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Development of web-based dynamic nomogram to predict survival in patients with gastric cancer: a population-based study

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ABSTRACT

Gastric cancer (GC) is the fifth most frequent malignancy worldwide and the third leading cause of cancer-associated mortality. The study's goal was to construct a predictive model and nomogram to predict the survival of GC patients. This historical cohort study assessed 733 patients who underwent treatments for GC. The univariate and multivariable Cox proportional hazard (CPH) survival analyses were applied to identify the factors related to overall survival (OS). A dynamic nomogram was developed as a graphical representation of the CPH regression model. The internal validation of the nomogram was evaluated by Harrell's concordance index (C-index) and time-dependent AUC. The results of the multivariable Cox model revealed that the age of patients, body mass index (BMI), grade of tumour, and depth of tumour elevate the mortality hazard of gastric cancer patients ($P < 0.05$). The built nomogram had a discriminatory performance, with a C-index of 0.64 (CI: 0.61, 0.67). We constructed and validated an original predictive nomogram for OS in patients with GC. Furthermore, nomograms may help predict the individual risk of OS in patients treated for GC.

Keywords: Gastric cancer, Dynamic nomogram, Cox proportional hazard regression model, Survival analysis.

Introduction

Gastric cancer (GC) is one of the most common malignancies, with high incidence and mortality rates, and ranks as the fifth most frequent cancer and the third leading cause of cancer-related deaths globally ¹. The cancer is most commonly diagnosed in men among five countries (Bhutan, China, Kyrgyzstan, Mongolia, and Vietnam) ². Despite the fact that the incidence of GC has reduced during the past decades in European countries, the prognosis stays poor ³. Also, the 5-year overall survival rate for GC patients is approximately 25 percent in the West ⁴. Though the incidence of GC has decreased in Western countries in recent decades, its incidence has remained high in some Eastern countries (e.g., China, Japan, and Korea). Basis on the cancer registry of Turkey, GC may be the 5th most common malignancy in both men and women ⁵. countries, two-thirds of new cases of stomach cancer are recorded, and survival is still low in both developed and developing countries ⁶.

The incidence is approximately 7300 cases per year among the Iranian population, which is the most common cancer in men ⁷. Moreover, mortality from GC can be the first leading factor of death due to cancer in both sexes ⁸. However, the incidence of the disease was higher in men than in women ⁹. Considering the low rate of 5-year survival of GC patients, identification and control of predictive factors remain the essential prevention methods ¹⁰.

Notwithstanding these technologies and therapeutic strategies have progressed over the last several decades, but GC patients' survival and risk factors remain unsatisfactory. It is crucial to recognize prognostic factors for those patients.

According to various statistical analyses, many researches have been performed to evaluate the prognosis factor on the survival of patients with GC ^{10,11}. Those methods incorporate several variables to predict a particular endpoint using traditional statistical methods (e.g., logistic or CPH regression models) ^{12,13}. Other studies have surveyed machine learning methods, which are a branch of artificial intelligence (AI) and computer science, on GC data ¹⁴⁻¹⁷. Almazat et al. applied the Kaplan-Meier method to estimate overall survival in patients with GC ¹⁸. The Cox and Frailty models of survival analysis were used and then compared with C-index ¹³. Other researchers have presented nomograms, which are the graphical representation to intuitive perception of clinicians in Colorectal cancer (CRC) and GC patients ^{11,19,20}. A nomogram, a simple graphical visualization combining and quantifying all independent prognostic factors, plays an increasingly vital role in medical sciences and clinical studies ²¹. Moreover, nomograms play a significant role in improving prognostic accuracy by combining all independent prognostic factors and quantifying their risks ^{22,23}.

The objective of this study was to establish a CPH regression model to explore prognosticators for OS in patients with GC. Then, a more dynamic nomogram was constructed to predict overall survival based on a relatively large historical cohort of patients with GC.

2. Materials and methods

Data sources and ethics statement

The demographical and clinicopathological data were extracted from a tertiary University-Hospital of Iran, Taleghani Hospital in Tehran, between 2013 and 2020. The data from Tehran city (n=733) was regarded. The Ethics Committee of Iran University of Medical Sciences approved the study (Ethical code: IR.IUMS.REC.1399.122). We obtained the patients' informed consent to be allowed to use their medical information. The methods were carried out in accordance with the relevant guidelines and regulations.

