MEDICAL SCIENCE MONITOR

DATABASE ANALYSIS

e-ISSN 1643-3750
© Med Sci Monit, 2020; 26: e923931
DOI: 10.12659/MSM.923931

Received: 2020.03.01
Accepted: 2020.04.06
Available online: 2020.06.18
Published: 2020.08.19

A Predictive Nomogram for Early Mortality in Stage IV Gastric Cancer

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

ACDE 1 Yuqian Feng*
ABDE 1 Kaibo Guo*
BC 1 Huimin Jin
D 1 Yuying Xiang
E 1 Yiting Zhang
AFG 2 Shanming Ruan

1 The First Clinical Medical College of Zhejiang Chinese Medical University, Hangzhou, Zhejiang, P.R. China
2 Department of Medical Oncology, The First Affiliated Hospital of Zhejiang Chinese Medical University, Hangzhou, Zhejiang, P.R. China

* Yuqian Feng and Kaibo Guo contributed equally to this study and should be considered as first co-authors

Corresponding Author: Shanming Ruan, e-mail: shanmingruan@zcmu.edu.cn

Source of support: National project of clinical collaboration of traditional Chinese and western medicine for the treatment of major diseases (Bin Lv, gastric cancer, *http://yzs.satcm.gov.cn*); Program for the Cultivation of Youth Talents in China Association of Chinese Medicine (QNRC2-C08); Zhejiang Provincial Project for the key discipline of traditional Chinese medicine (Yong Guo, no. 2017-XK-A09)

Background: The study was intended to establish predictive nomogram models for predicting total early mortality (the probability of surviving less than or equal to 3 months) and cancer-specific early mortality in patients with stage IV gastric cancer. This was the first study to establish prognostic survival in patients with stage IV gastric cancer.

Material/Methods: Patients from the SEER database were identified using inclusion and exclusion criteria. Their clinical characteristics were statistically analyzed. The Kaplan-Meier method and the log-rank test were used to compare the influences of different factors on survival time. Logistic regression models were conducted to explore the correlative factors of early mortality. A nomogram was established based on factors significant in the logistic regression model and an internal validation was performed.

Results: Of the 11,036 eligible patients included in the study, 4932 (44.7%) patients resulted in total early death (42.6% died of the cancer and 2.1% died of other reasons). Larger tumor size, poor differentiation, and liver metastasis were positively related to cancer-specific early mortality. Surgery was negatively related to total early mortality and cancer-specific early mortality, while cardia was only negatively associated with total early death. Predictive nomogram models for total early mortality and cancer-specific early mortality have been validated internally. The areas under the receiver operating characteristics curve were 73.5%, and 68.0%, respectively, and the decision curve analysis also proved the value of the models.

Conclusions: The nomogram models proved to be a suitable tool for predicting the early mortality in stage IV gastric cancer.

MeSH Keywords: Mortality, Premature • Nomograms • Stomach Neoplasms

Full-text PDF: https://www.medscimonit.com/abstract/index/idArt/923931

2816 3 8 34

Indexed in: [Current Contents/Clinical Medicine] [SCI Expanded] [ISI Alerting System] [ISI Journals Master List] [Index Medicus/MEDLINE] [EMBASE/Excerpta Medica] [Chemical Abstracts/CAS]

Background

Globally, gastric cancer ranks fifth and third in cancer incidence and mortality, respectively. There were more than 1.03 million newly diagnosed gastric cancer cases worldwide and approximately 783,000 death cases in 2018. Gastric cancer morbidity is the highest in eastern Asia [1]. Distant metastases to gastric cancer are common at the time of diagnosis [2]. Metastatic disease is found at the initial diagnosis of 35% to 40% of gastric cancer patients, and 4% to 14% of these have metastatic disease in the liver, followed by the lung, bone, and brain [3,4]. Many factors such as age, tumor location, tumor size, TNM (Tumor-Node-Metastasis), and surgery, affect the prognosis of cancer.

At present, the prognosis of solid cancer is decided by the American Joint Committee on Cancer (AJCC) TNM staging system [5,6]. However, the existing TNM staging does not reflect tumor prognosis well [7,8]. Based on this system, we cannot evaluate the prognosis between patients with stage IV gastric cancer. Therefore, we need to develop a new prognosis prediction model to accurately individualize the early mortality between advanced cancer patients. Large sample studies have been rarely performed, and are urgently needed at present.

This study was based on information about patients with stage IV gastric cancer from the Surveillance, Epidemiology, and End Results (SEER) database to analyze demographic and clinical characteristics, evaluate early mortality, and examine the risk factors of early death when first diagnosed. In addition, the work has produced a predictive nomogram that contained relevant factors for predicting early mortality and internal validation was performed to test the accuracy of the predictive model.

Material and Methods

Data

Data was obtained from the SEER database, which provides the cancer relevant factors and survival outcomes from established cancer registries across approximately one-third of the United States population. The database includes information about the clinical characteristics and survival outcomes for different cancer patients. It has certain standards for patient data collection, therefore, its accuracy is guaranteed. SEER*Stat Software version 8.3.5 (*https://seer.cancer.gov/seerstat/*, National Cancer Institute, Maryland, U.S.) was used to collect information about gastric cancer patients in the study. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The SEER Program collects data from population-based cancer registries with anonymous information. The SEER database has public-use data and our study did not require approval or a declaration of local ethics.

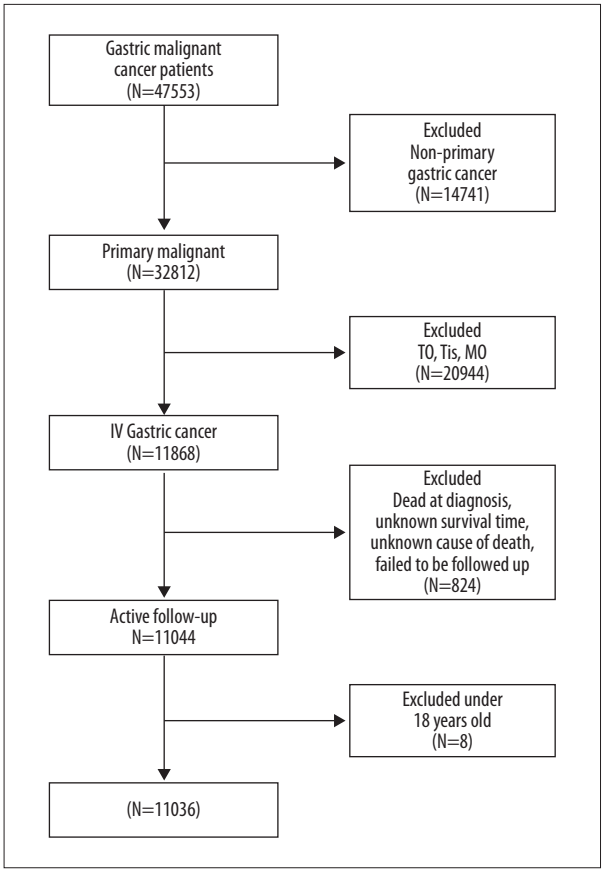


Figure 1. Flowchart for selection of the stage IV gastric cancer patients.

Study population

This was a population-based cohortstudy. The SEER database did not collect data on organ metastases until 2010. Therefore, the study included patients diagnosed with gastric cancer between 2010 and 2016 (with at least 3 months follow-up). Patients with non-primary tumors, T0, Tis, M0, dead at diagnosis, ambiguous survival time, unknown cause of death, failed to be followed up, or ≤18 years old were excluded. Inclusion criteria were patients with stage IV gastric cancer confirmed at the initial diagnosis (Figure 1). When cancer patients died within 3 months of initial diagnosis, it was defined as early death [9,10].

Indexed in: [Current Contents/Clinical Medicine] [SCI Expanded] [ISI Alerting System] [ISI Journals Master List] [Index Medicus/MEDLINE] [EMBASE/Excerpta Medica] [Chemical Abstracts/CAS]

Statistical analysis

The quantitative data involved in the study were described as mean±standard deviation and comparisons between different groups were analyzed using Student's *t* tests. The categorical data were mainly described as a percentage (%) and the difference between categorical variables were analyzed by the Pearson chi-squared test. The primary outcomes were total early death, cancer-specific early death, and non-cancer-specific early death. Non-cardia includes the fundus of the stomach, body of the stomach, lesser curvature of the stomach, greater curvature of the stomach, overlapping lesion of the stomach, gastric antrum, and pylorus. Influences of the correlative factors on survival time were compared by the Kaplan-Meier method, and the log-rank test was used. The study first used univariate logistic regression to derive factors related to early death. Then variables with $p<0.05$ were included in multivariate logistic regression. Incomplete information in the variables was excluded.

The predictive nomograms for total early mortality, and cancer-specific early mortality were based on the results of regression analysis using the R version 3.6.1 (Lucent Technologies, New Jersey, U.S.). Calibration plots for the nomograms were produced. The reliability of the nomograms was evaluated by the C-index, receiver operating characteristic curve, the area under the curve (AUC), and decision curve analysis (DCA). Due to the lack of relevant models for the early death prognosis of patients with stage IV gastric cancer, the nomogram and internal verification with the existing prognostic criterion could not be compared.

Results

Demographic and clinical characteristics

Information was initially collected from the database for 47,553 gastric cancer patients, and 11,036 eligible patients were included in the study after strict screening for inclusion and exclusion criteria. The average age of patients was 63.60±14.28 years, with 64.2% (N=7081) male and 35.8% (N=3955) female patients. The average age of females with gastric cancer was higher than that of males (64.10±15.76 years *vs.* 63.32±13.38 years, $p<0.001$). The majority of patients were Caucasians (71.7%, N=7911), 56.3% patients (N=6208) were married, 32.2% patients had cardia gastric cancer, and 88.0% patients had adenocarcinomas. Among the study population, the percentages of liver, lung, bone and brain metastases were 43.0%, 14.7%, 12.8%, and 2.0%, respectively. Patients' clinical characteristics are shown in Table 1.

