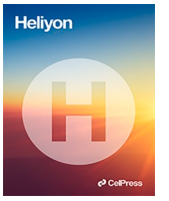
Heliyon 9 (2023) e21642

Contents lists available at ScienceDirect

Heliyon

journal homepage: www.cell.com/heliyon



A hierarchical prognostic model for Co-diabetes pancreatic adenocarcinoma

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ARTICLE INFO

Keywords:
Co-diabetes pancreatic adenocarcinoma
Prealbumin
Transferrin
Nomogram
Overall survival
Prognostic hierarchical

ABSTRACT

Background: Co-diabetes pancreatic adenocarcinoma has a poorer prognosis than pancreatic adenocarcinoma without diabetes. This study aimed to develop a reliable prognostic model for patients with co-diabetes pancreatic adenocarcinoma.
Method: Overall, 169 patients with co-diabetes pancreatic adenocarcinoma were included in our study. First, the independent risk factors affecting the prognosis of patients with co-diabetes pancreatic adenocarcinoma were determined by univariate and multivariate Cox regression analyses. Based on these identified risk factors, we developed a nomogram and evaluated its predictive ability using the concordance index, receiver operating characteristic curve, calibration plot, decision curve, and net reclassification index.
Results: In this study, prealbumin, transferrin, carcinoembryonic antigen, distant metastasis, tumor differentiation neutrophil count, lymphocyte count and fasting blood glucose were confirmed as significant prognostic factors. Based on these predictors, a new nomogram was developed. Compared with the American Joint Committee on Cancer 8 staging system and other models, the nomogram achieved a higher concordance index in the training (0.795) and validation (0.729) queues. The area under the nomogram's curve for predicting patient survival at 0.5, 1, and 1.5 years in the training queue was >0.8. Patients were risk-stratified using the nomogram, and Kaplan–Meier survival curves of subgroups were plotted. The Kaplan–Meier

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https://doi.org/10.1016/j.heliyon.2023.e21642
Received 2 March 2023; Received in revised form 24 October 2023; Accepted 25 October 2023
Available online 4 November 2023

curve also showed better separation than the American Joint Committee on Cancer 8 staging system, indicating that our model has a better risk hierarchical ability.
Conclusions: Compared to the American Joint Committee on Cancer 8 staging system and other predictive models, our model showed better predictive ability for patients with co-diabetes pancreatic adenocarcinoma. Our model will help in patients' risk stratification and improves their prognosis.

1. Introduction

Pancreatic adenocarcinoma(PAAD) is one of the most pernicious cancers and the seventh leading cause of cancer-related death worldwide [1]. The difficulty of early diagnosis, high malignant potential, and easy occurrence of distant metastasis are crucial reasons for poor prognosis [2,3]. There is increasing evidence that diabetes is closely related to the pathogenesis and development of PAAD, and clinical studies indicate that the risk of morbidity and mortality of PAAD increases nearly twice among diabetic patients [4–7]. Furthermore, patients with co-diabetes pancreatic adenocarcinoma have higher mortality rates and shorter median survival times than patients without diabetes [8]. The results showed that the influence of diabetes on the occurrence and development of PAAD may be related to insulin resistance, and as a characteristic of type 2 diabetes, it may be relevant to the high invasiveness of PAAD [8–10]. Therefore, accurately judging the prognosis of patients with co-diabetes pancreatic adenocarcinoma has a significant role in formulating treatment plans in this high-risk group.

Previous studies have shown that malnutrition and inflammation are common in patients with cancer, and are positively correlated with increased morbidity and mortality [11–14]. Common nutritional indicators, such as albumin or body mass index (BMI), which is often used to evaluate nutritional status, are also considered independent prognostic predictors in patients with cancer [15–19]. It is generally believed that overnutrition or being overweight may be involved in the occurrence of diabetes; however, some studies have pointed out that a considerable number of patients with diabetes have a lower weight than normal [20]. This study found that malnutrition is closely related to diabetes and that there are differences in hormone levels between patients with diabetes with low BMI and those with high BMI: higher insulin and glucagon levels, and other hormones such as adiponectin and resistin, which may be the cause of malnutrition in patients with diabetes, were observed [8,20–23]. In summary, diabetes, PAAD, and malnutrition were related. Recently, many inflammation-based indicators, such as the neutrophil-to-lymphocyte ratio (NLR), lymphocyte/monocyte ratio (LMR), and platelet-to-lymphocyte ratio (PLR), have been used to predict the prognosis of patients with different cancers [14,24–26]. Others have used some nutrition-based models, such as the albumin-globulin score (AGS) and albumin-to-globulin ratio (AGR) [27]. Several studies on tumor indicators have shown that tumor markers such as carcinoembryonic antigen (CEA), carbohydrate antigen (CA) 19-9, CA125 and other tumor indicators play important roles in the prognosis of PAAD [28–31]. In addition, the CEA may be superior to the CA 19-9 for predicting the prognosis of PAAD [31]. Therefore, models such as CA19-9 level-to-total bilirubin ratio, a combination of prognostic nutritional index (PNI = 10xSerum albumin (g/dL) + 0.005 × lymphocyte count (cells/mm^3)) and CA19-9 are used to predict patient prognosis [32,33]. Many prognostic models have emerged; however, we still use the traditional tumor staging system published by the American Joint Committee on Cancer (AJCC). The Tumor Node Metastasis (TNM) staging system is one of the most important staging systems for predicting the prognosis of PAAD [34,35]. However, it is difficult to obtain surgical specimens, which leads to difficulties in TNM staging. Moreover, it ignores critical imaging and serological characteristics [34].

To date, some studies have demonstrated that serum prealbumin and transferrin levels are independent risk factors for many malignant diseases, especially in identifying malnutrition and tumor patients with poor prognoses [15,36–40]. Furthermore, they are universally used to predict the outcomes of many diseases because of their simple determination methods [16,18,38–40]. However, the current prognostic models are mainly based on albumin, inflammatory indicators, and liver function enzymes. Only a few studies have investigated the nutritional indicators of prealbumin and transferrin, which are more sensitive than albumin [41,42].

This study aimed to investigate the independent risk factors influencing the prognosis of patients with co-diabetes pancreatic adenocarcinoma. Furthermore, we combined nutritional, tumor and inflammatory indicators to develop a novel nomogram based on the TNM staging system. We could screen high-risk patients and implement appropriate treatment schemes using our nomogram.

2. Materials and methods

2.1. Patients

This retrospective analysis was performed on 169 patients from 2015 to 2021 at the Pancreatic Center of Guangdong Provincial People's Hospital. All patients had PAAD, which was confirmed by pathological examination, and diabetes was confirmed based on the patient's medical history, blood glucose monitoring, serum insulin, and glycated hemoglobin levels [8]. The Ethics Committee of Guangdong Provincial People's Hospital approved this study, and all patients provided informed consent. The inclusion criteria for this study were as follows: 1) PAAD initially diagnosed by imaging and confirmed by pathological examination; 2) patients with type 2 diabetes; and 3) American Association of Anesthesiologists (ASA) score <3. The exclusion criteria were as follows: 1) incomplete clinical and pathological data and 2) patients with liver and kidney disease, thyroid disease, or other conditions that may cause changes in prealbumin or transferrin levels, such as multiple primary tumors (Fig. 1). Demographic, serological, radiological, and pathological information were collected for patients who conformed to the inclusion, such as age, sex, BMI, CA125, CEA, CA19-9,

serum albumin, prealbumin, transferrin, tumor size, tumor differentiation, fasting blood glucose (FBG), lymph node metastasis (LNM), distant metastasis, PLR, NLR, PNI, and AJCC stage. The AJCC staging system used for the patients was AJCC Version 8 (AJCC-8). The primary outcome is the overall survival (OS), which is defined as the date of diagnosis until death or the date of the last follow-up of survivors. The follow-up period was 3 years.

