Predictive value of CONUT score combined withserum CA199 levels in postoperative survival of patients with pancreatic ductaladenocarcinoma: a retrospective study

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Background: The preoperative controlling nutritional status (CONUT) score and serum carbohydrate antigen 199 (CA199) levels are individually correlated with the prognosis of pancreatic ductal adenocarcinoma (PDAC). The objective of this study aimed to investigate the efficacy of CONUT score and CA199 (CONUT-CA199) combination in predicting the prognosis of PDAC patients undergoing radical surgery.

Methods: We retrospectively analyzed the preoperative CONUT scores and serum CA199 levels of 294 patients with PDAC who underwent radical resection at the Affiliated Hospital of Southwest Medical University between March 2012 and July 2019. Patients were divided into four groups on the basis of their preoperative CONUT scores and serum CA199 levels: $CONUT^{low}/CA199^{low}$ (1), $CONUT^{low}/CA199^{high}$ (2), $CONUT^{high}/CA199^{low}$ (3), and $CONUT^{high}/CA199^{high}$ (4). The prognostic effects were compared among the groups.

Results: $CONUT^{high}$ was more frequent in patients with positive peripancreatic infiltration and Clavien-Dindo classification of ≥IIIa ($P < 0.001$). Kaplan-Meier analysis revealed obvious difference in overall survival (OS) and recurrence-free survival (RFS) among patients with PDAC having CONUT-CA199 scores of 1, 2, 3 and 4 ($P < 0.001$). Peripancreatic infiltration, lymph node metastasis, pTNM stage, CONUT score, serum CA199 levels, and CONUT-CA199 classification were found to be the independent prognostic factors for OS and RFS in multivariate analyses. In time-dependent receiver operating characteristic (ROC) analyses, the area of the CONUT-CA199 score under the ROC curve (AUC) was higher than that of the preoperative CONUT score or serum CA199 levels for the prediction of OS and RFS.

Conclusion: CONUT-CA199 classification may be more effective in predicting the postoperative prognosis of PDAC patients

1   **Predictive value of CONUT score combined with serum CA199 levels in**

2   **postoperative survival of patients with pancreatic ductal adenocarcinoma: a**

3   **retrospective study**

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36

37   **Abstract**

38   **Background:** The preoperative controlling nutritional status (CONUT) score and serum

39   carbohydrate antigen 199 (CA199) levels are individually correlated with the prognosis of

40   pancreatic ductal adenocarcinoma (PDAC). The objective of this study aimed to investigate the

41   efficacy of CONUT score and CA199 (CONUT-CA199) combination in predicting the prognosis

42   of PDAC patients undergoing radical surgery.

43   **Methods:** We retrospectively analyzed the preoperative CONUT scores and serum CA199

44   level of 294 patients with PDAC who underwent radical resection at the Affiliated Hospital of

45   Southwest Medical University between March 2012 and July 2019. Patients were divided into

46   four groups on the basis of their preoperative CONUT scores and serum CA199 levels:

47      $CONUT^{low}/CA199^{low}$ (1), $CONUT^{low}/CA199^{high}$ (2), $CONUT^{high}/CA199^{low}$ (3),   and

48      $CONUT^{high}/CA199^{high}$ (4). The prognostic effects were compared among the groups.

49   **Results:** $CONUT^{high}$ was more frequent in patients with positive peripancreatic infiltration

50   and Clavien-Dindo classification of $\geq$IIIa ($P < 0.001$). Kaplan-Meier analysis revealed obvious

51   difference in overall survival (OS) and recurrence-free survival (RFS) among patients with

52   PDAC having CONUT-CA199 scores of 1, 2, 3 and 4 ($P<0.001$). Peripancreatic infiltration,

53   lymph node metastasis, pTNM stage, CONUT score, serum CA199 levels, and CONUT-CA199

54   classification were found to be the independent prognostic factors for OS and RFS in

55   multivariate analyses. In time-dependent receiver operating characteristic (ROC) analyses, the

56   area of the CONUT-CA199 score under the ROC curve (AUC) was higher than that of the

57   preoperative CONUT score or serum CA199 levels for the prediction of OS and RFS.

58   **Conclusion:** CONUT-CA199 classification may be more effective in predicting the

59   postoperative prognosis of PDAC patients.

60   **Keywords:** pancreatic ductal adenocarcinoma; controlling nutritional status score;

61   carbohydrate antigen 199; prognosis

62

63   Pancreatic cancer (PC) is a malignant disease with strong invasiveness in humans, and it is
64   expected to be the second leading cause of cancer related death in the future (Rahib et al. 2014).
65   Pancreatic ductal adenocarcinoma (PDAC), which originates from the ductal epithelium, is the
66   most common histological type of PC, accounting for approximately 95% of pancreatic exocrine
67   tumors (Kamisawa et al. 2016). Currently, the only available treatment modality for PDAC is
68   surgical resection (Gong et al. 2013). However, the disease is often diagnosed at a later stage
69   owing to its initially unpredictable biological behavior. At that time, liver, lymph nodes,
70   peripheral vessels, and nerves are often affected, with the tumor showing rapid growth, resulting
71   in poor prognosis, and the 5-year survival rate has been stagnant at 6% for decades (El-Khayat et
72   al. 2018; Siegel et al. 2019). Numerous studies have shown that tumor size, lymph node
73   metastasis, vascular invasion and serum tumor markers (TMs) are vital prognostic factors for PC
74   (Karamitopoulou et al. 2013; Staal et al. 2019; Winter et al. 2013), Moreover, early detection of
75   postoperative recurrence can help improve the survival rate of patients with PDAC(Wu et al.
76   2019), therefore, it is important to determine the factors affecting the prognosis of these patients
77   after pancreatectomy. It is not difficult to obtain the serum TMs level of patients from clinical
78   data, which is of potential value for diagnosis, monitoring of postoperative recurrence and
79   predicting survival rate (Fujioka et al. 2007). The serum marker CA199 has shown diagnostic
80   potential in patients with latent and early PDAC (Haab et al. 2015; O'Brien et al. 2015), and can
81   predict disease progression (Duffy et al. 2010; Satake et al. 1985).

