NOMOGRAM CONSTRUCTING AND VERIFYING OF PANCREATIC BODY AND TAIL NEUROENDOCRINE CARCINOMA PATIENTS

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ABSTRACT

Objective: To establish and evaluate a prognostic survival model for Pancreatic neuroendocrine carcinoma (panNEC) of body and tail based on the Surveillance, Epidemiology, and End Results (SEER).

Materials and methods: A retrospective study was conducted to collect data on panNEC of body and tail from the SEER database between 2005 and 2019, including clinical information and treatment regimens. A total of 246 patients were included, and they were randomly divided into a training set and a validation set at a ratio of 8:2. Based on independent risk factors identified through COX multivariate analysis, a nomogram model was constructed and compared with the performance of the 8th edition of the American Joint Committee on Cancer (AJCC) staging system in predicting survival.

Results: Tumor differentiation, age, and treatment modality were identified as independent risk factors for prognosis in patients with pancreatic endocrine tumors (P<0.05). The area under the receiver operating characteristic curve (AUROC) for the 1-year, 3-year, and 5-year overall survival rates for the nomogram in the training and validation sets were 0.850 vs. 0.992, 0.899 vs. 0.979, and 0.879 vs. 0.856, respectively. The nomogram had a higher AUROC compared than the AJCC staging. Calibration curves showed good calibration for the nomogram, and clinical decision curves showed that the nomogram had higher accuracy compared with the AJCC staging.

Conclusion: Based on the SEER database, the nomogram model can predict individualized survival outcomes for patients with panNEC of body and tail more accurately than the AJCC staging, providing a reference for treatment and follow-up.

KEYWORDS

SEER database, Pancreatic neuroendocrine carcinoma, Nomogram, Prognosis

https://doi.org/10.17993/3cemp.2024.130153.196-212

INDEX

https://doi.org/10.17993/3cemp.2024.130153.196-212

1. INTRODUCTION

In addition to pancreatic cancer, the second most common epithelial malignant tumor of the pancreas is pancreatic neuroendocrine neoplasms (panNEN), accounting for about 2%-5% of all pancreatic tumors. Its prognosis is often better than pancreatic cancer [1-3]. panNEN belongs to a type of neuroendocrine tumor and is transformed from APUD cells that originated from the endoderm during embryonic development. panNEN includes well-differentiated neuroendocrine tumors (panNET) and poorly differentiated neuroendocrine carcinomas (panNEC). Among them, panNEC is further classified into small cell type and large cell type. According to the 2022 WHO classification definition of neuroendocrine tumors, panNEN is classified into three grades based on mitotic rate and ki67 labeling index: G1 level (mitotic count <2/2mm² and/or ki67 index <3%); G2 level (mitotic count 2-20/2mm² and/or ki67 index 3%-20%); well-differentiated G3 level (mitotic count >20/HPF and/or ki67 index >20%) is called pancreatic high-grade neuroendocrine tumor (panNET). Poorly differentiated G3 level (mitotic count >20/2mm² and/or ki67 index >70%) is called pancreatic low-grade neuroendocrine carcinoma (panNEC). The incidence of panNEC is increasing year by year, with an incidence of about 0.8/100,000 in the United States and about 1.27/100,000 in Japan [4]. panNEC is classified into functional and non-functional types based on whether patients exhibit hormone-related clinical manifestations. Functional panNEC accounts for about 34%, including insulinoma, gastrinoma, somatostatinoma, vasoactive intestinal peptide tumor, glucagonoma, etc. Functional panNEC patients often exhibit symptoms of hormone over secretion, so they are usually detected and treated early in clinical practice. Non-functional panNEC accounts for about 66%, which usually has a concealed onset and no typical clinical manifestations in the early stage. It often presents with non-specific symptoms such as abdominal pain, abdominal distension, indigestion, weight loss, biliary tract obstruction, duodenal obstruction, jaundice, etc. The prognosis of pancreatic head and tail panNEC is different. Pancreatic tail panNEC has a lower incidence and this study explores the prognostic factors of pancreatic tail panNEC based on precision medicine concepts.

2. MATERIALS AND METHODS

The SEER database is one of the commonly used public databases in clinical practice. It includes a large number of retrospective clinical tumor studies in some US states and counties (about 35% of the US population). The data is easily accessible and publicly available free of charge, making it popular among researchers. The included tumors include breast cancer, colorectal cancer, lung cancer, prostate cancer, reproductive system tumors, lymphoma, leukemia, and other digestive system tumors as well as other types of tumors that have not yet been clearly identified. The included variables include the number of patients with the disease, age, race, time of diagnosis, tumor size, degree of differentiation, TNM staging, primary or metastatic, treatment method, radiotherapy and chemotherapy, survival time, and survival status at the last follow-up.

https://doi.org/10.17993/3cemp.2024.130153.196-212

This study used a retrospective cohort study method to retrospectively analyze the clinical data of 686 patients with pancreatic body and tail panNEC in the SEER database from 2005 to 2019. The following inclusion and exclusion criteria were used:

<I> Inclusion criteria:

1. Age ≥ 18 years old;
2. Lesion is a primary malignant tumor;
3. Have a clear TNM staging;
4. Follow-up information is complete;
5. Histological diagnosis of pancreatic body and tail neuroendocrine cancer, with histological code 8246/3 in the tumor disease classification code (ICD-O-3).

