# Prognostic analysis of very early onset pancreatic cancer: a population based analysis

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**Background :** We aimed to use competing risk model to assess whether very early onset pancreatic cancer ( VEOPC ) (< 45 years) had a worse prognosis than older pancreatic cancer (PC) patients, and to build a competing risk nomogram for predicting the risk of death of VEOPC.

**Methods:** We selected pancreatic adenocarcinoma (PDAC) patients as our cohort from Surveillance, Epidemiology, and End Results (SEER) database. The impact of cancer specific death was estimated by competing risk analysis. Multivariate Fine-Gray regression for proportional hazards modeling of the subdistribution hazard (SH) model based nomogram was constructed, which was internally validated by discrimination and calibration with 1,000 bootstraps.

**Results:** Our cohort included 1,386 VEOPC patients and 53,940 older patients. We observed that in unresectablePDAC patients, VEOPC had better cancer specific survival (CSS) than each older group (45-59 years, 60-69 years, 70-79 years and > 79 years). There was no significant prognostic difference between VEOPC and each older group in resectablePDAC. Our competing nomogram showed well discrimination and calibration by internal validation.

**Conclusion:** For unresectable PDAC patients, VEOPC had better CSS than older patients. Our competing risk nomogram might be an easy-to-use tool for the specific death prediction of VEOPC patients with PDAC.

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2 # cancer: a population based analysis

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17 ## Abstract

18 **Background:** We aimed to use competing risk model to assess whether very early onset

19 pancreatic cancer (VEOPC) (< 45 years) had a worse prognosis than older pancreatic

20 cancer (PC) patients, and to build a competing risk nomogram for predicting the risk of

21 death of VEOPC.

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23 Surveillance, Epidemiology, and End Results (SEER) database. The impact of cancer

24 specific death was estimated by competing risk analysis. Multivariate Fine-Gray

25 regression for proportional hazards modeling of the subdistribution hazard (SH) model

26 based nomogram was constructed, which was internally validated by discrimination and

27 calibration with 1,000 bootstraps.

28 **Results:** Our cohort included 1,386 VEOPC patients and 53,940 older patients. We

29 observed that in unresectable PDAC patients, VEOPC had better cancer specific survival

30 (CSS) than each older group (45-59 years, 60-69 years, 70-79 years and > 79 years).

31 There was no significant prognostic difference between VEOPC and each older group in

32 resectable PDAC. Our competing nomogram showed well discrimination and calibration

33 by internal validation.

**Conclusion:** For unresectable PDAC patients, VEOPC had better CSS than older patients. Our competing risk nomogram might be an easy-to-use tool for the specific death prediction of VEOPC patients with PDAC.

**List of abbreviations:** PC, pancreatic cancer; VEOPC, very early onset pancreatic cancer; BMI, body mass index; OS, overall survival; PDAC; pancreatic adenocarcinoma; SEER, Surveillance, Epidemiology, and End Results; NOS, not otherwise specified; LNR, lymph nodes ratio; AJCC, American Joint Committee on Cancer; CID, cumulative incidences of death; CIF, cumulative incidences function; CSS, cancer specific survival; HR , hazard ratio; 95%CI, 95%confidence index; AUC, the area under the curve of receiver operating characteristic curve.

## Introduction

Pancreatic cancer (PC) patients have a 5 years survival lower than 10%(Siegel et al. 2018). According to American cancer society, the average age of PC patients at diagnosis is 70 years. Less than 3% of PC patients are under the age of 45 years at diagnosis (Surveillance 2019a), which was defined as very early onset PC (VEOPC)(McWilliams et al. 2016). Duo to its rareness, few data were reported regarding the clinicopathological features and treatment response of VEOPC patients(Grosfeld et al. 1990; Jaksic et al. 1992; Lack et al. 1983; McWilliams et al. 2016; Shorter et al. 2002).

The identification of prognostic factors of PC might improve the prediction of the survival and the selection of therapy for PC patients. The well-known PC prognostic factors comprised resection margins, lymph nodes status and lymph node ratio, perineural and blood vessel invasion, tumor localization and body mass index (BMI) and treatment such as chemotherapy(Bilici 2014; Lin et al. 2016). However, whether age is a prognostic factor of PC is currently controversial. Some studies found "younger" PC patients (with different definition of age < 45 years, age < 50 years, age < 60 years and age < 70 years) had better overall survival (OS) than the older PC patients(Baxter et al. 2007; He et al. 2013; Saad et al. 2018; Sugiura et al. 2017). While the other studies found younger age (with different definition of age < 65 years and age < 70 years)(Barbas et al. 2012; Miyazaki et al. 2016; van der Geest et al. 2016) was not associated with the survival of PC patients. To be noted, these studies had limited number of VEOPC patients or did not treat the VEOPC as a group.

68  Nomogram is a valuable tool to use different clinical variables to determine a
69  statistical prognostic model that generates a probability of clinical outcomes for a single
70  patient(Balachandran et al. 2015). Nomogram have been applied in various types of
71  cancers(Fakhry et al. 2017; Huang et al. 2016; Liang et al. 2015; Rose et al. 2015).
72  Nowadays, nomograms are commonly used to estimate prognosis in oncology and
73  medicine, which fit the trend of personalized medicine(Balachandran et al. 2015). It is
74  worthy to construct a nomogram for predicting the prognosis of VEOPC patients.

