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BRIEF ARTICLE

Log-normal censored regression model detecting prognostic factors in gastric cancer: A study of 3018 cases

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Abstract

AIM: To investigate the efficiency of Cox proportional hazard model in detecting prognostic factors for gastric cancer.

METHODS: We used the log-normal regression model to evaluate prognostic factors in gastric cancer and compared it with the Cox model. Three thousand and eighteen gastric cancer patients who received a gastrectomy between 1980 and 2004 were retrospectively evaluated. Clinic-pathological factors were included in a log-normal model as well as Cox model. The akaike information criterion (AIC) was employed to compare the efficiency of both models. Univariate analysis indicated that age at diagnosis, past history, cancer location, distant metastasis status, surgical curative degree, combined other organ resection, Borrmann type, Lauren's classification, pT stage, total dissected nodes and pN stage were prognostic factors in both log-normal and Cox models.

RESULTS: In the final multivariate model, age at diagnosis, past history, surgical curative degree, Borrmann type, Lauren's classification, pT stage, and pN stage were significant prognostic factors in both log-normal and Cox models. However, cancer location, distant metastasis status, and histology types were found to be significant prognostic factors in log-normal results alone. According to AIC, the log-normal model performed better than the Cox proportional hazard model (AIC value: 2534.72 *vs* 1693.56).

CONCLUSION: It is suggested that the log-normal regression model can be a useful statistical model to evaluate prognostic factors instead of the Cox proportional hazard model.

Key words: Gastric cancer; Log normal regression model; Cox proportional hazard model; Prognostic factors

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INTRODUCTION

The survival of patients with gastric cancer has recently been improved because of early detection, rational lymphadenectomy and several therapeutic modalities[1,2]. However, gastric cancer still remains the second leading cause

of cancer mortality in the world. It is acknowledged that surgery and systemic chemotherapy can clearly improve the survival of patients with gastric cancer[3,4]. However, a sensible treatment option must be fundamentally based on the current evaluation of prognostic factors, so a rational method to evaluate the prognostic factors is very important in establishing therapeutic strategies and evaluate prognosis.

Survival analysis is a branch of statistics which deals with death in biological organisms and failure in mechanical systems. The Cox model is the standard tool for assessing the effect of prognostic factors; however, there may be substantive differences in the estimated prognosis obtained by the Cox model rather than a log-normal model[5]. The Cox model is semiparametric, in that the baseline hazard takes on no particular form[6]. In contrast to Cox, a link to parametric survival models comes through alternative functions for the baseline hazard. In this case, one can let the baseline hazard be a parametric form such as log-normal. It is acknowledged that most of studies used the Cox proportional hazard model to find the relation between survival time and covariates of patients with gastric cancer[7-9]. On the other hand, some studies reported that log-normal regression could estimate the parameter more efficiently than the Cox model[5]. However, the efficiency of log-normal regression was still controversial.

The aim of this retrospective study was to elucidate the factors affecting the survival of patients with GC using log-normal regression, and to compare these results with the Cox model.

MATERIALS AND METHODS

Patients

In this study, three thousand and eighteen cases with gastric cancer were selected on whom an operation was performed at the China Medical University between 1980 and 2004. The selection criteria for inclusion were as follows: (1) an operation was performed; (2) lymph nodes were dissected and then pathologically examined; and (3) the patient medical records were available. All patients were periodically followed up through post letters, and/or telephone interviews with patients and their relatives. Clinical, surgical and pathological findings, and all follow-up information were collected and recorded in a database, and 5-year survival rate was calculated. The study protocol was approved by the Ethics Committee of China Medical University.