Based on the inclusion and exclusion criteria, the corresponding pathological, serological, and imaging data were collected from 169 eligible patients and retrospectively analyzed. The 169 patients were randomly assigned to two groups based on a 7:3 ratio, with 124 patients in the training queue for analysis and the other group (n = 45) in the validation queue for internal validation. The independent risk factors of patients with co-diabetes pancreatic adenocarcinoma were ascertained by Cox regression analysis. Considering the independent risk factors of the training queue, a nomogram was constructed and verified in the validation queue. The nomogram was found in conformity with the independent dangerous factors of the training queue and then verified by the validation queue. The forecasting ability of the nomogram was compared with the AJCC-8 staging system and other forecasting models. This study was conducted in accordance with the principles of the Declaration of Helsinki of the World Medical Association.

2.2. Statistical analysis

The demographic characteristics, pathological data, and serological and imaging examinations of patients were collected before treatment. Continuous variables, such as age, BMI, and levels of CA19-9, CA12-5, CEA, serum albumin, prealbumin, transferrin, leucocyte count, neutrophil count, monocyte count, lymphocyte count, FBG, PLR, NLR, and PNI, were converted into categorical variables. The receiver operating characteristic (ROC) curve was used, and the area under the curve (AUC) and Youden's index were compared to determine the best cut-off value for each index [43,44]. The BMI was calculated by measuring the patient's height (m) and weight (kg). BMI = weight (kg)/height [2] (m^2). According to the World Health Organization (WHO), adult BMI is divided into three categories: low weight (malnutrition, BMI <18.5), normal range (18.5–24.9), and overweight (≥25). Before treatment, imaging and pathological data were used to determine tumor size, LNM, and distance metastasis. According to the AJCC-8 staging system, the tumor size and LNM of the patients were divided into groups. Categorical data were compared using the Chi-square and Fisher's exact tests. The potential prognostic risk factors were determined by univariate and multivariate Cox proportional hazard regression analyses, and a nomogram was developed based on the determined independent risk factors. Furthermore, we evaluated the predictive ability of the nomogram by analyzing the concordance index (C-index) and ROC curve. A calibration plot was used to evaluate whether the probability predicted by the nomogram matched the probability of the real events. We then used the decision curve analysis (DCA) to evaluate the net income of the nomogram to meet the actual needs of clinical decision-making. The net reclassification index (NRI) was used to judge the accuracy of the nomogram and to compare the efficiency of nomograms with previous models. The nomogram was used to calculate the hazard points for each patient. Using the X-tile software, the patients were assigned into three groups based on their risk score: low, middle, and high-hazards groups. Kaplan–Meier analysis and log-rank test were used to evaluate the predictive ability of the nomogram for the three groups. Statistical analysis was performed using R software version 4.1.3 and SPSS (statistical product service solutions) version 25. Statistical significance was set at $P < 0.1$.

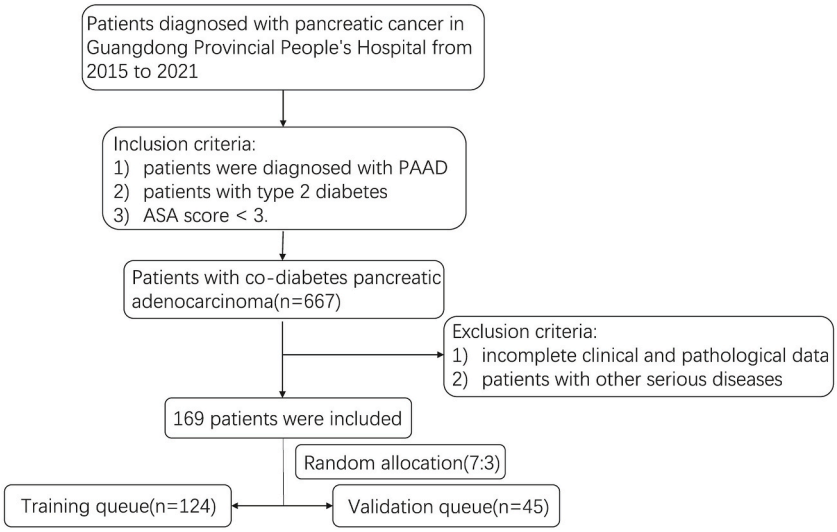

Fig. 1. Study design flowchart. A total of 169 patients with co-diabetes pancreatic adenocarcinoma with complete relevant information were enrolled in this study and then randomly separated into training and validation queues with a ratio of 7:3. PAAD, pancreatic adenocarcinoma; ASA, American Association of Anesthesiologists.

Table 1
A summary of clinicopathologic characteristics of the patients in training and validation queues.

Characteristics		Training Queue(n = 124)	Validation Queue(n = 45)	P-value
Gender				0.750
	Male	71 (57.3 %)	27(60.0 %)	
	Female	53 (42.7 %)	18(40.0 %)	
Age (Years)				0.994
	≤68	91(73.4 %)	33(73.3 %)	
	> 68	33(26.6 %)	12(26.7 %)	
BMI(kg/m^2)				
	≤18	30(24.2 %)	8(17.8 %)	0.644
	18–24	66(53.2 %)	27(60.0 %)	
	≥24	28(22.6 %)	10(22.2 %)	
Transferrin (g/L)				0.860
	≤1.88	57 (46 %)	20 (44.4 %)	
	> 1.88	67 (54 %)	25 (55.6 %)	
Prealbumin(mg/L)				0.465
	≤172.43	63(50.8 %)	20(44.4 %)	
	> 172.43	61(49.2 %)	25(55.6 %)	
Serum albumin(g/L)				0.264
	≤37	56(45.2 %)	16(35.6 %)	
	> 37	68(54.8 %)	29(64.4 %)	
CA19-9(U/mL)				0.723
	≤696.75	79(63.7 %)	30(66.7 %)	
	> 696.75	45(36.3 %)	15(33.3 %)	
CA125(U/mL)				0.055
	≤28	51 (41.1 %)	26 (57.8 %)	
	> 28	73 (58.9 %)	19 (42.2 %)	
CEA (ng/mL)				
	≤7.44	85 (68.5 %)	36 (80.0 %)	0.145
	> 7.44	39 (31.5 %)	9 (20.0 %)	
Location				0.699
	Head	67(54.0 %)	25(55.6 %)	
	Neck	5(4.0 %)	3(6.7 %)	
	Body	13(10.5 %)	2(4.4 %)	
	Tail	15(12.1 %)	7(l5.6 %)	
	Multiple	24(19.4 %)	8(17.8 %)	
Tumor size (cm)				0.959
	≤2	11(8.9 %)	4(8.9 %)	
	2–4	37(29.8 %)	15(33.3 %)	
	> 4	41(33.1 %)	15(13.3 %)	
	Blood Vessels	35(28.2 %)	11(24.4 %)	
LNM				0.367
	0	37(29.8 %)	18(40.0 %)	
	1–3	26(21.0 %)	10(22.2 %)	
	≥4	61(49.2 %)	17(37.8 %)	
Distant metastasis				0.298
	Absent	66(53.2 %)	28(62.2 %)	
	Present	58(46.8 %)	17(37.8 %)	
Treatment				0.211
	Un-treatment	12(9.7 %)	1(2.2 %)	
	Surgery	6(4.8 %)	4(8.9 %)	
	Chemotherapy	37(29.8 %)	9(20.0 %)	
	SPAC	62(50.0 %)	29(64.4 %)	
	Other	7(5.6 %)	2(4.4 %)	
Differentiation				0.083
	Poorly	24(19.4 %)	16(35.6 %)	
	Moderately	98(79.0 %)	28(62.2 %)	
	Well	2(1.6 %)	1(2.2 %)	
Leucocyte(10^{9}cells/L)				0.454
	≤4.90	34(27.4 %)	15(33.3 %)	
	>4.90	90(72.6 %)	30(66.7 %)	
Neutrophil(10^{9}cells/L)				0.078
	≤3.59	29(23.4 %)	5(11.1 %)	
	>3.59	95(76.6 %)	40(88.9 %)	
Monocyte(10^{9}cells/L)				0.232
	≤0.475	54(43.5 %)	15(33.3 %)	
	>0.475	70(56.5 %)	30(66.7 %)	
Lymphocyte(10^{9}cells/L)				0.057
	≤0.92	54(43.5 %)	12(26.7 %)	
	> 0.92	70(56.5 %)	33(73.3 %)	

