



Observational Study

Survival benefit of younger gastric cancer patients in China and the United States: A comparative study

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Abstract

BACKGROUND

The impact of racial and regional disparity on younger patients with gastric cancer (GC) remains unclear.

AIM

To investigate the clinicopathological characteristics, prognostic nomogram, and biological analysis of younger GC patients in China and the United States.

METHODS

From 2000 to 2018, GC patients aged less than 40 years were enrolled from the China National Cancer Center and the Surveillance Epidemiology and End Results database. Biological analysis was performed based on the Gene Expression Omnibus database. Survival analysis was conducted *via* Kaplan-Meier estimates and Cox proportional hazards models.

RESULTS

A total of 6098 younger GC patients were selected from 2000 to 2018, of which 1159 were enrolled in the China National Cancer Center, and 4939 were collected from the Surveillance Epidemiology and End Results database. Compared with the United States group, younger patients in China revealed better survival outcomes ($P < 0.01$). For race/ethnicity, younger Chinese cases also enjoyed a better prognosis than that in White and Black datasets ($P < 0.01$). After stratification by pathological Tumor-Node-Metastasis (pTNM) stage, a survival advantage was observed in China with pathological stage I, III, and IV (all $P < 0.01$), whereas younger GC patients with stage II showed no difference ($P = 0.16$). In multivariate analysis, predictors in China involved period of diagnosis, linitis plastica, and pTNM stage, while race, diagnostic period, sex, location, differen-

tiation, linitis plastica, signet ring cell, pTNM stage, surgery, and chemotherapy were confirmed in the United States group. Prognostic nomograms for younger patients were established, with the area under the curve of 0.786 in the China group and of 0.842 in the United States group. Moreover, three gene expression profiles (GSE27342, GSE51105, and GSE38749) were enrolled in further biological analysis, and distinctive molecular characteristics were identified in younger GC patients among different regions.

CONCLUSION

Except for younger cases with pTNM stage II, a survival advantage was observed in the China group with pathological stage I, III, and IV compared to the United States group, which might be partly due to differences in surgical approaches and the improvement of the cancer screening in China. The nomogram model provided an insightful and applicable tool to evaluate the prognosis of younger patients in China and the United States. Furthermore, biological analysis of younger patients was performed among different regions, which might partly explain the histopathological behavior and survival disparity in the subpopulations.

Key Words: Gastric cancer; Younger patients; Racial disparity; Regional disparity; Prediction model; Biological analysis

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Core Tip: The impact of racial and regional disparity on younger patients with gastric cancer (GC) is not clear. A total of 6098 younger GC patients were selected from 2000 to 2018, of which 1159 were enrolled in the China National Cancer Center, and 4939 were collected from the Surveillance Epidemiology and End Results database. Compared with the United States group, younger patients in China revealed better survival outcomes and a better prognosis. Three gene expression profiles from the Gene Expression Omnibus database were enrolled in further biological analysis, and distinctive molecular characteristics were identified in younger GC patients among different regions.

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INTRODUCTION

Gastric cancer (GC) is the fourth leading cause of cancer-related deaths worldwide[1], with the highest incidence among individuals aged 50-70 years. Only 2.0%-6.2% of documented cases are among patients younger than 40 years[2,3]. Although the incidence of GC has gradually declined, important age-specific details may be obscured by the overall trend [4]. During the last decades, the incidence of younger GC patients has remained stable or even increased in both Western and Eastern populations[5-7].

It was long thought that younger patients with GC had aggressive behavior and serious prognosis[8]. Further insight into which subpopulations were at the highest risk of dying remained a crucial requisite so that interventions could be initiated appropriately. Recently, several studies have demonstrated a wide survival discrepancy of GC in different regions or races[9,10]. Notably, GC patients in Asia had more favorable prognoses than patients in Western countries. The important difference has also been found in certain subtypes of GC, including sex and anatomic location[9,10]. For younger GC patients, however, knowledge concerning the regional and racial disparity is scarce. Chen *et al*[11] reported that younger patients in China have a longer survival time than younger patients in the United States, whereas Strong *et al*[12] showed no difference between the United States and Chinese cohorts. The inconsistent findings from these studies might derive from the small sample sizes, with the population records ranging from 336 to 1075.

As such, based on a unique combination of the Surveillance Epidemiology and End Results (SEER) database in the United States and a high-volume National Cancer Center Database in China, we sought to compare the clinicopathological features, survival outcomes, and prognostic nomograms in younger Chinese and United States patients. Moreover, biological analysis of younger GC patients was further evaluated, which might partly explain the histopathological behaviors and survival disparity among different regions and races.

MATERIALS AND METHODS

Data source and patient selection

The study queried clinical data from 2000 to 2018 based on the two large independent cohorts. The histologically confirmed GC cases in China were selected through the China National Cancer Center Gastric Cancer Database (NCCGCDB). As a single but high-volume cohort, NCCGCDB included more than 18000 patients from all regions of

China over the past 20 years. Meanwhile, the United States group was identified from the SEER database. The SEER database, supported by the National Cancer Institute, constituted approximately 27.8% of the United States population [13]. Younger patients were defined as GC cases younger than 40 years of age, which remains consistent with the majority of previous studies [14,15]. Clinical data abstracted from the NCCGCD and SEER databases included younger patients' demographics, clinicopathological characteristics, and survival variables. The stage of GC was assessed according to the 8th edition of the American Joint Committee on Cancer Tumor-Node-Metastasis (TNM) staging system. The primary endpoint of the study was overall survival (OS). Moreover, the gene expression sets evaluated in the study were obtained from the Gene Expression Omnibus (GEO) database (<https://www.ncbi.nlm.nih.gov/geo/>). The study protocol was approved by the ethics committee of National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College (No. 17-156/1412), and all methods were carried out in accordance with relevant guidelines and regulations in the ethics approval and consent.

Statistical analysis

The line chart was plotted to analyze the changing ratios of younger GC patients from 2000 to 2018. Categorical variables were compared using the χ^2 test. Comparisons were performed using the *t*-test for normally distributed continuous variables and the Mann-Whitney *U* test for variables not normally distributed. Survival curves for different regions and races were calculated with the Kaplan-Meier method, while the log-rank test estimated the relevant survival disparity. Univariate and multivariate Cox proportional hazards models were used to determine the prognostic factors for younger patients, while the corresponding hazard ratio and 95% confidence interval (CI) were generated. The covariates with a *P* value of < 0.10 in the univariate models were included in the multivariate analysis [16]. Statistical significance was set at a two-sided *P* value less than 0.05. The survival nomogram for China and the United States was formulated based on the multivariate analysis. Younger cases were randomized 7:3, which were adopted in the training set and the validation set, respectively. The area under the curves (AUC), the concordance index (C-index), and the calibration plots were performed to measure the effectiveness of nomograms. All statistical analyses in the study were conducted using R software v.3.6.3 (<http://www.r-project.org/>).

Bioinformatics analysis

Based on the GEO database, the differentially expressed genes (DEGs) analysis was further performed to evaluate gene discrepancy for younger patients among different regions, while genes that met the cutoff criteria, adjusted *P*-value < 0.05 and $|\log FC| > 2.0$, where FC represents fold change, were considered as DEGs. A heatmap was constructed with 50 differential genes from the DEGs analysis. The Search Tool for the Retrieval of Interacting Genes database (<http://string-db.org/>) was designed to analyze the protein-protein interaction (PPI) network, which was subsequently visualized by Cytoscape software (www.cytoscape.org/). As a plugin in Cytoscape, CytoHubba was used to calculate the degree of protein node, and the top 10 genes were identified as hub genes.

RESULTS

Demographic and clinicopathological features

From 2000 to 2018, a total of 6098 younger GC patients were selected, of which 1159 were enrolled in NCCGCD, and 4939 were collected from the SEER database. The mean age of younger patients was 33.77 ± 4.53 in China, and 32.91 ± 5.38 in the United States ($P < 0.0001$). As shown in Figure 1, time trends of younger patients from 2000 to 2018 have remained stable in both China and the United States sets (range 3.9%-6.7%, range 3.4%-3.8%, respectively). Compared to the United States group, the China group had a higher ratio of younger patients over periods.

