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Prognostic factors in gastric cancer using log-normal censored regression model

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***Background & objectives*: Gastric cancer is one of the most common cancers in the world. It is rarely detected early, and the prognosis remains poor. Cox proportional hazard model is used to examine the relationship between survival and covariates. Parametric survival models such as log normal regression model can also be used for this analysis. We used log normal regression model in this study to evaluate prognostic factors in gastric cancer and compared with Cox model.**

***Methods*: We retrospectively studied the 746 patients diagnosed with gastric cancer admitted in a referral hospital in Tehran, Iran, from February 2003 through January 2007. Age at diagnosis, sex, extent of wall penetration, histology type, tumour grade, tumour size, pathologic stage, lymph node metastasis and presence of metastasis were entered into a log normal model. Hazard rate (HR) was employed to interpret the risk of death and the results were compared with Cox regression. The AIC (Akaike Information Criterion) was employed to compare the efficiency of models.**

***Results*: Univariate analysis indicated that with increasing age the risk of death increased significantly in both log normal and Cox models. Patients with grater tumour size were also in higher risk of death followed by those with poorly differentiated and moderately differentiated in tumour grade and advanced pathologic stage. The presence of metastasis was significant prognostic factor only in log normal analysis. In final multivariate model, age was still a significant prognostic factor in Cox regression but it was not significant in log normal model. Presence of metastasis followed by histology type were other prognostic features found significant in log normal results. Based on AIC, log normal model performed better than Cox.**

***Interpretation & conclusion*: Our results suggest that early detection of patients in younger age and in primary stages and grade of tumour could be important to decrease the risk of death in patients with gastric cancer. Comparison between Cox and log normal models indicated that log normal regression model can be a useful statistical model to find prognostic factors instead of Cox.**

Key words Gastric cancer - log-normal regression - prognostic factors

Gastric cancer (GC) is an important cause of mortality[1,2] and has been predicted to be the eighth leading cause of all deaths worldwide in the year 2010[3]. In a large series from the United States, the percentage of these tumours among all gastric malignancies increased from 0.3 to 1.8 per cent and the proportion of carcinoids among all enteric carcinoids from 2.4 to 8.7 per cent[4]. Although the incidence of GC is decreasing,

majority of cases distant metastasis is seen at the time of diagnosis[5]. In approximately half of newly diagnosed patients, the carcinoma is advanced beyond its original local-regional boundaries[6].

Survival analysis is the modeling of time to event of death to evaluate the effects of treatment on survival time[7]. Many studies have been done to assess the impact of clinical and demographic characteristics on survival of patients with GC using Cox proportional hazard model to find the relation between survival time and covariates[8-11].

Although Cox proportional hazard model is a well known method to examine the relationship between survival and clinical or demographic covariates[12], certain parametric models can also estimate the parameter more efficiently than the Cox model[13]. The Cox model is semi parametric, in that the baseline hazard takes on no particular form[12]. 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. These parametric models can easily be used by maximum likelihood estimators and allow the researchers to explore the data through the different relationships consisting of linear trend, nonlinear ones or interactions and when the proportional hazard assumption dose not hold these methods, lead to acceptable conclusions[7].

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 Cox model.

Material & Methods

The data represented a cohort of all 746 patients admitted at Taleghani Hospital, Tehran, Iran, with a diagnosis of GC and treated from February 2003 through January 2007. This hospital is a referral center for gastrointestinal cancers and all these patients were diagnosed by endoscopy and biopsies, most of them undergoing subtotal gastrectomy and a few undergoing total gastrectomy. The exclusion criteria were the patients who had not completed document at hospital registry or treated beyond study period. The study protocol was approved by the Ethics Committee of the Research Centre for Gastroenterology and Liver Disease of Shaheed Beheshti Medical University.

Age at diagnosis, sex, extent of wall penetration, histologic type, tumour grade, tumour size, pathologic stage, lymph node metastasis and distant of metastasis were entered to a log normal censored regression in univariate and multivariate analysis in order to find the relationships between characteristic and prognostic factors with survival time. The term of relative risk (RR) was used to interpret the risk of death in parametric results and the term of AIC (Akaike Information Criterion) was employed to compare the efficiency of models[14]. The AIC is a measure of the goodness of fit of an estimated statistical model. Lower AIC indicates better likelihood.

All $P<0.05$ were considered as statistically significant and the analysis was carried out using STAT software.

Results

Of the 746 patients with GC included in this study, 530 (71%) were men and 216 (29.0%) women. The mean age at diagnosis was 59.6±12.9 yr (range: 20-88 yr). Overall, 285 patients (38.6%) died and 61.4 per cent have not experienced the event of death (right censored) until the January 2007.

