

*Original Article****Application Weibull regression in the study of survival patients evolved by Gastric cancer referred to Imam Khomeini hospital of Sari (Northern Iran) 2007- 2013***

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***Abstract:***

***Background and purpose:*** The survival rate of gastric cancer patients has significantly increased during the last decades because of the advances in this type of cancer treatment. The purpose of the current study was to examine the survival levels of gastric cancer through Weibull regression and its affective causes.

***Materials and methods:*** In this research, the records and personal information of 643 patients who were evolved by gastric cancer and referred to Imam Khomeini hospital of Sari (2007- 2013) were studied in order to determine their levels of survival. During the study, 74 cases of patients were exempted from the study due to their defective data, and the data collected from 569 cases were analyzed to obtain the results. In the current study, the impact of factors affecting Survival time was determined using the Weibull regression model. The analysis of data was performed using Stata statistical Software in 0.05 significance level.

***Results:*** The findings of the study showed that patients were estimated to experience 5 years of survival probability equal to 0.75, 0.68, 0.54, 0.41, 0.3 during the time period November – December, 2013 the 1, 2, 3, 4 with a median survival time equal to 19 months, resulting in a survival mean equal to 24.49 months. Based on the Univariate and Multivariate analyses methods, some variables like: stage and metastasis were determined as the affective factors on the survival probability (p-value <0.05).

***Conclusion:*** In this study, it was then concluded that the life span of examined patients is very low in comparison with developed countries, which might be because of late reference or delayed diagnosis and the lack of facilities for treatment. Thus, the factors such as earlier diagnosis of the problem and screen methods could certainly influence and increase the patients' survival rate.

***Keywords:*** Gastric Cancer; Survival Analysis; Weibull Regression

## 1. Introduction

There are three categorical methods for survival analysis. Nonparametric model (Kaplan-Meier, Nelson Allen and life table), semi-parametric model (Cox proportional hazards model), and parametric models (Exponential, Weibull, gamma, lognormal and etc). The advantage of parametric model to the other two methods is that with the distribution, it is possible to calculate the quantile. Many parametric methods such as accelerated failure time (AFT) model, and Weibull (AFT) model are among the most widely used alternatives to model, and has more flexibility than in Cox semi-parametric models. Because of the risk rate, and using the maximum likelihood method for estimating parameters, which model? is not constant over time (1-4).

Being one of the diverse types of cancers and one of the most important causes of death in all over the world, gastric cancer is caused by uncontrolled growth of gastric cells (5). Cancer is the first-ranked cause of death in developed countries, but the second in undeveloped (6). The gastric cancer is the second common type of cancers after lung cancer in men but the breast cancer is the most common one in women (7). Half of cancer cases occur in eastern Asia, and mainly in China (8). Despite the efforts done in the field of cancer prevention-occur, this disease has been spread increasingly and is raised as a cause of death all over the world. So, it is expected that cancer prevalence reach 17 cases in the year 2020 (9). It is documented that during the last 75 years, because of determining the causes of danger and some controlling measures, the level of death because of gastric cancer has

considerably been decreased. For instance, it is observed that in the United States of America, the level of death toll because of gastric cancer has been decreased from 28 to 5.8 per 100,000 people among men, while this census among women has been decreased from 27 toward 2.8 per 100,000 persons. Despite this census, new cases equal to 21260 have been diagnosed along the US, and 11210 of the American cancerous cases died in the year 2007. The cancer occurrence is still high in some countries like Japan, China, Chile, and Ireland (10, 11). Also in Iran, gastric cancer is ranked three as the cause of death after road accidents and cardiovascular diseases, and is considered as one of the most important health and cure problems. Based on the estimations of International Agency of Cancer Researches, during the year 2012, about 53,000 Iranian citizens had died because of cancer. The cancer of stomach system is the most important type of cancer that, according to medicals, is spread as a result of the involvement of environmental, biologic and dietary factors (12). Gastric cancer in Iran is known as the second common cancer with 11.4% of occurrence after breast cancer in the year 2015 (13). The northern and north-western areas of Iran are among the highly affected areas (14-17). Although it is expected that the level of gastric cancer to be decreased during the following years, it is documented that about 50% of its diagnostic cases are in their advanced stages, and it could be due to the fact that the early diagnosis of this cancer is very difficult (8,18). Therefore, it is very much important to have an exact census of cancer occurrence and the death toll because of cancer in order to take certain controlling steps and

design programs along this country. The aim of the current study was to evaluate the survival of patients with gastric cancer referring to Imam Khomeini Hospital from 2007 to 2014 through Weibull regression.