Notably, compared to the United States, younger GC patients in China predominantly had distal tumor location (83.7% *vs* 66.7%, $P < 0.0001$), poor differentiation (82.5% *vs* 78.5%, $P < 0.0001$), and signet ring cell carcinoma (52.9% *vs* 28.9%, $P < 0.0001$). Conversely, relatively higher percentages of proximal location (33.3% *vs* 16.3%, $P < 0.0001$), well differentiation (7.5% *vs* 1.2%, $P < 0.0001$), and pTNM stage IV tumors (52.5% *vs* 21.4%, $P < 0.0001$) were revealed in the United States patients (Table 1). As for treatment, the percentage of surgery (75.1% *vs* 41.4%, $P < 0.0001$), lymphadenectomy (67.4% *vs* 19.1%, $P < 0.0001$), and lymphadenectomy with at least 15 examined lymph nodes (ELNs ≥ 15) (52.4% *vs* 10.6%, $P < 0.0001$) were higher in China than those in the United States. In addition, nearly 60.6% of the patients in the United States cohort received chemotherapy compared with only 36.9% in the Chinese cohort ($P < 0.0001$).

Survival analysis in different regions and races

Survival trends of younger GC patients are summarized in Table 2 and Figure 2. Compared to the stable prognosis of the United States, a noticeable survival increment was shown in younger Chinese patients. The 3-year OS increased from 54.5% (95%CI: 41.7%-71.4%) in 2000-2003 to 66.5% (95%CI: 60.8%-72.7%) in 2014-2018, while the 5-year OS improved from 47.7% (95%CI: 35.0%-65.0%) in 2000-2003 to 51.6% (95%CI: 46.6%-57.2%) in 2009-2013.

Figure 3 depicts the Kaplan-Meier curves for different regions and races. The survival outcomes were much better in Chinese patients or patients diagnosed in China, compared with other races (mentioned in SEER dataset) or the United States patients (all $P < 0.0001$). To avoid the bias of pathological stage, further analysis was performed to evaluate prognosis of younger cases divided by pTNM stage. The left column of Figure 3 shows the survival curves of younger patients in China and the United States diagnosed as all pTNM stages (Figure 3A), pTNM stage I (Figure 3B), pTNM stage II (Figure 3C), pTNM stage III (Figure 3D), and pTNM stage IV (Figure 3E), while the right column evaluated the

Table 1 Demographic and clinicopathological characteristics of younger gastric cancer patients in China and the United States from 2000 to 2018

	China (<i>n</i> = 1159), <i>n</i> (%)		United States (<i>n</i> = 4939), <i>n</i> (%)		<i>P</i> value
Period of diagnosis					< 0.0001
1 (2000-2003)	194	16.7	972	19.7	
2 (2004-2008)	237	20.5	1248	25.3	
3 (2009-2013)	396	34.3	1280	25.9	
4 (2014-2018)	332	28.6	1439	29.1	
Race					< 0.0001
Chinese	1159	100.0	126	2.6	
White			3405	69.9	
Black			703	14.4	
Others			640	13.1	
Gender					0.135
Male	581	50.1	2599	52.6	
Female	578	49.9	2340	47.4	
Age (year), mean ± SD					0.005
	34		32.91		
	5		5.38		
Primary tumor location					< 0.0001
Proximal	176	16.3	1030	33.3	
Distal	903	83.7	2067	66.7	
Differentiation					< 0.0001
Well	9	1.2	211	7.5	
Moderate	124	16.3	394	14.0	
Poor/Undifferentiated	626	82.5	2214	78.5	
Linitis plastica					0.070
Yes	29	2.6	57	1.7	
No	1101	97.4	3279	98.3	
Signet ring cell carcinoma					< 0.0001
Yes	426	52.9	1429	28.9	
No	380	47.1	3510	71.1	
Pathologic T-stage (AJCC 8th)					< 0.0001
T1	197	22.2	498	24.3	
T2	97	10.9	266	13.0	
T3	143	16.1	509	24.9	
T4	452	50.8	773	37.8	
Pathologic N-stage (AJCC 8th)					< 0.0001
N0	412	41.8	1137	49.9	
N1	119	12.1	724	31.7	
N2	162	16.4	232	10.2	
N3	292	29.6	188	8.2	
Pathologic M-stage					< 0.0001

M0	869	79.4	1268	45.9	
M1	225	20.6	1492	54.1	
pTNM stage (AJCC TNM 8th)					< 0.0001
I	222	21.2	649	20.3	
II	169	16.1	377	11.7	
III	433	41.3	498	15.5	
IV	225	21.4	1687	52.5	
Surgery					< 0.0001
Yes	869	75.1	2047	41.4	
No	288	24.9	2892	58.6	
Chemotherapy					< 0.0001
Yes	428	36.9	2991	60.6	
No	731	63.1	1948	39.4	
Lymphadenectomy					< 0.0001
Yes	780	67.4	941	19.1	
No	377	32.6	3398	80.9	
Lymphadenectomy with at least 15 lymph nodes					< 0.0001
Yes	606	52.4	524	10.6	
No	551	47.6	4415	89.4	
Number nodes examined (n), mean ± SD					< 0.0001
	25		18.9		
	13		15.0		
Number positive nodes (n), mean ± SD					< 0.0001
	6		7.4		
	8		7.4		

AJCC: American Joint Committee on Cancer; pTNM: Pathological Tumor-Node-Metastasis; SD: Standard deviation.

OS among different races/ethnicities. Except for stage II GC patients ($P = 0.16$, $P = 0.22$, respectively), all other Kaplan-Meier curves revealed obvious survival advantages in patients who were Chinese or diagnosed in China (all $P < 0.01$).

Moreover, the univariate and multivariate analyses were performed to investigate the prognostic factors for younger GC patients in the China group and the United States group (Tables 3 and 4).

Significant variables on univariate analysis were enrolled in the multivariate modeling, followed by region, race, period of diagnosis, sex, location, differentiation, linitis plastica, signet ring cell carcinoma, pTNM, surgery, chemotherapy, ELNs ≥ 15 (all $P < 0.05$). For younger GC patients, the independent prognosis factors included region, period of diagnosis, poorly differentiated, linitis plastica, pTNM stage, surgery, chemotherapy, and ELNs ≥ 15 (all $P < 0.05$). However, significant predictors in China only involved period of diagnosis (all $P < 0.05$), linitis plastica ($P = 0.0005$), and pTNM stage (all $P < 0.0001$). For the United States patients, Black ethnicity, poorly differentiated, linitis plastica, signet ring cell, and later pathological stage were related to serious prognosis (all $P < 0.01$), whereas recent period, female, distal location, surgery, and chemotherapy emerged as protective factors (all $P < 0.05$).

Nomogram of younger GC patients

To predict OS of younger patients with GC, nomograms for China and the United States group were established separately based on the results of the Cox regression analysis. As illustrated in Figure 4, a total of four clinical parameters (including linitis plastica, surgery, ELNs ≥ 15 , and pTNM stage) were included in the Chinese models, while the nomogram for the United States identified the following parameters: Race, sex, tumor location, differentiation, pTNM stage, linitis plastica, signet ring cell, surgery, and chemotherapy.

According to the results of the validation set, the C-index for the China and United States models was 0.814 and 0.787, respectively. The AUC that was applied to evaluate the discernment of the nomogram models was 0.786 in the China group and 0.842 in the United States group (Supplementary Figure 1). In addition, high-quality calibration plots in both China and the United States models had been demonstrated (Supplementary Figure 2).

