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Reviewer A

The study is aimed at proposing a nomogram with a prognostic value for patients > 50 yrs affected by neuroendocrine carcinomas of pancreatic origin.

The idea is valid and with a good potential impact on clinical practice. However, I consider the present results as affected by a significant bias: the inclusion of therapeutic options as a variable for univariate/multivariate analysis. In fact, a patient eligible for surgery is expected to have a more limited disease (and thus with a better prognosis) than another one candidate to palliative radiotherapy, or palliative chemo, or no treatment. We also have to consider that a nomogram is useful especially when prognosis can be predicted at diagnosis, and not necessarily during treatments.

Response: Thank you for your comment. Regarding whether treatment methods should be included in the analysis, due to the rarity of PanNEC and its poor survival rates, there are few large cohort studies on treatment prognosis for PanNEC[1]. Meanwhile, a recent publication has also utilized treatments variables to construct a nomogram for the survival of PanNEC with liver metastasis[2].Therefore, we believe including such factors has a certain clinical significance and conducting multivarivate cox regression analysis (see Page 5, Lines 97; Page 6, Lines 98-100; Page 7, Lines 117-137; Page 8, Lines 138-140). However, we also agree with your opinion and have performed a Cox regression analysis excluding treatment-related variables (Table S1) and developed a nomogram (Figure S2), which is included in the supplementary materials.

Reference:

1. *Sorbye H, Grande E, Pavel M, Tesselaar M, Fazio N, Reed NS, Knigge U, Christ E, Ambrosini V, Couvelard A, Tiensuu Janson E. European Neuroendocrine Tumor Society (ENETS) 2023 guidance paper for digestive neuroendocrine carcinoma. J Neuroendocrinol. 2023 Mar;35(3):e13249. doi: 10.1111/jne.13249. Epub 2023 Mar 16. PMID: 36924180.*

2. *Luo W, Zhang T. Primary tumor resection enhances the survival of pancreatic neuroendocrine carcinoma patients with liver metastasis under the definition of 2019 WHO classification. J Cancer Res Clin Oncol. 2023 Sep;149(11):9201-9212. doi: 10.1007/s00432-023-04847-3. Epub 2023 May 15. PMID: 37184680.*

We now stated the revised sentences and Tables as follows:

"Materials and Methods

...We performed multivariate Cox regression analyses both including and excluding treatments in the training set .The results of univariate and multivariate Cox proportional hazards regression were expressed as hazard ratios and 95% confidence intervals. Variables with significance (P < 0.05) from the multivariate Cox regression were used to construct nomograms, either incorporating treatments or excluding them.

"Results

Independent risk factors for CSS in patients with elderly-onset PanNEC

We conducted univariate and multivariate Cox regression analyses in the training group, which consisted of 244 individuals, 184(75.4%) of whom experienced the outcome event. Univariate Cox regression analysis showed that age, TNM stage, liver metastasis, surgery, chemotherapy and lung metastasis were significantly (p<0.05) correlated with CSS. Multivariate Cox analysis showed that age (HR:1.56, 95%CI:1.10-2.22, P=0.013), surgery (HR:2.23, 95%CI:1.27-4.23, P=0.006), chemotherapy (HR:2.39, 95%CI:1.68-3.38, P＜0.001), TNM stage (HR:3.96, 95%CI:1.19-13.19, P=0.025), and liver metastasis (HR:1.75, 95%CI:1.16-2.65, P=0.008) were independent prognostic factors for CSS in patients with elderly-onset PanNEC (Table 2).

Furthermore, we also excluded several treatment variables in both univariate and multivariate Cox regression analyses. We found that age (HR:2.25, 95%CI:1.63-3.10, P＜0.001), TNM stage (HR:4.12, 95%CI:1.27-13.40, P=0.019), and liver metastasis (HR:1.76, 95%CI:1.17-2.66, P=0.007) were independent risk factors affecting patient prognosis (Table S1).

