Original Research Article

Predictive Model of Early Death of Resectable Pancreatic Ductal Adenocarcinoma After Curative Resection: A SEER-Based Study

Cancer Control
Volume 29: 1–10

DOI: 10.1177/10732748221084853
journals.sagepub.com/home/ccx
SAGE

Weikang Liu[1], Yongsu Ma[1], Bingjun Tang[1], Chang Qu[1], Yiran Chen[1], Yinmo Yang[1], and Xiaodong Tian[1]

Abstract

Objective: This study aims to determine the factors that predict early death and establish a predictive model for early death by analyzing clinical characteristics of patients with resectable pancreatic ductal adenocarcinoma (R-PDAC) who die early after radical surgery.

Materials and Methods: This was a retrospective study of patients who underwent radical surgical resection for R-PDAC in the Surveillance, Epidemiology, and End Results (SEER) database. Patients with overall survival ≤ 12 months were assigned as early death group and above 1 year as the late death group. Univariate and multivariate logistic regression was conducted to identify factors significantly associated with early death. An early death predictive model was constructed based on the identified independent risk factors.

Results: A total of 9695 patients were analyzed, and the total incidence of early death was 30.72%. Multivariable analysis showed that factors significantly associated with early death included age at diagnosis, race, marital status, tumor location, tumor size, tumor grade, number of positive lymph nodes, number of examined lymph nodes, positive lymph node ratio, chemotherapy, and radiotherapy. The predictive model showed good discrimination with a C-index of 0.722 (95% confidence interval: 0.711-0.733) and convincing calibration.

Conclusions: We developed a predictive model that may be easily applied to patients with R-PDAC after radical resection to predict the chance of death within 1 year. For patients with high risk of early death, neoadjuvant therapy should be considered. Even after radical resection, more aggressive adjuvant chemotherapy (with or without combined radiotherapy) must be used to minimize the chance of early death.

Keywords

pancreatic ductal adenocarcinoma, resectable, predictive model, early death

Introduction

Pancreatic ductal adenocarcinoma (PDAC) is one of the most lethal malignancies with an overall 5-year survival rate less than 9%.[1] Cancer-related death rate of PDAC is predicted to rank the second in the United States, and the third in Europe by 2030.[2] Radical resection remains the only curative therapy for PDAC, but the proportion of patients suitable for resection is only 20-25%, and the predicting prognosis is still unsatisfied. For the unselected PDAC patients, the overall 5-year survival after resection is only around 20%, and it has been widely accepted that high chance of long-term survival depends on the combination with either adjuvant or neoadjuvant systemic therapy. With the development of chemotherapy strategy, patients with advanced pancreatic cancer can achieve a median survival of 13.7 months on chemotherapy drugs alone.[3] However, in clinical practice,

[1]Peking University First Hospital, Beijing, China

Corresponding Authors:
Yinmo Yang, Department of General Surgery, Peking University First Hospital, 1st hospital, Beijing 100034, China.
Email: yangyinmosci@163.com

Xiaodong Tian, Peking Department of General Surgery, Peking University First Hospital, Xishiku Street, Beijing 100034, China.
Email: tianxiaodong@pkufh.cn

about 30% of patients with radically resected pancreatic cancer die within 1 year after surgery.[4,5] It is necessary to identify the risk factors for death in the patients who develop early death, avoid up-front surgery, and implement neoadjuvant therapy and aggressive postoperative adjuvant therapy.

Although tumor size, grade, margin status, and lymph node invasion are the main prognostic factors of PDAC, they are not sufficient to predict early death and the prognostic contributions of each factor have not been determined. The National Comprehensive Cancer Network (NCCN) guidelines recommend large tumor, significantly elevated serum CA19-9, regional lymph node enlargement, significant recent weight loss, and severe pain as risk factors for recurrence and metastasis after radical resection of PDAC, but it is unclear whether these factors affect patient survival less than 1 year. Several studies have explored risk factors for poor prognosis after resection of PDAC, including preoperative serum tumor markers (CEA+/CA125+/CA19-9 ≥ 1000 U/mL); hemoglobin < 10 g/dL; white blood cell count > 11,000/ml; platelet count, 350,000/ml; body mass index ≥ 35 kg/m^2; tumor > 2.5 cm; and other prognostic factors.[6-8] However, most of these studies have problems with small sample size and insufficient number of risk factors covered. Therefore, the prediction of survival after radical resection in patients with PDAC based on larger sample size and more prognostic factors is important.

In patients with resectable pancreatic ductal adenocarcinoma (R-PDAC), it is necessary to evaluate the timing of surgery. By comparing the early death group and the late death group, we could identify the risk factors of early death after the operation, so as to predict the prognosis of such patients and provide the strategies and timing of intervention. In this study, we identified eleven factors associated with early death through univariable and multivariable regression analyses. By using a nomogram approach, we demonstrated the contribution of various risk factors to the risk of early death. Our predictive model helps provide the strategies before and after surgery.

Methods

Data Collection

This study was approved by the Ethics Committee of Peking University First Hospital (No. 2019-167, June 26, 2019 in Beijing). The data was drawn from the Surveillance, Epidemiology, and End Results (SEER) database, and personal information of all patients was completely hidden. All information was collected from pancreatic adenocarcinoma patients who underwent radical surgery from 2004 to 2015 based on the SEER database (http://seer.cancer.gov/). According to the definition resectability of NCCN guideline (2020 version), the inclusion criteria were as follows: (1) All data contained ICD-O-3 histopathological classification, and only patients with ICD-O-3 histology codes 8140 (adenocarcinoma) and 8500 (ductal carcinoma) were selected. (2) All data have detailed information of tumor size, lymph nodes involvement, and distant metastasis. The exclusion criteria were as follows: (1) unknown age, (2) confirmed distant metastasis during surgery (stage M1), (3) unknown tumor type, (4) unknown tumor size, (5) unknown tumor grade, (6) no information of lymph node retrieved, (7) unknown survive data, (8) tumor contact artery or vein, and (9) death within a month after surgery. Based on the information of tumor size and number of positive lymph, the TNM stage for each enrolled case was redefined according to the eighth edition AJCC staging system. Finally, the data of 9695 patients with PDAC were included in this study. The patients were divided into 2 groups (the early death and late death) taking 1 year after radical operation as the boundary. The screening and statistical process was shown in Figure 1. The reporting of this study followed RECORD guidelines.[9]

