Int J Clin Exp Med 2020;13(1):164-172
www.ijcem.com /ISSN:1940-5901/IJCEM0095728

Original Article

A new nomogram-based on large population to predict survival in patients with operable small intestinal and gastric gastrointestinal stromal tumors

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Received April 20, 2019; Accepted December 3, 2019; Epub January 15, 2020; Published January 30, 2020

Abstract: The present research was designed to develop a novel risk stratification nomogram to predict long term cancer-specific survival (CSS) in patients with operable small intestinal and gastric gastrointestinal stromal tumors (GISTs). SEER database was employed to retrieve eligible subjects with small intestinal and gastric GISTs from 2004 through 2015, who underwent radical surgery. Risk adjusted Cox proportional hazard regression analysis as well as propensity score matched (PSM) model were utilized to evaluate the prognostic value of involved variables, followed by nomogram construction to predict 3-, 5- and 10-year CSS. Afterwards, the predictive accuracy of the nomogram was assessed by discrimination as well as calibration plots. We enrolled 2719 patients from the SEER database. The Cox regression model analysis showed that serosal invasion, older age (older than 62 years), marital status (widowed and never married), gender (male), mitotic count (> 5/50 HPF) grade, primary site (jejunum/ileum) as well as tumor size (> 5 cm) were independent risk factors for CSS in these subjects. Afterwards, these above variables were combined to construct nomograms. As a result, the C-index of the nomogram was 0.759, and calibration curves revealed the close correlation of nomograms-indicated CSS with actual outcome. This was the first study to construct nomograms in operable small intestinal and gastric GISTs, which could help to identify patients at high risk for intensive treatment or follow-up.

Keywords: Gastrointestinal stromal tumors, serosal invasion, nomograms, prognosis

Introduction

Gastrointestinal stromal tumors (GISTs) are the most prevalent type of sarcoma in the gastrointestinal (GI) tract, and are most generally detected in the stomach and small intestine. Nevertheless, only a limited portion of GISTs are detected in the colon, esophagus or other locations of the peritoneal cavity [1, 2]. The majority of GISTs typically express KIT, with activated KIT or PDGFRA mutations, which are mutually exclusive and critically drive cell proliferation in GISTs [3]. Imatinib mesylate (IM), a tyrosine kinase inhibitor (TKI), was approved by the FDA in 2002 for treating GISTs following a series of clinical trials which showed that IM was capable of prolonging the long-term outcomes of GIST patients with both moderate and high-risk [4].

There have been diverse systems to classify GISTs patients. In addition, the prognostic indicators associated with post-operative relapse have been examined, indicating that mitosis, tumor site, tumor size and tumor rupture are potential independent prognostic variables for tumor relapse in GIST patients undergoing R0 or R1 resection [1, 5-7]. The mortality rate of GIST patients has significantly declined due to the extensive administration of IM in clinics. However, the recurrence and metastasis rates are still high, particularly for patients with high risk [8].

We have previously investigated survival trends in operable small intestinal and gastric GISTs patients, and found that primary tumor location is not an independent prognostic factor [9]. Recently, other studies also have demonstrated similar OS and CSS in patients with intestinal and gastric GISTs [10, 11].

For more accurate prognostic prediction and probable correlation with IM efficiency as adju-

vant therapy in subjects with high-risk operable small intestinal and gastric GISTs, a novel risk classification nomogram was established and validated, which incorporated both tumor features and patient characteristics.

Materials and methods

Origins of materials

The SEER database, supported by NCI, gathers and registers information on tumor incidence as well as patient survival, which covers about 28% of the total American population by collecting information from 18 population-based cancer registries (from 2004-2015). The SEER database has no identifier, which is then publicly available to cancer-based epidemiological as well as health policy researches. Herein, after the acquisition of institutional approval, we were able to ascertain information from the SEER database.

Inclusion and exclusion criteria

The inclusion criteria were listed as follows: year of diagnosis (range: 2004-2015); the definition of GIST was based on GI tumour site codes as well as the GIST-specific histology code (ICD-O-3 code 8936); patients with small intestinal and gastric GISTs. In addition, only those with tissues sampled by R0 resection were included in the present study. Moreover, the exclusion criteria are as follows: patients with autopsy-based cancer diagnosis or via death certificate; subjects with metastatic stage; subjects without age documentation at diagnosis or younger than 18 years; subjects without pathological diagnosis; patients burdened with other types of malignancies cancers unless the GIST was the first diagnosed malignant tumour in order to obtain CSS information; patients who died within 1 month (possibly due to operative complications or rapid progression) following palliative surgery; patients with limited information of gender, race, tumor location, tumor size, mitotic count, marital status and serosal invasion.