## 2. Materials and methods

Being a historical cohort study, the statistical population of this research consisted of all the patients referred to the Imam Khomeini Hospital of Sari who were diagnosed with gastric cancer and had a cure record file in that hospital. The variables under study were three groups of demographic, biologic, and socio-economic variables. Demographic variables included patient age at diagnosis (age), Sex, familial history and city, biological variables included: stage, site of tumor, type of tumor, metastasis site at presentation, Undergo Surgery before Adjuvan Chemotherapy, Undergo Surgery after Neoadjuvan Chemotherapy, site of relaps, time to Relapse (months), progression, time to Progression (months), type of regimen, how many course, CT, diarrhea, neuropathy, neutropenia, cause of DC of chemotherapy, RT, Treat Compl and reson of chemo.DC, and socio-economic variables. The data was collected from the medical files of patients. The last statue of the patients' health was determined by telephone contact and recording in the check lists. The survival time of the patients was calculated by subtracting the date of disease diagnosis (by Endoscopy) from the date of death or censoring date based on its month. In the current study, the cases of censure included the alive patients at the end of study and the lost cases during follow up.

Also, for the cases who passed away during the study, the gastric cancer was considered as the cause of death.

The data were then analyzed using statistical Software 9.3 SAS analytical and statistical methods, and parametric Weibull regression was also used to examine the cumulative survival rate. The univariate analysis of the variables that had a significant level of less than 0.25 entered the multivariate analysis (19), and the significant levels of 0.05 influencing variables were identified.

## 3. Results

Among the 569 patients involved by gastric cancer under this study, 381 were male (70%), and 163 female (30%). The average age of the patients was also calculated to be 65.21 years. The mean age of cancer diagnosis among males was  $65.68 \pm 13.41$  years, while this mean was  $64.26 \pm 14.49$  for females. Also, 57.2% (318 patients) were among the cases with up to 65 years of age, and 9% (50 patients) of the patients were less than 45 years old. Only two of the patients were unmarried. Among the 565 patients with recorded job information, 154 men were working in agriculture sector, while 110 women were working in a non-agricultural job (housekeeping). 60.8% of the patients were residing in the urban and 30.2% in the rural areas. In 122 (40.1%) of the cases, the tumor was located in cardia, whereas in 98 (32.2%) of them it was located in the Antrum. There was not seen any significant relationship between the time of survival and the location of tumor.

The data regarding the type of tumor was in the medical files of only 398 of the patients among who, 90.2% showed the tumor type of Adenocarcinoma. Among these 397 patients with recorded stages of disease spread, 315 (79.4%) were in their third and fourth stages at the time of referring to the hospital. During this study, 329 (57.8%) of the sample cases experienced the event (death), and the rest of the patients equal to 240 (52.2%) faced censure event (either alive at the end of study, or lost life during the follow up). Mean, median, and standard deviation of the patients' survival was calculated to be 24.49, 19 and 0.84 months. The Weibull regression method was used in the univariable analysis, and the levels of survival of 1, 2, 3, 4, 5 years for the patients were calculated to be 0.77, 0.68, 0.52, 0.44, and 0.3. To compare survival in subgroup variables studied, according to univariate Weibull test variables, type of tumor, metastasis, undergo Surgery before (Adjuvan Chemotherapy), neuropathy, neutropenia, RT, reason of chemotherapy DC, stage, age categorical, the number of courses for Chemotherapy, significant level of less than 0.25 enter the multivariate analysis were as follows (Table 1 and 2).