Statistical Analysis

The receiver operating characteristics (ROC) curve was used to estimate the optimal threshold for LNR as risk factors for early death. The optimal cut-off value was determined to be the point of the ROC curve closest to the upper-left corner of the graph. All the variables were included as covariate in multivariable logistic regression models. Multivariable logistic regression analysis was used to estimate odds ratio (OR) with 95% confidence intervals (CIs). All P values were 2-sided, and a value < 0.05 was considered statistically significant. All significant predictors were used to build a predictive model for early death risk by using the cohorts. To quantify the discrimination performance of the early death nomogram, C-index was measured. The early death nomogram was subjected to bootstrapping validation (1000 bootstrap resamples) to calculate a relatively corrected C-index. Calibration curves were plotted to assess the calibration of the early death nomogram. All analysis were performed using the SPSS version 22.0 (IBM, Armonk, NY, USA) and R software (Version 3.6.1; https://www.R-project.org).

Results

Baseline Characteristics

The study population comprised 9695 patients, and their baseline demographic and clinical characteristics are shown in Table 1. The number of early death group and late death group were 2978 and 6717, respectively. 59.54% of patients aged ≥ 65 years; 82.61% of patients were Caucasian; 50.53% of patients were male; poor marital status (including divorce, separation, death of spouse) accounted for 23.38%; pathological staging, T1, T2, and T3, accounted for 17.91%, 60.65%, and 21.44%; N0, N1, and N2 accounted for 33.4%, 41.53%, and 25.07%; IA, IB, IIA, IIB, and III accounted for 8.7%, 18.81%, 5.89%, 41.53%, and 20.07%, respectively. The percentage of patients with tumors located at the head was 83.04%, and the percentage of tumors with well, moderately, and poorly differentiated was 10.06%, 52.91%, and 37.03%, respectively. During the perioperative period, 30.46% of patients did not receive

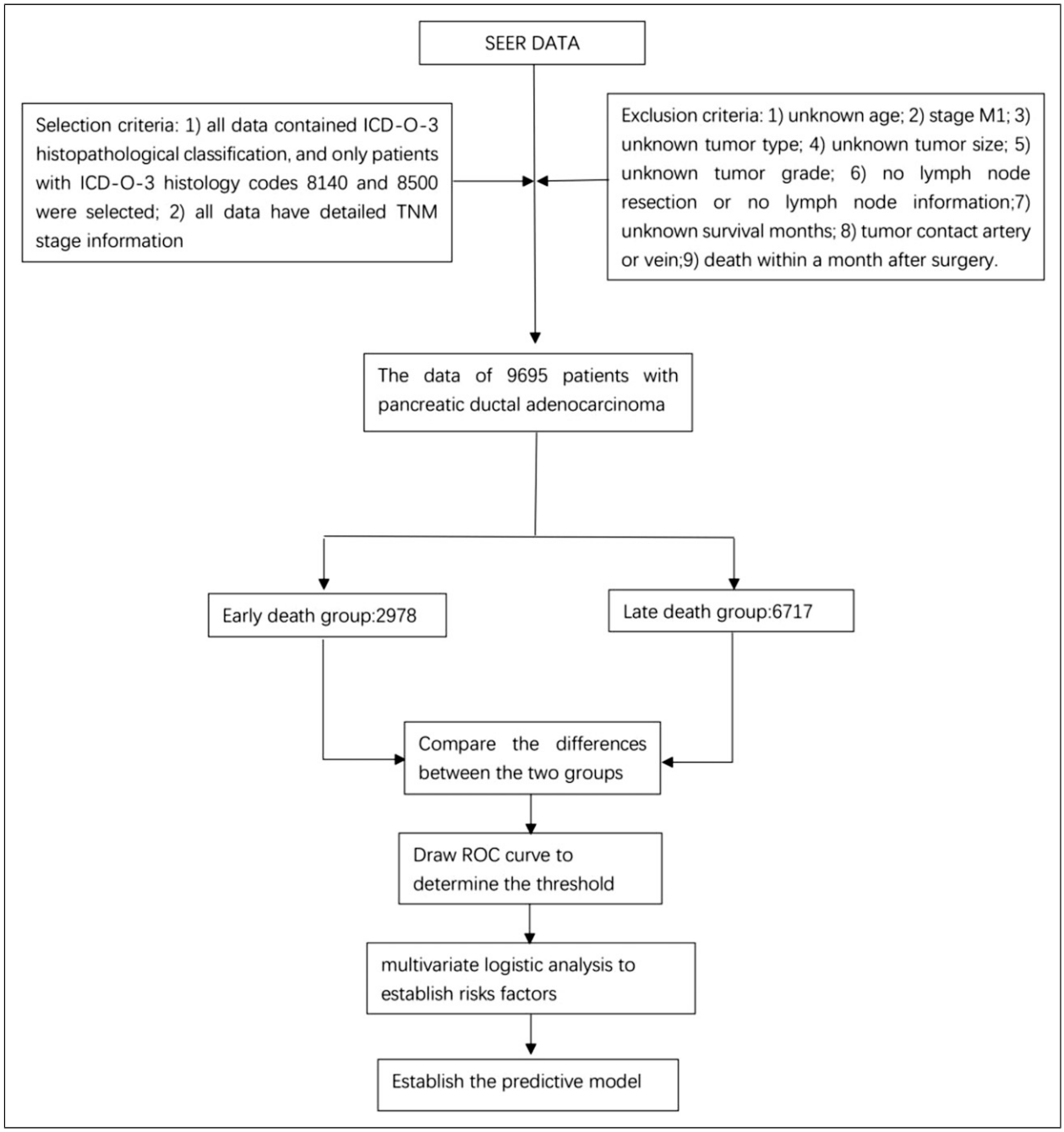

Figure 1. Flowchart for screening and statistical analysis of PDAC. SEER, Surveillance, Epidemiology, and End Results; PDAC, pancreatic ductal adenocarcinoma.

