Original Article

Alternative for the Cox Regression model: using Parametric Models to Analyze the Survival of Cancer Patients

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Abstract

Background: Although the Cox proportional hazard regression is the most popular model for analyzing the prognostic factors on survival of cancer patients, under certain circumstances, parametric models estimate the parameter more efficiently than the Cox model. The aim of this study was to compare the Cox regression model with parametric models in patients with gastric cancer who registered at Taleghani hospital, Tehran, Iran.

Methods: In a retrospective cohort study, 746 patients with gastric cancer were studied from February 2003 through January 2007. Gender, age at diagnosis, distant metastasis, extent of wall penetration, tumor size, histology type, tumor grade, lymph node metastasis and pathologic stage were selected as prognosis , and entered to the models. Lognormal, Exponential, Gompertz, Weibull, Log-logistic and Gamma regression were performed as parametric models ,and Akaike Information Criterion (AIC) were used to compare the efficiency of the models.

Results: Based on AIC, Log logistic is an efficient model. Log logistic analysis indicated that wall penetration and presence of pathologic distant metastasis were potential risks for death in full and final model analyses.

Conclusion: In the multivariate analysis, all the parametric models fit better than Cox with respect to AIC; and the log logistic regression was the best model among them. Therefore, when the proportional hazard assumption does not hold, these models could be used as an alternative and could lead to acceptable conclusions.

Key words: Cox; Parametric model; Gastric cancer; Survival analysis

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Introduction

Characterizing the different survival distributions that correspond to different subgroups within a heterogeneous population is the objective of many studies. A descriptive summary of such a comparison could consist of parametric or semi parametric methods. There are two major regression models used for right censored data: proportional hazards model (Cox) as a semi parametric method [1] , and accelerated failure time model or linear model representation in log time as a parametric model. Many of the standard parametric models such as Weibull, Exponential and Lognormal are accelerated failure time models.

Although the Cox regression model is the most favorable employed technique in survival analysis, parametric models [2] lead to a number of benefits.

Researchers in medical sciences often tend to prefer semi parametric models instead of the parametric due to its less assumptions .However; some studies recommended that under certain circumstances, parametric models estimate the parameters more efficiently than the Cox model [3, 4]. In the parametric model, we often use the maximum likelihood procedure to estimate the

unknown parameters, and this technique and its interpretation are well-known to researchers. In addition, accelerated failure time can be used as a relative risk with similar interpretation in the Cox regression model.

Gastric cancer is an important cause of mortality [5], and is predicted to be the eighth leading cause of all deaths worldwide in the year 2010 [6].

Many researchers have been conducted to assess the impact of clinical and demographic characteristics of those patients who survived Gastric cancer. Most of these studies used the Cox proportional hazard model to find the relation between survival time and covariates [7-10]. In the survival models, the hazard function for a given individual describes the instantaneous risk of experiencing an event of interest within an infinitesimal interval of time, given that the individual has not yet experienced that event.

Cox [1] proposed a semi-parametric model for the hazard function that allows the addition of explanatory variables, or covariates, but keeps the baseline hazard as an arbitrary, unspecified, nonnegative functional of time.

Its baseline hazard is defined as the hazard function for that individual with zero on all covariates. Because the baseline hazard is not assumed to be of a parametric form, Cox's model is referred to as a semi-parametric model for the hazard function [11] and several methods are available for estimating the baseline hazard function [12].

Cox's model has become the most used procedure for modelling the relationship of covariates to a survival or other censored outcomes [13]. However, it has some restrictions. One of the restrictions of using the Cox model with time-fixed covariates is its proportional hazards assumption; it means the hazard ratio between two sets of covariates is constant over time. This is due to the common baseline hazard function canceling out in the ratio of the two hazards. The Cox model is semi parametric, in that the baseline hazard takes on no particular form. In contrast to Cox, a link to parametric survival models comes through alternative functions for the baseline hazard. In this case we can allow the baseline hazard to take a parametric form such as Weibull, Gompertz, Exponential, and Lognormal etc.

These parametric baseline hazards then assume parametric survivorship, such as a smooth downward slope of the survival plot. Although the parametric models might be somewhat more efficient, they have more assumptions. Nevertheless, if the assumptions are met, the analysis will be more powerful.

The aim of this study is to use the Cox regression model and alternative parametric models to evaluate the prognostic factors of gastric cancer survival, and to compare the efficacy of the models.

