Original Article

Determining the Effective Factors on Gastric Cancer Using Frailty Model in South-East & North of Iran

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Abstract

Background and Purpose*:* Gastric cancer is the third leading cause of mortality in Iran after cardiovascular diseases and accidents. The aim of the present study was to assess survival and it's affecting factors in gastric cancer patients through using Cox and parametric models along with frailty.

Materials and Methods: In this study, the medical records of gastric cancer patients treated from 2008 to late 2010 were collected in Afzalipour and Bahonar Hospitals in Kerman and Imam Khomeini Hospital in Sari. 383 patients entered the study and were followed up for at least five years. The survival of patients was assessed by using Cox proportional hazard, log-normal and log-logistic models under gamma and inverse-Gaussian distributions, as two special models for frailty. Models efficiency comparison criteria were Akaike information criterion and Cox-Snell residuals.

Results: Out of 196 patients in Kerman, 132(67.3%) were males and 64(32.7%) were females. The average age of the patient was 61yr and 59 yr for the males and females, respectively. Also, the survival rates after 1, 3, and 5 years of the diagnosis were 62%, 50%, and 45%, respectively. In the city of Sari, 69% (129 people) of the patients were male and 31% were female. The mean ages of male and female were 66 and 62 yr, respectively. At the same time, 1, 3, and 5 year survival rates of patients were 58%, 36%, and 30%, respectively. Based on Akaike information criterion, Cox-Snell residuals, and non-monotonic failure rate, log-logistic model along with gamma frailty was more fitted in comparison with other models. Using this model, radiotherapy, heartburn, and tumor grade were found as significant predictors.

Conclusion: Radiotherapy, heartburn, and tumor grade could be considered as more affected factors. According to rejection of the proportional hazard assumption, assessments of residual figures, and according to non-significant frailty effect by log-normal model, log-logistic model along with gamma frailty was found to be the best fitted model.

Keywords: Gastric cancer; Proportional Hazard Model; Parametric models; Frailty models -AIC

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1. Introduction

Gastric cancer is one of the most prevalent causes of mortality in developed and developing countries, such as Iran (3). It is the second most prevalent cancer in Iran, and the most prevalent one in men. It is also the third most prevalent cancer in women after breast and esophageal cancers (1, 5). Based on an estimate in 2002, Age Standardized incidence Rate (ASR) in women and men was reported to be 26.1 and 11.1 in 100000 person/year (1, 6). The prevalence of gastric cancer is different around the world (7). Since in most of the cases it is diagnosed in advanced stages, gastric cancers has low survival rate (8). 5-year survival rate of this cancer has been reported 12.3% in Chili, 9% in Brazil, 29.6% in China, 4.4% in Thailand, 37% in United States of America, and 22% in Japan. In Iran, over 80% of gastric cancer patients are diagnosed in advanced stages, where treatment strategy will have subtle effects (9-13). Most of the northern and southeastern regions in Iran are located in vulnerable area to gastric cancer (14). Ardabil and East Azerbaijan Provinces have the most incidence rate for gastric cancer in Iran. While central and eastern provinces of Iran are moderate, and southern regions of Iran are considered as low risk areas (5). Kerman province, located in southeastern part of Iran, has low incidence rate for gastric cancer with 10.2 and 5.1 rates for men and women, respectively (15). The main purpose of survival studies is to determine the important diseases and the demographic factors in the occurrence of an event, such as recurrence of a disease, death of patient, recovery, and other factors (16, 17). Standard survival methods are based on this assumption that survival data of patients are independent of each other and distribution time, until the intended event for various patients are independent and identical. While in most of the cases, the studied communities have heterogeneous combination of individuals with different hazards, and the evaluation of this heterogeneity is difficult and sometimes can contribute to inappropriate and reductive hazard functions, which are due to neglecting some unobservable, non-measurable, and unknown genetic or environmental factors, which cause heterogeneity in the target communities and are effective on distribution time of survival and hazard function. These factors are usually individual effects, which are not measurable by using apparent covariate, and because of excluding them in the regression model, estimating parameters are biased by using usual Cox proportional hazard model, and to resolve this problem in survival analysis, random effects as frailty models have been proposed during the last decade. In the current study, gamma and inverse-Gaussian distributions were used to estimate frailty (18-24), and the aim of this study was to assess the survival of patients and the factors affecting it in gastric cancer patients using log-normal and log-logistic parametric models along with gamma frailty. It also wanted to compare the results of these models with Cox Model.

