The development and external validation of a nomogram predicting overall survival for gastric cancer patients with inadequate lymph nodes based on an international database

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Research article

Keywords: Gastric cancer, Nomogram, Lymphadenectomy, Prognosis

Posted Date: October 2nd, 2019

DOI: <https://doi.org/10.21203/rs.2.15591/v1>

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Version of Record: A version of this preprint was published at International Journal of Clinical Oncology on March 31st, 2021. See the published version at <https://doi.org/10.1007/s10147-021-01875-2>.

Abstract

Background The inadequate lymph nodes could lead to stage migration and indicate a poor prognosis for gastric cancer after curative surgery. Some emerging novel predictors and the methodology of nomogram could increase the accuracy of survival prediction. **Methods** An international database regarding gastric cancer was employed as the primary cohort. The patients with inadequate (<30) lymph nodes (LN) were analyzed by Cox proportional hazards regression. Based on the selected model, a nomogram was plotted and calibrated by the external validation database. **Results** A total of 1109 patients were included in the primary cohort, and 6584 patients in the validation cohort. There were significant differences regarding the clinical characteristics between the two cohorts. The model containing age, T stages, N stages, metastatic lymph nodes (mLN), and the number of total LN retrieved (TLN) showed superiority over the conventional TNM stages. The Harrell's concordance index of the nomogram and TNM stages was 0.744 and 0.717 respectively. The external validation demonstrated a good concordance with the nomogram-predicted survival. **Conclusions** The nomogram containing age, T stages, N stages, mLN, and TLN had a better accuracy than the conventional TNM staging system in predicting overall survival for gastric cancer patients with inadequate (<30) LNs.

Background

Gastric cancer remains the fifth most prevalent and third leading cause of cancer death worldwide according to the latest epidemiologic data[1]. A radical gastrectomy is crucial for treating gastric cancer, and the extended peri-gastric lymphadenectomy (D2 surgery) was considered standard procedure for the locally advanced stages[2]. Along with the enlarged surgical field, the number of lymph nodes (LN) retrieved could theoretically be increased, meaning that the LN count could be regarded as a criterion for surgical quality control[3]. A lower LN count could imply a deficiency in the surgical treatment and lead to an unfavorable prognosis[4, 5].

Meanwhile, the number of LN retrieved is also a prerequisite for applying the American Joint Committee on Cancer (AJCC) TNM classification system for gastric cancer[6], which is the most universally accepted prognostic indicator. According to AJCC system, at least 16 regional nodes should be removed or assessed pathologically, and the removal or evaluation of more nodes (≥ 30) is desirable[6]. A substandard LN count could lead to N stage migration[7, 8] and the subsequent underestimation of the survival risk. To increase the predictive values of LN-related parameters, some novel predictors have been studied and introduced in clinical practice. According to multiple studies[9–12], the predictors, including the ratio of metastatic LN, the ratio of negative to positive LN, and the log odds of positive lymph nodes (LODDS), have confirmed the superiority over the conventional AJCC N stage in predicting survival.

Additionally, besides the attempts to mend the predictors related to LN status, the parameters[13, 14] related to tumor volume have been investigated and also showed some values in survival prediction. Based on the hypothesis that adding additional information to the conventional AJCC staging system might help to increase the predictive accuracy, we carried out this study accordingly. An international

database was employed to minimize the bias, and the nomogram was used to maximize the clinical practical value.

Methods

Primary database and external validation database

The primary database was composed by the IMIGASTRIC database and the PUCH database. The former was an international database dedicated to international study on minimally invasive surgery for gastric cancer. The database was established and run by St. Mary's Hospital of Terni and "La Sapienza" University of Rome. The latter was a prospectively collected and maintained database for gastric cancer, established and run by Peking University Cancer Hospital. As the biggest database providing the information on cancer statistics, the Surveillance, Epidemiology, and End Results (SEER) database was chosen as the external validation.

Inclusion and exclusion criteria

The inclusion criteria for case selection in the primary database were as follows: (1) histologically confirmed gastric adenocarcinoma; (2) gastrectomy was performed with D2 lymphadenectomy; (3) the number of total LN retrieved (TLN) was less than 30, and (4) the follow-up time was longer than 60 months or end point (death) reached.