Construction and validation of a nomogram for predicting CSS in patients with elderly-onset PanNEC

The nomogram was based on independent variables of the training set (Figure 2). The most significant risk factor for CSS was TNM stage (Figure S1). We also developed a nomogram that excluded treatment, as shown in Figure S2. The calibration curve based on independent prognostic factors incorporating treatment demonstrated consistent predicted and observed results for 6-month, 1-year, and 2-year CSS (Figure 3). The calibration curve excluding treatments yielded similar results (Figure S3). The AUCs for 6-month, 1-year, and 2-year CSS in the model incorporating treatment were 0.826, 0.791, and 0.800 in the training set and 0.848, 0.775, and 0.781 in the validation set (Figure 4), while the model excluding treatment achieved AUCs of 0.725, 0.758, and 0.807 in the training set and 0.692, 0.683, and 0.695 in the validation set (Figure S4), demonstrating high accuracy in predicting CSS. Furthermore, DCA indicated that the nomogram had clinical benefits (Figure 5, FigureS5).

Table S1: Univariate and multivariate cox regression analyses of prognostic factors for CSS of elderly-onset PanNEC without treatment.

Variables	Univariate analysis		Multivariate analysis	
	HR (95%CI)	*P value*	HR (95%CI)	*P value*
Age				
<75	1.00 (Reference)		1.00 (Reference)	
≥75	2.09 (1.54 ~ 2.85)	<.001	2.25 (1.63 ~ 3.10)	<.001
Sex				
Female	1.00 (Reference)			

Male	0.97 (0.72 ~ 1.30)	0.830		
Race				
White	1.00 (Reference)			
Black	1.06 (0.69 ~ 1.64)	0.793		
Others	1.05 (0.64 ~ 1.71)	0.855		
Marital status				
Married	1.00 (Reference)			
Others	0.84 (0.61 ~ 1.16)	0.292		
Primary site				
Body and Tail	1.00 (Reference)			
Head	1.26 (0.88 ~ 1.80)	0.205		
Others	1.32 (0.89 ~ 1.97)	0.169		
Tumor size				
≤20	1.00 (Reference)			
21-40	0.74 (0.39 ~ 1.38)	0.340		
>40	0.83 (0.45 ~ 1.51)	0.539		
Unknown	0.89 (0.45 ~ 1.75)	0.727		
TNM stage				
I	1.00 (Reference)		1.00 (Reference)	
II/III	3.51 (1.04 ~ 11.79)	0.042	2.88 (0.84 ~ 9.87)	0.093
IV	5.97 (1.89 ~ 18.87)	0.002	4.12 (1.27 ~ 13.40)	0.019
Liver metastasis				
No	1.00 (Reference)		1.00 (Reference)	
Yes	2.04 (1.46 ~ 2.84)	<.001	1.76 (1.17 ~ 2.66)	0.007
Lymph nodes metastasis				

No	1.00 (Reference)			
Yes	0.94 (0.68 ~ 1.29)	0.704		
Unknown	0.93 (0.48 ~ 1.77)	0.816		
Bone metastasis				
No	1.00 (Reference)			
Yes	1.29 (0.82 ~ 2.01)	0.271		
Unknown	2.34 (0.95 ~ 5.72)	0.063		
Brain metastasis				
No	1.00 (Reference)			
Yes	1.34 (0.55 ~ 3.28)	0.521		
Unknown	2.18 (0.96 ~ 4.94)	0.063		
Lung metastasis				
No	1.00 (Reference)		1.00 (Reference)	
Yes	0.99 (0.66 ~ 1.50)	0.976	0.80 (0.53 ~ 1.22)	0.309
Unknown	3.70 (1.35 ~ 10.12)	0.011	2.34 (0.85 ~ 6.44)	0.101

Another relevant bias to consider is declared in the discussion at lines 165-167: "....part of the PNEC in the SEER database diagnosed before 2010 was classified as 167 NET G3". The Authors must exclude these cases!

Response: Thank you for your comment. We re-screened the SEER database according to the 2019 WHO criteria for pancreatic neuroendocrine tumors, selecting patients with ICD-O-3 codes 8013 (Large cell neuroendocrine carcinoma) and 8041 (Small cell carcinoma, NOS) with primary sites in the pancreas. Due to database updates, we included data from 2010 to 2021, excluding data prior to 2010.(See Page 5, Lines 70-73) The clinical features of the patients are summarized in Table 1.