82   Relevant reports have shown that the prognosis of tumor is closely related to the
83   inflammatory status, immune function and nutritional status of patients(Mantzorou et al. 2017;
84   Ni et al. 2019; van Dijk & Pot 2016; Xiao et al. 2019). Numerous studies have found that
85   malnutrition significantly increases postoperative complications and has a negative impact on the
86   quality of life, hospital stay, anti-cancer treatment effect and overall survival in cancer
87   patients(Borre et al. 2018; Fujiya et al. 2018; Lin et al. 2019).Furthermore, the latest research
88   shows that there is a close relationship between nutritional status and prognosis of patients with
89   cancer, including PDAC (Abe et al. 2018; Balzano et al. 2017; Gilliland et al. 2017). The

90 controlling nutritional status (CONUT) score, a system for scoring immune nutritional status that

91 emerged in 2005, has garnered the attention of researchers (Ignacio de Ulibarri et al. 2005), it

92 includes the measurement of serum albumin and total cholesterol levels as well as peripheral

93 blood lymphocytes. This scoring system has been considered as a predictor of prognosis for

94 postoperative liver cancer, gastric cancer, colorectal cancer, and PDAC (Iseki et al. 2015; Kato et

95 al. 2018; Shoji et al. 2017; Takagi et al. 2017). The patient's serum TMs are mostly determined

96 by the tumor itself, whereas the CONUT score reflects the overall immune and nutritional status

97 of patients. Both indicators demonstrate their role in assessing the prognosis of patients with

98 PDAC. However, the value of their joint application is still unclear, this study aims to use these

99 two indicators in combination to evaluate the prognosis of patients with PDAC.

Materials and Methods

101 **Study population**

102   All patients with PC who received radical resection in the affiliated hospital of the

103 Southwest Medical University between March 2012 and July 2019 were retrospectively analyzed;

104 a total of 294 cases met the inclusion criteria of this study. Inclusion criteria were as follows:

105 patients 1) with histopathological confirmation of PDAC; 2) who had undergone radical

106 resection; 3) who did not receive any neoadjuvant chemotherapy and/or radiotherapy before

107 surgery; 4) with no history of other malignant tumors; 5) with complete clinical and follow-up

108 data; and 6) in whom no metastatic lesions were found in the whole body before surgery.

109 Exclusion criteria were as follows: patients 1) with acute or chronic infectious diseases

110 preoperatively; 2) with preoperative complications of blood system diseases, kidney diseases, or

111 cardiovascular and cerebrovascular diseases; 3) with any other known autoimmune disease; 4)

112 with history of steroid medication use within 15 days before operation; 5) who received

113 preoperative immune enhancement therapy or had a recent history of blood transfusion; and 6)

114 who died within 30 days after operation.

115 **Investigational Variables**

116   All preoperative clinicopathological data were obtained from the electronic medical record

117   system; the data included age, gender, height, weight, serum CA199 levels and

118   carcinoembryonic antigen (CEA), tumor location, tumor size, histopathological type. Invasion

119   and metastasis of peripancreatic, lymph nodes, lymphatic vessels and blood vessels, and pTNM

120   staging were performed. Prognostic nutrition index (PNI) and CONUT score were calculated by

121   blood routine results. Complications were presented by clavien-dindo classification and

122   incidence of pancreatic fistula. Blood samples were collected 1 week before surgery and assessed

123   for serum albumin and total cholesterol levels as well as total peripheral lymphocyte count.

124   CONUT scores and PNI (Ignacio de Ulibarri et al. 2005; Pinato et al. 2012) were calculated

125   according to previously described methods, as shown in Table 1. Postoperative complications

126   were presented by the Clavien-Dindo classification system(Clavien et al. 2009) and the 2016

127   version of the postoperative pancreatic fistula grading system released by the International Study

128   Group on Pancreatic Surgery (Bassi et al. 2017). The largest diameter of the tumor in the

129   pathological sampling was considered as tumor size, and tumor staging was performed according

130   to the TNM staging criteria of AJCC version 8 (van Roessel et al. 2018). We communicated with

131   the patients before surgery and their consent was orally obtained for our study. Our research was

132   supported by the Ethics Committee of the Affiliated Hospital of Southwest Medical University

133   (NO.KY2019053).