(*continued on next page*)

Table 1 (*continued*)

Characteristics		Training Queue(n = 124)	Validation Queue(n = 45)	P-value
NLR				0.916
	≤3.81	81 (65.3 %)	29 (64.4 %)	
	> 3.81	43 (34.7 %)	16 (35.6 %)	
PLR				0.368
	≤178.38	73 (58.9 %)	23 (51.1 %)	
	> 178.38	51 (41.1 %)	22 (48.9 %)	
PNI				0.105
	≤41.71	83 (66.9 %)	24 (53.3 %)	
	> 41.71	41 (33.1 %)	21 (46.7 %)	
AJCC Stage				0.737
	IA	5 (4.0 %)	2 (4.4 %)	
	IB	9 (7.3 %)	6 (13.3 %)	
	IIA	12 (9.7 %)	6 (13.3 %)	
	IIB	24 (19.4 %)	9 (20.0 %)	
	III	16 (12.9 %)	6 (13.3 %)	
	IV	58 (46.8 %)	16 (35.6 %)	
FBG (mmol/L)				0.710
	≤7.35	31(25.0 %)	10(22.2 %)	
	> 7.35	93(75.0 %)	35(77.8 %)	

BMI-Body mass index; CA19-9-Carbohydrate Antigen 19-9; CA125-Carbohydrate Antigen 125; CEA-Carcinoembryonic Antigen; multiple-tumor sites≥2; LNM- Lymph node metastasis; SPAC-Surgery and Postoperative adjuvant chemotherapy; AJCC-American Joint Committee on Cancer; FBG- Fasting blood glucose.

3. Results

3.1. Patient characteristics and follow-up

Overall, 169 patients with co-diabetes pancreatic adenocarcinoma at the Pancreatic Center of Guangdong Provincial People's Hospital were enrolled according to the inclusion and exclusion criteria. According to a ratio of 7:3, 169 patients were randomly assigned into two groups, with 124 patients in the training queue and the other 45 patients in the validation queue [45–47]. Table 1 summarizes the clinicopathological features of the training and validation queues. The median ages of participants in the training and validation queues were 63 and 59 years, respectively, of which 71 were men and 53 women in the training queue and 27 men and 18

Table 2
Univariate and multivariate cox regression analysis for overall survival.

Patient characteristics		Univariate analysis		Multivariate analysis	
		HR (95 % CI)	P-value	HR (95 % CI)	P-value
Gender	Male/Female	0.726(0.478,1.102)	0.133		
Age (Years)	≤68/ > 68	0.731(0.465,1.151)	0.177		
BMI (kg/m^2)	<18/18–24/≥24	1.293(0.666,2.511)	0.717		
Tumor Location	Head/neck/body/tail/multiple	0.611(0.362,1.032)	0.017	1.094(0.942,1.272)	0.239
Tumor size(cm)	≤2/2–4/ > 4/blood vessels	0.378(0.166,0.862)	0.004	0.927(0.714,1.204)	0.570
LNM	0/1–3/≥4	0.494(0.308,0.795)	0.000	1.107(0.808,1.518)	0.526
Distant metastasis	Absent/Present	2.727(1.795,4.143)	0.000	3.631(1.935,6.816)	0.000
Treatment	t0/t1/t2/t3/t4	1.199(0.462,3.112)	0.000	0.761(0.592,0.978)	0.033
Differentiation	Poorly/Moderately/well	4.650(0.573,37.732)	0.212	0.433(0.239,0.783)	0.006
Albumin(g/L)	≤37.42/ > 37.42	1.363(0.909,2.045)	0.134		
Prealbumin(mg/L)	≤172.43/ > 172.43	1.934(1.280,2.922)	0.002	1.873(1.030,3.406)	0.040
Transferrin(g/L)	≤1.88/ > 1.88	2.268(1.502,3.424)	0.000	0.542(0.304,0.964)	0.037
CA19-9(U/mL)	≤696.75/>696.75	0.635(0.420,0.960)	0.031	0.698(0.422,1.155)	0.162
CA125(U/mL)	≤28/>28	2.297(1.478,3.569)	0.000	0.824(0.454,1.498)	0.526
CEA (ng/mL)	≤7.44/>7.44	0.390(0.256,0.595)	0.000	2.646(1.586,4.416)	0.000
Leucocyte(10^9cells/L)	≤4.90/>4.90	0.620(0.378,1.020)	0.060	1.107(0.526,2.333)	0.789
Neutrophil(10^9cells/L)	≤3.59/>3.59	0.490(0.320,0.750)	0.001	1.844(0.953,3.565)	0.069
Monocyte(10^9cells/L)	≤0.475/>0.475	0.879(0.581,1.332)	0.544		
Lymphocyte(10^9cells/L)	≤0.92/>0.92	1.857(1.177,2.930)	0.008	0.491(0.257,0.939)	0.031
NLR	≤3.81/ > 3.81	0.373(0.245,0.569)	0.000	1.040(0.524,2.064)	0.912
PLR	≤178.38/ > 178.38	0.634(0.420,0.957)	0.030	0.897(0.495,1.624)	0.719
PNI	≤41.71/ > 41.71	2.269(1.496,3.442)	0.000	0.814(0.462,1.434)	0.475
FBG (mmol/L)	≤7.35/ > 7.35	0.654(0.398,1.072)	0.092	1.654(0.947,2.891)	0.077

BMI-Body mass index; Location: multiple- Tumor sites≥2; LNM- Lymph node metastasis; Treatment: T0-untreatment, T1-surgery, T2-chemotherapy, T3-Surgery and Postoperative adjuvant chemotherapy (SPAC), T4-other treatments; CA19-9-Carbohydrate Antigen 19-9; CA125-Carbohydrate Antigen 125, CEA-Carcinoembryonic Antigen; NLR-neutrophil-to-lymphocyte ratio, PLR-platelet-to-lymphocyte ratio, PNI- prognostic nutritional index; FBG- Fasting blood glucose.

women in the validation queue. Most patients in the training queue were AJCC-8 stage IV (n = 58, 46.8 %), followed by stage IA (4.0 %), IB stage 9 (7.3 %), stage IIA 12 (9.7 %), stage IIB 24 (19.4 %), stage III 16 (12.9 %). In the validation queue, most patients were AJCC-8 stage IV 16 (35.6 %), followed by stage IA 2 (4.4 %), stage IB 6 (13.3 %), stage IIA 6 (13.3 %), stage IIB 9 (13.3 %), and stage III 6 (13.3 %). The best cutoff values for age, serum albumin, prealbumin, transferrin, CEA, CA125, CA19-9, leucocyte count, neutrophil count, monocyte count, lymphocyte count, FBG, NLR, PLR, and PNI were 68, 37.42 g/L, 172.43 mg/L, 1.88 g/L, 7.44 ng/mL, 28U/mL, 696.75U/mL, 4.9 × 10^9cells/L, 3.59 × 10^9cells/L, 0.475 × 10^9cells/L, 0.92 × 10^9cells/L, 7.35 mmol/L, 3.81, 178.38, and 46, respectively (Supplementary Fig. 1). The median duration of observation was 17 months. In summary, the median follow-up periods of the training and validation queues were 8.7 months and 13 months, respectively. The 0.5-year, 1-year, and 1.5-year OS rates in the training queue were 31 %, 15 %, and 10 %, respectively, whereas those in the validation queue were 55 %, 21 %, and 13 %, respectively.