We now stated the revised sentences and Table1 as follows:

"Materials and Methods

*Eligible patients were screened from the SEER database using SEER*Stat version 8.4.3. According to the latest WHO classification criteria, we collected data from the SEER database for patients diagnosed between 2010 and 2021, with primary tumors in the pancreas and histological codes ICD-O-3 8013 (Large cell*

neuroendocrine carcinoma) and 8041 (Small cell carcinoma, NOS). The exclusion criteria were (1) patients with missing demographic and crucial clinical information, (2) patients aged <50 years at diagnosis, and (3) patients with incomplete survival data.

Table 1. Demographic and clinicopathological characteristics in patients with elderly-onset PanNEC.

Variables	Total set (n=407)	Training set (n=244)	Validation set (n=163)	*P value*
Age, n(%)				0.373
<75	282 (69.29)	165 (67.62)	117 (71.78)	
≥75	125 (30.71)	79 (32.38)	46 (28.22)	
Sex, n(%)				0.697
Female	180 (44.23)	106 (43.44)	74 (45.40)	
Male	227 (55.77)	138 (56.56)	89 (54.60)	
Race, n(%)				0.939
White	313 (76.90)	189 (77.46)	124 (76.07)	
Black	49 (12.04)	29 (11.89)	20 (12.27)	
Others	45 (11.06)	26 (10.66)	19 (11.66)	
Marital status, n(%)				0.736
Married	281 (69.04)	170 (69.67)	111 (68.10)	
Others	126 (30.96)	74 (30.33)	52 (31.90)	
Primary site, n(%)				0.962
Body and Tail	112 (27.52)	66 (27.05)	46 (28.22)	
Head	183 (44.96)	110 (45.08)	73 (44.79)	
Others	112 (27.52)	68 (27.87)	44 (26.99)	
Tumor size, n(%)				0.915
≤20	29 (7.13)	16 (6.56)	13 (7.98)	
21-40	124 (30.47)	76 (31.15)	48 (29.45)	
>40	190 (46.68)	115 (47.13)	75 (46.01)	
Unknown	64 (15.72)	37 (15.16)	27 (16.56)	
Surgery, n(%)				0.710
Yes	47 (11.55)	27 (11.07)	20 (12.27)	
No	360 (88.45)	217 (88.93)	143 (87.73)	
Radiation, n(%)				0.101
Yes	47 (11.55)	23 (9.43)	24 (14.72)	
No/Unknown	360 (88.45)	221 (90.57)	139 (85.28)	
Chemotherapy, n(%)				0.921
Yes	251 (61.67)	150 (61.48)	101 (61.96)	
No/Unknown	156 (38.33)	94 (38.52)	62 (38.04)	
TNM stage, n(%)				0.985
I	18 (4.42)	11 (4.51)	7 (4.29)	
II/III	46 (11.30)	28 (11.48)	18 (11.04)	
IV	343 (84.28)	205 (84.02)	138 (84.66)	
Liver metastasis, n(%)				0.651

No	125 (30.71)	77 (31.56)	48 (29.45)	
Yes	282 (69.29)	167 (68.44)	115 (70.55)	
Lymph nodes metastasis, n(%)				0.190
No	270 (66.34)	156 (63.93)	114 (69.94)	
Yes	122 (29.98)	76 (31.15)	46 (28.22)	
Unknown	15 (3.69)	12 (4.92)	3 (1.84)	
Bone metastasis, n(%)				0.822
No	351 (86.24)	209 (85.66)	142 (87.12)	
Yes	47 (11.55)	30 (12.30)	17 (10.43)	
Unknown	9 (2.21)	5 (2.05)	4 (2.45)	
Brain metastasis, n(%)				0.012
No	373 (91.65)	230 (94.26)	143 (87.73)	
Yes	23 (5.65)	7 (2.87)	16 (9.82)	
Unknown	11 (2.70)	7 (2.87)	4 (2.45)	
Lung metastasis, n(%)				0.784
No	332 (81.57)	198 (81.15)	134 (82.21)	
Yes	67 (16.46)	42 (17.21)	25 (15.34)	
Unknown	8 (1.97)	4 (1.64)	4 (2.45)	

Only an updated version of the results excluding treatments from the cox-regression analysis, and excluding patients diagnosed from 2000 to 2010 can prove the validity of results, and make this study eligible for publication.