chemotherapy and 35.95% of patients received radiotherapy. The area under the curve (AUC) of LNR was 0.607, with an optimal threshold of 10% for predicting early death, and the sensitivity was 60.4% and the specificity was 55.9% (Figure 2).

Factors Associated With Early Death

In Table 1, age, race, marital status, T stage (AJCC eighth), N stage (AJCC eighth), tumor site, pathology grade, number of examined lymph node, LNR, chemotherapy, and radiotherapy were identified as potential factors for early death. In multivariate logistic regression (Table 2), eleven variables were independently associated with early death, including age ≥ 65 (OR, 1.260; 95% CI, 1.141-1.391; P < .001), black race (OR, 1.339; 95% CI, 1.145-1.565; P < .001), poor marital status (OR, 1.129; 95% CI, 1.009-1.264; P = .034), T2 stage (OR, 1.525; 95% CI, 1.328-1.751; P < .001), T3 stage (OR, 2.400; 95% CI, 2.047-2.814; P < .001), N1 stage

Table 1. Clinical Features of Early Death and Late Death Cohorts.

Variable	Total Subjects	Early Death	Late Death	P
Age at diagnosis				< 0.001
< 65 (%)	3923 (40.46%)	1014 (10.46%)	2909 (30.01%)	
≥ 65 (%)	5772 (59.54)	1964 (20.26)	3808 (39.28)	
Race				0.119
White (%)	8009 (82.61%)	2436 (25.13%)	5573 (57.48%)	
Black (%)	948 (9.78%)	319 (32.90%)	629 (6.49%)	
Others (%)	738 (7.61%)	223 (2.3%)	515 (5.31%)	
Gender				0.121
Male (%)	4899 (50.53%)	1540 (15.88%)	3359 (34.65%)	
Female (%)	4796 (49.47%)	1438 (14.93%)	3358 (34.64%)	
Marital status				< 0.001
Divorced/separated/widowed	2267 (23.38%)	782 (8.07%)	1485 (15.32%)	
Married/domestic partner/single/unknown	7428 (76.62%)	2196 (22.65%)	5232 (54.00%)	
T (AJCC eighth)				< 0.001
T1 (%)	917 (17.91%)	353 (3.64%)	1383 (14.27%)	
T2 (%)	5880 (60.65%)	1779 (18.35%)	4101 (42.30%)	
T3 (%)	2079 (21.44%)	846 (8.73%)	1233 (12.72%)	
N (AJCC eighth)				< 0.001
N0 (%)	3238 (33.40%)	734 (7.57%)	2504 (25.83%)	
N1 (%)	4026 (41.53%)	1274 (13.14%)	2752 (28.39%)	
N2 (%)	2431 (25.07%)	970 (10.01%)	1461 (15.07%)	
Stage(AJCC eighth)				< 0.001
IA (%)	843 (8.70%)	140 (1.44%)	703 (7.25%)	
IB (%)	1824 (18.81%)	412 (4.25%)	1412 (14.56%)	
IIA (%)	571 (5.89%)	182 (1.88%)	389 (4.01%)	
IIB (%)	4026 (41.53%)	1274 (13.14%)	2752 (28.39%)	
III (%)	2431 (20.07%)	970 (10.01%)	1461 (15.07%)	
Tumor site				0.035
Head (%)	8051 (83.04%)	2509 (25.88%)	5542 (57.16%)	
Body/tail (%)	1644 (16.96%)	469 (4.84%)	1175 (12.12%)	
Tumor grade				< 0.001
Well (%)	975 (10.06%)	175 (1.81%)	800 (8.25%)	
Moderately (%)	5130 (52.91%)	1380 (14.23%)	3750 (38.68%)	
Poorly (%)	3590 (37.03%)	1423 (14.68%)	2167 (22.35%)	
Lymph nodes examined				
≤15 (%)	5360 (55.29%)	1751 (18.06%)	3609 (37.22%)	
>15 (%)	4335 (44.71%)	1227 (12.67%)	3108 (32.06%)	
LNR	.1(0−.25%)	.15(.03−.33%)	.08(0−.22%)	< 0.001
Chemotherapy				< 0.001
Yes (%)	6742 (69.54%)	1552 (16.01%)	5590 (57.66%)	
No/unknown (%)	2953 (30.46%)	1426 (14.71%)	1527 (15.75%)	
Radiotherapy				< 0.001
Yes (%)	3485 (35.95%)	772 (7.96%)	2713 (27.98%)	
No/unknown (%)	6210 (64.05%)	2206 (22.75%)	4004 (41.30%)	

Abbreviations: LNR, positive lymph nodes ratio.

(OR, 1.398, 95% CI, 1.202-1.625; P < .001), N2 stage (OR, 1.864; 95% CI, 1.514-2.295; P < .001), moderately differentiated (OR, 1.634; 95% CI, 1.359-1.964; P < .001), poorly differentiated (OR, 2.916; 95% CI, 2.419-3.516; P < .001), LNR > 10% (OR, 1.38; 95% CI, 1.186-1.607; P < .001), body/tail location (OR, .868; 95% CI, 0.761—.989; P < .001), number of examined lymph node > 15 (OR, .738; 95% CI, 0.666-.818; P < .001), chemotherapy (OR, .32; 95% CI, 0.287-.357; P < .001), and radiotherapy (OR, .783; 95% CI, 0.700-.875; P < .001).