Incidence of early death

In the present study, 4932 (44.7%) gastric cancer patients had total early deaths, where 4697 (42.6%) patients died of the cancer and 235 (2.1%) patients died of other reasons. Early mortality for males with gastric cancer was higher than females, however, there was no statistical difference (28.6% *vs.* 16.1%, $\chi^2=0.19$, $p>0.05$). The incidence of total early death fluctuated significantly with age. Early mortality in patients aged 18–40 years decreased with age, while early mortality increased for the other age groups. Trends in early mortality were roughly the same for males and females in the various age groups (Figure 2A).

Early mortality varied with the location of primary tumors. In females, the lowest early mortality was for tumors in the lesser curvature of the stomach (38.6%), followed by the body of the stomach (39.7%) and cardia (40.3%). However, the tumors of the greater curvature of the stomach (49.1%) and fundus of the stomach (48.6%) contributed to higher early mortality. In males, the lowest early mortality was seen in patients with tumors in the cardia (37.8%). However, patients with tumors in the greater curvature of the stomach (52.0%), overlapping lesion of the stomach (48.5%), and body of the stomach (48.1%) contributed to higher early mortality. The cardia cancer (38.3%) presented significantly lower early mortality than the non-cardia cancer (45.0%) ($\chi^2=38.98$, $p< 0.001$) (Figure 2B).

Gastric cancer patients with brain metastases had the highest early mortality (59.0%), followed by lung (53.8%), bone (52.4%), and liver metastases (49.6%). In females, early mortality due to brain metastases (68.3%) was higher than that in males (55.4%) and the total group (59.0%) (Figure 2C).

The early mortality of gastric cancer patients was positively correlated with the number of metastatic organ sites ($\chi^2=164.29$, $p<0.001$). Male patients presented with similar results ($\chi^2=81.435$, $p<0.001$). For males, early mortality in four organ metastases (66.7%) was higher than three organ metastases (58.9%). However, for females, early mortality in four organ metastases (60.0%) was slightly lower than three organ metastases (61.1%) (Figure 2D).

The median survival time of different age groups varied. Patients older than 85 years had the shortest median survival time ($p<0.001$) compared with the other listed age groups (Figure 3A). Amongst the study population, the median survival time of non-cardia cancer was significantly shorter than patients with cardia gastric cancer ($p<0.001$) (Figure 3B). Patients with liver metastases had significantly shorter survival times than patients without liver metastases. Similar results were seen for lung metastases ($p<0.001$) (Figure 3C, 3D). Compared to patients with a lower histological grade, those

Indexed in: [Current Contents/Clinical Medicine] [SCI Expanded] [ISI Alerting System] [ISI Journals Master List] [Index Medicus/MEDLINE] [EMBASE/Excerpta Medica] [Chemical Abstracts/CAS]

Table 1. Univariable logistic regression for analyzing the risk factors for early death.

Factors	Patients no.(%)			
	No early death	Total early death	Cancer-specific early death	Non-cancer-specific early death
Age				
≤55	2040 (33.42)	1022 (20.72)	992 (21.12)	30 (12.77)
56–65	1793 (29.37)	1181 (23.95)	1126 (23.97)	55 (23.40)
66–75	1365 (22.36)	1203 (24.39)	1134 (24.14)	69 (29.36)
≥76	906 (14.84)	1526 (30.94)	1445 (30.76)	81 (34.47)
Race				
White	4382 (71.79)	3529 (71.55)	3362 (71.58)	167 (71.06)
Black	766 (12.55)	717 (14.54)	677 (14.41)	40 (17.02)
Asian or Pacific Islander	863 (14.14)	603 (12.23)	576 (12.26)	27 (11.49)
American Indian/Alaska Native	69 (1.13)	66 (1.34)	65 (1.38)	1 (0.43)
Unknown	24 (0.39)	17 (0.34)	17 (0.36)	0 (0.00)
Sex				
Female	2176 (35.65)	1779 (36.07)	1697 (36.13)	82 (34.89)
Male	3928 (64.35)	3153 (63.93)	3000 (63.87)	153 (65.11)
Marital status				
Unmarried	2086 (34.17)	2228 (45.17)	2120 (45.14)	108 (45.96)
Married	3718 (60.91)	2490 (50.49)	2375 (50.56)	115 (48.94)
Unknown	300 (4.91)	214 (4.34)	202 (4.30)	12 (5.11)
Insurance status				
Uninsured	280 (4.59)	290 (5.88)	284 (6.05)	6 (2.55)
Insured	5706 (93.48)	4520 (91.65)	4300 (91.55)	220 (93.62)
Unknown	118 (1.93)	122 (2.47)	113 (2.41)	9 (3.83)
Primary site				
Non-cardia	2912 (47.71)	2387 (48.40)	2270 (48.33)	117 (49.79)
Cardia	2194 (35.94)	1364 (27.66)	1300 (27.68)	64 (27.23)
Unknown	998 (16.35)	1181 (23.95)	1127 (23.99)	54 (22.98)
Pathological type				
Adenocarcinoma(exclude signet ring cell)	4083 (66.89)	3235 (65.59)	3078 (65.53)	157 (66.81)
Signet ring cell	1381 (22.62)	1011 (20.50)	970 (20.65)	41 (17.45)
Others	640 (10.48)	686 (13.91)	649 (13.82)	37 (15.74)
Tumor size (cm)				
<3	450 (7.37)	256 (5.19)	243 (5.17)	13 (5.53)
≥3 <5	740 (12.12)	454 (9.21)	429 (9.13)	25 (10.64)
≥5 <7	717 (11.75)	447 (9.06)	428 (9.11)	19 (8.09)
≥7 <9	358 (5.87)	221 (4.48)	209 (4.45)	12 (5.11)
≥9	335 (5.49)	262 (5.31)	251 (5.34)	11 (4.68)
Unknown	3504 (57.40)	3292 (66.75)	3137 (66.79)	155 (65.96)

Indexed in: [Current Contents/Clinical Medicine] [SCI Expanded] [ISI Alerting System] [ISI Journals Master List] [Index Medicus/MEDLINE] [EMBASE/Excerpta Medica] [Chemical Abstracts/CAS]

Table 1 continued. Univariable logistic regression for analyzing the risk factors for early death.

Factors	Patients no.(%)			
	No early death	Total early death	Cancer-specific early death	Non-cancer-specific early death
T stage				
T1	962 (15.76)	780 (15.82)	730 (15.54)	50 (21.28)
T2	333 (5.46)	168 (3.41)	162 (3.45)	6 (2.55)
T3	1029 (16.86)	454 (9.21)	431 (9.18)	23 (9.79)
T4	1325 (21.71)	973 (19.73)	931 (19.82)	42 (17.87)
Others	2455 (40.22)	2557 (51.85)	2443 (52.01)	114 (48.51)
Lymphatic metastasis				
N0	1979 (32.42)	1860 (37.71)	1766 (37.60)	94 (40.00)
N1	2272 (37.22)	1438 (29.16)	1368 (29.12)	70 (29.79)
N2	447 (7.32)	199 (4.03)	189 (4.02)	10 (4.26)
N3	489 (8.01)	219 (4.44)	210 (4.47)	9 (3.83)
Others	917 (15.02)	1216 (24.66)	1164 (24.78)	52 (22.13)
Histological grade				
I	125 (2.05)	55 (1.12)	52 (1.11)	3 (1.28)
II	1166 (19.10)	714 (14.48)	667 (14.20)	47 (20.00)
III	3494 (57.24)	2698 (54.70)	2593 (55.21)	105 (44.68)
IV	68 (1.11)	76 (1.54)	74 (1.58)	2 (0.85)
Others	1251 (20.49)	1389 (28.16)	1311 (27.91)	78 (33.19)
Liver metastases				
Yes	2392 (39.19)	2351 (47.67)	2231 (47.50)	120 (51.06)
No	3464 (56.75)	2372 (48.09)	2268 (48.29)	104 (44.26)
Others	248 (4.06)	209 (4.24)	198 (4.22)	11 (4.68)
Lung metastases				
Yes	751 (12.30)	873 (17.70)	825 (17.56)	48 (20.43)
No	5028 (82.37)	3720 (75.43)	3547 (75.52)	173 (73.62)
Others	325 (5.32)	339 (6.87)	325 (6.92)	14 (5.96)
Bone metastases				
Yes	672 (11.01)	741 (15.02)	714 (15.20)	27 (11.49)
No	5144 (84.27)	3881 (78.69)	3690 (78.56)	191 (81.28)
Others	288 (4.72)	310 (6.29)	293 (6.24)	17 (7.23)
Brain metastases				
Yes	89 (1.46)	128 (2.60)	126 (2.68)	2 (0.85)
No	5705 (93.46)	4468 (90.59)	4254 (90.57)	214 (91.06)
Others	310 (5.08)	336 (6.81)	317 (6.75)	19 (8.09)
Surgery				
Yes	861 (14.11)	275 (5.58)	254 (5.41)	21 (8.94)
No	123 (2.02)	133 (2.70)	128 (2.73)	5 (2.13)
Unknown	5120 (83.88)	4524 (91.73)	4315 (91.87)	209 (88.94)

Indexed in: [Current Contents/Clinical Medicine] [SCI Expanded] [ISI Alerting System] [ISI Journals Master List] [Index Medicus/MEDLINE] [EMBASE/Excerpta Medica] [Chemical Abstracts/CAS]

Table 1 continued. Univariable logistic regression for analyzing the risk factors for early death.

