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Parametric Model Evaluation in Examining the Survival of Gastric Cancer Patients Andits Influencing Factors

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Abstract

Background: Cox proportional hazard model is the most common technique to analysis the variables effect on survival time, but under certain circumstances, parametric models may offer advantages over Cox's model. In this study we use cox regression and alternative parametric models such as Weibull, exponential, log-normal, logistics and gamma model to evaluate factors affecting survival of patients with gastric cancer. Comparisons were made to find the best model.

Method: In this study, data from 643 patients with gastric cancer who were referred to Imam Khomeini hospital with personal details during 2007 to 2013 have been reviewed in order to determine the survival rate of gastric cancer. It was observed that 74 cases were eliminated due to incomplete information and 569 persons were examined. Akaike Information model was used for comparison between models.

Result: Of a total of 569 patients, 329 (57.8%) died during the period. The figure of Cox-Snell residuals indicates that only the exponential model does not have better fitness. Weibull, log-normal, log-logistic and gamma models show the better fitness because points are on straight line. At the time of diagnosis, stage with ($p<0.0008$) and metastasis with ($p<0.0219$) were subjected to higher risk of death.

Conclusion: Based on Akaike's criterion, the Weibull model with Akaike value of 257.165 is the most favorable for survival data.

Keywords: parametric models, akaike's criterion, gastric cancer, survival analysis

1. Introduction

Analysis of survival data is a set of methods that is applied for analyzing data at which response variable is the time of occurrence a special event. The features of time data are positivity and skewed to the right. Another characteristic of survival time is existence of incomplete (unfinished or censored) data. The study of survival data is of longitudinal type and person has been followed up until the occurrence of an event or being censored (Kleinbaum & Klein, 2012; Ravangard et al., 2011). There are three methods for analysis of survival data: Nonparametric method (Kaplan-Meier, Nelson Allen and life table), semi-parametric method (Cox regression), and Parametric method (exponential, Weibull, gamma, lognormal, etc.). The advantage of parametric method over the other two methods shows that having distribution may calculate the quantiles. More adaptations for survival function, simplicity and completeness are other reasons for the popularity of parametric distributions (Kleinbaum & Klein, 2012).

Cox semi-parametric method is also used widely for modeling these data (Ravangard et al., 2011; Zhu et al.,

2011). These methods show the relationship between survival and some concomitant variables such as age, sex, family history of disease and etc. A primary reason for using Cox method is the existence of fewer pre-assumptions in this technique. However, in some cases, parametric methods present more accurate estimations (Zhu et al., 2011; Pourhoseingholi et al., 2007). In parametric models, the direct effect on survival variables by conditional probability (such as Cox model) can be studied. Most of the parametric methods such as Weibull model are Accelerated Failure Time-AFT (Kleinbaum & Klein, 2012; Klein, 2012; Pourhoseingholi et al., 2007). Among the most widely used parametric models is Weibull model and it showed more flexibility than Cox semi-parametric model (Zhu et al., 2011; Binti Abdullah, 2013) because its risk rate is not time constant and estimates of unknown parameters may be obtained using maximum likelihood method (Zhu et al., 2011).

One of the most common cancers is Gastric cancer that is the cause of non-controlling growth of malignant cells in the stomach. Cancer is the first cause of death in developed countries and the second cause of death in less developed countries (Nazir et al., 2014). The gastric cancer is the most common type of cancer in men after lung cancer while the breast cancer is considered the most common cancer in women (Fock, 2014). Half of the incidence cases happen in East Asia and mainly in China (Biglarian et al., 2009). Despite great efforts in the prevention and treatment of cancer, the disease has increased substantially and is still a killer factor in the worldwide. So, it is expected that its prevalence reaches 17 cases per year in 2020 (Vinod et al., 2009). The cancer disease is the third cause of death after road accidents and cardiovascular disease in Iran and is considered as one of the most important health problems. Northern and northwestern Iran is among high-risk areas for this disease (Malekzadeh, Derakhshan, & Malekzadeh, 2009; Kolahdoozan et al., 2010; Kavousi et al., 2014). This study aims at investigation of parametric models in the evaluation of patients survival with cancer and its' affecting factors.

