

Evaluating Long-Term Survival of Patients with Esophageal Cancer using Parametric Non-Mixture Cure Rate Models

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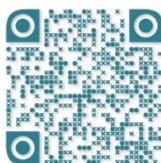
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ABSTRACT

Background & Objective: Esophageal cancer (EC) has been identified as one of the most common cancers in the northeastern regions of Iran. In our study, parametric non-mixture cure rate model was applied to evaluate the effects of risk factors on the long-term survival of patients with EC in East Azerbaijan, Northeastern Iran.

Materials & Methods: This retrospective cohort study of 127 patients with EC registered at Iran National Cancer Registry office in the period 2009-2010. These patients were followed up for 5 years in East Azerbaijan, Iran until 2015. The best parametric cure rate model was identified and the risk factors of survival in patients with EC were measured by Akaike Information Criteria and parametric non-mixture cure rate model, respectively.

Results: The survival time of EC patients ranged 0.10-69.03 months. Male sex (Odds Ratio (OR) =0.08, 95% confidence interval (CI): 0.02-0.32, $P<0.001$), patients who underwent esophagectomy surgery (OR=6.11, 95%CI: 1.46-25.55, $P=0.013$) had a significant effect on the survival and the cure fraction of EC patients. Population cure rate was 0.11 (95%CI: 0.07-0.19) and cure fraction was estimated 4.9%.

Conclusion: The Weibull non-mixture cure rate model was the most appropriate statistical tool to identify potential risk factors that affect both survival and cure fraction of EC patients. It is a recommended tool for analyzing the long-term survival of patients with EC.

Keywords: Esophageal neoplasms, Survival analysis, Non-mixture Cure Rate models



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Introduction

In recent decades, cancer has become a serious public health problem worldwide. Cancer rates are decreasing in western countries such as the United States, while in less developed and developing countries, including Eastern European countries, which have an unhealthy western lifestyle, cancer rates are increasing (1, 2). According to the National Cancer Registry (NCR) reports, after coronary disease, accidents, and natural phenomena, cancer is considered as the third main cause of death, in Iran (3). Esophageal cancer (EC) is a deadly malignancy which has caused the premature death in patients in advanced stages (4, 5). Based on the recent meta-analysis conducted on the incidence of esophageal cancer, the incidence rate of this cancer was reported eighty-four percent in developing countries (6). Also in 2013, 442000 new cases of esophageal cancer were diagnosed and 440000 patients with esophageal cancer experienced death due to this cancer worldwide (7). It is anticipated that the prevalence rates of esophageal cancer will

increase by 140% by 2025 (8). EC is the 8th most common cancer with regard to incidence and the 6th highest with regard to mortality (9). Medical researchers have achieved advanced progress in Diagnosis and treatment of esophageal cancer, but the survival rate of patients with esophageal cancer ranges from 15% to 20%. Patients who are diagnosed in the early stages have had the high survival rate associated with disease (5). Geographic and racial differences have had an important role in the incidence of esophageal cancer across the world (4). Surgery is known as a definitive treatment for esophageal cancer. However, surgical techniques can also impact the increase of survival in patients with EC (4). Radiotherapy and chemotherapy are other major treatment options in patients with esophageal cancer. Previous medical research shows that using chemotherapy and radiotherapy improved the treatment and survival of patients with locally advanced esophageal cancer (10, 11). Upper gastrointestinal tract cancers were

observed as the most common cause of death in the Caspian littoral of Iran. Furthermore, esophageal, stomach and colon cancer had had a high incidence in this region and the Eastern Azerbaijan province (12-14). Recent studies revealed that the incidence rate of esophageal cancer is higher in women than in men and that patients with esophageal cancer aged 50-70 years old have had highest incidence rates (12, 15). Multiple epidemiological studies revealed that smoking consumption, alcohol drinking, socioeconomic status, gender and the age at diagnosis are important risk factors that affect the survival of patients with esophageal cancer (15-20). According to reports from the Iranian Ministry of Health, gastrointestinal tract cancers such as esophageal and gastric cancers are the most common cancers in the East Azerbaijan province (21). Unfortunately, few studies have been conducted on the occurrence of gastrointestinal tract cancers, their survival rates and the risk factors associated with this diseases (22).

