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ORIGINAL ARTICLE

The incidence, prevalence, and survival analysis of pancreatic neuroendocrine tumors in the United States

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Abstract

Purpose The incidence of pancreatic neuroendocrine tumors (pNETs) was increasing. The main purpose of this study was to statistically analyze the incidence and prevalence of pNETs and the main risk factors for the prognosis.

Methods Based on the Surveillance, Epidemiology, and End Results (SEER) database, with three registries integrated, this study comprehensively displayed the annual age adjust incidence of pNETs from 1975 to 2018, the estimated 20-year limited-duration prevalence, and conducted the univariate and multivariate survival analysis.

Results The incidence of pNETs has increased to about 1.5 per 100,000 population, and the prevalence has reached about 0.008% with the aged, Grade 1 and nonfunctional tumors accounting for the majority. The average median overall survival (OS), 5-year survival rate, and median disease-free survival (DFS) of pNETs patients from 1975 to 2018 were 85 months, 57.55%, and 220 months, respectively. From 2000 to 2018, the median OS was 94 months, and the 5-year survival rate was 59.94%. In multivariate survival analysis, the greatest risk factor was Grade 3&4 with HR = 3.62 (3.10–4.28), followed by distant stage with HR = 2.77 (2.28–3.36), and aged over 80 years old with HR = 2.26 (1.33–3.83). Surgery was a protective prognostic factor with HR = 0.34 (0.29–0.40).

Conclusion The incidence and prevalence of pNETs were still increasing, but the trend was gradual and aging in recent years. The survival time of pNETs was longer but has not changed much in recent years. The degrees of malignancy, stage, and operation were the most important prognosis factors.

Keywords Pancreatic neuroendocrine tumors · Incidence · Prevalence · Survival analysis · SEER

Abbreviations

NETs	Neuroendocrine tumors
pNETs	Pancreatic neuroendocrine tumors
SSAs	Somatostatin analogs
PRRT	Peptide receptor-mediated radionuclide therapy
SSTR	Somatostatin receptor
SEER	Surveillance, Epidemiology, and End Results
OS	Overall survival
DFS	Disease-free survival
CT	Computed tomography
SRI	Somatostatin receptor imaging
111In-SRS	Indium-111 somatostatin receptor scintigraphy
68 Ga-PET	Gallium-68 positron emission tomography
FDG-PET	Fluorodeoxyglucose positron emission tomography

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Introduction

Neuroendocrine tumors (NETs) are a relatively rare type of neoplasms originating from the diffuse neuroendocrine system; pancreas is a relatively common site of neoplasms originating from islet cells [1]. In recent years, the incidence of pancreas neuroendocrine tumors (pNETs) has been increasing [2,3], especially with the progress of examination technology and the improvement of people's awareness of health examinations [4–7]. At the same time, with the deepening of the understanding of pNETs, the application of somatostatin analogs (SSAs) [8] and chemotherapy [9], and the improvement of

surgical techniques and decision-making [10,11], the survival rate of pNETs was also improved.

The onset of pNETs is insidious, and the biological behavior is highly heterogeneous, showing either inert growth or invasive growth or even early metastasis, and the biological characteristics may change with the progression of the disease [12]. pNETs can lead to hormone-related symptoms or syndromes due to the hormone secretion function of tumors, and there are significant differences in the prognosis of pNETs with different grades and stages [11]. Therefore, the treatment and the prognosis assessment of pNETs require a comprehensive consideration of each impact and an individualized treatment plan [13].

Surgery remains the main curative treatment for pNETs. Biological therapy, targeted therapy, chemotherapy, and peptide receptor-mediated radionuclide therapy (PRRT) are used as systemic therapies for un-resectable and metastatic pNETs [14,15]. SSAs have anti-proliferative effects and are mainly composed of lanreotide and octreotide long-acting release drugs. They are currently the first-line biological therapy drugs for advanced-stage well-differentiated (Grade 1 or 2) pNETs with Ki-67 < 10% and somatostatin receptor (SSTR)-positive [16–18]. Approved by the U.S. Food and Drug Administration, everolimus (rapamycin inhibitor) and sunitinib (tyrosine kinase inhibitor) are the two drugs currently for the targeted therapy of pNETs, which have been proposed as the second-line therapy for patients with SSTR-positive expression after SSAs therapy, and the first-line therapy for those with SSTR-negative expression [16]. Systematic chemotherapy is recommended for advanced, metastatic pNETs with high tumor grade, high tumor burden, high Ki-67 index and rapid disease progression to shrink the tumor size before surgery. For Grade 1 and Grade 2 pNETs, temozolomide monotherapy or combination regimen is recommended, and capecitabine (CAPTEM) scheme is preferred. For Grade 3 pNETs, a combination therapy based on temozolomide is a treatment option [19,20].

For the development of diagnosis and treatment technology in recent years, the incidence and prognosis of pancreatic neuroendocrine tumors may have undergone great changes. This study cited the multi-center data in the Surveillance, Epidemiology, and End Results (SEER) [21] open database to comprehensively demonstrate the incidence, prevalence, survival rates and prognostic factors of pNETs in recent years, providing the reference evidence for treatment decision-making and prognosis assessment.

Methods

Data source

We used SEER program SEER*Stat database released on April 15, 2021: version 8.3.9.2 in our study. SEER collects cancer patient demographics, primary tumor site, tumor morphology, stage at diagnosis, first course of treatment, and survival status data from population-based cancer registries covering approximately 34.6% of the U.S. population.