134   **Follow-up**

135   We follow up all patients in a standardized way. Follow-up examination included

136   abdominal ultrasound, chest X-ray, routine blood work, blood biochemistry (liver function, renal

137   function), and TMs assessment. Contrast-enhanced computed tomography, magnetic resonance

138   imaging, positron emission tomography, and other modalities were used depending on the

139   situation if a suspicious lesion was detected and the nature of the lesion could not be defined. In

140   accordance with the Chinese comprehensive guidelines for the diagnosis and treatment of PC

141   (Pancreatic Cancer Committee of Chinese Anti-Cancer 2018), the patients were reexamined

142   every 3 months during the first year after surgery, followed by every 3–6 months in next 2–3

143 years. After 3 years, the follow-up period changed to 6 months. Survival data were obtained

144 through patient outpatient visits and telephone follow-up. We counted the interval between the

145 completion of surgery and death or the last follow-up, and the interval between the completion of

146 surgery and tumor recurrence or the last follow-up, respectively expressed as the overall survival

147 (OS) and Recurrence-free survival (RFS). Tumor recurrence included local recurrence and

148 distant metastasis (liver and peritoneum, lungs, bone, etc.). The follow-up deadline was August

149 2019.

Definition of preoperative CONUT-CA199 score

151 The optimal cut-off value of preoperative CONUT score was 3, which was used as the

152 criterion to divide 294 patients into low group (<3; n = 194) and high group (≥3; n = 100).

153 Patients were divided into the following two groups according to the optimal cut-off value of

154 serum CA199 levels (36.6 ng/mL): CA199^{low} (<36.6; n = 148), CA199^{high} (≥36.6; n = 146).

155 Based on the cut-off values of preoperative CONUT and CA199, we defined the CONUT-

156 CA199 score. patients with CONUT^{low}/CA199^{low} (n = 95) were assigned a score of 1; those with

157 CONUT^{low}/CA199^{high} (n = 99) were assigned a score of 2; those with CONUT^{high}/CA199^{low} (n =

158 53) were assigned a score of 3; and those with CONUT^{high}/CA199^{high} (n = 47) were assigned a

159 score of 4.

Statistical analyses

161 The classified data were summarized using a number (%), and the difference between each

162 group of variables is detected by chi-square test. A post hoc power analysis was completed. The

163 power of the Peripancreatic infiltration and the Clavien-Dindo classification group was 0.64 and

164 0.98, respectively. The optimal cut-off values of CONUT score, CA199, CEA, age, size, PNI,

165 and the area under the curve (AUC) were obtained by receiver operating characteristic (ROC)

166 curve analysis. Survival curves were presented using the Kaplan-Meier method and the

167 differences were compared by log-rank test. Firstly, univariate analysis was carried out for

168 various clinical and pathological variables, and covariates with P value <0.05 were included in

169 multivariate analysis. Cox proportional hazard model and stepwise analysis were used to obtain

170 independent influencing factors of OS and RFS. IBM SPSS Statistics package v.24.0 (Chicago,

171 IL, USA) was used for statistical analysis, $P < 0.05$ was considered statistically significant.

Results

173 294 patients who met the criteria were enrolled [163 men (55.4%) and 131 women (44.6%);

174 age range, 29–78 years; mean age, 55.5 ± 10.8 years].

175 Among the enrolled patients, 214 (72.8%) had tumors in the pancreatic head, 63 (21.4%)

176 had tumors in the pancreatic body and tail, and 17 (5.8%) had tumors that were diffuse in the

177 pancreas. Among all patients, 131 (44.5%) had poorly differentiated, 96 (32.7%) had moderately

178 differentiated, and 67 (22.8%) had highly differentiated tumors. There were 70 (23.8%), 125

179 (42.5%), and 99 (33.7%) patients with stage I, II, and III tumors, respectively. The general

180 situation of the two groups of patients is shown in table 2. CONUT^{high} was more frequent in

181 patients with positive peripancreatic infiltration and Clavien-Dindo classification $\geq$IIIa ($P <$

182 0.001).

183 The 5-year OS of the CONUT^{low} group (11.0%) was significantly higher than that of the

184 CONUT^{high} group (2.9%) ($P < 0.0001$) (Fig. 1A). The 5-year OS rate of the CA199^{high} group

185 (4.7%) was lower than that of the CA199^{low} group (13.3%) ($P < 0.013$)(Fig. 1B).

186 Patients were divided into four groups to determine the impact of combining the CONUT

187 scores and serum CA199 levels (CONUT-CA199) on prognosis. The 5-year OS rates of

188 patients with CONUT^{low}/CA199^{low}, CONUT^{low}/CA199^{high}, CONUT^{high}/CA199^{low}, and

189 CONUT^{high}/CA199^{high} were 15.3%, 9.1%, 6.1%, and 0%, respectively ($P < 0.0001$) (Fig. 2A). In

190 addition, the similar 5-year RFS rates were 9.2%, 7.9%, 4.7%, and 0%, respectively ($P < 0.0001$)

191 (Fig. 2B).ROC analysis was used to further evaluate the effect of three independent factors on

192 prognosis in our research. The results showed that the preoperative CONUT-CA199 scores were

193 more predictive of OS and RFS in patients with PDAC than preoperative CONUT scores or

194 preoperative serum CA199 levels alone (OS: AUC = 0.685, 95% CI: 0.625–0.746; $P < 0.001$;

195 RFS: AUC = 0.692, 95% CI: 0.632–0.751; $P < 0.001$; Fig. 3A-B).

196   Univariate analyses showed that age (<52 vs. ≥52 years; $P < 0.05$), serum CA199 levels

197 (<36.6 vs. ≥36.6 ng/mL; $P < 0.001$), tumor size (<3.1 vs. ≥3.1 cm; $P < 0.05$), histopathological

198 type (poorly differentiated vs. moderate-highly differentiated; $P < 0.001$), peripancreatic

199 infiltration (positive vs. negative; $P < 0.001$), lymph node metastasis (positive vs. negative; $P < $

200 0.001), superior mesenteric artery invasion (positive vs. negative; $P < 0.001$), portal vein system

201 invasion (positive vs. negative; $P < 0.05$), nerve plexus invasion (positive vs. negative; $P < 0.05$),

202 pTNM stage (I/II vs. III; $P < 0.001$), PNI (<46.1 vs. ≥46.1; $P < 0.001$), the CONUT score (low

203 vs. high; $P < 0.001$), the CONUT-CA199 score (1 vs. 2 vs. 3 vs. 4; $P < 0.001$) were related to OS

204 and RFS (Table 3).