Reference standard

Lymph nodes were meticulously dissected from the en bloc specimens, and the classification of the dissected lymph nodes was determined by surgeons who reviewed the excised specimens after surgery based on the Japanese Classification of Gastric Carcinoma[10]. Accordingly, lymphadenectomy was classified as D1, dissection of all the Group 1 lymph nodes; D2, dissection of all Group 1 and Group 2 lymph nodes; and D3, dissection of all the Group 1, Group 2 and Group 3 lymph nodes. pN category was defined as pN0 (no metastatic lymph node), pN1 (1-6 metastatic lymph nodes), pN2 (7-15 metastatic lymph nodes) and pN3 (> 15 metastatic lymph nodes), according to the 5th Edition of UICC[11]. The location of tumors was defined as upper, middle and lower third gastric cancer, according to JCGC[10] and the histological grade was defined as poorly differentiated, moderately differentiated and well differentiated, according to the latest World Health Organization (WHO) classification[12]. The Borrmann type was defined as Borrmann Ⅰ, Borrmann Ⅱ, Borrmann Ⅲ and Borrmann Ⅳ, according to JCGC[10]. The histological type was determined according to Lauren's classification.

Statistical analysis

All data were analyzed using STAT statistics software (Version 10.0, Stata Corp LP). Clinic-pathologic factors were entered to a log-normal censored regression, as well as a Cox proportional hazard model in univariate and multivariate analysis in order to find the prognostic factors. The term of relative risk (RR) was used to interpret the risk of death in parametric results and the term of Akaike Information Criterion (AIC) was employed to compare the efficiency of models. Disease-specific survival was analyzed using the Kaplan-Meier method. The log-rank test was used to analyze survival differences. Lower AIC indicates better likelihood. A P value of less than 0.05 was considered statistically significant.

RESULTS

Clinic-pathological characteristics of patients with gastric cancer

The male-to-female ratio among the 3018 patients enrolled was 2.74:1 and the mean age was 57.54 years (range: 19 to 90 years) at operation. 269, 1362 and 608 cases received D1, D2 and more than D2 lymph node dissection respectively. In addition, six hundred and fifty seven cases received palliative surgery. From 3018 cases, a total of 46081 lymph nodes were removed and examined, and the mean number of examined lymph nodes was 15.27. One thousand six hundred and forty three cases were observed lymph node metastasis. Thus, the incidence of lymph node metastasis was 54.44%. The last follow-up was Jan 1, 2009, with a total follow-up rate of 70.68%. More clinic-pathologic factors are shown in Table 1.

Multivariate analysis of prognostic factors in gastric cancer

Univariate analysis indicated that age at diagnosis, past history, cancer location, distant metastasis status, surgical curative degree, combined other organ resection, Borrmann type, Lauren's classification, pT stage, total dissected nodes and pN stage were prognostic factors in both log-normal and Cox models. In the final multivariate model, age at diagnosis, past history, surgical curative degree, Borrmann type, Lauren's classification pT stage, and pN stage were significant prognostic factors in both

Table 1 Clinicopathological characteristics of 3018 gastric cancers included in the study *n* (%)

Variable	Subgroups	Frequency
Gender ratio	Male	2211 (73.26)
	Female	807 (26.74)
Age at diagnosis (mean ± SD; yr)		57.54 ± 11.24
Past history		
	Without	2234 (74.02)
	With	784 (25.98)
Family history	Without	2467 (81.74)
	With	551 (18.26)
Cancer number	Single	2883 (96.65)
	Multiple	100 (3.35)
Cancer location	Lower stomach	1873 (62.64)
	Middle stomach	492 (16.46)
	Upper stomach	355 (11.87)
	Total stomach	270 (9.03)
Distant metastasis status	Without	2540 (85.04)
	With	447 (14.96)
Maximum tumor diameter (mean ± SD, cm)		5.85 ± 3.30
Surgical curative degree	Absolutely radical	1396 (49.73)
	Relatively radical	809 (28.82)
	Palliative	602 (21.45)
Lymph node dissection	More than D2	608 (20.99)
	D2	1362 (47.03)
	D1	269 (9.29)
	Palliative surgery	657 (22.69)
Combined other organ resection	Without	2016 (76.80)
	With	609 (23.20)
Histological type	Well differentiated	755 (27.43)
	Middle differentiated	382 (13.88)
	Poor differentiated	1615 (58.69)
Borrmann classification	Ⅰ	70 (2.98)
	Ⅱ	426 (18.15)
	Ⅲ	1571 (66.94)
	Ⅳ	280 (11.93)
Lauren classification	Intestinal type	1170 (43.89)
	Diffuse type	1496 (56.11)
pT stage	pT1	328 (11.89)
	pT2	1486 (53.88)
	pT3	737 (26.72)
	pT4	207 (7.51)
Total dissected lymph node (mean ± SD)		15.27 ± 13.11
Pathological lymph node status	pN0	1375 (45.56)
	pN1	1039 (34.43)
	pN2	432 (14.31)
	pN3	172 (5.70)