Statistical analysis

Age at diagnosis, sex, race, marital status, tumor location, tumor size, mitotic count, serosal invasion, survival (months) and cause of mortality were retrieved from the SEER database. OS and CSS were taken as the outcomes according to specific codes in SEER. Moreover, non-cancer specific mortality was considered as a censored observation.

Pearson's χ^2 test or Fisher's exact test was utilized to compare categorical variables between groups. Kaplan-Meier (KM) method was employed to plot survival rates, along with log-rank tests for analysis of survival differences. Cox proportional hazards model was employed for calculation of adjusted hazard ratios (HRs) and 95% confidence intervals (CIs). Nomograms for 3-, 5-, and 10-year CSS predictions were conducted on the basis of the multivariate logistic regression analysis, which served as a visualizing tool to acquire predicted values manually from the multivariate logistic regression analysis. The internal validation of nomogram was tested by discrimination and calibration [12]. To be specific, the discrimination was estimated by Concordance index (C-index), ranging from 0.5-1.0. C-index of 0.5 suggested completely random outcomes, while 1.0 indicated perfect discrimination. Calibration plot was generated to evaluate the correlation between the nomogram-predicted risk and the actual risk. Additionally, propensity score-matched (PSM) analysis was performed using a 1:2 "nearest neighbor" match paradigm, aiming at adjusting for possible differences in baseline data and minimizing bias. R version 3.5.2. was used for statistical analysis and GraphPad Prism 6.0 (GraphPad Software, San Diego, CA) was employed to plot survival curves. A $P < 0.05$ indicated statistically significant.

Results

Clinicopathologic features of patients

In this study, 2719 eligible patients diagnosed with small intestinal and gastric GISTs who received complete R0 resection were enrolled from January 2004 through December 2015. The last follow-up was set at November 2017, with a median follow-up period of 56 months (range: 1 to 143 months). The median age was 62 years old (range: 18 to 98 years of age). The clinical features and mean OS by individual clinical parameters or tumor features were displayed in **Table 1**. Log-rank (Mantel-Cox) test was applied, which showed that the median OS of patients without tumor serosal invasion were significantly longer than those

Table 1. Association of clinical and pathological variables with overall survival

Characteristic	n (%) Total N = 2719	Mean (months) 95% CI	Statistic	*P*
Age (Median = 62 years)			126.576	< 0.001
≤ 62	1398	126.50 (124.02-128.98)		
> 62	1321	102.48 (99.03-105.92)		
Gender			6.901	0.009
Female	1325	117.93 (114.88-120.98)		
Male	1394	112.32 (109.25-115.39)		
Race			1.616	0.446
White	1846	115.10 (112.52-117.68)		
Black	467	112.68 (107.14-118.20)		
Other*	406	116.89 (111.24-122.53)		
Primary Site			1.478	0.478
Stomach	1771	115.60 (112.87-118.34)		
Duodenum	180	116.57 (108.50-124.64)		
Jejunum/ileum	768	113.16 (109.19-117.13)		
Mitotic Count			18.716	< 0.001
≤ 5 per 50 HPF	2351	116.22 (114.00-118.43)		
> 5 per 50 HPF	368	97.25 (90.55-103.96)		
Marital status			65.607	< 0.001
Married	1708	118.63 (116.06-121.20)		
Divorced/Separated	256	120.16 (113.33-126.99)		
Widowed	311	94.17 (86.95-101.39)		
Never married	444	111.66 (106.03-117.30)		
Serosal invasion			20.970	< 0.001
No	1856	118.46 (115.87-121.06)		
Yes	863	107.92 (104.10-111.75)		
Tumor size, cm			35.598	< 0.001
0-2	195	123.19 (115.00-131.38)		
2.1-5	931	121.44 (117.85-125.03)		
5.1-10	976	114.77 (111.29-118.26)		
> 10 cm	617	105.35 (100.61-110.09)		
Year of diagnosis			2.354	0.502
2004-2006	536	113.24 (109.49-117.00)		
2007-2009	626	91.84 (89.54-94.14)		
2010-2012	740	65.08 (63.90-66.25)		
2013-2015	817	33.52 (33.05-33.99)		

*American Indian/AK Native, Asian/Pacific Islander.

with serosal invasion (HR = 0.6552, 95% CI: 0.5268 to 0.7731, P < 0.001). Consistently, the median CSS of patients without tumor serosal invasion were significantly prolonged over those with serosal invasion (HR = 0.4493, 95% CI: 0.3216 to 0.5439, P < 0.001). The MK curves of OS (**Figure 4A**) and CSS (**Figure 4B**) of subjects without tumor serosal invasion in comparison to those with resection were shown in **Figure 4**.