Table 2 Overall survival rates by background characteristics from 2000 to 2018

Characteristics	China			United States		
	1-yr, % (95%CI)	3-yr, % (95%CI)	5-yr, % (95%CI)	1-yr, % (95%CI)	3-yr, % (95%CI)	5-yr, % (95%CI)
Total						
Period of diagnosis						
1 (2000-2003)	75.0 (63.2-89.0)	54.5 (41.7-71.4)	47.7 (35.0-65.0)	58.4 (55.3-61.7)	40.7 (37.7-44.0)	36.2 (33.2-39.4)
2 (2004-2008)	80.1 (74.5-86.1)	59.7 (52.9-67.3)	54.1 (47.4-61.9)	58.1 (55.4-61.0)	42.3 (39.6-45.2)	38.4 (35.7-41.3)
3 (2009-2013)	76.7 (72.3-81.3)	57.1 (52.1-62.6)	51.6 (46.6-57.2)	60.8 (58.1-63.6)	44.0 (41.2-46.9)	39.7 (37.0-42.6)
4 (2014-2018)	88.6 (85.1-92.3)	66.5 (60.8-72.7)		61.6 (58.9-64.4)	43.0 (39.9-46.4)	
Race						
Chinese	81.4 (78.9-84.1)	60.9 (57.6-64.3)	52.3 (48.8-56.0)	66.0 (58.1-75.1)	52.9 (44.4-62.9)	42.9 (34.4-53.5)
White				59.7 (58.1-61.5)	41.7 (40.0-43.6)	37.8 (36.0-39.6)
Black				58.0 (54.3-61.8)	42.7 (39.0-46.7)	38.2 (34.6-42.3)
Others				59.4 (55.6-63.5)	43.3 (39.4-47.6)	37.2 (33.3-41.6)
Gender						
Male	82.2 (78.7-85.8)	61.5 (57.1-66.2)	53.6 (49.0-58.7)	57.0 (55.0-59.0)	39.6 (37.6-41.7)	34.8 (32.8-36.9)
Female	80.6 (76.9-84.5)	60.2 (55.5-65.3)	50.7 (45.7-56.2)	63.0 (61.0-65.1)	46.2 (44.1-48.4)	42.2 (40.1-44.4)
Primary tumor location						
Proximal	76.7 (69.8-84.2)	47.7 (39.8-57.2)	42.7 (34.7-52.4)	59.0 (56.0-62.2)	35.8 (32.8-39.1)	30.5 (27.5-33.7)
Distal	84.5 (81.8-87.3)	66.3 (62.8-70.1)	57.4 (53.5-61.5)	64.6 (62.5-66.7)	48.0 (45.8-50.4)	42.9 (40.6-45.3)
Differentiation						
Well	100.0 (100.0-100.0)	100.0 (100.0-100.0)	85.7 (63.3-100.0)	92.5 (88.9-96.2)	83.3 (78.0-89.0)	78.8 (72.6-85.6)
Moderate	90.4 (84.7-96.6)	76.1 (67.6-85.6)	66.3 (56.4-78.0)	72.3 (67.9-76.9)	50.1 (45.2-55.5)	44.6 (39.6-50.1)
Poor/Undifferentiated	87.7 (84.8-90.7)	69.6 (65.4-74.0)	61.6 (57.0-66.5)	48.3 (46.3-50.5)	25.7 (23.9-27.6)	19.9 (18.2-21.8)
Linitis plastica						
Yes	57.1 (39.5-82.8)	14.3 (5.0-40.7)	4.8 (0.7-32.2)	49.5 (37.8-65.0)	14.8 (7.6-29.0)	12.3 (5.8-26.4)
No	83.9 (81.4-86.6)	68.7 (65.4-72.2)	63.8 (60.2-67.5)	60.0 (58.6-61.4)	43.1 (41.6-44.6)	38.6 (37.1-40.1)
Signet ring cell carcinoma						
Yes	91.0 (87.9-94.2)	80.3 (75.8-85.0)	76.9 (72.1-82.1)	49.5 (37.8-65.0)	14.8 (7.6-29.0)	12.3 (5.8-26.4)
No	90.2 (86.7-93.8)	75.1 (70.0-80.6)	70.8 (65.2-76.8)	60.0 (58.6-61.4)	43.1 (41.6-44.6)	38.6 (37.1-40.1)
pTNM stage (AJCC TNM 8th)						
I	100.0 (100.0-100.0)	99.4 (98.4-100.0)	99.4 (98.4-100.0)	91.5 (89.3-93.8)	86.4 (83.6-89.2)	83.4 (80.2-86.6)
II	97.1 (94.3-99.9)	83.6 (77.5-90.3)	69.8 (61.9-78.7)	84.2 (80.4-88.2)	68.4 (63.4-73.8)	61.0 (55.5-67.0)
III	83.5 (79.4-87.9)	54.9 (49.3-61.0)	42.6 (37.0-49.2)	74.8 (70.9-78.8)	41.0 (36.5-46.1)	29.6 (25.3-34.7)
IV	51.2 (43.8-59.7)	17.4 (12.3-24.8)	9.9 (6.0-16.3)	29.7 (27.5-32.1)	10.4 (8.8-12.1)	7.1 (5.7-8.7)
Surgery						
Yes	89.6 (87.3-92.0)	72.4 (69.0-76.0)	63.4 (59.5-67.5)	82.6 (80.9-84.3)	61.2 (59.0-63.5)	53.6 (51.3-56.1)
No	58.4 (51.8-65.9)	33.4 (26.9-41.5)	28.7 (22.2-37.0)	43.2 (41.3-45.1)	29.1 (27.4-31.0)	27.0 (25.3-28.9)
Chemotherapy						
Yes	89.1 (85.8-92.6)	67.0 (61.9-72.6)	52.7 (47.1-59.1)	55.9 (54.1-57.8)	32.7 (31.0-34.6)	27.4 (25.7-29.2)
No	76.8 (73.3-80.4)	57.2 (53.1-61.6)	51.9 (47.7-56.5)	66.4 (64.2-68.6)	59.2 (56.9-61.6)	56.2 (53.9-58.7)

Lymphadenectomy						
Yes	90.8 (88.4-93.2)	77.7 (74.3-81.3)	73.7 (69.9-77.6)	70.9 (67.9-73.9)	39.4 (36.2-42.8)	29.2 (26.1-32.6)
No	64.0 (58.3-70.3)	41.4 (35.4-48.5)	35.1 (29.0-42.5)	57.2 (55.6-58.8)	43.7 (42.1-45.4)	40.7 (39.1-42.4)
Lymphadenectomy with at least 15 lymph nodes						
Yes	91.8 (89.3-94.3)	79.9 (76.2-83.3)	76.2 (72.2-80.6)	77.3 (73.7-81.1)	43.4 (39.4-48.6)	32.4 (28.1-37.2)
No	86.5 (80.4-93.1)	69.0 (60.9-78.3)	64.1 (55.6-73.8)	63.0 (58.4-67.9)	34.0 (29.6-39.1)	25.3 (21.2-30.2)

AJCC: American Joint Committee on Cancer; CI: Confidence interval pTNM: Pathological Tumor-Node-Metastasis.

DEGs analysis, PPI network, and hub gene identification from GEO database

To evaluate gene disparities according to different races, we performed DEGs analysis for younger GC patients from the GEO database. Three gene expression profiles (GSE27342, GSE51105, and GSE38749), which contained 8 younger cases from China, and 12 samples from the Americas and Oceania, were included in this study. After DEGs analysis was performed among different regional sets, 50 significant DEGs were selected (Figure 5). Compared to other regions, certain genes were downregulated in China (Figure 5A), while *C11orf58*, *TLK1*, *ARHGAP5*, *MRPL2*, and *RBMX2* were upregulated. Moreover, the PPIs among the DEGs were performed with the Search Tool for the Retrieval of Interacting Genes. A total of 200 nodes and 245 edges were involved in the PPI network (Figure 5B and C). The top 10 genes evaluated by connectivity degree in the PPI network were as follows: *CTNNB1*, *APP*, *CTSB*, *UBA52*, *RHOA*, *ATP5B*, *EEF2*, *FN1*, *RPL11*, and *CTSD*.