Of the total patients, 184 have had pathologic distant metastasis, 244 had tumour size >35mm, 254 diagnosed with stage IV of GC, 203 with poorly differentiated grade of tumour, 532 with histology type of adenocarcinoma NOS, 219 in T4 level of extent of wall penetration and 64 in N3 level of regional lymph nodes metastasis (Table I).

According to the univariate analysis (Table II) as age increased, the risk of death increased significantly in both log normal and Cox model with similar results. Patients with larger tumour size were also in higher risk of death followed by those with poorly differentiated and moderately differentiated tumour grade (only log normal significant results) and advanced pathologic stage. The presence of metastasis was another significant prognostic factor only in log normal analysis. Neither log normal nor Cox model showed sex, lymph node metastasis and histology type as a prognostic factors.

In multivariate adjusted model there was a major difference between Cox and log normal models (Table III). Although age was still a significant prognostic factor in final model of Cox regression, it was not significant in log normal results. Distant of metastasis followed by histology type were other prognostic factors found significant in log normal for both full and final model but not significant for Cox results. There

Table I. Clinical characteristics of patients with gastric cancer

Variable	Subgroup	Frequency	
		n	%
Grade of tumour (n=455)	Well differentiated	112	24.6
	Moderately differentiated	140	30.8
	Poorly differentiated	203	44.6
Tumour size (n=337)	<35 mm	93	27.6
	>35 mm	244	72.4
Histology type (n=734)	Adenocarcinoma NOS	532	72.5
	Signet cell car. & mucin-producing adeno. & mucinous adeno.	72	9.8
	Other type of histology	130	17.7
Extent of wall penetration* (n=567)	T1	18	3.2
	T2	70	12.3
	T3	260	45.9
	T4	219	38.6
Regional lymph nodes metastasis** (n=457)	N1	130	28.4
	N2	263	57.5
	N3	64	14.0
Pathologic distant metastasis (n=506)	Absent	322	63.6
	Present	184	36.4
Pathologic stage*** (n=619)	I (0,IAIB)	53	8.6
	II	108	17.5
	III (IIIA,IIIB)	204	32.9
	IV	254	41.0

* T1, Tumour invades lamina propria or submucosa; T2, Tumour invades muscularis propria or subserosa; T3: Tumour penetrate serosa (visceral peritoneum) without invasion of adjacent structures; T4: Tomour invades adjacent structures; **N1, Metastasis in 1 to 6 regional lymph nodes; N2, Metastasis in 7 to 15 regional lymph nodes; N3, metastasis in more than 15 regional lymph nodes; ***I and II: early stage, III and IV: advanced stage.

Table II. Univariate model of Cox and log-normal regression with prognostic factors

	Cox HR (CI: 95%)	Log normal HR (CI: 95%)
Age at diagnosis	1.01* (1.00-1.02)	1.02* (1.01-1.03)
Sex		
Male	1.04 (0.8-1.32)	0.92 (0.70-1.22)
Female	1.00	1.00
Distant metastasis		
Absent	1.00	1.00
Present	1.01 (0.62-1.61)	2.14* (1.60-2.86)
Extent of wall penetration		
T1		
T2	1.24 (0.35-4.35)	2.44* (1.85-3.12)
T3	2.52 (0.79-8.00)	1.53* (1.16-2.02)
T4	4.83* (1.53-15.24)	2.92* (1.78-4.81)
Tumour size		
<35 mm	1.00	1.00
>35 mm	1.66* (1.40-2.56)	2.19* (1.33-3.60)
Histology type		
Adenocarcinoma	1.00	1.00
Signet ring cells &	1.22 (0.91-1.64)	0.79 (0.58-1.06)
Other	0.95 (0.80-1.129)	1.06 (0.90-1.26)
Tumour grade		
Well differentiated	1.00	1.00
Moderately differentiated	1.13 (0.73-1.75)	1.47* (1.06-2.00)
Poorly differentiated	1.50* (1.01-2.23)	1.27* (0.90-1.80)
Lymph node metastasis		
N1	1.00	1.00
N2	0.98 (0.70-1.34)	0.96 (0.69-1.32)
N3	1.02 (0.72-1.45)	1.09 (0.76-1.55)
Pathologic stage		
Early	1.00	1.00
Advanced	1.84* (1.41-2.41)	2.08* (1.56-2.78)

*Statistically significant ($P<0.05$)
HR, Hazard ratio; CI, Confidence interval

were similar results for extent of wall penetration in both Cox and log normal multivariate analysis.

Based on AIC, log normal model performed better than Cox (Table III) in full model and final model. The AIC for log normal models was approximately half of Cox model.

Discussion

Many retrospective studies have indicated pathologic, clinical and patient characteristics as multiple variables with respect to survival[15,16].