Demographic and clinical variables

Survival time, based on months elapsed from the cancer diagnosis until death, was considered the outcome variable. The demographical and clinical variables, including sex, marital status, smoking status, body mass index (BMI), family history, type of treatment, grade of tumour, depth of tumour, number of involved lymph nodes were predictors. The patients' survival status was collected based on alive or dead.

Statistical analysis

The continuous variables were described as Mean $\pm$ SD. Also, the frequency and percentage of categorical variables were reported. Missing data were imputed by fully conditional specification²⁴. The Kaplan-Meier was used in order to estimate the survival function. We applied a univariable CPH model to explore the relationship between a patient's survival and explanatory variables. The selected variables with $P < 0.2$ in the univariable analysis were subjected to multivariable regression modelling. Then, the nomogram was illustrated according to the multivariable CPH model. At last, C-index and time-dependent area under the roc curve were calculated to assess the internal validation. Also, internal calibration using bootstrap resampling was assessed by plotting the predicted probabilities from the model versus actual survival probabilities. The analysis was performed using the SPSS 23 and Stata 11. The survival, DynNom, rms, and hdnom packages in R 4.1.0 software were used to create a dynamic nomogram and to perform validation and calibration.

Results

The study population consisted of 733 confirmed patients with GC who underwent treatment. The median of follow-up time is 9.55 months (IQR=4-19.13, Range= 0.1-84). The Mean $\pm$ SD age of patients was 59.49 $\pm$ 13.47 years, with ranges from 14 to 89 years. 932 (69.1%) of patients were male, and 417 (30.9%) were female. Six hundred ninety-nine (51.8%) patients were censored, and 643 (47.7%) of patients died at the end of follow-up. Other demographic and pathological characteristics of GC patients are given in Table 1. Also, the table revealed factors related to survival rate according to the univariable CPH regression model.

Table 1. Univariable Cox regression analyses for survival in patients with GC

		Status		HR(CI)	P-value
		censored	dead		
Survival time (month), Median (IQR)		10.8(2.9-21.8)	10.0(5.3-16.7)	-	-
Age, Mean (SD)		61.0(12.45)	60.3(13.26)	1.01(1.005, 1.02)	0.003
Sex	Male	318(60.9)	204(39.1)	1.02(0.79, 1.32)	0.877
	Female	132(62.6)	79(37.4)	ref	
Marital status	Married	441(61.3)	278(38.7)	1.35(0.37, 4.89)	0.543
	Single	8(80.8)	2(20.0)	ref	
Smoking	Never used	285(63.6)	165(36.7)	ref	0.272
	Previous or current user	143(57.0)	108(43.0)	1.14(0.90, 1.45)	
BMI	≤18.5	49(46.7)	56(53.3)	1.33(0.96, 1.84)	0.082
	18.5-25	192(63.6)	110(36.4)	ref	
	25-30	48(80.0)	12(20.0)	0.61(0.34, 1.12)	0.114
	≥30	8(72.7)	3(27.3)	0.62(0.19, 1.97)	0.426
Family history	no	314(61.0)	201(39.0)	ref	0.152
	yes	108(62.1)	66(37.9)	0.82(0.62, 1.07)	
Type of treatment	Surgery treatment	288(64.4)	159(35.6)	ref	<0.001
	Other treatments	162(56.6)	124(43.4)	1.61(1.27, 2.04)	
Tumour grade	Well	76(68.5)	35(31.5)	ref	
	Moderately	89(65.0)	48(35.0)	1.19(0.77, 1.85)	0.622
	Poorly	120(60.0)	80(40.0)	1.44(0.97, 2.14)	0.072
	Undifferentiated	165(57.9)	120(42.1)	1.43(0.98, 2.09)	0.061
Depth of tumour	T1	13(81.3)	3(18.8)	0.37(0.12, 1.12)	0.078
	T2	55(80.9)	13(19.1)	0.33(0.19, 0.57)	<0.001
	T3	175(68.1)	82(31.9)	0.62(0.48, 0.81)	<0.001
	T4	90(41.9)	125(58.1)	ref	
Number of involved lymph node	N1	86(66.7)	43(33.3)	ref	
	N2	159(62.4)	96(37.6)	1.11(0.74, 1.66)	0.582
	N3	44(68.8)	20(31.3)	1.02(0.63, 1.66)	0.914

The results showed that age of diagnosing, BMI, family history, type of treatment, grade of tumour, and depth of tumour were significant in the univariable CPH model ($P < 0.05$).