DISCUSSION

Our study compared younger GC patients in China and the United States at clinical and biological levels. Survival advantages of younger GC patients in China were demonstrated from two high-volume databases. These data were stronger than previous studies[17], and high-quality nomograms were further constructed for younger patients according to different regions. Compared to western regions, DEGs in China were confirmed, which might partly explain the histopathological behaviors and survival disparity.

Staying in line with the previous results[11,18], our conclusions showed that younger patients in China were more prominent in the distal location, while GC in the proximal location was more common in the United States. The above discrepancy was presumably related to certain predisposing factors[19-21]. In Western countries, obesity and gastroesophageal reflux were associated with proximal GC[20], whereas *Helicobacter pylori* infection in China may partially account for a high incidence of the distal location[21]. Additionally, Chinese cases were more likely diagnosed with an early pathological stage than those in the United States. This might partially be due to the improvement of cancer screening and early detection programs in China, which have expanded to 31 provinces since 2015[22,23]. When considering surgical patterns, it was thought that gastrectomy with D2 lymphadenectomy was the standard treatment for GC in Eastern Asia[24]. However, most patients in Western countries undergo D1 lymphadenectomy, and D2 lymphadenectomy was only recommended rather than the therapeutic norm[25,26]. These treatment differences might explain the higher percentage of ELNs ≥ 15 and the larger number of nodes examined for Chinese younger patients in our study.

With a direct comparison from a high-volume GC cohort in China and the SEER database, we reported significant survival differences for younger GC patients. Consistent with the previous studies[11,18], our findings revealed that younger cases had a better prognosis in China than in the United States. With the exception of pTNM stage II, significantly better OS was observed in the China group with stages I, III, and IV. Notably, the survival advantage of younger Chinese patients could partially be attributed to a remarkable improvement in the quality of clinical services, such as improved access to primary healthcare, early cancer screening, and individual multimodal therapies[22,23,27]. Moreover, it was well known that gastrectomy with D2 lymphadenectomy was common in Asian areas, while the vast majority of GC cases in Western countries undergo D1 lymphadenectomy[24]. The above type of surgical procedures might be associated with the survival disparity among different regions. In addition, the later tumor stage and some other factors including lifestyle and high body mass index in the United States patients might also in part explain the poor prognosis[28].

As a convenient statistical predictive tool, nomograms have been widely applied for physicians to clarify a diagnosis and predict survival[29,30]. To our best knowledge, the present study, which used the largest sample sizes, constructed survival nomograms for younger GC patients in China and the United States. Compared with previous models[18], nomograms not only avoid the bias of regions but also achieve reliable predictive performance, which was reflected by an AUC of 0.786 for China and 0.842 for the United States. In addition, the calibration plots of the training set and validation set (Supplementary Figure 1) illustrated great agreement between nomogram prediction and actual observation, thus further suggesting a robust predictive ability of nomograms in the present study.

Although specific gene expression among regions and races was not yet fully ascertained, several studies demonstrated a strong association between regional/racial-related genes and the prognosis of GC[31,32]. Loh *et al*[31] reviewed the genetic polymorphisms of GC among different races/ethnicities. The results showed that 37 polymorphisms

Table 3 Univariate Cox regression analysis of younger gastric cancer patients in China and the United States

Characteristics		Total			China			United States			China vs United States		
		HR	95%CI	P value	HR	95%CI	P value	HR	95%CI	P value	HR	95%CI	P value
Region	China	1											
	United States	2.06	1.84-2.31	< 0.0001									
Race	Chinese	1						1			1.24	1.00-1.54	0.11
	White	2.08	1.85-2.33	< 0.0001				1.22	0.95-1.56	0.12			
	Black	2.14	1.85-2.47	< 0.0001				1.26	0.97-1.63	0.08			
	Others	2.07	1.79-2.38	< 0.0001				1.26	0.97-1.64	0.08			
Period of diagnosis	Period 1 (2000-2003)	1			1			1			1.12	0.83-1.49	0.55
	Period 2 (2004-2008)	0.90	0.81-0.99	0.009	0.67	0.45-1.00	0.05	0.95	0.85-1.05	0.30	1.52	1.27-1.80	< 0.0001
	Period 3 (2009-2013)	0.87	0.78-0.96	0.008	0.84	0.57-1.22	0.35	0.91	0.82-1.01	0.09	1.36	1.19-1.55	< 0.0001
	Period 4 (2014-2018)	0.84	0.76-0.94	0.008	0.74	0.49-1.10	0.14	0.91	0.82-1.02	0.10	2.03	1.72-2.41	< 0.0001
Gender	Male	1			1			1			1.70	1.51-1.91	< 0.0001
	Female	0.85	0.80-0.91	< 0.0001	1.05	0.87-1.26	0.64	0.82	0.76-0.88	< 0.0001	1.52	1.27-1.80	< 0.0001
Primary tumor location	Proximal	1			1			1			1.30	1.08-1.57	0.02
	Distal	0.68	0.62-0.75	< 0.0001	0.59	0.47-0.75	< 0.0001	0.77	0.70-0.85	< 0.0001	1.56	1.40-1.74	< 0.0001
Differentiation	Well	1			1			1			1.10	0.33-3.62	0.90
	Moderate	2.82	2.05-3.88	< 0.0001	1.62	0.39-6.76	0.51	3.17	2.28-4.42	< 0.0001	2.14	1.56-2.94	< 0.0001
	Poor/Undifferentiated	5.27	3.91-7.11	< 0.0001	2.19	0.54-8.83	0.27	6.15	4.53-8.35	< 0.0001	3.20	2.83-3.62	< 0.0001
Linitis plastica	Yes	1.95	1.58-2.40	< 0.0001	3.69	2.41-5.65	< 0.0001	1.89	1.41-2.52	< 0.0001	1.03	0.66-1.60	0.91
	No	1			1			1			2.25	2.03-2.50	< 0.0001
Signet ring cell carcinoma	Yes	1.61	1.52-1.72	< 0.0001	0.80	0.61-1.05	0.18	2.01	1.86-2.17	< 0.0001	6.53	5.33-7.99	< 0.0001
	No	1			1			1			2.45	2.02-2.96	< 0.0001
pTNM stage (AJCC TNM 8 th)	1			1	1			1			9.88	4.28-22.83	< 0.0001
	2-85	2.25-3.60	< 0.0001	2.85	19.50	7.04-54.05	< 0.0001	2.27	1.76-2.93	< 0.0001	1.27	0.96-1.67	0.16
	6-18	5.04-7.58	< 0.0001	6.18	46.77	17.36-125.96	< 0.0001	4.88	3.93-6.07	< 0.0001	1.31	1.13-1.53	0.003
	19-52	16.09-23.68	< 0.0001	19.52	137.73	50.88-372.83	< 0.0001	14.25	11.69-17.36	< 0.0001	1.46	1.26-1.68	< 0.0001

Surgery	Yes	0.36	0.34-0.38	< 0.0001	0.23	0.19-0.28	< 0.0001	0.41	0.37-0.44	< 0.0001	1.29	1.15-1.45	0.0002
	No	1			1			1			1.25	1.08-1.25	0.01
Chemotherapy	Yes	1.71	1.59-1.84	< 0.0001	0.93	0.77-1.13	0.45	1.80	1.66-1.95	< 0.0001	2.10	1.84-2.40	< 0.0001
	No	1			1			1			0.97	0.87-1.09	0.69
Lymphadenectomy with at least 15 lymph nodes	Yes	0.56	0.49-0.63	< 0.0001	0.64	0.47-0.87	< 0.0001	0.73	0.63-0.86	0.0001	2.49	2.12-2.91	< 0.0001
	No	1			1			1			3.86	3.21-4.65	< 0.0001

AJCC: American Joint Committee on Cancer; CI: Confidence interval; HR: Hazard ratio; pTNM: Pathological Tumor-Node-Metastasis.

across 27 genes were significantly related to GC in Asians, while 12 polymorphisms across 11 genes were found in Caucasians. Then, Li *et al*[32] found significant gene disparity among White, Black, and Asian patients. Four core genes, including *GYG2P1*, *RPS4Y1*, *TXLNG*, and *EIF1AX*, were demonstrated in White ethnicity, which were relevant for RNA binding and transcription pathways. Black ethnicity with GC was mainly enriched in cell structural changes, and *DNAJC5*, *HDAC10*, *NEO1*, and *SMG5* were identified. For Asian patients, *TMSB4Y*, *UTY*, *ZFY*, and *ZNF787* were screened based on the relationship between gene expression and DNA methylation. In our study, we first evaluated the race/ethnicity-associated genes for younger GC patients. After the construction of PPI networks and screening according to the degree of the protein node, the hub genes of younger GC patients were as follows: *CTNNB1*, *APP*, *CTSB*, *UBA52*, *RHOA*, *ATP5B*, *EEF2*, *FN1*, *RPL11*, and *CTSD*. Further mechanistic studies are warranted to confirm the related signaling and action mechanisms.

