A nomogram based on Aspartate Aminotransferase/Alanine Aminotransferase (AST/ALT) ratio after surgery to predict the prognostic value in patients with gastric cancer

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Abstract

Background This study aimed to develop an effective nomogram for predicting overall survival (OS) in surgically treated gastric cancer.

Methods We retrospectively evaluated 190 gastric cancer in this study. Cox regression analyses were performed to identify significant prognostic factors for OS in patients with resectable gastric cancer. The predictive accuracy of nomogram was assessed by calibration plot, concordance index (C-index) and decision curve, and then were compared with the traditional TNM staging system. Based on the total points (TPS) by nomogram, we further divided patients into different risk groups.

Results On multivariate analysis of the 190 cohort, independent factors for survival were age, clinical stage and Aspartate Aminotransferase/Alanine Aminotransferase (SLR), which were entered into the nomogram. The calibration curve for the probability of OS showed that the nomogram-based predictions were in good agreement with actual observations. And the C-index of the established nomogram for predicting OS had a superior discrimination power compared with the TNM staging system [0.768 (95% CI: 0.725-0.810) vs 0.730 (95% CI: 0.688-0.772), $p < 0.05$]. Decision curve also demonstrated that the nomogram was better than TNM staging system. Based on the TPS of the nomogram, we further subdivided the study cohort into 3 groups: low risk ($TPS \leq 158$), middle risk ($158 < TPS \leq 188$), high risk ($TPS > 188$), the differences of OS rate were significant in the groups.

Conclusions The established nomogram resulted in more accurate prognostic prediction for individual patient with resectable gastric cancer.

Background

Gastric cancer (GC), or stomach cancer is one of the common malignant cancers and the second leading cause of cancer related death in the world, especially in East Asia (Takahashi et al. 2013; Yamaoka et al. 2008). And the most common type of GC is adenocarcinoma (GA). There are over 26000 new gastric cancer cases diagnosed and 10730 deaths from GC yearly in the United States (Siegel et al. 2016). Surgery represents the primary treatment for patients with resectable gastric cancer, early gastric cancer has a favorable long-term survival when treated with curative surgical resection, but most GC patients are discovered at advanced stages which requiring multimodality therapy. The poor early detection, recurrence and metastasis, all these factors lead to the low overall survival (OS) rates of GC (Noh et al. 2014). At present, TNM stage has been considered as the main factor to predict the prognosis in gastric cancer (Fujitani et al. 2018; Sasako et al. 2011). However, the outcomes of GC patients with the same stage might be completely different. Therefore, identification of other ways to increase the predictive accuracy of prognosis in GC patients is essential.

Numerous studies had reported that most common serum examinations were considered as prognostic factors of cancer patients. AST and ALT were the common liver function tests, and there was increasing evidence that serum AST and ALT could effectively predict outcomes in patients with hepatocellular

carcinoma, renal cell carcinoma and breast cancer(Ishihara et al. 2017; Thornburg et al. 2008; Zhang et al. 2015). In addition, serum AST/ALT ratio (SLR) or ALT/AST ratio (LSR) had been used as biomarker to assess tumor, liver cirrhosis, insulin resistance, and alcoholic liver disease(Bezan et al. 2015; Gleeson et al. 2009; Kawamoto et al. 2012; Nyblom et al. 2006).

Recently, a growing studies reported that nomogram combined with the common serum examinations could predict prognosis more accurately in a variety of tumors, including lung cancer, colorectal cancer, hepatocellular carcinoma, and so on(Li et al. 2016; Zeng et al. 2017; Zou et al. 2016). Additionally, our pervious study had reported that LSR is a prognostic factor of GC patients, and patients with lower LSR had a greater risk of death than those with higher LSR(Chen et al. 2016).Our aim of this study was to establish a prognostic nomogram for resectable GC based on the SLR and clinicopathological parameters, and to assess whether this model had a more accurate prediction of GC patient survival.