Clinical researchers have achieved progress in the treatment of chronic diseases in last few decades. These achievements have increased the proportion of cured patients from many types of cancers (23). In this case, the population group could be split into two sub groups including long-term survivors (those who are being cured) and short-term survivors (those who are non-cured). In such situations, using common survival approaches like proportional hazard model could not provide accurate estimations due to a large number of censoring items at the end of the follow-up period which, accurately, could not estimate the survival probability of those with long-term survival (24). Nevertheless, a non-mixture cure model or bounded cumulative hazard model uses a different approach for modeling survival and cure fraction parts of the model (25).

In the Current study, we compare the parametric forms of non-mixture cure rate model in a retrospective cohort study to analyze the effects of risk factors on survival and cure fraction of patients with esophageal cancer.

Materials and Methods

This registry-based retrospective cohort study was conducted in East-Azerbaijan on 399 patients with gastrointestinal cancers during the years 2009-2010 who registered at Iran National Cancer Registry office in Iran's Cancer Registration Program and were followed up till 2015. In this national program, all pathology centers, health centers, and hospitals in provinces are obligated to report their data to the Cancer Office of Disease Control and Prevention (26). Sampling was done in a full-census manner and the dataset of this study was collected from 127 cases of patients with EC who lived in cities including Azarshahr, Osku, Ahar, Bostanabad, Bonab, Tabriz, Jolfa, Chroyrnagh, Sarab, and Shabestar in the East-Azerbaijan Province.

The type of cancer site in this study was defined according to the International Classification of Diseases, 10th revision. 127 EC patients was defined by code C15. In order to assess the potential risk factors of EC, patients

with prior cancers were excluded from this study. Also, there is no loss to follow-up in this study. Figure 1 showed Flow chart of patients who met inclusion/exclusion criteria for the study population. In addition, the current study data is extracted from an MSc thesis which was checked and approved by the Ethics Committee of the TUMS (IR.TUMS.DDRI.REC.1396.4148).

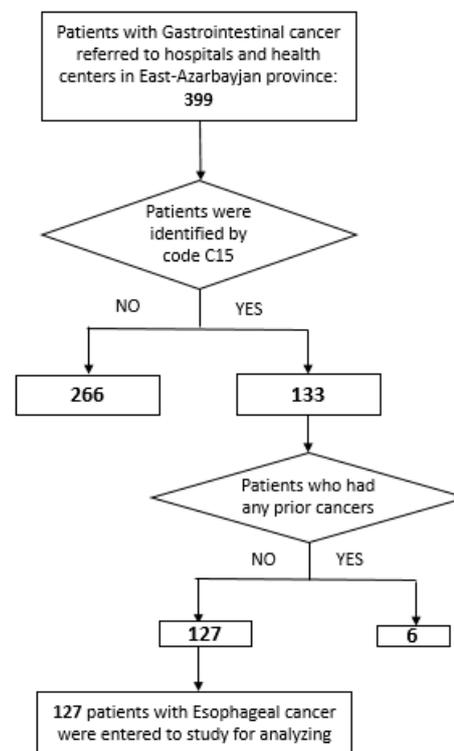


Figure 1. Flow chart of patients who met inclusion/exclusion criteria for the study population

The patients that were referred to health centers and hospitals in this province were followed up for five years until 2015. The patients' information were extracted from their records in hospitals and health centers. The patients were contacted via phone to collect data on their health and survival information. The beginning of the study was assumed as the pathologic diagnosis of the cancer. The study outcome was considered death due to EC. Survival time was calculated by the difference between the dates of death and the first report of their cancer pathology. Patients who survived by the end of the study were considered as right censored. Dying as a result of esophageal cancer was considered as failure in this study. Furthermore, the survival time in long-term survival group was measured as the time interval between the date of EC diagnosis and the date of EC patients' last follow-up time. Meanwhile, for short-term survivors the interval time between the date of EC diagnosis and the date of their death due to EC was regarded as their survival time.