Our study has certain strengths. First, two high-volume databases based on the SEER and the NCCGCDB were comprehensively evaluated for the regional and racial disparity of younger GC patients. Second, our study, utilizing the largest sample sizes globally, constructed prognostic nomograms for younger GC patients in China and the United States, thus providing an intuitive accessible tool for physicians to predict survival and develop resurvey schedules. Moreover, to our best knowledge, it was the first study to perform biological analysis for younger patients among different regions, which provided a molecular interpretation for the survival discrepancy. Despite all this, several limitations need to be considered in the present study. Some of the key baseline prognostic factors, including body mass index, smoking, drinking, and the efficacy of neo/adjuvant therapy were absent in the SEER database. In addition, as a high-volume single center, some findings from NCCGCDB might not be strongly generalizable to China, which should be replicated in a larger multicenter experience. Lastly, even after correcting by batch effects (Supplementary Figure 3), there was also potential bias during encoding samples from GEO database. These factors might affect the accuracy of the results.

CONCLUSION

In conclusion, younger GC patients diagnosed in China had a better prognosis than those in the United States. Except for younger cases with pTNM stage II, a survival advantage was observed in the China group with pathological stages I, III, and IV. Moreover, utilizing the largest sample sizes globally, prognostic nomograms in China and the United States were constructed and showed robust predictive performance. Further large-scale studies are warranted to investigate more molecular characteristics and related mechanisms for younger GC patients among different regions and races.

Table 4 Multivariate Cox regression analysis of younger gastric cancer patients in China and the United States

Characteristics		Total ¹		P value	China ²		P value	United States ³		P value
		HR	95%CI		HR	95%CI		HR	95%CI	
Region	China	1								
	United States	2.42	1.35-4.33	0.01						
Race	Chinese	1						1		
	White	0.80	0.45-1.41	0.52				1.21	0.94-1.55	0.13
	Black	0.84	0.46-1.53	0.63				1.48	1.14-1.92	0.003
	Others	0.76	0.42-1.38	0.45				1.19	0.91-1.55	0.20
Period of diagnosis	Period 1 (2000-2003)	1			1			1		
	Period 2 (2004-2008)	0.62	0.27-0.78	0.02	0.51	0.29-0.89	0.047	0.55	0.47-0.64	< 0.0001
	Period 3 (2009-2013)	0.54	0.25-0.73	0.01	0.39	0.22-0.67	0.004	0.50	0.43-0.59	< 0.0001
	Period 4 (2014-2018)	0.48	0.16-0.49	0.0002	0.07	0.03-0.14	< 0.0001	0.47	0.40-0.56	< 0.0001
Gender	Male	1						1		
	Female	0.92	0.80-1.07	0.35				0.85	0.79-0.92	< 0.0001
Primary tumor location	Proximal	1			1			1		
	Distal	0.92	0.75-1.12	0.47	0.88	0.60-1.29	0.58	0.88	0.80-0.98	0.02
Differentiation	Well	1						1		
	Moderate	2.89	0.88-9.48	0.14				1.90	1.36-2.65	0.0002
	Poor/Undifferentiated	4.77	1.47-15.44	0.03				2.97	2.16-4.07	< 0.0001
Linitis plastica	Yes	1.73	1.12-2.68	0.04	6.70	2.72-16.50	0.0005	1.63	1.21-2.19	0.001
	No/unknown	1			1			1		
Signet ring cell carcinoma	Yes	1.07	0.92-1.24	0.47				1.48	1.36-1.61	< 0.0001
	No/unknown	1						1		
pTNM stage (AJCC TNM 8 th)	I	1			1			1		
	II	10.96	5.05-23.75	< 0.0001	18.69	5.55-62.96	< 0.0001	2.35	1.81-3.04	< 0.0001
	III	27.32	12.87-58.00	< 0.0001	58.95	18.18-191.13	< 0.0001	4.51	3.57-5.69	< 0.0001
	IV	57.20	26.58-123.10	< 0.0001	158.6	43.85-573.93	< 0.0001	8.26	6.72-10.16	< 0.0001
Surgery	Yes	0.50	0.36-0.70	0.0005	0.46	0.20-1.03	0.11	0.42	0.37-0.46	< 0.0001
	No	1			1			1		
Chemotherapy	Yes	0.69	0.58-0.84	0.001				0.82	0.75-0.90	< 0.0001
	No	1						1		
Lymphadenectomy with at least 15 lymph nodes	Yes	0.74	0.63-0.86	0.001	0.88	0.64-1.20	0.49	1.04	0.90-1.20	0.64
	No	1			1			1		

¹Adjusted factors for total patients: region, race, period, sex, primary tumor location, differentiation, linitis plastica, signet ring cell carcinoma, pathological Tumor-Node-Metastasis (pTNM) stage, surgery, chemotherapy, lymphadenectomy with at least 15 lymph nodes.

²Adjusted factors for patients from China cohort: period, primary tumor location, linitis plastica, pTNM stage, surgery, lymphadenectomy with at least 15 lymph nodes.

³Adjusted factors for patients from the United States cohort: race, period, sex, primary tumor location, differentiation, linitis plastica, signet ring cell carcinoma, pTNM stage, surgery, chemotherapy, lymphadenectomy with at least 15 lymph nodes.

AJCC: American Joint Committee on Cancer; CI: Confidence interval; HR: Hazard ratio.