3.2. *Determination of the risk factors affecting the prognosis of patients with co-diabetes pancreatic adenocarcinoma*

Tumor location, tumor size, LNM, distant metastasis, prealbumin, transferrin, CEA, CA125, CA19-9, leucocyte count, neutrophil count, lymphocyte count, FBG, PLR, NLR, and PNI were identified as potential prognostic risk factors (P value < 0.1) by univariate Cox regression analysis, and the potential risk factors were analyzed by pluralistic Cox regression analysis. The results showed that prealbumin, transferrin, CEA, distant metastases, neutrophil count, lymphocyte count and FBG were independent risk factors for participants with co-diabetes pancreatic adenocarcinoma (Table 2). A previous study has indicated that tumor differentiation is an independent risk factor for the prognosis of various malignancies [34,48]. Therefore, although the analysis suggests that tumor differentiation was not a potential risk factor for patient clinical outcomes, regression analysis incorporating this predictor into multivariate Cox suggests that tumor differentiation is an independent risk factor for patient clinical outcomes. Schoenfeld residual analyses were used to confirm whether the Cox proportional risk model conforms to the proportional risk hypothesis. The P-values for prealbumin, transferrin, CEA, distant metastasis, tumor differentiation, neutrophil count, lymphocyte count and FBG were 0.4536, 0.5117, 0.6053, 0.1733, 0.3224, 0.1873, 0.2795 and 0.468, respectively. The global test had a P-value of 0.2481. The selection of prognostic factors was in accordance with the proportional hazard hypothesis (Fig. 2 A-H). Furthermore, Kaplan–Meier analyses validated that lower CEA levels were significantly associated with better survival, while lower prealbumin and transferrin levels were associated with poorer survival (Fig. 3 A-H). In summary, combined with the results of Table 2 and Figs. 2 and 3, revealed that

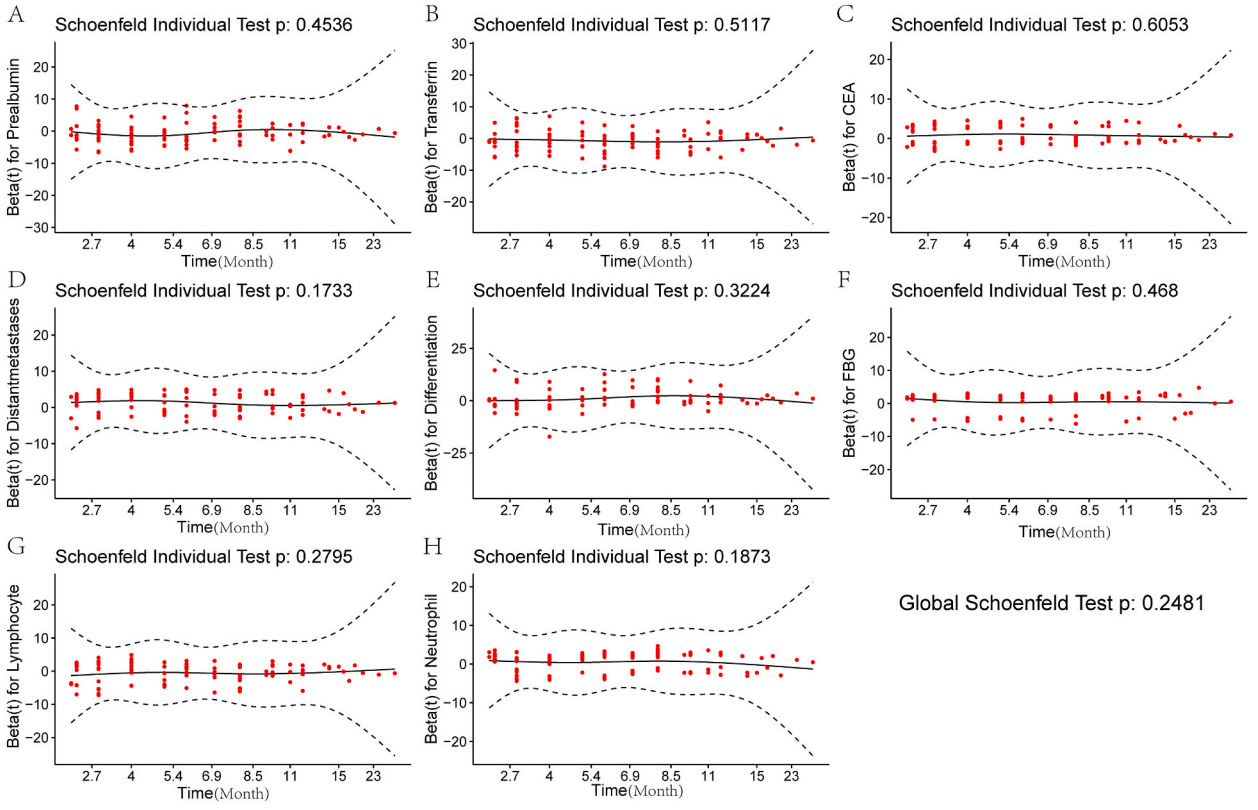

Fig. 2. Schoenfeld residuals vs ranked survival time for prealbumin (A), transferrin(B), carcinoembryonic antigen (CEA) (C), distant metastasis (D), differentiation (E), FBG(F), lymphocyte(G) and neutrophil(H). The P-value for the global test was 0.2481. All selected clinicopathologic factors were satisfied with the proportional hazards assumption.

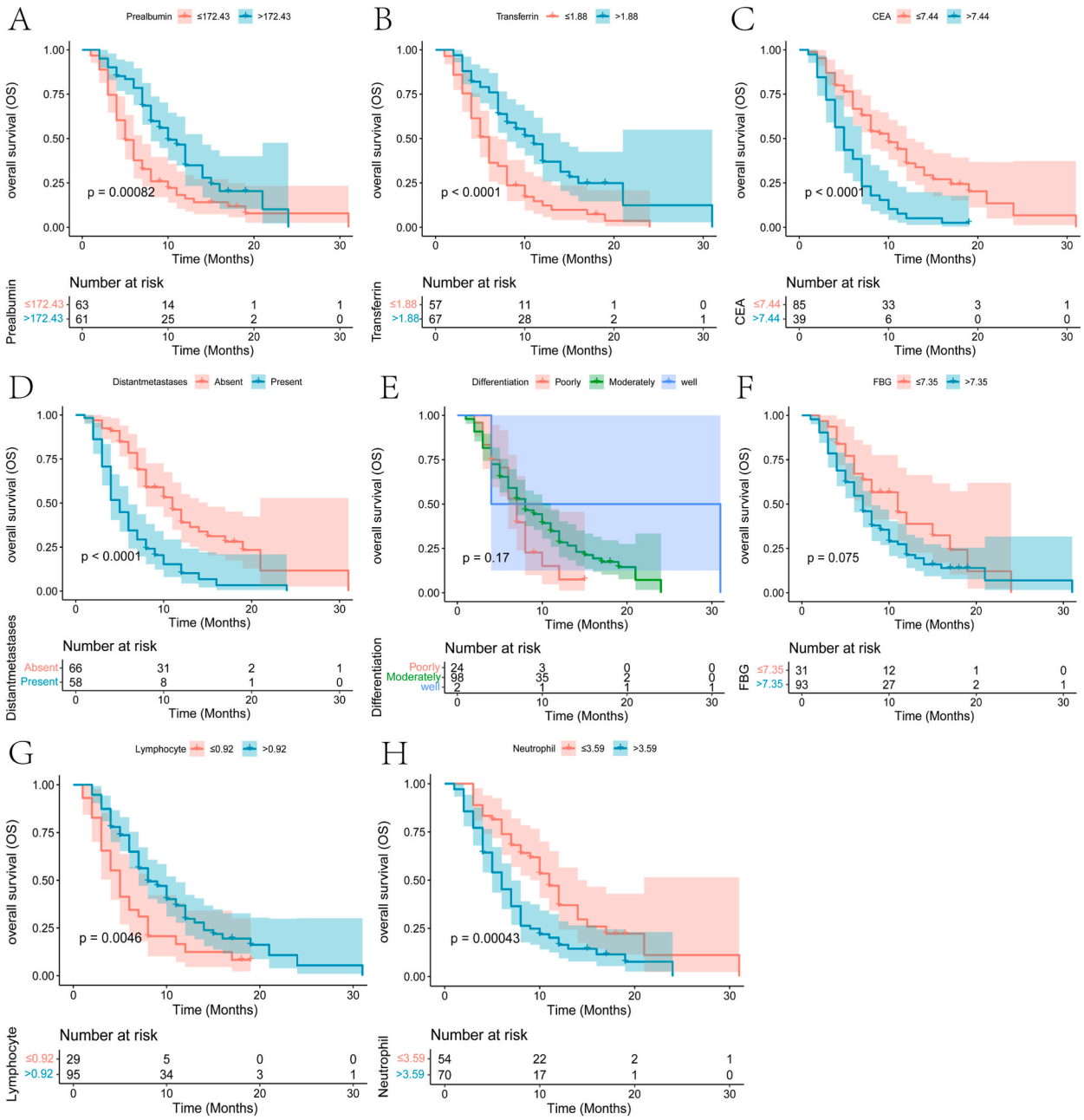

Fig. 3. Overall survival rates stratified by the selected predictors (A) prealbumin; (B) transferrin; (C) CEA; (D) distant metastasis; (E) differentiation (F) FBG, (G) lymphocyte and (H) neutrophil.