2. Materials and Methods

In the present study, the medical records of 383 gastric cancer patients treated from 2008 to late 2010 in Afzalipour and Bahonar Hospitals in Kerman and Imam Khomeini Hospital in Sari were included in the study. The target patients were then followed up for at least five years. City, gender, place of residence, opium, radiotherapy, chemotherapy, family history of cancer, surgery, dysphasia, weight loss, heartburn, hypertension, constipation, tumor grade, and tumor Histology were all taken into account as the variables in this study. Various models were assessed, and AIC values were calculated for parametric and semiparametric models. Then, according to Schoenfeld test, the proportional hazard assumption of the studied data was investigated. To compare the efficiency of parametric models, the Akaike information criterion and Cox-Snell residuals were used to assess the goodness of fit of a model, hence the lower value of AIC suggested a better model. The survival of patients was also assessed using Cox proportional hazard model, log-logistic, and log-normal models under gamma and inverse-Gaussian distributions, while considering two special models for frailty (36). All statistical analysis were done applying Stata V.11 (Stata Corporation, College Station, TX, USA) with a significant P value <0.05. This model was, at first, introduced by D.COX, a famous English statistician in 1972 to assess the effects of explanatory variables (independent) affecting survival time (25). It is a semi-parametric model, so that the form of baseline hazard function $\lambda_0(t)$ in this model is unknown, and no special distribution is considered for it. While in parametric models, survival times follow specific distributions, such as Weibull, exponential, log-normal, and log-logistic.

Cox hazard function for x explanatory variable, is a function as follows:

$$H(t;x) = h_0(t)\exp(X'\beta)$$

One of the limitations of this model is the proportional hazard assumption, which considers that hazard rate between two or more groups of explanatory variables should be stable over time (26, 27). The survival function for this model is as follows:

$$S(t;x) = \exp[-\exp(X'\beta)\int_0^t h_0(u)du$$

In the above models, $\lambda_0(t)$ is baseline hazard function, while β and X are vectors of regression coefficients and explanatory variables, respectively (27). The condition of using Cox model in the state of univariate survival data is that, regardless of covariate effects, there is no heterogeneity between survival times. To cope with this heterogeneity, a non-measurable random effect (frailty effect) is placed in hazard function (28). Frailty random effect variable (z) is an invisible and non-negative effect which has probability density function of $f(z)$ with the mean of 1 and variance of σ^2. This presumption is then called the standard condition of frailty effect. σ^2 Parameter demonstrates the rate of heterogeneity in the community. Significant frailty effect implies that patients with identical explanatory variables have various death risks. The term ‘frailty’ was, first, introduced by Vaupel et al. (1979) to define the differences between at-risk individuals in mortality data. Lancaster (1979) also assessed the time of unemployment with random effect, and made common mixed proportional hazards model in economic studies. Hougard (1986) initially suggested power variance distribution to present solutions for heterogeneity problem. Then, frailty models were applied for the studies of age at the time of death by Zelterman (1992), for the unemployment period by McCall (1994), pregnancy of women by Aalen (1987), and migration by Lindstrom (1996) (18, 29-35). Conditional survival and hazard function of the effect of frailty is as follows:

$$h_i(t) = h(t|z_i) = z_i h_0(t)\exp(X'\beta)$$

$$S_i(t) = S(t|z_i) = \exp\{-\int_0^t h(s|z_i)ds\} = (S(t))^{z_i}$$

In this model, z_i is a component of frailty for ithperson. β is a vector of regression coefficient, and X is a vector for explanatory variables in the model. $h_o(t)$ is the baseline hazard function which means that its’ value of explanatory variables equals zero (27).