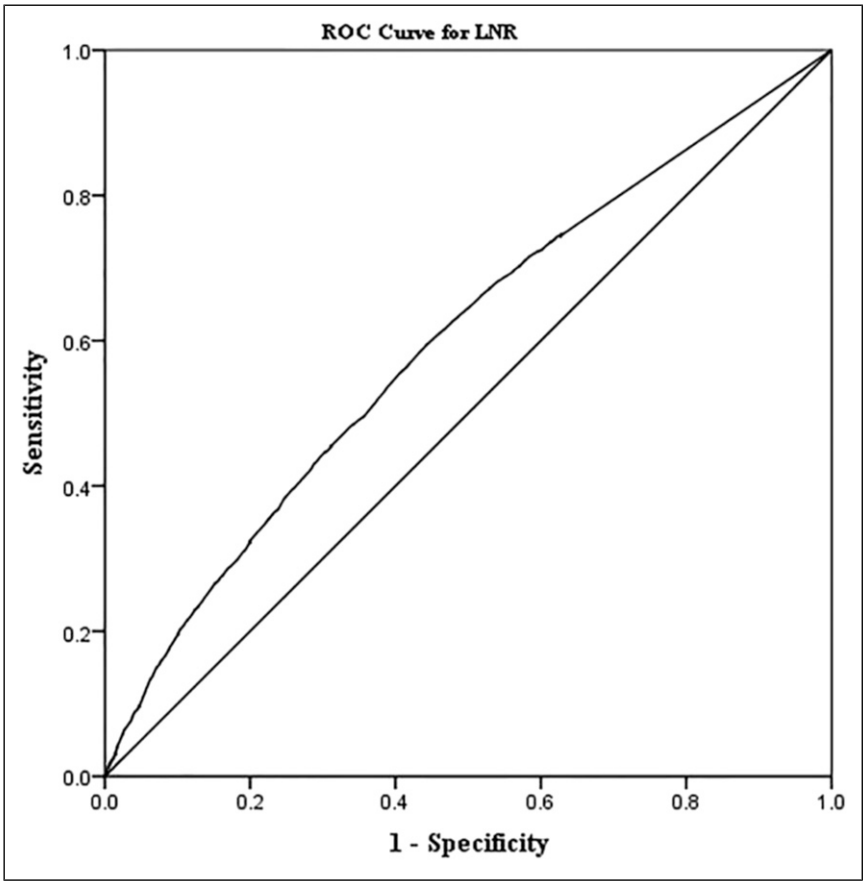

Figure 2. The receiver operating characteristics curve for LNR for predicting early death (< 12 months). The area under the curve (area under the curve) was .607 (95% CI: .595-.619), and the best cut-off value for predicting early death was 10% with a sensitivity of 60.4% and specificity of 55.9%. (P = .006). LNR, positive lymph nodes ratio.

Establishment and Validation of Early Death Predictive Model

We developed the predictive model that incorporated the above independent predictors and presented as the nomogram (Figure 3). Among the factors, tumor size, tumor grade, number of positive lymph nodes, and chemotherapy were important factors associated with early death. Assuming a 60-year-old white patient with the following situation: the size of the pancreatic head tumor is 50 mm, the number of lymph nodes examined is 10, the number of positive lymph nodes is 2, the LNR is 20% , and the tumor is moderately differentiated, from which we can calculate the risk of early death of this patient. The estimated risk of early death is 58% if the patient does not receive chemotherapy and radiotherapy, and 26% if he receives chemotherapy and radiotherapy. The calibration curve of the early death risk nomogram in R-PDAC patients demonstrated good agreement in this cohort (Figure 4). The x-axis represented the predicted early death risk. The y-axis represented the actual diagnosed early death. The diagonal dotted line represented a perfect prediction by an ideal model. The solid line represented the performance of the nomogram, of which a closer fit to the diagonal dotted line represented a better prediction. The C-index for the prediction nomogram was 0.722 (95% CI: 0.807-0.907) for the cohort, and was confirmed to be 0.720 by internal validation, suggesting the good discrimination of the model.

Discussion

In this study, we identified a set of parameters based on demographic characteristics and tumor characteristics that may help identify patients at high risk of early mortality after surgical resection for PDAC. These parameters were collected in all patients with PDAC who underwent radical surgery to facilitate focused intervention in high-risk patients and help improve clinical outcomes. Data on the definition of early death after radical resection for pancreatic cancer are limited and inconsistent.[4,8,10-12] We defined 12 months postoperatively as early death because, with advances in chemotherapy regimens, current median survival time for advanced pancreatic cancer using chemotherapy regimens alone is close to or greater than 12 months.

A previous study has identified preoperative independent predictive risk factors for early recurrence in patients with

Table 2. Multivariable Logistic Regression for Early Death and Late Death Groups.

Variables	Levels	OR (95% CI)	*P*
Age at diagnosis	< 65	Reference	
	≥ 65	1.260 (1.141-1.391)	< 0.001
Race	White	Reference	
	Black	1.339 (1.145-1.565)	< 0.001
	Others	1.071 (0.897-1.280)	0.447
Gender	Male	Reference	
	Female	0.924 (0.839-1.017)	0.107
Marital status	Married/domestic partner/single/unknown	Reference	
	Divorced/separated/widowed	1.129 (1.009-1.264)	0.034
Tumor size	T1	Reference	
	T2	1.525 (1.328-1.751)	< 0.001
	T3	2.400 (2.047-2.814)	< 0.001
Positive lymph nodes	N0	Reference	
	N1	1.398 (1.202-1.625)	< 0.001
	N2	1.864 (1.514-2.295)	< 0.001
Tumor site	Head	Reference	
	Body/tail	0.868 (0.761-0.989)	0.034
Tumor grade	Grade 1	Reference	
	Grade 2	1.634 (1.359-1.964)	< 0.001
	Grade 3	2.916 (2.419-3.516)	< 0.001
Lymph nodes Examined	≤ 15	Reference	
LNR	> 15	0.738 (0.666-0.818)	< 0.001
	≤ 10%	Reference	
Chemotherapy	> 10%	1.38 (1.186-1.607)	< 0.001
	No/unknown	Reference	
Radiotherapy	Yes	0.320 (0.287-0.357)	< 0.001
	No/unknown	Reference	
	Yes	0.783 (0.700-0.875)	< 0.001

Abbreviations: CI indicates confidence interval; OR, Odds ratio; LNR, positive lymph nodes ratio.