Factors	Total early death		Cancer-specific early death		Non-cancer-specific early death	
	OR (95% CI)	P-value	OR(95% CI)	P-value	OR (95% CI)	P-value
Age						
≤55	Ref	1	Ref	1	Ref	1
56–65	1.315 (1.184–1.461)	<0.001	0.889 (0.771–1.024)	0.103	1.904 (1.226–3.014)	0.005
66–75	1.759 (1.579–1.960)	<0.001	0.981 (0.845–1.140)	0.802	2.791 (1.183–4.357)	<0.001
≥76	3.362 (3.009–3.759)	<0.001	1.474 (1.249–1.743)	<0.001	3.482 (2.309–5.391)	<0.001
Race						
White	Ref	1	Ref	1	Ref	1
Black	1.162 (1.040–1.299)	0.008	1.030 (0.876–1.216)	0.726	1.285 (0.895–1.803)	0.159
Asian or Pacific Islander	0.868 (0.775–0.971)	0.014	0.860 (0.737–1.007)	0.058	0.870 (0.565–1.288)	0.506
American Indian/Alaska Native	1.188 (0.844–1.670)	0.322	1.598 (0.919–3.060)	0.123	0.346 (0.020–1.558)	0.292
Unknown	NA	NA	NA	NA	NA	NA
Sex						
Female	Ref	1	Ref	1	Ref	1
Male	0.982 (0.908–1.062)	0.646	0.913 (0.814–1.023)	0.12	1.043 (0.798–1.373)	0.76
Marital status						
Unmarried	Ref	1	Ref	1	Ref	1
Married	0.627 (0.580–0.678)	<0.001	0.863 (0.769–0.967)	0.012	0.735 (0.564–0.959)	0.023
Unknown	NA	NA	NA	NA	NA	NA
Insurance status						
Uninsured	Ref	1	Ref	1	Ref	1
Insured	0.765 (0.646–0.905)	0.002	0.923 (0.712–1.179)	0.533	2.067 (1.000–5.261)	0.081
Unknown	NA	NA	NA	NA	NA	NA
Primary site						
Non-cardia	Ref	1	Ref	1	Ref	1
Cardia	0.758 (0.695–0.827)	<0.001	0.998 (0.885–1.127)	0.98	0.811 (0.593–1.099)	0.183
Unknown	NA	NA	NA	NA	NA	NA
Pathological type						
Adenocarcinoma(exclude signet ring cell)	Ref	1	Ref	1	Ref	1
Signet ring cell	0.924 (0.841–1.014)	0.097	1.187 (1.035–1.366)	0.015	0.795 (0.555–1.114)	0.196
Others	NA	NA	NA	NA	NA	NA
Tumor size (cm)						
<3	Ref	1	Ref	1	Ref	1
≥3 <5	1.078 (0.890–1.309)	0.443	1.288 (1.015–1.631)	0.036	1.140 (0.589–2.310)	0.704
≥5 <7	1.096 (0.903–1.331)	0.354	1.416 (1.111–1.802)	0.005	0.885 (0.438–1.844)	0.736
≥7 <9	1.085 (0.864–1.362)	0.481	1.455 (1.090–1.951)	0.012	1.128 (0.503–2.506)	0.765
≥9	1.375 (1.100–1.718)	0.005	1.787 (1.326–2.426)	<0.001	1.001 (0.436–2.254)	0.999
Unknown	NA	NA	NA	NA	NA	NA

Indexed in: [Current Contents/Clinical Medicine] [SCI Expanded] [ISI Alerting System] [ISI Journals Master List] [Index Medicus/MEDLINE] [EMBASE/Excerpta Medica] [Chemical Abstracts/CAS]

Table 1 continued. Univariable logistic regression for analyzing the risk factors for early death.

Factors	Total early death		Cancer-specific early death		Non-cancer-specific early death	
	OR (95% CI)	P-value	OR(95% CI)	P-value	OR (95% CI)	P-value
T stage						
T1	Ref	1	Ref	1	Ref	1
T2	0.622 (0.505–0.765)	<0.001	0.710 (0.545–0.933)	0.0126	0.410 (0.157–0.889)	0.041
T3	0.544 (0.470–0.629)	<0.001	0.712 (0.587–0.863)	<0.001	0.533 (0.318–0.867)	0.013
T4	0.906 (0.799–1.027)	0.122	1.024 (0.850–1.231)	0.804	0.630 (0.414–0.953)	0.029
Others	NA	NA	NA	NA	NA	NA
Lymphatic metastasis						
N0	Ref	1	Ref	1	Ref	1
N1	0.673 (0.614–0.738)	<0.001	0.921 (0.808–1.050)	0.22	0.766 (0.559–1.046)	0.095
N2	0.474 (0.396–0.565)	<0.001	0.587 (0.476–0.728)	<0.001	0.626 (0.305–1.150)	0.163
N3	0.477 (0.401–0.565)	<0.001	0.696 (0.564–0.865)	<0.001	0.513 (0.240–0.966)	0.057
Others	NA	NA	NA	NA	NA	NA
Histological grade						
I	Ref	1	Ref	1	Ref	1
II	1.392 (1.005–1.950)	0.05	1.715 (1.187–2.437)	0.003	1.513 (0.547–6.272)	0.491
III	1.755 (1.280–2.437)	<0.001	2.237 (1.568–3.134)	<0.001	1.018 (0.379–4.163)	0.976
IV	2.540 (1.616–4.023)	<0.001	2.867 (1.555–5.550)	0.001	0.831 (0.108–5.080)	0.84
Others	NA	NA	NA	NA	NA	NA
Liver metastases						
Yes	Ref	1	Ref	1	Ref	1
No	0.697 (0.645–0.753)	<0.001	0.822 (0.735–0.920)	<0.001	0.699 (0.535–0.911)	0.008
Others	NA	NA	NA	NA	NA	NA
Lung metastases						
Yes	Ref	1	Ref	1	Ref	1
No	0.636 (0.572–0.708)	<0.001	0.797 (0.676–0.935)	0.006	0.662 (0.483–0.925)	0.013
Others	NA	NA	NA	NA	NA	NA
Bone metastases						
Yes	Ref	1	Ref	1	Ref	1
No	0.684 (0.611–0.766)	<0.001	0.561 (0.461–0.677)	<0.001	1.110 (0.753–1.704)	0.616
Others	NA	NA	NA	NA	NA	NA
Brain metastases						
Yes	Ref	1	Ref	1	Ref	1
No	0.545 (0.413–0.714)	<0.001	0.760 (0.483–1.142)	0.209	2.310 (0.734–14.004)	0.241
Others	NA	NA	NA	NA	NA	NA
Surgery						
Yes	Ref	1	Ref	1	Ref	1
No	3.385 (2.559–4.485)	<0.001	3.132 (2.054–4.986)	<0.001	1.058 (0.350–2.624)	0.911
Unknown	NA	NA	NA	NA	NA	NA

Ref – reference; OR – odds ratio; NA – not available.

Indexed in: [Current Contents/Clinical Medicine] [SCI Expanded] [ISI Alerting System] [ISI Journals Master List] [Index Medicus/MEDLINE] [EMBASE/Excerpta Medica] [Chemical Abstracts/CAS]

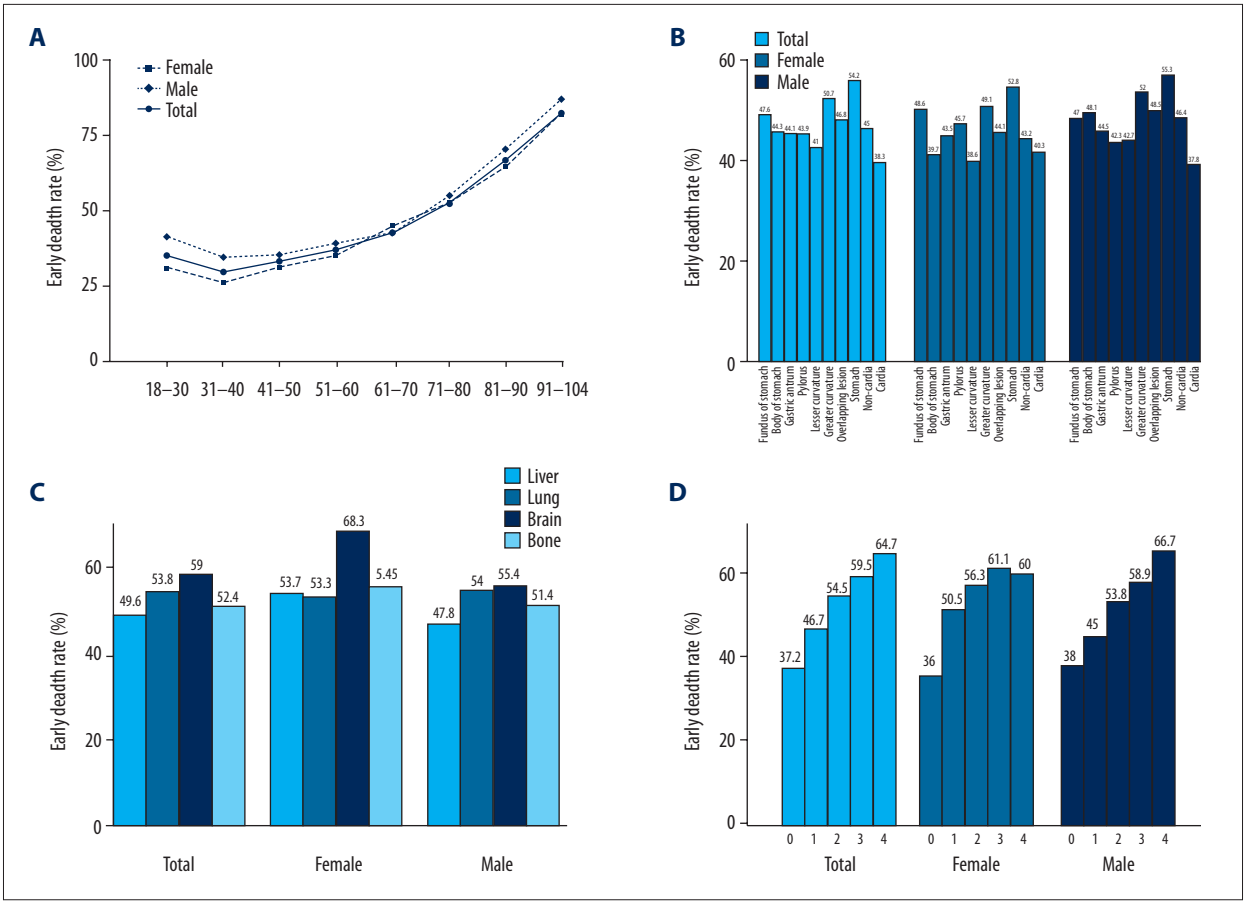


Figure 2. Trend and distribution of early mortality of stage IV gastric cancer patients stratified by: age (**A**), gastric cancer sites (**B**), distant metastases by organs (**C**), number of metastasized organs (**D**).

with a higher histological grade had worse survival prognosis (p<0.001) (Figure 3E). Surgical treatment significantly extended patients' survival time (p<0.001) (Figure 3F).