In the current study, in order to compare the efficiency of parametric and Cox models, Akaike information criterion (AIC) was used. This criterion was presented by Akaike and aimed to measure the goodness of fit for model which is calculated trough the following equation:

$$AIC = -2*\log(likelihood) + 2*(a+c)$$

In this equation, a is the number of parameters presented in the model, and c is the constant coefficient which is dependent on the type of the model, and is zero for Cox model, while the value of c is 2 for applied parametric models (36).

3. Results

In the current study, 383 gastric cancer patients were assessed with the mean age of 63.49 and standard deviation of 15.124. Of these patients, 261 (68.1%) were men and 122 (31.9%) were women. The median survival of these patients was 612 days. 1-year, 3-year, and 5-year survival rates of these patients were 60%, 43%, and 37%, respectively. Of 383 gastric cancer patients, 229 of them died during the study, whereas a number equal to 154 (40.2%) of the patients were still alive or there was no accurate information regarding their survival rate or considered as right-censored observations. In the city of Kerman, 67.3% (132 patients) were male and 32.6% were female. Of 196 patients, 102 of them died during the study (94 patients were considered as right-censored). The mean ages of the male and female patients were 61.89 and 59.2 years, respectively. 1-year, 3-year, 5-year and median survival rates of these patients in Kerman and Sari are listed in table 2. As it is evident, patients in Kerman had more survival rates in comparison with Sari's patients. In the city of Sari, 67.9% (127 patients) were male and 32.1% were female. Of 187 patients, 129 of them died during the study (54 patients were considered as right-censored). It should also be noted that the mean ages of the male and female patients were 67.48 and 62.95 years, respectively.

Table1. Characteristics of gastric cancer patients.

Variables		n(%)	p-value
City	Kerman	196(51.2)	0.009*
	Sari	187(48.8)	
Gender	Female	122(31.9)	0.070
	Male	261(68.1)	
Place of residence	Rural	162(42.3)	0.970
	Urban	221(57.7)	
Opium	N0	260(67.9)	0.120
	Yes	123(32.1)	
Radiotherapy	N0	325(84.9)	0.409
	Yes	58(15.1)	
Chemotherapy	N0	185(48.3)	0.744
	Yes	198(51.7)	
Family of Cancer	N0	340(88.8)	0.230
	Yes	43(11.2)	
Surgery	N0	99(25.8)	0.447
	Yes	284(74.2)	
Dysphasia	N0	315(82.2)	0.054
	Yes	68(17.8)	
Weight loss	N0	100(26.1)	0.731
	Yes	283(73.9)	
Heartburn	N0	326(85.1)	0.063
	Yes	57(14.9)	
Hypertension	N0	316(82.5)	0.401
	Yes	67(17.5)	
Constipation	N0	343(89.6)	0.705
	Yes	40(10.4)	
Tumor grade	Well-differentiated	29(7.6)	0.000*
	Moderately-differentiated	202(52.7)	
	Poorly-differentiated	152(39.7)	
Tumor Histology	Adenocarcinoma	307(80.2)	0.070
	Others	76(19.8)	

* Significant at 0.05 level

Table2. Survival characteristics of patients with Gastric cancer

Survival rate	One year	Three year	Five year	Median(day)
Kerman	62%	50%	45%	1044
Sari	58%	36%	30%	512

All present variables were used to perform the analysis for this study. As a result, the researchers tried to assess the influence of these variables on survival of gastric cancer patients.

At first, according to Schoenfeld test, the proportional hazard assumption of the collected data was rejected, and as a result, Cox model was excluded. Then, AIC values were calculated for Weibull (1308.699), exponential (1419.556), log-normal (1290.168), and log-logistic (1294.096) models. According to the lower rate of Akaike information for log-logistic, Weibull, and log-normal models in comparison with other models, they were nominated to fit the model for the data. During the next stage, according to Cox-Snell residual plot (Figure 1), log-logistic and log-normal parametric models were selected. In order to correct the heterogeneity of observations, gamma frailty and inverse-Gaussian parameters were added to these models, the significance level of which was obtained in log-logistic model (p= 0.001, $\theta = 1.294$). Table 2 and Table 3 demonstrate the findings obtained from multivariate analysis of parametric models (with and without frailty effect).