75  Pancreatic adenocarcinoma (PDAC) is the main type of PC, which has a worse
76  prognosis than other histology types. The current study selected PDAC patients as our
77  cohort. To be noted, the competing event of death is widely existing in the prognostic
78  analysis of cancer. The failure to account for such competing events, such as Kaplan–
79  Meier method and standard Cox proportional hazards regression analysis, might result in
80  an overestimate of the cumulative incidences(Satagopan et al. 2004). The competing risk
81  model considers both the disease-specific death and other causes of death, which was
82  fit to the analysis in the presence of competing risk events (Kim 2007). The competing
83  risk analysis was often missed in previous studies when included with very aged PC
84  patients. The aim of our study was to use competing risk model to estimate the prognostic
85  value of age in PDAC patients and construct competing nomogram for cancer–specific
86  death prediction of VEOPC patients by using the data from Surveillance, Epidemiology,
87  and End Results (SEER) database of the National Cancer Institute of United States,
88  which currently collects and publishes cancer incidence and survival data from
89  population-based cancer registries covering approximately 34.6 percent of the United
90  States population(Surveillance 2019b).

91

## Methods

92

### *Cohort selection*

93

94  The cohort was selected by SEER*Stat 8.3.5 software (SEER ID: daid) with the
95  following criteria: (1) it should be a primary PDAC patients (ICD-O-3 histology codes 8140
96  and 8500) registered equal or after year of 2004; (2) it should be a patient who has a
97  survival time over than 0 month with records of survival status; (3) it should have at least
98  one year follow up time to capture enough events to ensure a meaningful analysis. We
99  also excluded few patients with unclear information of race, surgery, number
100 of regional lymph nodes examined, radiotherapy and marital status. Finally, we excluded
101 1 patient with cancer in the islets of langerhans. The detailed data selection process was
102 shown in Supplemental Figure 1.

103

### *Study variables and endpoints*

105  We included 14 variables into our analysis, which were listed as the follows: age at
106  diagnosis, sex (Females and males), race (Caucasian, African American, American
107  Indian/Alaska Native and Asian or Pacific Islander), tumor location (Head of pancreas,
108  body of pancreas, tail of pancreas, pancreatic duct, other specified parts of pancreas,
109  overlapping lesion of pancreas and Pancreas, NOS (Not otherwise specified)), surgery
110  experience (No surgery, local or partial pancreatectomy, local or partial pancreatectomy
111  and duodenectomy, total pancreatectomy with or without gastrectomy or duodenectomy,
112  pancreatectomy NOS or surgery NOS), tumor size, LNR (Lymph nodes ratio, which is
113  defined as the ratio of the number of positive lymph nodes to the total number of lymph
114  nodes examined), 6th American Joint Committee on Cancer (AJCC) tumor TNM stage,
115  grade, radiotherapy and chemotherapy experience and marital status. The value of age
116  at diagnosis, tumor size and LNR were classified into small categorical variables to fit the
117  linear assumption. The widowed or single (Never married or having a domestic partner)
118  or divorced or separated patients was defined as "Single". The median observed survival
119  time was referred to median follow-up time.

120

### *Statistical analyses*

122  The difference of each variable between VEOPC and other PC patients was
123  evaluated by Chi-Squared tests. Cumulative incidences of death (CID) was estimated for
124  deaths caused by cancer or other reasons by using the cumulative incidences function
125  (CIF) analysis. Multivariate SH model was used to assess the cancer specific survival
126  (CSS). All the variables were included in the multivariate analysis. Hazard ratio (HR) and
127  95%confidence index (95%CI) were calculated.

128  Multivariate SH model-based nomogram was constructed by multivariate logistic
129  regression model to predict the 6 months, 12 months, 18 months and 24 months cancer
130  specific death of VEOPC patients. The internal validation of nomogram was performed
131  by discrimination and calibration with 1,000 time bootstraps(Balachandran et al. 2015).
132  The discrimination was estimated by the area under the curve of receiver operating
133  characteristic curve (AUC, which was also referred as C-statistics). The AUC ranges from
134  0.5-1.0, with 0.5 indicates the outcomes is totally random and 1.0 indicates the perfect
135  discrimination. The calibration was assessed by calibration curves, which shows how
136  close the nomogram estimated risk was to the observed risk. All the statistical analyses
137  were performed by "R" version 3.6.0. The CIF test and multivariate SH analysis were
138  performed by "R" package "cmprsk". The competing risk nomogram was constructed by

139   "R" package "mstate" and plotted by "R" package "regplot". The calibration curve was
140   drawn by "R" package "riskRegression". The AUC was calculated by "R" package
141   "riskRegression" and plotted by "R" package "ggplot2". A two tailed p-value less than 0.05
142   was considered statistically significant.

143

## Results

145   ### Cohort selection

146   We included the patients diagnosed equal to or before 2015 to ensure an enough
147   follow-up time. There were 1,386 VEOPC patients and 53,940 older PDAC patients (>=
148   45 years). The median survival time of VEOPC and older patients were 9 and 7 months,
149   respectively. Significant differences were found between VEOPC and other PC patients.
150   The VEOPC patients had more males, fewer Caucasians, more surgery rates, fewer LNR,
151   higher TNM stage, higher grade, more experience of chemotherapy and radiotherapy and
152   fewer of married status (p < 0.001, Table 1) than the older patients. We also provided a
153   table with characteristics for all patients (Supplemental Table 1). We divided the older
154   patients into 4 groups with different age ranges (45-59 years, 60-69 years, 70-79 years
155   and >79 years) for further analysis.

156

157   ### Prognostic analysis of age in PDAC patients

158   The CIF plot showed VEOPC patients had a decreased risk of cancer death than
159   older patients (p < 0.001, Figure 1a). Further subgroup analyses by surgery showed that
160   VEOPC patients had better prognosis than the older patients whether they performed
161   surgery or not (p < 0.001, Figure 1b-c). Moreover, multivariate SH model with all the
162   included variables showed that in unresectable PDAC patients, the VEOPC had better
163   CSS than older patients. While in the resected PDAC patients, no significant difference
164   was found between VEOPC and older patients (Table 2).