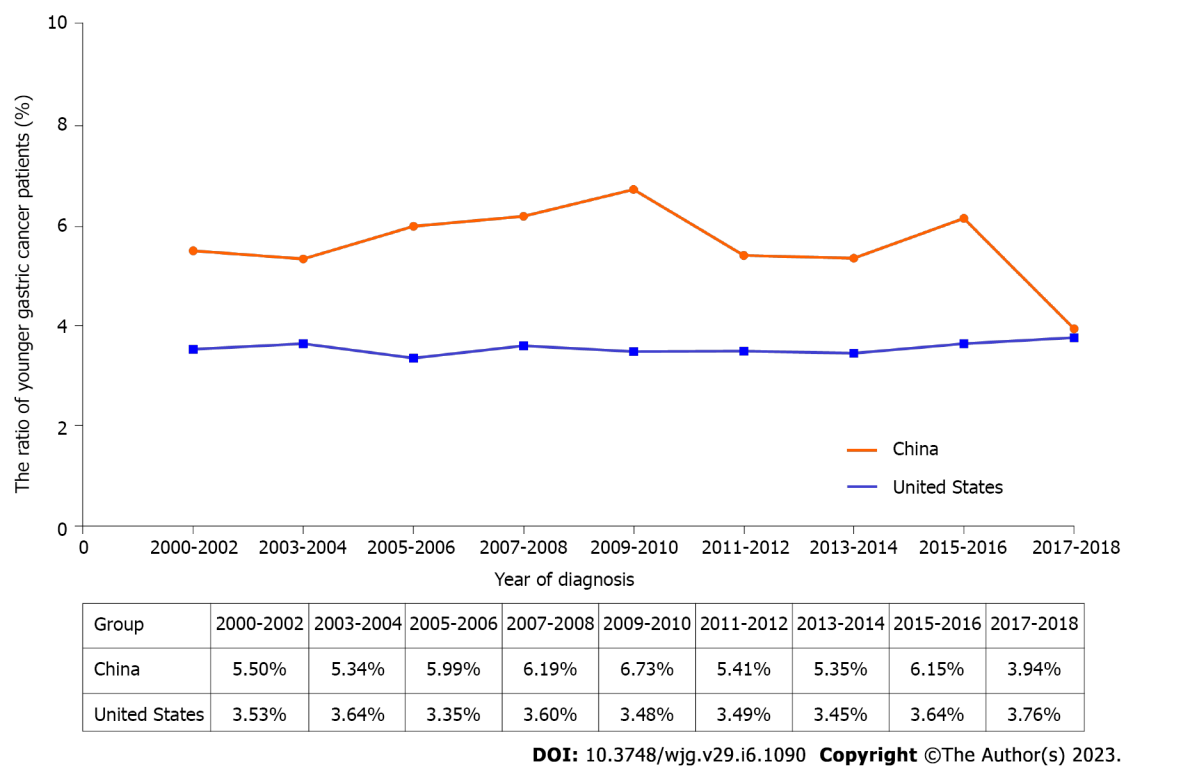


Figure 1 The ratio of younger patients with gastric cancer based on the China National Cancer Center and Surveillance Epidemiology and End Results databases from 2000 to 2018.

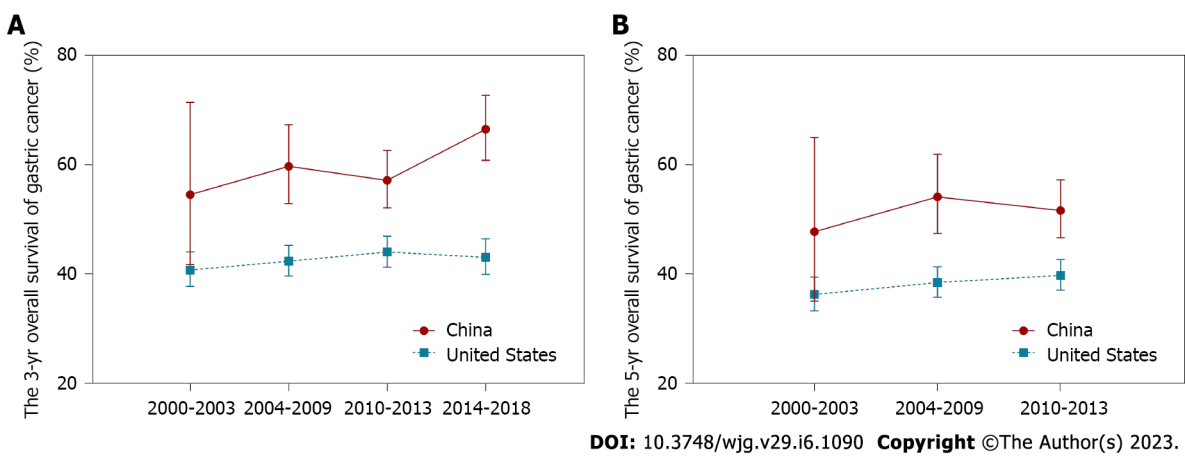
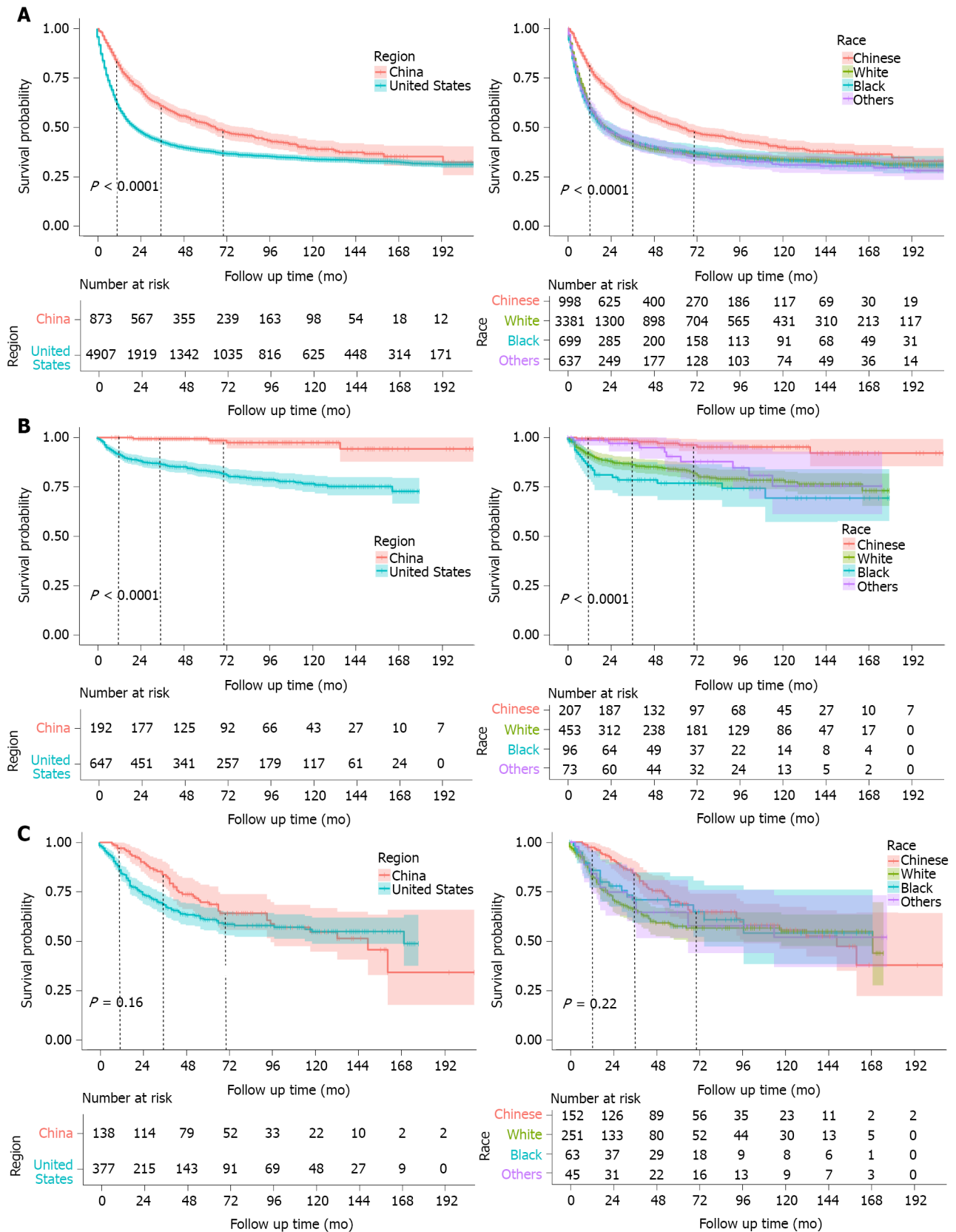
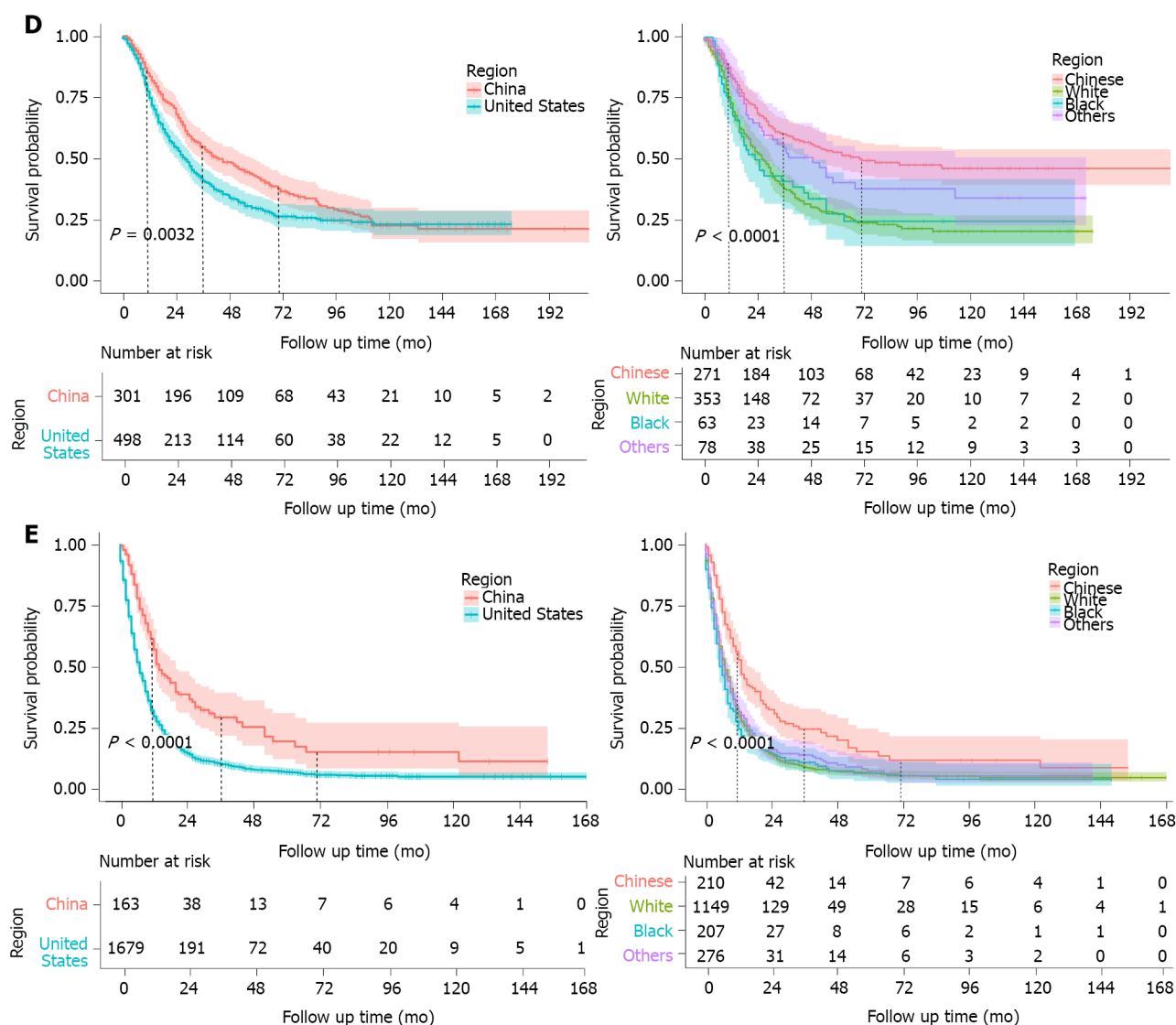