205   Since the CONUT-CA199 score includes the CONUT score and serum CA199 levels, two

206 multi-factor Cox proportional models were set up to avoid colinearity problems. Among them,

207 peripancreatic infiltration ($P < 0.05$), lymph node metastasis ($P < 0.001$), pTNM stage ($P < 0.05$),

208 the CONUT score ($P < 0.001$), serum CA199 levels ($P < 0.001$), and the CONUT-CA199 score

209 ($P < 0.001$) were independent prognostic factors for OS and RFS in multivariate analyses (Table

210 4).

211 **Discussion**

212   The CONUT score has been suggested as an indicator of immune-nutritional status of the

213 host (Ignacio de Ulibarri et al. 2005; Tokunaga et al. 2017). Increasing body of documents have

214 suggested that patients with high preoperative CONUT scores generally have poor nutritional

215 and pro-tumor immunity status, potentially leading to tumor invasion and metastasis. A growing

216 number of studies have shown that patients with high preoperative CONUT score are generally

217 poorer in nutritional status and pro-tumour immunity status, and promote tumor invasion and

218 metastasis (Liang et al. 2017; Shoji et al. 2017), which is significant for survival prognosis in

219 postoperative patients with multiple cancers (Harimoto et al. 2018; Liu et al. 2018; Yang et al.

220   2019a). Related studies have shown that the CONUT score is associated with survival prognosis

221   of patients with unresectable PDAC and is an independent predictor of survival of patients with

222   PDAC after pancreatectomy (Asama et al. 2018; Kato et al. 2018). Similar to previous reports,

223   the finding of our report indicate that the preoperative CONUT score has value in predicting the

224   postoperative prognosis of PADC patients. As the highest protein in human plasma produced by

225   the liver, albumin can be used to assess the nutritional status of the body. Patients with low

226   serum albumin levels are associated with poor nutritional and immune status, which can be a

227   favorable condition for tumor invasion and metastasis (Liu et al. 2016). Lymphocyte expression

228   in tumor defense is critical by inducing cytotoxic cell death. Therefore, a decrease in the amount

229   of such cells in the blood may be related to impaired tumor immune function, allowing for tumor

230   progression (Berntsson et al. 2016; Gooden et al. 2011; Jacobson 2006; Tang et al. 2014). PNI,

231   which includes serum albumin levels and total lymphocyte count, is one of the most commonly

232   used indicators of nutritional status (Kanda et al. 2011). It is known to be closely related to the

233   prognosis of various cancers (Mohri et al. 2013; Sun et al. 2015; Yamamoto et al. 2019).

234   Compared with PNI, the CONUT score includes the measurement of total serum cholesterol

235   levels as well. Cholesterol, as an important component of cell membranes, is involved in many

236   signaling pathways related to tumor development, progression, and immunogenicity; furthermore,

237   cholesterol levels act as an important nutritional index (Haghikia & Landmesser 2018; Jacobs et

238   al. 2012; Yang et al. 2019b). Therefore, the CONUT score is considered to be a better nutritional

239   and immune prognostic factor than PNI. In our study, PNI was found to be associated with OS

240   and RFS of patients with PDAC after surgery, but it was not an independent predictor; however,

241   the preoperative CONUT score was an independent predictor of OS and RFS in patients with

242   PDAC after surgery.

243   The Clavien–Dindo grading system is currently the most commonly used statistical

244   classification system for complications. High CONUT scores correlate with an increased

245   incidence of postoperative pneumonia, length of hospital stay, and incidence of serious

246   complications after gastric cancer (Lin et al. 2019). In our study, patients were divided into two

247   groups based on the CONUT score by calculating a cut-off value, and it was found that the high

248   CONUT score group was more prone to severe postoperative complications and peripancreatic

249   invasion, but was not more likely to develop postoperative pancreatic fistula. The reason for

250   these results may be that the three blood indicators measured under the CONUT score, which

251   reflect the immune and nutritional status of the body, show an increased incidence of serious

252   postoperative complications. However, the development of pancreatic fistula is mostly related to

253   the hardness of the pancreas, whether is accompanied by pancreatitis, surgical technique,

254   anastomosis type, and reconstruction mode, and the effects of immune and nutrition status on

255   pancreatic fistula development seem to be insignificant.