165

166   ### Independent prognostic factors of CSS of VEOPC

167   As shown in Table 3, multivariate SH model was used to find independent prognostic
168   factors for the CSS of VEOPC patients. We found the female, race of Asian or Pacific
169   Islander, PC located in pancreatic duct, no surgery, high LNR, high M stage, high grade,
170   lack of chemotherapy, and single status were risk factors of the VEOPC patients ($P <$
171   $0.05$).

172

173   ### Nomogram development and validation

174    The nomogram was constructed by multivariate SH model. A weighted total score
175    calculated from each variable was used to estimate the 6 months, 12 months, 18 months
176    and 24 months cancer specific death of VEOPC patients (Figure 2). The sex, race,
177    location, surgery strategy, tumor size, LNR, TNM stage, grade, chemotherapy and marital
178    status were found to be significantly important for the prognosis of VEOPC patients
179    (Variables with asterisk in Figure 2). The calibration plots showed well correlation
180    between observed CSS and nomogram predicted CSS (Figure 3a-d).Time dependent
181    AUC plot suggested well discrimination of our nomogram (AUC >= 0.736, Figure 3e).
182    Furthermore, we equally stratified the whole VEOPC into three groups based on their
183    level of competing nomogram scores and performed a CIF analysis. The CIF plot (Figure
184    4) showed VEOPC with higher scores of our competing nomogram was at high risk of
185    cancer related death. It indicated that our competing nomogram was useful for risk
186    stratification of the prognosis of VEOPC patients. The detailed competing nomogram
187    scores for all variables were listed in Supplemental Table 2.

188

## Discussion

190    No previous competing analysis was performed to analyze the prognostic difference
191    between VEOPC and older PC patients. The current study used competing risk model to
192    estimate the prognostic difference between VEOPC and older patients by using the data
193    from SEER. We found that among the unresectable PDAC patients, the VEOPC had
194    better CSS than older patients. And among resected PDAC patients, there was no
195    significant prognostic difference between VEOPC and older patients. We also built the
196    first competing nomogram for primary VEOPC patients with histology type of PDAC.
197    Age was observed as an independent prognostic factor for many cancers. Previous
198    studies identified that younger patients had worse prognosis than older patients in
199    colorectal cancer(van Eeghen et al. 2015) and breast cancer(Chen et al. 2016) while
200    younger patients had better prognosis than older patients in lung cancer(Arnold et al.
201    2016), liver cancer(Zhang & Sun 2015) and prostate cancer (Pettersson et al. 2018). A
202    study found that the <45 years PDAC patients had better survival than > 70 years PDAC
203    patients (He et al. 2013). Another study found <50 years PDAC patients had no significant
204    difference on prognosis when compared with their whole cohort(Tingstedt et al. 2011). To
205    be noted, these studies only included with limited samples. A SEER based study found
206    the risk of cancer-specific death decreases with age in resectable PDAC patients(He et
207    al. 2018). However, we found the age was not an independent prognostic factor for
208    resectable PDAC patients. This difference might be caused by the difference of inclusion

209 criteria that our study included more variables in the multivariate SH model. We provided
210 a detailed inclusion workflow in the Supplemental Figure 1. We found the VEOPC
211 patients, despite with a higher TNM stage, had a better CSS than the older patients in
212 unresectable patients (Supplemental Table 3). It might be explained by the well accepted
213 fact that younger patients had more tolerance to chemotherapy. Indeed, in the
214 unresectable group, the VEOPC patients had a 17.5% higher rate to have chemotherapy
215 than the older patients.

216 Males had higher rate of PC incidence in United States(Yadav & Lowenfels 2013).
217 We observed the males had 15% higher rate than the females in VEOPC. Previous study
218 found males had worse prognosis than females in patients under 60 years but not in
219 VEOPC patients(McWilliams et al. 2016). It might be caused by the sample size. Our
220 study had much higher amount of VEOPC patients than this study and we found the males
221 had worse CSS than females.

222 Marriage status was linked to the improvements in cardiovascular, endocrine,
223 immune function, and cancer prognosis(Aizer et al. 2013; Gallo et al. 2003; Herberman
224 & Ortaldo 1981). Previous study observed that unmarried patients were at significantly
225 higher risk of presentation with metastatic cancer, undertreatment, and death resulting
226 from their cancer(Aizer et al. 2013). We found the VEOPC patients with married status
227 had better CSS than patients with single status, which provided new hint to the
228 association between support care and cancer prognosis.

229 Our SH model based nomogram was well validated by discrimination and calibration.
230 The variables included in our nomogram were easy to be obtained, allowing a feasible
231 translation into the future clinical use. To be noted, we included both the significant
232 variables and the insignificant variables into our nomogram, since if a nomogram only
233 includes statistically significant variables, it might tend to exert an inappropriately large
234 influence, leading to falsely narrowed confidence intervals, which would make this
235 nomogram appear more accurate than it is(Nicholas J Vogelzang 2005). Patients with
236 higher competing nomogram scores of our study were found to have higher CID,
237 indicating that our nomogram was useful for risk stratification of the prognosis of VEOPC
238 patients.

239 Our study had some limitations. First, the detailed strategy of chemotherapy or
240 radiotherapy was missed in current study as well as other therapies such as
241 immunotherapy. Second, although the current nomogram was well validated by internal
242 validation, there was a lack of an external validation by cohort other than SEER. Third, it
243 should be noted that only factors available in the SEER registry were examined. The
244 results from this study might only fit the population from United States. Fourth, our study

245 has no exploration of molecular mechanism, which was of interest but cannot be
246 conducted at this time with data currently available.
247

## Conclusions

249 The current study showed that for unresectable PDAC, VEOPC had better CSS than
250 older patients. For the VEOPC patients, we built a SH model based nomogram to estimate
251 their CSS. This nomogram was shown to have good discrimination and calibration.
252

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348

349 **Figure legends**

350 **Figure 1.** CIF plots of the association between age and the prognosis of PDAC patients
351 Legends: a-c, The CIF plots of the association between age and the prognosis of all
352 cohort (a), patients with surgery (b) or without surgery (c).