The data analysis showed that radiotherapy variable was significant only with frailty effect (p<0/05). City, heartburn, tumor grade, and histopathology type of tumor were significant in log-normal and log-logistic models (Table 2, Table3). The results of the multivariate analysis of the log-logistic model with gamma frailty demonstrated that survivals of gastric cancer patients with radiotherapy treatment were 3.88 times more than patients without this treatment. Furthermore, those patients with heartburn had 2.41 times more survival rates in comparison with other patients. Hence, if gastric cancers are diagnosed in early stages, like other cancers, patients have more life time. In the current study, likewise, the same results were obtained, which meant that the patients with moderate tumor grade survived 0.386 times less than those with well tumor grade. Furthermore, those patients with poor tumor grade survived 0.099 times less than those with well tumor grade (Table 2).

Table 2. Results of log-logistic parametric models with and without frailty effect in multivariate survival analysis of gastric cancer patients

variables	loglogistic								
	without frailty			gamma frailty			invgauss frailty		
	γ	p-value	RR	γ	p-value	RR	γ	p-value	RR
City	3.047	0.000*	0.429	1.421	0.309	0.671	1.558	0.194	0.591
Gender	1.385	0.234	0.781	0.994	0.982	1.007	1.076	0.789	0.916
Place of-residence	1.138	0.614	0.906	1.171	0.522	0.836	1.13	0.63	0.865
Opium	0.67	0.199	1.355	0.795	0.445	1.298	0.778	0.412	1.346
Radiotherapy	2.023	0.054	0.586	3.884	0.000*	0.215	3.819	0.000*	0.204
Chemotherapy	1.115	0.685	0.92	1.201	0.472	0.812	1.204	0.48	0.803
Family History-of cancer	0.766	0.486	1.225	1.309	0.47	0.737	1.248	0.563	0.769
Surgery	0.568	0.06	1.536	0.706	0.226	1.485	0.689	0.205	1.556
Dysphasia	1.689	0.139	0.672	1.163	0.678	0.842	1.236	0.555	0.778
Weight loss	0.948	0.859	1.041	0.796	0.426	1.296	0.796	0.437	1.31
Heartburn	2.098	0.043*	0.57	2.413	0.015*	0.368	2.517	0.010*	0.335
Hypertension	0.687	0.266	1.33	0.603	0.125	1.776	0.602	0.131	1.824
Constipation	0.934	0.873	1.053	0.822	0.62	1.25	0.81	0.603	1.284
Tumor grade									
Moderately-differentiated	0.382	0.063	2.076	0.386	0.049*	2.941	0.401	0.065	2.953
Poorly-differentiated	0.095	0.000*	5.963	0.099	0.000*	13.786	0.098	0.000*	15.689
Tumor Histology									
Adenocarcinoma	2.119	0.022*	0.566	1.654	0.11	0.565	1.681	0.107	0.541
AIC		1294.096			1285.358			1285.569	
theta					1.294181			2.526526	
p-value					0.001*			0.001*	

* Significant at 0.05 level
γ, Accelerated failure time
RR, Relative risk

Table 2 demonstrates that frailty variance of gamma distribution in log-logistic models was significantly more than zero. This meant that individual and specific characteristics of patients are effective in survival. Those patients with identical explanatory variables had various death risks. None of sex, place of residence, chemotherapy, surgery, opium consumption, family history of cancer, dysphasia, hypertension, weight loss variables were significant. Although opium consumption variable was not significant, but in 56% of the cases, those patients with consumption of opium had 0.79 times lower survival in comparison with those patients with no consumption of it. Furthermore, in 53% of the cases (Table 2), the patients treated with chemotherapy had 1.2 times more survival in comparison with those patients without chemotherapy. At the same time, 77% of the cases with surgery had 0.7 times lower survival rates than those with no surgery. 57% of the patients with weight loss had 0.8 times lower survival rate in comparison with those with no weight loss. It was also found that 88% of the patients with hypertension had 0.6 times lower survival rates than those with no hypertension, while 38% of the cases with constipation had 0.82 times lower survival rates in comparison with those without constipation. Finally, 89% of the sample patients with adenocarcinoma histopathology tumor had 1.654 times more survival rates than those patients without adenocarcinoma tumors.