R-PDAC.[11] However, our study is the first to use a large sample size of patients with R-PDAC to predict early death after radical resection. We developed and validated a risk predictive model for early death in patients with R-PDAC by integrating risk factors from demographic characteristics, disease characteristics, and treatment characteristics into a user-friendly nomogram. While a predictive model only using preoperative factors is valuable, the addition of perioperative factors into the model increases the accuracy of the prediction.

Demographically, our study found that age > 65 years, poor marital status, and black race are independent risk factors for early death for R-PDAC. Consistent with previous reports, no significant difference in cancer survival was found between men and women.[13] The impact of age on prognosis has been well studied. The 5-year survival of patients aged 20-40 years was almost 3 times that of patients aged > 40 years, and the mortality risk of PDAC patients aged 40-80 years was twice that of patients aged < 40 years.[14] Marital status is suggested to be an important factor in prognosis,[15] while another study showed that marital status has no effect on the prognosis of pancreatic cancer.[16] Our study showed that blacks had a higher risk of early death after radical PDAC surgery than whites, as demonstrated in other studies.[17,18] Compared with white patients, black PDAC patients were younger, staged later, and received less treatment. These findings may only be partially related to socioeconomic differences. When disease staging and treatment were controlled, there was no reduction in survival rates for black patients.

For oncological features, tumor location at the head of the pancreas had higher risk of early death than body/tail for R-PDAC. Prognostic significance of tumor location in pancreatic cancer is still controversial. Pancreatic body and tail tumors, due to the late symptoms, tend to be more advanced and larger, and have worse prognoses.[19,20] Poor prognosis for overall survival has been reported for tumors located at the pancreatic head.[21] According to the Japanese Pancreas Society, the head of the pancreas has complex lymphatic drainage system compared to the distal pancreas.[22] Some studies have shown that the lymph nodes of pancreatic body/tail tumors are less invaded, leading to a better prognosis.[23,24] The impact of pancreatic cancer tumor location on prognosis is yet to be further confirmed by prospective studies in large, high-quality samples. Many studies have shown that LNR is an important indicator of pancreatic cancer prognosis.[25-27] By

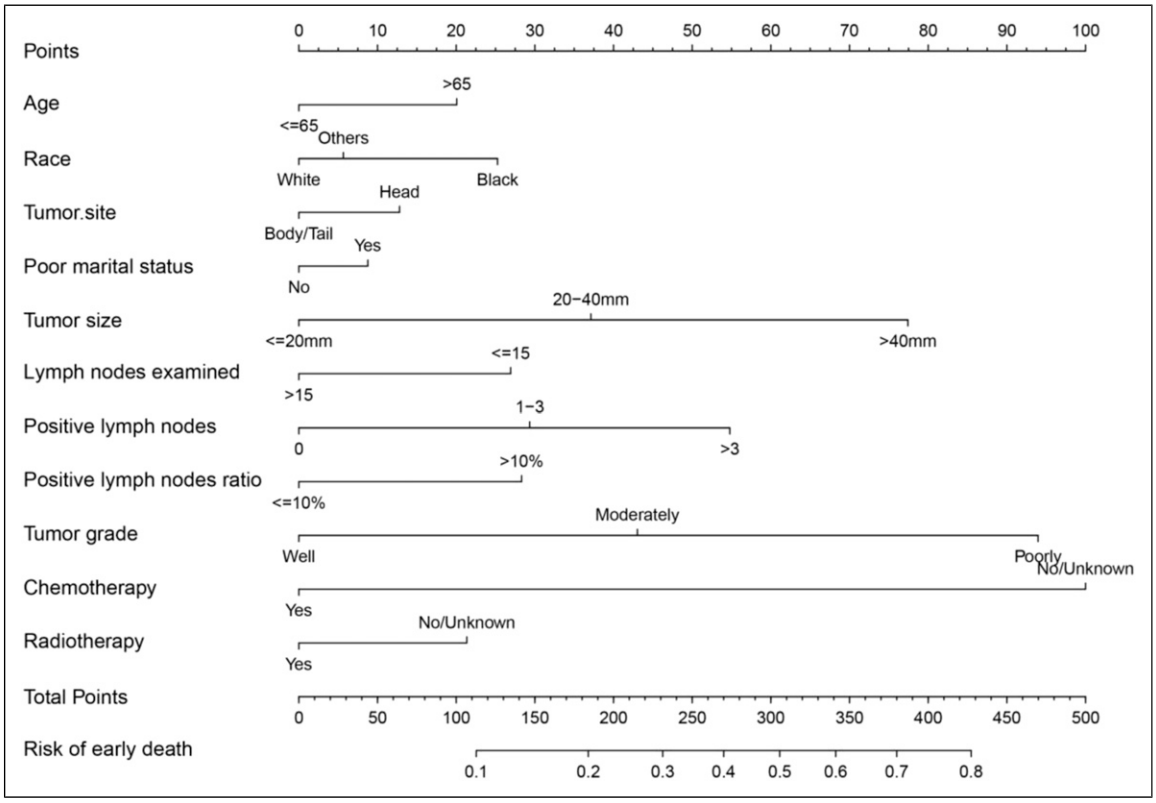

Figure 3. Developed early death nomogram. The early death nomogram was developed in the cohort, with age, race, tumor site, poor marital status, tumor size, lymph nodes examined, positive lymph nodes, positive lymph nodes ratio, tumor grade, chemotherapy, and radiotherapy incorporated.

using an ROC curve, we defined the optimal cut-off value for the LNR, which was significantly associated with early death.