Independent risk factors related to OS and CSS in this cohort

Cox proportional hazards regression analysis was utilized for the exploration of the possible effects of clinicopathological features on OS and CSS. Consequently, patients with serosal invasion harbored a significantly worse OS compared to those without serosal invasion (HR = 1.387, 95% CI: 1.143 to 1.682, P =

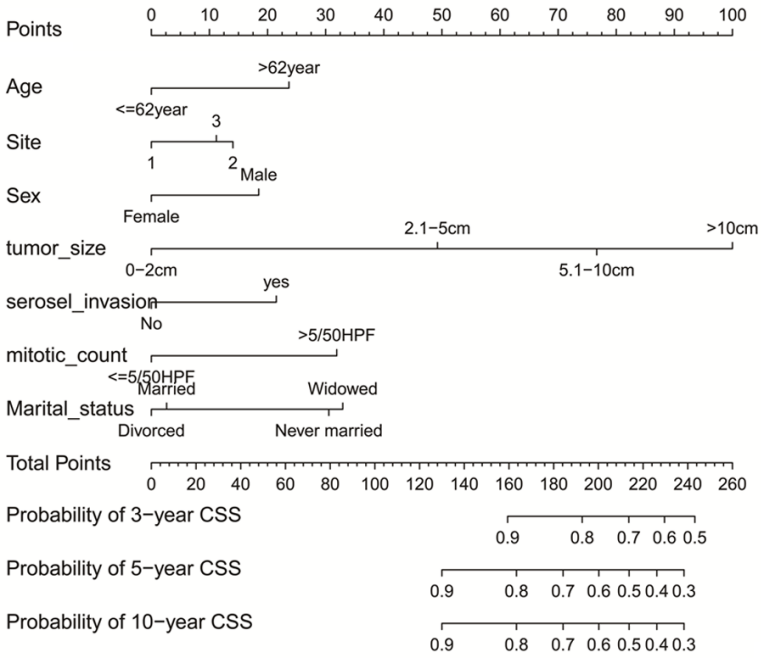

Figure 1. Nomogram for predicting 3-year, 5-year and 10-year CSS in operable small intestinal and gastric GISTs. The nomogram is used by summing the points identified on the top scale for each independent variable and drawing a vertical line from the total points scale to the 3-year, 5-year and 10-year CSS to obtain the probability of survival. The total points projected to the bottom scale indicate the % probability of the 3-year, 5-year and 10-year CSS. Site: 1 = Stomach, 2 = Jejunum/ileum, 3 = Duodenum.

0.001). Similarly subjects with serosal invasion also had a significantly worse CSS (HR = 1.636, 95% CI: 1.261 to 2.122, P < 0.001) than those without serosal invasion. Moreover, we found that older age (62 years), marital status (widowed and never married), gender (male), mitotic count (> 5/50 HPF), primary tumor location (jejunum/ileum) as well as tumor size (> 5 cm) were independent risk factors for CSS in the above population. Detailed characteristics of patients were listed in **Table 2**.

Nomogram development and internal validation

A total of 2719 eligible patients with adequate follow-up time were incorporated to construct the nomogram, which involved these characteristics by utilizing a Cox proportional hazards model. A weighted total score calculated from each variable was used to predict the 3-year, 5-year and 10-year CSS (**Figure 1**). Discrimination and calibration were analyzed in the nomogram as internal validation. As a result, C-index was 0.759, indicating relatively good discrimination of the nomogram. The calibration curves for 3-year, 5-year and 10-year CSS were displayed in **Figure 2**, which showed good correlation between observed CSS and nomogram-predicted CSS.