**Table 1.** Analysis of Maximum Likelihood Parameter Estimates

Parameter	variables	DF	Estimate	Standard Error	95% Confidence Limits		Chi-Square	Pr > ChiSq
Intercept		1	3.3271	1.2831	0.8123	5.8420	6.72	0.0095
Type of tumor	Adenocarcinoma	1	0.6743	0.3997	-0.1091	1.4577	2.85	0.0916
	SCC+GIST+ADENO SIGNETRING	0	0.0000					
Metastasis site at presentation	Ascitis	1	-1.9631	0.7550	-3.4428	-0.4833	6.76	0.0093
	bone	1	-1.2387	0.6392	-2.4914	0.0141	3.76	0.0526
	liver	1	-1.4430	0.7992	-3.0094	0.1234	3.26	0.0710
	liver+lung	1	-1.2652	1.1229	-3.4660	0.9356	1.27	0.2598
	no	1	-2.0552	0.7013	-3.4296	-0.6808	8.59	0.0034
	other	0	0.0000					
OP.BEFOR	no	1	0.0391	0.4811	-0.9039	0.9821	0.01	0.9353
	yes	0	0.0000					
neuropathy	no	1	0.0316	0.5861	-1.1171	1.1804	0.00	0.9570
	yes	0	0.0000					
neutropenia	no	1	0.4799	0.4012	-0.3063	1.2662	1.43	0.2316
	yes	0	0.0000					
RT	no	1	0.3503	0.3074	-0.2522	0.9527	1.30	0.2545
	yes	0	0.0000					
Reson of chemotherapy DC	adverse reaction	1	0.2310	0.4289	-0.6095	1.0716	0.29	0.5901
	low performance	1	-0.3829	0.6199	-1.5978	0.8320	0.38	0.5368
	progressive	0	0.0000					
Stage	1	1	1.9226	0.7805	0.3928	3.4524	6.07	0.0138
	2	1	1.8230	0.6713	0.5072	3.1388	7.37	0.0066
	3	1	1.6121	0.4506	0.7290	2.4953	12.80	0.0003
	4	0	0.0000					
Age categorical	1	1	-0.2056	0.8391	-1.8502	1.4391	0.06	0.8065
	2	1	0.3472	0.2775	-0.1967	0.8911	1.57	0.2108
	3	0	0.0000					
How many course Chemotherapy	1	1	-0.9623	0.9508	-2.8258	0.9012	1.02	0.3115
	2	1	-0.8340	0.7952	-2.3927	0.7246	1.10	0.2943
	3	1	-0.9805	0.8570	-2.6602	0.6992	1.31	0.2526
	4	1	8.2246	52985.38	-103841	103857.7	0.00	0.9999
	5	1	-1.2519	0.8592	-2.9359	0.4321	2.12	0.1451
	6	0	0.0000					
Scale		1	0.3934	0.0612	0.2900	0.5336		
Weibull Shape		1	2.5419	0.3954	1.8740	3.4481		

**Table 2.** Type III Analysis of Effects

Effect	DF	Wald	
		Chi-Square	Pr > ChiSq
Type of tumor	1	2.8463	0.0916
metastasis	5	13.1649	0.0219
OP.BEFOR	1	0.0066	0.9353
neuropathy	1	0.0029	0.9570
neutropenia	1	1.4312	0.2316
RT	1	1.2987	0.2545
Reason of Chemotherapy DC	2	2.3116	0.3148
stage	3	16.8351	0.0008
Age Categorical	2	2.6394	0.2672
How many course Chemotherapy	5	2.5791	0.7645

A significant level of 0.05 variables such as: stage of (p<0.0008) and metastasis (p<0.0219) were identified as risk factors, so that the patients who were in advanced stages of disease were associated with lower survival. And metastasis was used as a factor affecting the survival of patients.

#### 4. Discussion

The results of the current study showed that the stage and metastasis were the significant variables on the survival of the patients affected by gastric cancer, and the highest age was obtained in the seventh decade of life, and also the most common type of cancer diagnosed was adenovirus Published anatomical carcinoma and cardiac and antrum of the stomach, and then according to Zhou et al. (3, 11), Weibull model was used for the survival of stomach cancer patients in a retrospective study. Hence, 1715 patients with colorectal cancer were examined

regarding their age at diagnosis, gender, family history, drug history, tumor location, tumor size, lymph node status, and tumor stage Pathology and depth, which were all selected as potential factors corresponding with the only variable of pathological stage study. The Global statistics showed that despite the considerable decreasing trend of gastric cancer among the European countries like Spain (20) and Italy (21), in a large number of developing countries like Korea (22) Iran (11) and Portugal (23), it has an increasing trend. The trend of cancer occurrence in the west of Iran is increasing among both males and females. Some of these increased incidences, the cancer registry system in the country shows that improving the ratio may be due to certain changes in risk factors for this cancer (24).

According to the findings of the present study, not any significant relationship was found between sexuality and the life length of the patients. This result was consistent with the findings of scholars like Kitagawa et al. lieu et al. and Jamali et al. who did not find any significant relationship between sexuality and life length of the patients (25-27). Based on the sexual distribution of the population, 381 cases (70%) of the patients were men and 163 cases (30%) were women, and based on the data, the ratio of men to women was 3:2, which was consistent with the results of the studies done in Ardabil (28) and Fars (29) provinces. But based on the results, the sexual ratio was more than some of the studies and less than some others. In the current study, the age of diagnosis is not considered as one of the determining causes affecting the patients' survival and is coincident with the results of Sirius et al., Xhang et al., and Ismaeeli et al. (30-32), but at the same time, is not coincident with Speech et al., Iunee et al. Roshanaee et al., Yazdanband and Moqimi Dehkordi et al (29, 33-36). The mean age of the patients in the current study was equal to 65.21 years (65.68 years for the men suffering from gastric cancer, and 64.26 years for the women, which meant that the mean was more than mean estimations among the other studies (29, 37). The results of the current study showed that the most common contagion occurs in the seventh decade of life, which was a finding consistent with the other studies (13, 29, 38). A similar study done in the University of Newcastle showed that most of the patients with gastric cancer were in the decade of 50-70 (39). The age difference among the patients based on the variables of location and situation of residency

