RESEARCH COMMUNICATION

Comparing Cox Regression and Parametric Models for Survival of Patients with Gastric Carcinoma

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Abstract

Background: Researchers in medical sciences often tend to prefer Cox semi-parametric instead of parametric models for survival analysis because of fewer assumptions but under certain circumstances, parametric models give more precise estimates. The objective of this study was to compare two survival regression methods - Cox regression and parametric models - in patients with gastric adenocarcinomas who registered at Taleghani hospital, Tehran. Methods: We retrospectively studied 746 cases from February 2003 through January 2007. Gender, age at diagnosis, family history of cancer, tumor size and pathologic distant of metastasis were selected as potential prognostic factors and entered into the parametric and semi parametric models. Weibull, exponential and lognormal regression were performed as parametric models with the Akaike Information Criterion (AIC) and standardized of parameter estimates to compare the efficiency of models. Results: The survival results from both Cox and Parametric models showed that patients who were older than 45 years at diagnosis had an increased risk for death, followed by greater tumor size and presence of pathologic distant metastasis. Conclusion: In multivariate analysis Cox and Exponential are similar. Although it seems that there may not be a single model that is substantially better than others, in univariate analysis the data strongly supported the log normal regression among parametric models and it can be lead to more precise results as an alternative to Cox.

Key Words: Cox - parametric model - AIC - gastric carcinoma

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Introduction

The objective of many studies is to characterize the different survival distributions that correspond to different subgroups within a heterogeneous population. 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 (Cox , 1972) and accelerated failure time model as a parametric model. Many of the standard parametric models such as Weibull, Exponential and Lognormal are accelerated failure time models.

However Cox regression is the most widely employed model in survival analysis, parametric models (Lawless, 1998) lead to some benefits.

Researchers in medical sciences often tend to prefer semi parametric instead of parametric because of its less assumptions but some comments recommended that under certain circumstances, parametric models estimate the parameter more efficient than Cox (Efron , 1977; Oakes , 1977). In parametric model we often use maximum likelihood procedure to estimate the unknown parameters and this technique and its interpretation are familiar for researchers. Also accelerated failure time can be used as relative risk with similar interpretation in Cox regression.

Gastric cancer is the second leading cause of cancer death in the world (Pisani et al., 1999). The incidence and mortality rates for gastric cancer are declining throughout the world (Toossens et al., 1981) and it is predicted to be the eighth leading cause of all deaths worldwide in the year 2010 (Murray et al., 1997). The aim of this study is use Cox regression and alternative parametric models to evaluate the effect of Gender, age at diagnosis, family history of cancer, tumor size and presence of pathologic distant metastasis on survival of patients with gastric cancer who registered at Taleghani hospital in Tehran and their survivals followed from February 2003 through January 2007.

Cox regression and Weibull, Exponential and Lognormal models were applied to the data and comparisons were made to find the best model.

Patients and Methods

Cox Proportional Hazards Model

In survival models, the hazard function for a given individual describes the instantaneous risk of experiencing

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an event of interest within an infinitesimal interval of time, given that the individual has not yet experienced that event. Cox (1972) 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. The Cox hazard function for fixed-time covariates, x, is:

$$\lambda(t;x) = \lambda(\mathrm{t}) \exp (\chi\beta)$$

Due to the construction of equation above, the 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. The survival function corresponding is then (Lawless, 1982).

$$S(t;x) = \exp\left[-\exp(x'\beta)\int_0^t \lambda_0(u)du\right]$$

This integral is called the baseline cumulative hazard function. Several methods are available for estimating the baseline cumulative hazard function (Klein et al., 1997).

Cox's model has become the most used procedure for modeling the relationship of covariates to a survival or other censored outcome (Therneau et al., 2000). However, it has some restrictions. One of the restrictions to 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.

Parametric models

The Cox model is semi parametric, in that the baseline hazard takes on no particular form. That means we have no particular parametric model for hazard and time. Suppose we assume a nonparametric baseline hazard. Then there will be a nonparametric baseline survivorship function. But that really means that we take the baseline survival experience as we see it. A link to parametric survival models comes through alternative functions for the baseline hazard. In this case we can let the baseline hazard be a parametric form such as Weibull, Gompertz, Exponential, and Lognormal. For example in Exponential regression the baseline survivorship function is in follows:

$$S(t;x,\beta) = \exp\left[{-t}/{\exp(\beta_0 + \beta_1 x)}\right]$$

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. Why use a parametric survival model?

If the assumptions are met, the analysis is more powerful.We have considered Weibull and Exponential models with respect to the assumptions of constant and monotone baseline hazard respectively and lognormal model because its baseline hazard has value 0 at t=0, increases to maximum and then decreases, approaching 0 as becomes large.