Factors associated with early death

Univariate logistic regression showed advanced age, marital status, higher T stages, and liver, and lung metastases were all closely related to the total early death, cancer-specific early death and non-cancer-specific early death. Poor differentiation, higher N stages, bone metastases, and surgery were only related to total early death and cancer-specific early death (Table 1).

After incorporating the significant factors into multivariable logistic regression, the results showed that advanced age, primary site, poor differentiation, liver metastases, lung metastases, and surgery were significantly related to total early death. While tumor size, poor differentiation, liver metastases, and surgery were only significantly related to cancer-specific early death. Poor differentiation, liver metastases, and surgery were significantly related to total early death and cancer-specific early death (Table 2).

Establishment of nomograms for predicting early mortality

Based on the previously mentioned factors (age, primary site, tumor size, histological grade, liver metastases, lung metastases, surgery) according to the multivariable model, significant factors related to non-cancer-specific early death were insufficient, only two nomograms were established to predict total early mortality, and cancer-specific early mortality among stage IV gastric cancer patients, respectively. The probability of total early death ranged from 0.05 to 0.90, while cancer-specific early death ranged from 0.10 to 0.95. Therefore, not every total score would have a corresponding probability. The line for the histological grade was the longest in the two prediction models, suggesting that histological grade had the most value in predicting early mortality. In the nomogram for predicting cancer-specific early mortality, surgery and T stage also had great predictive value (Figure 4A, 4B). Internal verification showed that the C-index for the total early mortality nomogram was 0.627 and cancer early mortality was 0.656. The solid lines of the calibration curves approach at a 45°, suggesting accurate prediction by these two models. (Figure 5A, 5B). Moreover, the AUC for the two nomograms

Indexed in: [Current Contents/Clinical Medicine] [SCI Expanded] [ISI Alerting System] [ISI Journals Master List] [Index Medicus/MEDLINE] [EMBASE/Excerpta Medica] [Chemical Abstracts/CAS]

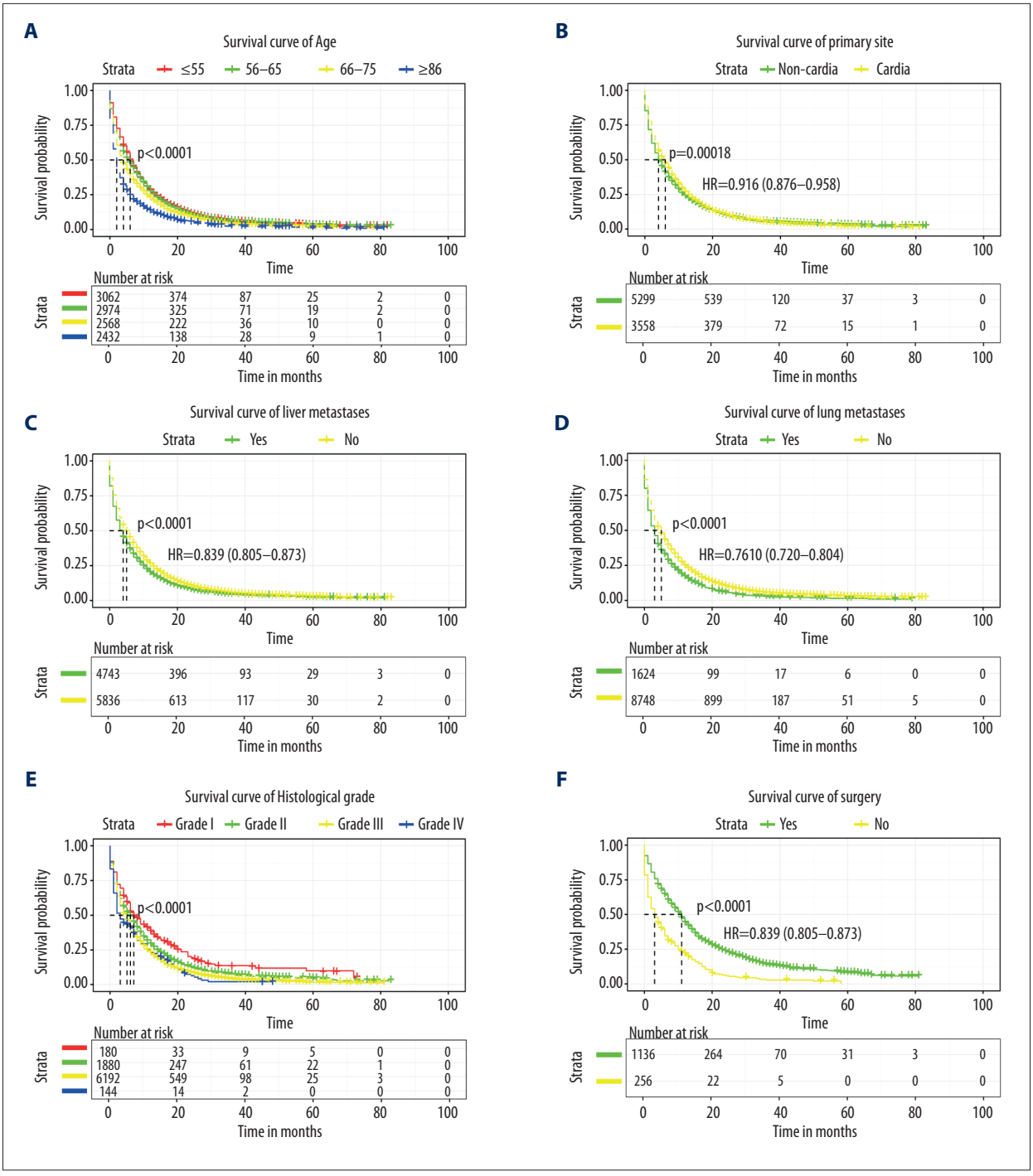


Figure 3. Kaplan-Meier survival curve for (**A**) age, (**B**) primary site, (**C**) liver metastases, (**D**) lung metastases, (**E**) histological grade, (**F**) surgery in stage IV gastric cancer patients.

Indexed in: [Current Contents/Clinical Medicine] [SCI Expanded] [ISI Alerting System] [ISI Journals Master List] [Index Medicus/MEDLINE] [EMBASE/Excerpta Medica] [Chemical Abstracts/CAS]

Table 2. Multivariable logistic regression for analyzing the risk factors for early death.

Factors	Total early death		Cancer-specific early death		Non-cancer-specific early death	
	OR (95% CI)	P-value	OR (95% CI)	P-value	OR(95% CI)	P-value
Age						
≤55	Ref	1	Ref	1	Ref	1
56–65	0.853 (0.436–1.582)	0.582	0.931 (0.551–1.575)	0.787	1.879 (1.208–2.979)	0.17
66–75	3.252 (1.827–5.899)	<0.001	1.050 (0.607–1.828)	0.863	2.729 (1.785–4.273)	<0.001
≥76	3.441 (1.927–6.265)	<0.001	1.333 (0.747–2.410)	0.335	3.258 (2.154–5.059)	<0.001
Race						
White	Ref	1	Ref	1	Ref	1
Black	1.081 (0.600–1.909)	0.792	NS	NS	NS	NS
Asian or Pacific Islander	0.615 (0.356–1.033)	0.073	NS	NS	NS	NS
American Indian/Alaska Native	1.886 (0.116–25.241)	0.632	NS	NS	NS	NS
Unknown	NA	NA	NA	NA	NA	NA
Sex						
Female	Ref	1	1	1	Ref	1
Male	NS	NS	NS	NS	NS	NS
Marital status						
Unmarried	Ref	1	Ref	1	Ref	1
Married	0.724 (0.474–1.108)	0.136	1.007 (0.664–1.518)	0.972	0.754 (0.577–0.987)	0.13
Unknown	NA	NA	NA	NA	NA	NA
Insurance status						
Uninsured	Ref	1	Ref	1	Ref	1
Insured	1.719 (0.624–6.101)	0.34	NS	NS	NS	NS
Unknown	NA	NA	NA	NA	NA	NA
Primary site						
Non-cardia	Ref	1	Ref	1	Ref	1
Cardia	0.307 (0.138–0.627)	0.002	NS	NS	NS	NS
Unknown	NA	NA	NA	NA	NA	NA
Pathological type						
Adenocarcinoma(exclude signet ring cell)	Ref	1	Ref	1	Ref	1
Signet ring cell	NS	NS	1.023 (0.616–1.715)	0.93	NS	NS
Others	NA	NA	NA	NA	NA	NA
Tumor size (cm)						
<3	Ref	1	Ref	1	Ref	1
≥3 <5	0.850 (0.392–1.902)	0.685	1.456 (0.765–2.749)	0.248	NS	NS
≥5 <7	0.693 (0.318–1.558)	0.364	1.435 (0.741–2.754)	0.28	NS	NS
≥7 <9	1.104 (0.484–2.583)	0.817	1.842 (0.895–3.809)	0.097	NS	NS
≥9	0.916 (0.401–2.145)	0.836	2.414 (1.114–5.333)	0.027	NS	NS
Unknown	NA	NA	NA	NA	NA	NA

Indexed in: [Current Contents/Clinical Medicine] [SCI Expanded] [ISI Alerting System] [ISI Journals Master List] [Index Medicus/MEDLINE] [EMBASE/Excerpta Medica] [Chemical Abstracts/CAS]

Table 2 continued. Multivariable logistic regression for analyzing the risk factors for early death.

