in patients with PC. In addition, we aimed to stratify survival probability with non-anatomic information, including the identified nutritional indexes.

## Materials and Methods

### *Patients*

For this retrospective study, we acquired data from a prospectively maintained database on consecutive patients with histologically-proven PC that underwent surgery at the First Department of Surgery, Nagoya University Hospital, between January 2008 and December 2018. Patients with intraductal papillary mucinous carcinoma were excluded. This study was approved by the Human Research Review Committee of Nagoya University Hospital (No. 2019-0430).

All patients received multidetector-row CT within 1 month prior to surgery. Patients with jaundice and/or cholangitis underwent percutaneous or endoscopic biliary drainage. In general, we did not perform surgery until the serum total bilirubin level was normalized (≤2.0 mg/dl). We also did not perform surgery when patients have a symptom of cholangitis. Blood sampling and the evaluation of the nutritional status were performed when these conditions were stabilized.

Based on the preoperative findings and according to the tumor location and stage, patients were assigned to one of the following operative procedures: pancreaticoduodenectomy (PD), distal pancreatectomy (DP), and total pancreatectomy (TP). A modified Child's method was used for reconstruction after PD; with a jejunal limb, an end-to-side pancreaticojejunostomy, biliojejunostomy, and gastro/duodenojejunostomy were performed in the order listed. Similarly, reconstruction for TP was performed with a biliojejunostomy and gastro/duodenojejunostomy, in the order listed. A portal vein and/or superior mesenteric vein resection was performed when necessary.

To assess postoperative complications systematically, we applied the Clavien-Dindo classification and the grading system established by the International Study Group of Pancreatic Surgery [15-17].

### *Blood test and body composition indexes*

In the present study, four blood test indexes (NLR, PLR, PNI, and mGPS) were calculated as previously described **(Table 1)** [2-6, 10, 11]. For the NLR, PLR, and PNI, patients were dichotomized, based on the worst tertile.

Preoperative body composition status was assessed with the following four indexes (Table 1): preoperative total psoas muscle area, normalized by patient height (nTPA); total elector spine muscle area, normalized by patient height; the mean CT value of the psoas muscle; and the mean CT value of the elector spine muscle [8, 18-20]. The muscle areas were evaluated at the level of the third lumbar vertebra, by examining the initial preoperative abdominal/pelvic CT images (**Figure 1**). The borders of the psoas muscle and the elector spine muscle were manually traced on both sides, and both the area and the mean CT values were automatically calculated. The cohort was dichotomized as either low nutritional and/or frail status or other nutritional status, and the cut-off value was based on the worst tertile for each nutritional index.

***Pathological assessment and adjuvant therapy***

Pathological findings were evaluated with the Tumor-Node-Metastasis classification of malignant tumors established by the Union for International Cancer Control, 8th edition [21].

Patients were treated with adjuvant chemotherapy, which included gemcitabine [22] or S-1, unless contraindicated by a patient’s condition. S-1 was mainly used after 2013 [23].

***Statistical analysis***

Continuous variables were expressed as the median and range. Continuous variables were evaluated with the Mann-Whitney U test and categorical variables were evaluated with the $\chi^2$ test or Fisher’s exact probability test, as appropriate. Overall survival was determined from the time of surgery to the time of death or the date of the most recent follow-up, whichever came first. Postoperative overall survival was calculated with the Kaplan-Meier method, and differences in survival curves were compared with the log-rank test. All variables with *P*-values <0.05 in univariable analyses were subsequently entered into a multivariable Cox proportional hazards model to identify independent predictors of survival. The Cox analysis was performed with a stepwise forward selection, with entry and removal limits of *P* <0.05 and *P* ≥0.10, respectively. A *P*-value <0.05 was considered statistically significant. These calculations were performed with the IBM SPSS 24 software package (IBM Japan Inc., Tokyo, Japan).

To assess the performance of the risk scores, the concordance index (C-index) was calculated in the data set followed by a bootstrapping resample method (n = 1000) (internal validation). Comparisons between the scoring system and other prognostic factors were evaluated by the C-index. The larger the C-index, the more accurate was the prognostic prediction. Validation data were statistically analyzed with the R program (https://www.r-project.org/).

## Results

### *Patient characteristics*

The study included 187 patients. Patient characteristics are summarized in **Table 2**. Primary tumors were categorized as resectable in 123 patients (66%), borderline resectable in 52 (28%), and locally advanced unresectable in 12 patients (6%) [24]. The most common procedure was a PD (n = 125, 67%), followed by DP (n = 40, 21%), and TP (n = 22, 12%). Portal vein resections were performed in 67 patients (36%). Grade B/C pancreatic fistulae were observed in 13 patients (7%) [16]. According to the Clavien-Dindo classification [17], grade 3a or greater complications occurred in 20 patients (11%), and 2 patients died of postoperative complications. Preoperative and postoperative chemotherapy was administered in 34 (18%) and 147 (79%) patients, respectively; adjuvant radiotherapy was performed in only one patient. The last follow-up was in June 2020. The median follow-up period was 1194 days, and 125 (67%) patients died. One patient was lost to follow-up within 1 year after the operation.

### *Predictive value of nutritional indexes for overall survival*

The univariate analysis showed that four of the eight indexes (NLR, PNI, mGPS, and nTPA) could potentially predict overall survival (**Table 3**). The multivariate analysis indicated that NLR ≥3.0 and PNI <36 independently predicted poor survival (hazard ratios: 1.54 and 1.60, respectively). **Table 4** shows the relationship between these two indexes and the tumor-related clinicopathologic factors. The tumor marker and pathological factors were not significantly different between patients with poor nutritional condition and patients with other nutritional conditions, based on either of the two nutritional indexes. Meanwhile, a few of radiographic findings (tumor location in PNI and resectability classification in NLR) showed difference between the two nutritional conditions of either index.