Propensity score adjustment for serosal invasion

PSM analysis was conducted by decreasing the differences between groups on confounding variables. Additionally, PSM was performed for serosal invasion. The mean difference between treated group and control group of all variables was eliminated into minimum after matching. The histograms after PSM were much more similar than the left side ones without matching, indicating the success of our matching (**Figure 3**). The median OS of patients with serosal invasion was significantly shorter compared to those without serosal invasion (HR = 1.412, 95% CI: 1.149 to 1.735, P < 0.001) (**Figure 4A** and **4D**). Additionally, subjects with serosal invasion also had a significantly worse CSS (HR = 1.845, 95% CI: 1.403 to 2.425, P < 0.001) than those without serosal invasion (**Figure 4C** and **4D**). Finally, we used Cox proportional hazards regression model to explore the effects of serosal invasion as well as other clinicopathological characteristics on CSS. Consequently, CSS of patients burdened with serosal invasion were shortened than those without serosal invasion (HR = 1.685, 95% CI: 1.288 to 2.206, P < 0.001).

Discussion

In total, 2719 eligible patients were retrieved from the SEER database and further analyzed. Each variable was evaluated for its prognostic value by Cox regression model. As a result, multivariate analyses revealed that serosal invasion, older age (62 years), marital status (widowed and never married), gender (male), mitotic count (> 5/50 HPF), primary tumor site (jeju-

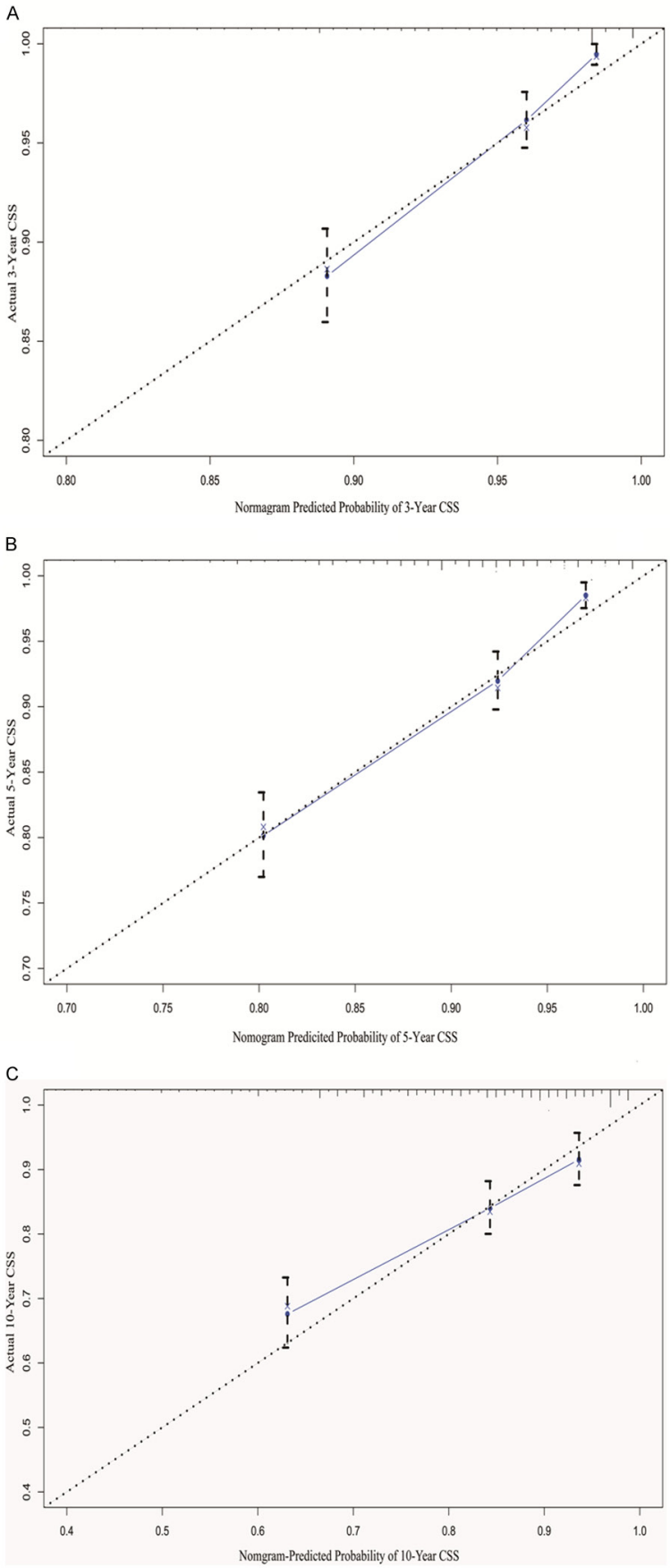

Figure 2. Nomogram model calibration curves. A. 3-year calibration curves; B. 5-year calibration curves; C. 10-year calibration curves; The x-axis shows the nomogram predicted probability, and the y-axis gives the actual survival as estimated by the Kaplan-Meier method.