Materials and Methods

The data represent a historical cohort study of 746 patients who were admitted to Taleghani hospital with a diagnosis of gastric cancer, and were treated from February 2003 through January 2007. This hospital is a referral center for patients with gastrointestinal cancers (GI). All the patients were diagnosed by endoscopy and biopsies, and most of them were undergoing subtotal gastrectomy , and a minority were undergoing total gastrectomy. The following patients were excluded from the study: the patients who did not complete the forms at the hospital reception or those who were treated before or after the time frame of February 2003 to January 2007. The study protocol was approved by the ethics committee of the Research Centre for Gastroenterology and Liver Disease of Shahid Beheshti University of Medical Sciences. Patients' deaths were confirmed trough contacting their family members, and clinical information was extracted from the hospital documents during two months.

The Cox proportional hazard model was used to determine the difference of survival time (in month) between sub groups of gender, age at diagnosis, distant metastasis, extent of wall penetration, tumor size, histology type, tumor grade and lymph node metastasis. Pathologic stage was defined as early stage (0, IA, IB, II, IIA, IIB) and advanced stage (IIIA, IIIB, IV) according to the TNM classification. In addition, histology type of tumor was defined as Adenocarcinoma NOS, Signet Cell Carcinoma, Mucin-producing adenocarcinoma, Mucinous adenocarcinoma and other type of histology. Histological grade of tumor was classified according to the World Health Organization classification as well differentiated, moderately differentiated, and poorly differentiated.

On the other hand, we have considered parametric models including Weibull and Exponential models with respect to the assumptions of constant and monotone baseline hazard respectively. We also considered the lognormal model because its baseline hazard has the value of 0 at t=0, which increases to maximum and then decreases, and becomes large when approaching 0 . We also used Gompertz because it turns into the straight hump-shaped line within logarithmic co-

ordinate and log logistic and it increases initially when having a hazard rate, and, it then decreases.

One way to compare the parametric and semi parametric models is to base the decision on minimum Akaike Information Criterion (AIC). The AIC is a measure of the goodness of fit of an estimated statistical model [14]. It is grounded in the concept of entropy. The AIC is an operational way of trading off the complexity of an estimated model against how well the model fits the data.

For our models discussed, the AIC is given by

$$AIC = -2 \log(\text{likelihood}) + 2(p+k)$$

Where p is the number of parameter, k=1 for the exponential model, k=2 for the Weibull, log logistic, and log normal models and k=3 for generalized gamma [14]. Lower AIC indicates better likelihood.

Results

A total number of 746 patients with gastric cancer entered to this study, of whom, 530 were male (71%) and 216 were female (29.0%). The mean age at diagnosis was 59.6±12.9 (Range: 20-88 years). In general, 285 patients (38.6%) have died and 61.4% did not die (right censored) up to January of 2007.

Table 1. Clinicopathological Characteristics of Gastric Cancer patients

Variable	Subgroup	Frequency	
		n	%
Grade of tumor(n=746)	Well differentiated	112	24.6
	Moderately differentiated	140	30.8
	Poorly differentiated	203	44.6
Tumor size(n=337)	<35mm	93	27.6
	>35mm	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=576)	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: Tumor invades lamina propria or submucosa, T2: Tumor invades muscularis propria or subserosa, T3: Tumor penetrates serosa (visceral peritoneum) without invasion of 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

Of the total patients, 36.4% had pathologic distant metastasis, 72.4% had more than 35 mm tumor size, 41.0% were diagnosed with stage IV of GC, 44.6% with poorly differentiated grade of tumor, 72.5% with histology type of adenocarcinoma NOS, 38.6% in T4 level of extent of wall penetration , and 14.0% in N3 level of regional lymph nodes metastasis (Table 1).