2. Method

The data represent a historical cohort study. The statistical population consists of patients with gastric cancer who referred to Imam Khomeini hospital of Sari City for treatment since the beginning of November 2007 until the end of October 2013 and has medical records at this center. Patients were followed up periodically by telephone during the study and their survival status was determined as failure time until the end of October 2013. In this study, information on variables such as demographic variables including age of patient at the time of diagnosis, Sex, familial history and city; biological variables such as stage, site of tumor, type of tumor metastasis site at presentation, op before, op after, site of relapse, time of relapse, progression, time of prognostic, type of regimen, CT, diarrhea, neuropathy, neutropenia, cause CT dc, RT, Treat Compl and reason of chemo D.C; Socio-economic variables such as patient's job have been recorded using cancer registry forms. This information were extracted from medical records of patients and health status of patients was conducted by phone and registration in prepared check lists. The survival time of patients is calculated by subtracting the date of diagnosis (through endoscopic) from the date of death or censoring in months. In this study, censored cases include alive people at the end of the study and missing people on follow-up and the gastric cancer is considered the cause of death for all of the people who died.

Descriptive statistics and analytical methods and the best fitted model to the data that are identified using Cox-Snell residuals figures and Akaike criteria have been used in order to investigate the effect of prognostic factors on gastric cancer. Variables with less than 0.25 significance level in the univariate analysis were entered the multivariate analysis (Hosmer, Lemeshow, & May, 2008) and influential variables are determined at 0.05 significance level.

The evaluation criteria: for comparative evaluation models in this paper, the Akaike criterion (AIC) was used which was proposed in 1974 by Akaike (1092 (25)). AIC is a measure for fitness of statistical models and indicates which model is more appropriate for data analysis. AIC criterion formula is calculated as follows:

$$AIC = -2 \{\log (likelihood)\} + 2 (P+K)$$

Where p, is the number of parameters, k=1 (constant coefficient) for exponential model and k=2 for Weibull and lognormal models (26, 1092). Lower AIC indicates better likelihood. All calculations were carried out by SAS (version 9.3) software.

3. Result

Of the 569 patients with gastric cancer examined in the study, 163 (28.6%) were women (28.6%) and 381 (67%) were men and the rest are just censorship. The mean age of patients was 65.21 years. The mean age at the time of diagnosis was 65.68±13.14 years in men and 62.26±14.49 years in women with gastric cancer. About 57.2% (318) patients are above 65 year and 9 % (50) of patients are younger than 45 years. Only two were single. Job

information availability of 565 patients indicates that 154 men are in agricultural group and 110 women are doing other than non-agricultural work (housekeeper). It is observed that 60.8 percent of patients have lived in urban and 30.2 percent in rural areas. The tumor site was in cardia in 122 (40.1%) patients and it was in gastric antrum in 98 (32.2%) patients where there is not any significant relationship in terms of survival time of patients and the tumor site. The information on the type of tumor was available only in 398 cases of patients, of which, Adenocarcinoma tumor was detected in majority of 398 (90.2%) patients. Of 397 patients that progression stage of disease was listed in their records, 315 (79.4%) of them were referred for treatment in stage 3 and 4 of disease. In this study, 329 (57.8%) patients of total patients experienced death and 240 (42.2%) patients were censored (including alive people at the end of study and missing people at follow-up).

The mean, median and standard deviation of survival are 24.49, 19 and 0.84 months respectively.

The Cox-Snell figure shows that the exponential model has no good fitness on data and Weibull, lognormal, log logistic and Gamma models are more favorable models of which points are almost in a straight line.