Material And Methods

Sample collection and laboratory analysis

We consecutively collected 190 gastric cancer patients (ages 23–79 years, median 56 years, 132 males and 58 females) who underwent gastric resection at Sun Yat-Sen University Cancer Center from January 2008 to December 2015. Inclusion criteria were as follows: (1) patients confirmed as gastric cancer by pathological. Pathologic slides were reviewed by two independent observers to classify histologic subtypes. (2) Patients who underwent radical resection and had not previously take anti-inflammatory medicines were included. (3) The absence of second carcinomas was assessed by clinical history, gastroscopy, computed tomography (CT) and routine laboratory tests. Patients with the following conditions were excluded in the study: history of inflammatory disease that may modify AST and ALT levels; with multiple stomach tumors; bacterial or viral infection, fever of unknown origin.

Clinicopathologic parameters of each patient were collected as follows: age, gender, smoking history, family history, tumor status, serous infiltration, ABO blood group, pathologic TNM stage, AST, ALT, SLR, CRP, ALB, CRP/ALB. Clinical stage was assessed according to the seventh edition of the Union for International Cancer Control (UICC). OS of patients was followed up by clinic or telephone call. The date from surgery to death or to January 2017 was considered as survival time. The authenticity of this article has been validated by uploading the key raw data onto the Research Data Deposit (RDD) public platform () with the approval RDD number as RDDB2019000518.

All the samples were collected at the time after surgery. The serum levels of AST, ALT, CRP, and ALB were measured by an Automatic Biochemical Analyzer (Hitachi 7600, Japan) according to the manufacturer's instructions.

Statistical analysis

Statistical analyses were performed using SPSS software, version 20.0 (SPSS Inc., Chicago, IL, USA). Nomogram for possible prognostic factors associated with OS were established by R software (version 3.5.1). The cut-off values of AST, ALT, CRP and ALB were estimated by median, and other continuous

variables were transformed into categorical variables based on the cut-off values of the X-tile program(Camp et al. 2004). The Kaplan-Meier curves were used to calculate the survival rate, and the Log-rank test was used to compare them. The Cox proportional hazards regression was used for multivariate analysis. All variables with $p < 0.05$ in the multivariable model were used to develop a dynamic prediction nomogram model. The performance of the prediction nomogram model was evaluated by concordance index (C-index) and decision curve. The difference was considered statistically significant when $p < 0.05$.

Results

Clinicopathologic Characteristics

190 patients with gastric cancer who received surgery were enrolled for our study. The clinical characteristics of patients were shown in Table 1. The median age was 56 (range from 23 to 79). There existed 132 male patients (69.5%) and 58 female patients (30.5%). Patients had smoking history and family history were 58 (30.5%) and 18 (9.5%). The number of early stage and advanced stage patients were 34 (17.9%) and 156 (82.1%). Lymph node metastasis was confirmed pathologically in 133 (70.0%) patients. Only 16 (8.4%) patients have distant metastasis. And all the patients are adenocarcinoma (AC).

Table 1
Clinical and laboratory characteristics of 190 patients associated with overall survival (OS)

Characteristics	No. of patients	OS (Months) Mean (95% CI)	p-Value
Age			0.022
≤ 51	63	70.76 (63.31–78.21)	
> 51	127	58.97 (52.70–65.23)	
Gender			0.429
Female	58	60.46 (51.39–69.53)	
Male	132	63.66 (57.87–69.44)	
Family History			0.287
Yes	18	62.22 (56.94–67.51)	
No	171	68.48 (55.05–81.90)	
Smoking Behavior			0.25
Yes	58	67.09 (58.61–75.57)	
No	132	61.26 (55.25–67.26)	
Tumor status			< 0.001
T1/T2	34	89.13 (86.82–91.41)	
T3/T4	156	57.09 (51.59–62.58)	
Lymph node metastasis			< 0.001
Yes	133	53.57 (47.36–59.77)	
No	57	84.40 (80.87–87.94)	
Distant metastases			< 0.001
Yes	16	33.06 (19.26–46.85)	
No	174	65.69 (60.66–70.72)	
Clinical stage			< 0.001
I	22	86.65 (83.46–89.85)	
II	46	85.78 (81.48–90.08)	
III	81	58.85 (51.51–66.18)	

OS, overall survival; ALT, alanine aminotransferase; AST, aspartate aminotransferase; SLR: AST/ALT ratio; ALB, albumin; CRP, C-reaction protein.