num/ileum) and tumor size (> 5 cm) were significantly associated with CSS of subjects with operable small intestinal and gastric GISTs. Furthermore, novel nomograms were successfully constructed for prediction of 3-, 5-year and 10-years CSS in operable small intestinal and gastric GISTs. Subsequent internal validation showed good discrimination and calibration of the nomogram.

There have been considerable evolution of GISTs prognostic systems ever since the introduction of NIH consensus criteria in 2002, with diverse proposed modifications of existing systems as well as novel systems [1, 5, 7, 13]. Nevertheless, unlike the majority of other types of malignancies which adopt TNM classification, there is no universally adopted prognostic system for GISTs. Traditionally constructed prognostic systems for GISTs generally involve tumor size, mitotic count, primary tumor location as well as tumor rupture. Tumor rupture, an unfavorable prognostic factor suggested by modified NIH criteria, is categorized into two clinical situations, including spontaneous tumor rupture before surgery and a consequence of the surgical manipulation [14]. Nevertheless, tumor rupture was not included in the present investigation due to the inadequate informa-

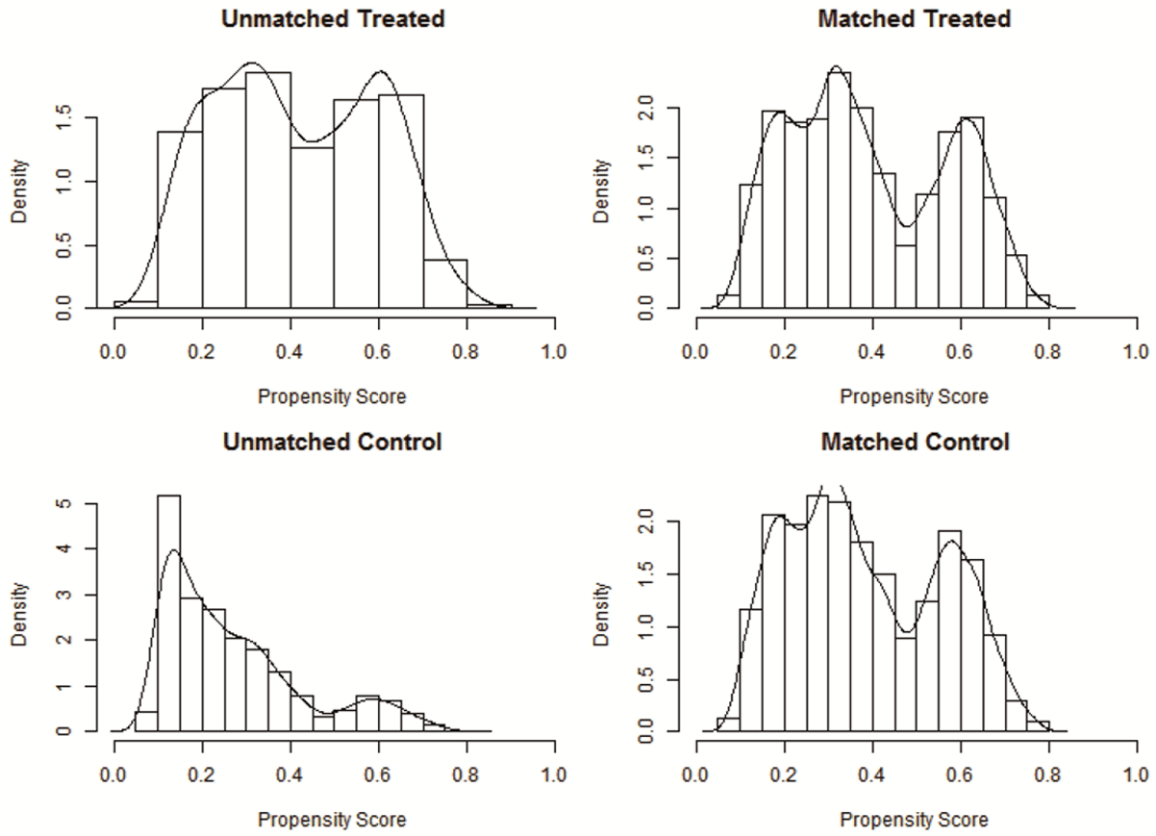

Figure 3. The histogram of unmatched data and matched data for serosal invasion. The histograms before matching on the left while the histograms after matching on the right. The similarity between treated and control group was correlated with the success of matching.