353

354 **Figure 2.** Nomogram for predicting 6 months, 12 months, 18 months and 24 months
355 cancer specific death of VEOPC patients
356 Legends: The nomogram is used by summing the points identified on the top scale for
357 each independent variable and drawing a vertical line from the total points scale to the 6
358 months, 12 months, 18 months and 24 months cancer specific death to obtain the
359 probability of survival. The total points projected to the bottom scale indicate the
360 probability of the 6 months, 12 months, 18 months and 24 months cancer specific death.
361 Sex: 1 = Male, 2 = Female; Race: 1 = Caucasian, 2 = African American, N = Other race;

362 Location: 250 = Head of pancreas, 251 = Body of pancreas, 252 = Tail of pancreas, 253
363 = Pancreatic duct, 257 = Other specified parts of pancreas, 258 = Overlapping lesion of
364 pancreas, 259 = Pancreas, NOS; Surgery, 0 = No surgery, 1 = Local or partial
365 pancreatectomy, 2 = Local or partial pancreatectomy and duodenectomy, 3 = Total
366 pancreatectomy with or without gastrectomy or duodenectomy, 4 = Pancreatectomy NOS
367 or surgery NOS; Tumor size: 2 = <=2cm, 4 = 2cm to 4cm, 6 = 4cm to 6cm, 8 = >6cm, 9
368 = Unknown; LNR: 0 = 0, 1 = <=0.2, 2 = 0.2-0.4, 3 = >0.4, 4 = No nodes were examined;
369 T stage: 1 = T1-T2, 2 = T3-T4, 9 = Unknown; N stage: 0 = NO, 1 = N1, 9 = Unknown; M
370 stage: 0 = M0, 1 = M1, 9 = Unknown; Grade: 1 = I-II, 2 = III-IV, 9 = Unknown;
371 Chemotherapy: 0 = none/unknown and 1 = yes; Radiotherapy: 0 = none/unknown or
372 refused, 1 = beam radiation or combination of beam with implants or isotopes or radiation
373 with method or source not specified or radioactive implants or radioisotopes and N =
374 Recommended, unknown if administered; Marital status: 0 = married; 1 = widowed or
375 single (never married or having a domestic partner) or divorced or separated. The asterisk
376 means significant.

377

378 **Figure 3.** Calibration curves and time dependent AUC plot for internal validation of SH
379 based nomograms
380 Legends: a-d, the calibration plots for 6 months (a), 12 months (b), 18 months (c) and 24
381 months (d) cancer specific death prediction of VEOPC patients; The x-axis shows the
382 nomogram predicted probability while the y-axis is the actual survival estimated by the
383 SH method, the black thick line overlaps the grey line indicating near perfect calibration;
384 e, time dependent AUC plots of SH-based nomograms.

385

386 **Figure 4.** CIF plot based on the competing nomogram scores for the VEOPC patients
387 Legends: the whole cohort of VEOPC patients were divided into three equally distributed
388 groups. The groups were named "High", "Intermediate" and "Low" according to the levels
389 of patients' competing nomogram scores.

The demographic and treatment data of VEOPC and older PC (>=45 years) patients

All variables showed significant differences between VEOPC and older PC patients (p < 0.001).

1   **Table 1. The demographic and treatment data of VEOPC and older PC (>=45 years)**
2   **patients**

| Characteristics | VEOPC (N = 1386) | | Older PC (N = 53932) | |
|---|---|---|---|---|
| | No. of patients | % | No. of patients | % |
| **Sex** | | | | |
| Male | 796 | 57.4% | 27337 | 50.7% |
| Female | 590 | 42.6% | 26595 | 49.3% |
| **Race** | | | | |
| Caucasian | 1026 | 74.0% | 43089 | 79.9% |
| African American | 207 | 14.9% | 6522 | 12.1% |
| American Indian/Alaska Native | 13 | 0.9% | 287 | 0.5% |
| Asian or Pacific Islander | 140 | 10.1% | 4034 | 7.5% |
| **Location** | | | | |
| Head of pancreas | 738 | 53.2% | 29410 | 54.5% |
| Body of pancreas | 154 | 11.1% | 6921 | 12.8% |
| Tail of pancreas | 182 | 13.1% | 6458 | 12.0% |
| Pancreatic duct | 12 | 0.9% | 319 | 0.6% |
| Other specified parts of pancreas | 18 | 1.3% | 805 | 1.5% |
| Overlapping lesion of pancreas | 113 | 8.2% | 4049 | 7.5% |
| Pancreas, NOS | 169 | 12.2% | 5970 | 11.1% |
| **Surgery** | | | | |
| No surgery | 1040 | 75.0% | 41989 | 77.9% |
| Local or partial pancreatectomy | 43 | 3.1% | 1517 | 2.8% |
| Local or partial pancreatectomy and duodenectomy | 242 | 17.5% | 8175 | 15.2% |
| Total pancreatectomy with or without gastrectomy or duodenectomy | 50 | 3.6% | 1978 | 3.7% |
| Pancreatectomy NOS or surgery NOS | 11 | 0.8% | 273 | 0.5% |
| **Tumor size (cm)** | | | | |
| <=2 | 144 | 10.4% | 4883 | 9.1% |
| 2 to 4 | 524 | 37.8% | 23278 | 43.2% |
| 4 to 6 | 333 | 24.0% | 12388 | 23.0% |
| >6 | 104 | 7.5% | 3840 | 7.1% |
| Unknown | 281 | 20.3% | 9543 | 17.7% |