Table 3. Results of log-normal parametric models with and without frailty effect in multivariate survival analysis of gastric cancer patients.

variables	**lognormal**								
	without frailty			**gamma frailty**			**Inv-gauss frailty**		
	γ	p-value	RR	γ	p-value	RR	γ	p-value	RR
City	2.823	(0.001)*	0.633	2.047	0.053	0.686	2.213	(0.023)*	0.664
Gender	1.493	0.153	0.838	1.332	0.327	0.86	1.394	0.249	0.843
Place of-residence	1.052	0.843	0.978	1.046	0.866	0.977	1.039	0.884	0.98
Opium	0.635	0.154	1.221	0.679	0.228	1.226	0.661	0.197	1.238
Radiotherapy	2.282	(0.033)*	0.696	3.267	(0.005)*	0.537	3.058	(0.007)*	0.562
Chemotherapy	1.219	0.477	0.917	1.288	0.369	0.876	1.282	0.382	0.880
Family History-of cancer	0.817	0.617	1.093	1.085	0.85	0.958	1.019	0.964	0.990
Surgery	0.583	0.072	1.268	0.655	0.174	1.249	0.636	0.14	1.263
Dysphasia	1.733	0.114	0.785	1.559	0.213	0.792	1.601	0.181	0.785
Weight loss	0.875	0.662	1.06	0.799	0.469	1.125	0.807	0.492	1.117
Heart burn	2.141	(0.042)*	0.715	2.389	(0.021)*	0.633	2.347	(0.024)*	0.644
Hypertension	0.679	0.256	1.185	0.659	0.229	1.245	0.659	0.230	1.240
Constipation	0.854	0.707	1.072	0.734	0.478	1.177	0.756	0.518	1.155
Tumor grade									
Moderately-differentiated	0.3936296	0.080	1.507	0.4173196	0.095	1.583	0.413028	0.094	1.578
Poorly-differentiated	0.0978442	(0.000)*	2.780	0.1025753	(0.000)*	3.310	0.1008627	(0.000)*	3.266
Tumor Histology									
Adenocarcinoma	1.998	(0.036)*	0.738	1.832	0.075	0.727	1.865	0.065	0.725
AIC	1290.168			1289.617			1289.973		
Theta				0.6155348			0.6853536		
p-value				0.055			0.069		