tion in SEER database, which is also common in other studies. In a multi-center study by Joensuu et al. [15], information on tumor rupture was inaccessible in 53.2% cases in pooled population-based cohort as well as 100% cases in validation [7]. In fact, the majority of patients with pre-operative spontaneous tumor rupture are generally burdened with military nodules since cases with implantation metastasis and without R0 resection were eliminated from our research. In the case of iatrogenic tumor rupture, it is mainly dependent on subjective assessment as well as active reporting of surgeons. Serosal invasion is a widely-accepted pathological risk factor in many malignancies, which could increase the positive peritoneal cytology, possibly resulting in poor prognosis. Serosal invasion has rarely been mentioned in GIST as a risk factor [15, 16]. The merits of serosal invasion were less interfering with subjective factors and surgical parameters in comparison to tumor rupture, which could be easily detected during operation and feasibly diagnosed by pathologists. Multivariate Cox proportional hazards model and PSM-based analysis both showed serosal invasion was significantly associated with shortened OS and CSS in subjects with operable small intestinal and gastric GISTs. Therefore, serosal invasion should be enrolled in the guidelines, which might be a prognostic factor in operable small intestinal and gastric GISTs.

Primary tumor location is another potent prognostic indicator in GISTs and thus enrolled in NIH criteria, however, there is controversy on it in terms of small intestinal GISTs with certain limitations [9-11]. The present study has shown that only the jejunum/ileum being the primary tumor location was an independent risk factor for CSS in these patients. Several studies have reported that age is an important prognostic factor in GISTs [2, 17]. Here, multivariate analysis revealed that older age was an independent risk factor for OS and CSS, suggesting poorer outcomes in older subjects, which was consistent with the findings of Wei Song's study in GISTs [18]. In addition, we found that male