log-normal and Cox models. However, cancer location, distant metastasis status and histology types were found as significant prognostic factors in log-normal results alone (Table 2). According to AIC, the log-normal model performed better than the Cox proportional hazard model (AIC value: 2534.72 *vs* 1693.56) (Table 3).

Survival outcomes

Overall, the 5-year disease-specific survival rate was 29.57%. The survival was observed significantly different in patients with different cancer locations (5-year disease-specific survival rate, L tumor *vs* M tumor *vs* U tumor *vs* T tumor: 33.11% *vs* 30.46% *vs* 25.66% *vs* 7.59%, χ^2 = 190.27, P = 0.000) (Figure 1). In addition, the cases with distant metastasis received a poorer prognosis than those without distant metastasis (5-year disease-specific survival

Table 2 Univariate model of Cox and log normal regression with prognostic factors

	HR (95% CI)	
	Cox	Log normal
Sex		
Male	0.953 (0.843-1.078)	0.925 (0.818-1.046)
Female	1.00	1.00
Age at diagnosis	1.015[1] (1.009-1.020)	1.016[1] (1.011-1.021)
Past history		
Without	1.00	1.00
With	0.715[1] (0.631-0.831)	0.694[1] (0.612-0.787)
Family history		
Without	1.00	1.00
With	0.871 (0.752-1.009)	0.875 (0.754-1.014)
Cancer number		
Single	1.00	1.00
Multiple	0.870 (0.622-1.218)	0.924 (0.661-1.294)
Cancer location		
Lower third	1.00	1.00
Middle third	1.181[1] (1.017-1.373)	1.302[1] (1.233-1.374)
Upper third	1.436[1] (1.212-1.701)	1.695[1] (1.429-1.897)
Total stomach	2.464[1] (2.062-2.944)	2.207[1] (2.011-2.677)
Distant metastasis		
Absent	1.00	1.00
Present	2.554[1] (2.194-2.973)	2.596[1] (2.227-3.027)
Surgical curative degree		
Absolutely radical	1.00	1.00
Relatively radical	1.835[1] (1.593-2.114)	2.159[1] (2.020-2.308)
Palliative	4.236[1] (3.714-4.832)	4.661[1] (4.214-4.759)
Lymph node dissection		
> D2	1.00	1.00
D2	0.989 (0.859-1.138)	1.536[1] (1.458-1.619)
D1	1.056 (0.853-1.307)	2.359[1] (2.121-2.574)
< D1	3.310[1] (2.854-3.839)	3.624[1] (3.231-3.862)
Combined other organ resection		
Without	1.00	1.00
With	1.981[1] (1.749-2.245)	2.070[1] (1.825-2.348)
Histologic types		
Well differentiated	1.00	1.00
Middle differentiated	0.706[1] (0.592-0.843)	0.976 (0.918-1.039)
Poor differentiated	0.918 (0.814-1.036)	0.952 (0.897-1.011)
Borrmann classification (*n* (%))		
Ⅰ	1.00	1.00
Ⅱ	1.005 (0.892-1.340)	0.981 (0.894-1.019)
Ⅲ	1.247[1] (1.173-1.638)	1.176[1] (1.074-1.293)
Ⅳ	2.512[1] (1.842-3.075)	2.610[1] (2.416-3.153)
Lauren classification (*n* (%))		
Intestinal type	1.00	1.00
Diffuse type	1.245[1] (1.082-1.184)	1.171[1] (1.015-1.384)
pT stage		
pT1	1.00	1.00
pT2	2.936[1] (2.299-3.751)	1.787[1] (1.666-1.916)
pT3	4.305[1] (3.357-5.522)	3.193[1] (3.066-3.321)
pT4	7.697[1] (5.759-10.287)	5.707[1] (5.579-5.833)
Total dissected nodes	0.993[1] (0.988-0.998)	0.994[1] (0.988-0.998)
pN stage		
pN0	1.00	1.00
pN1	1.555[1] (1.372-1.764)	1.633[1] (1.533-1.740)
pN2	2.510[1] (2.133-2.953)	2.667[1] (2.561-2.772)
pN3	3.669[1] (2.901-4.640)	4.355[1] (4.249-4.460)