**LNR**

| | | | | |
|---|---|---|---|---|
| 0 | 137 | 9.9% | 4542 | 8.4% |
| <=0.2 | 126 | 9.1% | 3983 | 7.4% |
| 0.2-0.4 | 57 | 4.1% | 2180 | 4.0% |
| 0.4-1 | 55 | 4.0% | 2116 | 3.9% |
| No nodes were examined | 1011 | 72.9% | 41111 | 76.2% |
| **T stage** | | | | |
| T1-T2 | 275 | 19.8% | 11774 | 21.8% |
| T3-T4 | 865 | 62.4% | 33301 | 61.7% |
| Unknown | 246 | 17.7% | 8857 | 16.4% |
| **N stage** | | | | |
| N0 | 603 | 43.5% | 26845 | 49.8% |
| N1 | 584 | 42.1% | 19325 | 35.8% |
| Unknown | 199 | 14.4% | 7762 | 14.4% |
| **M stage** | | | | |
| M0 | 582 | 42.0% | 26570 | 49.3% |
| M1 | 786 | 56.7% | 25678 | 47.6% |
| Unknown | 18 | 1.3% | 1684 | 3.1% |
| **Grade** | | | | |
| I-II | 326 | 23.5% | 11939 | 22.1% |
| III-IV | 256 | 18.5% | 8755 | 16.2% |
| Unknown | 804 | 58.0% | 33238 | 61.6% |
| **Chemotherapy** | | | | |
| No | 312 | 22.5% | 20586 | 38.2% |
| Yes | 1074 | 77.5% | 33346 | 61.8% |
| **Radiotherapy** | | | | |
| No | 1021 | 73.7% | 42283 | 78.4% |
| Yes | 365 | 26.3% | 11649 | 21.6% |
| **Marital status** | | | | |
| Married | 768 | 55.4% | 32013 | 59.4% |
| Single | 618 | 44.6% | 21919 | 40.6% |

3 All variables showed significant differences between VEOPC and older PC patients ($p < 0.001$).

Multivariate SH analysis of CSS for the association between age and the prognosis of PDAC patients

We included all variables in the SH multivariate analysis. HR, Hazard ratio; 95%CI,

95%confidence index; Significant results (p < 0.05) were bolded.

1    **Table 2. Multivariate SH analysis of CSS for the association between age and the prognosis of PDAC patients**

| Age (Years) | For the whole cohort | | For patients with surgery | | For patients without surgery | |
|---|---|---|---|---|---|---|
| | HR (95%CI) | p value | HR (95%CI) | p value | HR (95%CI) | p value |
| <45 | Reference | | Reference | | Reference | |
| 45-59 | **1.08 (1.02-1.14)** | **0.010** | 0.98 (0.86-1.12) | 7.50E-01 | **1.10 (1.03-1.16)** | **0.003** |
| 60-69 | **1.10 (1.04-1.17)** | **<0.001** | 1.01 (0.89-1.15) | 9.00E-01 | **1.13 (1.06-1.20)** | **<0.001** |
| 70-79 | **1.16 (1.09-1.23)** | **<0.001** | 1.04 (0.91-1.19) | 5.70E-01 | **1.19 (1.12-1.26)** | **<0.001** |
| >79 | **1.17 (1.10-1.24)** | **<0.001** | 1.00 (0.87-1.17) | 9.60E-01 | **1.19 (1.12-1.27)** | **<0.001** |

2    We included all variables in the SH multivariate analysis. HR, Hazard ratio; 95%CI, 95%confidence index; Significant results ($p < 0.05$) were bolded.

Multivariate SH analyses of CSS for each variable in VEOPC patients

We included all variables in the SH multivariate analysis. HR, Hazard ratio; 95%CI, 95%confidence index; Significant results (p < 0.05) were bolded.

1 **Table 3. Multivariate SH analyses of CSS for each variable in VEOPC patients**

| Characteristics | HR (95%CI) | p value |
|---|---|---|
| **Sex** | | |
| Male | Reference | |
| Female | **0.87 (0.77-0.98)** | **0.021** |
| **Race** | | |
| Caucasian | Reference | |
| African American | 1.02 (0.84-1.23) | 0.880 |
| American Indian/Alaska Native | 1.00 (0.67-1.50) | 1.000 |
| Asian or Pacific Islander | **1.54 (1.30-1.83)** | **<0.001** |
| **Location** | | |
| Head of pancreas | Reference | |
| Body of pancreas | 0.89 (0.73-1.08) | 0.220 |
| Tail of pancreas | 1.07 (0.87-1.32) | 0.530 |
| Pancreatic duct | **2.01 (1.34-3.02)** | **0.001** |
| Other specified parts of pancreas | 0.65 (0.33-1.29) | 0.220 |
| Overlapping lesion of pancreas | 0.92 (0.72-1.18) | 0.520 |
| Pancreas, NOS | **1.28 (1.03-1.60)** | **0.025** |
| **Surgery** | | |
| No surgery | Reference | |
| Local or partial pancreatectomy | **0.40 (0.26-0.61)** | **<0.001** |
| Local or partial pancreatectomy and duodenectomy | **0.46 (0.36-0.60)** | **<0.001** |
| Total pancreatectomy with or without gastrectomy or duodenectomy | **0.41 (0.28-0.61)** | **<0.001** |
| Pancreatectomy NOS or surgery NOS | 0.77 (0.36-1.64) | 0.490 |
| **Tumor size** | | |
| <=2cm | Reference | |
| 2 to 4 | 1.07 (0.87-1.32) | 0.510 |
| 4 to 6 | 1.11 (0.88-1.41) | 0.360 |
| >6 | 1.28 (0.94-1.74) | 0.110 |
| Unknown | 1.01 (0.78-1.32) | 0.930 |
| **LNR** | | |
| 0 | Reference | |
| <=0.2 | **1.39 (1.02-1.90)** | **0.037** |
| 0.2-0.4 | **1.80 (1.30-2.51)** | **<0.001** |
| 0.4-1 | **1.90 (1.37-2.64)** | **<0.001** |
| No nodes were examined | **1.33 (1.04-1.70)** | **0.021** |
| **T stage** | | |
| T1-T2 | Reference | |
| T3-T4 | 1.16 (0.98-1.37) | 0.082 |
| Unknown | 0.95 (0.73-1.22) | 0.680 |