<II> Exclusion criteria:

1. Polymorphic tumor;
2. Follow-up information is incomplete;
3. Treatment method is unclear;
4. Tumor type and TNM staging are incomplete.

After strict inclusion and exclusion criteria, a total of 246 cases were included out of the original 686 data. The influencing factors studied included ethnicity, age, gender, marital status, number of primary tumors, tumor size, TNM stage, tumor differentiation, chemotherapy, and surgical intervention. The observation indices were the overall survival time (OS), which refers to the time interval from the date of diagnosis to death due to any cause, and the survival status at the last follow-up.

Collected clinical data and treatment methods of patients with pancreatic body and tail panNEC diagnosed clinically from the SEER database between 2005 and 2019. 246 collected data were randomly divided into a training set and a validation set at a ratio of 8:2. The training set was used for model establishment and internal validation, while the validation set was used for external validation. IBM SPSS was used for data analysis. Factors with significant univariate Cox regression analysis ($p<0.05$) were included in multivariate Cox regression analysis. Variables with $p<0.05$ in multivariate Cox analysis were plotted using the Kaplan-Meier survival curve. Multivariate analysis results ($p<0.05$) were used to construct nomograms using RStudio, and compared with the eighth edition of the American Joint Committee on Cancer (AJCC) staging system. The prognostic performance of the models was compared using consistency index (C-index), calibration curve, and area under the receiver operating characteristic curve (AUROC). Decision curve analysis (DCA) was used to quantify the net benefit at different threshold probabilities to evaluate the clinical utility of the model.

https://doi.org/10.17993/3cemp.2024.130153.196-212

3. RESULTS

The 246 cases were randomly divided into a training set (197 cases) and a validation set (49 cases) at a ratio of 8:2. The baseline data of the patients is shown in Table 1.

COX univariate analysis using IBM SPSS produced the following results: race (p=0.64), gender (p=0.44), age (p=0.01), marital status (p=0.39), T staging (p<0.01), N staging (p=0.09), M staging (p<0.01), tumor size (p<0.01), tumor number (p=0.25), systemic therapy (p=0.41), tumor differentiation (p<0.01), and surgical intervention (p<0.01). The variables with p<0.05 in the COX univariate analysis were included in the COX multivariate analysis, which produced the following results: age (p<0.01), T staging (p=0.96), M staging (p=0.40), tumor size (p=0.93), tumor differentiation (p<0.01), and surgical intervention (p<0.01). The training set univariate and multivariate analysis results are shown in Table 2.

Table 1. Characteristics of training cohort and validation cohort

Variable	Total (n=246)	Training Cohorts (n=197)	Validation Cohorts (n=49)
Age			
≤54	74 (30.08%)	62 (31.47%)	12 (24.49%)
55~74	137 (55.69%)	109 (55.33%)	28 (57.14%)
≥75	35 (14.23%)	26 (13.20%)	9 (18.37%)
Gender			
Male	146 (59.35%)	115 (58.38%)	31 (63.27%)
Female	100 (40.65%)	82 (41.62%)	18 (36.73%)
Race			
White	181 (73.58%)	146 (74.11%)	35 (71.43%)
Black	25 (10.16%)	21 (10.66%)	4 (8.16%)
Other	40 (16.26%)	30 (15.23%)	10 (20.41%)
Marital status			
Married	159 (64.63%)	127 (64.47%)	32 (65.31%)
Unmarried	87 (35.37%)	70 (35.53%)	17 (34.69%)
Chemotherapy			
Yes	20 (8.13%)	17 (8.63%)	3 (6.12%)
No	226 (91.87%)	180 (91.37%)	46 (93.88%)
Surgery			

https://doi.org/10.17993/3cemp.2024.130153.196-212

Yes	207 (84.15%)	163 (82.74%)	44 (89.80%)
No	39 (15.85%)	34 (17.26%)	5 (10.20%)
T			
T1	73 (29.67%)	57 (28.93%)	16 (32.65%)
T2	81 (32.93%)	64 (32.49%)	17 (34.69%)
T3	77 (31.30%)	64 (32.49%)	13 (26.53%)
T4	15 (6.10%)	12 (6.09%)	3 (6.12%)
N			
N0	168 (68.29%)	133 (67.51%)	35 (71.43%)
N1	78 (31.71%)	64 (32.49%)	14 (28.57%)
M			
M0	182 (73.98%)	145 (73.60%)	37 (75.51%)
M1	64 (26.02%)	52 (26.40%)	12 (24.49%)
Differentiation			
Highly	165 (67.07%)	137 (69.54%)	28 (57.14%)
Moderately	47 (19.11%)	32 (16.24%)	15 (30.61%)
Poorly	34 (13.82%)	28 (14.21%)	6 (12.24%)
Tumor size			
≤2cm	81 (32.93%)	63 (31.98%)	18 (36.73%)
＞2cm	165 (67.07%)	134 (68.02%)	31 (63.27%)
Tumor number			
Single	170 (69.11%)	139 (70.56%)	31 (63.27%)
Multiple	76 (30.89%)	58 (29.44%)	18 (36.73%)

https://doi.org/10.17993/3cemp.2024.130153.196-212

Table 2. Univariate and multivariate analysis for panNEC of the training cohort.