Characteristics	No. of patients	OS (Months) Mean (95% CI)	p-Value
IV	41	31.14 (21.90-40.37)	< 0.001
Serous infiltration			
S0/S1	67	75.24 (68.54–81.94)	
S2/S3	123	56.24 (49.91–62.56)	0.143
AST			
≤ 28	99	66.64 (59.87–73.40)	
> 28	91	57.43 (50.65–64.21)	0.552
ALT			
≤ 25	97	64.90 (57.94–71.85)	
> 25	93	60.40 (53.59–67.21)	0.028
SLR			
≤ 1.24	135	66.72 (61.05–72.39)	
> 1.24	55	52.55 (43.55–61.55)	0.804
CRP			
≤ 68.48	94	63.93 (56.95–70.91)	
> 68.48	96	61.36 (54.43–68.30)	0.024
ALB			
≤ 34	94	57.49 (50.21–64.76)	
> 34	96	67.92 (61.49–74.34)	0.616
CRP/ALB			
≤ 1.15	94	64.66 (57.71–71.60)	
> 1.15	96	60.65(53.69–67.60)	0.283
Blood type			
A	50	58.01 (48.19–67.82)	
B	52	59.97 (50.92–69.02)	
AB	11	48.09 (31.35–64.83)	

OS, overall survival; ALT, alanine aminotransferase; AST, aspartate aminotransferase; SLR: AST/ALT ratio; ALB, albumin; CRP, C-reaction protein.

Characteristics	No. of patients	OS (Months) Mean (95% CI)	p-Value
0	77	68.22 (60.88–75.55)	
OS, overall survival; ALT, alanine aminotransferase; AST, aspartate aminotransferase; SLR: AST/ALT ratio; ALB, albumin; CRP, C-reaction protein.			

Association of serum SLR level after surgery with clinical characteristics

Median survival time in the present group of patients was 40.1 months (range 6.8–73.4 months), the 1-, 3-, 5-year survival rate were 90.5%, 66.8%, 63.2%, respectively. Patient characteristics and correlations between postoperative SLR level and clinicopathological parameters are shown in Table 2. SLR was associated with ALT ($p < 0.001$), ALB ($p = 0.045$) and overall survival ($p = 0.042$). Compared to the patients with better prognosis, the poor outcome patients had higher postoperative SLR ($p = 0.042$). There was no correlation between SLR and age, gender, family history, smoking behavior, tumor status, lymph node metastasis, distant metastases, clinical stage, serous infiltration, CRP, blood type.

Table 2
Correlation between AST/ALT and clinicopathological variables of gastric cancer patients

Characteristics	No of patients	AST/ALT ratio		p ^a
		≤ 1.24	> 1.24	
Patients	190	135	55	
Age				
≤ 51	63	49 (77.8%)	14 (22.2%)	0.150
> 51	127	86 (67.7%)	41 (32.3%)	
Gender				
Female	58	40 (69.0%)	18 (31.0%)	0.674
Male	132	95 (72.0%)	37 (28.0%)	
Family History				
Yes	171	122 (71.3%)	49 (28.7%)	0.678
No	18	12 (66.7%)	6 (33.3%)	
Smoking Behavior				
Yes	58	46 (79.3%)	12 (20.7%)	0.096
No	132	89 (67.4%)	43 (32.6%)	
Tumor status				
T1/T2	34	27 (79.4%)	7 (20.6%)	0.236
T3/T4	156	108 (69.2%)	48 (30.8%)	
Lymph node metastasis				
Yes	133	91 (68.4%)	42 (31.6%)	0.222
No	57	44 (77.2%)	13 (22.8%)	
Distant metastases				
Yes	16	10 (62.5%)	6 (37.5%)	0.431
No	174	125 (71.8%)	49 (28.2%)	
Clinical stage				
I	22	19 (86.4%)	3 (13.6%)	0.292