was not significant (like the cases observed in Iran (27)). Despite this observation, in another study conducted in France (40), the location of residency was shown as a factor affecting the patients' survival. In this study, the variable of family background was also not shown as an affective factor which is a result consistent with the results of Moqimi Dehkordi (29), Yazdanband (28) and Biglorian (8), but could also be inconsistent with the research findings in other countries.

Based on the current study, the most common type of cancer is Adonocarsinium which consists of 90.2% of the total population of the studied persons and the rate of contagion among men was reported to be more than women, which is again consistent with the studies conducted by Norouzinia et al. (41). This census confirms the censuses of Iran (42). The most common anatomic location for cancer is Cardia parts (40.1%) and then the Antrum part (32.25) that confirms the results shown by Sediqhi et al. (37). Also, Noroozinia (41) showed the Ednocarsinium as the first ranked part of cancer engagement and Cardia part as the second. The results of a study by Davood abadi et al. showed the Antrum part as the main part of involvement (44%) but noted that during the last two years and in the final stage of his study, the involvement of Cardia has been increased considerably (42). Also, another study done by Taqhavi et al. showed that among the patients involved by gastric cancer with proportional abundance equal to 53.6, Cardia is the most common involved part (18.9%), and then Antrum ( 17.2%). The noted locations were found based on the performed endoscopic Biopsy, and can include Cardia,



Antrum and Fundus. Also, in the current study, the variable of existence or absence of metastasis was shown significant against some other previous studies that had shown a contrary relationship between metastasis existence and patients' survival (26, 35). The results of the current study was also not consistent with the findings of Lieu et al., yoni et al., and noori kajoori et al. (26, 34, 43), but is consistent with the results of Ghorbani, Yazdani, Xhang, Jamali and Speech (27, 31, 33, 44, 45).

The results of Multivariate Weibull also showed that there was a significant difference between the patients' longevity and the stage of cancer advances. The patients who had referred to the hospital at the fourth stage of the disease had less survival, a result consistent with the results is accordance with all previous studies done in or out of Iran (29,46,47). In the current study, the 1, 2, 3, 4 and 5 years of survival for the patients were calculated to be 0.77,0.65,0.52,0.44 and 0.27, respectively, but Youni et al. reported the one and three year survival of the patients with gastric cancer equal to 75% and 42%, respectively( 34). Xhang et al. during a study had reported the survival of 1, 3 and 5 years equal to 87%, 61% and 32%, respectively (31). The results of the study conducted by Esmaeeli (48) in Mazandaran province (North of Iran) and by Yazdanbod (28) in Ardabil province (in the north-west of Iran) are almost consistent with the current study, but the findings of studies done by Zera'ati (49) in Tehran (3 years survival: 0.31 and 5 years survival: 0.18) and Beiglorian (46) in Tehran (3 years survival 0.32) are not consistent as much with the results

of the current study. The five years of survival for some developed countries like the United States, Switzerland, France, China, Japan had been reported 0.37, 0.22, 0.30, 0.30 and 0.35, respectively, and the 5 years survival for most of the other countries has been reported between 10- 30 % ( 50-52).

In the present study, the method of treatment was not determined as a factor affecting the patients' survival. But in the studies done in Northern America (53), Sun in China (11,54) and in the Europe (55), a positive effects of complementary chemotherapy and chemotherapy- radiotherapy is reported leading to the patients' survival. Finally, this study showed that the survival of the patients involved with the gastric cancer referring to the Touba Treatment Clinic Center of Sari is in low level, which might be because of the few facilities for on time diagnosis and any strategic program to control this kinds of cancers in Mazandaran province. The ranking of the stages of the cancer is the most important action to increase the survival of patients involved with gastric cancer. Therefore, due to the late diagnosis of the patients' problems, a considerable decrease could be observed in the hope for survival in these patients.

#### ***Conflict of Interests***

The Authors have no conflict of interest

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