Overall survival was stratified according to the number of risk factors (i.e., NLR ≥3.0 and/or PNI <36; **Figure 2**). The 3-year survival rates were 54% for patients with no risk factors, 31% for those with one risk factor, and 18% for those with two risk factors. The 88 patients with no factors had a significantly better survival rate than those with one or two factors (*P* = 0.007 and *P* = 0.001, respectively). Although overall survival rates were not significantly different between groups with 1 and 2 risk factors (*P* = 0.253), the 25 patients with two risk factors had a worse prognosis during the first 2 years compared to the 74 patients with one risk factor.

***Non-anatomic scoring system for presurgical prognostic assessment***

We generated a novel scoring system that included both the blood test indexes (NLR and PNI) and a statistically significant non-anatomic tumor marker, CA19-9 (**Table 3**). The two indexes and CA19-9 were evaluated separately in the scoring system (**Supplementary table 1**), as follows: (*a*) one point was given to patients with either or both of the two nutritional risk factors (i.e., NLR ≥3.0 and/or PNI <36); and (*b*) one point was given to patients with CA19-9 ≥37. Subsequently, patients were classified with scores of 0, 1, and 2, based on the sum, *a*+*b*. We found that survival probability decreased stepwise with increasing scores (*P* <0.05); the 3-year survival rates were 76%

for a score of 0, 42% for a score of 1, and 21% for a score of 2 (**Figure 3**).

**Table 5** shows the relationship between three scoring groups and the tumor-related clinicopathologic factors. Presurgical radiographic findings were not significantly different among the three groups, while 3 of 10 pathological findings (venous invasion, anterior serosal infiltration, and positive margin) were significantly different among the groups.

The C-index of the scoring system for predicting survival was 0.625 (95% CI, 0.580–0.670), which was higher than those of the independent prognostic factors such as NLR (0.571), PNI (0.558), CA19-9 (0.586), and margin status (0.585), indicating that the scoring system was better able to stratify patients for survival than the others.

## Discussion

To the best of our knowledge, this study was the first to reveal the impact of different preoperative nutritional assessments, based on both blood tests and body composition indexes, in patients undergoing resections for PC. The present study demonstrated that the blood test indexes, NLR and PNI, independently affected postoperative survival, and that these indexes combined with the CA19-9 level could effectively stratify survival. The prognostic scoring system presented in this study emphasizes the importance of assessing non-anatomical information in the presurgical setting.

At present, clinical tumor staging, based on the T (primary tumor) N (regional lymph node) M (distant metastasis) classifications is the most important prognostic criteria for patients with PC. However, nutritional status should be taken into consideration when determining a therapeutic strategy. The multivariate analysis in this study indicated that both NLR and PNI were significant prognostic factors, in addition to CA19-9, but the T and N stages were not significantly prognostic. This result implied that an anatomic assessment alone was inadequate for evaluating the preoperative PC status. Although our results did not elucidate the mechanism underlying a worse prognosis in patients with poor non-anatomic status, these two nutritional indexes, composed of distinct blood test variables, are typically available for presurgical prognostic predictions.

To improve the confidence in non-anatomic diagnostic nutritional indexes, we added the serum CA19-9 level, which is the most reliable tumor marker for PC [25-27]. We added CA19-9 to the scoring system because, (*a*) it was a non-anatomic biomarker, (*b*) it was identified as a significant prognostic factor in the present analysis (**Table 3**), and (*c*) it provided definitive tumor information, in contrast to radiographic findings, which might be inconsistent with pathological findings. A survival curve analysis showed that our novel 3-tier scoring system, with CA19-9, NLR, and PNI, could successfully stratify the risk of localized PC. Thus, this non-anatomical assessment could provide additional preoperative information about patients with PC.

Standardization of these nutritional assessments as prognostic factors for PC requires a consensus on uniform cut-off values for the continuous variables. In some studies, cut-off values were calculated with a receiver operating characteristic curve [3, 6, 8] or with the minimum *P*-value approach [11]. However, in other studies, a specific value was set without a clear explanation [2, 5-7, 10]. As a result, the cut-off value for NLR varied from 2.5 to 5.0 [2-6, 10, 11], and the cut-off for PNI ranged from 38 to 48.5 [2, 4, 6, 10, 11]. In the present study, we used the worst tertile (3.0 in NLR and 36 in PNI) as the cut-off value, because it specified a subset of patients with poor nutritional status. Nonetheless, we assessed these cut-off values in our cohort (data not shown) with the receiver operating characteristic curve (results showed cutoffs of 2.9 in NLR and 39 in PNI) analysis and the minimum *P*-value approach (results showed cutoffs of 3.0 and 34, respectively). Interestingly, both those cut-off values were similar to the original cut-offs determined with the worst tertile. Although the cut-off values used in this study remain under debate, these values were useful for stratifying the prognosis in our 187 patients that underwent surgery for PC. More multi-institutional data analyses are necessary to reach a definitive conclusion about cut-off values.

The current results have shown the clinical importance of preoperative nutritional status, but it remains unknown whether improving nutritional status could lead to a better surgical outcome. Our previous studies demonstrated that prehabilitation (preoperative exercise and nutritional therapies) improved muscle volume and nutritional status (indicated by the serum albumin levels and PNI) in patients with hepato-pancreato-biliary malignancies [28], and that the average level of preoperative physical activity was significantly associated with PNI and mGPS [29, 30]. Although those previous studies focused on the short-term postoperative outcomes and lacked survival analyses, they suggested that patients with PC should exercise and undertake nutritional therapies before surgery.

This study had several limitations. First, it was a single-institution, retrospective study. Although it was supported by internal validation, the accuracy of the scoring system and the presented cut-off values should be validated with an external sample or multi-institutional approach. Second, due to the small sample size, this study might have been insufficiently powered for detecting statistically significant results for nTPA and mGPS, which were marginally associated with patient survival. In future comprehensive analyses, the body composition indexes and the blood tests might be identified as prognostic factors. Third, although recent patients in this study received our prehabilitation program [28-30] and some patients showed an improvement of nutritional status by this program, the impact of prehabilitation on the long-term survival after surgery for PC is still unclear. This issue, therefore, should be further investigated in a future study. Considering these limitations, the present study can be considered a pioneering study that could lead to a future large-scale study on gastrointestinal cancers and PC.