Characteristics	No of patients	AST/ALT ratio		p ^a
		≤ 1.24	> 1.24	
II	46	32 (69.6%)	14 (30.5%)	
III	81	58 (71.6%)	23 (28.4%)	
IV	41	26 (63.4%)	15 (36.6%)	
Serous infiltration				
S0/S1	67	48 (71.6%)	19 (28.4%)	0.895
S2/S3	123	87 (70.7%)	36 (29.3%)	
AST				
≤ 28	99	69 (69.7%)	30 (30.3%)	0.667
> 28	91	66 (72.5%)	25 (27.5%)	
ALT				
≤ 25	97	51 (52.6%)	46 (47.4%)	< 0.001*
> 25	93	84 (90.3%)	9 (9.7%)	
CRP				
≤ 68.48	94	64 (68.1%)	30 (31.9%)	0.372
> 68.48	96	71 (74.0%)	25 (26.0%)	
ALB				
≤ 34	94	61 (64.9%)	33 (35.1%)	0.045*
> 34	96	74 (77.1%)	22 (22.9%)	
CRP/ALB				
≤ 1.15	94	65 (69.1%)	29 (30.9%)	0.576
> 1.15	96	70 (72.9%)	26 (27.1%)	
Blood type				
A	50	36 (72.0%)	14 (28.0%)	0.929
B	52	38 (73.1%)	14 (26.9%)	
AB	11	7 (63.6%)	4 (36.4%)	
O	77	54 (70.1%)	23 (28.9%)	

Characteristics	No of patients	AST/ALT ratio		
		≤ 1.24	> 1.24	p ^a
Overall survival				
Alive	118	90 (76.3%)	28 (23.7%)	0.042*
Death	72	45 (62.5%)	27 (37.5%)	
Note: a Using Chi-squared test, * p < 0.05 was considered statistically significant.				

Univariate and multivariate analyses of factors associated with patient prognosis

The univariate analysis show that postoperative SLR level was found to be associated with OS (p = 0.034), along with other variables, such as age (p = 0.017), tumor status (p < 0.001), lymph node metastases (p < 0.001), distant metastases (p = 0.003), clinical stage (p < 0.001), serous infiltration (p < 0.001), albumin (p = 0.024) (Table 3). Moreover, multivariate analysis showed that age (HR = 2.193, 95% CI: 1.169–3.746, p = 0.013), clinical stage (HR = 2.975, 95% CI: 1.706–5.187, p < 0.001) and SLR (HR = 1.672, 95% CI: 1.030–2.714, p = 0.038) were independent prognostic factors of OS for GC patients using the Cox proportional hazard model.

Table 3

Univariate and multivariate COX regression analyses for Overall Survival in patients with gastric cancer

Variables	Univariate Analysis			Multivariate Analysis		
	HR	CI	p	HR	CI	p
Age	1.874	1.087–3.229	0.017	2.09	1.169–3.746	0.013
Gender	0.822	0.506–1.336	0.434	-	-	-
Family History	0.613	0.247–1.522	0.258	-	-	-
Smoking Behavior	0.732	0.429–1.249	0.241	-	-	-
Tumor status	20.187	2.803–145.358	< 0.001	3.402	0.427–27.105	0.248
Lymph node metastasis	8.318	3.347–20.676	< 0.001	1.765	0.586–5.315	0.313
Distant metastases	3.079	1.614–5.872	0.003	1.044	0.479–2.279	0.913
Clinical stage	3.565	2.541–5.001	< 0.001	2.975	1.706–5.187	< 0.001
Serous infiltration	2.982	1.634–5.441	< 0.001	1.215	0.649–2.274	0.542
AST	1.414	0.888–2.251	0.143	-	-	-
ALT	1.151	0.724–1.828	0.552	-	-	-
SLR	1.699	1.054–2.738	0.034	1.672	1.030–2.714	0.038
CRP	1.06	0.668–1.684	0.804	-	-	-
Albumin	0.584	0.365–0.936	0.024	0.806	0.491–1.323	0.395
CRP/ALB ratio	1.126	0.709–1.788	0.616	-	-	-
Blood type	0.849	0.706–1.020	0.084	-	-	-
p < 0.05, statistically significant. CI = confidence interval; HR = hazard ratio.						