Our nomogram showed that tumor grade and tumor size affected early death risk, in agreement with previous studies.[15,28-30] Tumor size > 3 cm was independently associated with early recurrence which is often considered an important sign of poor prognosis.[31] With the development of imaging technology, preoperative examinations are increasingly able to accurately measure tumor diameter. While it has been shown that preoperative computed tomography (CT) scans may underestimate tumor size compared to pathological tumor size in PDAC patients, endoscopic ultrasound (EUS) has higher accuracy than CT for determining the size of smaller tumors.[32] Therefore, early death risk scores obtained from preoperative imaging measurements of tumor size may be higher than they actually are.

Currently, although NCCN guidelines recommend routine biopsy for patients receiving neoadjuvant therapy, routine sampling of resectable patients is debatable. Although the risk of biopsy-related complications is small, negative biopsies may not alter patient management. However, the accuracy, sensitivity, and specificity of EUS biopsy for diagnosing malignancy have been reported to be 97.6%, 96.6%, and 99.0%, respectively.[33] The number of positive lymph nodes is an indicator of the N stage in the AJCC guidelines, and our study showed that the number of positive lymph nodes was strongly associated with early death in R-PDAC patients. It has been shown that at least 11 to 17 lymph nodes should be dissected to accurately assess lymph node metastases for accurate N staging, and clearing > 15 lymph nodes can significantly improve prognosis.[34]

The role of adjuvant chemotherapy in pancreatic adenocarcinoma is well established and currently remains the standard of care by expert guidelines for PDAC. The Gastrointestinal Tumor Study Group (GITSG) study was the first randomized controlled trial in pancreatic adenocarcinoma to demonstrate survival benefit from adjuvant therapy following surgery, and treatment group had a median overall survival of 20 vs 11 months for surgery alone.[35] Moreover, clinical prognosis of patients has been greatly improved with the continuous improvement of chemotherapy regimens.[36-38] These reports are consistent with our findings that chemotherapy was associated with early mortality in our predictive model. For radiation therapy, there is currently less data on radiotherapy for PDAC, and further studies are needed to evaluate its significance.

This study has several limitations. First, our study is retrospective and selection bias is difficult to avoid. Second, we excluded all patients with vascular invasion based on tumor extension, which resulted in sample size smaller than the total number of patients judged to have R-PDAC, preoperatively. Third, the definition of perioperative chemotherapy in the

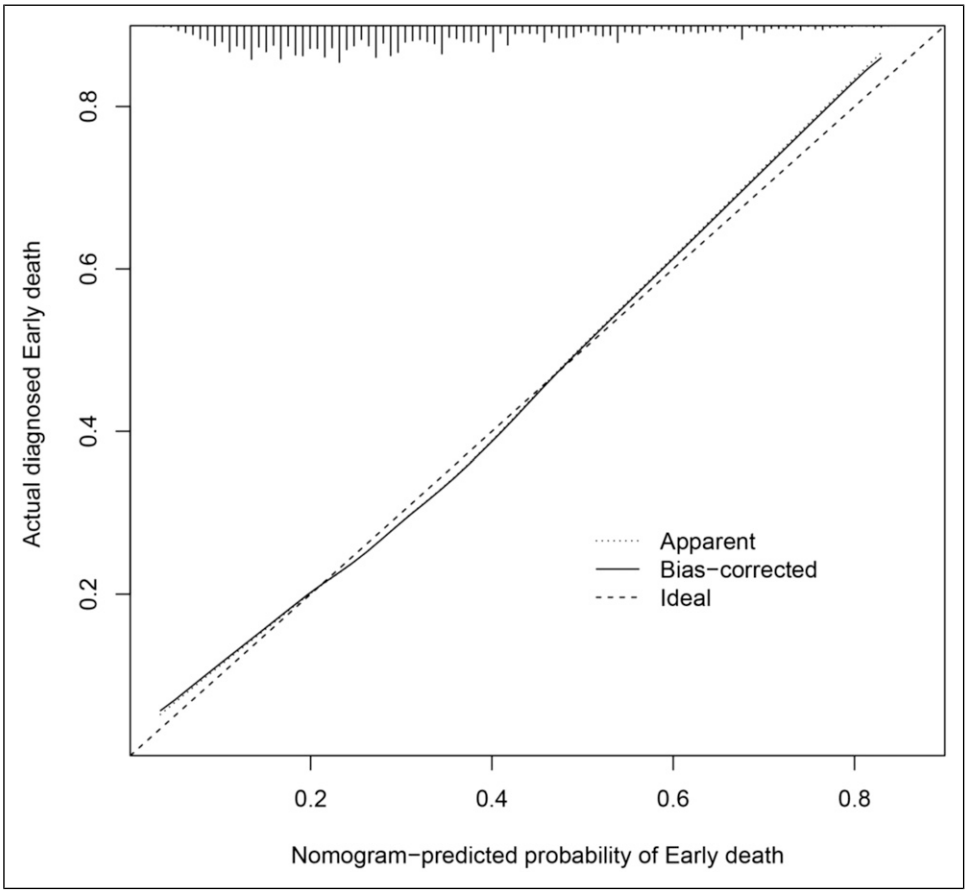

Figure 4. Calibration curves of the early death nomogram prediction in the cohort. The x-axis represented the predicted early death risk. The y-axis represented the actual diagnosed early death. The diagonal dotted line represented a perfect prediction by an ideal model. The solid line represented the performance of the nomogram, of which a closer fit to the diagonal dotted line represented a better prediction.