256   Serum CA199 levels are a classic TMs commonly used in the management of patients with

257   PC (Locker et al. 2006). This study also proved serum CA199 levels to be an independent factor

258   that may predict postoperative survival and prognosis of patients with PDAC. However, serum

259   CA199 levels are elevated not only in the case of PC but also in other cancers and certain

260   inflammatory diseases. Therefore, as a diagnostic tool for PDAC, serum CA199 levels have low

261   sensitivity and specificity (Liu et al. 2019; Zeng et al. 2019). Serum CA199 levels mainly

262   reflects the status of the tumor, whereas the CONUT score reflects the overall status of the

263   patient, including nutritional and immune status. We found that the combination of these two

264   factors (CONUT-CA199 score) may provide more accurate prognostic information for patients

265   with PDAC after surgery than either single factor, as indicated by the present ROC analyses. In

266   addition, the CONUT-CA199 score was shown to be an independent prognostic indicator on

267   multivariate analysis. These results suggest that the combination of serum CA199 levels and the

268   CONUT score is more effective and provides more predictive value than serum CA199 levels or

269   the CONUT score alone in evaluating patients with PDAC after surgery.

270   However, this study has some limitations. First, the sample size of our study is relatively

271   small. According to the measure of AUCs benchmark(Ceci & Bjork 2000), the AUC value is

272   lower, this study may be related to poor specificity of CA199 regionalization related cases,

273   inadequate sample size, source, and then through joint COUNT after scoring and CA199 levels,

274 found the AUC value is increased significantly, close to 0.7, and compared with the single use,

275 obvious advantages, significant difference, therefore, with the enlargement of the sample size

276 and the study population, the COUNT combined CA199 levels is expected to become effective

277 predictor of PDAC survival in patients with postoperative prognosis.

278 In summary, our study is the first to demonstrate that the preoperative CONUT-CA199

279 score is an independent prognostic factor for OS and RFS in patients with PDAC undergoing

280 radical resection. As a novel, economical, and reliable biomarker, the preoperative CONUT-

281 CA199 score has potential application in the development of individualized treatments and

282 follow-up plans.

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290 **Competing of interests**

291 The author states that there is no conflict of interest between them.

292 **Author contributions**

293 Ankang Wang and Bo Sun wrote the manuscript and performed data analyses; Hao Shi,

294 Zhiwei Huang, Tao He, and Tianxiang Zheng collected the clinical data; Qiu Li, Wenguang Fu,

295 and Yu Jiang reviewed the manuscript.

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481

Scoring system for the controlling nutritional status (CONUT)

* CONUT score =Serum albumin score + total lym phocyte score + total cholesterol score

2 **Table 1** Scoring system for the controlling nutritional status (CONUT)

Degree of undernutrition	CONUT score	Serum albumin (g/dl)	Total lymphocyte (/mm^3)	Total cholesterol (mg/dl)
Normal	0-1	≥3.50 (0)	≥1600 (0)	≥180 (0)
Mild	2-4	3.00-3.49 (2)	1200-1599 (1)	140-179 (1)
Moderate	5-8	2.50-2.99 (4)	800-1199(2)	100-139 (2)
Severe	9-12	<2.50 (6)	<800 (3)	<100 (3)

3 *CONUT score=Serum albumin score+total lymphocyte score+total cholesterol score

Relationships between CONUTscore and clinicopathological characteristics of 294 PDAC patients

Notes: *indicates P<0.05. PDAC, Pancreatic ductal adenocarcinoma; BMI, body mass index; p TNM , Pathologic tumour-node-metastasis; CONUT, controlling nutritional status; The cut off value of CONUT score is 3, according to the ROC analyses;

1 **Table 2** Relationships between CONUT score and clinicopathological characteristics of 294 PDAC
2 patients

Variable	CONUT^low (n= 194)	CONUT^high (n= 100)	χ^2 value	*P* value
Gender			0.401	0.526
Male	105 (54%)	58 (58%)		
Female	89 (46%)	42 (42%)		
Age (years)			3.205	0.073
<52	87 (45%)	34 (34%)		
≥52	107 (55%)	66 (66%)		
BMI (kg/m2)			3.455	0.178
<18.5	36 (19%)	25 (25%)		
≥18.5, <25.0	128 (66%)	61 (61%)		
≥25.0	30 (15%)	14 (14%)		
Tumour location			3.036	0.219
Pancreatic head	145 (75%)	69 (69%)		
Pancreatic body and tail	41 (21%)	22 (22%)		
Dispersed	8 (4%)	9 (9%)		
Tumor size (cm)			1.925	0.165
<3.1	134 (69%)	61 (61%)		
≥3.1	60 (31%)	39 (39%)		
Histopathological type			2.546	0.111
Poorly differentiated	80 (41%)	51 (51%)		
medium-high differentiation	114 (59%)	49 (49%)		
Peripancreatic infiltration			4.447	**0.035***
Positive	144 (74%)	85 (85%)		
Negative	50 (26%)	15 (15%)		
Lymph node metastasis			0.866	0.352
Positive	84 (43%)	49 (49%)		
Negative	110 (57%)	51 (51%)		
Lymphatic vessel invasion			0.365	0.546
Positive	146 (75%)	72 (72%)		
Negative	48 (25%)	28 (28%)		
Invasion of portal vein system			2.356	0.125
Positive	53 (27%)	36 (36%)		
Negative	141 (73%)	64 (64%)		
Superior mesenteric artery invasion			1.522	0.217
Positive	58 (30%)	37 (37%)		
Negative	136 (70%)	63 (63%)		
Nerve plexus invasion			1.081	0.299