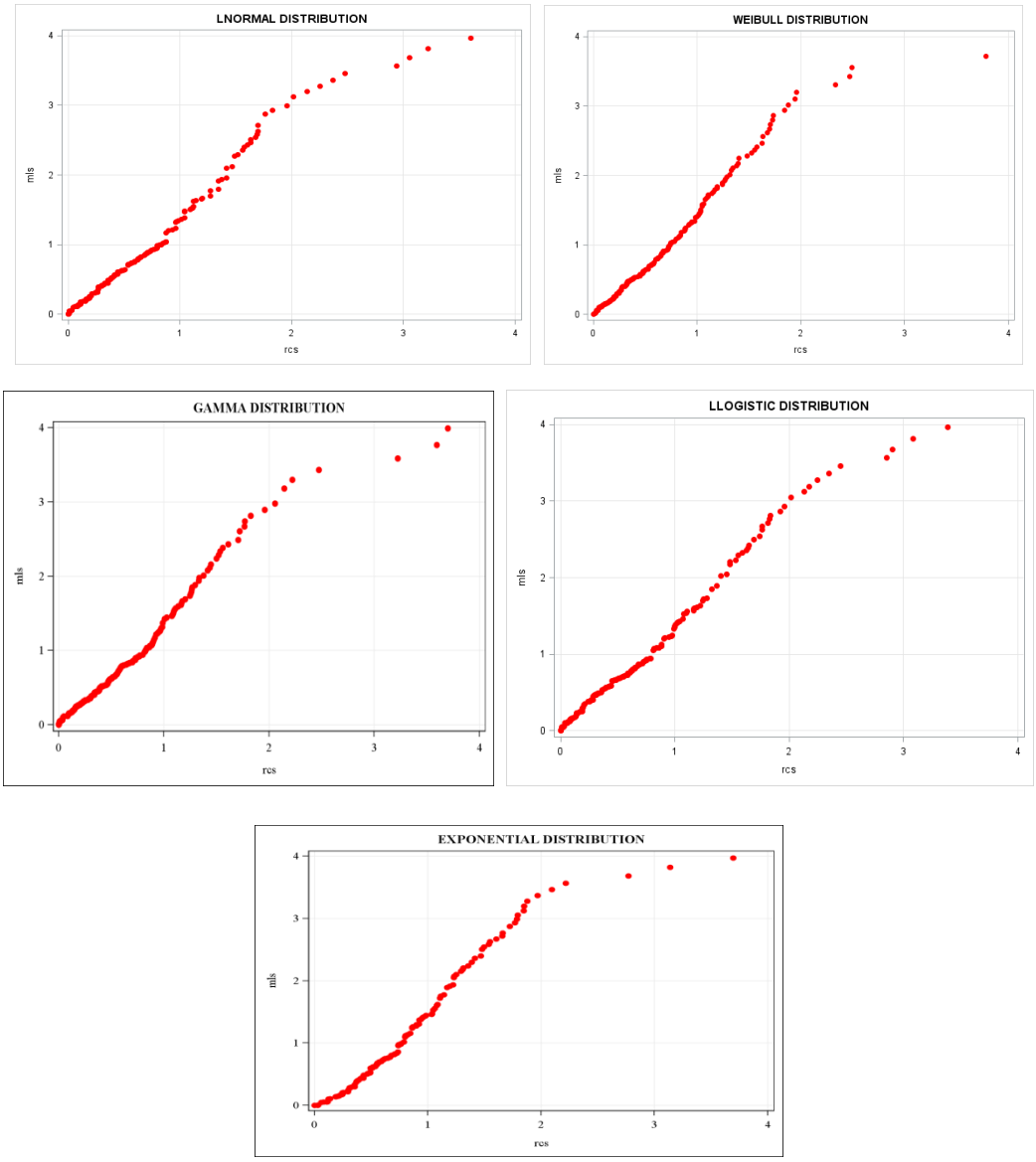

Figure 1. Cox-Snell residuals

Thus, Weibull model is introduced as best model using Akaike criterion because its Akaike value is less as shown in Table 1.

Table 1. Akaike's values

Model	Exponential	Weibull	Lognormal	Log logistic	Gamma
Akaike criterion	612.605	257.165	453.886	334.517	264.063

In order to compare the survival rates in studied variables subgroups, according to the univariate test of Weibull, exponential, log-normal, log-logistic and gamma, site of tumor, type of tumor, metastasis, OPBEFOR, CT, neuropathy, neutropenia, RT, reason of chemo DC, stage, age, variables have significant level less than 0.25 which enter the multivariate analysis as follows (Table 2).