The likelihood value and standardized of parameter estimates were employed to comparison among parametric and semi parametric models.

Evaluation Criteria

For the aim of comparison among parametric and semi parametric models we used Akaike Information Criterion (AIC) and standardized of parameter estimates.

The AIC proposed in Akaike (1974), is a measure of the goodness of fit of an estimated statistical model (Akaike, 1974). 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

$$AIC = -2 * \log(likelihood) + 2(p + k)$$

Where p is the number of parameter, k=1 for the exponential model, k=2 for the Weibull, log logistic, and log normal models (Klein et al., 1997). Lower AIC indicates better likelihood.

Standardized measure of variability,

sv

$$(sv = {\sigma_\beta}/{|\beta|})$$

analogous to the coefficient of variation.

Study of Gastric Cancer Survival

The data represent a retrospective review of all patients treated from February 2003 through January 2007, 746 patients whom were admitted at Taleghani hospital with a diagnosis of gastric cancer and entered into the study (71% male and 29% female). In general 285 patients (38.6%) have died and 61.4% have not experienced the event of death (right censored).

The 111 patients (15%) are less than 45 years at diagnosis, 322 patients (36.4%) have had pathologic distant metastasis, and 93 patients (26.6%) have more than 35 mm tumor size and 179 patients (25.5%) have a family history of cancer.

Cox proportional hazard model was used to determine the difference of survival time (in month) between sub groups of age at diagnosis, tumor size and pathologic distant of metastasis. Parametric models were performed as alternative ones.

Results

A total number of 746 patients with gastric carcinoma entered to this study. The mean age at diagnosis was 59.6±12.9 and values of parametric and semi parametric models were compared by using AIC. According to the graphical test (not shown hear) the proportional hazard assumption holds. Tables 1 and 2 show the results of univariate and multivariate analyses. Based on AIC, the Cox and Exponential model in multivariate analysis are the best. According to the results from both Cox and parametric models patients who were upper than 45 years

Table 1. Cox and Parametric Models of Gastric Carcinoma Survival in Multivariate Analysis

Factors	Cox Standardized variability	AIC	Weibull Standardized variability	AIC	Exponential Standardized variability	AIC	Lognormal Standardized variability	AIC
Gender	1.11 (HR=1.26)	743	1.21 (RR=1.20)	780	1.20 (RR=1.25)	743	0.84 (RR=1.33)	776
Age at diagnosis	0.46*(HR=2.17)		0.34*(RR=1.02)		0.39*(RR=1.02)		0.62*(RR=1.02)	
Tumor size	0.44*(HR=1.85)		0.42*(RR=1.75)		0.45*(RR=1.82)		0.36*(RR=2.04)	
Pathologic distant metastasis	0.48*(HR=1.80)		0.53*(RR=1.60)		0.48*(RR=1.80)		0.42*(RR=2.01)	
Family History	3.44 (HR=0.92)		10.3 (RR=0.98)		3.95 (RR=0.93)		2.25 (RR=0.89)	

*significant at the 5% level

Table 2. Cox and Parametric Models of Gastric Carcinoma Survival in Univariate Analysis

Factors	Cox Standardized variability	AIC	Weibull Standardized variability	AIC	Exponential Standardized variability	AIC	Lognormal Standardized variability	AIC
Gender	5.08 (HR=1.03)	3247	4.06 (RR=1.03)	2609	4.26 (RR=1.03)	2607	2.35 (RR=1.06)	2560
Age at diagnosis	1.16 (HR=1.28)	3243	0.72*(RR=1.25)	2637	0.79*(RR=1.22)	2637	1.30*(RR=1.15)	2630
Tumor size	0.47*(HR=1.59)	1002	0.52*(RR=1.47)	1007	0.54*(RR=1.54)	1008	0.43*(RR=1.64)	1004
Pathologic distant metastasis	0.21*(HR=1.88)	2346	0.25*(RR=1.73)	1994	0.24*(RR=1.73)	1992	0.19*(RR=2.14)	1978
Family History	0.78 (HR=0.83)	3032	0.68 (RR=0.83)	2494	0.74 (RR=0.83)	2494	0.75 (RR=0.82)	2480

*significant at the 5% level

at diagnosis had an increased risk for death in term of hazard ration in Cox regression and relative risk in parametric models followed by those with tumor size greater than 35 mm and presence of pathologic distant metastasis ($P<0.05$). Although the Hazard Ratio in Cox model and accelerated failure time in parametric ones are approximately similar, according to AIC, Cox and Exponential are the most favorable in multivariate analysis. But with respect to lower variability Exponential seems better.