[1]Statistically significant (P < 0.05). HR: Hazard radio; CI: Confidence interval.

Table 3 Multivariate model of Cox and log normal regression with prognostic factors (full model and final model)

	Cox HR (95% CI)		Log normal HR (95% CI)	
	Full model (AIC = 1508.49)	Final model (AIC = 2534.72)	Full model (AIC = 913.34)	Final model (AIC = 1693.56)
Sex				
Male	0.91 (0.801-1.034)		0.886 (0.781-1.005)	
Female	1.00			
Age at diagnosis	1.014[1] (1.009-1.02)	1.011[1] (1.006-1.017)	1.015[1] (1.010-1.021)	1.015[1] (1.009-1.020)
Past history				
Without	1.00	1.00	1.00	1.00
With	0.840[1] (0.738-0.955)	0.858[1] (0.755-0.975)	0.813[1] (0.716-0.914)	0.809[1] (0.713-0.919)
Family history				
Without	1.00		1.00	1.00
With	0.957 (0.8254-1.11)		0.967 (0.833-1.234)	
Cancer number				
Single	1.00		1.00	
Multiple	1.21 (0.861-1.701)		1.312 (1.935-1.840)	
Cancer location				
Lower third	1.00		1.00	1.00
Middle third	1.033 (0.885-1.205)		1.135[1] (1.073-1.199)	1.129[1] (1.069-1.194)
Upper third	1.406[1] (1.173-1.686)		1.288[1] (1.224-1.353)	1.277[1] (1.211-1.338)
Total stomach	1.466[1] (1.214-1.771)		1.462[1] (1.365-1.558)	1.439[1] (1.343-1.535)
Distant metastasis				
Absent	1.00		1.00	1.00
Present	1.21[1] (1.013-1.447)		1.205[1] (1.011-1.437)	1.198[1] (1.009-1.424)
Surgical curative degree				
Absolutely radical	1.00	1.00	1.00	1.00
Relatively radical	1.389[1] (1.197-1.611)	1.383[1] (1.194-1.601)	1.724[1] (1.537-1.934)	1.672[1] (1.538-1.817)
Palliative	3.889[1] (2.583-5.855)	2.687[1] (2.316-3.116)	2.972[1] (2.770-3.174)	2.796[1] (2.653-2.938)
Lymph node dissection				
> D2	1.00		1.00	
D2	0.908 (0.784-1.051)		0.967 (0.892-1.049)	
D1	0.901 (0.712-1.14)		0.935 (0.855-1.015)	
< D1	0.607[1] (0.395-0.935)		0.904 (0.784-1.024)	
Combined other organ resection				
Without	1.00		1.00	
With	1.406[1] (1.227-1.61)		1.447[1] (1.264-1.657)	
Histologic types				
Well differentiated	1.00		1.00	1.00
Middle differentiated	1.056 (0.878-1.271)		1.110[1] (1.042-1.183)	1.120[1] (1.051-1.193)
Poor differentiated	1.179[1] (1.035-1.343)		1.232[1] (1.160-1.304)	1.254[1] (1.182-1.327)
Borrmann classification				
Ⅰ	1.00	1.00	1.00	1.00
Ⅱ	1.142 (0.957-1.319)	1.201 (1.068-1.433)	1.018 (0.943-1.106)	1.015 (0.941-1.102)
Ⅲ	1.315[1] (1.113-1.672)	1.394[1] (1.205-1.741)	1.246[1] (1.052-1.539)	1.241[1] (1.047-1.533)
Ⅳ	2.126[1] (1.758-3.119)	2.253[1] (1.827-3.284)	2.530[1] (2.376-2.713)	2.526[1] (2.372-2.708)
Lauren classification				
Intestinal type	1.00		1.00	1.00
Diffuse type	1.131[1] (1.012-1.358)		1.307[1] (1.154-1.528)	1.302[1] (1.148-1.523)
pT stage				
pT1	1.00	1.00	1.00	1.00
pT2	1.851[1] (1.431-2.394)	1.971[1] (1.528-2.542)	1.195[1] (1.102-1.297)	1.193[1] (1.100-1.294)
pT3	1.981[1] (1.511-2.598)	2.19[1] (1.678-2.858)	1.428[1] (1.328-1.527)	1.423[1] (1.324-1.522)
pT4	2.344[1] (1.699-3.235)	2.501[1] (1.821-3.435)	1.706[1] (1.557-1.855)	1.697[1] (1.549-1.847)
Total dissected nodes	0.987[1] (0.981-0.993)		0.988[1] (0.982-0.993)	
pN stage				
pN0	1.00	1.00	1.00	1.00
pN1	1.281[1] (1.123-1.461)	1.266[1] (1.11-1.444)	1.507[1] (1.393-1.620)	1.500[1] (1.387-1.622)
pN2	2.139[1] (1.783-2.566)	2.095[1] (1.749-2.51)	2.271[1] (2.151-2.391)	2.250[1] (2.130-2.370)
pN3	3.24[1] (2.446-4.292)	3.325[1] (2.52-4.386)	3.422[1] (3.242-3.602)	3.375[1] (3.196-3.554)