* Significant at 0.05 level
γ, Accelerated failure time
RR, Relative risk

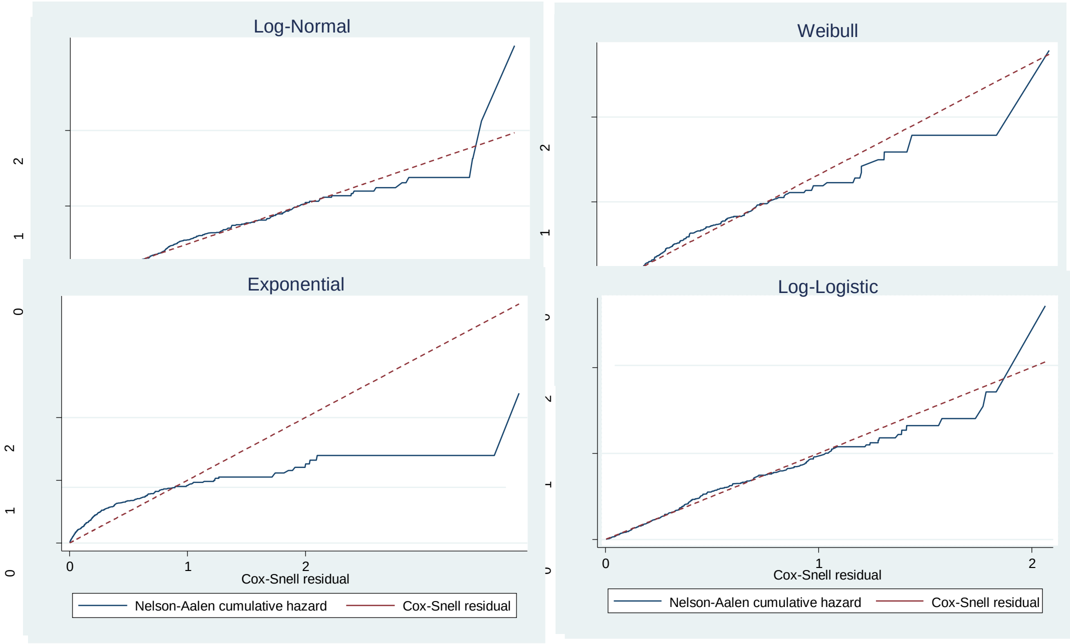

Figure 1. Cox-Snell residuals in parametric models.