prealbumin, transferrin, CEA, tumor differentiation, distant metastasis neutrophil count, lymphocyte count and FBG were independent risk factors for patients with co-diabetes pancreatic adenocarcinoma.

3.3. Development and verification of the nomogram

Establishment of prognostic nomogram on the basis of independent risk factors affecting the prognosis of patients with co-diabetes pancreatic adenocarcinoma (Fig. 4). According to the nomogram, each independent risk factor was given a score: prealbumin >172.43 g/L, transferrin >1.88 g/L, CEA≤7.44 ng/mL, FBG≤7.35, lymphocyte > 0.92, neutrophil≤3.59, well tumor differentiation and absence of distant metastasis were given a score of 0; while prealbumin≤172 g/L, transferrin≤1.88 g/L, CEA >7.44 ng/mL, FBG > 7.35, lymphocyte≤0.92 and neutrophil > 3.59 were given 37, 41, 54, 37, 40, 31 points, respectively. In addition, the presence of distant metastases scored 81 points. Furthermore, moderate and poorly differentiated tumors were assigned 58 and 100 points,

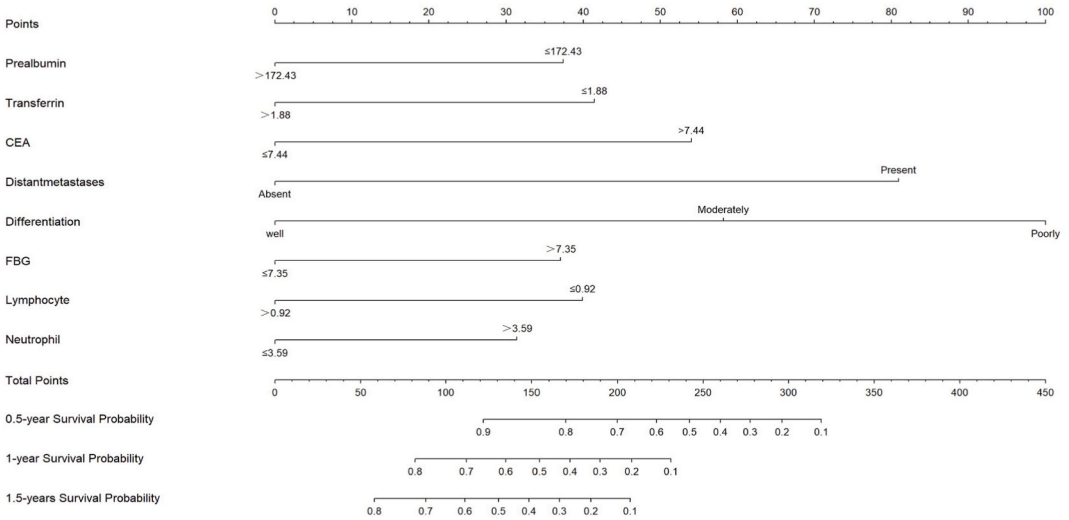

Fig. 4. Nomogram to predict 0.5-, 1-, and 1.5-year survival of patients with co-diabetes pancreatic adenocarcinoma. Prealbumin>172.43 g/L, transferrin>1.88 g/L, CEA ≤7.44 ng/mL, FBG≤7.35, lymphocyte > 0.92, neutrophil≤3.59, well tumor differentiation and absence of distant metastasis were given a score of 0; prealbumin≤172 g/L, transferrin≤1.88 g/L, CEA >7.44 ng/mL, FBG > 7.35 mmol/L, lymphocyte≤0.92 × 10^9cells/L and neutrophil > 3.59 × 10^9cells/L were given 37, 41, 54, 37, 40, 31 points, respectively; moderate and poorly differentiated tumors were assigned 58 and 100 points; the presence of distant metastases scored 81 points.

respectively. Finally, the total scores were summed and converted to 0.5-, 1-and 1.5-year survival rates.

We evaluated the predictive ability of the nomogram using the C-index and area under the ROC curve (AUC) and compared it with that of the AJCC and other models. As presented in Table 3, the nomogram achieved a high C index, including the training queue [0.795(95 % confidence interval, 0.751–0.840)] and the validation queue [0.729 (95 % confidence interval, 0.650–0.808)]. In addition, the C-index of our model was

Higher than those of the AJCC-8 staging system and other predicting models. The AUC values of 0.5-, 1-, and 1.5-year survival rates predicted by our nomogram were 0.894, 0.862, and 0.852 in the training queue(Fig. 5 A-C) and 0.785, 0.746, and 0.932 (Fig. 5 D-F) in the validation queue, respectively, which are also higher than those of the AJCC-8 staging system and other predicting models.

Furthermore, we used the calibration curve to predict the actual and predicted occurrence of the nomogram. The calibration curve of nomogram indicated that the prediction of the 0.5-year, 1-year, and 1.5-year survival rates by this model was in good agreement with the real survival rates (Fig. 6 A-F). We then used DCA to evaluate the nomogram's clinical efficacy in meeting the actual needs of clinical decision-making. The results showed that in the 0.5-, 1-, and 1.5-year survival training queues, the DCA curve of the nomogram showed a better net benefit than the AJCC-8 staging system, indicating that our model may have better clinical utility and benefit more patients (Fig. 7 A-F). In addition, we used the NRI to observe whether the nomogram's ability to predict the prognosis of patients with co-diabetes pancreatic adenocarcinoma was better than the AJCC-8 staging system. The results showed that the predictive ability of our model was better than that of the AJCC-8 staging system (Fig. 8 A-C). In summary, combining the C-index, AUC curve, calibration curve, and DCA, our nomogram can better help clinicians promote clinical decision-making and improve the prognosis of these high-risk patients.

3.4. Hierarchy of prognosis based on the co-diabetes pancreatic adenocarcinoma nomogram

To explore the prognostic hierarchy ability of the nomogram, after calculating the scores of each patient, the patients were assigned to three subgroups using the X-tile software, according to the scores: high (high-risk ≥267), medium (221 ≤ middle-risk <267), and

Table 3
Comparison of the C-index between models and AJCC-8 staging.

Patients		Overall Survival
		C-index (95 % CI)
Training queue	Nomogram	0.795(0.751–0.840)
	Itoh's model	0.560(0.455–0.665)
	AJCC-8staging	0.786(0.712–0.859)
Validation queue	Nomogram	0.729(0.650–0.808)
	Itoh's model	0.701(0.568–0.834)
	AJCC-8 staging	0.632(0.446–0.817)

AJCC-American Joint Committee on Cancer.