The exclusion criteria were as follows: (1) neoadjuvant treatments was applied; (2) previous surgery history related to stomach; (3) non-curative surgery was confirmed, including positive margin, positive cytology; (4) metastatic disease was confirmed before or at the time of surgery, including distant metastasis, distant LN metastasis, and peritoneal dissemination; and (5) combined with other malignancy.

As for validation database, the inclusion and exclusion criteria were the same with the primary, except that the surgical procedure had to be defined as gastrectomy roughly (coded as 30, 40, 50, 60, and 80 in the variable "RX Summ–Surg Prim Site") as a inclusion criteria instead of D2 lymphadenectomy, because there was no corresponding variable coding the D2 lymphadenectomy in SEER database. Additionally, in order to minimize the impact of inadequacy in surgical treatment in the SEER database, the minimum LN retrieved was required to be no less than 8, in keeping with the number in the primary database. Cases of unnatural death and any missing data on the number of metastatic LN and the TLN, the T stage, the tumor size were excluded as well.

Parameter definition

The depth invasion of tumor (T stage), LN metastasis (N stage), and the overall stage (TN stage) were categorized with the 8th edition of the American Joint Committee on Cancer (AJCC) staging system for gastric cancer[6].

In pursuit to the simplicity and practicability of the prognostic factors used for the nomogram, we only adopted some common, simple and easy-to-calculate parameters related to tumor volume and LN metastasis, including the tumor diameter defined as the longest length of tumor volume, the tumor index (TI)[14] calculated as tumor diameter $\times$ T stage, the number of metastatic lymph nodes (mLN), and the ratio of mLN to total lymph nodes examined (mLNR). The overall survival (OS) was defined as the time (in months) from the surgery to the date of death from any cause or the last follow-up.

Factor and model selection

The univariate analyses were performed in the primary cohort to identify the significant prognostic factors for OS. Then the factors with a p-value less than 0.1 in the univariate analyses were included in the multivariate analyses to find out the independent prognostic factors. The selected model was compared with the control model by Akaike Information Criterion (AIC), and the Harrell's concordance index (C-index). A smaller AIC and a larger C-index indicate a more accurate and effective model.

Nomogram development and external validation

The nomogram was plotted with RStudio (version 1.1.463, with packages “Hmisc”, “lattice”, “Formula”, “ggplot2”, and “rms”) according to Zhang's method[15]. The selected factors in the primary cohort were introduced into the Cox proportional hazard model, and a visualized risk diagram was drawn based on the model. As for the external validation, the calibration curves for 3- and 5-year survival rates were plotted by comparing the means of the nomogram-predicted OS with the observed Kaplan–Meier estimate of actual OS in both the primary and the validation cohorts. The bootstrapping method (1000 repetitions) was used to reduce the estimate bias.

Statistical analyses

Categorical data were presented as the numbers (percentage); continuous data were presented as the mean ($\pm$ standard deviation) if normally distributed or as the median (interquartile range) if not normally distributed. Differences of categorical and continuous data were analyzed by Chi-square tests and independent-samples T tests, respectively. The difference of OS was analyzed by log-rank test.

For the univariate analyses, Cox proportional hazards regressions were performed to determine the predicting factors of OS. The multivariate analysis was performed with bidirectional stepwise method. All

analyses were performed with SPSS® (version 23.0) and RStudio (version 1.1.463). Statistical significance was declared with two-sided $p < 0.05$ for all tests.

Results

The clinical characteristics and survival

A total of 1109 patients were included in the primary cohort, and 6584 patients in the validation cohort. The age, sex, race, tumor location, T stage, N stage, TNM stage, tumor diameter, TI, mLN, mLNR, and the total LN were significantly different between the two cohorts (Table 1). In summary, the population in primary cohort were younger, had more male patients, was dominated by Asian patients, had more cancers located in the middle and upper third of stomach, had more patients in early stages, and had smaller tumor diameter compared to the validation cohort. Although the mLN was similar between the two cohorts, the mLNR was lower in the primary cohort due to the higher number of TLN. The 3-year and 5-year OS was significantly higher in the primary cohort than the validation cohort (all $p < 0.001$) (Table 1) (Figure 1).

The univariate and multivariate analyses

The univariate analyses presented a significant correlation between the age, T stages, N stages, tumor diameter, TI, mLN, mLNR and the OS (all $P < 0.001$). The multivariate analysis showed that the age, T stages, N stages and mLN were the independent prognostic factors for OS (Table 2).