Variable	Univariate analysis HR(95%CI)	P-value	Multivariate analysis HR(95%CI)	P-value
Age				
≤54	2.274(1.382-3.743)	0.01	0.831 (0.337-2.049)	688
55~74			4.131 (1.615-10.562)	3
≥75				
Gender				
Male	1.289(0.673-2.470)	444		
Female				
Race				
White	1.101(0.737-1.645)	639		
Black				
Other				
Marital status				
Married	0.757(0.402-1.426)	389		
Unmarried				
Chemotherapy				
Yes	1.483(0.581-3.788)	410		
No				
Surgery				
Yes	0.076(0.039-0.151)	＜0.01	0.195 (0.070-0.542)	＜0.01
No				
T				
T1	2.158 (1.489-3.130)	＜0.01	——	938
T2				938
T3				940
T4				——
N				

https://doi.org/10.17993/3cemp.2024.130153.196-212

N0	1.703 (0.913-3.177)	94		
N1				
M				
M0	4.832 (2.582-9.040)	＜0.01	1.452 (0.615-3.429)	395
M1				
Differentiation				
Highly	3.275(2.274-4.717)	＜0.01	1.860 (0.690-5.017)	220
Moderately			4.367 (1.714-11.123)	＜0.01
Poorly			——	——
Tumor size				
≤2cm	9.618 (2.319-39.900)	＜0.01	——	926
＞2cm				
Tumor number				
Single	1.455 (0.766-2.766)	252		
Multiple				

The univariate analysis showed that age, T staging, M staging, surgery, tumor size, and tumor differentiation were related factors affecting the prognosis of patients with pancreatic body and tail panNEC ($p<0.05$). Multivariate analysis showed that age, tumor differentiation, and surgical intervention were independent risk factors for the prognosis of patients with pancreatic body and tail panNEC ($p<0.05$). Based on the results of the three multivariate analyses, a Kaplan-Meier curve was plotted, as shown in Figure 1.

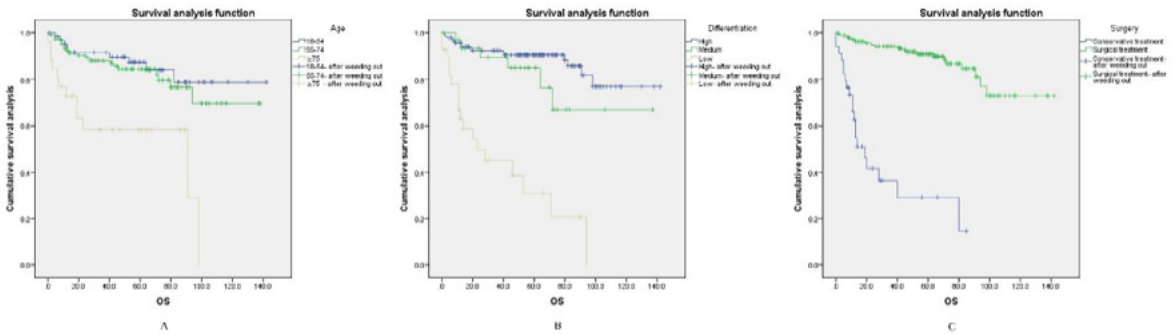

Figure 1. Kplan-Meier analysis for independent risk factor of panNEC: age(A), differentiation (B), surgery (C)

From Figure 1, it can be observed that as survival time increases, patients of older age have a faster decrease in survival probability. Patients who receive conservative

https://doi.org/10.17993/3cemp.2024.130153.196-212

treatment have a faster decrease in survival probability compared to those who undergo surgery. Additionally, lower tumor differentiation corresponds to a faster decrease in survival probability. This is consistent with previous research findings.

3.1. CONSTRUCTION OF NOMOGRAM

Nomogram, also known as an alignment diagram, is a graph that uses a family of disjoint line segments in a two-dimensional Cartesian coordinate system to represent a function with two independent variables. This type of graph is primarily used to express the relationships between variables in predictive models and can be applied in many fields, including medicine, meteorology, and economics.

In the field of medicine, nomograms can combine various clinical characteristics to predict individualized outcomes, allowing for more convenient and rapid access to targeted predictive outcomes, as well as intuitive observation of the results of regression analysis. For example, in tumor prognosis studies, nomograms can be used to predict the survival, prognosis, and recurrence risk of tumor patients. By constructing a multi-factor regression model, integrating multiple predictive indicators, and then using a graduated line segment drawn on a common plane according to a certain proportion, the relationship between each variable in the predictive model can be expressed. In this way, researchers can intuitively understand the patient's condition, predict the disease's development trend, and evaluate the treatment effect by observing the nomogram based on the patient's specific situation.