This study evaluated the association between survival of patients with gastric cancer and several prognosis factors such as age at diagnosis, sex, extent of wall penetration, histologic type, tumour grade, tumour size, pathologic stage, lymph node metastasis and distant of metastasis. Some studies reported better survival rate for women[17]. Curtis *et al*[18] showed that the prognosis was better in women according to age and stage. In our results sex had no effect on survival rates as also reported earlier[19].

Age at diagnosis was a strong and independent prognostic factor, and our finding in univariate analysis was similar with previous reports[20,21] indicating better survival for younger patients.

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

	Cox HR (CI: 95%)		Log normal HR (CI: 95%)	
	Full Model AIC=905.7	Final Model AIC=2394.2	Full Model AIC=467.3	Final Model AIC=1055.24
Age at diagnosis	1.01 (0.99-1.03)	1.02* (1.00-1.03)	0.99 (0.98-1.01)	
Sex				
Male	1.03 (0.62-1.69)		1.02 (0.64-1.61)	
Female	1.00		1.00	
Distant metastasis				
Absent	1.00		1.00	1.00
Present	1.38 (0.67-2.85)		2.09* (1.7-3.20)	2.02* (1.14-3.53)
Extent of wall penetration				
T1	1.00	1.00	1.00	1.00
T2	8.97* (1.16-69.39)		6.67* (1.56-33.33)	
T3	6.18 (0.83-45.87)	4.08* (2.42-6.88)	4.76* (1.15-20.00)	4.00* (1.29-6.67)
T4	2.86 (0.36-22.91)	2.03* (1.18-3.49)	2.27 (0.5-11.11)	2.04* (1.28-3.22)
Tumour size				
<35 mm	1.00		1.00	
>35 mm	0.50 (0.19-1.34)		11.82* (4.35-32.14)	
Histology type				
Adenocarcinoma	1.00		1.00	1.00
Signet ring cell &	1.20 (0.88-1.64)		5.92* (3.00-11.70)	3.67* (3.06-4.39)
Other			41.68* (11.02-156.02)	16.28* (11.59-22.65)
Tumour grade				
Well differentiated	1.00		1.00	
Moderately differentiated	0.39 (0.81-2.41)		0.87 (0.52-1.46)	
Poorly differentiated	1.00 (0.56-1.78)		1.11 (0.65-1.87)	
Lymph node metastasis				
N1	1.00		1.00	
N2	1.44 (0.68-3.03)		1.31 (0.70-2.50)	
N3	2.06 (0.92-4.60)		1.64 (0.81-3.33)	
Pathologic stage				
Early	1.00		1.00	
Advanced	1.51 (0.80-2.84)		1.51 (0.83-2.78)	

*Statistically significant ($P<0.05$)
HR, Hazard ratio; CI, Confidence interval

Metastasis is another important prognostic factor of GC and many studies showed that the survival depends on the presence of metastasis[22]. The results in both univariate and multivariate analyses showed a higher risk of death for patients with distant metastasis. Our findings were in agreement with these observations showing an association with distant metastasis, which was also found in multivariate analysis[23,24].

Size and grade of tumour were other significant factors which affected the survival probability of patients in univariate analysis for both log normal and Cox model. This finding was similar to a study which pointed a higher hazard ratio of death for patients with larger tumour or worse grade of tumour[25]. Orsenigo *et al*[23] also reported similar conclusion for tumour size in a univariate analysis.

Depth of invasion has been a superior prognostic discriminator in both univariate and multivariate analysis. Our results, confirmed by other studies[26,27] showed that depth of penetration influenced on patient's survival.

Patients with adenocarcinoma showed a better survival in our study. The reason of poor survival in other groups could be because mucinous gastric cancer correlates with advanced disease at diagnosis. These patients had significantly more metastatic lymph nodes and lymphatic and venous invasion[28,29].

The evaluation criteria in our study indicated log normal regression to be more powerful in comparison

to Cox not only in full model but also in final one. Although it seemed that in term of interpretation the values obtained for all prognostic factors in univariate analysis were similar, the data strongly supported the log normal regression in full and final model and might lead to more precise results as an alternative for Cox.

A good discrimination among parametric models requires the censoring percentage not to exceed 40-50 per cent[30] although in our data the censoring was about 60 per cent, the parametric results were not performed bad.

Unfortunately complete information on the treatment given to patients was not available and also the site of metastases was another limitation due to the poor registry in these years.

In conclusion, our study showed that age at diagnosis, tumour size and grade, presence of distant metastasis, wall penetration and histology type were associated factors for survival time in patients with GC. One of the most important reasons seemed to be delayed consultation and diagnosis. According to these results the early detection of patients at younger age and in primary stages and grade of tumour may be important to decrease the risk of death in patients with GC. Also, comparison between Cox and log normal models indicated that parametric models like log normal regression can be a useful statistical model to find prognostic factors.

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