PNET classification and variable selection

According to the International Classification of Disease for Oncology 3rd edition (ICD-O-3), the pancreas were defined in the tumor site, and the classification of neuroendocrine tumors includes non-function: carcinoid tumor (8240), enterochromaffin cell tumors (8241), enterochromafn-like cell tumors (8242), goblet cell carcinoid (8243), mixed adeno-neuro-endocrine carcinoma (8244), adeno-carcinoid tumor (8245), neuroendocrine carcinoma (8246) and atypical carcinoid (8249); function: islet cell carcinoma (8150), insulinoma (8151), glucagonoma (8152), gastrinoma (8153), mixed pancreatic endocrine and exocrine tumor (8154), VIPoma (8155) and somatostatinoma (8156). Selected cases were older than 15 years old, the survival factors included: Sex, Race, Grade, Surgery, Tumor Primary Site, and Stage. Survival months and Living status were collected as variables in the database. Grade classification according to SEER was that: Grade 1, well differentiated; Grade 2, moderately differentiated; Grade 3, poorly differentiated and Grade 4, undifferentiated or anaplastic. Grade 3 and Grade 4 were combined into one category as "Grade 3 & 4" for analysis in this study. According to the scope of tumor invasion, the Stage level included localized, regional and distant in the SEER database.

Statistical analysis

To maximize the representativeness and avoid repetition of the study, in the age adjust incidence statistics, we combined three data sets groupings by the duration of piecewise, case of data during 1975–1991 from 9 Registries Nov 2020 Sub (1975–2018), during 1992–1999 from 13 Registries Nov 2020 Sub (1992–2018), and during 2000–2018 from 18 Registries Nov 2020 Sub (1992–2018).

The age-adjusted 20-year limited-duration prevalence rates were calculated and integrated for each year from 2000 to 2018 by SEER*Stat software (8.3.9.2), using two data registries: the case of data during 2000–2012 from 9 Registries Nov 2020 Sub (1975–2018), and during (2012–2018) 13 Registries Nov 2020 Sub (1992–2018). The incidence rates and the prevalence rates curves were calculated using weighted proportions of corresponding age groups in the 2000 U.S. standard population, plotted with Graph Pad Prism 9.3.0.

The data used in the univariate survival analysis was collected and integrated from the corresponding data as previously stated, maximum 8486 cases were included.

Kaplan–Meier survival analysis and log-rank tests were employed and plotted by Graph Pad Prism 9.3.0.

For multivariate survival analysis, which was carried out by Cox proportional-hazards model, 3453 cases were included totally in the calculation after removing data for blank and unknown variables; Forest plot and Nomogram of the model were calculated and drawn by R software (version 4.1.2).

Results

Annual incidence

During the 43 years from 1975 to 2018, with the increasing incidence of NETs, the annual age-adjusted incidence of pNETs increased, it went from a low of 0.2 per 100,000 population in 1976 to a high of 1.5 per 100,000 population in 2017, which was 7.5-fold higher than before accounting for about 15% of all neuroendocrine tumors (Fig. 1a). In contrast to the gradual growth of NETs, the incidence of pNETs increased dramatically between 2008 and 2013, from 0.6 to 1.3 per 100,000 population. The incidence was markedly higher in older patients, especially those aged over 65 years (Fig. 1b). The total of the statistical incidence of cases was 13,158, in addition to missing data, 7274 (55.28%) were men, 10,487 (80.13%) were White, 10,939 (83.14%) were the non-function tumor, and 4320 (35.14%) were Grade 1 (Supplement Table 1). In gender, since 1992, the incidence in men has been higher than that in women, and the gap has gradually increased. In 2018, it was 1.6 per 100,000 population for males as 1.2 for females, while it was the same as 0.2 between the two genders in 1977 (Fig. 1c). In the race group, the incidence was higher and more similar in Whites and Blacks, and the incidence among Asians has increased in recent years (Fig. 1d). Notably, mainly and sharply increased incidence of pNETs was observed in the G1 well-differentiated and nonfunctional tumors, especially in the last 10 years (Fig. 1e, f).

Prevalence

In line with the general trend of the incidence, the 20-year limited-duration age-adjusted prevalence of pNETs was increasing year by year. From 2000 to 2018, the prevalence increased from 0.0016% to 0.00789% with a total increase of 4.9-fold and an almost fivefold increase in 5 years. Compared with the steady growth of the prevalence of NETs, pNETs began to show a considerable increase from 2012 (Fig. 2a, Supplement Table 2). Similarly, the prevalence continued to increase in patients older than 65–74 years old obviously (Fig. 2b). The prevalence was higher in males than females as the trends in the incidence (Fig. 2c). Along with the increase, the prevalence of Blacks has surpassed that of Whites (Fig. 2d). Besides, the rise in Grade 1 and nonfunctional tumors was most pronounced in both the Grade and nonfunctional groups (Fig. 2e).

Survival

From 1975 to 2018, the average median OS of pNETs patients was 85 months (7.1 years). The 5-year survival rate and 10-year survival rate were 57.55% and 41.30%, respectively (Table 1, Fig. 3a), and the median DFS was 220 months (Table 2, Fig. 3b). The survival rate was increased as time gone by, and it was higher in the 2000s than that of last century: during 1975–1991 (9 Registries), the 5-year and 10-year survival rates were 35.84% and 22.86% respectively, and the median OS was 34.5 months (2.9 years); while during 2000–2018 (13 Registries), the 5-year survival rate, 10-year survival rate, and median OS rose to 59.94%, 43.70%, and 94 months (7.8 years), respectively (Table 1, Fig. 3c). Notably, the 5-year survival rate increased by 67.24%, and the median survival time increased 2.7-fold.

In univariate survival analyses for each group, the patients ≤ 30 years, Female, Asian, tumor size ≤ 2 cm, tumors in the tail of the pancreas, Grade 1, nonfunctional tumors, localized, and surgical patients had a relatively well prognosis (Table 1, Figs. 3e and 4). Among them, the median OS of the tumor size ≤ 2 cm group was the longest (197 months) (Table 1, Fig. 4c), and the survival rate of patients with localized tumor was the highest (5-year survival rate was 85.37%, 10-year survival rate was 72.05%) (Table 1, Fig. 4h). The patients with Grade 1 had a better survival with the median OS = 171 months, and the 5-year survival rate = 79.54%. In contrast, in the Grade 3&4 group, patients' median OS was only 13 months, and the 5-year survival rate was 22.53% (Table 1, Fig. 4g). According to the results, surgery significantly improved the prognosis: the median OS of patients undergoing surgery was 167 months, the 5-year survival rate was 79.10%, and the 10-year survival rate was 62.29%; while the median OS of patients without surgery was 23 months, the 5-year survival rate was 27.87%, and the 10-year survival rate was only 13.91% (Table 1, Fig. 3d).