Factors	Total early death		Cancer-specific early death		Non-cancer-specific early death	
	OR (95% CI)	P-value	OR (95% CI)	P-value	OR(95% CI)	P-value
T stage						
T1	Ref	1	Ref	1	Ref	1
T2	0.395 (0.073–1.713)	0.237	0.968 (0.338–2.775)	0.952	0.443 (0.169–0.966)	0.113
T3	1.076 (0.405–3.062)	0.886	1.698 (0.713–4.002)	0.226	0.581 (0.346–0.949)	0.076
T4	1.726 (0.656–4.882)	0.283	2.287 (0.951–5.440)	0.061	0.693 (0.455–1.052)	0.155
Others	NA	NA	NA	NA	NA	NA
Lymphatic metastasis						
N0	Ref	1	Ref	1	Ref	1
N1	0.711 (0.349–1.448)	0.345	0.991 (0.531–1.834)	0.977	NS	NS
N2	0.649 (0.312–1.351)	0.246	1.587 (0.822–3.061)	0.167	NS	NS
N3	0.819 (0.427–1.600)	0.552	1.524 (0.820–2.796)	0.177	NS	NS
Others	NA	NA	NA	NA	NA	NA
Histological grade						
I	Ref	1	Ref	1	Ref	1
II	3.591 (0.586–70.424)	0.25	2.339 (0.689–8.178)	0.171	NS	NS
III	6.768 (1.149–131.038)	0.082	3.363 (1.011–11.525)	0.047	NS	NS
IV	11.195 (1.438–240.700)	0.044	7.594 (1.302–64.796)	0.035	NS	NS
Others	NA	NA	NA	NA	NA	NA
Liver metastases						
Yes	Ref	1	Ref	1	Ref	1
No	0.447 (0.285–0.699)	<0.001	0.564 (0.346–0.903)	0.019	0.822 (0.626–1.078)	0.667
Others	NA	NA	NA	NA	NA	NA
Lung metastases						
Yes	Ref	1	Ref	1	Ref	1
No	0.223 (0.102–0.485)	<0.001	0.642 (0.255–1.457)	0.314	0.723 (0.526–1.014)	0.027
Others	NA	NA	NA	NA	NA	NA
Bone metastases						
Yes	Ref	1	Ref	1	Ref	1
No	0.813 (0.296–2.525)	0.701	0.640 (0.178–1.800)	0.438	NS	NS
Others	NA	NA	NA	NA	NA	NA
Brain metastases						
Yes	Ref	1	Ref	1	Ref	1
No	0.125 (0.018–1.282)	0.051	NS	NS	NS	NS
Others	NA	NA	NA	NA	NA	NA
Surgery						
Yes	Ref	1	Ref	1	Ref	1
No	2.835 (1.005–7.888)	0.045	11.912 (2.338–218.646)	0.018	NS	NS
Unknown	NA	NA	NA	NA	NA	NA

Ref – reference; OR – odds ratio; NA – not available; NS – not significant.

Indexed in: [Current Contents/Clinical Medicine] [SCI Expanded] [ISI Alerting System] [ISI Journals Master List] [Index Medicus/MEDLINE] [EMBASE/Excerpta Medica] [Chemical Abstracts/CAS]

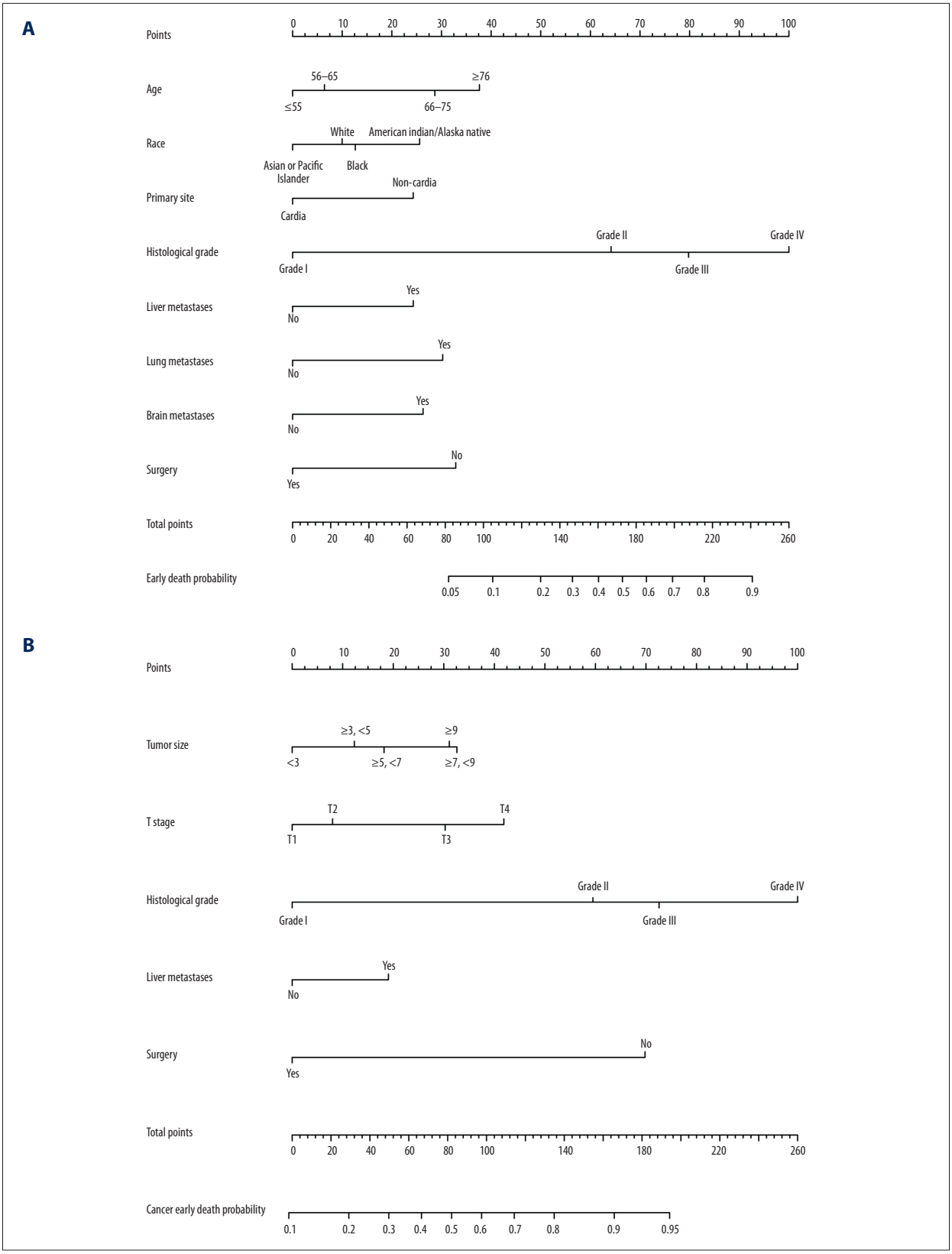


Figure 4. Nomogram for predicting all causes of early mortality (**A**) and cancer-specific early mortality in stage IV gastric cancer patients (**B**).

Indexed in: [Current Contents/Clinical Medicine] [SCI Expanded] [ISI Alerting System] [ISI Journals Master List] [Index Medicus/MEDLINE] [EMBASE/Excerpta Medica] [Chemical Abstracts/CAS]

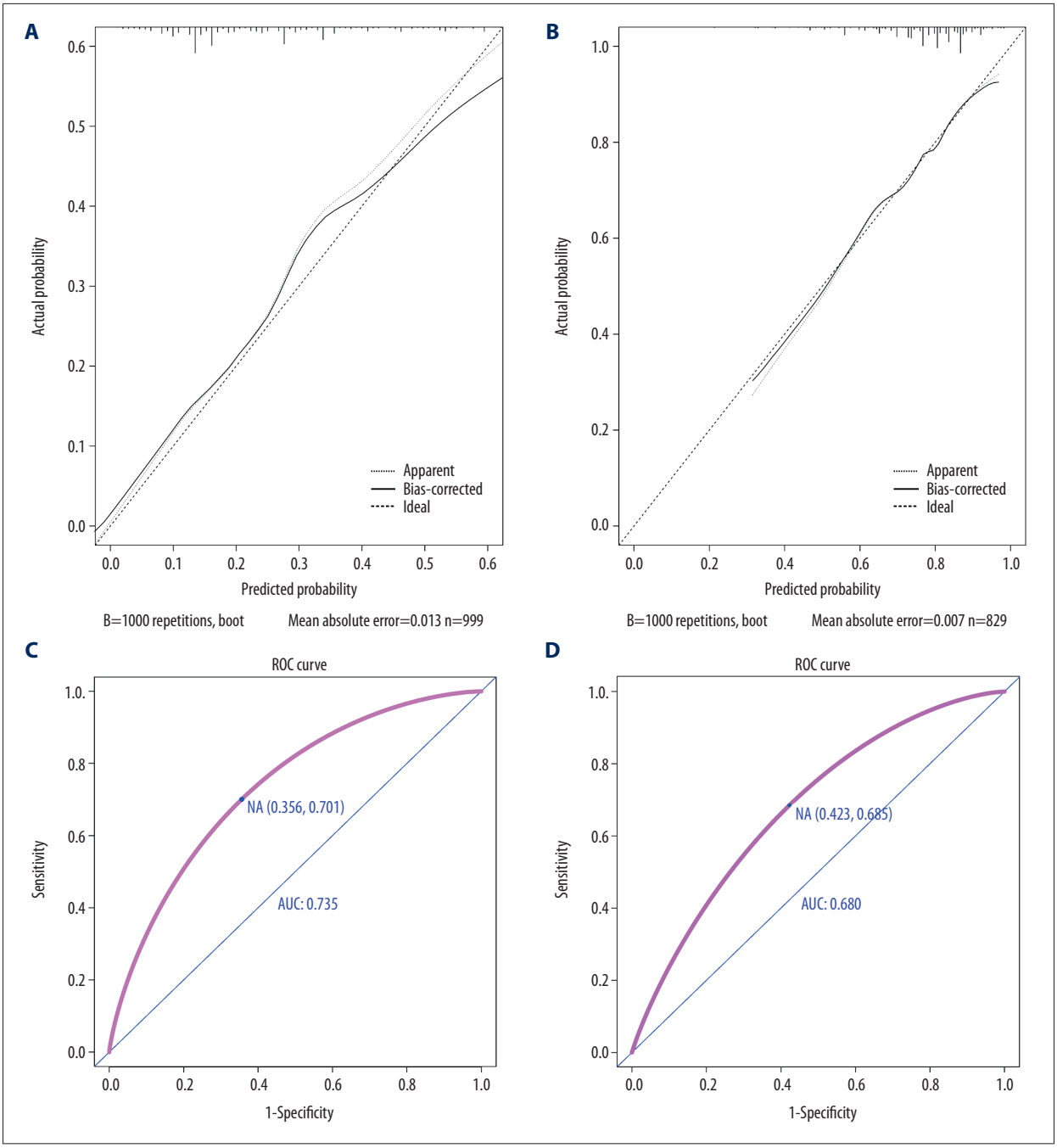


Figure 5. The calibration curve and receiver operating characteristics curve for assessing the calibration and discrimination of the nomogram in predicting all causes of early mortality (**A, C**) and cancer-specific early mortality (**B, D**).

were 73.5%, and 68.0%, respectively, exhibiting good discrimination (Figure 5C, 5D). The DCA also proved the value of the two models. The net benefit of our risk models were larger than that in other two scenarios (all screening or none-screening) in a wide range of threshold probabilities (Figure 6A, 6B).