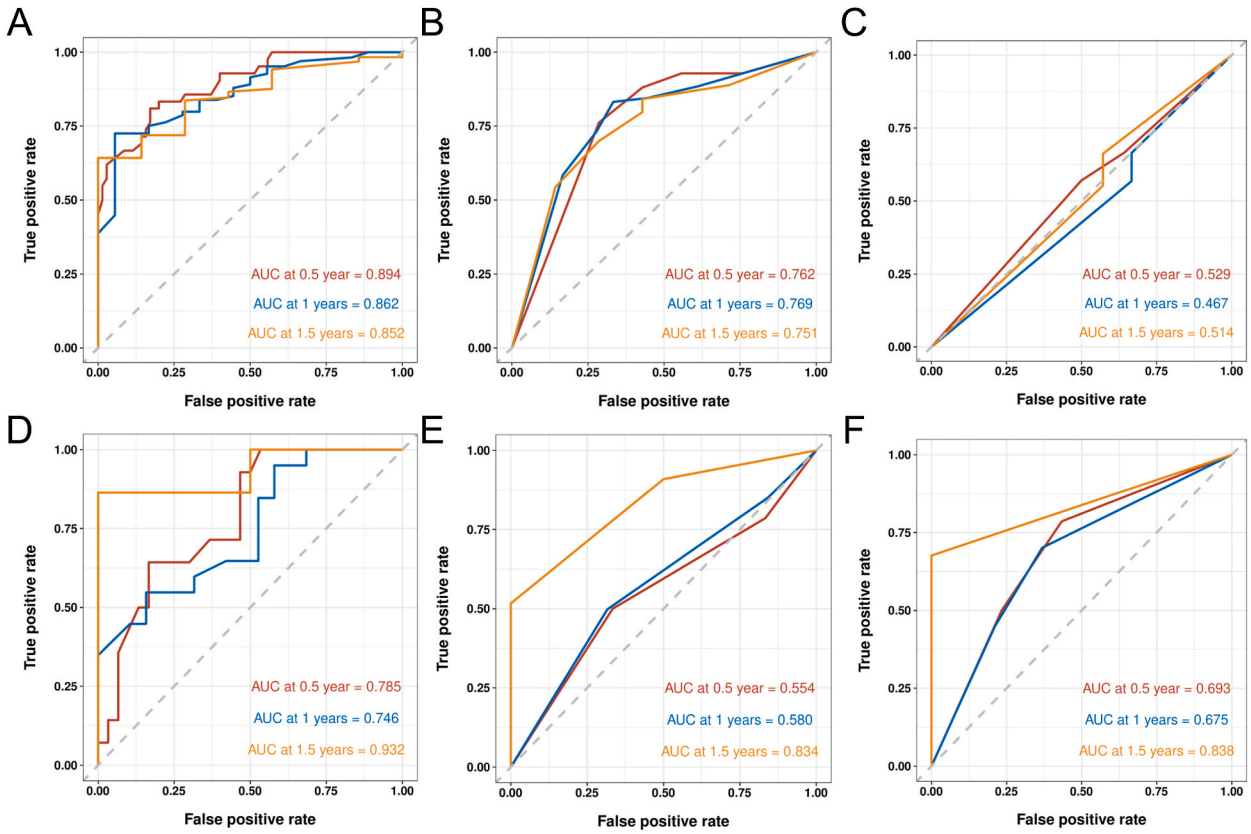

Fig. 5. Comparison of receiver operating characteristic (ROC) curves of the nomogram, AJCC-8 staging system and Itoh's model in the training(A-C) and validation queues (D–F) of 0.5, 1, and 1.5 years.

low-risk (low-risk <221) groups. Kaplan–Meier analysis was performed to determine the OS of the three subgroups (Fig. 9A). We found that the survival rate of the high-risk group was lower than that of the low-risk group, and there was statistical significance among the subgroups ($P < 0.1$), indicating that our model had a good ability to stratify prognosis. We also determined the OS of patients with AJCC-8 stages I, II, and III (Fig. 9B) and Itoh's model scores of 0, 1, and 2 (Fig. 9C). The results showed that the survival curves of the three subgroups were better separated than those of AJCC-8 stages and Itoh's model, and our nomogram had a better ability to stratify prognosis.

4. Discussion

In this study, we examined the preoperative parameters of the patients, such as age, sex, BMI, prealbumin, transferrin, albumin, serological examination, CEA, CA125, CA19-9, tumor size, LNM, and distant metastasis. Furthermore, through analysis, we ascertained the risk factors independently influencing the prognosis of patients with co-diabetes pancreatic adenocarcinoma. Our findings revealed that prealbumin, transferrin, CEA, distant metastases, the degree of tumor differentiation, neutrophil count, lymphocyte count and FBG are independent risk factors for such high-risk patients, and new nomograms were developed based on patients-independent risk factors. Moreover, our findings revealed higher C-index and AUC values than those of the AJCC-8 grading system. Based on the nomogram, we assigned patients into three subgroups: high-, middle-, and low-risk, which will help clinicians to judge the prognosis of such high-risk groups based on more accessible examinations of patients, make early and close follow-up plans, and make more reasonable treatment plans.

Many studies have confirmed that diabetes plays a significant role in the progression of PAAD [4–6,8,19]. A large queue study from South Korea showed that the close relationship between diabetes and PAAD was mainly associated with insulin resistance, and diabetes can increase the risk of PAAD-related death [8]. Another study from the US found that patients with diabetes who had high serum insulin levels had a significantly higher risk of PAAD compared with patients with low serum insulin levels [49]. Other studies have shown that insulin resistance in patients with diabetes increases the invasiveness of pancreatic cancer [9]. Some basic experiments have shown that insulin promotes the growth of pancreatic cancer cell lines [8,50]. Other theories suggest that insulin can promote the occurrence and development of PAAD by promoting the expression of insulin-like growth factor 1 (IGF-1) and its receptor-mediated signaling pathway [23,51,52]. Others believe that the relationship between diabetes and PAAD may be related to the changes in adiponectin levels [22,53]. In summary, the morbidity and mortality of patients with co-diabetes pancreatic adenocarcinoma were