Multivariable analysis of OS

Multivariate Cox regression survival analysis of OS (Table 2, Fig. 5a, b) was performed to compare the proportion of factors contributing to the overall outcome and the role of each stratification in each subgroup with log-rank test p value $= 9.82 \times 10^{-256}$ and C-index = 0.81 (Fig. 5a). The forest map showed that the risk of death of Grade 3&4 was 3.62-fold that of Grade 1 (95% CI

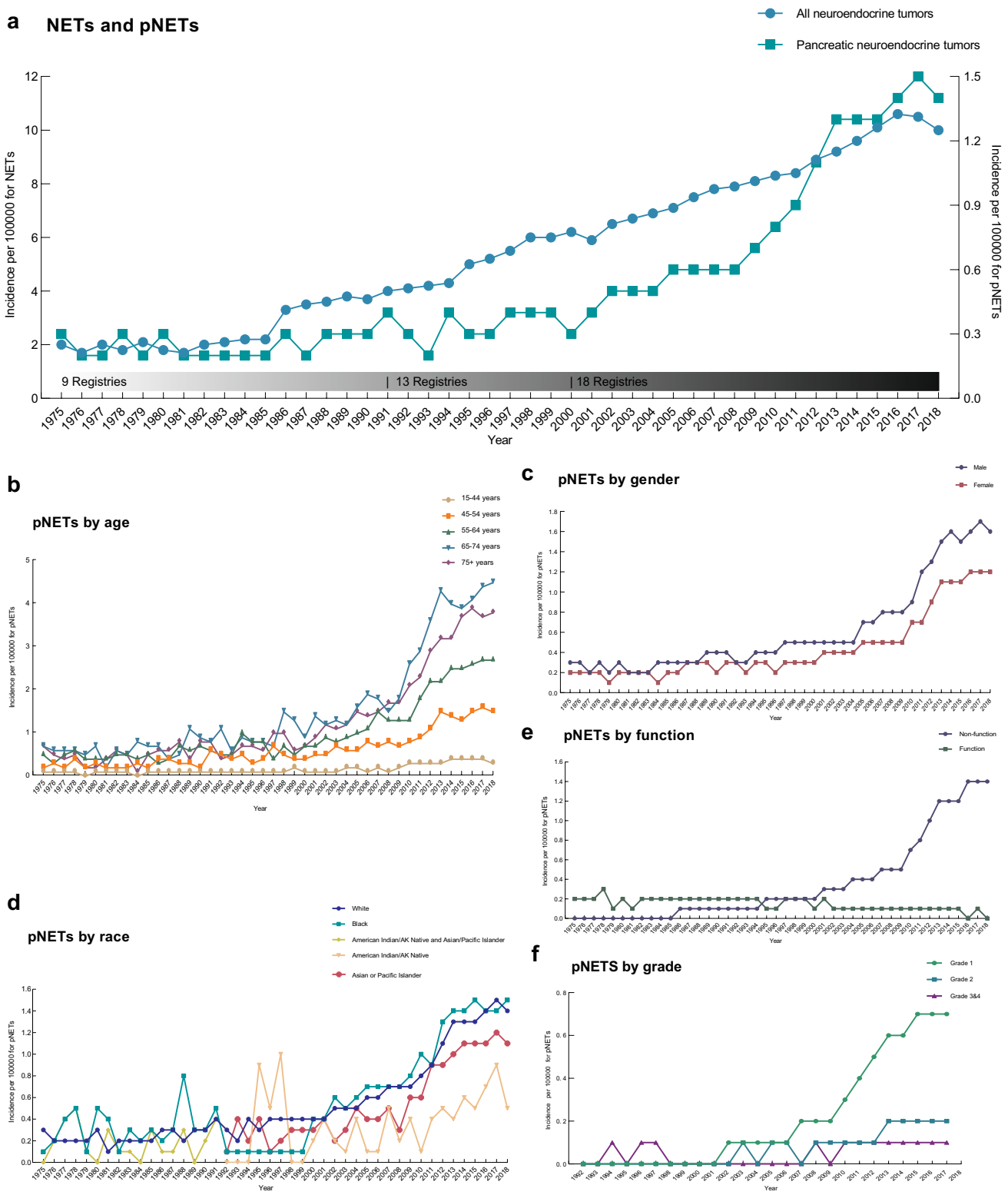

Fig. 1 The incidence of pNETs from SEER database in 1975–2018 at 9 Registries, 13 Registries, and 18 Registries. **a**–**f** 1975–1991 data from 9 Registries, 1992–1999 data from 13 Registries, 2000–2018 from 18 Registries. **a** The incidence of NETs and pNETs. **b** The incidence of pNETs by age. **c** The incidence of pNETs by gender. **d** The incidence of pNETs by race. **e** The incidence of pNETs by function. **f** The incidence of pNETS by grade. pNETs, pancreatic neuroendocrine tumors

Table 1 Median survival month and survival rate of total and each group by univariate survival analysis