Discussion

Gastric cancer is one of the main causes of cancer death worldwide [1]. It has been proposed that patients with stage IV gastric cancer have pessimistic survival time. Qiu et al. reported that median survival time for them was less than 4 months [11–13]. From the 11,036 patients included in this study, 42.6% succumbed to the disease within three months after the initial

Indexed in: [Current Contents/Clinical Medicine] [SCI Expanded] [ISI Alerting System] [ISI Journals Master List] [Index Medicus/MEDLINE] [EMBASE/Excerpta Medica] [Chemical Abstracts/CAS]

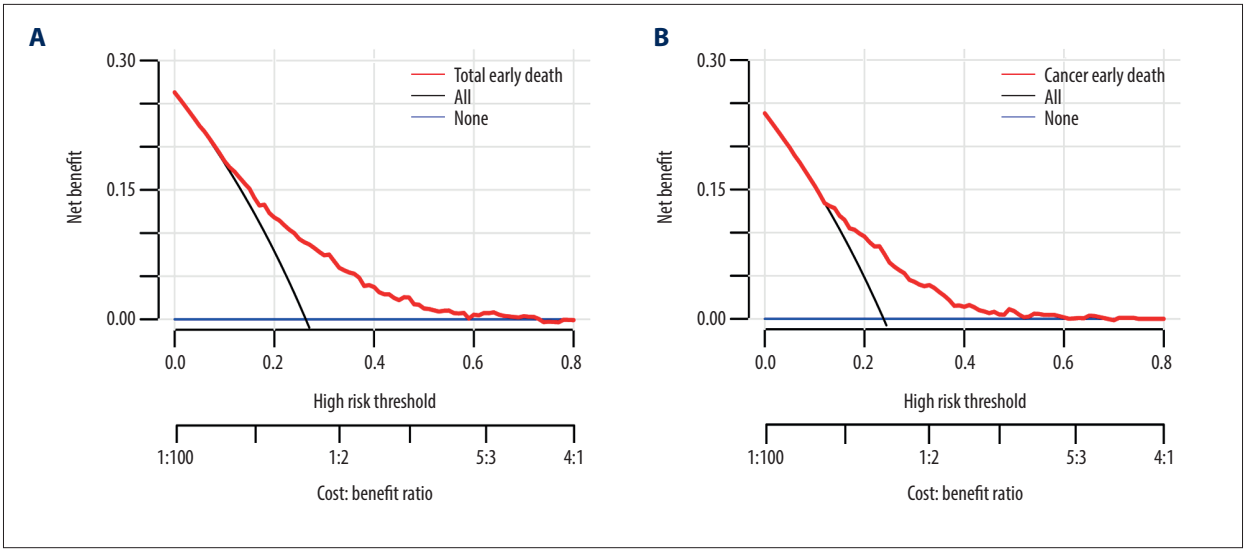


Figure 6. The decision curve analysis for assessing clinical utility of the nomogram in predicting all causes of early mortality (**A**) and cancer-specific early mortality (**B**).

diagnosis. Therefore, knowledge of the factors (age, primary site, tumor size, histological grade, liver metastases, lung metastases, surgery) that affect the early death of patients can help formulate corresponding therapeutic schemes in advance, to improve the survival rate. To the best our knowledge, this study is the first to explore early death prediction for patients with stage IV gastric cancer.

In this study, some factors were found to be positively related to early mortality in stage IV gastric cancer, including advanced age, non-cardia, high histological grade (grade III, IV), tumor size, and distant metastases (liver and lung). Surgery on primary sites was negatively related to early death.

Previous studies reported advanced age as one of the risk factors affecting the prognosis of gastric cancer. Compared with younger patients, the survival time of elderly patients is significantly shorter [14,15]. Our study showed that the early death rate roughly increased when patients were older than 40, for males and females. The link between advanced age and early death had also been explored. Elderly patients always have a higher incidence of serious complications, weak immune systems, and muscle atrophy is related to poor prognosis and early death [16–18]. Young patients are in better basic physical condition and have fewer comorbidities, such as heart disease, high blood pressure, etc. and are more likely to tolerate the side effects of adjuvant therapy [19]. Compared to elderly patients, young patients are more willing to try other treatments [16,20]. However, the early death rate among patients aged 18-40 years declined with age. Another study analyzed a group of young patients aged 30 years or younger with unique clinicopathological features such as advanced stage cancer, a positive family history of cancer, undifferentiated and diffuse histologic type. Based on the aforementioned factors, their prognosis would be relatively poorer than others [21].

A series of studies investigated the differences between cardia gastric cancer and non-cardia gastric cancer. They concluded that cardia gastric cancer patients were generally considered to have worse prognosis than the patients with non-cardia gastric cancer because of the different clinicopathological features [22–24]. In general, cardia gastric cancer was assumed to have more aggressive biological behavior and was more prone to lymph node metastasis and recurrence [25]. However, in our study, cardia gastric cancer was less likely to cause early death than non-cardia gastric cancer. This result is contradictory and we investigated the cause for this result. The previous study reported that the five-year survival rates of patients with cardia gastric cancer who underwent R0 resection were no lower than those with non-cardia cancer [24]. Patients found to have lymph node metastases would be more likely to undergo lymphadenectomy. Therefore, other adjuvant therapies and R0 resection may influence the result. The relatively small sample of the cardia gastric cancer group in the present study may be another potential reason. Because other factors associated with early death, such as age, primary site, tumor size, histological grade, etc. can greatly interfere with the result.

Tumor size, considered to be the largest diameter of a solid tumor, is another important clinical indicator of prognoses [26], which can be accurately obtained by gastroscopy or imaging. This parameter has also been confirmed as an independent prognostic factor in solid cancers [27–29]. It is often used as an indicator to decide whether surgery is needed. Tumor size has been incorporated into the TNM staging systems to assess the prognosis, such as non-small-cell lung cancer [30].

Indexed in: [Current Contents/Clinical Medicine] [SCI Expanded] [ISI Alerting System] [ISI Journals Master List] [Index Medicus/MEDLINE] [EMBASE/Excerpta Medica] [Chemical Abstracts/CAS]

The optimal cutoff value for tumor size was 4 cm. Large tumor sizes often indicated poor prognoses, which was consistent with the result of this study [31].

Liver and lung metastases were related to unfavorable prognoses in gastric cancer patients as vital organ damage and tumor load increase to lethal levels [11]. The median survival time for gastric cancer patients with liver metastases was 2–3 months and 0–10% patients can survive longer than 5 years [32]. While only 2–4% patients with lung metastases can survive longer than 5 years[33]. This study also found that early death was associated with liver and lung metastasis. In addition, a positive correlation between prognosis and the number of metastatic organs was seen.

Stage IV gastric cancer patients already had distant metastasis, and the need for surgery remains controversial. Previous National Comprehensive Cancer Network guidelines suggest that for patients with distant metastasis, surgery can only be used as a means of palliative treatment. Previous studies have shown that for patients with advanced gastric cancer, the survival benefits of undergoing surgical treatment compared to no surgery are obvious. However, the option of surgery needs to be treated with caution and more rigorous research should be conducted in the future to explore the impact of surgery on patients with distant organ metastases [14,34].

The Cox regression model was also used in our research. We incorporated meaningful values ($p<0.05$) from the multivariate Cox regression model to construct nomograms for early mortality and cancer early mortality. However, upon verification of the calibration curve, we found that the solid line of the curve did not approach in the direction of 45°. Therefore, the logistic regression model was chosen for establishment of the nomogram (Supplementary Table 1, Supplementary Figures 1, 2).

Limitations

There are several limitations in our study. Firstly, our study only included patients who were initially diagnosed with stage IV gastric cancer, and patients who subsequently developed metastases were not included. The SEER database includes approximately 30% of the total US population only, therefore, the research sample is not extensive enough. Secondly, some factors related to gastric cancer have not been explored and may affect the predictive ability of the nomogram, such as helicobacter pylori, sarcopenia, cachexia, some inflammatory indices, and the Eastern Cooperative Oncology Group performance score. Further studies need to be conducted with consideration of these factors related to gastric cancer. Thirdly, only an internal validation of the nomogram was performed, and external verification is still necessary. We will do our best to validate this prognostic model in future clinical practice.

Conclusions

Based on the aforementioned factors (age, primary site, tumor size, histological grade, liver metastases, lung metastases, surgery), a predictive nomogram was set up. It has a good ability to predict early mortality in patients with stage IV gastric cancer. This model can be widely used in clinical practice, allowing clinicians to develop more personalized treatments for patients with advanced gastric cancer, to give them the best possible prognosis.

Conflict of interest

None.

Indexed in: [Current Contents/Clinical Medicine] [SCI Expanded] [ISI Alerting System] [ISI Journals Master List] [Index Medicus/MEDLINE] [EMBASE/Excerpta Medica] [Chemical Abstracts/CAS]

Supplementary Data

Supplementary Table 1. Multivariable Cox regression for analyzing the risk factors for early death.