The model selection

In the multivariate model, the “N3b” stage did not reached the statistical significance, and the hazard ratio (HR) was even lower than the “N3a” stage, which was inconsistent with the clinical impression obviously. The result might be explained by the limited number of “N3b” stage in the primary cohort ($n=71$, 6.4%). Besides, the case number of “T4b” was even lower ($n=26$, 2.3%), so we combined the stage “N3b” with “N3a” as “N3”, and the stage “T4b” with “T4a” as “T4” in the subsequent analyses (Table 1 and 2).

Apparently, the mLNR had a constant mathematical relationship with mLN and TLN, given the strong correlation between the two factors, the multivariate analysis might be biased by the collinearity between mLN and mLNR. On the other hand, since the TLN was documented to be the independent prognostic factor in multiple studies[4, 5], and was recommended to be above 30 for a favourable prognosis[6], we introduced the mLN and TLN in the model selection for clinical benefits.

Generally, the model was evaluated by its discriminative capability and the goodness of fit. The C-index and AIC was used as the assessment criteria for the two above features respectively. As the controlled

model, the TNM stage model had a C-index of 0.717, and an AIC of 6662.988, which was inferior to other models. Interestingly, all other models had a same C-index of 0.744, however, the model (age + T stages + N stages + mLN + TLN) had the lowest AIC (6607.119), which implied a superiority in goodness of fit, in spite of the minor difference among the models (Table 3).

The nomogram development and external validation

The model containing age, T stages, N stages, mLN, and TLN was selected to develop the nomogram (Figure 2). The nomogram was used to predict the patient's 3-year and 5-year OS by measuring all the variables on the "Points" scale and summing up all the scores, the projective point of the "Total points" on the "survival" scale could read the survival rate. The C-index of the nomogram was 0.744, which was close to the cutoff point of 0.75, and indicated a relatively good discriminative capability.

The calibration curves in the validation cohort demonstrated a good concordance with the nomogram-predicted survival either for 3-year or for 5-year (Figure 3). The C-index of the nomogram in validation cohort was 0.694 and 0.690 for 3-year and 5-year OS respectively. It was notable that, even there was a significant difference of survival rate between the primary cohort and the validation cohort, the nomogram still had a good accuracy in predicting survival in the range out of the primary cohort.

Discussion

For clinical practice, the survival prediction is the foundation upon which to generate the treatment strategy. As the universally adopted predicting tool, the N staging system for gastric cancer has been challenged by the emerging novel parameters, and the AJCC has made some important modifications regarding the N stages. In the latest version, the TNM stage groupings have been reclassified, and the "N3a" and "N3b" contribute to the TNM grouping separately, which refines the role of N stages in TNM classification. This modification could yield a more accurate prediction of survival[16]. However, a prerequisite is in place for applying the system, which is that the minimum of TLN should be no less than 16[6]. As regards the presence of inadequate TLN, the AJCC TNM staging system still leaves a blank.

The definition of "inadequate" has varied greatly among different studies. In terms of stage migration, the number 15 is generally regarded as the cutoff value[7, 8]. Patients with substandard TLN could be underestimating their survival risk based on the false N stages. Furthermore, in terms of survival benefits, the number defined as "inadequate" could increase to a range of 25-30[5, 17, 18]. For a total gastrectomy, the "adequate" number could even be as high as 40[19]. The patients left in the gap between the two definitions of "inadequate" should not be neglected and deserve further investigations to avoid a misleading survival prediction. In the present study, we adopted 30 as the cutoff value for deeper clinical significance.

The nomogram developed in this study showed superiority over the conventional AJCC TNM staging system with regard to its discriminative capability and applicability. For better practicability, we only included certain simple and easy-to-calculate parameters. The independent prognostic factors selected in the primary cohort were similar to those of other studies related to the prediction of nomogram for gastric cancer after D2 lymphadenectomy[20, 21]. The selection of independent predictors was the crucial process for nomogram development, especially when highly correlated factors were evident such as the commonly used parameters (mLN, mLNR, TLN, LODDS, and so on) related to LN involvement. Because no standard and effective statistical methods were available to handle the collinearity problem, the predictor selection based on clinical consideration was permitted. In the present study, both mLN and mLNR were the significant predictors in the univariate analysis; however, in the multivariate analysis with the stepwise method, mLNR was deleted in the first step. In any case, we attempted to test the discriminative capability of the combination containing mLNR and found the same C-index (0.744) with the combination containing mLN, with a tiny difference of AIC (6609.483 vs 6609.415) presented. Interestingly, we also found that mLN combined with TLN could improve the goodness of fit for the predicting model, which was in agreement with most of the aforementioned studies; as such, we finally used the model containing age, T stage, N stage, mLN, and TLN to plot the nomogram.