	Median survival month	5 years survival rate (%)	10 years survival rate (%)	Log-rank tests *P* value
OS of pNETs	85	57.55	41.30	
DFS of pNETs	220	72.29	60.94	
Years				
1975–1991 (331)	34.5	35.84	22.86	**p < 0.001**
1992–1999 (459)	42	42.70	28.97	
2000–2018 (7658)	94	59.94	43.70	
Age				
≤ 30 (183)	163	64.54	52,78	**p < 0.001**
> 30 ≤ 60 (3644)	119	65.58	49.76	
> 60 ≤ 80 (4062)	73	53.61	36.08	
> 80 (597)	21	27.33	9.62	
Gender				
Male (4706)	73	55.25	38.20	**p < 0.001**
Female (3780)	100	61.14	45.10	
Grade				
Grade 1 (2982)	171	79.54	64.13	**p < 0.001**
Grade 2 (941)	109	66.88	45.53	
Grade 3&4 (631)	13	22.53	11.69	
Race				
Whites (6651)	82	57.22	40.53	**p = 0.012**
Blacks (1133)	80	55.10	39.11	
Asian or Pacific Islander (660)	126	65.80	54.39	
American Indian/Alaska Native (42)	57	46.96	46.96	
Tumor size				
≤ 2 cm (2110)	197	81.28	68.69	**p < 0.001**
> 2 cm ≤ 5 cm (3041)	88	58.14	43.23	
> 5 cm (1735)	65	51.97	34.15	
Primary site				
Pancreatic head (2680)	73	55.00	38.30	**p < 0.001**
Pancreatic neck and tail (3863)	112	64.27	47.53	
Function				
Non-function (3103)	87	58.56	41.46	**p = 0.047**
Function (1383)	71	53.86	39.28	
Surgery or not				
No surgery (3646)	23	27.87	13.91	**p < 0.001**
Surgery (4802)	167	79.10	62.29	
Tumor stage				
Localized (2918)	203	85.37	72.05	**p < 0.001**
Regional (3555)	124	68.89	51.38	
Distant (1773)	25	30.21	15.96	

OS overall survival, *DFS* disease-free survival, *pNETs* pancreatic neuroendocrine tumors

Bold is meant to emphasize statistical significance

3.10–4.24) with the maximum hazard ratio (HR) value among all factors. Older than 80 years old and larger invasion stage were also more important factors affecting survival rate ($p < 0.05$). Women had a better prognosis than men with HR = 0.8 (95% CI 0.70–0.90), while Blacks had a worse prognosis than Whites with HR = 1.37 (95% CI 1.14–1.65). Besides, the risk of death was 1.20 times higher for functional tumors than for nonfunctional tumors (95% CI 1.00–1.43) with p value = 0.047. Surgery was an effective intervention to reduce mortality and