Stage and Metastasis variables are significant in Weibull model which is the best likelihood model in this study. Neuropathy and neutropenia variables are also significant in log logistic model.

Table 2. Multivariate analysis

Type III Analysis of Effects											
		Weibull		Exponential		Log normal		Log-logistic		Gamma	
Effect	DF	Wald Chi-Square	Pr>ChiSq	Wald Chi-Square	Pr>ChiSq	Wald Chi-Square	Pr>ChiSq	Wald Chi-Square	Pr>ChiSq	Wald Chi-Square	Pr>ChiSq
Siteoftumor	5							8.1303	0.1492		
Type Of Tumor	1	2.8463	0.0916					1.3112	0.2522		
Metastasis	5	13.1649	0.0219			2.9231	0.9391			15.3295	0.0320
Opbefor	1	0.0066	0.9353	2.3284	0.1270	2.9587	0.0854	0.2638	0.6075	3.4515	0.0632
Ct	1					3.1204	0.0773	0.0840	0.7719		
Neuropathy	1	0.0029	0.9570	1.3368	0.2476	3.6152	0.0573	6.7411	0.0094		
Neutropenia	1	1.4312	0.2316	0.4995	0.4797	0.0014	0.9697	6.2162	0.0127	0.2816	0.5957
Rt	1	1.2987	0.2545	0.0938	0.7594	0.0000	0.9954	2.8167	0.0933	0.1536	0.6952
Reson Of Chemo DC	2	2.3116	0.3148								
Stage	3	16.8351	0.0008	24.2403	<.0001	29.4162	<.0001	46.1327	<.0001	8.1418	0.0432
Age Categorical	2	2.6394	0.2672								
Howmany Course	5	2.5791	0.7645							4.4788	0.4827
Aic		257/165		612/605		453/886		334/517		264/063	

4. Discussion

Researchers of medical field often tend to use Cox proportional hazards model instead of the same parametric models in analyzing the impact of explanatory variables on survival of patients. A systematic model on the cancer Journals shows that the assumptions of this model are investigated only in 0.5% of studies which use Cox model (Altman et al., 1995). If the proportional hazards assumptions do not hold then the results of Cox model will not be reliable. Thus, parametric models such as Weibull, exponential, lognormal and etc. can be better choices in such a situation. These models fit the model by assuming the existence of a special distribution for time variable and without having to assume proportional hazards.

This study aims at investigation of parametric models in the analysis of patients' survival with gastric cancer and their affecting factors. For cooperation of models the Akaike's criterion was used. In this study, the proportional hazards assumption was hold for all of the models and residuals figure indicates that fitting the models was appropriate. Results showed that in multivariate analysis, parametric models were carter from other models and the Weibull model had the best likelihood among the parametric models.

Nardi and Schemper (2003) compared the Cox regression and parametric models in three clinical trials. They used remnants of deviation from normal (Nardi & Schemper, 1999) to consider the assumptions of parametric models. In Nardi and Schemper models the Weibull model was better than other models that are consistent with

our study. A good discrimination among parametric models requires the right censoring percentage not to exceed 40–50% (Nardi & Schemper, 2003). Although in this study the percent of censoring was 42.2% but parametric models had appropriate fitness. In Pour Hossein Goli and his colleagues study, the exponential model in multivariate analysis and log normal model in univariate case were obtained for patients with gastric cancer despite the high percentage of censor that is not consistent with our study (Pourhoseingholi et al., 2007). Yazdani et al. compared the parametric models in patients with gastric cancer using AIC criterion. In this study, the Weibull model is more efficient than gamma and exponential models that is consistent with our study (Yazdani et al., 2011). Also in the Ghadimi et al study (Ghadimi et al., 2011), the log logistic model (with and without its fragility) was better than other models.

5. Conclusion

Despite the desire of many researchers to apply Cox model in survival analytical studies, the parametric models have the ability to present better results than Cox model in cases where the censorship is relatively low, whether the appropriate hazards assumption holds or not. Therefore, it is suggested to choose the best and efficient model in the examining the results of all the different models of survival analysis.

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Competing Interests Statement

The authors declare that there is no conflict of interests regarding the publication of this paper.

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