Positive	120 (62%)	68 (68%)		
Negative	74 (38%)	32 (32%)		
pTNM stage			3.642	0.056
I-II	136 (70%)	59 (59%)		
III	58 (30%)	41 (41%)		
Clavien-Dindo classification			24.342	**<0.001***
<IIIa	170 (88%)	63 (63%)		
≥IIIa	24 (12%)	37 (37%)		
Pancreatic fistula			0.269	0.604
Presence	34 (18%)	20 (20%)		
Absence	160 (82%)	80 (80%)		

3 Notes: *indicates P<0.05. PDAC, Pancreatic ductal adenocarcinoma; BMI, body mass index;
4 pTNM, Pathologic tumour-node-metastasis; CONUT, controlling nutritional status; The cut off
5 value of CONUT score is 3, according to the ROC analyses;

Univariate analyses offactors associated with overall survival and recurrence-free survival of PDACpatients

Notes: *indicates P<0.05. PDAC, Pancreatic ductal adenocarcinoma; HR, hazard ratio; CI, confidence interval; OS, overall survival; RFS, recurrence-free survival; BMI, body mass index; p TNM, Pathologic tumour-node-metastasis; CEA, carcinoembryonic antigen; CA199; carbohydrate antigen 199; PNI, prognostic nutritional index; CONUT, controlling nutritional status;

1 Table 3 Univariate analyses of factors associated with overall survival and recurrence-free
2 survival of PDAC patients

Variable	OS			RFS		
	HR	95%CI	*P* value	HR	95%CI	*P* value
Gender (Male vs. Female)	0.78	0.57-1.08	0.137	0.85	0.63-1.16	0.311
Age (<52 vs. ≥52 years)	1.51	1.08-2.11	0.015*	1.49	1.09-2.03	0.013*
Preoperative CEA (<6.4 vs. ≥6.4 ng/ml)	1.41	0.95-2.11	0.092	1.29	0.87-1.91.	0.200
Preoperative CA199 (<36.6 vs. ≥36.6ng/ml)	3.03	2.15-4.27	<0.001*	2.22	1.63-3.04	<0.001*
BMI (<18.5 vs.≥18.5, <25.0 vs. ≥25.0 kg/m2)	1.10	0.85-1.44	0.471	1.04	0.81-1.33	0.789
Tumour size (<3.1 vs. ≥3.1 cm)	1.49	1.07-2.07	0.018*	1.58	1.16-2.16	0.004*
Tumour Location (Head vs. Body and tail vs. Dispersed)	0.89	0.68-1.17	0.402	0.83	0.63-1.08	0.157
Histopathological type (Poor vs. medium-high)	0.54	0.38-0.75	<0.001*	0.55	0.40-0.80	<0.001*
Peripancreatic infiltration (Positive vs. Negative)	0.34	0.21-0.53	<0.001*	0.40	0.26-0.59	<0.001*
Lymph node metastasis (Positive vs. Negative)	0.28	0.20-0.41	<0.001*	0.31	0.22-0.43	<0.001*
Lymphatic vessel invasion (Positive vs. Negative)	0.92	0.62-1.35	0.657	0.93	0.65-1.33	0.686
Superior mesenteric artery invasion (Positive vs. Negative)	0.45	0.32-0.63	<0.001*	0.50	0.36-0.69	<0.001*
Invasion of portal vein system (Positive vs. Negative)	0.55	0.39-0.78	0.001*	0.54	0.39-0.76	<0.001*
Nerve plexus invasion (Positive vs. Negative)	0.67	0.48-0.95	0.023*	0.66	0.48-0.90	0.010*
pTNM stage (I-II vs. III)	2.86	2.05-4.00	<0.001*	2.44	1.78-3.35	<0.001*
Clavien-Dindo classification (<IIIa vs. ≥IIIa)	1.54	1.06-2.24	0.123	1.42	0.99-2.04	0.059
Pancreatic fistula (Presence vs. Absence)	0.92	0.62-1.38	0.700	0.94	0.64-1.38	0.749
Preoperative PNI(<46.1 vs. ≥46.1)	0.51	0.37-0.71	<0.001*	0.58	0.43-0.79	0.001*
Preoperative COUNT score (Low vs. High)	3.50	2.52-4.87	<0.001*	2.68	1.95-3.69	<0.001*
Preoperative CONUT-CA199 score (1 vs. 2 vs. 3 vs.4)	2.10	1.81-2.44	<0.001*	1.78	1.54-2.05	<0.001*

3 Notes: *indicates P<0.05. PDAC, Pancreatic ductal adenocarcinoma; HR, hazard ratio; CI,
4 confidence interval; OS, overall survival; RFS, recurrence-free survival; BMI, body mass index;
5 pTNM, Pathologic tumour-node-metastasis; CEA, carcinoembryonic antigen; CA199;
6 carbohydrate antigen 199; PNI, prognostic nutritional index; CONUT, controlling nutritional
7 status;

9
10

Multivariate analyses offactors associated with overall survival and recurrence-free survival of PDACpatients

Notes: *indicates P<0.05. PDAC, Pancreatic ductal adenocarcinoma ; HR, hazard ratio; CI, confidence interval; OS, overall survival; DFS, disease- freesurvival; p TNM, Pathologic tumour-node-metastasis; CEA, carcinoembryonic antigen; CA199; carbohydrate antigen 199; PNI, prognostic nutritional index; CONUT, controlling nutritional status;

1 Table 4 Multivariate analyses of factors associated with overall survival and recurrence-free
2 survival of PDAC patients