According to the results of the three COX multivariate analyses, we used RStudio to construct nomograms for predicting 1-, 3-, and 5-year survival rates. (Figure 2)

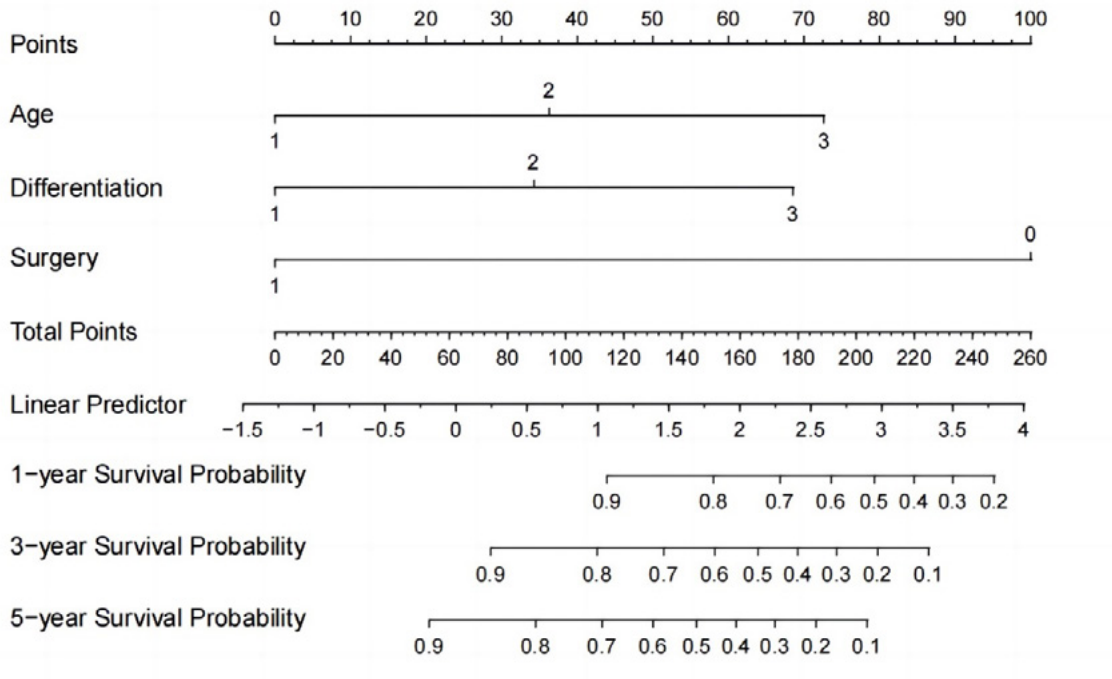

Figure 2. Prognostic nomogram for patients with pancreatic body and tal panNEC

https://doi.org/10.17993/3cemp.2024.130153.196-212

3.2. VALIDATION OF NOMOGRAM:

The C-index of Nomogram in the training set was 0.835, and in the validation set was 0.861. Calibration curves of Nomogram and AJCC staging were plotted in the training and validation sets (Figure 3). The 1-year overall survival rate calibration curve of Nomogram was in good agreement with the ideal slope of 1, suggesting that compared with AJCC staging, using the Nomogram established in this study to predict overall survival rate was more consistent with the actual results and more accurate. ROC curves of Nomogram and AJCC staging were plotted in the training and validation sets, including 1-year, 3-year, and 5-year survival rates (Figure 4). In the training set, the AUROC of Nomogram was 0.850, 0.899, and 0.879, while the AUROC of AJCC staging was 0.875, 0.830, and 0.777; in the validation set, the AUROC of Nomogram was 0.992, 0.979, and 0.856, while the AUROC of AJCC staging was 0.832, 0.817, and 0.836. From the above data, it can be seen that both in the training and validation sets, Nomogram had higher C-index and AUROC, showing better predictive performance without significant overfitting. To further evaluate the clinical value of Nomogram, clinical decision curves for 1-year, 3-year, and 5-year overall survival rates were plotted (Figure 5). The trend of DCA curve represented the predictive ability and accuracy of the model under different decision thresholds. The upper the curve is, the higher the predictive ability and accuracy of the model are. Obviously, DCA curve showed that Nomogram had better predictive efficiency than AJCC staging in this study.