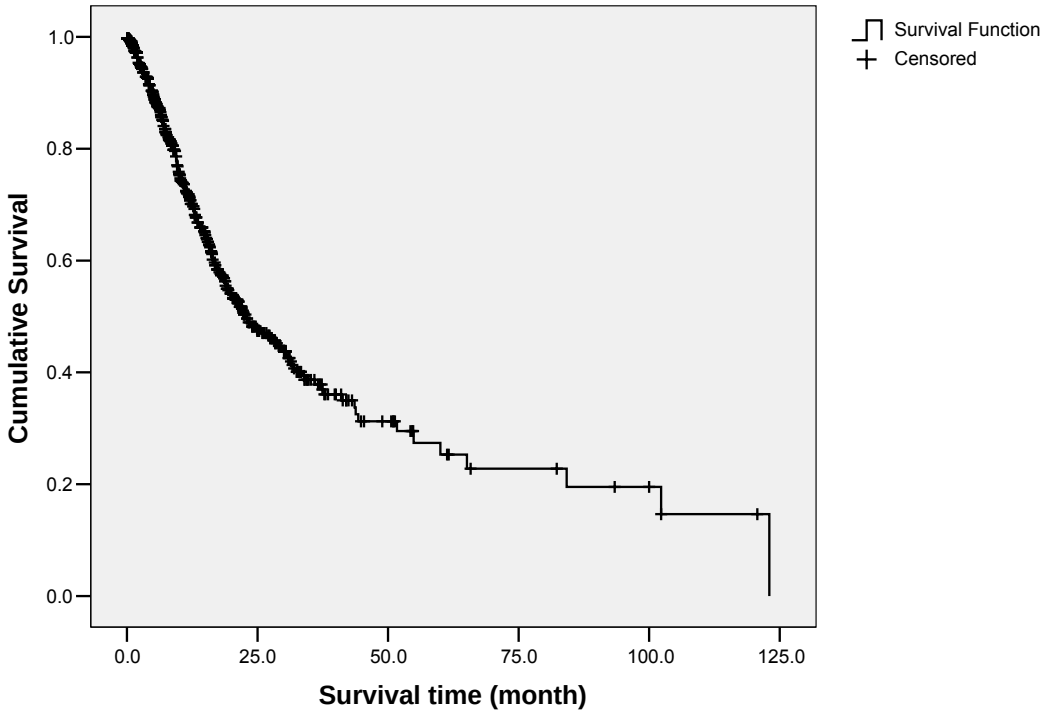

Figure1. Overall survival curves for patients with gastric cancer

The mean and median of overall survival time were 42.45 and 22.8 months respectively (Range: 1-93.4 months), figure 1 depicts the overall survival curves of patients with gastric cancer.

The values of parametric and semi parametric models were compared using AIC. Table II and table III demonstrate the results for the full model and the final model in multivariable analysis, representing results from 533 cases respectively.

According to the graphical test (not shown here), the proportional hazard assumption holds for all the subgroups. To assess the goodness of fit for the parametric models, residual graphs were performed, indicating perfect fit for all the parametric models.

Based on AIC, all parametric models were performed better than the Cox model not only in the full model but also in the final model. And it should be noted that the Log logistic model is the most efficient among all models in the full and final multivariable analysis. According to the results from the Log logistic model, patients who were in the level of T4 and T3 of wall penetration had an increased risk for death in term of hazard ratio in the full model , but in the final model, only T4 level was significant. Moreover, patients with presence of pathologic distant metastasis were 1.88 (95% CI: 1.59-2.27) times more at the risk of death in the full model and 1.67 more at risk of death(95% CI: 1.14-2.38) in the final model according to the Log logistic analysis.

Neither the Cox, nor the parametric models showed any evidence about significant differences in gender and tumor grade in final models.

Discussion

In the final multivariate analysis, only distant metastasis and depth of invasion remain as the best efficient models in the Log logistic model. Depth of invasion -as expected- a highly superior prognostic discriminator in both full and final model in all analyses. Our results, also confirmed by other studies [15, 16] ,showed that depth of penetration influence patients' survival. Metastasis is another important prognostic factor of gastric cancer [17] .Many authors stated that the survival rate depends on the presence of metastasis. Our findings are in agreement with these observations indicating an association with distant metastasis, which is maintained in multivariate analysis [18, 19].

The limitation of this study is missing data due to incomplete patients' record. Surgical curability is one of the most important prognostic factors, but unfortunately no information was available on the results of curative operation as most of the patients

referred from other cities or hospitals and we only had access to registry information not to their original documents. We faced the same situation for the regional lymph node metastases. Up to 60% of the patients had a history of lymph node metastases according to registry data (categorized as N1, N2 and N3), but no more information existed for other patients (lymph node metastases or not). Therefore, this incomplete covariate can seriously influence the results of this prognostic factor.

In a review of survival analyses in cancer journals [20], it was found that only 5 per cent of all studies used the Cox model with respect to checking the underlying assumptions. If this assumption does not hold, the Cox model can lead to unreliable conclusions. Therefore, the parametric models such as Lognormal, Weibull, Exponential, Gompertz and log logistic are the common options. These models provide the interpretation based on a specific distribution for duration times without need to proportional hazard assumptions.

The evaluation criteria in our study indicated that parametric models are most powerful compared to the Cox model. However, it seems that in term of interpretation, the values obtained for all the parametric models are similar. The data strongly supported the log logistic regression model in full and final model, and it can lead to more precise results as an alternative for the Cox model.