The Nomogram For The Prediction Of Os

According to multivariate Cox regression model, we know that age ≥ 51 , advanced clinical stage, and SLR ≥ 1.24 were poor prognostic factors for OS. So a nomogram containing age, clinical stage, and SLR was established to predict OS of GC patients (Fig. 1). The nomogram model achieved a C-index of 0.794 (95% CI: 0.749–0.839), which was higher than the C-index of the TNM staging system 0.730 (95% CI: 0.688–0.772, $p < 0.05$), and the predictive accuracies for OS of GC between the nomogram and the TNM system were compared by calculating the Harrell's C-index (Table 4). Calibration curves for the probability of survival at 1-, 3-, 5-years after surgery showed optimal agreement between the prediction established in

the nomogram and the actual observation (Fig. 2). The results of the decision curve analysis at 5 years were presented in Fig. 3. Compared to the traditional TNM staging system, the established nomogram model had a higher overall net benefit across a wide range of threshold probabilities.

Table 4
The C-index of nomogram model and TNM stage for prediction of OS

Variables	C-index (95%CI)	p
Nomogram Model	0.794 (0.749–0.839)	
TNM stage	0.730 (0.688–0.772)	
Nomogram Model vs TNM stage		< 0.05
C-index = concordance index; CI = confidence interval.		

Performance of the nomogram model in stratifying risk of patients

Based on the predictor of nomogram, three subgroups were divided in GC patients by total score: low risk group (score: 0-158), middle risk group (score: 158–188), and high risk group (score: ≥ 188) (Table 5). The results suggested that patients of GC with higher score corresponded to worse prognoses. The low risk group with survival probabilities of 100%, 98.2% and 94.8% for 1, 3 and 5 years, respectively. The middle risk group with survival probabilities of 94.4%, 65.3% and 62.5% for 1, 3 and 5 years, respectively. The high risk group had the lowest probability of survival of 76.7% for 1 year, 38.3% for 3 years and 33.3% for 5 years, respectively. Then Kaplan-Meier curve was plotted based on the cutoff values. The OS medians of these three group were 86.70, 63.47 and 38.56 months, respectively. This stratification could effectively discriminate the survival outcomes for the three risk groups (Fig. 4, $p < 0.001$).

Table 5
Point Assignment and Prognostic Score of the nomogram model

Variable and Prognostic Score	Score	Estimated 1-Year OS (%)	Estimated 3-Year OS (%)	Estimated 5-Year OS (%)
Age group points				
≤ 51	0			
> 51	20			
Stage group points				
I	0			
II	33			
III	67			
IV	100			
SLR group points				
≤ 1.24	0			
> 1.24	13			
Total prognostic Score				
0-158		100	98.2	94.8
158–188		94.4	65.3	62.5
≥ 188		76.7	38.3	33.3

Discussion

GC is an aggressive cancer with high incidence and death rate in worldwide (Parkin et al. 2001). H. Pylori infection, inflammation and other factors may increase risk of GC, which are related to cancer development (Li et al. 2013; Mbulaiteye et al. 2009; Talley et al. 1991). The survival of individual patients within the same stage are remarkably heterogeneous in GC. Currently, surgical resection remains the best treatment for patients with GC. However, patients after gastrectomy often experience recurrence or metastasis within 5 years (Liu et al. 2018). Thus, it is important to identify independent prognostic factors to optimize postoperative treatments. Nomogram is a statistical prediction tool that generates a numerical probability of death and cancer recurrence. It can incorporate all prognostic factors to estimate the survival outcome for cancer patients (Albert et al. 2012; Valentini et al. 2011). In recent years, nomograms have been widely demonstrated in a variety of cancers, compared to the traditional staging system, some of them have more accurate prediction (Li et al. 2016; Sternberg 2006). In our previous

study, we found that LSR is an independent prognostic factor for patients of GC, patients with higher LSR were associated with better survival than those with lower LSR(Chen et al. 2016). However, it did not comprehensively evaluate the significance of serum Aminotransferase and clinicopathological parameters in patients of GC.