[1]Statistically significant (< 0.05); HR: Hazard radio; CI: Confidence interval; AIC: Akaike Information Criterion.

rate, 33.50% *vs* 7.56%, χ^2 = 372.21, P = 0.000) (Figure 2). Furthermore, the cases with different histologic types were investigated with a different prognosis (5-year disease-specific survival rate, well differentiated tumors *vs* middle differentiated tumors *vs* poor differentiated tumors: 39.27% *vs* 29.67% *vs* 25.03%, χ^2 = 12.37, P = 0.002) (Figure 3).

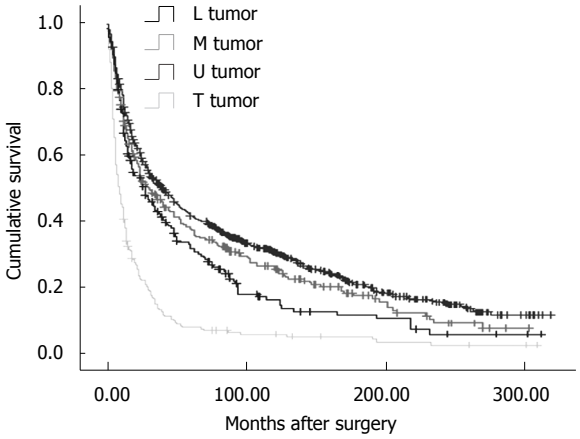

Figure 1 Disease-specific survival analysis according to cancer locations (χ^2 = 190.27, *P* = 0.000, Log Rank test). L tumor: Lower third tumors; M tumor: Middle third tumors; U tumor: Upper third tumors; T tumor: Tumor occupied the total stomach.

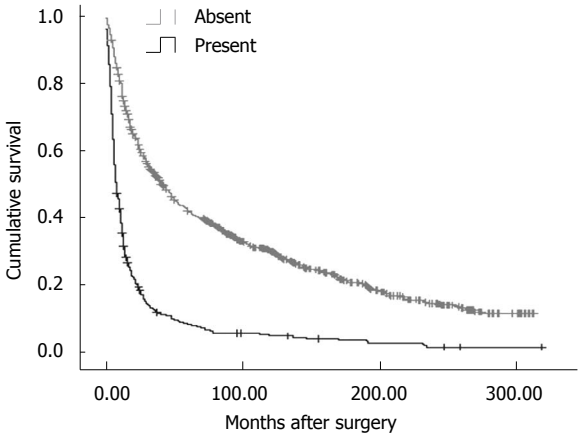

Figure 2 Disease-specific survival analysis according to distant metastasis status (χ^2 = 372.21, *P* = 0.000, Log Rank test).