In conclusion, we showed that NLR and PNI were prognostic risk factors in resectable PC, and when combined with serum CA19-9 levels, they could enhance the ability to stratify survival. The present scoring system, a non-anatomic approach in the presurgical setting, might serve as an alternative prognostic staging system, along with conventional anatomical tumor staging.

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**Figure legends**

**Figure 1.** Abdominal CT images at the level of the third lumbar vertebra. (A) Manual tracings of the right and left psoas muscle areas (yellow), which comprise the total psoas muscle area (TPA). Normalized TPA = measured TPA [$mm^2$]/height [m]$^2$. The mean CT value of the psoas muscle was measured simultaneously. (B) Manual tracings of the right and left elector spine muscle areas (yellow), which comprise the total elector spine muscle area (TESA). Normalized TESA = measured TESA [$mm^2$]/height [m]$^2$. The mean CT value of the elector spine muscle was measured simultaneously.

**Figure. 2.** Cumulative survival rates of patients after surgery for PC, according to the number of preoperational nutritional risk factors (i.e., NLR ≥3.0, PNI <36). *P*-values are based on log-rank tests. NLR: neutrophil-to-lymphocyte ratio; PNI: prognostic nutritional index

**Figure 3**: Presurgical prognostic stratification, based on a non-anatomic scoring system. One point was assigned for one or two nutritional risk factors (i.e., NLR ≥3.0 and/or PNI <36); and one point was assigned for CA19-9 ≥37. The cumulative survival rates are shown for patients with total scores of 0, 1, and 2; *P*-values are based on log-rank tests. NLR: neutrophil-to-lymphocyte ratio; PNI: prognostic nutritional index

**References**


1. Okusaka T, Nakamura M, Yoshida M, Kitano M, Uesaka K, Ito Y, et al. Clinical Practice Guidelines for Pancreatic Cancer 2019 From the Japan Pancreas Society: A Synopsis. Pancreas. 2020;49:326-35.
2. Yamada S, Fujii T, Yabusaki N, Murotani K, Iwata N, Kanda M, et al. Clinical Implication of Inflammation-Based Prognostic Score in Pancreatic Cancer: Glasgow Prognostic Score Is the Most Reliable Parameter. Medicine (Baltimore). 2016;95:e3582.
3. Asari S, Matsumoto I, Toyama H, Shinzeki M, Goto T, Ishida J, et al. Preoperative independent prognostic factors in patients with borderline resectable pancreatic ductal adenocarcinoma following curative resection: the neutrophil-lymphocyte and platelet-lymphocyte ratios. Surg Today. 2016;46:583-92.
4. Watanabe J, Otani S, Sakamoto T, Arai Y, Hanaki T, Amisaki M, et al. Prognostic indicators based on inflammatory and nutritional factors after pancreaticoduodenectomy for pancreatic cancer. Surg Today. 2016;46:1258-67.
5. Garcea G, Ladwa N, Neal CP, Metcalfe MS, Dennison AR, Berry DP. Preoperative neutrophil-to-lymphocyte ratio (NLR) is associated with reduced disease-free survival following curative resection of pancreatic adenocarcinoma. World J Surg. 2011;35:868-72.
6. Kanda M, Fujii T, Kodera Y, Nagai S, Takeda S, Nakao A. Nutritional predictors of postoperative outcome in pancreatic cancer. Br J Surg. 2011;98:268-74.
7. Delitto D, Judge SM, George TJ, Jr., Sarosi GA, Thomas RM, Behrns KE, et al. A clinically applicable muscular index predicts long-term survival in resectable pancreatic cancer. Surgery. 2017;161:930-8.
8. Okumura S, Kaido T, Hamaguchi Y, Fujimoto Y, Masui T, Mizumoto M, et al. Impact of preoperative quality as well as quantity of skeletal muscle on survival after resection of

pancreatic cancer. Surgery. 2015;157:1088-98.

9. Kawai M, Hirono S, Okada KI, Miyazawa M, Shimizu A, Kitahata Y, et al. Low lymphocyte monocyte ratio after neoadjuvant therapy predicts poor survival after pancreatectomy in patients with borderline resectable pancreatic cancer. Surgery. 2019;165:1151-60.

10. Abe T, Nakata K, Kibe S, Mori Y, Miyasaka Y, Ohuchida K, et al. Prognostic Value of Preoperative Nutritional and Immunological Factors in Patients with Pancreatic Ductal Adenocarcinoma. Ann Surg Oncol. 2018;25:3996-4003.

11. Onoe S, Maeda A, Takayama Y, Fukami Y, Takahashi T, Uji M, et al. The Prognostic Impact of the Lymphocyte-to-Monocyte Ratio in Resected Pancreatic Head Adenocarcinoma. Med Princ Pract. 2019;28:517-25.

12. Pecorelli N, Carrara G, De Cobelli F, Cristel G, Damascelli A, Balzano G, et al. Effect of sarcopenia and visceral obesity on mortality and pancreatic fistula following pancreatic cancer surgery. Br J Surg. 2016;103:434-42.

13. Sandini M, Bernasconi DP, Fior D, Molinelli M, Ippolito D, Nespoli L, et al. A high visceral adipose tissue-to-skeletal muscle ratio as a determinant of major complications after pancreatoduodenectomy for cancer. Nutrition. 2016;32:1231-7.

14. Pecorelli N, Capretti G, Sandini M, Damascelli A, Cristel G, De Cobelli F, et al. Impact of Sarcopenic Obesity on Failure to Rescue from Major Complications Following Pancreaticoduodenectomy for Cancer: Results from a Multicenter Study. Ann Surg Oncol. 2018;25:308-17.