Factors	Total early death		Cancer-specific early death		Non-cancer-specific early death	
	OR (95% CI)	P-value	OR (95% CI)	P-value	OR(95% CI)	P-value
Age						
≤55	Ref	1	Ref	1	Ref	1
56–65	0.853 (0.481–1.513)	0.587	0.917 (0.707–1.188)	0.510	1.472 (0.877–2.472)	0.144
66–75	2.625 (1.601–4.302)	<0.001	1.586 (1.210–2.079)	<0.001	3.138 (1.938–5.083)	<0.001
≥76	2.532 (1.534–4.179)	<0.001	1.461 (1.106–1.930)	0.008	3.790 (2.328–6.172)	<0.001
Race						
White	Ref	1	Ref	1	Ref	1
Black	1.031 (0.644–1.652)	0.898	NS	NS	NS	NS
Asian or Pacific Islander	0.627 (0.400–0.981)	0.041	NS	NS	NS	NS
American Indian/Alaska Native	1.563 (0.314–7.778)	0.585	NS	NS	NS	NS
Unknown	NA	NA	NA	NA	NA	NA
Sex						
Female	Ref	1	Ref	1	Ref	1
Male	NS	NS	NS	NS	NS	NS
Marital status						
Unmarried	Ref	1	Ref	1	Ref	1
Married	0.750 (0.532–1.056)	0.099	0.992 (0.814–1.209)	0.934	0.808 (0.592–1.103)	0.180
Unknown	NA	NA	NA	NA	NA	NA
Insurance status						
Uninsured	Ref	1	Ref	1	Ref	1
Insured	1.710 (0.618–4.731)	0.301	1.172 (0.769–1.786)	0.460	1.575 (0.577–4.297)	0.375
Unknown	NA	NA	NA	NA	NA	NA
Primary site						
Non-cardia	Ref	1	Ref	1	Ref	1
Cardia	0.336 (0.171–0.660)	0.002	0.832 (0.623–1.113)	0.215	NS	NS
Unknown	NA	NA	NA	NA	NA	NA
Pathological type						
Adenocarcinoma(exclude signet ring cell)	Ref	1	Ref	1	Ref	1
Signet ring cell	NS	NS	0.968 (0.761–1.231)	0.791	0.808 (0.538–1.213)	0.304
Others	NA	NA	NA	NA	NA	NA
Tumor size (cm)						
<3	Ref	1	Ref	1	Ref	1
≥3 <5	0.998 (0.530–1.878)	0.994	1.513 (1.046–2.191)	0.028	NS	NS
≥5 <7	0.745 (0.422–1.497)	0.477	1.259 (0.873–1.815)	0.218	NS	NS
≥7 <9	1.093 (0.563–2.121)	0.792	1.380 (0.932–2.042)	0.108	NS	NS
≥9	1.020 (0.531–1.961)	0.953	1.237 (0.831–1.843)	0.295	NS	NS
Unknown	NA	NA	NA	NA	NA	NA

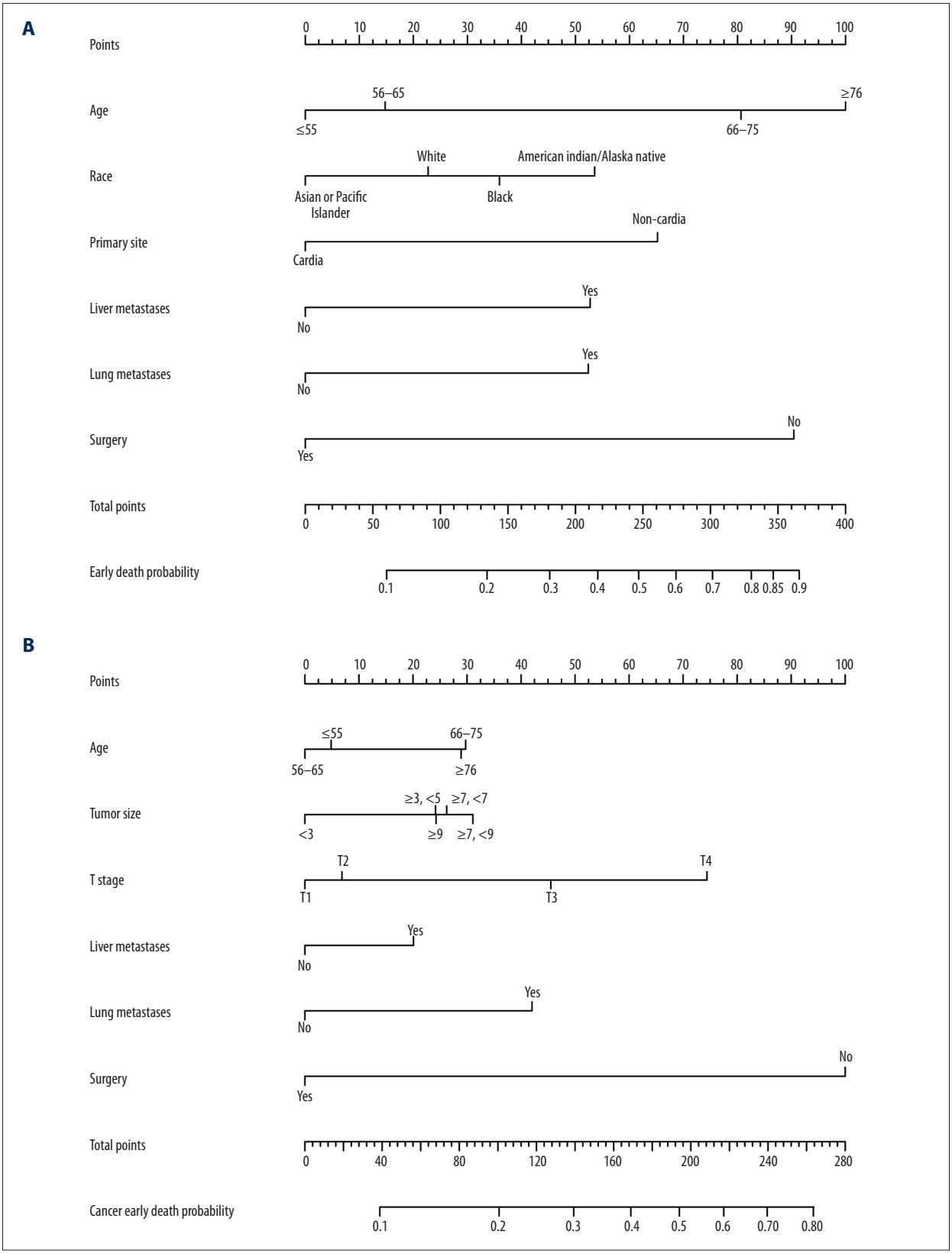
Indexed in: [Current Contents/Clinical Medicine] [SCI Expanded] [ISI Alerting System] [ISI Journals Master List] [Index Medicus/MEDLINE] [EMBASE/Excerpta Medica] [Chemical Abstracts/CAS]

Supplementary Table 1 continued. Multivariable Cox regression for analyzing the risk factors for early death.

Factors	Total early death		Cancer-specific early death		Non-cancer-specific early death	
	OR (95% CI)	P-value	OR (95% CI)	P-value	OR(95% CI)	P-value
T stage						
T1	Ref	1	Ref	1	Ref	1
T2	0.404 (0.107–1.524)	0.181	0.842 (0.436–1.626)	0.609	0.767 (0.408–1.442)	0.410
T3	0.876 (0.399–1.922)	0.741	1.394 (0.843–2.306)	0.195	0.735 (0.484–1.119)	0.151
T4	1.273 (0.590–2.750)	0.539	1.825 (1.091–3.055)	0.022	1.065 (0.736–1.541)	0.739
Others	NA	NA	NA	NA	NA	NA
Lymphatic metastasis						
N0	Ref	1	Ref	1	Ref	1
N1	0.943 (0.543–1.637)	0.834	0.888 (0.626–1.259)	0.504	NS	NS
N2	0.897 (0.493–1.632)	0.723	1.284 (0.912–1.807)	0.152	NS	NS
N3	0.971 (0.574–1.643)	0.913	1.343 (0.972–1.857)	0.074	NS	NS
Others	NA	NA	NA	NA	NA	NA
Histological grade						
I	Ref	1	Ref	1	Ref	1
II	3.265 (0.428–24.917)	0.254	1.338 (0.556–3.219)	0.515	NS	NS
III	5.162 (0.692–38.548)	0.109	1.781 (0.749–4.237)	0.192	NS	NS
IV	8.019 (0.945–68.084))	0.056	2.669 (0.989–7.202)	0.053	NS	NS
Others	NA	NA	NA	NA	NA	NA
Liver metastases						
Yes	Ref	1	Ref	1	Ref	1
No	0.496 (0.347–0.711)	<0.001	0.696 (0.560–0.866)	0.001	NS	NS
Others	NA	NA	NA	NA	NA	NA
Lung metastases						
Yes	Ref	1	Ref	1	Ref	1
No	0.334 (0.196–0.568)	<0.001	0.457 (0.305–0.685)	<0.001	0.665 (0.446–0.992)	0.045
Others	NA	NA	NA	NA	NA	NA
Bone metastases						
Yes	Ref	1	Ref	1	Ref	1
No	0.795 (0.336–1.881)	0.601	0.650 (0.399–1.060)	0.084	NS	NS
Others	NA	NA	NA	NA	NA	NA
Brain metastases						
Yes	Ref	1	Ref	1	Ref	1
No	0.503 (0.119–2.129)	0.351	0.657 (0.282–1.530)	0.330	NS	NS
Others	NA	NA	NA	NA	NA	NA
Surgery						
Yes	Ref	1	Ref	1	Ref	1
No	2.920 (1.363–6.255)	0.006	4.654 (2.874–7.536)	<0.001	NS	NS
Unknown	NA	NA	NA	NA	NA	NA