DISCUSSION

There were several studies that have investigated the factors influencing prognosis[13,14]. The conclusions of the reports were controversial, though most of them used the Cox proportional hazard model to find the relation between survival time and patient characteristics, and clinical and pathological factors in patients with gastric cancer.

After evaluating the clinic-pathological factors of 738 patients, Kulig *et al*[7] reported that patient age, depth of tumor infiltration, tumor location, and metastatic node ratio were identified as independent prognostic factors in a Cox proportional hazards model. In addition, Shiraishi *et al*[15] reported that independent prognostic factors of gastric cancer were serosal invasion, extragastric lymph node metastasis and liver metastasis, but survival was not significantly associated with any of the patient factors or operation factors, including the extent of lymph node dissection. In our study, age at diagnosis, past history, surgical curative degree, Borrmann type, Lauren's classification, pT stage, and pN stage were significant prognostic factors in Cox models. There was a small difference between our study and other reports. In the final model of log-normal analysis, we investigated that cancer location, distant metastasis and histologic types were significantly related to the survival. The outcomes were also verified by disease-specific survival analysis. However, the association between above factors and survival were not observed. In log-normal analysis, Pourhoseingholi *et al*[5] observed that distant metastasis, histology type and pT stage were significant prognostic factors after retrospectively studying 746 Iranian patients. Moreover, distant metastasis was a significant prognostic factor only in log-normal analysis, not in the Cox model.

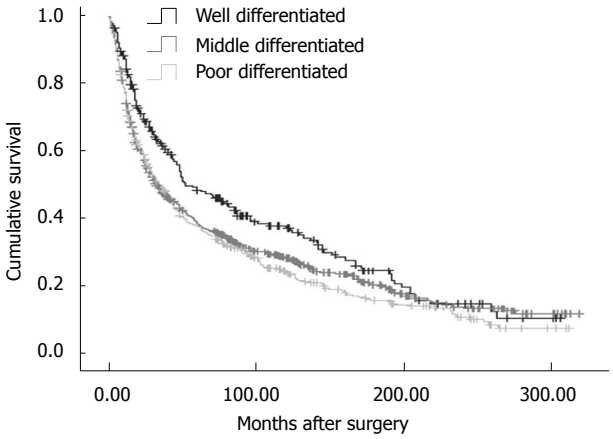

Figure 3 Disease-specific survival analysis according to histologic types (χ^2 = 12.37, *P* = 0.002, Log Rank test).

Compared to the Cox model, the evaluation criteria in our study indicated log-normal regression was more powerful not only in the full model, but also in the final one. In the final model, the selected prognostic factors in the log-normal model were different compared to those in the Cox model. Furthermore, the data strongly supported the log-normal regression in the full and final models, and might lead to more precise results as an alternative for Cox.

In conclusion, according to the results of our study, age at diagnosis, past history, cancer location, distant metastasis status, surgical curative degree, combined other organ resection, histology types, Borrmann type, Lauren's classification, pT stage, total dissected nodes and pN stage were significant prognostic factors of gastric cancer. It is suggested that log-normal regression model can be a useful statistical model to evaluate prognostic factors instead of the Cox proportional hazard model.

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COMMENTS

Background

Most of studies used the Cox proportional hazard model to find the relation between survival time and covariates of patients with gastric cancer (GC). On the other hand, some studies reported that log-normal regression could estimate

the parameter more efficiently than the Cox model. However, the efficiency of log-normal regression was still controversial.

Research frontiers

In this retrospective study, the authors elucidated the factors affecting the survival of patients with GC using log-normal regression, and to compare these results with the Cox model.

Applications

It is suggested that log-normal regression model can be a useful statistical model to evaluate prognostic factors instead of the Cox proportional hazard model.

Peer review

Overall the study was well designed, performed, and analyzed. The very minor, but important parameters should be added in analysis.

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