SEER database did not clearly distinguish between preoperative neoadjuvant chemotherapy or postoperative adjuvant chemotherapy. Fourth, for multivariate analysis, the number of positive lymph nodes, number of examined lymph nodes, and positive lymph node ratio are confounding factors. Fifth, some risk factors affecting the prognosis of PDAC, such as preoperative serum tumor markers, marginal status, weight loss, and severe pain, were not recorded in the SEER database, so these factors were not included in this model. Sixth, it is well-known that there is significant difference between distal pancreatectomy and the Whipple procedure to early postoperative death after surgery for pancreatic cancer. However, in the prediction model of this study, the tumor location is only used as a factor in the prediction model, and this factor has a relatively small influence on predicting the early death of pancreatic cancer after surgery. This discordance may indicate a weakness of our prediction model with mixed-up types of surgery. Further studies are needed to establish a prediction model for each type of surgery.

In summary, this study is the first to use a large sample size of R-PDAC patients to establish a predictive model which can be conveniently applied to patients with R-PDAC after curative resection to predict the probability of death within 1 year. For patients with a high risk of early death, neoadjuvant therapy before surgery may be considered. Even after radical resection, aggressive adjuvant chemotherapy with or without combined radiotherapy is necessary to minimize the probability of early mortality.

Authors' Contribution

Weikang Liu, Yongsu Ma, Bingjun Tang, Chang Qu, and Yiran Chen collected and analyzed the data, and drafted the manuscript. Yinmo Yang and Xiaodong Tian designed the study and wrote the manuscript. All authors read and approved the manuscript.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This work was supported by the grants from the National Natural Science

Foundation of China (No. 81871954, 82171722), Beijing Municipal Natural Science Foundation (No. 7212111) and the Interdisciplinary Clinical Research Project of Peking University First Hospital.

Ethical Approval

This study was approved by the Ethics Committee of Peking University First Hospital (No, 2019-167).

Informed Consent

All patients provided written informed consent.

ORCID iD

Yinmo Yang https://orcid.org/0000-0002-6202-6535

References

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2020. *CA Cancer J Clin*. 2020;70(1):7-30.
2. Rahib L, Smith BD, Aizenberg R, Rosenzweig AB, Fleshman JM, Matrisian LM, et al. Projecting cancer incidence and deaths to 2030: The unexpected burden of thyroid, liver, and pancreas cancers in the United States. *Cancer Res*. 2014;74(11): 2913-2921.
3. Ozaka M, Matsumura Y, Ishii H, Omuro Y, Itoi T, Mouri H, et al. Randomized phase II study of gemcitabine and S-1 combination versus gemcitabine alone in the treatment of unresectable advanced pancreatic cancer (Japan clinical cancer research organization PC-01 study). *Cancer Chemother and Pharmacol*. 2012;69(5):1197-1204.
4. Balzano G, Dugnani E, Crippa S, Scavini M, Pasquale V, Aleotti F, et al. A preoperative score to predict early death after pancreatic cancer resection. *Dig Liver Dis*. 2017;49(9):1050-1056.
5. Dias-Santos D, Ferrone CR, Zheng H, Lillemoe KD, Castillo CFD. The Charlson age comorbidity index predicts early mortality after surgery for pancreatic cancer. *Surgery*. 2015;157(5):881-887.
6. Zhang D, Fu SY, Xu J, Sun X. Clinical significance of CA-199 and LINC01197 in pancreatic cancer. *Oncologie*. 2020;22(2): 95-105.
7. Liu L, Xu H, Wang W, Wu C, Chen Y, Yang J, et al. A preoperative serum signature of CEA+/CA125+/CA19-9 >/= 1000 U/mL indicates poor outcome to pancreatectomy for pancreatic cancer. *Int J Cancer*. 2015;136(9):2216-2227.
8. Sohal DP, Shrotriya S, Glass KT, Pelley RJ, McNamara MJ, Estfan B, et al. Predicting early mortality in resectable pancreatic adenocarcinoma: A cohort study. *Cancer*. 2015;121(11): 1779-1784.
9. Benchimol EI, Smeeth L, Guttmann A, Harron K, Moher D, Petersen I, et al. The REporting of studies conducted using observational routinely-collected health data (RECORD) statement. *PLoS Med*. 2015;12(10):e1001885.
10. Hsu CC, Wolfgang CL, Laheru DA, Pawlik TM, Swartz MJ, Winter JM, et al. Early mortality risk score: Identification of poor outcomes following upfront surgery for resectable pancreatic cancer. *J Gastrointest Surg*. 2012;16(4):753-761.
11. Clark W, Silva M, Donn N, Luberice K, Humphries LA, Paul H, et al. Targeting early deaths following pancreaticoduodenectomy to improve survival. *J Gastrointest Surg*. 2012;16(10):1869-1874.
12. Siddiqui A, Heinzerling J, Livingston EH, Huerta S. Predictors of early mortality in veteran patients with pancreatic cancer. *Am J Surg*. 2007;194(3):362-366.
13. Quaresma M, Coleman MP, Rachet B. 40-year trends in an index of survival for all cancers combined and survival adjusted for age and sex for each cancer in England and Wales, 1971-2011: A population-based study. *Lancet*. 2015;385(9974): 1206-1218.
14. Wang H, Liu J, Xia G, Lei S, Huang X, Huang X. Survival of pancreatic cancer patients is negatively correlated with age at diagnosis: A population-based retrospective study. *Sci Rep*. 2020;10(1):7048.
15. Smith BJ, Mezhir JJ. An interactive Bayesian model for prediction of lymph node ratio and survival in pancreatic cancer patients. *JAMIA*. 2014;21(e2):e203-e211.
16. Reyngold M, Winter KA, Regine WF, Abrams RA, Safran H, Hoffman JP, et al. Marital status and overall survival in patients with resectable pancreatic cancer: Results of an ancillary analysis of NRG Oocology/RTOG 9704. *Oncol*. 2020;25(3): e477-e483.
17. Nipp R, Tramontano AC, Kong CY, Pandharipande P, Dowling EC, Schrag D, et al. Disparities in cancer outcomes across age, sex, and race/ethnicity among patients with pancreatic cancer. *Cancer Med*. 2018;7(2):525-535.
18. Heller DR, Nicolson NG, Ahuja N, Khan S, Kunstman JW. Association of treatment inequity and ancestry with pancreatic ductal adenocarcinoma survival. *JAMA Surg*. 2019:e195047.
19. Wentz SC, Zhao ZG, Shyr Y, Shi CJ, Merchant NB, Washington K, et al. Lymph node ratio and preoperative CA 19-9 levels predict overall survival and recurrence-free survival in patients with resected pancreatic adenocarcinoma. *World J Gastrointest Oncol*. 2012;4(10):207-215.
20. Bilici A. Prognostic factors related with survival in patients with pancreatic adenocarcinoma. *World J Gastroenterol*. 2014; 20(31):10802-10812.
21. Zheng Z, Wang M, Tan C, Chen Y, Ping J, Wang R, et al. Disparities in survival by stage after surgery between pancreatic head and body/tail in patients with nonmetastatic pancreatic cancer. *PLoS One*. 2019;14(12):e0226726.
22. Kawarada Y. [New classification of pancreatic carcinoma–Japan Pancreas Society]. *Nihon Shokakibyo Gakkai zasshi = Jpn J Gastroenterol*. 2003;100(8):974-980.
23. Sohn TA, Yeo CJ, Cameron JL, Koniaris L, Kaushal S, Abrams RA, et al. Resected adenocarcinoma of the pancreas-616 patients: results, outcomes, and prognostic indicators. *J Gastrointest Surg*. 2000;4(6):567-579.
24. Moon HJ, An JY, Heo JS, Choi SH, Joh JW, Kim YI. Predicting survival after surgical resection for pancreatic ductal adenocarcinoma. *Pancreas*. 2006;32(1):37-43.
25. Tol JA, Brosens LA, van Dieren S, van Gulik TM, Busch OR, Besselink MG, et al. Impact of lymph node ratio on survival in