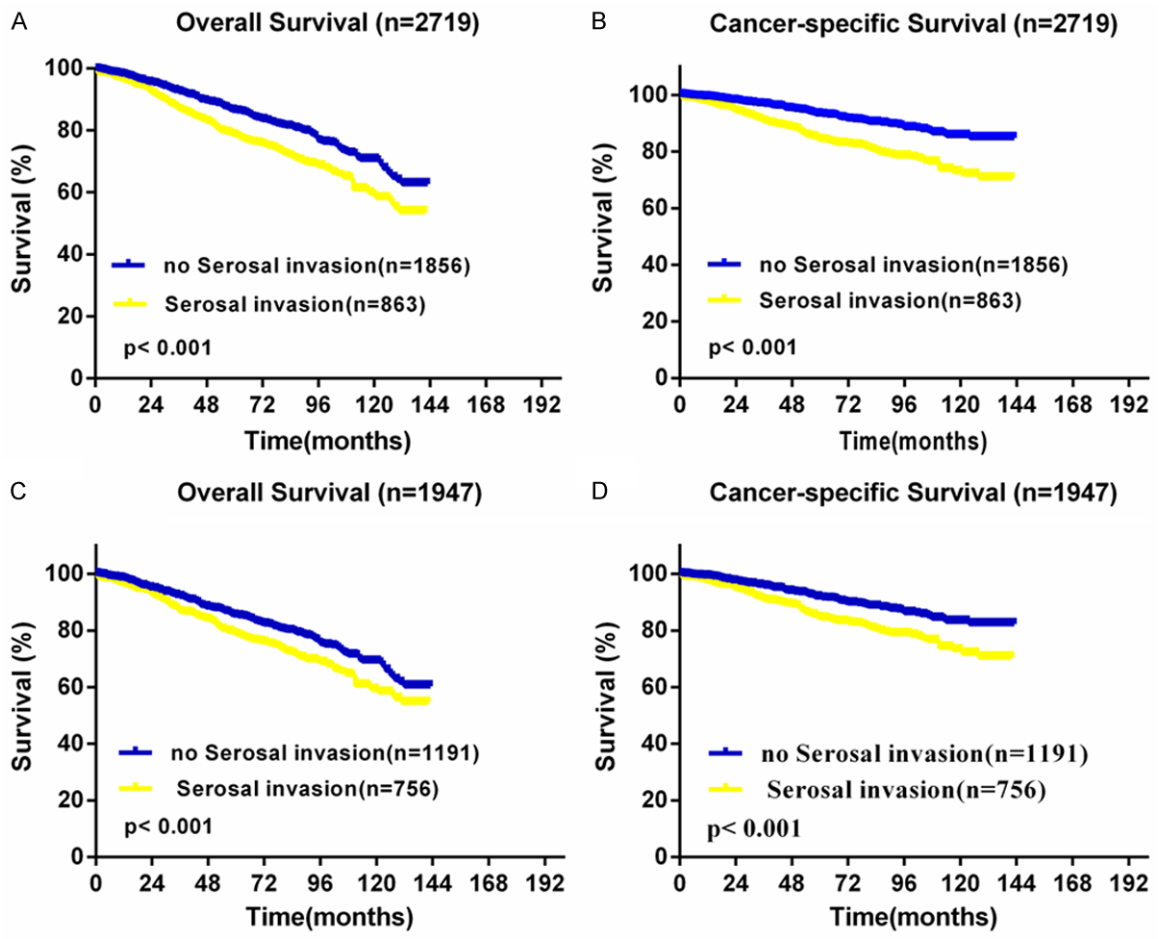

Figure 4. Kaplan-Meier curves for overall and cancer-specific survival. (A and B) Depict the overall and cancer-specific survival in the original data set, and (C and D) depict the overall and cancer-specific survival after propensity score matching.

patients harbored a worse prognosis compared to females with operable small intestinal and gastric GISTs, consistent with previous studies [7, 18]. In recent years, the effects of mental health on human health have attracted accumulative attention. Married populations are likely to acquire more social support and emotional comfort, which might lead to better prognosis [19]. Our study found that being widowed or never married was an independent risk factor in this cohort.

The presently-established nomogram demonstrates good discrimination with a C-statistic of 0.759. Easily available clinical variants are utilized, which provide convenience to the clinical utility of the nomogram. Of note, our nomogram is especially proper to facilitate clinicians in handling complicated situations without clinical guidelines. Furthermore, the clinicopathological data of GISTs patients collected from the SEER database were detailed, ensuring the accurate constriction of the prognostic nomogram.

There are some limitations in our study. First, RFS information is unavailable from the SEER dataset. Secondly, information on TKIs used as well as pathologic features (including type of PDGFR or KIT mutations, tumour necrosis, and imatinib adjuvant therapy information) are inaccessible, either. Thirdly, this model was simplified with available and acceptable parameters, which absolutely fail to enrol all possible variants affecting the clinical outcomes. Finally, our nomogram was based on a retrospective cohort, with relative low level of clinical evidence, thus, further validation in prospective clinical trials is required.

Table 2. Univariate and Multivariable Cox regression model for overall survival and cancer-specific survival in operable small intestine and gastric gastrointestinal stromal tumors patients