15. Wente MN, Bassi C, Dervenis C, Fingerhut A, Gouma DJ, Izbicki JR, et al. Delayed gastric emptying (DGE) after pancreatic surgery: a suggested definition by the International Study Group of Pancreatic Surgery (ISGPS). Surgery. 2007;142:761-8.

16. Bassi C, Dervenis C, Butturini G, Fingerhut A, Yeo C, Izbicki J, et al. Postoperative

pancreatic fistula: an international study group (ISGPF) definition. Surgery. 2005;138:8-13.

17. Dindo D, Demartines N, Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. Ann Surg. 2004;240:205-13.

18. Baumgartner RN, Koehler KM, Gallagher D, Romero L, Heymsfield SB, Ross RR, et al. Epidemiology of sarcopenia among the elderly in New Mexico. Am J Epidemiol. 1998;147:755-63.

19. Mourtzakis M, Prado CM, Lieffers JR, Reiman T, McCargar LJ, Baracos VE. A practical and precise approach to quantification of body composition in cancer patients using computed tomography images acquired during routine care. Appl Physiol Nutr Metab. 2008;33:997-1006.

20. Otsuji H, Yokoyama Y, Ebata T, Igami T, Sugawara G, Mizuno T, et al. Preoperative sarcopenia negatively impacts postoperative outcomes following major hepatectomy with extrahepatic bile duct resection. World J Surg. 2015;39:1494-500.

21. James DB, Mary KG, Christian W. TNM classification of malignant tumours. 8th ed: Wiley-Blackwell; 2017.

22. Oettle H, Post S, Neuhaus P, Gellert K, Langrehr J, Ridwelski K, et al. Adjuvant chemotherapy with gemcitabine vs observation in patients undergoing curative-intent resection of pancreatic cancer: a randomized controlled trial. Jama. 2007;297:267-77.

23. Uesaka K, Boku N, Fukutomi A, Okamura Y, Konishi M, Matsumoto I, et al. Adjuvant chemotherapy of S-1 versus gemcitabine for resected pancreatic cancer: a phase 3, open-label, randomised, non-inferiority trial (JASPAC 01). Lancet. 2016;388:248-57.

24. Japan Pancreas Society. Classification of Pancreatic Carcinoma 4th English Edition. Tokyo: Kanehara; 2017.

25. Humphris JL, Chang DK, Johns AL, Scarlett CJ, Pajic M, Jones MD, et al. The prognostic and predictive value of serum CA19.9 in pancreatic cancer. Ann Oncol. 2012;23:1713-22.

26. Hartwig W, Strobel O, Hinz U, Fritz S, Hackert T, Roth C, et al. CA19-9 in potentially resectable pancreatic cancer: perspective to adjust surgical and perioperative therapy. Ann Surg Oncol. 2013;20:2188-96.

27. Tsai S, George B, Wittmann D, Ritch PS, Krepline AN, Aldakkak M, et al. Importance of Normalization of CA19-9 Levels Following Neoadjuvant Therapy in Patients With Localized Pancreatic Cancer. Ann Surg. 2020;271:740-7.

28. Nakajima H, Yokoyama Y, Inoue T, Nagaya M, Mizuno Y, Kadono I, et al. Clinical Benefit of Preoperative Exercise and Nutritional Therapy for Patients Undergoing Hepato-Pancreato-Biliary Surgeries for Malignancy. Ann Surg Oncol. 2019;26:264-72.

29. Nakajima H, Yokoyama Y, Inoue T, Nagaya M, Mizuno Y, Kayamoto A, et al. How Many Steps Per Day are Necessary to Prevent Postoperative Complications Following Hepato-Pancreato-Biliary Surgeries for Malignancy? Ann Surg Oncol. 2020;27:1387-97.

30. Hayashi K, Yokoyama Y, Nakajima H, Nagino M, Inoue T, Nagaya M, et al. Preoperative 6-minute walk distance accurately predicts postoperative complications after operations for hepato-pancreato-biliary cancer. Surgery. 2017;161:525-32.

Table 1. Summary of the nutritional indexes used in the present study.

| Abbreviation | Long form | Definition and Calculation |
|---|---|---|
| Blood test indexes | | |
| NLR | Neutrophil-to-lymphocyte ratio | Neutrophil count [/mm$^3$] / lymphocyte [/mm$^3$] |
| PLR | Platelet-to-lymphocyte ratio | Platelet count [/μl] / lymphocyte [/mm$^3$] |
| PNI | Prognostic nutritional index | 10 × serum albumin concentration [g/dl] + 0.005 × lymphocyte count [/mm$^3$] |
| mGPS | Modified Glasgow prognostic score | |
| Score 0 | | CRP concentration ≤10 mg/l |
| Score 1 | | CRP concentration >10 mg/l and Albumin concentration ≥35 g/l |
| Score 2 | | CRP concentration >10 mg/l and Albumin concentration <35 g/l |
| Body composition indexes | | |
| nTPA | Normalized total psoas muscle area | Right and left psoas muscles area* [mm$^2$] / height [m]$^2$ |
| nTESA | Normalized total elector spine muscle area | Right and left elector spine muscles area* [mm$^2$] / height [m]$^2$ |
| P-CTv | Mean CT value of psoas muscle | Mean CT value of psoas muscle* |
| E-CTv | Mean CT value of elector spine muscle | Mean CT value of elector spine muscle* |

*CT, computed tomography; CRP, C-reactive protein.*

** The index was evaluated using the cross-sectional CT images at the level of the third lumbar vertebra.*

Table 2. Clinicopathological characteristics of the study patients with pancreatic carcinoma.