Notably, this study was based on an international database. Both the primary and validation cohorts had relatively large samples. The data were collected from multiple centers and contained multiple races, which could make the results more convincing than those of monocentric research with mono-ethnicity. The data on clinical characteristics revealed significant differences between the primary and validation cohorts in tumor features, T stages, N stages, and TNM stages. Above all, even with the significant difference in survival, the nomogram could still predict the survival in the validation cohort.

The present study, although carefully conducted, has some limitations. First, the discriminative capability of the nomogram belonged to the median accuracy (C-index=0.744), which was lower than the nomograms developed at Seoul National University Hospital (C-index=0.78)[20] and Catholic University St. Mary's Hospital (C-index=0.87)[21]. The latter two studies had different populations, of which the majority had LN of more than 15 and no upper limitations; thus, the predicting accuracy could be higher than ours. Second, based on the lack of information on the adjuvant treatment in the primary cohort, we did not take the adjuvant chemotherapy into account for inclusion criteria, which could lead to diversity in treatment strategies and subsequent survival difference.

Conclusions

The nomogram containing age, T stages, N stages, mLN, and TLN was superior than the conventional AJCC TNM staging system in predicting OS for gastric cancer patients with inadequate (<30) LNs. The continuous improvements on AJCC TNM staging system was advocated, especially for the patients having a limited number of LNs to be examined.

Declarations

Ethics approval and consent to participate

Not applicable (This was a retrospective study, and no individual data were analyzed)

Consent for publication

Not applicable

Availability of data and materials

The datasets of IMIGASTRIC and PUCH are available from the corresponding authors on reasonable request. The dataset of SEER was retrieved from the software “SEER Data Viewer”, which was available in “<https://seer.cancer.gov/seerstat/>”.

Competing interests

The authors declare that they have no conflict of interest.

Funding

No funding supported this study

Authors' contributions

SXL and JD designed the study, retrieved the datasets, analyzed the data and wrote the manuscript. ZYL, FT, JFJ and AP revised the manuscript. All authors have read and approved the final version of this manuscript.

Acknowledgements

We thank the IMIGASTRIC program for its contribution in promoting the collaborative work between Peking University Cancer Hospital and St. Mary's Hospital.

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Tables

Table 1 The clinical characteristics and survival

	Primary cohort	Validation cohort	P value
	(n=1109)	(n=6584)	
Age	63.0 ($\pm$ 11.8)	68.6 ($\pm$ 13.2)	<0.001
Sex			<0.001
Male	812 (73.2%)	3800 (57.7%)	
Female	297 (26.8%)	2784 (42.3%)	
Race			<0.001
Asian or Pacific Islander	895 (80.7%)	1582 (24.0%)	
Black	0 (0.0%)	1087 (16.5%)	
Caucasian	214 (19.3%)	3845 (58.4%)	
Others	0 (0.0%)	70 (1.1%)	
Tumor location			<0.001
Upper third	327 (29.5%)	294 (4.5%)	
Middle third	243 (21.9%)	766 (11.6%)	
Lower third	539 (48.6%)	2815 (42.8%)	
Unknown	0 (0.0%)	2709 (41.1%)	
T stage			<0.001
T1	315 (28.4%)	1253 (19.0%)	
T2	156 (14.1%)	819 (12.4%)	
T3	290 (26.1%)	2456 (37.3%)	
T4a	322 (29.0%)	1573 (23.9%)	
T4b	26 (2.3%)	483 (7.3%)	
N stage			0.001
N0	449 (40.5%)	2272 (34.5%)	
N1	180 (16.2%)	1078 (16.4%)	
N2	187 (16.9%)	1302 (19.8%)	
N3a	222 (20.0%)	1517 (23.0%)	
N3b	71 (6.4%)	415 (6.3%)	
TNM stage			<0.001
IA	268 (24.2%)	965 (14.7%)	
IB	109 (9.8%)	553 (8.4%)	
IIA	126 (11.4%)	916 (13.9%)	
IIB	115 (10.4%)	797 (12.1%)	
IIIA	208 (18.8%)	1363 (20.7%)	
IIIB	204 (18.4%)	1421 (21.6%)	
IIIC	79 (7.1%)	569 (8.6%)	
Tumor diameter (cm)	4.4 ($\pm$ 2.5)	5.3 ($\pm$ 4.2)	<0.001
TI	12.0 (3.5~20.0)	13.5 (6.0~23.2)	<0.001