patients with pancreatic and periampullary cancer. *Br J Surg*. 2015;102(3):237-245.
26. John BJ, Naik P, Ironside A, Davidson BR, Fusai G, Gillmore R, et al. Redefining the R1 resection for pancreatic ductal adenocarcinoma: Tumour lymph nodal burden and lymph node ratio are the only prognostic factors associated with survival. *HPB*. 2013;15(9):674-680.
27. Riediger H, Keck T, Wellner U, Hausen A, Adam U, Hopt UT, et al. The lymph node ratio is the strongest prognostic factor after resection of pancreatic cancer. *J Gastrointest Surg*. 2009;13(7): 1337-1344.
28. Botsis T, Anagnostou VK, Hartvigsen G, Hripcsak G, Weng C. Modeling prognostic factors in resectable pancreatic adenocarcinomas. *Cancer Inform*. 2010;7:281-291.
29. Brennan MF, Kattan MW, Klimstra D, Conlon K. Prognostic nomogram for patients undergoing resection for adenocarcinoma of the pancreas. *Ann Surg*. 2004;240(2):293-298.
30. Paniccia A, Hosokawa P, Henderson W, Schulick RD, Edil BH, McCarter MD, et al. Characteristics of 10-year survivors of pancreatic ductal adenocarcinoma. *JAMA Surg*. 2015;150(8): 701-710.
31. Groot VP, Gemenetzis G, Blair AB, Rivero-Soto RJ, Yu J, Javed AA, et al. Defining and predicting early recurrence in 957 patients with resected pancreatic ductal adenocarcinoma. *Ann Surg*. 2019;269(6):1154-1162.
32. Arvold ND, Niemierko A, Mamon HJ, Fernandez-del Castillo C, Hong TS. Pancreatic cancer tumor size on CT scan versus pathologic specimen: Implications for radiation treatment planning. *Int J Radiat Oncol Biol Phys*. 2011;80(5):1383-1390.
33. Krishna NB, LaBundy JL, Saripalli S, Safdar R, Agarwal B. Diagnostic value of EUS-FNA in patients suspected of having pancreatic cancer with a focal lesion on CT scan/MRI but without obstructive jaundice. *Pancreas*. 2009;38(6):625-630.
34. Marmor S, Burke EE, Portschy PR, Virnig BA, Jensen EH, Tuttle TM. Lymph node evaluation for treatment of adenocarcinoma of the pancreas. *Surg Oncol*. 2015;24(3):284-291.
35. Kalser MH, Ellenberg SS. Pancreatic cancer. Adjuvant combined radiation and chemotherapy following curative resection. *Arch surg*. 1960;120(8):899-903.
36. Liu W, Lu Y, Zhang D, Shi L, Zu G, Yan H, et al. MicroRNA-708 inhibits the proliferation and chemoresistance of pancreatic cancer cells. *Biocell*. 2020;44(1):73-80.
37. Huang H, Miao H, Wang J, Wu D, Lei Q, Wang S, et al. Advances on anticancer new drugs in China and the USA in 2020: From ongoing trial to drug approval. *J Natl Cancer Inst*. 2021;1(4):147-152.
38. Neoptolemos JP, Palmer DH, Ghaneh P, Psarelli EE, Valle JW, Halloran CM, et al. Comparison of adjuvant gemcitabine and capecitabine with gemcitabine monotherapy in patients with resected pancreatic cancer (ESPAC-4): A multicentre, open-label, randomised, phase 3 trial. *Lancet*. 2017;389(10073):1011-1024.