https://doi.org/10.17993/3cemp.2024.130153.196-212

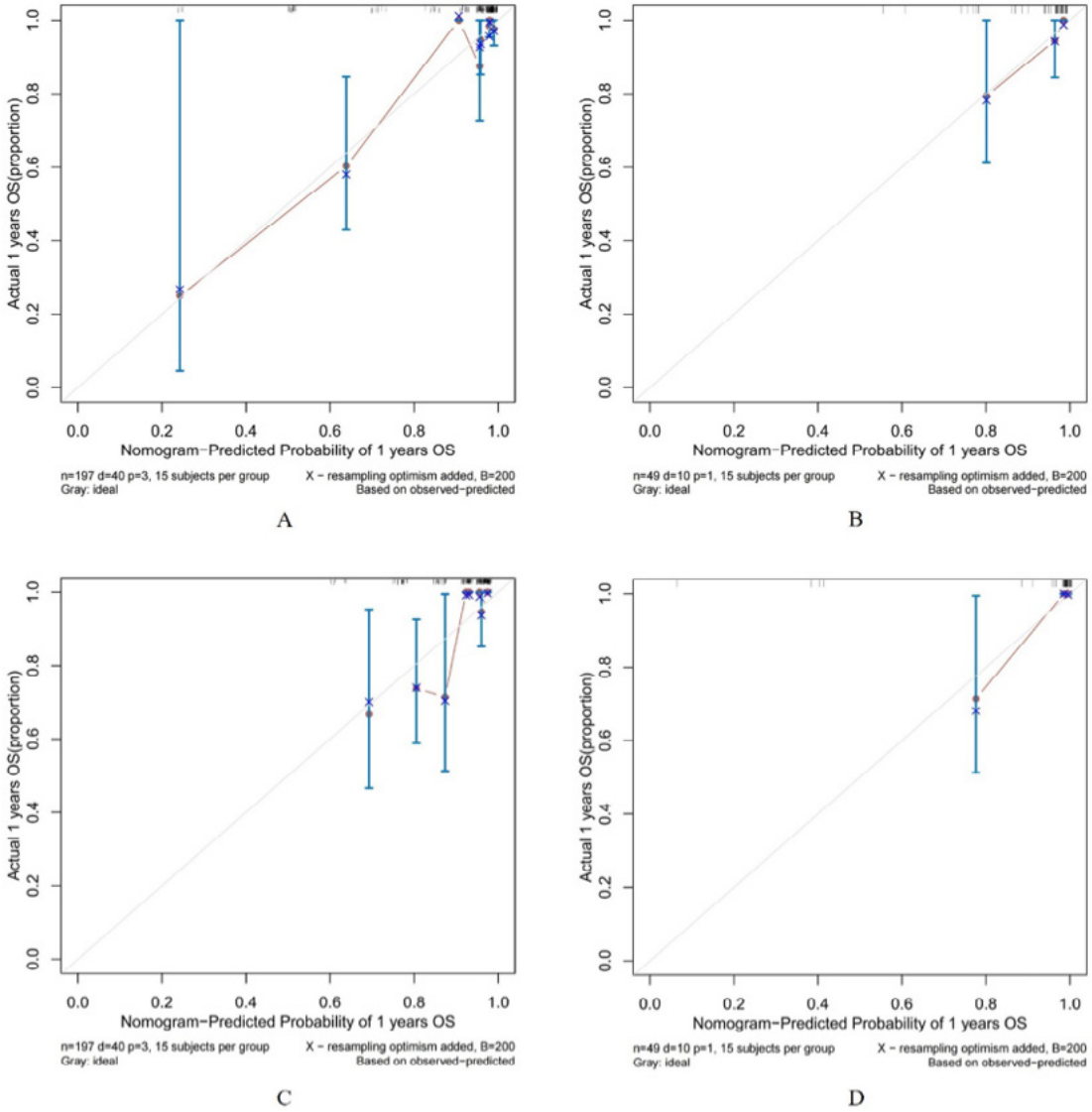

Figure 3. Calibrationcurves of nomogram and AJCC staging (A: training calibrationcurve, B: validation calibrationcurve, C: AJCC training calibrationcurve, D: AJCC calibrationcurve)