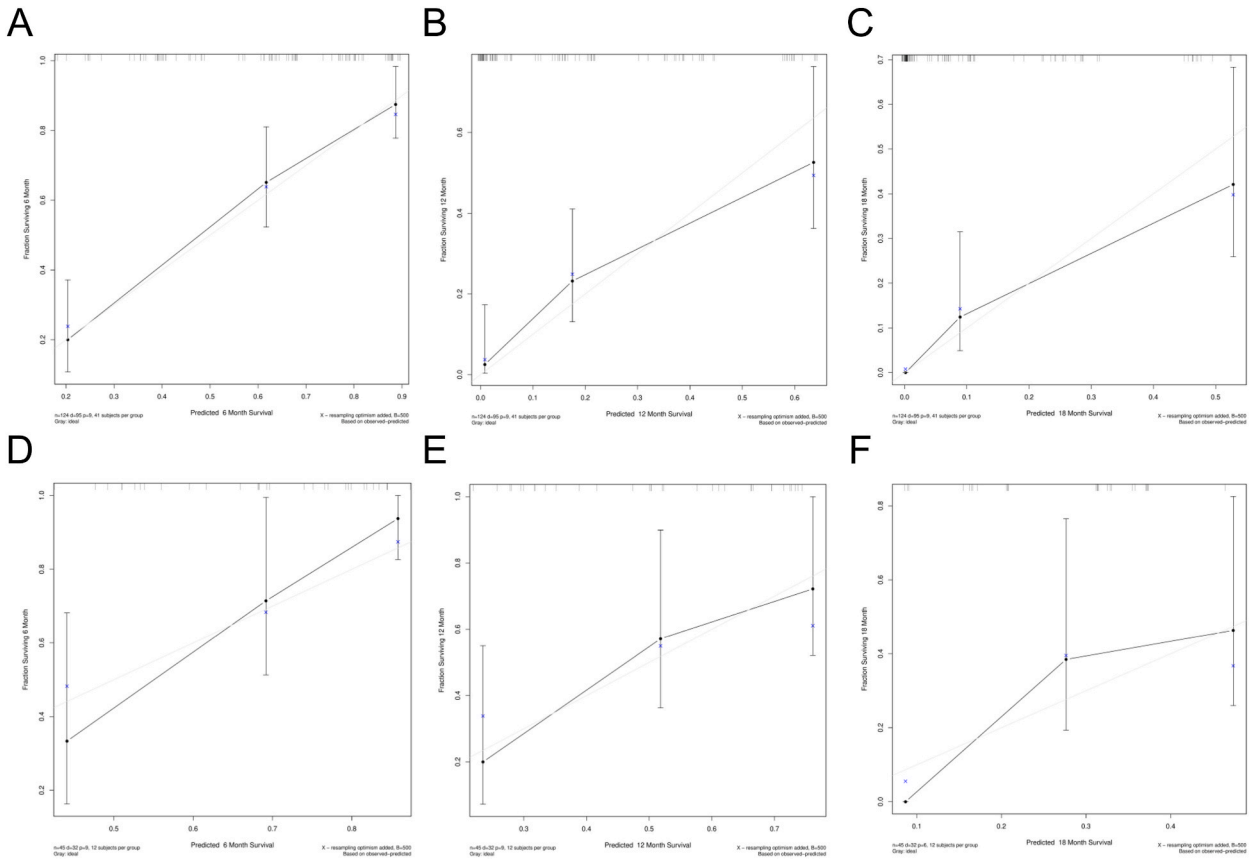

Fig. 6. Calibration plots of the nomogram for 0.5-, 1-, and 1.5-year overall survival (OS) prediction in the training queue (A–C) and validation queue (D–F).

higher than in patients without diabetes. Therefore, it was necessary to develop a model to assess the prognosis of this high-risk group.

Recent studies have shown that malnutrition has become a risk factor affecting the prognosis of various cancers [12,13,33,36]; however, previous nutritional prediction models less involved indicators such as prealbumin and transferrin, and more concerned with albumin, BMI and other indicators [17–19]. This study included two new nutritional indicators such as prealbumin and transferrin. Previous studies have shown that prealbumin and transferrin outperform nutritional indicators such as albumin in identifying malnutrition and poor prognosis [36,41,42,54]. In this study, the results showed that prealbumin and transferrin levels were independent risk factors affecting prognosis, whereas serum albumin levels were not significantly correlated with patient prognosis ($P > 0.1$). These results are consistent with those of previous studies. Serum prealbumin is a small-molecule protein synthesized by the liver, which is used to identify malnutrition, and is a prognostic marker in patients with malignant tumors. Prealbumin is a plasma transporter with a short half-life of approximately 1.9 days, which is shorter than that of albumin (approximately 12.5–21.0 days). When malnutrition occurs in the human body, it usually takes approximately 14 days for albumin to change in the blood; therefore, albumin cannot quickly make relevant changes. Serum prealbumin level in blood can forecast the state of nutritional intake balance of patients. Whether it is a positive or negative balance, it can play a rapid response role and be used as an index to predict malnutrition [40,42,54]. Transferrin is a single-chain glycosylated protein that is mainly synthesized in the liver and is found in high concentrations in human plasma. Transferrin is an indispensable component of body fluids, the main iron protein in the plasma, and has a comprehensive physiological function. Serum transferrin has a half-life of approximately 8 days and can participate in hundreds of iron-ion cycles. Under normal circumstances, the content of transferrin in the human body is relatively stable, and the level of transferrin in the human body has important implications for human health. Studies have shown that transferrin, an acute protein in the plasma, is inhibited when inflammation occurs. Therefore, the level of serum transferrin may decrease during acute inflammation and malnutrition, and its level is negatively correlated with disease severity [36,41,55,56]. In summary, preoperative blood albumin and transferrin levels may be better predictors of prognosis in patients with tumors than other nutritional indicators, such as albumin.

Previous studies have shown that serum tumor markers can be used as an adjunct to guide clinical practice for screening, tumor staging and even monitoring the prognosis of various types of cancer [28,30,31,34]. According to the literature, CEA and CA19-9 are independent risk factors that influence the prognosis of PAAD, and they can be used to assist in diagnosis and determine the resectability and curative effect of surgery [31,34]. Moreover, CEA may be better than CA19-9 for predicting patient prognosis [31]. The recommended cut-off value for CEA is broad, and the optimal cut-off remains debatable; for instance, using a higher cut-off can lead to

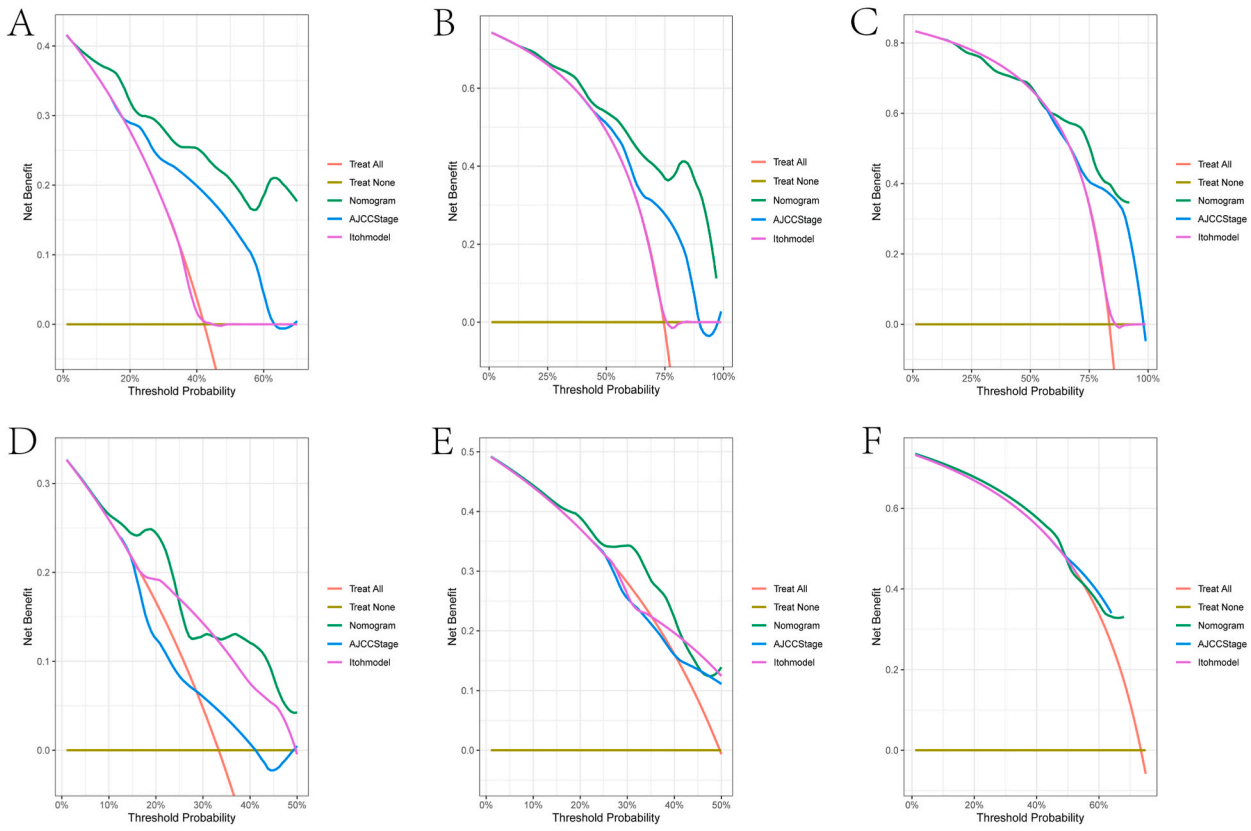

Fig. 7. Decision curve analysis of the nomogram for 0.5-, 1-, and 1.5-year overall survival (OS) prediction of patients in the training (A–C) and validation (D–F) queues. The nomogram had a better net benefit with a wider range of threshold probabilities than AJCC-8 staging system for both 0.5-, 1-, and 1.5-year OS.