| | n = 187 | |
|---|---|---|
| Preoperative characteristics | | |
| Age, year | 68 | (36-85) |
| Gender | | |
| Male | 109 | (58%) |
| Female | 78 | (42%) |
| Body hight, cm | 162 | (133-185) |
| Body weight, kg | 55 | (31-79) |
| ASA physical status ≥2 | 139 | (74%) |
| Biliary drainage | 95 | (51%) |
| Preoperative pancreatitis | 20 | (11%) |
| Preoperative cholangitis | 23 | (12%) |
| Tumor location | | |
| Head | 135 | (72%) |
| Body/Tail | 52 | (28%) |
| Resectability classification † | | |
| Resectable | 123 | (66%) |
| Borderline resectable | 52 | (28%) |
| Locally advanced unresectable | 12 | (6%) |
| Results of blood test | | |
| Albumin, g/dl | 3.8 | (2.1-5.0) |
| C-reactive protein (CRP), mg/dl | 0.15 | (0.0-22.2) |
| Platelet count, $10^3/\mu l$ | 22.1 | (5.3-481.0) |
| Neutrophil count, $10^3/\mu l$ | 3.2 | (0.6-25.5) |
| Lymphocyte count, $10^3/\mu l$ | 1.3 | (0.3-3.6) |
| CA19-9, U/ml | 94 | (0-10090) |
| Surgery | | |
| Surgical procedure | | |
| Pancreaticoduodenectomy | 125 | (67%) |
| Distal pancreatectomy | 40 | (21%) |
| Total pancreatectomy | 22 | (12%) |
| Portal vein resection | 67 | (36%) |
| Operative time, min | 466 | (149-1126) |
| Blood loss, ml | 1000 | (48-8335) |
| Homologous transfusion | 55 | (29%) |
| Soft pancreas | 23 | (12%) |
| Postoperative course | | |
| Hospital stay, day | 23 | (6-131) |
| Pancreatic fistula (Grade B/C) * | 13 | (7%) |
| Delayed gastric emptying (Grade B/C) * | 6 | (3%) |
| Clavien-Dindo grade ≥3a | 20 | (11%) |
| Mortality | 2 | (1%) |
| Perioperative chemotherapy | | |
| Preoperative therapy | 34 | (18%) |
| Postoperative therapy | 147 | (79%) |
| Pathological classification ¶ | | |
| pT1/2/3/4 | 59/102/16/7 | (32%)/(55%)/(9%)/(4%) |
| pN1/2 | 95/17 | (51%)/(9%) |
| pM1 | 9 | (5%) |
| Margin status, R0 | 117 | (63%) |

*Expressed as n (%) or median (range); ASA, American Society of Anesthesiologists; CA19-9, carbohydrate antigen 19-9*

** According to the International Study Group of Pancreatic Surgery (15, 16)*

*† Classification of pancreatic carcinoma (24) , ¶ UICC 8th (21)*

Table 3. Univariate and multivariate analysis for the predictive value of the nutritional and tumor indexes in 187 patients.

| Variable | No. of patients | Survival (%) 1-year | Survival (%) 2-year | *P* (Log-rank test) | Multivariate Hazard ratio (95% CI) | Multivariate *P* |
|---|---|---|---|---|---|---|
| NLR | | | | *0.008* | | *0.021* |
| < 3.0 | 125 | 89.5 | 63.4 | | *1.00* | |
| ≥ 3.0 | 62 | 77.4 | 51.6 | | *1.54 (1.07-2.21)* | |
| PLR | | | | *0.630* | | |
| < 220 | 125 | 84.7 | 57.3 | | | |
| ≥ 220 | 62 | 87.1 | 64.4 | | | |
| PNI | | | | *0.011* | | *0.011* |
| < 36 | 62 | 75.8 | 49.9 | | *1.60 (1.11-2.30)* | |
| ≥ 36 | 125 | 90.3 | 64.3 | | *1.00* | |
| mGPS | | | | *0.016* | | |
| Score 0 | 155 | 89.0 | 63.5 | | | |
| Score 1, 2 | 32 | 68.8 | 40.6 | | | |
| nTPA | | | | *0.032* | | |
| < 672 | 62 | 75.8 | 53.0 | | | |
| ≥ 672 | 125 | 90.3 | 62.8 | | | |
| nTESA | | | | *0.962* | | |
| < 1750 | 62 | 85.5 | 62.9 | | | |
| ≥ 1750 | 125 | 85.5 | 57.8 | | | |
| P-CTv | | | | *0.563* | | |
| < 33 | 62 | 82.3 | 54.8 | | | |
| ≥ 33 | 125 | 87.1 | 61.8 | | | |
| E-CTv | | | | *0.062* | | |
| < 26.5 | 62 | 82.3 | 49.9 | | | |
| ≥ 26.5 | 125 | 87.1 | 64.3 | | | |
| CA19-9 | | | | *0.001* | | *0.002* |
| < 37 | 68 | 91.2 | 76.3 | | *1.00* | |
| ≥ 37 | 119 | 82.2 | 50.0 | | *1.83 (1.24-2.69)* | |
| Tumor location | | | | *0.035* | | |
| Head | 135 | 82.1 | 55.1 | | | |
| Body/Tail | 52 | 94.2 | 71.0 | | | |
| Resectability classification † | | | | *0.696* | | |
| Resectable | 123 | 90.2 | 62.1 | | | |
| Borderline resectable/Unresectable | 64 | 76.6 | 54.6 | | | |
| Postoperative chemotherapy | | | | *0.069* | | |
| Present | 147 | 88.4 | 62.1 | | | |
| Absent | 40 | 75.0 | 49.9 | | | |
| T stage ¶ | | | | *0.938* | | |
| Classification pTis/1/2 | 164 | 85.9 | 58.1 | | | |
| Classification pT3/4 | 23 | 82.6 | 69.6 | | | |
| N stage ¶ | | | | *0.001* | | |
| Classification pN0 | 75 | 90.7 | 70.5 | | | |
| Classification pN1/2 | 112 | 82.0 | 53.6 | | | |
| Margin status | | | | *<0.001* | | *<0.001* |
| R0 | 117 | 90.5 | 66.2 | | *1.00* | |
| R1/2 | 70 | 77.1 | 48.5 | | *2.08 (1.44-3.00)* | |

*NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; PNI, prognostic nutritional index; mGPS, modified Glasgow prognostic score; nTPA, normalized total psoas muscle area; nTESA, normalized total elector spine muscle area; P-CTv, mean CT value of psoas muscle; E-CTv, mean CT value of elector spine muscle; CA19-9, carbohydrate antigen 19-9*

*† Classification of pancreatic carcinoma (24) , ¶ UICC 8th (21)*

Table 4. Comparison of the tumor-related factors according to the nutritional status.

| | NLR | | | | | PNI | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | ≥ 3.0 (n = 62) | | < 3.0 (n = 125) | | *P* | < 36 (n = 62) | | ≥ 36 (n = 125) | | *P* |
| Tumor location, Head | 43 | (69%) | 92 | (74%) | *0.542* | 52 | (84%) | 83 | (66%) | *0.012* |
| Resectability classification †, Resectable | 34 | (55%) | 89 | (71%) | *0.026* | 39 | (63%) | 84 | (67%) | *0.560* |
| Postoperative chemotherapy | 52 | (34%) | 95 | (76%) | *0.217* | 44 | (71%) | 103 | (82%) | *0.073* |
| CA19-9, U/ml | 128 | (0-3880) | 65 | (1-10090) | *0.720* | 116 | (1-3880) | 89 | (0-10090) | *0.797* |
| Tumor size, ≥ 2.0cm | 46 | (74%) | 75 | (60%) | *0.056* | 42 | (68%) | 79 | (63%) | *0.541* |
| Poorly differentiatied adenocarcinoma | 11 | (18%) | 19 | (15%) | *0.656* | 12 | (19%) | 18 | (14%) | *0.385* |
| Microscopic lymphatic invasion | 47 | (76%) | 99 | (79%) | *0.597* | 48 | (77%) | 98 | (78%) | *0.879* |
| Microscopic venous invasion | 36 | (58%) | 71 | (57%) | *0.869* | 38 | (61%) | 69 | (55%) | *0.428* |
| Microscopic perineural invasion | 53 | (86%) | 110 | (88%) | *0.628* | 56 | (90%) | 107 | (86%) | *0.363* |
| Microscopic anterior serosal infiltration | 52 | (84%) | 89 | (71%) | *0.058* | 46 | (74%) | 95 | (76%) | *0.787* |
| Microscopic retroperitoneal invasion | 56 | (90%) | 111 | (89%) | *0.751* | 53 | (86%) | 114 | (91%) | *0.234* |
| Microscopic plexus invasion | 9 | (15%) | 19 | (15%) | *0.902* | 11 | (18%) | 17 | (14%) | *0.455* |
| Microscopic PV/SMV invasion | 26 | (42%) | 36 | (29%) | *0.072* | 16 | (26%) | 46 | (37%) | *0.133* |
| Lymph node metastasis | 36 | (58%) | 76 | (61%) | *0.719* | 36 | (58%) | 76 | (61%) | *0.719* |
| Microscopic positive margin | 29 | (47%) | 91 | (33%) | *0.063* | 27 | (44%) | 43 | (34%) | *0.224* |

*Expressed as n (%) or median (range), † Classification of pancreatic carcinoma (24)*

*NLR, neutrophil-to-lymphocyte ratio; PNI, prognostic nutritional index; CA19-9, carbohydrate antigen 19-9; PV, portal vein; SMV, superior mesenteric vein*

Table 5. Comparison of the tumor-related factors according to the presurgical prognostic scores.

| | Score 0 n = 33 | Score 1 n = 90 | Score 2 n = 64 | *P* |
|---|---|---|---|---|
| Tumor location, Head | 20 (61%) | 64 (71%) | 51 (80%) | *0.132* |
| Resectability classification †, Resectable | 26 (79%) | 59 (66%) | 38 (59%) | *0.161* |
| Postoperative chemotherapy | 26 (79%) | 71 (79%) | 50 (78%) | *0.993* |
| Tumor size, ≥ 2.0cm | 19 (58%) | 53 (59%) | 49 (77%) | *0.050* |
| Poorly differentiatied adenocarcinoma | 3 (9%) | 12 (13%) | 15 (23%) | *0.118* |
| Microscopic lymphatic invasion | 22 (67%) | 69 (77%) | 55 (86%) | *0.085* |
| Microscopic venous invasion | 14 (42%) | 47 (52%) | 46 (72%) | *0.009* |
| Microscopic perineural invasion | 27 (82%) | 78 (87%) | 58 (91%) | *0.461* |
| Microscopic anterior serosal infiltration | 16 (49%) | 71 (79%) | 54 (84%) | *<0.001* |
| Microscopic retroperitoneal invasion | 28 (85%) | 80 (89%) | 59 (92%) | *0.553* |
| Microscopic plexus invasion | 5 (15%) | 11 (12%) | 12 (19%) | *0.534* |
| Microscopic PV/SMV invasion | 8 (24%) | 31 (34%) | 23 (36%) | *0.479* |
| Lymph node metastasis | 16 (49%) | 54 (60%) | 42 (66%) | *0.264* |
| Microscopic positive margin | 10 (30%) | 27 (30%) | 33 (52%) | *0.016* |

*Expressed as n (%) or median (range), † Classification of pancreatic carcinoma (24)*