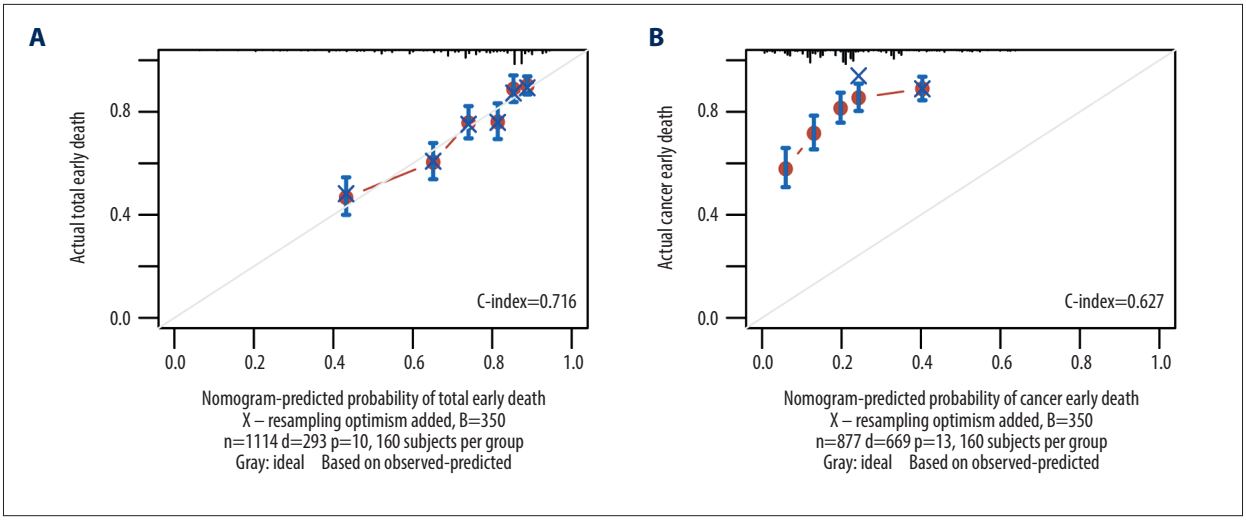
Ref – reference; OR – odds ratio; NA – not available; NS – not significant.

Indexed in: [Current Contents/Clinical Medicine] [SCI Expanded] [ISI Alerting System] [ISI Journals Master List] [Index Medicus/MEDLINE] [EMBASE/Excerpta Medica] [Chemical Abstracts/CAS]



Supplementary Figure 1. Nomogram for predicting all causes of early mortality (**A**) and cancer-specific early mortality in stage IV gastric cancer patients (**B**).

Indexed in: [Current Contents/Clinical Medicine] [SCI Expanded] [ISI Alerting System] [ISI Journals Master List] [Index Medicus/MEDLINE] [EMBASE/Excerpta Medica] [Chemical Abstracts/CAS]



Supplementary Figure 2. The calibration curve for assessing the calibration of the nomogram in predicting all causes of early mortality (**A**) and cancer-specific early mortality (**B**).

References:

1. Bray F, Ferlay J, Soerjomataram I et al: Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. Cancer J Clin, 2018; 68(6): 394–424
2. Rodriguez-de-Santiago E, Hernanz N, Marcos-Prieto HM et al : A multicentric Spanish study on the characteristics and survival of gastric adenocarcinoma under the age of 60. Gastroenterol Hepatol, 2019; 42(10): 595–603
3. Thomassen I, van Gestel YR, van Ramshorst B et al: Peritoneal carcinomatosis of gastric origin: A population-based study on incidence, survival and risk factors. Int J Cancer, 2014; 134(3): 622–28
4. Martella L, Bertozzi S, Londero AP et al: Surgery for liver metastases from gastric cancer: A meta-analysis of observational studies. Medicine, 2015; 94(31): e1113
5. Edge SB, Compton CC: The American Joint Committee on Cancer: The 7th edition of the AJCC cancer staging manual and the future of TNM. Ann Surg Oncol, 2010; 17(6): 1471–74
6. Cao LL, Lu J, Li P et al: Evaluation of the Eighth Edition of the American Joint Committee on Cancer TNM Staging System for Gastric Cancer: An analysis of 7371 patients in the SEER database. Gastroenterol Res Pract, 2019, 2019: 6294382
7. Zhou R, Wu Z, Zhang J et al: Clinical significance of accurate identification of lymph node status in distant metastatic gastric cancer. Oncotarget, 2016; 7(1): 1029–41
8. Fuse N, Bando H, Chin K et al: Adjuvant capecitabine plus oxaliplatin after D2 gastrectomy in Japanese patients with gastric cancer: A phase II study. Gastric Cancer, 2017; 20(2): 332–40
9. Jochems A, El-Naqa I, Kessler M et al: A prediction model for early death in non-small cell lung cancer patients following curative-intent chemoradiotherapy. Acta Oncol, 2018; 57(2): 226–30
10. Inoue T, Tamiya M, Tamiya A et al: Analysis of early death in Japanese patients with advanced non-small-cell lung cancer treated with nivolumab. Clin Lung Cancer, 2018; 19(2): e171–76
11. Qiu MZ, Shi SM, Chen ZH et al: Frequency and clinicopathological features of metastasis to liver, lung, bone, and brain from gastric cancer: A SEER-based study. Cancer Med, 2018; 7(8): 3662–72
12. Sun Z, Zheng H, Yu J et al: Liver metastases in newly diagnosed gastric cancer: A population-based study from SEER. J Cancer, 2019; 10(13): 2991–3005
13. Sleeman J, Steeg PS: Cancer metastasis as a therapeutic target. Eur J Cancer, 2010; 46(7): 1177–80
14. Han J, Tu J, Tang C et al: Clinicopathological characteristics and prognosis of cT1N0M1 gastric cancer: A population-based study. Dis Markers, 2019, 2019; 5902091
15. Yagi Y, Seshimo A, Kameoka S: Prognostic factors in stage IV gastric cancer: Univariate and multivariate analyses. Gastric Cancer, 2000; 3(2): 71–80
16. Wong JU, Tai FC, Huang CC: An examination of surgical and survival outcomes in the elderly (65–79 years of age) and the very elderly (>/=80 years of age) who received surgery for gastric cancer. Current Med Res Opin, 2020; 36(2): 229–33
17. Wang F, Liu X, Mao P et al: Relationship between the body mass index and tumor site postoperative complications and prognosis in gastric adenocarcinoma. Am Surg, 2018; 84(12): 1861–68
18. Troncone E, Marafini I, Stolfi C, Monteleone G: Transforming growth factor-beta1/Smad7 in intestinal immunity, inflammation, and cancer. Front Immunol, 2018; 9: 1407
19. O'Connell JB, Maggard MA, Livingston EH, Yo CK: Colorectal cancer in the young. Am J Surg, 2004; 187(3): 343–48
20. Zu H, Wang H, Li C et al: Clinico-pathological features and prognostic analysis of gastric cancer patients in different age groups. Hepatogastroenterology, 2015; 62(137): 225–30
21. Park HJ, Ahn JY, Jung HY et al: Clinical characteristics and outcomes for gastric cancer patients aged 18–30 years. Gastric Cancer, 2014; 17(4): 649–60
22. Zhao J, Zhao J, Du F et al : Cardia and non-cardia gastric cancer have similar stage-for-stage prognoses after R0 resection: A large-scale, multicenter study in China. J Gastrointest Surg, 2016; 20(4): 700–7
23. Nguyen TH, Mallepally N, Hammad T et al: Prevalence of *Helicobacter pylori* positive non-cardia gastric adenocarcinoma is low and decreasing in a US population. Dig Dis Sci, 2019; 14: 1–9
24. Amini N, Spolverato G, Kim Y et al: Clinicopathological features and prognosis of gastric cardia adenocarcinoma: A multi-institutional US study. J Surg Oncol, 2015; 111(3): 285–92
25. Saito H, Fukumoto Y, Osaki T et al: Distinct recurrence pattern and outcome of adenocarcinoma of the gastric cardia in comparison with carcinoma of other regions of the stomach. World J Surg, 2006; 30(10): 1864–69
26. Marchegiani G, Andrianello S, Malleo G et al: Does size matter in pancreatic cancer?: Reappraisal of tumour dimension as a predictor of outcome beyond the TNM. Ann Surg, 2017; 266(1): 142–48
27. Tran B, Roshan D, Abraham E et al: The prognostic impact of tumor size in papillary thyroid carcinoma is modified by age. Thyroid, 2018; 28(8): 991–96
28. Wang HM, Huang CM, Zheng CH et al: Tumor size as a prognostic factor in patients with advanced gastric cancer in the lower third of the stomach. World J Gastroenterol, 2012; 18(38): 5470–75
29. Wang X, Wan F, Pan J et al: Tumor size: A non-neglectable independent prognostic factor for gastric cancer. J Surg Oncol, 2008; 97(3): 236–40

Indexed in: [Current Contents/Clinical Medicine] [SCI Expanded] [ISI Alerting System] [ISI Journals Master List] [Index Medicus/MEDLINE] [EMBASE/Excerpta Medica] [Chemical Abstracts/CAS]

30. Zhang J, Gold KA, Lin HY et al: Relationship between tumor size and survival in non-small-cell lung cancer (NSCLC): An analysis of the surveillance, epidemiology, and end results (SEER) registry. J Thorac Oncol, 2015; 10(4): 682–90
31. Dai CY, Lin CY, Tsai PC et al: Impact of tumor size on the prognosis of hepatocellular carcinoma in patients who underwent liver resection. J Chin Med Assoc, 2018; 81(2): 155–63
32. Bernards N, Creemers GJ, Nieuwenhuijzen GA et al: No improvement in median survival for patients with metastatic gastric cancer despite increased use of chemotherapy. Ann Oncol, 2013; 24(12): 3056–60
33. Kong JH, Lee J, Yi CA et al: Lung metastases in metastatic gastric cancer: Pattern of lung metastases and clinical outcome. Gastric Cancer, 2012; 15(3): 292–98
34. Lasithiotakis K, Antoniou SA, Antoniou GA et al: Gastrectomy for stage IV gastric cancer. a systematic review and meta-analysis. Anticancer Res, 2014; 34(5): 2079–85

Indexed in: [Current Contents/Clinical Medicine] [SCI Expanded] [ISI Alerting System] [ISI Journals Master List] [Index Medicus/MEDLINE] [EMBASE/Excerpta Medica] [Chemical Abstracts/CAS]