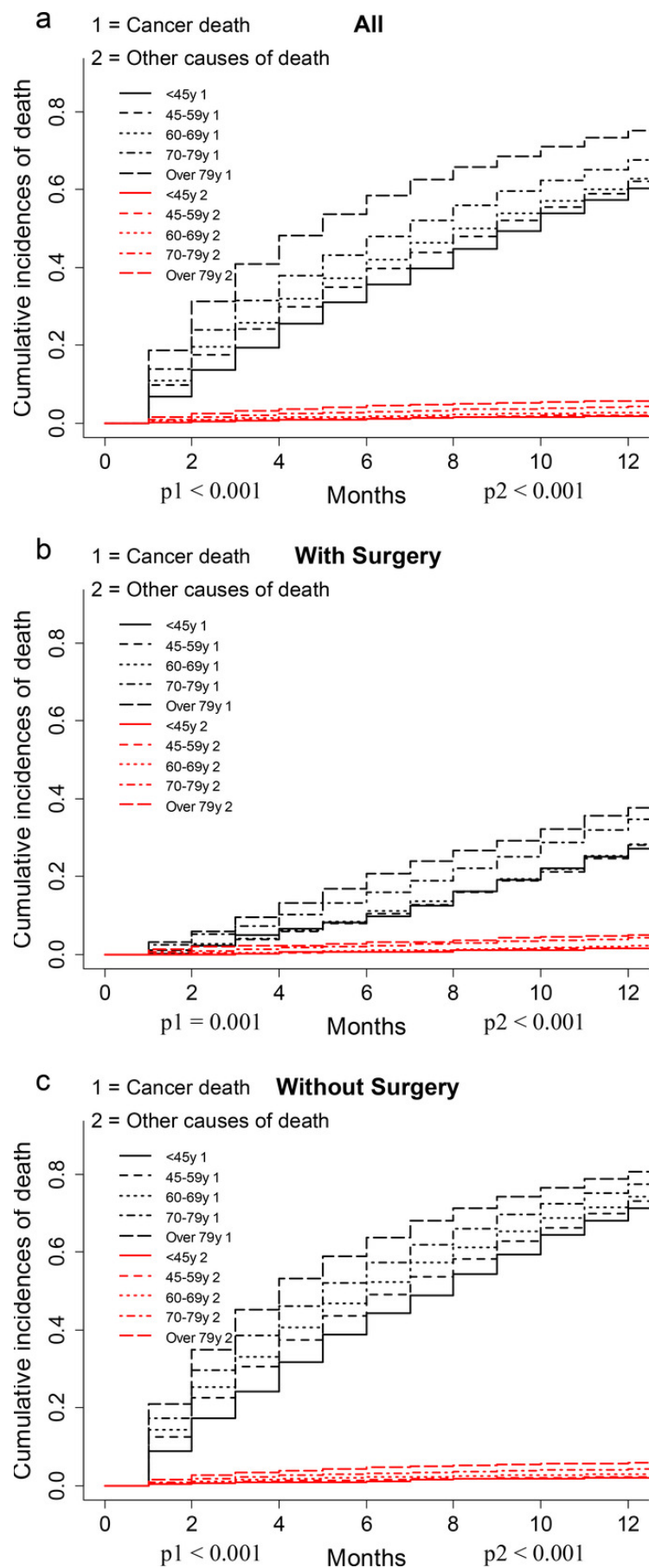
| | | |
|---|---|---|
| **N stage** | | |
| N0 | Reference | |
| N1 | 1.12 (0.95-1.31) | 0.170 |
| Unknown | **1.34 (1.09-1.66)** | **0.005** |
| **M stage** | | |
| M0 | Reference | |
| M1 | **1.48 (1.25-1.75)** | **<0.001** |
| Unknown | 1.09 (0.60-1.96) | 0.780 |
| **Grade** | | |
| I-II | Reference | |
| III-IV | **1.29 (1.07-1.56)** | **0.007** |
| Unknown | 1.09 (0.93-1.29) | 0.290 |
| **Chemotherapy** | | |
| No | Reference | |
| Yes | **0.63 (0.53-0.76)** | **<0.001** |
| **Radiotherapy** | | |
| No | Reference | |
| Yes | 1.09 (0.94-1.25) | 0.250 |
| **Marital status** | | |
| Married | Reference | |
| Single | **1.15 (1.02-1.30)** | **0.021** |