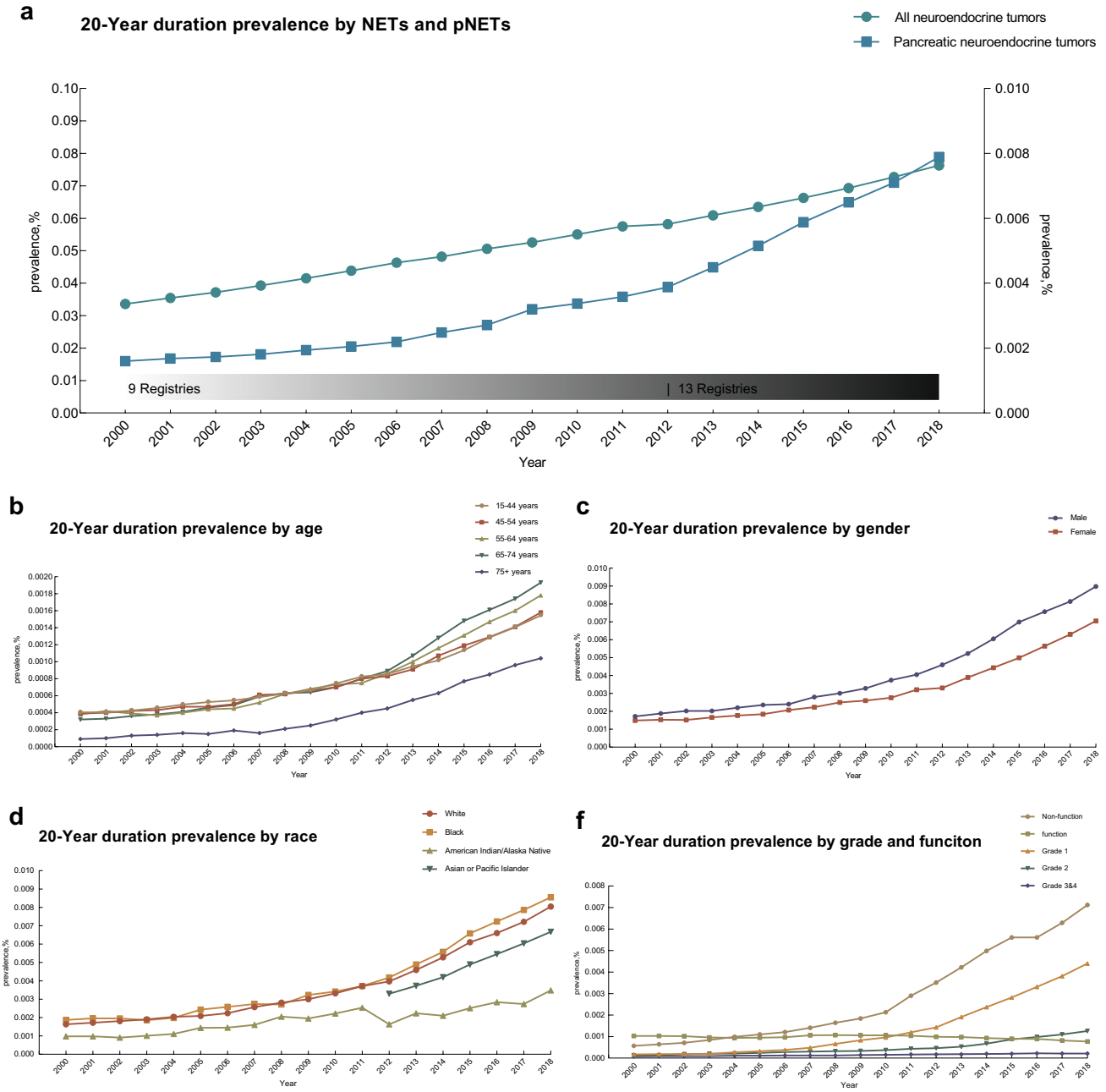

Fig. 2 The 20-year duration prevalence of pNETs from SEER database in 2000–2018 at 9 Registries, 13 Registries, and 18 Registries. **a–e** 2000–2011 data from 9 Registries, data from 13 Registries. **a** The 20-year duration prevalence of NETs and pNETs. **b** The 20-year duration prevalence of pNETs by age. **c** The 20-year duration prevalence of pNETs by gender. **d** The 20-year duration prevalence of pNETs by race. **e**, The 20-year duration prevalence of pNETs by grade and function. pNETs, pancreatic neuroendocrine tumors

improve prognosis with HR = 0.34 (95%CI 0.29–0.40). The primary site of tumor had no significant effect on prognosis ($p > 0.05$) (Fig. 5a). The nomogram of the Cox proportional-hazards model clearly showed the influence of various factors on the prognosis and death risk evaluation of individual cases. Tumor Grade 3&4 had the greatest influence on prognosis, followed by no surgery, and the distant stage of tumor. Asians and Pacific Islanders had lower risk scores than Blacks and Whites. Tumor size alone had the least influence on the prognosis compared to the other groups. A nonfunctional tumor had better prognosis than a functional tumor (Fig. 5b). The calibrations of the nomogram for 5-year and 10-year survival rates were satisfactory (Fig. 5c, d).

Table 2 Demographics and baseline characteristics of patients with pNETs for Multivariate survival analysis

Characteristics	Alive ($N=2450$)	Dead ($N=1003$)	Overall ($N=3453$)
Age			
≤30	57 (2.3%)	16 (1.6%)	73 (2.1%)
>30<60	1175 (48.0%)	353 (35.2%)	1528 (44.3%)
>60≤80	1138 (46.4%)	525 (52.3%)	1663 (48.2%)
>80	80 (3.3%)	109 (10.9%)	189 (5.5%)
Sex			
Male	1284 (52.4%)	622 (62.0%)	1906 (55.2%)
Female	1166 (47.6%)	381 (38.0%)	1547 (44.8%)
Race			
White	1908 (77.9%)	784 (78.2%)	2692 (78.0%)
Black	301 (12.3%)	142 (14.2%)	443 (12.8%)
Asian or Pacific Islander	234 (9.6%)	70 (7.0%)	304 (8.8%)
American Indian/Alaska Native	7 (0.3%)	7 (0.7%)	14 (0.4%)
Grade			
Grade 1	1884 (76.9%)	479 (47.8%)	2363 (68.4%)
Grade 2	481 (19.6%)	205 (20.4%)	686 (19.9%)
Grade 3&4	85 (3.5%)	319 (31.8%)	404 (11.7%)
Tumor size			
≤2 cm	1036 (42.3%)	183 (18.2%)	1219 (35.3%)
>2 cm≤5 cm	1038 (42.4%)	517 (51.5%)	1555 (45.0%)
>5 cm	376 (15.3%)	303 (30.2%)	679 (19.7%)
Primary site			
Pancreatic head	829 (33.8%)	461 (46.0%)	1290 (37.4%)
Pancreatic body and tail	1621 (66.2%)	542 (54.0%)	2163 (62.6%)
Function			
Non-function	2259 (92.2%)	854 (85.1%)	3113 (90.2%)
Function	191 (7.8%)	149 (14.9%)	340 (9.8%)
Surgery or not			
No surgery	188 (7.7%)	408 (40.7%)	596 (17.3%)
Surgery	2262 (92.3%)	595 (59.3%)	2857 (82.7%)
Stage			
Localized	1502 (61.3%)	236 (23.5%)	1738 (50.3%)
Regional	669 (27.3%)	279 (27.8%)	948 (27.5%)
Distant	279 (11.4%)	488 (48.7%)	767 (22.2%)

Discussion

This study integrated the three data registry parts of SEER database over time, was a large multi-center clinical study of pNETs analysis, covering a period of 43 years from 1975 to 2018, and provided a comprehensive picture of the incidence and prognosis of pNETs. For the incidence of pNETs, it has increased obviously even after 2012. It went from 1.0 to the highest 1.5 per 100,000 population (the prevalence increased from 0.00388% to 0.00789%) and accounted for about 15% in the overall NETs increasingly. The previously reported that the incidence rate was 1.0 per 100,000 population, accounting for approximately 10% of NETs [2,22,23]. The improvement and widespread application of examination technology are one of the essential reasons. With a sensitivity of 82%, computed tomography (CT) has become a universal screening tool [4], not only that, but more sensitive and specific somatostatin receptor imaging (SRI), including indium-111 somatostatin receptor scintigraphy (111In-SRS), gallium-68 positron emission tomography (68 Ga-PET) and fluorodeoxyglucose positron emission tomography (FDG-PET) have been widely used in the last decade for pNETs diagnosis [12,24,25]. The improvement and wide application of ultrasonic imaging and ultrasonic endoscopy improved the detection rates and the incidence [4,7,26]. It could be seen from the results that the incidence and the prevalence of patients over 65 years old also increased clearly. The patients over 60 years old accounted for more than half of the total, and the incidence was the highest in patients aged 65–75, especially since