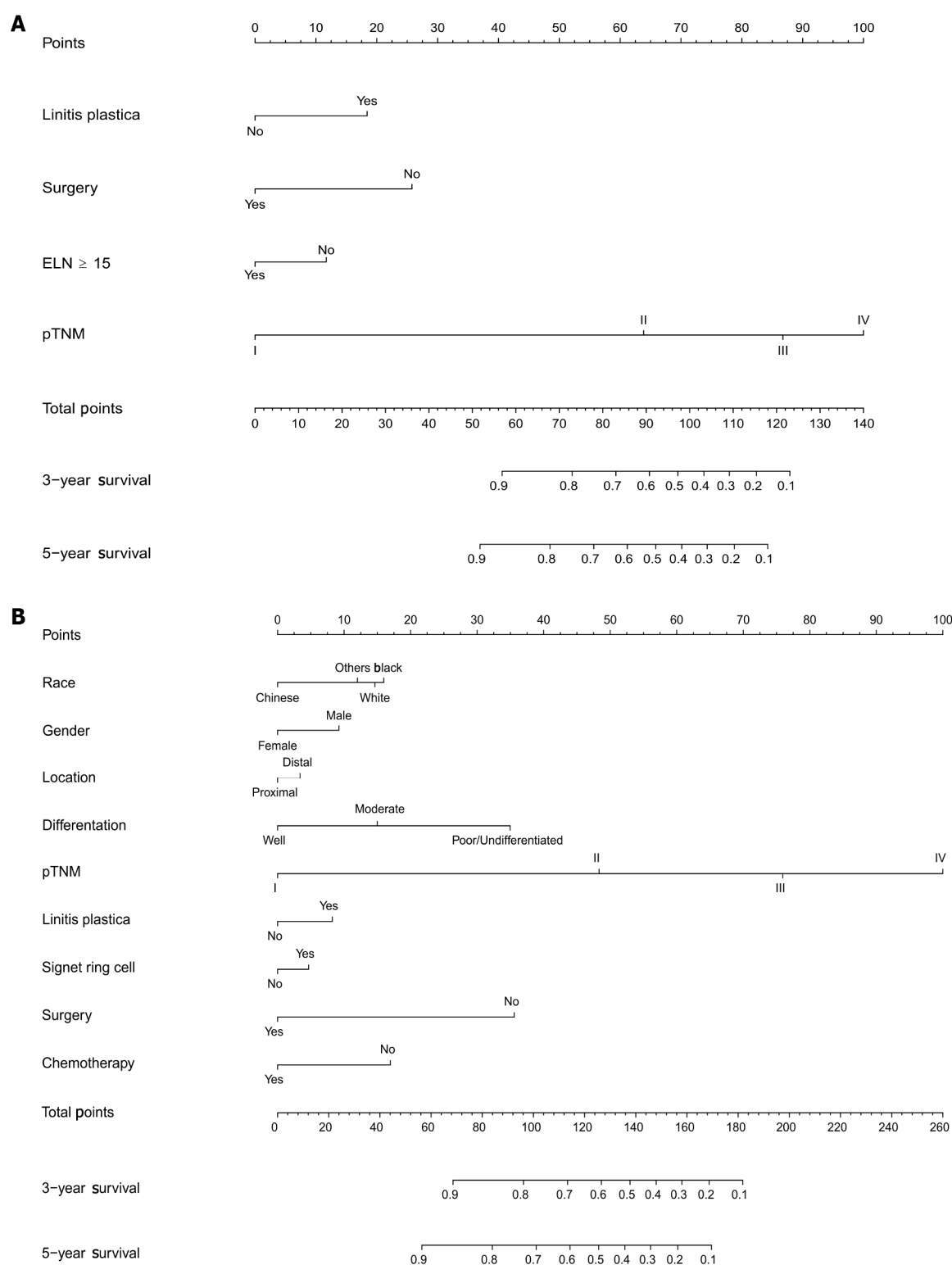
Figure 2 The survival trends of younger patients with gastric cancer based on the China National Cancer Center and Surveillance Epidemiology and End Results databases. A: Trends of the 3-year overall survival; B: Trends of the 5-year overall survival.