With regard to Kaplan–Meier plot, the 1-year survival rate was 70.9%, while 3-year and 5-year survival rates were at 36.4% and 19.7%, respectively.

The results of the multivariable CPH were presented in Table 2. Variables that had $P < 0.2$ in the univariable analysis were candidates for the multivariable regression analysis. The table showed that age of diagnosis, BMI, grade of the tumour, and depth of tumour are significant in the multivariable CPH model ($P < 0.05$).

Table 2. Multivariable Cox regression model for survival in GC patients.

		HR(CI)	P-value
Age		1.01(1.005, 1.02)	0.003
BMI	≤18.5	1.27(0.97, 1.66)	0.075
	18.5-25	Ref	
	25-30	0.54(0.32, 0.90)	0.020
	≥30	1.20(0.69, 2.08)	0.518
Family history	No	ref	
	Yes	0.93(0.70, 1.23)	0.629
Type of treatment	Surgery treatment	Ref	
	Other treatments	1.33(0.99, 1.78)	0.057
Tumour grade	Well	1.04(0.69, 1.56)	0.853
	Moderately	1.22(0.84, 1.76)	0.281
	Poorly	1.57(1.14, 2.15)	0.005
	Undifferentiated	ref	
Depth of tumour	T1	0.38(0.15, 0.95)	0.039
	T2	0.39(0.22, 0.68)	0.001
	T3	0.66(0.49, 0.90)	0.009
	T4	Ref	

The result showed that for every ten years of increasing the age, the hazard rate increases by 10% (HR=1.01, P-value<0.05). The HR in patients with the overweight range was 46% less than the normal group (HR = 0.54, P < 0.05); however, obese patients had higher HR than normal weight, which is non-significant (HR=1.2, P=0.518).

Also, the hazard ratio in patients who underwent chemotherapy, radiotherapy, and immunotherapy, presented as other treatments in the table, is 33% more than the people who had surgery; however, the type of treatment was non-significant (HR=1.33, P=.057). Moreover, HR of tumour grade in patients with undifferentiated tumour grade was 57% more than people with well grade (HR=1.57, P<0.05). When the depth of the tumour deteriorated, the HR was soared significantly in GC patients. Thus, the higher the tumour depth, the higher HR (P<0.05).

The results of the multivariable CPH model were presented as a nomogram in Figure 1. The probability of survival for a GC patient can be predicted at a specific time point using this nomogram. The patient's characteristics have been plotted on each variable axis. To predict the survival probability of a patient, a vertical line is drawn from the patient's characteristics value to the top points scale. In this way, the number of points that were assigned by that variable value is determined. Then, the points from each variable value are summed. Finally, the sum on the total points is vertically projected onto the bottom axis, and a personalized probability survival time is obtained. Figure 2 shows the image of a web-based nomogram which is accessible in the <https://nbshiny.shinyapps.io/GastricDynNom/>.

Fig 1. Predictive nomogram for survival in Gastric cancer patients.

Dynamic Nomogram

Age
 20 22 24 26 28 30 32 34 36 38 40 42 44 46 48 50 52 54 56 58 60 62 64 66 68 70 72 74 76 78 80 82 84 86 88 90
 77

BMI
 25= $\leq$ <30

Familyhistory
 No

Treatment
 Other treatment

Grade
 Poorly

PT
 T3

☐ Predicted Survival at this Follow Up

☐ Alpha blending (transparency)

Predict

Fig 2. Web-based survival rate calculator ([Dynamic Nomogram \(shinyapps.io\)](https://shinyapps.io/dynamic-nomogram/)) to predict the survival of GC patients; Two patients who are 77 years old, no surgery, no family history, PT3 and $25 \leq \text{BMI} < 30$, but have different grade, well (black line) and poorly (blue line), according to the web survival rate calculator.