In univariate analysis similar results were observed for age at diagnosis, tumor size and pathologic distant metastasis. All parametric models showed better likelihood in compare to Cox except for tumor size where seems that Cox is the first choice but the result from Lognormal is dramatically similar it. While age at diagnosis is significant in parametric model, it is insignificant in Cox regression for univariate analysis. On the other hand according to AIC, Lognormal is the efficient one among parametric model in univariate analysis.

In multivariate models, Cox and Exponential are the same with respect to AIC and standardized variability. But in univariate, all parametric ones are better than Cox except for tumor size and the Lognormal is the first choice among parametric models.

Neither Cox, nor parametric models in both univariate and multivariate analysis show any evidence about significant differences in gender and family history.

Discussion

Researchers in the field of medical sciences are often interested in Cox proportional hazard model more than parametric models but In a recent review of survival analyses in cancer journals (Altman et al., 1985), it was found that only 5 per cent of all studies using the Cox PH model with respect to checking the underlying assumptions. If this assumption does not hold, the Cox model can lead to the unreliable conclusions so Parametric models such as Lognormal, Weibull and Exponential are the common choices. These models provide the interpretation based on a specific distribution for duration times without need to proportional hazard assumptions.

The aim of this study was to investigate the comparative performance of Cox and parametric models in a survival analysis of patients with gastric carcinoma. We used Akaike Information Criterion (AIC) to evaluate among models. In our example the proportional hazard assumptions were hold and the all parametric model residual (not shown here) indicated a perfect fit. We explored the impact of gender, age at diagnosis, tumor size, pathologic distant metastasis and family history of cancer on survival time and all parametric and semi parametric models in both univariate and multivariate analysis showed an increased risk of death for patients who were upper than 45 years at diagnosis, tumor size greater than 35 mm and presence of pathologic distant metastasis.

Age at diagnosis was a strong and independent prognostic factor for gastric cancer, and our finding in univariate analysis is in conformity with previous reports (Arveux et al., 1992; Haugstvedt et al., 1993) indicated better survival for young patients.

Metastasis is another important prognostic factor of gastric cancer (Adachi et al., 1996; Shiraishi et al., 2000) many authors show that the survival depends on the presence of metastasis. In this study we transformed and categorized distant of metastasis in two levels; the presence of metastasis tumor or not. The results in both univariate and multivariate analysis showed a higher relative risk of death for patients with distant metastasis. Our findings are in agreement with these observations showing an association with distant metastasis, which is maintained in multivariate analysis (Orsenigo et al., 2005;

Costa et al., 2007).

Size of tumor is another significant factor where affected the survival probability of patients in both univariate and multivariate analysis. This finding is similar to some other study where pointed a higher hazard ratio of death for patients with larger tumor or worse grade of tumor (Coburn et al., 2003). Another study (Orsenigo et al., 2005) also repotted same conclusion for tumor size in a univariate analysis.

The evaluation criteria indicated Cox and Exponential model are similarly the best models in multivariate analysis and some same conclusions in univariate analysis. Although it seems that there may not be a single model that is substantially better than others, the data strongly supported the log normal regression among parametric models in univariate analysis and it can be lead to more precise results as an alternative for Cox.

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 (Nardi et al., 2003) although in our data the censoring was about 60 per cent, the parametric results were not performed bad. In addition, Oakes (Oakes, 1977) discussed that; asymptotically well fitted parametric models should be more efficient than Cox if parameter values are far from zero.

Nardi and Schemper (Nardi et al., 2003) compared Cox and parametric models in tree clinical studies. They used Normal-deviate residuals (Nardi, 1999) to verify the parametric model assumptions. In Nardi's study where there were some parameters far from zero the Weibull regression produced standardized variability. In our study this case holds and Exponential (in multivariate) and lognormal (in univariate) are the perfect one among parametric models.

Orbe, Ferreira and Nunez-Anton conducted a simulation study to comparing Cox and accelerated failure time models (Orbe et al., 2002). They used the methodology that proposed by Stute (Stute et al., 1993), 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 model when the proportional hazard assumption holds or dos not hold. They also presented this comparison in a gastric cancer data set that the proportional hazard assumption did not hold. The findings showed a perfect fitting for lognormal and Stute's methodology with same parameter estimations.

However the Cox parameter estimations are familiar for researchers in the field of medical sciences, the results in accelerated failure times can interpret as the relative risk that is not unknown for medical scientists. So these parameters can be interpreted as factor accelerating or decelerating similarly in the interpretation of Cox' odds ratio. These parametric models can easily conducted by maximum likelihood estimators and let the researchers to explore the data through the different relationships consist of leaner trend, nonlinear ones or interactions and when the proportional hazard assumption dose not hold these methods lead to acceptable conclusions.

In spite of this advantage further study should be carried out to evaluate the effects of practical cases such as small sample size, large censoring and changing in proportional hazard assumption or duration time's distribution.

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