Response: Thank you for your comment. First, we have presented the results of the multivariate Cox regression analysis excluding treatments in the supplementary materials (Table S1). We have also reconstructed the nomogram (Figure S2) and the corresponding ROC curve (Figure S3), calibration curve (Figure S4), and decision curve analysis (DCA) curve (Figure S5). Additionally, as per your request, we excluded patients from before 2010 to ensure a more accurate study population.

Other minor issues to change are the following:

- consider to use "PanNEN" (or PanNET or PanNEC) instead of PNEN, etc.

Response: Thank you for your comment. We have revised them in the text.

- lines 39-40 " The prognosis of pancreatic neuroendocrine tumors is poor, with a median survival time of about 67 months" is unnecessary in the text, to be deleted.

Response: Thank you for your comment. We have deleted the sentence in the text.

- Why did the Authors exclude patients aged <50 years at diagnosis? This choice might also affect the results with a bias, and would limit the application of the nomogram to younger patients. Please, explain in the discussion.

Response: Thank you for your comment. First, literature indicates that PanNEC

can be classified into early-onset PanNEC for patients under 50 years old and classic or late-onset PanNEC for those 50 years or older. The former has a better prognosis but is less common, while the latter constitutes the primary patient group with a poorer prognosis and distinct clinical characteristics. In our study cohort of 476 PanNEC patients, only 47 were under 50, making subgroup analysis challenging. Therefore, to ensure the accuracy of our results, we only analyzed patients aged 50 and older. We also make some relevant explanations added to the discussion. (See Page 9, Lines 146-150)
We now stated the revised sentences as follows:
"Discussion
...We excluded PanNEC patients under 50 years old from our study due to literature indicating that PanNEC can be categorized by age into early-onset PanNEC (under 50) and classic or late-onset PanNEC (50 and older), with differences in prognosis and clinical characteristics[12,14]. The early-onset PanNEC constitutes less than 10% of cases in our study. To ensure the accuracy of our results, we focused solely on elderly-onset PanNEC patients aged 50 and older.

- line 59: " patients with poorly differentiated and undifferentiated tumors (grade III or IV)," Which grading classification is mentioned? NECs are expected to be G3 according to Rindi's Gradind system. Please specify what you mean, and add the appropriate reference.
Response: Thank you for your comment. The grading system used in the SEER database categorizes PanNEC based on the pathological differentiation reported by the hospitals, with Grade III indicating poorly differentiated tumors and Grade IV indicating undifferentiated tumors. In our previous research, we aimed to exclude well-differentiated types from earlier versions of PanNEC to define a new category of PanNEC. However, due to the updated differentiation criteria in the 2010 WHO classification, data prior to 2010 may not fully align with the current definition of PanNEC. Additionally, the 2019 WHO classification has redefined PanNEC into only two types: large cell neuroendocrine carcinoma and small cell carcinoma, NOS, without mentioning differentiation grades. To ensure the accuracy of our study, we redefined our dataset to include only pancreatic neuroendocrine carcinomas diagnosed with ICD-0-3 codes 8013 (Large cell neuroendocrine carcinoma) and 8041 (Small cell carcinoma, NOS) between 2010 and 2021.(See Page 5, Lines 70-73)

- What about immunotherapy in your population?
Response: Thank you for your comment.Due to the types of variables available in the SEER database, information on immunotherapy is not included. We will address this limitation in the discussion section of our study. (See Page 10, Lines 193-195)
"Discussion
...First, family history, history of drinking and smoking, and immunotherapy were not obtained from the SEER database.

- Why were extra-abdominal metastases not considered as a variable for cox-analysis?

Response: Thank you for your comment. Due to the absence of information on part of extra-abdominal metastases in the SEER database before 2010, this data was not included in previous analyses. We have now incorporated the available variables related to extra-abdominal metastases into our Cox regression analysis. Our new findings indicate that liver metastases are an independent prognostic factor affecting patient outcomes.