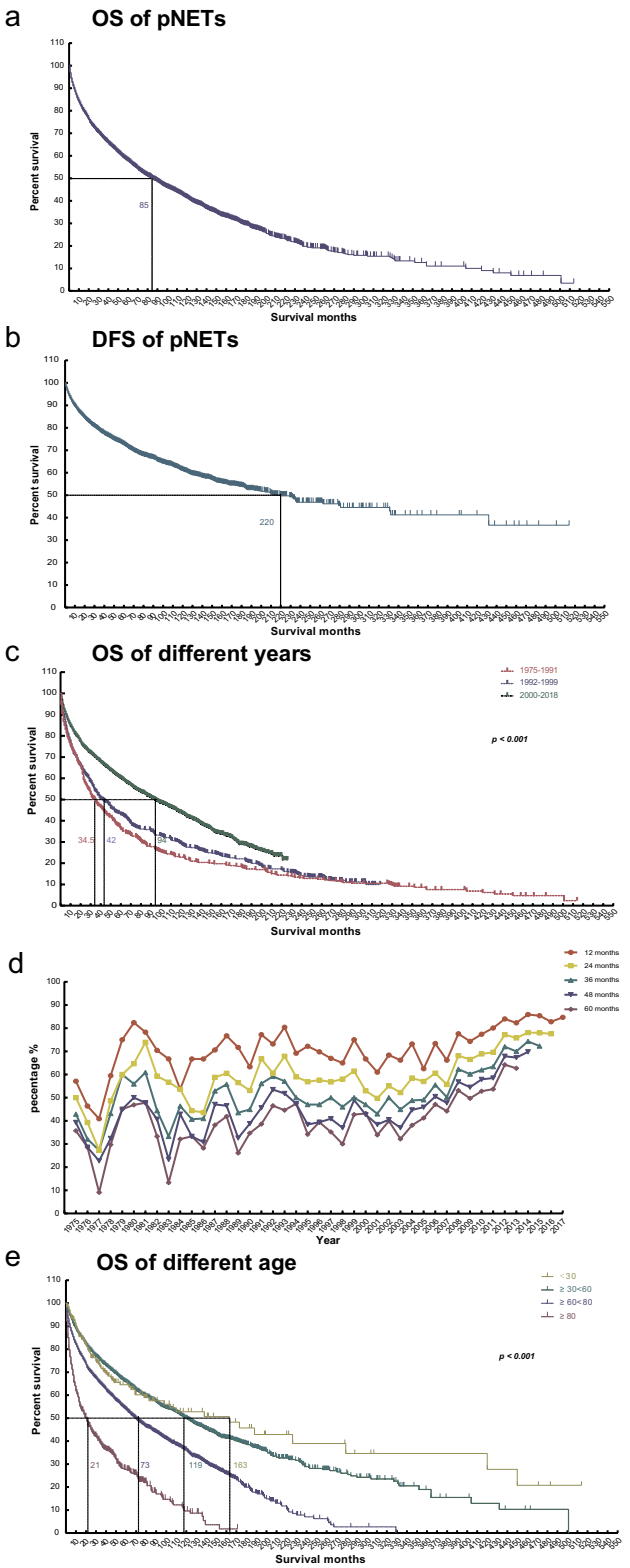

Fig. 3 Survival analysis of pNETs. **a** OS of pNETs. **b** DFS of pNETs. **c**, Survival analysis of pNETs by different yeas with Kaplan–Meier. **d** Trends of 12–60 months (1–5 years) survival rate of pNETs. **e**, Survival analysis of pNETs by different age. P value of Log-Rank test with Kaplan–Meier. *OS* overall survival, *DFS* disease-free survival, *pNETs* pancreatic neuroendocrine tumors

2010. It might be due to an aging population, like other cancer diseases [27,28]. In terms of gender, in recent years, the incidence and prevalence of males were higher than that of females, and the gap tended to increase, which have been proved by the previous studies [23,29]. Men also had a shorter survival time than women, which might be related to factors, such as pressure, lifestyle, obesity and smoking, but there was no literature report to prove these.

Almost the same as the previous study [30], the 5-year survival rate in the 1990s was about 42%, and it increased to about 59.94% from 2000 to 2018. Overall, the survival rates and median survival time of pNETs have improved over the past 3 decades. Sonbol MB et al. analyzed the data of pNETs from the SEER database 18 registries (2000–2016), and the result showed that the median survival time was 46 months from 2000 to 2007. In contrast, the median survival time increased to 85 months from 2009 to 2016 [22]. The 9 registries (1987–2016) SEER dataset analyzed by Wang J et al. also showed increased trend of the survival time [23]. Increased incidence was a correlate of improved survival rates due to the improvement of detection rates as advances in detection technology allow tumors to be detected early and treated promptly [31]. Another important reason was a better understanding of pNETs and improvement of treatment modalities. However, the increase of the survival rate of pNETs was limited over the last 5 years (2012–2017). Therefore, to improve survival time, the choice of future treatment may require more consideration of various influencing factors and the formulation of a more individualized treatment plan.

According to our Cox regression analysis and nomogram results, the weights of factors influencing pNETs presence were the grade (Grade 3&4), age (older than 80 years old), stage (invasion area), surgery, race, gender (male), function, tumor location and Tumor size. The high grade was the most independent risk factor, as reported in other literature [32–34]. The survival outcome of the grade had a qualitative change between Grade 2 and Grade 3&4 with the 5-year survival rates of 66.88% and 22.53% respectively, and the nomogram score differs by nearly 60 points in this study. The research on the grading system was still improving, but it was beyond doubt that the malignant degree of tumor itself mainly determines the prognosis [35].