2  We included all variables in the SH multivariate analysis. HR, Hazard ratio; 95%CI, 95%confidence index;

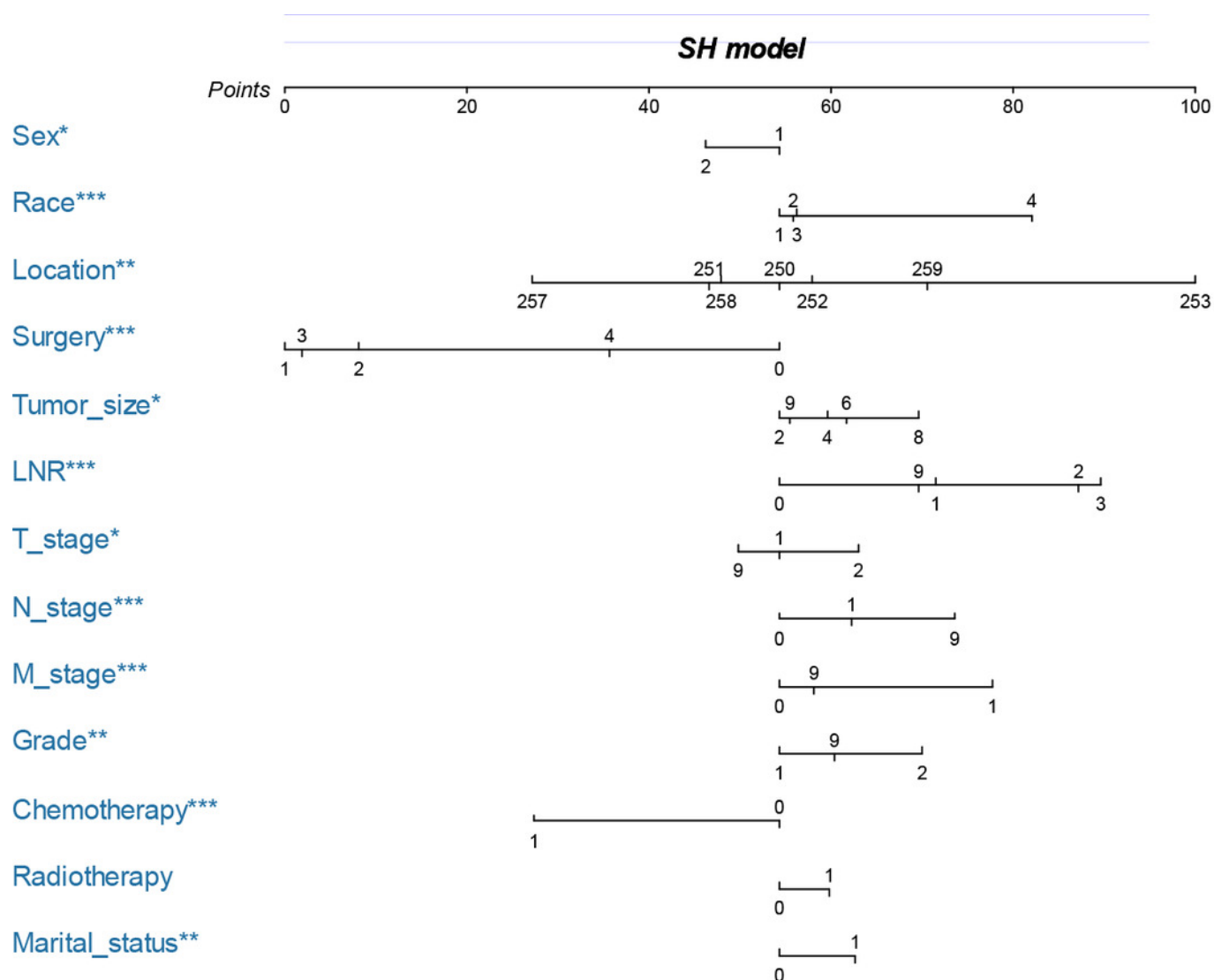
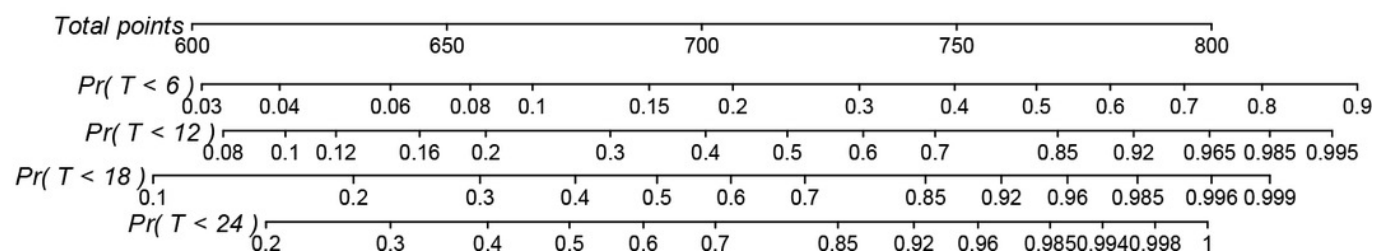
3  Significant results (p < 0.05) were bolded.