https://doi.org/10.17993/3cemp.2024.130153.196-212

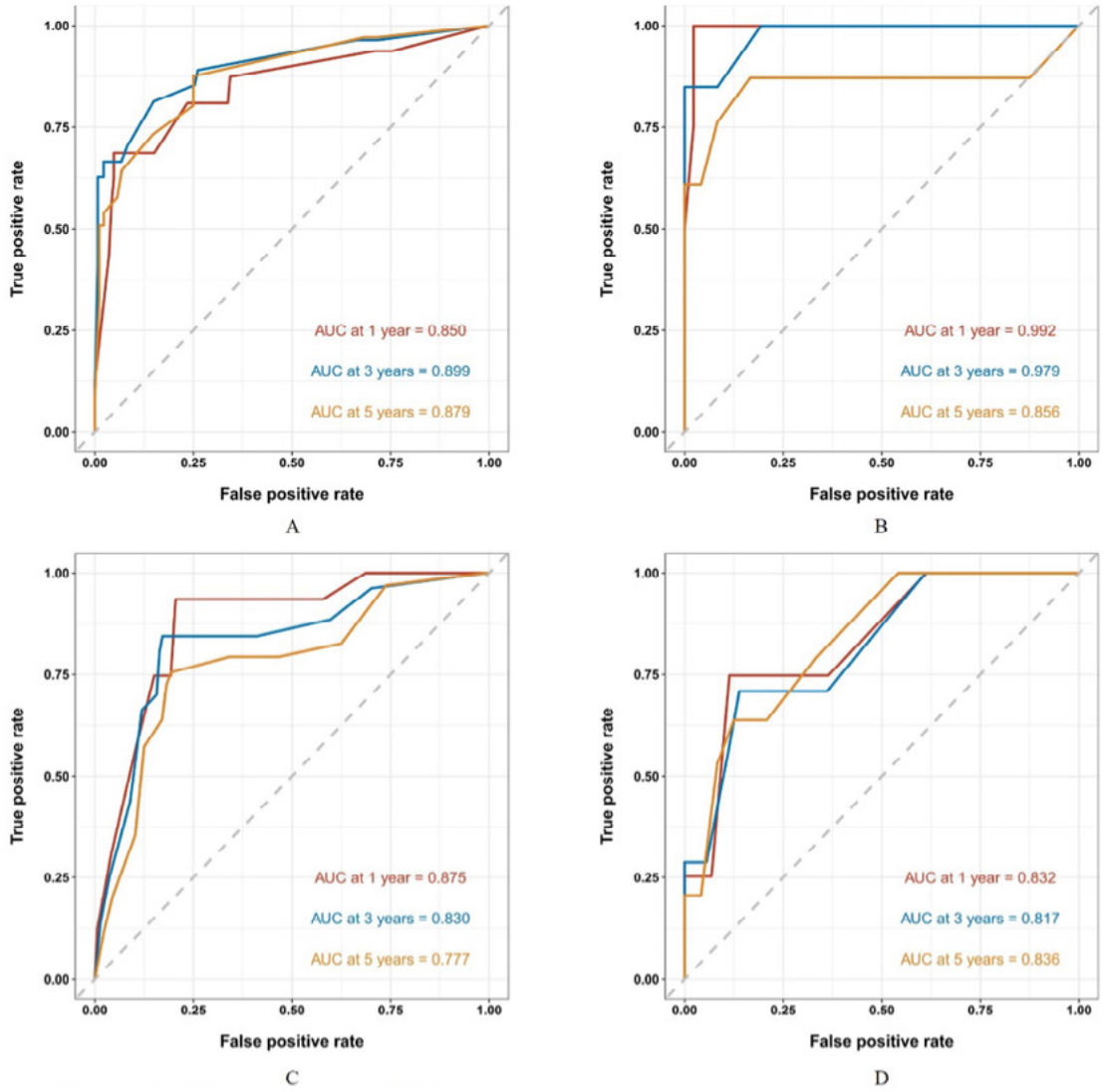

Figure 4. AUROC of nomogram and AJCC staging (A: training AUROC, B: validation AUROC C: AJCC training AUROC D: AJCC validation AUROC)