A limitation of this data is the percent of censoring. A good discrimination among parametric models requires the censoring percentage not to exceed 40-50 per cent [21] ,although in our data the censoring was about 60 per cent. The parametric results were not performed badly. In addition, Oakes [4] discussed that asymptotically well fitted parametric models should be more efficient than the Cox model if parameter values are far from zero.

Nardi and Schemper [21] compared Cox and parametric models in tree clinical studies. They used Normal-deviate residuals [22] to verify the parametric model assumptions. In Nardi's study where there were some parameters far from zero, the Weibull regression produced standardized variability. This also holds in our study; however, the results still supported parametric models as the perfect option.

Orbe, Ferreira and Nunez-Anton conducted a simulation study to compare Cox and accelerated failure time models [23]. They used the methodology that proposed by Stute [24], which can be used to estimate linear regression models with censored observations. The strong evidence appeared in their simulation to support Stute, log-logistic and lognormal models when the proportional hazard assumption holds or dos not hold. They also presented this comparison in a gastric cancer data and stated that the proportional hazard assumption did not hold. The findings showed a perfect fitting for lognormal and Stute's methodology with same parameter estimations.

Moghimi-Dehkordi et al compared Cox and parametric models in survival of patients with gastric cancer in southern of Iran [25]. They showed that although the hazard ratio in the Cox model and the parametric ones are approximately similar, according to Akaike Information Criterion, the Weibull and Exponential models are the most favorable for survival analysis.

Although the Cox parameter estimations are well-known to the researchers in the field of medical sciences, the results in accelerated failure times can be interpreted as the relative risk that is not unknown to medical scientists. Thus, these parameters can be interpreted as factor accelerating or decelerating similarly in the interpretation of Cox' hazard ratio. These parametric models can be easily conducted 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.

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Conflict of Interest

None to declare

Authors' Contribution

MAP conceived, designed the study, interpreted the results and drafted the manuscript. AP and MV participated in writing and revising the manuscript. BMD and AS designed and carried out the analyses. SA contributed to data gathering and data entry to the software. MRZ revised and approved the final manuscript. All authors read and improved the final manuscript.

Table 2. Prognostic Factors of Gastric Cancer using Cox and Parametric Models, Full model

Prognostic factors	Cox HR (CI: 95%)	Lognormal HR (CI: 95%)	Exponential HR (CI: 95%)I	Gompertz HR (CI: 95%)	Weibull HR (CI: 95%)	Log-logistic HR (CI: 95%)	Generalized Gamma HR (CI: 95%)
Age at diagnosis	1.01* (1.00-1.02)	1.02* (1.01-1.03)	1.01 (0.99-1.03)	1.01 (0.99-1.03)	1.01 (0.99-1.03)	0.99 (0.97-1.00)	0.99 (0.97-1.00)
Sex							
Male	1.04 (0.80-1.32)	0.92 (0.70-1.22)	1.25 (0.75-2.04)	1.23 (0.97-1.01)	1.32 (0.81-2.18)	1.14 (0.76-1.71)	1.19 (0.78-1.82)
Female	1.00	1.00	1.00	1.00	1.00	1.00	1.00
Distant metastasis							
Absent	1.00	1.00	1.00	1.00	1.00	1.00	1.00
Present	1.01 (0.62-1.61)	1.92* (1.56-2.32)	1.82* (1.05-2.22)	1.82* (1.50-2.22)	1.83* (1.50-2.23)	1.88* (1.59-2.27)	1.89* (1.54-2.28)
Extent of wall penetration							
T1	1.00	1.00	1.00	1.00	1.00	1.00	1.00
T2	1.24 (0.35-4.35)	2.44* (1.85-3.12)	2.99 (0.37-23.90)	3.00 (0.37-23.95)	2.87 (0.36-22.93)	2.08 (0.50-9.09	2.32 (0.48-11.11)
T3	2.52 (0.79-8.00)	1.53* (1.16-2.02)	6.08 (0.82-45.01)	6.08 (0.82-45.02)	6.14 (0.83-45.57)	4.17* (1.03-16.67)	4.54* (1.01-20.83)
T4	4.83* (1.53-15.24)	2.92* (1.78-4.81)	9.02* (1.17-69.51)	9.01* (1.17-69.46)	9.57* (1.23-74.19)	5.88* (1.35-25.00)	6.67* (1.37-33.34)
Tumor size							
<35mm	1.00	1.00	1.00	1.00	1.00	1.00	1.00
>35mm	1.66* (1.40-2.56)	2.19* (1.33-3.60)	1.96 (0.73-5.26)	1.94 (0.73-5.15)	1.90 (0.71-5.07)	1.63 (0.76-3.49)	1.69 (0.77-3.71)
Histology type							
Adenocarcinoma	1.00	1.00	1.00	1.00	1.00	1.00	1.00
Signet ring cell&…	1.22 (0.91-1.64)	0.79 (0.58-1.06)	1.13 (0.83-1.54)	1.13 (0.83-1.54)	1.16 (0.85-1.58)	0.92 (0.73-1.22)	0.91 (0.69-1.19)
Other	0.95 (0.80-1.129)	1.06 (0.90-1.26)					
Tumor grade							
Well differentiated	1.00	1.00	1.00	1.00	1.00	1.00	1.00
Moderately differentiated	1.13 (0.73-1.75)	1.47* (1.06-2.00)	0.91 (0.52-1.58)	0.91 (0.52-1.59)	0.88 (0.50-1.55)	1.07 (0.67-1.71)	1.08 (0.67-1.73)