*PV, portal vein; SMV, superior mesenteric vein*

Figure 1

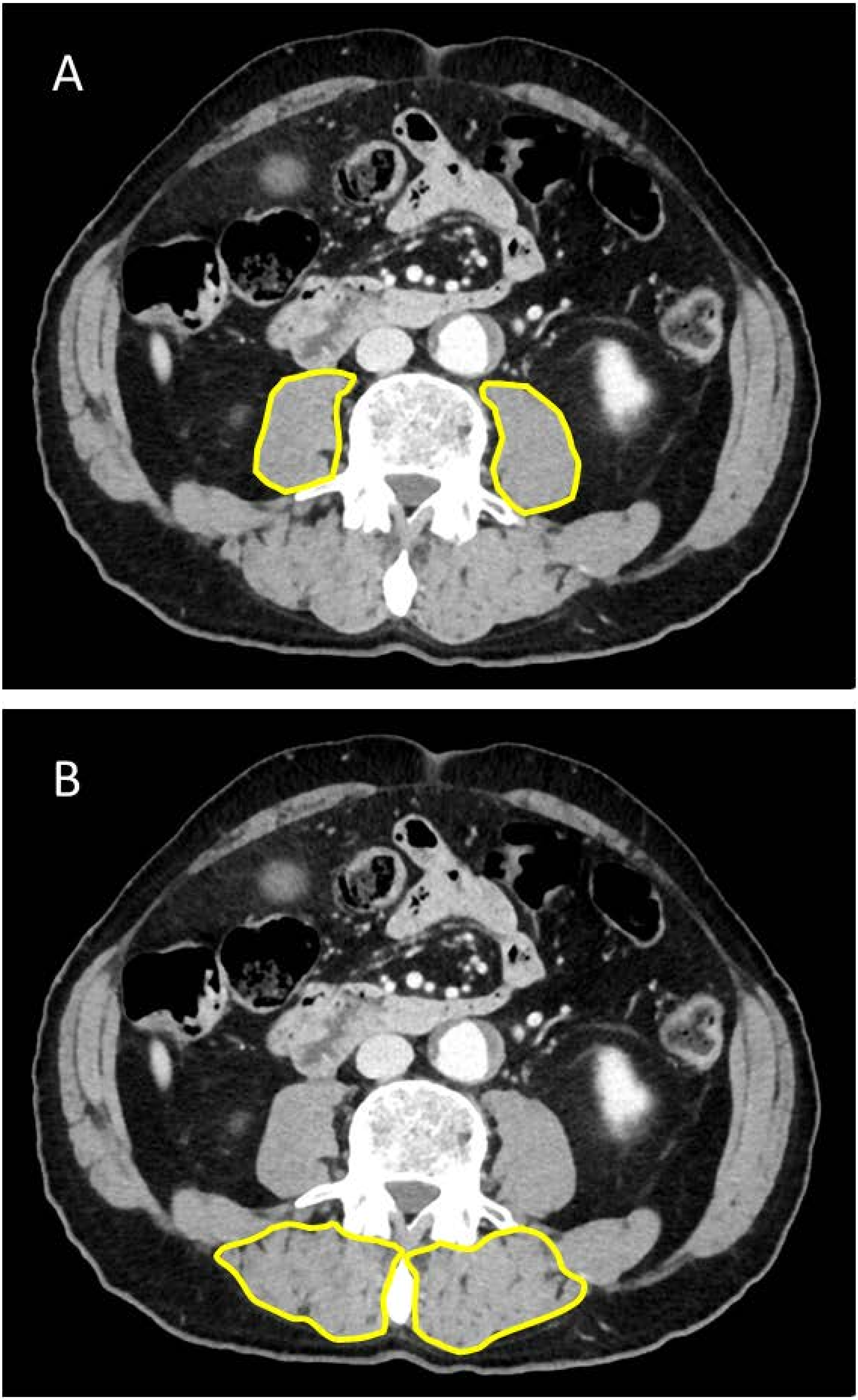
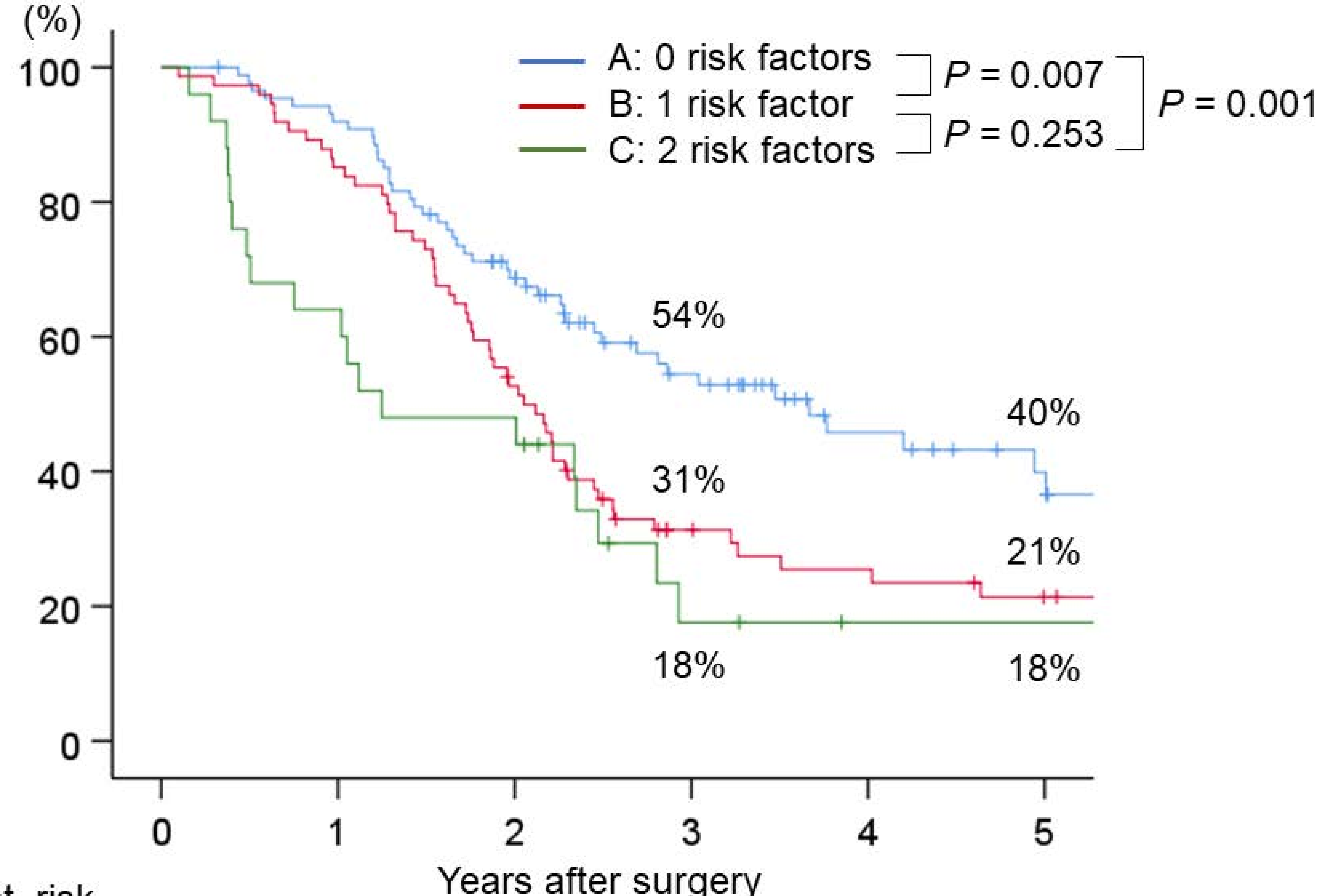
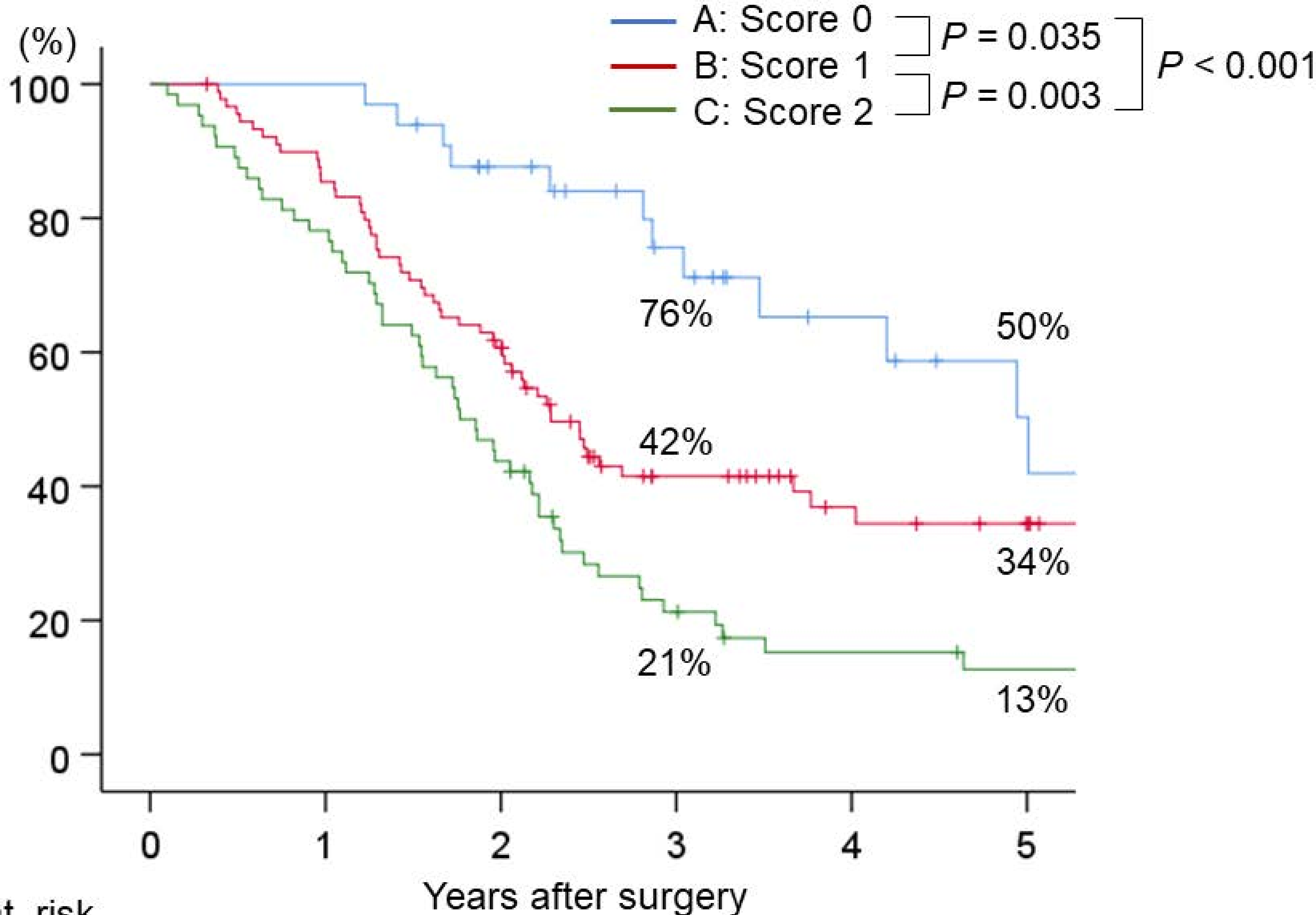


Figure 2




| No. at risk | 0 | 1 | 3 | 5 |
|---|---|---|---|---|
| A | 88 | 80 | 34 | 12 |
| B | 74 | 63 | 17 | 9 |
| C | 25 | 16 | 3 | 1 |

# Figure 3




No. at risk

| | | | | |
|---|---|---|---|---|
| A | 33 | 33 | 17 | 6 |
| B | 90 | 76 | 25 | 11 |
| C | 64 | 50 | 12 | 5 |

Supplementary table 1. A scoring system for preoperative prognostic assessment.

| Predictive index | Scores contributed |
|---|---|
| Nutritional index (NLR ≥3.0, PNI <36) | |
| With no factor. | 0 point |
| With either or both of the two factors. | 1 point |
| Tumor index (CA19-9) | |
| < 37 U/ml | 0 point |
| ≥ 37 U/ml | 1 point |