# Figure 1

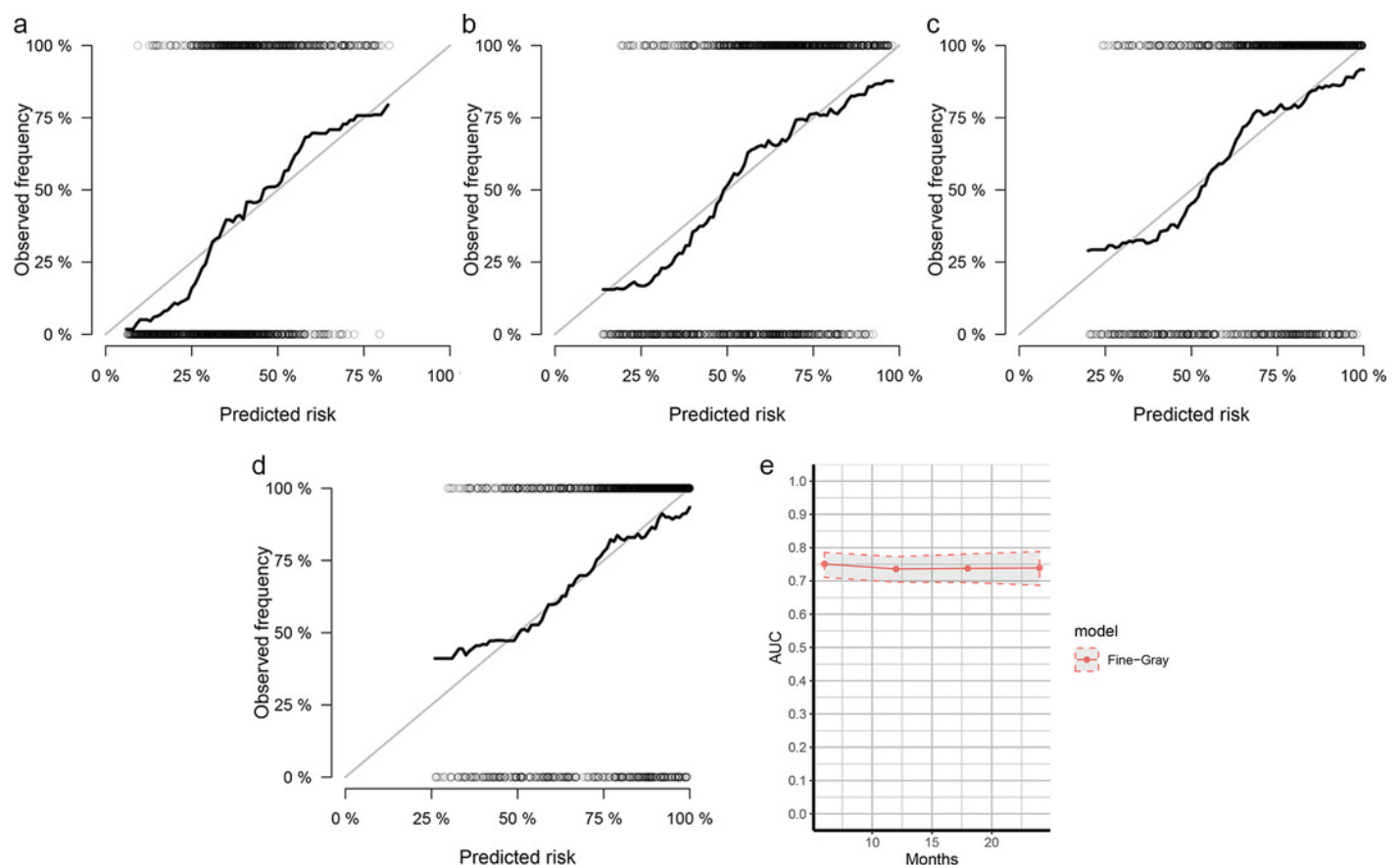
CIF plots of the association between age and the prognosis of PDAC patients

a-c, The CIF plots of the association between age and the prognosis of all cohort (a), patients with surgery (b) or without surgery (c).

# Figure 2

Nomogram for predicting 6 months, 12 months, 18 months and 24 months cancer specific death of VEOPC patients

The nomogram is used by summing the points identified on the top scale for each independent variable and drawing a vertical line from the total points scale to the 6 months, 12 months, 18 months and 24 months cancer specific death to obtain the probability of survival. The total points projected to the bottom scale indicate the probability of the 6 months, 12 months, 18 months and 24 months cancer specific death. Sex: 1 = Male, 2 = Female; Race: 1 = Caucasian, 2 = African American, N = Other race; Location: 250 = Head of pancreas, 251 = Body of pancreas, 252 = Tail of pancreas, 253 = Pancreatic duct, 257 = Other specified parts of pancreas, 258 = Overlapping lesion of pancreas, 259 = Pancreas, NOS; Surgery, 0 = No surgery, 1 = Local or partial pancreatectomy, 2 = Local or partial pancreatectomy and duodenectomy, 3 = Total pancreatectomy with or without gastrectomy or duodenectomy, 4 = Pancreatectomy NOS or surgery NOS; Tumor size: 2 = <=2cm, 4 = 2cm to 4cm, 6 = 4cm to 6cm, 8 = >6cm, 9 = Unknown; LNR: 0 = 0, 1 = <=0.2, 2 = 0.2-0.4, 3 = >0.4, 4 = No nodes were examined; T stage: 1 = T1-T2, 2 = T3-T4, 9 = Unknown; N stage: 0 = NO, 1 = N1, 9 = Unknown; M stage: 0 = M0, 1 = M1, 9 = Unknown; Grade: 1 = I-II, 2 = III-IV, 9 = Unknown; Chemotherapy: 0 = none/unknown and 1 = yes; Radiotherapy: 0 = none/unknown or refused, 1 = beam radiation or combination of beam with implants or isotopes or radiation with method or source not specified or radioactive implants or radioisotopes and N = Recommended, unknown if administered; Marital status: 0 = married; 1 = widowed or single (never married or having a domestic partner) or divorced or separated. The asterisk means significant.

# Figure 3

Calibration curves and AUC plots for internal validation of SH based nomograms

a-d, the calibration plots for 6 months (a), 12 months (b) , 18 months (c) and 24 months (d) cancer specific death prediction of VEOPC patients; The x-axis shows the nomogram predicted probability while the y-axis is the actual survival estimated by the SH method, the black thick line overlaps the grey line indicating near perfect calibration; e, time dependent AUC plots of SH-based nomograms.

# Figure 4

CIF plots based on the competing nomogram scores for the VEOPC patients

the whole cohort of VEOPC patients were divided into three equally distributed groups. The groups were named "High", "Intermediate" and "Low" according to the levels of patients' competing nomogram scores.