https://doi.org/10.17993/3cemp.2024.130153.196-212

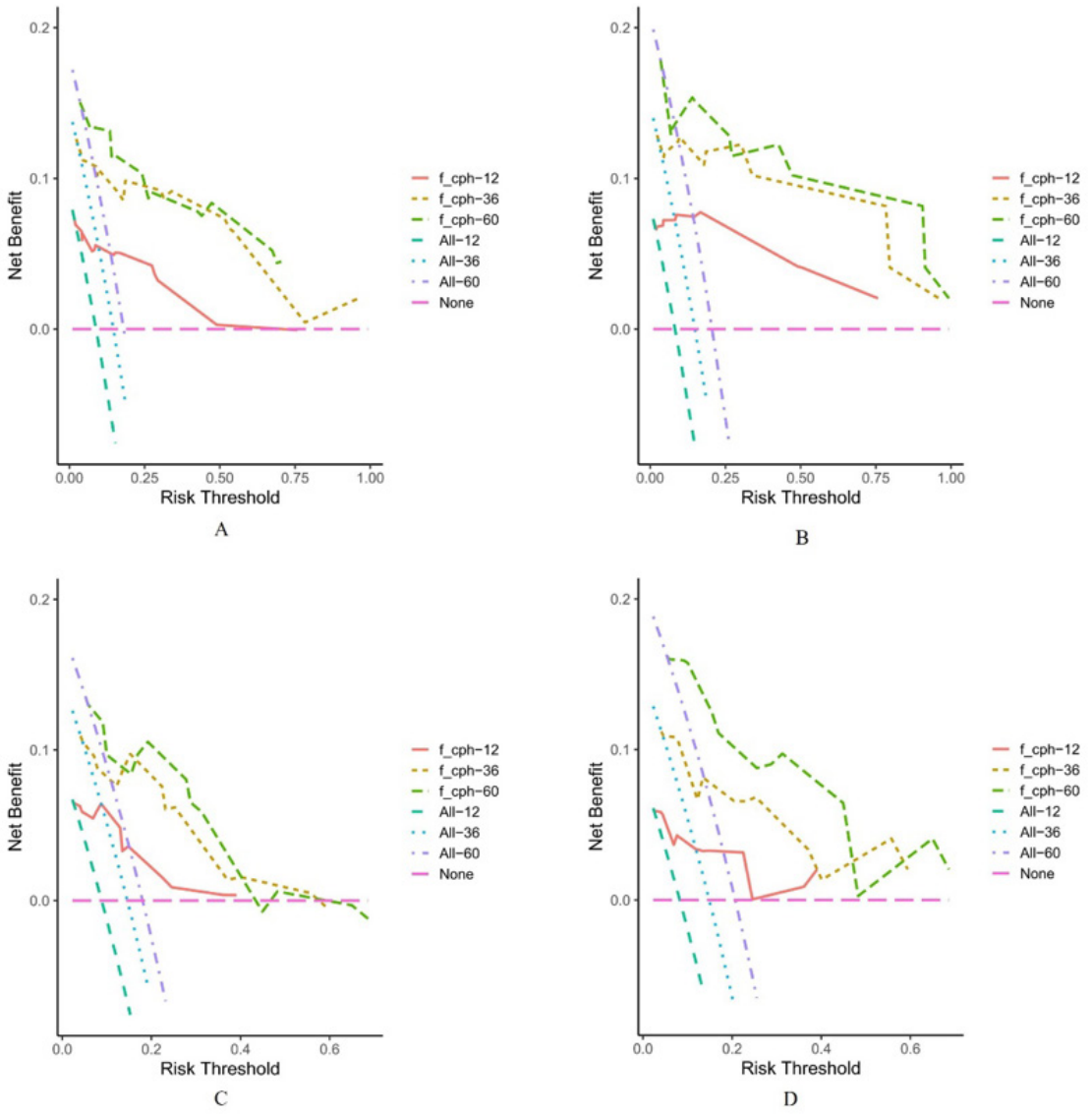

Figure 5. Decision curve of nomogram and AJCC staging (a: DCA of training, b: DCA of validation, c: DCA of AJCC training, d: DCA of AJCC validation)

4. DISCUSSION

4.1. THE IMPACT OF AGE ON PROGNOSIS

The COX multivariate analysis shows that age is an independent risk factor for the prognosis of patients with pancreatic endocrine neoplasms (panNEC) in the body and tail of the pancreas. This may be related to the following aspects:

1. Previous studies have shown that with increasing age, immune function decreases and DNA repair abnormalities increase, which directly leads to tumorigenesis [5]. Epidemiological investigations have also suggested that elderly patients with cancer have a poor prognosis, which is consistent with the conclusion of this study.

https://doi.org/10.17993/3cemp.2024.130153.196-212

2. The mechanism of poor prognosis in elderly patients may be related to the overactivation of related signaling pathways [6]. Compared with non-elderly patients, there are differences in the expression of tumor-related genes in elderly patients. With increasing age, mutations in tumor suppressor genes lead to the loss of control of tumor signaling, with the Akt/mTOR-representing pro-tumor signaling pathway expression increasing, making tumors more prone to development, growth, and metastasis.

3. Elderly patients often have more underlying diseases, more conservative treatment options, early symptoms not obvious, poor family economic conditions, and less active treatment, which leads to a worse prognosis compared to younger patients.

4.2. THE IMPACT OF SURGERY ON PROGNOSIS

The COX multivariate analysis shows that surgical resection is an independent risk factor for the prognosis of patients with pancreatic endocrine neoplasms (panNEC) in the body and tail of the pancreas. The Kaplan-Meier curve shows that patients who undergo surgery have a better prognosis than those who receive conservative treatment. This is consistent with previous literature reports, where surgical treatment is the preferred treatment option for most resectable panNEC patients [7-8]. Surgery can reduce disease-related symptoms, alleviate patient suffering, and improve quality of life and survival time. Whether patients with metastatic panNEC require aggressive surgical intervention has long been controversial. Some studies have shown that for patients with panNEC who cannot undergo radical resection, debulking surgery (removing as much of the tumor as possible, including the primary tumor and metastatic deposits) can also alleviate clinical symptoms and improve long-term outcomes [9-12]. Haugvik [13]and colleagues studied 119 patients with panNEC and found that patients who underwent radical resection had a 3-year survival rate of 69%. Even for patients with metastatic disease, removing the primary tumor can improve patient prognosis. For elderly patients, patients with poor general condition, or patients who cannot tolerate surgery, if conservative treatment has no significant effect, palliative surgery can still be performed to treat tumor-related complications [14].

4.3. THE EFFECT OF TUMOR DIFFERENTIATION ON PROGNOSIS

The COX multivariate analysis shows that tumor differentiation is an independent risk factor for the prognosis of patients with pancreatic endocrine neoplasms (panNEC) in the body and tail of the pancreas. The degree of tumor differentiation has a significant impact on the prognosis of panNEC. Generally speaking, the higher the degree of tumor differentiation, the better the prognosis is usually. This is consistent with multi-center studies [15-18]. In panNEC, well differentiated tumors have a cell

https://doi.org/10.17993/3cemp.2024.130153.196-212

morphology and biological behavior similar to normal neuroendocrine cells, with a lower proliferation rate and lower aggressiveness. This type of tumor is usually associated with a good prognosis and a longer survival time after surgical resection. In contrast, poorly differentiated tumors have a cell morphology and biological behavior that differ significantly from normal neuroendocrine cells, with a higher proliferation rate and stronger aggressiveness. This type of tumor is prone to metastasis and recurrence, usually has a poor prognosis, and a shorter survival time.

4.4. THE SHORTCOMINGS OF THIS STUDY

Despite the large volume of data in the SEER database, which covers a majority of the US population and has follow-up data for each patient, this study extracted data with the same characteristics. However, there are still some unavoidable limitations: (1) The database does not include specific information on radiotherapy and chemotherapy, with only whether the patient received chemotherapy being recorded, without specific regimens and doses; radiotherapy information only includes the site and some techniques (such as particle implantation or external irradiation, etc.), without important treatment information such as surgical margin status. (2) The follow-up outcome only includes death and the cause of death, which limits research on recurrence, metastasis, or progression. (3) Some cases in the database have incompletely recorded surgical methods.