We now displayed the revised Table 2.

Table 2. Univariate and multivariate cox regression analyses of prognostic factors for CSS of elderly-onset PanNEC.

Variables	Univariate analysis		Multivariate analysis	
	HR (95%CI)	*P value*	HR (95%CI)	*P value*
Age				
<75	1.00 (Reference)		1.00 (Reference)	
≥75	2.09 (1.54 ~ 2.85)	<.001	1.56 (1.10 ~ 2.22)	0.013
Sex				
Female	1.00 (Reference)			
Male	0.97 (0.72 ~ 1.30)	0.830		
Race				
White	1.00 (Reference)			
Black	1.06 (0.69 ~ 1.64)	0.793		
Others	1.05 (0.64 ~ 1.71)	0.855		
Marital status				
Married	1.00 (Reference)			
Others	0.84 (0.61 ~ 1.16)	0.292		
Primary site				
Body and Tail	1.00 (Reference)			
Head	1.26 (0.88 ~ 1.80)	0.205		
Others	1.32 (0.89 ~ 1.97)	0.169		

Tumor size				
≤20	1.00 (Reference)			
21-40	0.74 (0.39 ~ 1.38)	0.340		
>40	0.83 (0.45 ~ 1.51)	0.539		
Unknown	0.89 (0.45 ~ 1.75)	0.727		
Surgery				
Yes	1.00 (Reference)		1.00 (Reference)	
No	2.56 (1.52 ~ 4.30)	<.001	2.32 (1.27 ~ 4.23)	0.006
Radiation				
Yes	1.00 (Reference)			
No/Unknown	1.44 (0.86 ~ 2.40)	0.168		
Chemotherapy				
Yes	1.00 (Reference)		1.00 (Reference)	
No/Unknown	2.02 (1.49 ~ 2.72)	<.001	2.39 (1.68 ~ 3.38)	<.001
TNM stage				
I	1.00 (Reference)		1.00 (Reference)	
II/III	3.51 (1.04 ~ 11.79)	0.042	3.28 (0.96 ~ 11.27)	0.059
IV	5.97 (1.89 ~ 18.87)	0.002	3.96 (1.19 ~ 13.19)	0.025
Liver metastasis				
No	1.00 (Reference)		1.00 (Reference)	
Yes	2.04 (1.46 ~ 2.84)	<.001	1.75 (1.16 ~ 2.65)	0.008
Lymph nodes metastasis				
No	1.00 (Reference)			
Yes	0.94 (0.68 ~ 1.29)	0.704		
Unknown	0.93 (0.48 ~ 1.77)	0.816		

Bone metastasis				
No	1.00 (Reference)			
Yes	1.29 (0.82 ~ 2.01)	0.271		
Unknown	2.34 (0.95 ~ 5.72)	0.063		
Brain metastasis				
No	1.00 (Reference)			
Yes	1.34 (0.55 ~ 3.28)	0.521		
Unknown	2.18 (0.96 ~ 4.94)	0.063		
Lung metastasis				
No	1.00 (Reference)		1.00 (Reference)	
Yes	0.99 (0.66 ~ 1.50)	0.976	0.83 (0.55 ~ 1.27)	0.398
Unknown	3.70 (1.35 ~ 10.12)	0.011	2.21 (0.80 ~ 6.07)	0.125

Reviewer B

1. If available, please update your reference list by including related literatures published within a year. Some of the references are outdated.

Response: Thank you for your suggestion. We now have updated the related literatures.

2. The main text should be organized in Introduction, Methods, Results, Discussion, and Conclusions.

Response: Thanks for your comment. We add the conclusions to our text (See page 10, Line 199).

3. Please add the age unit in Figures 2 and S2 and Tables 1-2 and S1.

Response: Thanks for your comment. We have added the unit of age.

4. Abbreviation should be spelled out the first time it is used in the Abstract/Highlight Box/Body Text/Figure/Table/Supplementary.

Response: Thanks for your comment. We have revised them.

5. Add the unit of tumor size in Tables 1-2 and S1.

Response: We have revised the article according to your requirements.