Variable	OS			DFS		
	HR	95%CI	*P* value	HR	95%CI	*P* value
Model 1						
Age (<52 vs. ≥52 years)	0.98	0.68-1.42	0.933	0.89	0.61-1.30	0.546
Tumour size (<3.1 vs. ≥3.1 cm)	1.11	0.76-1.62	0.608	1.09	0.74-1.60	0.657
Histopathological type (Poor vs. medium-high)	0.94	0.65-1.36	0.735	1.11	0.76-1.61	0.590
Peripancreatic infiltration (Positive vs. Negative)	0.60	0.38-0.94	0.027*	0.60	0.40-0.91	0.017*
Lymph node metastasis (Positive vs. Negative)	0.33	0.23-0.49	<0.001*	0.37	0.26-0.53	<0.001*
Superior mesenteric artery invasion (Positive vs. Negative)	1.07	0.62-1.86	0.800	1.11	0.64-1.93	0.707
Invasion of portal vein system (Positive vs. Negative)	0.85	0.58-1.25	0.411	0.77	0.52-1.14	0.193
Nerve plexus invasion (Positive vs. Negative)	0.85	0.59-1.24	0.408	0.98	0.68-1.42	0.914
pTNM stage (I-II vs. III)	1.87	1.30-2.70	0.001*	1.63	1.16-2.29	0.005*
Preoperative PNI(<46.1 vs. ≥46.1)	0.89	0.62-1.29	0.548	0.81	0.55-1.20	0.289
Preoperative COUNT score (Low vs. High)	4.00	2.82-5.67	<0.001*	2.93	2.10-4.10	<0.001*
Preoperative CA199 (<36.6 vs. ≥36.6ng/ml)	2.23	1.57-3.17	<0.001*	1.66	1.20-2.29	0.002*
Model 2						
Age (<52 vs. ≥52 years)	0.99	0.69-1.43	0.951	0.96	0.68-1.37	0.832
Tumour size (<3.1 vs. ≥3.1 cm)	1.11	0.76-1.62	0.593	1.20	0.84-1.71	0.309
Histopathological type (Poor vs. medium-high)	0.92	0.64-1.33	0.661	0.94	0.67-1.33	0.723
Peripancreatic infiltration (Positive vs. Negative)	0.59	0.37-0.94	0.026*	0.60	0.40-0.91	0.017*
Lymph node metastasis (Positive vs. Negative)	0.33	0.22-0.49	<0.001*	0.37	0.26-0.53	<0.001*
Superior mesenteric artery invasion (Positive vs. Negative)	1.06	0.61-1.83	0.839	1.12	0.65-1.92	0.689
Invasion of portal vein system (Positive vs. Negative)	0.86	0.59-1.26	0.434	0.78	0.54-1.11	0.164
Nerve plexus invasion (Positive vs. Negative)	0.85	0.58-1.24	0.412	0.83	0.59-1.18	0.303
pTNM stage (I-II vs. III)	1.91	1.33-2.73	<0.001*	1.62	1.16-2.27	0.005*
Preoperative PNI(<46.1 vs. ≥46.1)	0.90	0.62-1.30	0.576	0.94	0.66-1.32	0.701
Preoperative CONUT-CA199 score (1 vs. 2 vs. 3 vs.4)	2.04	1.74-2.40	<0.001*	1.70	1.46-1.98	<0.001*

3 Notes: *indicates P<0.05. PDAC, Pancreatic ductal adenocarcinoma; HR, hazard ratio; CI,
4 confidence interval; OS, overall survival; DFS, disease- freesurvival; pTNM, Pathologic tumour-
5 node-metastasis; CEA, carcinoembryonic antigen; CA199; carbohydrate antigen 199; PNI,
6 prognostic nutritional index; CONUT, controlling nutritional status;

8
9
10

Figure 1

Fig. 1. Overall survival curves for pancreatic ductal adenocarcinoma patients according to CONUT score (A) and serum CA199 level (B).

CONUT, Controlling Nutritional Status; CA199; carbohydrate antigen 199.
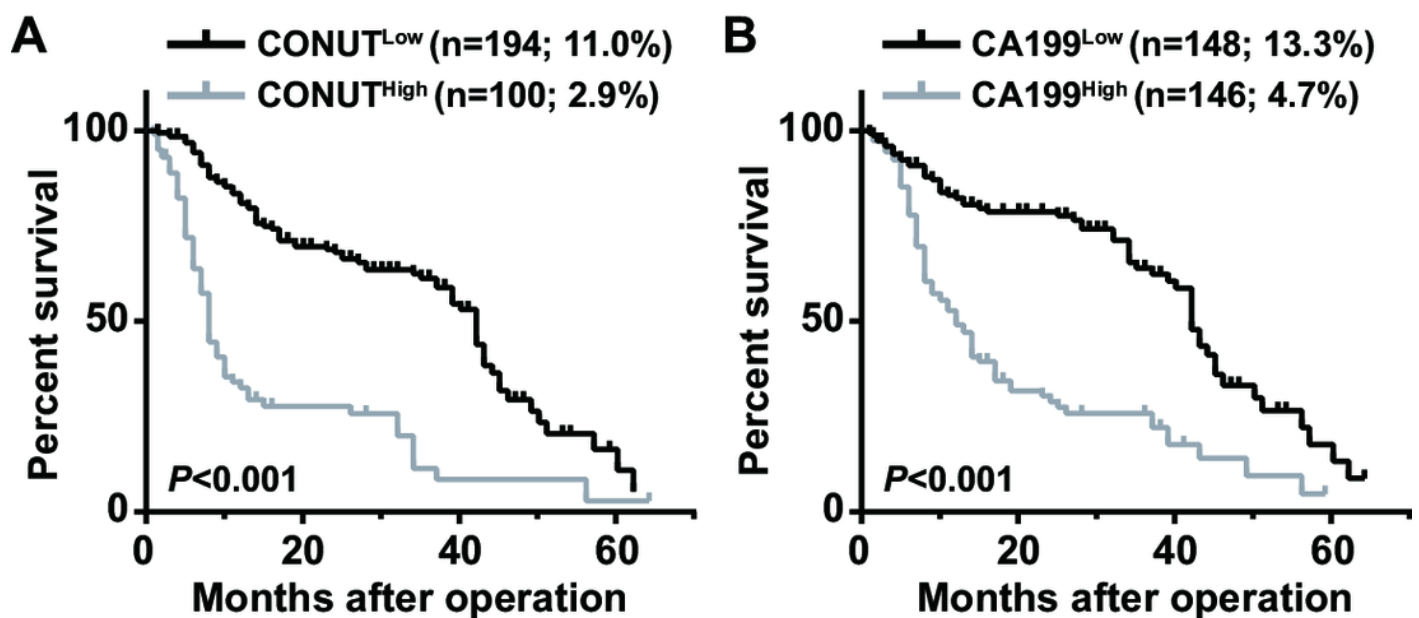
Figure 2