The results in this study indicated that the survival rate of Asians was higher with 5-year survival rate of 65.80% comparing with that of Whites (57.22%) and Blacks (55.10%). American Indian/Alaska Native had the lowest survival rates. In a study for the Japanese that included 245 cases, the 5-year survival rate of pNETs was 79.3% with a median survival time of 202 months between 1987 and 2016 [36], also suggesting a better prognosis for Asians. Some studies have reported that Blacks had lower survival rates than Whites because of the lower rates of surgery [30,37]. From

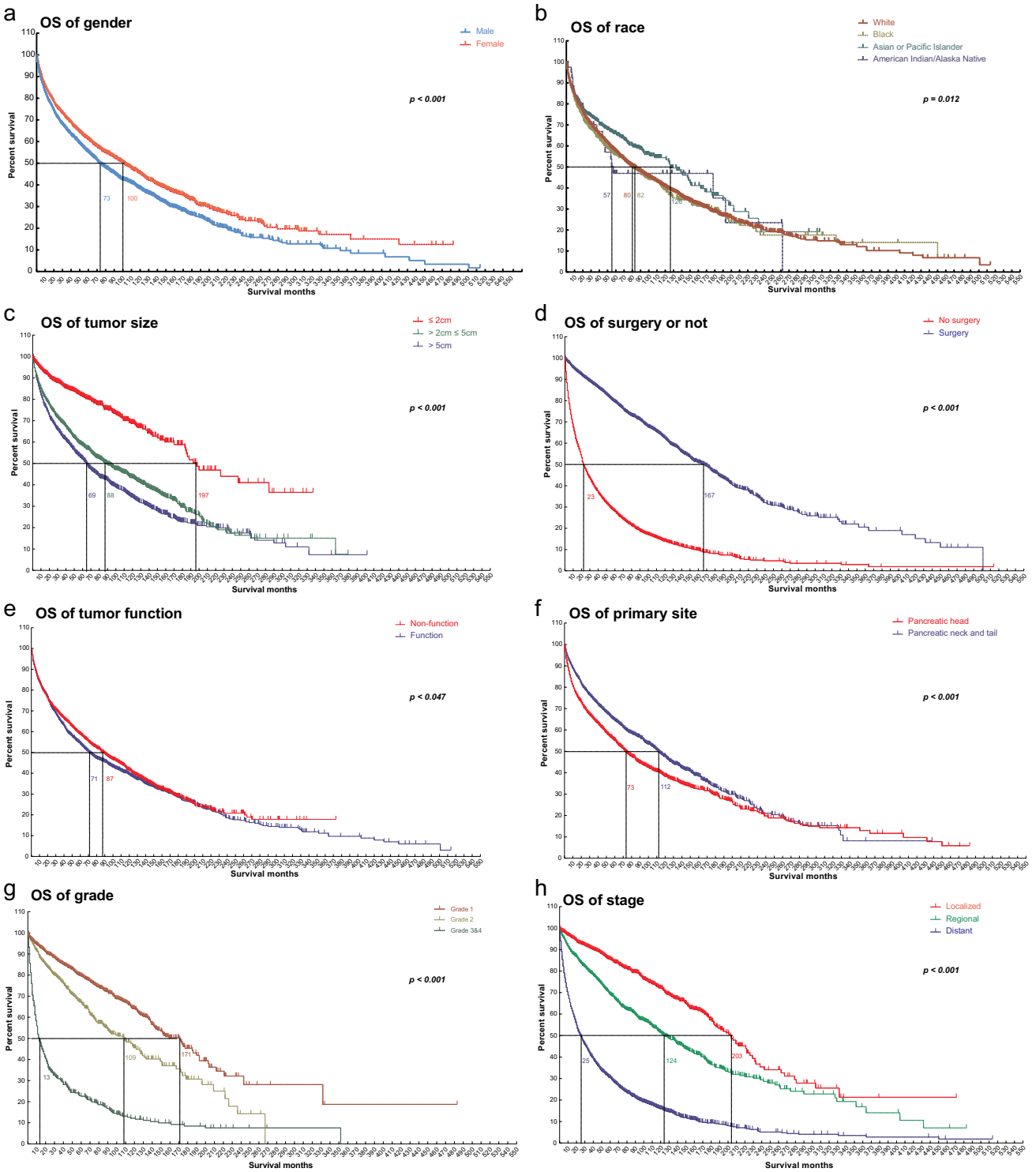

Fig. 4 Survival analysis of pNETs with different factors. **a** Survival analysis of pNETs by gender. **b** Survival analysis of pNETs by race. **c** Survival analysis of pNETs by tumor size. **d** Survival analysis of pNETs by surgery or not. **e** Survival analysis of pNETs by tumor function. **f** Survival analysis of pNETs by primary site. **g**, Survival analysis of pNETs by grade. **h** Survival analysis of pNETs by stage. *p* value of Log-Rank test with Kaplan–Meier. *pNETs* pancreatic neuroendocrine tumors