5. CONCLUSION

In summary, in this study, age, treatment modality, and tumor differentiation were independent risk factors for the prognosis of patients with pancreatic endocrine neoplasms in the body and tail ($p<0.05$). The nomogram based on the SEER database can more accurately assess patient prognosis and predict survival time, providing a feasible prediction model for clinicians to better individualize treatment plans for patients, which has certain significance.

REFERENCES

(1) Jeune F, Taibi A, Gaujoux S. Update on the Surgical Treatment of Pancreatic Neuroendocrine Tumors. Scand J Surg. 2020 Mar;109(1):42-52. doi: 10.1177/1457496919900417.

(2) Fang JM, Shi J. A Clinicopathologic and Molecular Update of Pancreatic Neuroendocrine Neoplasms With a Focus on the New World Health Organization Classification. Arch Pathol Lab Med. 2019 Nov;143(11):1317-26. doi: 10.5858/arpa.2019-0338-RA.

(3) Mpilla GB, Philip PA, El-Rayes B, Azmi AS. Pancreatic neuroendocrine tumors: Therapeutic challenges and research limitations. World J Gastroenterol. 2020 Jul 28;26(28):4036-54. doi: 10.3748/wjg.v26.i28.4036.

(4) Regolo M, et al. Pancreatic Neuroendocrine Tumor (Pan-NET) Presented by Abdominal Pain: A Case Report and Literature Review. J Clin Med. 2023 Oct 19;12(20). doi: 10.3390/jcm12206617.

https://doi.org/10.17993/3cemp.2024.130153.196-212

(5) Van Herck Y, et al. Is cancer biology different in older patients? Lancet Healthy Longev. 2021 Oct;2(10). doi: 10.1016/s2666-7568(21)00179-3.

(6) Marchese U, et al. Multimodal Management of Grade 1 and 2 Pancreatic Neuroendocrine Tumors. Cancers (Basel). 2022 Jan 15;14(2). doi: 10.3390/cancers14020433.

(7) Akerström G, Hellman P, Hessman O, Osmak L. Surgical treatment of endocrine pancreatic tumours. Neuroendocrinology. 2004;80 Suppl 1:62-6. doi: 10.1159/000080744.

(8) Maharjan CK, Ear PH, Tran CG, Howe JR, Chandrasekharan C, Quelle DE. Pancreatic Neuroendocrine Tumors: Molecular Mechanisms and Therapeutic Targets. Cancers (Basel). 2021 Oct 12;13(20). doi: 10.3390/cancers13205117.

(9) Kjaer J, et al. Benefit of Primary Tumor Resection in Stage IV, Grade 1 and 2, Pancreatic Neuroendocrine Tumors: A Propensity-Score Matched Cohort Study. Ann Surg Open. 2022 Mar;3(1). doi: 10.1097/as9.0000000000000151.

(10) Sarmiento JM, Heywood G, Rubin J, Ilstrup DM, Nagorney DM, Que FG. Surgical treatment of neuroendocrine metastases to the liver: a plea for resection to increase survival. J Am Coll Surg. 2003 Jul;197(1):29-37. doi: 10.1016/s1072-7515(03)00230-8.

(11) Li AY, Visser BC, Dua MM. Surgical Indications and Outcomes of Resection for Pancreatic Neuroendocrine Tumors with Vascular Involvement. Cancers (Basel). 2022 May 6;14(9). doi: 10.3390/cancers14092312.

(12) Zhang X, et al. A Nomogram to Accurately Identify Pancreatic Neuroendocrine Tumors Metastasizing to Distant Organs: A Study Based on Two National Population-Based Cohorts From the United States and China. Clin Med Insights Oncol. 2022;16:11795549221099853. doi: 10.1177/11795549221099853.

(13) Foubert F, et al. Survival and prognostic factors analysis of 151 intestinal and pancreatic neuroendocrine tumors: a single center experience. J Gastrointest Oncol. 2019 Feb;10(1):103-11. doi: 10.21037/jgo.2018.09.13.

(14) Wu Z, Wang W, Zhang K, Fan M, Lin R. The impact of surgery and survival prediction in patients with gastroenteropancreatic neuroendocrine tumors: a population-based cohort study. Int J Surg. 2023 Jun 1;109(6):1629-38. doi: 10.1097/js9.0000000000000336.

(15) Crook C, Zhang YH, Li D. Pharmacotherapeutic Management of Well-Differentiated Neuroendocrine Tumors in Older Patients: Current Status and Potential Therapies. Drugs Aging. 2022 Apr;39(4):257-69. doi: 10.1007/s40266-022-00934-1.

(16) Li X, et al. Risk factors for lymph node metastasis in gastric neuroendocrine tumor: a retrospective study. BMC Surg. 2021 Mar 31;21(1):174. doi: 10.1186/s12893-021-01174-7.

(17) Wang H, et al. Validation and modification of staging Systems for Poorly Differentiated Pancreatic Neuroendocrine Carcinoma. BMC Cancer. 2020 Mar 6;20(1):188. doi: 10.1186/s12885-020-6634-9.

(18) Chopde, et al. Prognostic predictors for recurrence following curative resection in grade I/II pancreatic neuroendocrine tumours. Langenbecks Arch Surg. 2023 May 22;408(1):204. doi: 10.1007/s00423-023-02943-z

https://doi.org/10.17993/3cemp.2024.130153.196-212