Fig. 2. Overall survival curves (A) and recurrence-free survival curves (B) for pancreatic ductal adenocarcinoma patients according to the combination of CONUT score and serum CA199 level.

CONUT, Controlling Nutritional Status; CA199; carbohydrate antigen 199.
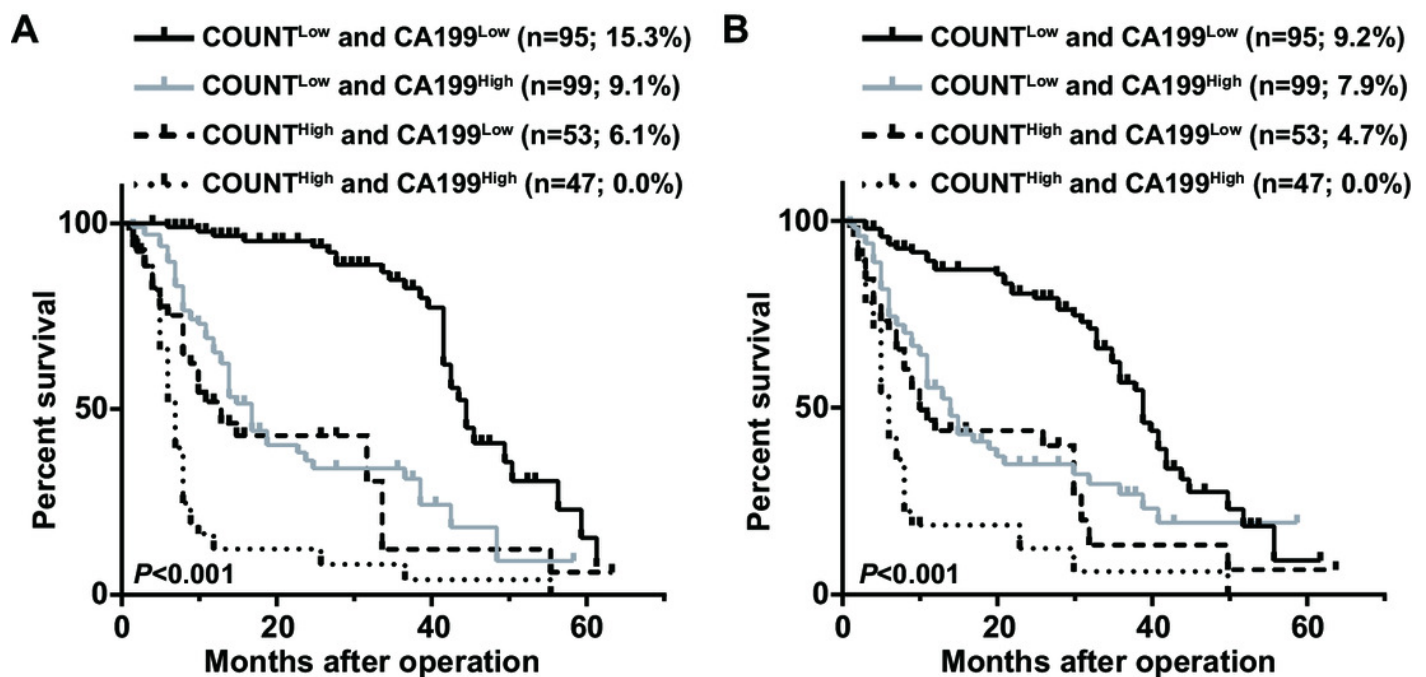
Figure 3

Fig. 3. Time-dependent ROCcurves of preoperative CONUT score, serum CA199 level, and CONUT-CA199 scorefor the prediction of pancreatic ductal adenocarcinoma patients' outcomes.

A. Overall survival . B. Recurrence-free survival. CONUT, controlling nutritional status; CA199; carbohydrate antigen 199; ROC, receiver operating characteristic; AUC, area under curve; CI, confidence interval.