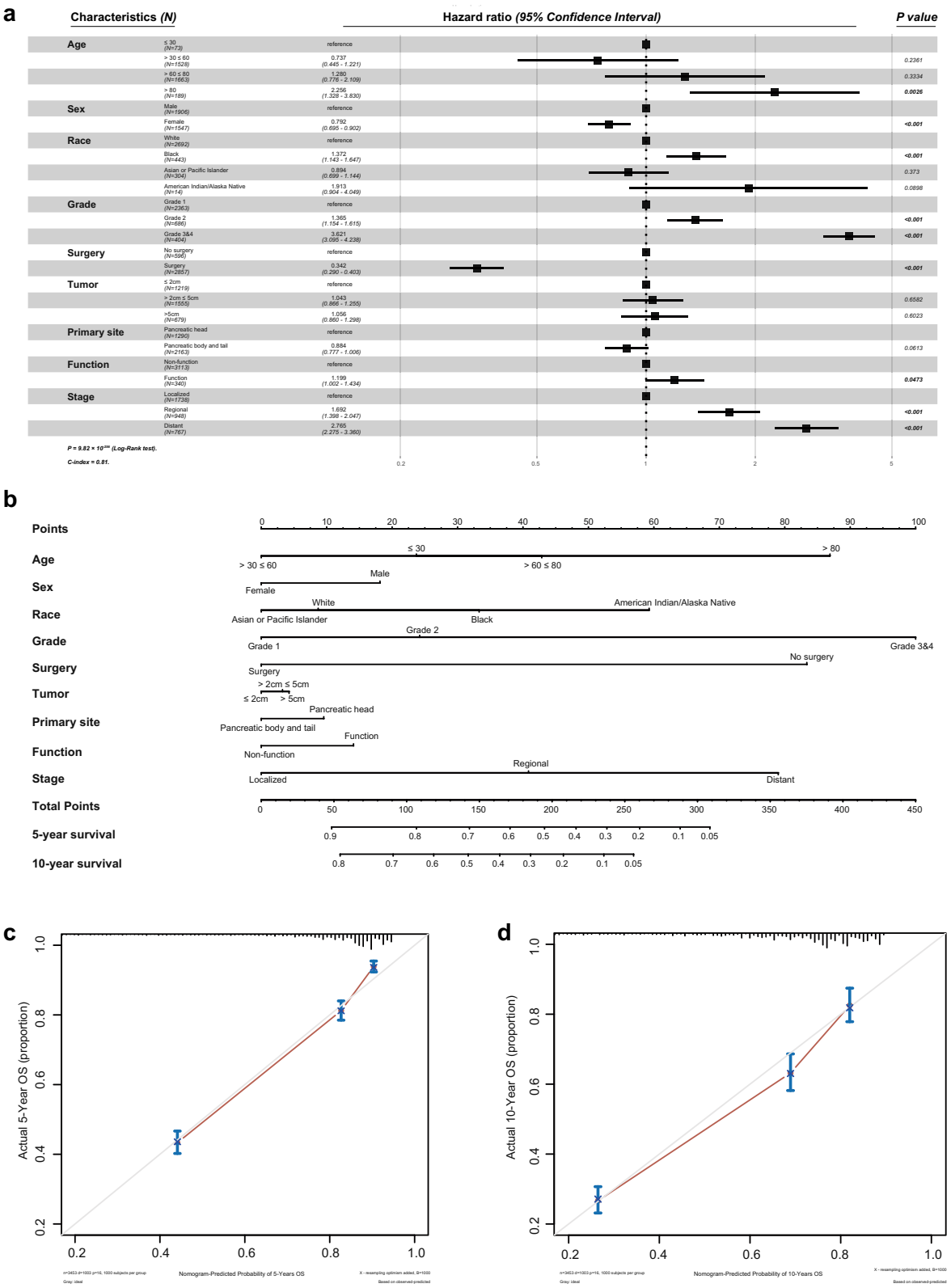

Fig. 5 The multivariate survival analysis of pNETs by Cox proportional-hazards model. **a** The forest map of the multivariate survival analysis of pNETs by Cox proportional-hazards model. $p = 9.28 \times 10^{-256}$ (Log-Rank test). C-index = 0.81. pNETs, pancreatic neuroendocrine tumors. **b** Nomogram of the multivariate survival analysis of pNETs by Cox proportional-hazards model. **c** The calibration of the nomogram for 5-year OS. **d** The calibration of the nomogram for 10-year OS. *pNETs* pancreatic neuroendocrine tumors, *OS* overall survival, *OS* overall survival

that, we could speculate that the difference in race might relate to their medical willingness, and medical conditions. Further research is needed to determine whether there is a physical or genetic difference between races.

The correlation between functionality and prognosis still seems to be controversial. Nonfunctional pNETs seemed to have a worse prognosis [38]. Some reports suggested that functionality was not an independent prognostic indicator of pNETs [39]. In our study, the univariate and multivariate analyses showed that the survival rates of the nonfunctional pNETs were better than the functional pNETs, and the 5-year survival rates were 53.86% and 58.56%, respectively, with log-rank tests = 0.047 and hazard ratio = 1.20 ($p = 0.047$). In addition, data in the ENET guidelines suggested that a higher percentage of functional pNETs was malignant [40]. However, functional pNETs such as insulinoma had a better prognosis [40,41].

Tumor size is relatively easy to obtain from preoperative examination. Still, the simple tumor size may have little effect on prognosis, which needs to be determined by combining factors, such as grade and stage (invasion scope). Currently, for the nonfunctional, Grade 1/2 and tumor size < 2 cm patients, the treatment of choice between observation and surgery is still under discussion. The current trend was that patients' tumor size < 1 cm can be selected for observation, whether to operate and the scope of operation at 1–2 cm needed further study and discussion [40,42]. However, in our nomogram model, the risk score (almost 84 point) was higher in no surgery patients with tumors smaller than 2 cm, non-function, localized and Grade 1 than in surgical patients with tumors larger than 2 cm, regional, functional and Grade 2 (almost 72 point). From this point of view, even if the tumor is smaller than 2 cm, surgical treatment is still the most important way to improve the prognosis. Therefore, it is still a desirable direction to improve the accuracy of preoperative tumor localization and to improve surgical techniques and methods.

At present, drug therapy is becoming more prominent in the treatment of pNETs [43,44]. We also introduced some current applications of drug therapy in pNETs in the introduction. However, there were no records of endocrine therapy and detailed descriptions of chemotherapy, radiotherapy and other drugs in SEER data. So, the effect of drug therapy on the survival of pNETs was not evaluated and calculated in our study. That was the main limitation of this paper.

In general, the incidence and the prevalence of pNETs were increasing, it has seemed to be stable in recent years. The incidence was about 1.5 per 100,000 population, accounted for about 15% in the overall NETs, and the prevalence has reached about 0.008%. The aged, Grade 1, and nonfunctional pNETs increased obviously. The survival time of pNETs was longer, but has not changed much in recent years. The grade, age, surgery and stage were the main prognosis factors, and the gender, race, tumor size, the primary site of tumor, and function were also the prognostic factors.

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Declarations

Conflict of interest The authors have no conflicts of interest to declare.

Research involving human participants and/or animals This article does not contain any studies with human participants or animals performed by any of the authors.

Informed consent For this type of study, formal consent is not required.

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