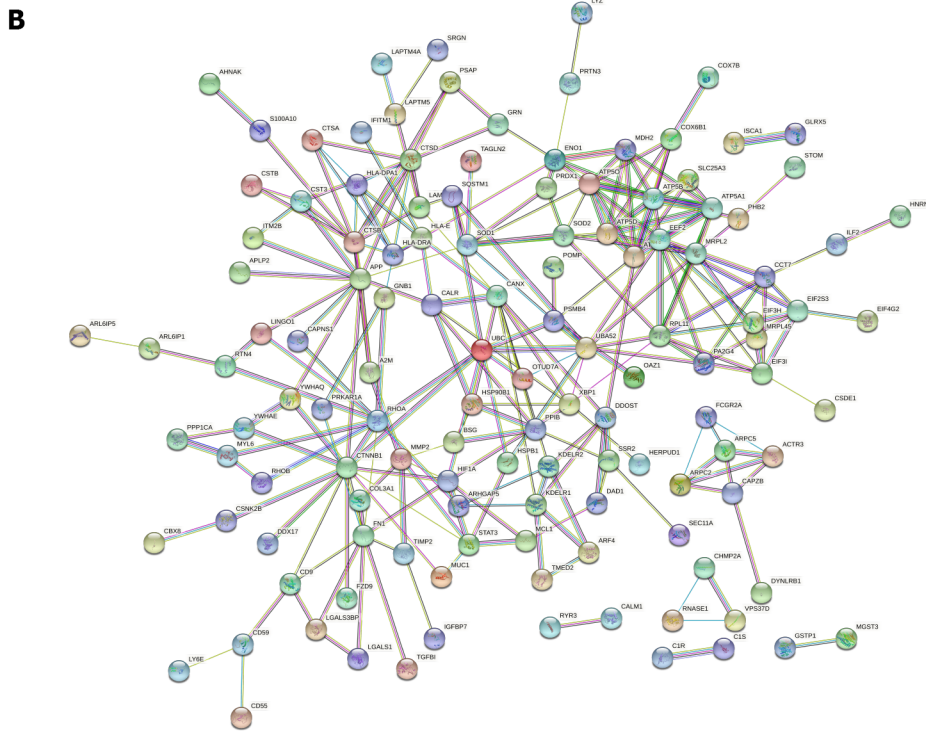
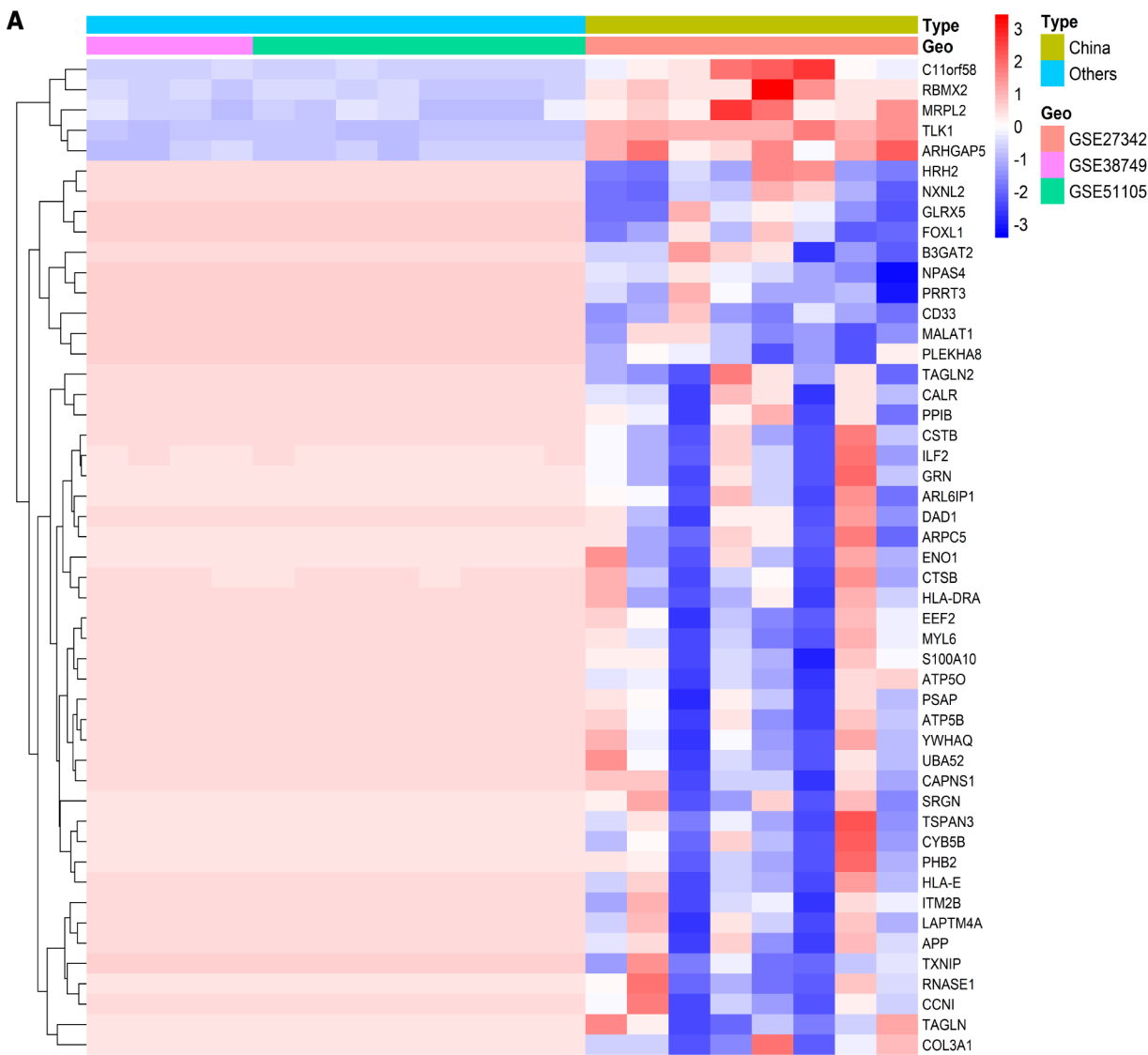
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Figure 3 Kaplan-Meier survival curves of different regions and races from the China National Cancer Center and Surveillance Epidemiology and End Results databases from 2000 to 2018. A: All gastric cancer; B: Gastric cancer diagnosed as Tumor-Node-Metastasis (TNM) stage I; C: Gastric cancer diagnosed as TNM stage II; D: Gastric cancer diagnosed as TNM stage III; E: Gastric cancer diagnosed as TNM stage IV.



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Figure 4 Prognostic nomogram for younger gastric cancer patients. A: Nomogram based on the China National Cancer Center; B: Nomogram based on the Surveillance Epidemiology and End Results database. ELN: Examined lymph nodes; pTNM: Pathological Tumor-Node-Metastasis.





ARTICLE HIGHLIGHTS

The impact of racial and regional disparity on younger patients with gastric cancer (GC) remains unclear.

This study aimed to provide a national view of younger GC patients in China and the United States.

To investigate the clinicopathological characteristics, prognostic nomogram, and biological analysis of younger GC patients in China and the United States.

From 2000 to 2018, GC patients aged less than 40 years were selected from the China National Cancer Center and the Surveillance Epidemiology and End Results database. Biological analysis was enrolled from the Gene Expression Omnibus database.

A total of 6098 younger GC patients were selected from 2000 to 2018, of which 1159 were enrolled in the China National Cancer Center, and 4939 were collected from the Surveillance Epidemiology and End Results database. Compared with the United States group, younger patients in China revealed better survival outcomes ($P < 0.01$). For race/ethnicity, younger Chinese cases also enjoyed a better prognosis than that in White and Black subsets ($P < 0.01$). Prognostic nomograms for younger patients were established, with area under the curves of 0.786 for China and 0.842 for the United States. Moreover, three gene expression profiles (GSE27342, GSE51105, and GSE38749) were enrolled in further biological analysis, and distinctive molecular characteristics were identified in younger GC patients in different regions.

Except for younger cases with pathological Tumor-Node-Metastasis stage II, a survival advantage was observed in the China group with pathological stages I, III, and IV. Biological analysis of younger patients was performed among different regions, which might partly explain the histopathological behaviors and survival disparity in the subpopu-

lations.

Research perspectives

Further large-scale studies are warranted to investigate more molecular characteristics and related mechanisms for younger GC patients among different regions and races.

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FOOTNOTES

Author contributions: Niu PH, Zhao LL, and Wang WQ contributed equally to this work and share first authorship. All authors made substantial contributions to the intellectual content of this paper.

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Informed consent statement: Patients were not required to give informed consent to the study because the analysis used anonymous data that were obtained after each patient agreed to treatment by written consent.

Conflict-of-interest statement: All authors report no relevant conflicts of interest for this article.

Data sharing statement: The data used to support the findings of this study are included within the article in Tables.

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