Internal Validation and Calibration

The internal validation was checked using C-Index and time-dependent AUC at evaluation time points. The C-index was calculated as 0.64 (CI: 0.61, 0.67). also, we validate the performance of the CPH model with bootstrap resampling every year from the first year to the sixth year. The time-dependent AUC at 1, 2-, 3-, 4-, 5- and 6-years follow-up have been presented in figure 3 (upper left). In addition, the internal calibration using bootstrap resampling was assessed by plotting the predicted probabilities from the model versus actual survival probabilities. In this way, the samples were split into ten risk groups, and the survival probabilities at 1 and 2 years were obtained and summarized as calibration plots in figure 3 (right).

Fig 3. Time-Dependent AUC Summary at Evaluation Time Points (upper left). Internal calibration using bootstrap resampling at 1 year (lower left) and 2 years (lower right).

Discussion

This study provided a significant contribution through the use of a historical cohort of patients with GC who were treated in Iran from 2009 to 2020. The multivariable CPH model presented that

age of diagnosing, BMI, family history, type of treatment, grade of tumour, and depth of tumour were statistically significant. Furthermore, we construct a nomogram to predict OS, which could provide individualized estimates of potential survival and aid individualized management decisions for GC. The C-index was applied to evaluate the model internal validation, and found that the prognostic model has high accuracy.

Nomogram is a precise and useful clinical tool that can help clinicians predict the probability of an outcome event, that is, survival time. A variety of nomograms have been built to predict the therapeutic benefits, the postoperative survival rate in patients with GC²⁵⁻²⁷. Here, we constructed a nomogram to predict the survival rate in GC patients. According to previous studies, a C-index >0.6 indicated that the built model had an acceptance accuracy²⁸⁻³⁰. The value of this index was consistent with our study. In general, a few studies have applied AUC to predict the OS^{25,27,31}. The AUC values of ROC were more than 60% for 1-, 3-, and 5-year of survival, which are compatible with our study.

Our multivariable CPH regression model discovered that age of diagnosis, BMI, grade of the tumour and tumour depth were independent risk factors in GC. Most of the previous studies focused on independent variables associated with GC and found that tumour depth, differentiation grade, size, and lymphatic invasion were closely associated with patients' survival^{32,33}. Lu et al. reported age, differentiation, tumour size, number of examined lymph nodes, pT stage, pN stage, and adjuvant chemotherapy as associated with GC²⁹. They showed that the hazard ratio increased with age, which means that, the older patients get, the higher the hazard. Similarly, our study found that age and pT stage were significant in the CPH model. In our multivariable CPH regression model, the groups with $25 \leq \text{BMI} < 30$ had significantly higher than the group with a $\text{BMI} \leq 18.5$ cm, suggesting that the BMI was a powerful predictor in patients with GC. The built nomogram finally corroborated that the BMI was one of the main risk factors in predicting survival of GC patients^{26,30}. Regarding the grade of tumour, most previous studies reported that the tumour grade was a main predictor for patients with GC^{14,15,22,25,26,28,29}. Similarly, our study found the grade of tumour can be a strong predictor in patients with GC. That means the worse the tumor grade, the greater the hazard ratio.

Study limitation

The key strength of this study is the long-term follow-up period. Also, we had several limitations. First, some variables, such as *Helicobacter pylori* infection status, location of tumour, demarcation line of tumour lesion, tumour markers, nutritional status, and Charlson Comorbidity Index, may also be potential risk factors in patients with GC and need to be incorporated into our model. Second, Statistical analysis was performed using internal validation. It is suggested that in future studies, external validation can be performed using another test dataset.

Conclusion

We successfully established a novel nomogram using patient data from the GC database in Taleghani University-Hospital. Furthermore, the age at diagnosing, BMI, tumour grade, depth of tumour made a significant contribution in predicting OS of patients with GC.

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