mLN	2.0 (0.0~7.0)	2.0 (0.0~8.0)	0.018
mLNR	0.07 (0.00~0.31)	0.16 (0.00~0.50)	<0.001
TLN	22.4 ($\pm$ 4.7)	16.5 ($\pm$ 6.0)	<0.001
3-year OS	86.9%	42.4%	<0.001
5-year OS	74.3%	33.8%	<0.001

TI, tumor index (=Tumor diameter $\times$ T stage); TLN, the number of total lymph nodes retrieved; mLN, the number of metastatic lymph nodes; mLNR, the ratio of mLN to TLN; OS, overall survival

Table 2 The univariate and multivariate analyses

Factors	Univariate analysis			Multivariate analysis		
	HR	95% CI	P value	HR	95% CI	P value
Age	1.026	1.018~1.034	<0.001	1.031	1.023~1.039	<0.001
Sex						
Female	ref					
Male	1.044	0.8621~1.264	0.659			
T stages						
T1	ref			ref		
T2	3.803	2.512~5.757	<0.001	2.621	1.697~4.046	<0.001
T3	8.409	5.870~12.045	<0.001	5.059	3.235~7.911	<0.001
T4a	12.106	8.512~17.218	<0.001	6.578	3.592~12.046	<0.001
T4b	16.334	9.591~27.818	<0.001	8.632	3.329 ~22.383	<0.001
N stages						
N0	ref			ref		
N1	2.817	2.095~3.788	<0.001	1.536	1.116~2.113	0.008
N2	4.871	3.703~6.408	<0.001	1.929	1.349~2.758	<0.001
N3a	7.937	6.166~10.217	<0.001	2.260	1.327~3.851	0.003
N3b	9.066	6.602~12.449	<0.001	2.147	0.613~4.043	0.346
Tumor diameter (cm)	1.186	1.156~1.218	<0.001	1.127	0.965~1.316	0.131
TI	1.044	1.038~1.050	<0.001	0.966	0.925~1.009	0.120
mLN	1.093	1.082~1.105	<0.001	1.046	1.000~1.094	0.049
mLNR	9.612	7.363~12.55	<0.001			
TLN	1.011	0.9924~1.029	0.255			

CI, confidence interval; HR, hazard ratio; TI, tumor index (= Tumor diameter $\times$ T stage); TLN, the number of total lymph nodes retrieved; mLN, the number of metastatic lymph nodes; mLNR, the ratio of mLN to TLN; ref, reference.

Table 3 The comparison of models by C-index and AIC

Model composition	C-index	AIC
TNM stage (control model)	0.717	6662.988
age + T stages + N stages + mLN	0.744	6609.415
age + T stages + N stages + mLNR	0.744	6609.483
age + T stages + N stages + mLN + TLN	0.744	6607.119
age + T stages + N stages + mLNR + TLN	0.744	6608.932

AIC, Akaike Information Criterion; C-index, Harrell's concordance index; TLN, the number of total lymph nodes retrieved; mLN, the number of metastatic lymph nodes; mLNR, the ratio of mLN to TLN.

Figures

Figure 1

The 3-year and 5-year overall survival curves for the primary and validation cohorts

Figure 2

A nomogram predicting 3-year and 5-year overall survival for gastric cancer patients with inadequate lymph nodes. The nomogram is used to predict the 3-year and 5-year overall survival by measuring all the variables on the “Points” scale and summing up all the points. The survival rate can be read from the projective point of the “Total points” on the “Survival” scale.

Figure 3

The calibration curves for the nomogram predicting overall survival. The x-axis represents the nomogram-predicted survival, and the y-axis represents the actual survival and 95% confidence interval by the Kaplan–Meier analysis. A. Calibration curve for 3-year overall survival; B. Calibration curve for 5-year overall survival.