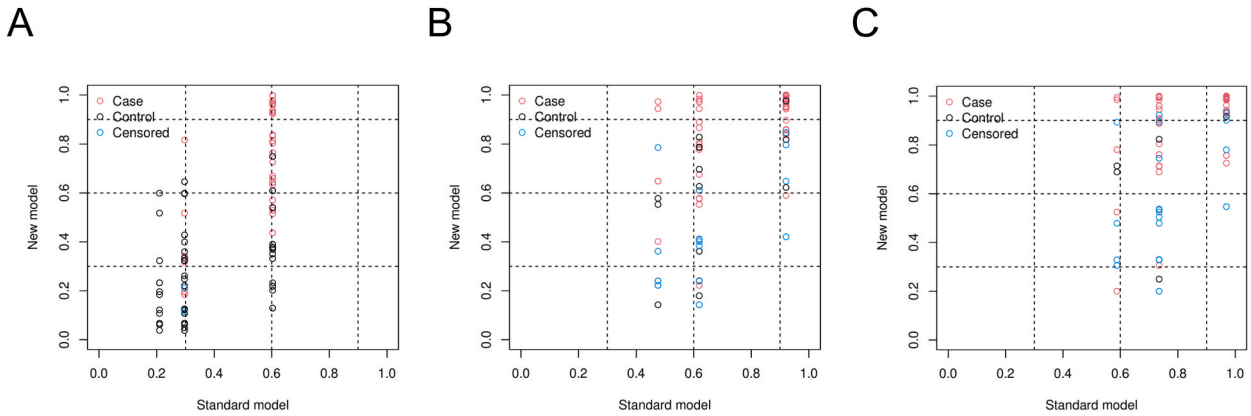

Fig. 8. Net Reclassification Index (NRI) of the nomogram for 0.5-, 1-, and 1.5-year in the training cohort (A–C). The results showed that the NRI of nomogram in 0.5-year, 1-year and 1.5-year were all >0, indicating that the ability of nomogram to predict the prognosis of patients with co-diabetes pancreatic adenocarcinoma was improved compared with AJCC-8 staging system.

missing many patients with poor prognoses, and using a lower cut-off reduces the sensitivity and specificity of predicting patient clinical outcomes. According to the characteristics of the patients, the best cut-off value of CEA was determined using the ROC curve, which was 7.88 ng/mL. CEA was identified as an independent risk factor affecting the prognosis of patients with co-diabetes pancreatic adenocarcinoma. Labrinus reportedly suggest 7.0 ng/mL as the best cut-off value and showed that CEA could be used to independently predict the occurrence of advanced pancreatic cancer [31]. This is consistent with the findings of our study. The best cutoff values of various predictive indicators may be different between studies, which may be related to different studies and patient selection

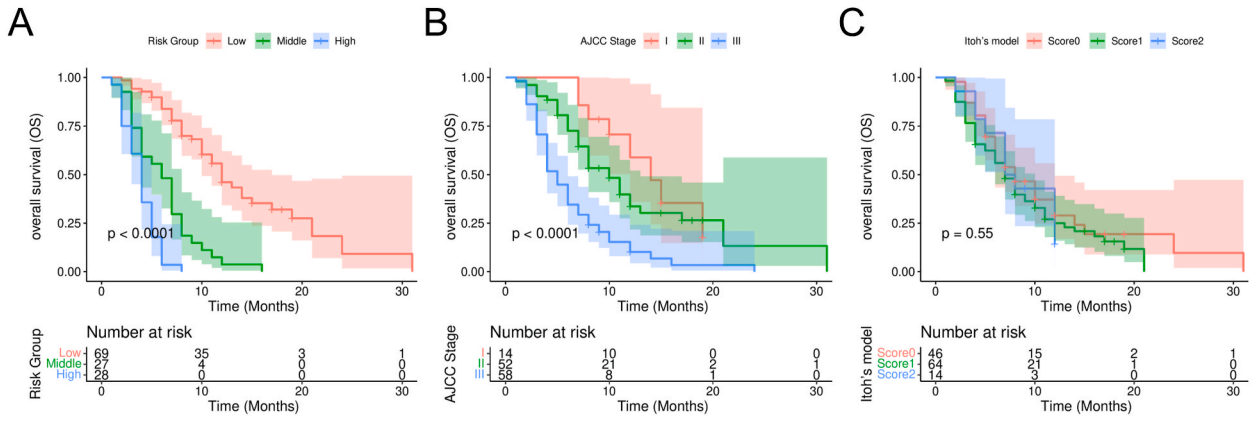

Fig. 9. (A) Kaplan–Meier analysis was performed to evaluate overall survival (OS) among three subgroups stratified by the risk scores. (B) Kaplan–Meier analysis was performed to evaluate OS among patients of AJCC-8 stage I, II, III and IV. (C) Kaplan–Meier analysis was performed to evaluate OS among patients of Itoh's model. The survival curves for the three subgroups stratified by the risk scores had better separation than those for the AJCC-8 stage system and Itoh's models.

methods.

Overall, our nomogram had the following advantages: 1) To the best of our knowledge, this was the first time to analyze the prognosis of patients with co-diabetes pancreatic adenocarcinoma, a high-risk group, and establish a simple and repeatable model. 2) Our model included novel nutritional indicators, such as prealbumin and transferrin. Studies have shown that it is more relevant and sensitive to malnutrition and tumors than albumin, BMI and other nutritional indicators. 3) Our model achieved a high C-index and AUC area, and the DCA curve also proved that this model can help clinicians guide clinical decisions and improve the prognosis of this high-risk group. 4) Our model also includes the characteristics of tumor itself, such as tumor differentiation grade and distant metastasis, which undoubtedly made our model more reliable. This study had some limitations. First, this was a single-center study. In the future, we expect multicenter and large-scale cooperative studies to prove the prognostic significance of each index and the prediction model in this high-risk population. Second, this study was a retrospective study, and there are no prospective studies; thus, determining the best cut-off value for each factor may be difficult. Moreover, our study did not explore more nutritional indicators and the influence of inflammatory indicators, and previous studies have shown that apolipoprotein A1, serum cholesterol level, and high-density lipoprotein are the factors influencing tumor prognosis [21,57–60]. In the future, we will further explore the potential link between diabetes and PAAD, and the correlation between systemic inflammation and malnutrition.

5. Conclusion

We discovered that prealbumin, transferrin, CEA levels, distant metastasis, tumor differentiation neutrophil, lymphocyte and FBG are significant risk factors for the prognosis of patients with co-diabetes pancreatic adenocarcinoma. Based on these factors, an effective prognostic model was developed, which will aid in the establishment of long-term treatment options for high-risk patients.

Funding statement

This study was supported by the National Natural Science Foundation of China (Project No. 82072635, 82173149,82173149 and 82102961), Basic and Applied Basic Research Foundation of Guangdong Province (Project No: 2021A1515012441), Special Events Supported by Heyuan People's Hospital (Project No: YNKT202202), the Science and Technology Program of Heyuan (23051017147335) and the Science and Technology Program of Huizhou Daya Bay (2021002).

Data availability statement

Data associated with our study are not deposited into publicly available repositories. Data will be made available on request.

Ethics declarations

This study was reviewed and approved by the Ethics Committee of Guangdong Provincial People's Hospital, with the approval number: KY-Z-2020-169.

CRediT authorship contribution statement

Zelong Wu: Writing – original draft, Data curation. **Chunsheng Liu:** Writing – original draft, Data curation. **Zuyi Ma:** Writing –

original draft, Data curation. **Zhenchong Li:** Investigation, Formal analysis, Data curation. **Shujie Wang:** Software, Formal analysis, Data curation. **Yubin Chen:** Software, Formal analysis, Data curation. **Mingqian Han:** Resources, Data curation. **Shanzhou Huang:** Software, Project administration, Data curation, Conceptualization. **Qi Zhou:** Resources, Project administration, Conceptualization. **Chuanzhao Zhang:** Funding acquisition, Data curation, Conceptualization. **Baohua Hou:** Resources, Project administration, Data curation, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgment

The authors gratefully acknowledge the contribution of the study participants.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2023.e21642.

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