4. Discussion

Cancer is one of the most important health problems worldwide, hence most of the health equipment in developing countries is allocated to these diseases (37). Survival rate in this disease is relatively low, and after diagnosis, people will not live for a long time (38). Numerous studies have been conducted in the field of identifying factors affecting survival of this disease (39-41). For various reasons, such as the support of most statistical software and the existence of fewer assumptions, most of the investigators tend to use Cox proportional hazard model to identify the factors affecting survival of patients. Whereas, in a systematic study conducted by Altman et al. on 43 articles, 5% of them assessed proportional hazard assumption in Cox Model. Failure to establish this assumption causes the results of the model not to be completely reliable. As a consequence in these conditions, parametric models will be a more appropriate selection. Such models with the assumption of a specific distribution for time variable and without any need to proportional hazard assumption will fit the model (42-44). The aim of the current study was to assess and compare log-logistic and log-normal parametric models with Cox Model and to evaluate the entry of frailty effect in survival analysis of gastric cancer patients. The studied variables in this research included city (Kerman and Sari), sex (Male, female), residency (urban, rural), radiotherapy, family history of cancer, chemotherapy, consumption of opium, surgery, heartburn, dysphasia, hypertension, weight loss, constipation, tumor grade (poor, moderate, good), and histophatologic type of tumor (Adenocarcinoma, others). In the current study, sex proportion was 2.14, which was a value higher than the estimated sex proportion by the study of Ghadimi et al. and lower than some other studies (2, 45-47). The mean age of patients in the present study was 63.49 years old (64.65 years old for men and 60.99 years old for women), which was relatively similar to a 5-year study conducted by Biglaran et al. in Tehran, but higher than some other studies (46, 48), and lower than mean estimations in the study of Yazdani et al. (50). In this study, radiotherapy, heartburn, and tumor grades were considered as the important predictors of survival in gastric cancer patients, so that those people treated by radiotherapy had higher survival rate, as well as the patients with heartburn. It should be noted that the diagnosis of a disease in the early stages is a factor affecting survival of a patient. In the previously conducted studies, it had been documented that those patients with family history of cancer had lower survival rate (2, 51-53), while the family history of cancer was not a significant variable in the current study, and these findings were in congruence with the findings of Pour Hossiengholi, Yazdan Band, and Baeradeh (54, 55, 56) in their conducted studies. One of the reasons for such inconsistency could be due to the fact that about 88.8% of the patients in the current research reported no family history of cancer. As expected, tumor grade variable in the current study was identified as a factor affecting survival in gastric cancer patients. So that, those people diagnosed in poor tumor grade had the lower survival rate. Whereas, those patients with moderate or poor disease grade had 2.941 and 13.782-time more relative risk than those with a good tumor grade. In a study conducted in China, it was observed that the effect of tumor grade was significant, and the relative risk of those patients with a moderate and poor tumor grade was 1.14 and 1.34 times more than those patients with a good tumor grade, respectively. Furthermore, in a study conducted by Moghimi-Dehcordi in Fars Province, the effect of tumor grade was seen to be significant, and the relative risk of those patients with a poor tumor grade was observed to be 1.56 times higher than those with good grade tumor (57, 58). In the present study, the type of tumor histopathology in the ultimate model was found to be not significant, which was consistent with the studies of Zeraati and Biglarian (59, 60). Furthermore, in some background studies, it had been demonstrated that sex was an important predictive factor for survival in patients (2, 51), while this variable was also not significant in the present study, which was consistent with some other studies (51, 54, 61, 62). In the current research, the relative risk in those patients with radiotherapy was 0.215 times more than those cases without radiotherapy. As observed in the literature, radiotherapy variable was significant in a study conducted by Whitson et al., and the relative risk in those patients with radiotherapy was 0.63 times more than those cases without radiotherapy, the current study was in congruence with this study (63). The results of this research demonstrated that based on Akaike information criterion and according to rejection of proportional hazard assumption, the parametric models of log-logistic along with gamma frailty were better fitted in comparison with the other existing models. In this model, except for radiotherapy, heartburn, and tumor grade, the other variables did not have any significant effect on the survival of patients. Rajaeifard et al. evaluated the factors affecting the survival of gastric cancer patients by using Cox, Weibull, exponential, and log-normal models, and demonstrated that the results of Cox and parametric models were relatively similar; however, they found that by using Akaike information criterion, Weibull parametric model was better fitted (47). It should be noted that in the current investigation, this case was true for log-logistic model (with gamma frailty). In another study conducted on gastric cancer patients in Taleghani Hospital of Tehran, Pour Hossiengholi et al. compared the efficacy of Cox and parametric models by using Akaike information criterion and residuals figures. They concluded that log-normal parametric mode had the best fit, and could be used as a replacement for Cox Model in the survival analysis of gastric cancer patients (27). Ghadimi et al. in a study on gastric cancer patients in the city of Babol concluded that log-normal and log-logistic parametric models in multivariate analysis as well as univariate analysis had relatively similar results, and that because of the rejection of proportional hazard assumption, Akaike information criterion, and assessment of residuals, log-logistic model was best fitted, and was considered as a suitable replacement for Cox Model (2). Zare et al. conducted a study regarding the efficacy of parametric and Cox Models by using Akaike information criterion and Cox-Snell residuals, and concluded that parametric models were best fitted in comparison with Cox Model, as a suitable replacements for it (64). Orbe et al. conducted a study regarding simulated and real data of gastric cancer patients in order to decide whether the proportional hazard assumption is established or not. The efficacy of log-logistic, log-normal, and stute model was better than Cox Model (65). In the studies of Ghadimi et al. regarding the efficacy of Cox and parametric models with frailty effect, it was concluded that when proportional hazard effect was not established, log-logistic model with frailty effect was better fitted than Cox Model (51, 66), which was consistent with the finding of the current study. In order to compare the models, Akaike information criterion and assessment Cox-Snell residuals were used. In the present study, it was also found and established that parametric models are better fitted if the percentage of a right-censor is not more than 40 to 50% (44). Based on the findings, log-logistic model with gamma frailty was the best statistical model amongst parametric models for the survival analysis of gastric cancer patients. The current study demonstrated that radiotherapy, tumor grade, and heartburn were the most prognostic effective factors affecting lifetime of gastric cancer patients. Furthermore, it was observed that the survival of patients treated by radiotherapy was higher than those without radiotherapy treatment, and those patients with heartburn had higher survival rate. The diagnosis of a disease at early stages was also found to contribute to higher survival rates. Increasing awareness of public toward prognosis of this disease and diagnosis at early stages can be effective in a higher survival rate. Since the proportional assumption was rejected about the data, and according to Akaike information criterion and assessment of residuals and significant gamma frailty effect, log-logistic model with gamma frailty can be an appropriate replacement for Cox Model to determine the factors affecting the survival of gastric cancer patients.

Advantage and disadvantage:

In Cox and parametric models, the hazard function may depend on unknown or non-measurable factors that can cause the regression coefficients being estimated by such models to be biased. As a result, the frailty models were introduced in order to overcome the problem and better model the survival of patients. Frailty models are even used to explain the random variation of the survival function due to unknown risk factors, such as genetic and environmental factors.

Conflicts of interest

The Authors have no conflict of interest.

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