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Poorly differentiated	1.50* (1.01-2.23)	1.27* (0.90-1.80)	1.26 (0.74-2.13)	1.26 (0.74-2.13)	1.34 (0.79-2.28)	0.88 (0.55-1.38)	0.84 (0.52-1.32)
Lymph node metastasis							
N1	1.00	1.00	1.00	1.00	1.00	1.00	1.00
N2	0.98 (0.70-1.34)	0.96 (0.69-1.32)	0.66 (0.41-1.05)	0.66 (0.41-1.07)	0.60 (0.38-0.97)	1.35 (0.90-2.03)	1.40 (0.92-2.12)
N3	1.02 (0.72-1.45)	1.09 (0.76-1.55)	0.41 (0.18-0.92)	0.41 (0.18-0.93)	0.38 (0.17-0.85)	1.91 (0.99-3.67)	2.01* (1.03-3.97)
Pathologic stage							
Early	1.00	1.00	1.00	1.00	1.00	1.00	1.00
Advanced	1.84* (1.41-2.41)	2.08* (1.56-2.78)	1.34 (0.71-2.53)	1.34 (0.71-2.53)	1.27 (0.66-2.44)	1.37 (0.80-2.38)	1.33 (0.76-2.32)
AIC	905.7	467.3	465.30	463.30	461.81	455.94	460.86

*Statistically significant
HR: Hazard Ratio, CI: Confidence Interval

Table 3. Prognostic Factors of Gastric Cancer using Cox and Parametric Models, Final model

Prognostic factors	Cox HR (CI: 95%)	Lognormal HR (CI: 95%)	Exponential HR (CI: 95%)l	Gompertz HR (CI: 95%)	Weibull HR (CI: 95%)	Log-logistic HR (CI: 95%)	Generalized Gamma HR (CI: 95%)
Age at diagnosis	1.02* (1.00-1.03)		1.02* (1.01-1.03)			0.98 (0.97-0.99)	
Sex							
Male							
Female							
Distant metastasis							
Absent		1.00	1.00	1.00	1.00	1.00	1.00
Present		1.69* (1.17-2.51)	1.75* (1.08-2.81)	1.75* (1.09-2.82)	1.74* (1.08-2.81)	1.67* (1.14-2.38)	1.66* (1.13-2.46)
Extent of wall penetration							
T1	1.00	1.00	1.00	1.00	1.00	1.00	1.00
T2							
T3	4.08* (2.42-6.88)	4.00* (1.29-6.67)	1.92* (1.14-3.25)	2.07* (1.22-3.49)	2.16* (1.27-3.64)	1.96* (1.25-3.03)	2.04* (1.28-3.22)

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T4	2.03* (1.18-3.49)	2.04* (1.28-3.22)	3.73* (2.25-6.19)	3.77* (2.26-6.26)	3.91* (2.35-6.48)	3.84 (0.41-5.88)	3.86* (2.44-6.25)
Tumor size							
<35mm			1.00	1.00	1.00		1.00
>35mm			1.67 (0.92-3.03)	1.89* (1.06-3.45)	1.92* (1.07-3.44)		1.78* (1.06-3.02)
Histology type							
Adenocarcinoma		1.00					
Signet ring cell&…		3.67* (3.06-4.39)					
Other		16.28* (11.59-22.65)					
Tumor grade							
Well differentiated							
Moderately differentiated							
Poorly differentiated							
Lymph node metastasis							
N1							
N2							
N3							
Pathologic stage							
Early							
Advanced							
AIC	2394.2	1055.24	1025.96	1034.30	1038.30	1003.96	1020.54

*Statistically significant
HR: Hazard Ratio, CI: Confidence Interval

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