Variable	Cox regression for overall survival				Cox regression for Cancer-specific survival			
	Unadjusted[a]	*P*	Adjusted[b]	*P*	Unadjusted[a]	*P*	Adjusted[b]	*P*
	HR (95% CI)		HR (95% CI)		HR (95% CI)		HR (95% CI)	
Age (Median = 62 years)								
≤ 62	1.00 (reference)		1.00 (reference)		1.00 (reference)		1.00 (reference)	
> 62	2.95 (2.42-3.59)	< 0.001	3.13 (2.53-3.88)	< 0.001	1.52 (1.18-1.95)	0.001	1.78 (1.35-2.34)	< 0.001
Gender								
Female	1.00 (reference)		1.00 (reference)		1.00 (reference)		1.00 (reference)	
Male	1.28 (1.06-1.53)	0.009	1.48 (1.21-1.80)	< 0.001	1.47 (1.14-1.90)	0.003	1.49 (1.14-1.96)	0.004
Race								0.710
White	1.00 (reference)		1.00 (reference)		1.00 (reference)		1.00 (reference)	
Black	1.12 (0.88-1.43)	0.348	1.09 (0.85-1.40)	0.502	1.20 (0.87-1.65)	0.275	1.08 (0.77-1.52)	0.664
Other*	0.91 (0.69-1.20)	0.501	0.89 (0.67-1.18)	0.427	0.95 (0.65-1.38)	0.781	0.89 (0.61-1.31)	0.564
Primary Site								0.046
Stomach	1.00 (reference)		1.00 (reference)		1.00 (reference)		1.00 (reference)	
Duodenum	1.12 (0.92-1.36)	0.263	1.32 (0.89-1.95)	0.167	1.10 (0.52-1.84)	0.731	1.29 (0.75-2.19)	0.356
Jejunum/ileum	1.20 (0.65-1.39)	0.797	1.20 (0.97-1.46)	0.085	1.48 (1.14-1.92)	0.003	1.40 (1.07-1.83)	0.014
Mitotic Count								
≤ 5/50 HPF	1.00 (reference)		1.00 (reference)		1.00 (reference)		1.00 (reference)	
> 5/50 HPF	1.86 (1.40-2.47)	< 0.001	2.03 (1.46-2.82)	< 0.001	2.67 (1.90-3.75)	< 0.001	3.28 (2.15-5.02)	< 0.001
Marital status								
Married	1.00 (reference)		1.00 (reference)		1.00 (reference)		1.00 (reference)	
Divorced/Separated	0.91 (0.64-1.31)	0.625	1.120 (0.78-1.62)	0.549	0.81 (0.49-1.37)	0.436	0.95 (0.56-1.61)	0.855
Widowed	2.46 (1.95-3.11)	< 0.001	2.08 (1.61-2.68)	< 0.001	1.84 (1.30-2.62)	0.001	1.92 (1.31-2.82)	0.001
Never married	1.34 (1.04-1.73)	0.025	1.73 (1.33-2.26)	< 0.001	1.69 (1.23-2.31)	0.001	1.82 (1.31-2.54)	< 0.001
Serosal invasion								
No	1.00 (reference)		1.00 (reference)		1.00 (reference)		1.00 (reference)	
Yes	1.53 (1.27-1.83)	< 0.001	1.39 (1.14-1.68)	0.001	2.23 (1.74-2.86)	< 0.001	1.64 (1.26-2.12)	< 0.001
Tumor size, cm								
0-2	1.00 (reference)		1.00 (reference)		1.00 (reference)		1.00 (reference)	
2.1-5	1.02 (0.63-1.64)	0.931	0.88 (0.55-1.42)	0.603	3.60 (0.87-14.89)	0.078	3.08 (0.74-12.77)	0.121
5.1-10	1.41 (0.89-2.45)	0.142	1.11 (0.70-1.77)	0.658	7.65 (1.89-31.05)	0.004	5.48 (1.35-22.30)	0.017
> 10	2.04 (1.28-3.25)	0.003	1.55 (0.96-2.49)	0.074	14.72 (3.64-59.59)	< 0.001	9.20 (2.26-37.51)	0.002
Year of diagnosis								
2004-2006	1.00 (reference)		1.00 (reference)		1.00 (reference)		1.00 (reference)	
2007-2009	0.95 (0.76-1.20)	0.951	0.99 (0.79-1.25)	0.939	0.83 (0.61-1.12)	0.230	0.87 (0.64-1.18)	0.366
2010-2012	1.55 (0.62-1.07)	0.811	1.55 (0.49-0.90)	0.008	0.55 (0.38-0.81)	0.002	0.37 (0.24-0.58)	< 0.001
2013-2015	0.96 (0.64-1.43)	0.957	0.94 (0.53-1.23)	0.314	0.91 (0.54-1.51)	0.701	0.641 (0.36-1.13)	0.127

*American Indian/AK Native, Asian/Pacific Islander. a: univariate Cox regression analysis, b: multivariable Cox regression analysis full model.

Conclusion

In summary, this was the first study to construct and validate nomograms for prediction of 3-year, 5-year and 10-year CSS using a large population-based cohort. The established nomograms could help clinicians identify subjects with operable small intestinal and gastric GISTs at high risk of cancer-specific mortality within 10 years.

Acknowledgements

The authors acknowledge the efforts of the Surveillance, Epidemiology, and End Results (SEER) Program tumor registries in the creation of the SEER database. The interpretation and reporting of these data are the sole responsibility of the authors. This study was supported by the Natural Science Foundation of Ningbo (grant No. 2015A610230), the Oncology Key Special Subject of Ningbo (2016-55), Key Laboratory of Diagnosis and Treatment of Digestive System Tumors of Zhejiang Province (2019E10020).

Disclosure of conflict of interest

None.

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