In this study, our result show that the clinical characteristics of AST, ALB and overall survival were associated with SLR levels. Using univariable analysis and subsequent multivariable analysis, we identified age, clinical stage and SLR as independent prognostic factors for surgically treated GC patients. We evaluated the prognostic power of SLR in GC patients, and established an effective predictive nomogram model for GC patients. The nomogram model which included age, stage status, and SLR. The C-index of the nomogram model predicted OS with an accuracy of 0.794 (95% CI: 0.749–0.836). It had a better accuracy than the current TNM classification system 0.730 (95% CI: 0.688–0.772). In addition, the nomogram model had a higher overall net benefit than the TNM staging system at 5 years. To our knowledge, this is the first study providing a nomogram based on SLR and clinical characteristics to predict the survival of resectable GC patients. According to the nomogram model scores, GC patients were divided into three risk groups. Each group had distinct survival outcome, and the high risk group had shortest OS in the three risk groups. Such a nomogram model provided clinicians a consistent and reliable tool to predict outcomes in patients of GC after gastrectomy.

The potential mechanism of the established nomogram based on SLR predicting patient prognosis can be explained as follows: At first, liver is the main organ in metabolism, secretion, and immunity(Adesanoye et al. 2010; Wolf 1999). Serum AST and ALT activity has long been used as an inflammatory marker to evaluate the functional status of liver(Drotman et al. 1978; Frederiks et al. 1984). Lin et al reported that LSR is a strong risk of hepatic steatosis in patients with chronic HCV infection(Lin et al. 2015). AST and ALT levels reflect the condition of inflammatory response. Inflammation could relate to cancer development. Numerous studies had shown us that the presence of inflammatory response is linked to poor survival in many cancers(Li et al. 2016; Toiyama et al. 2013). Moreover, it has been reported that there is an increased production of reactive oxygen species (ROS) and DNA damage in liver injury. ROS include hydrogen peroxide (H_2O_2), superoxide and hydroxyl free radicals. Meanwhile, ROS was considered as a toxic product of cellular metabolism, and it was known to modify protein activity for cell growth and survival(AbdulSalam et al. 2016; Concepcion Navarro et al. 1993). DNA damage could lead cell to apoptosis. It is an essential cell apoptosis process of programmed cell death in multicellular organisms(Fulda et al. 2010).

The established nomogram could predict survival more precise for resectable GC patients. However, there are still several limitations. First, it lacks validation cohort. Second, our study was a retrospective study, and we cannot avoid potential biases. Third, this is a single-center study and a small sample size of 190 patients. Therefore, our results need to be further verified by multi-center studies which using greater sample sizes. Despite these limitations, this model provided an effective tool to predict the OS of GC patients, and it is helpful to make individualized treatment decision for patients.

Conclusions

In conclusion, we established a nomogram containing age, clinical stage and SLR for predicting survival of patients with resected GC, and it shows a better level of discrimination ability than the traditional TNM classification. This model is a simple, precise and easy-to-use scoring system for clinicians to estimate the survival of GC patients.

Abbreviations

OS: overall survival; ALT: alanine aminotransferase; AST: aspartate aminotransferase; SLR: AST/ALT ratio; ALB: albumin; CRP: C-reaction protein.

Declarations

Acknowledgments

Not applicable.

Authors' contributions

LFL, SX, NX: conception and design; QYZ, SLC: administrative support; LFL, MTW, YQL: collection and assembly of data; QXX, LMF, QYZ: data analysis and interpretation; All authors reviewed and edited the manuscript and approved the final version of the manuscript.

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Availability of data and materials

The datasets analyzed during the current study are not publicly available due to patient privacy concerns, but are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

This study was approved by the Clinical Research Ethics Committee of the Sun Yat-sen University Cancer Center, and all patients provided written informed consent at the first visit to our center

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Figures

Figure 1

Nomogram convey the results of prognostic models using age, clinical stage and SLR characteristics predict OS. The nomogram was used summing the points identified on the points scale for each variable. The total points projected on the bottom scales indicate the probability of 1-, 3- and 5-year survival.

Figure 2

The calibration curves for predicting patient OS at 1 year (A), 3 years (B) and 5 years (C) in the primary cohort. Nomogram model-predicted OS is plotted on the x-axis; actual OS is plotted on the y-axis. The reference line is 45 degree and indicates perfect calibration.

Figure 3

Decision curve analysis for 5-year survival predictions. In the decision curve analysis, the y-axis indicates net benefit. The straight line represents the assumption that all patients will die, and the horizontal line represents the assumption that no patients will die.

Figure 4

Kaplan-Meier curve of GC patients OS for three groups based on the predictor from the nomogram model.