The data collection included demographic information (e.g., the age at the time of diagnosis, gender, educational status, marital status, and employment status) and the biological and clinical variables (e.g., non-communicable

disease (NCD) affected status, smoking habits, Esophagectomy surgery, chemotherapy, and radiotherapy). In addition, socioeconomic status (SES) obtained based on a checklist of wealth and social position characteristics such as household fuel consumption, residential facilities, personal family facilities, and household appliances used by the family, total monthly household income, education status, and job status. Principle component factor analysis was applied to obtain the socioeconomic status (KMO=0.722, Bartlett's Sphericity test $P<0.001$). The extracted score categorized by the median to low and high level.

Statistical Analysis

Demographic, biological and clinical characteristics of patients were entered in the log-rank test to assess the unadjusted effect of variables. Descriptive characteristics of the patients were expressed as the mean \pm standard deviation (SD) and frequency (percentage) for continuous categorical variables.

The Kaplan-Meier survival plot was used to reveal if the plot reached zero with the current amount of follow up time. The plot contributed to finding the proportion of survived cases. In the case of a high survival rate, Cox regression model leads to bias estimates. In this situation, Cure rate models can be proper tools to investigate what risk factors are associated with survival of cured and uncured patients. Cure rate models are categorized into two major forms; mixture cure rate model and non-mixture cure rate model (27). In 1999, the second method was presented as a non-mixture cure rate model by Chen et al. (28). A non-mixture cure rate model is known as a bounded cumulative hazard model. This model uses different approaches to model the survival and cure fraction parts of the model. Covariates interpretation is not the same for these two kinds of cure rate models (29, 30).

In this model, a log-log link function was used and the survival function can be written as follows:

$$S(t) = p^{F_0(t)} = \exp(\ln(p) F_0(t)),$$

Where $F_0(t) = 1 - S_0(t)$ is expressed as the cumulative distribution function for the non-cured group (29).

In order to determine the best subset which has the best fit on a Cox proportional hazards model, stepwise selection could be a suitable approach. Therefore, this method was applied in this study to obtain a subset with variables having $0.2 < P < 0.1$ to achieve the most accurate estimations. Another method which was taken to account to check the indicators of multicollinearity among variables was Variance Inflation Factor (VIF). This method provides an opportunity to measure the value of variance of the estimated regression coefficient' inflation through calculating the amount of correlation between model's predictor variables. It should be noted that the

chosen subset fitted to parametric non-mixture cure models was the one which was already used to fit the Cox proportional hazards model in this study.

In current study, estimating the quality of parametric non-mixture cure rate models was determined by Akaike Information Criteria (Log-logistic, Log-Normal, Weibull and Exponential are used as parametric distributions in non-mixture cure rate model).

Odds ratio (OR) estimations of Weibull non-mixture cure rate model were displayed as our results. It should be taken into consideration that OR estimations in a non-mixture cure rate model defined by a logit link could demonstrate that in which variable group the odds of being cured is higher than the other one. Therefore, in this model if the value of odds is higher than one, it could be, indeed, true that the odds of being cured is greater than the baseline group and vice versa (29).

Moreover, the 95% confidence intervals for the estimated effect sizes were demonstrated as 95% Confidence Interval (CI). The data were analyzed using R software version 3.4.2, and the figures was prepared by STATA version 12. The P value < 0.05 was considered statistically significant.

Results

Our study was performed on 127 esophageal cancer patients, aged 35-88 years old. A total of 113 (89%) cases experienced the death due to esophageal cancer and 14 (11%) were alive by the end of the study. The survival time ranges of patients with EC were from 0.10 to 69.03 months. One, three and five-year survival probabilities were 0.44 (95% confidence interval (CI): 0.36-0.54), 0.2 (95% CI: 0.14-0.28) and 0.13 (95% CI: 0.08-0.2) respectively. The mean (\pm standard deviation) age at diagnosis was 66.92 (\pm 11.95) years old. The mean and median survival time in non-cure group were 16.99 (95% CI: 13.46-20.52) and 10.06 (95% CI: 6.49-13.63) months respectively. The patients' characteristics and Log-rank test results are shown in Table 1.

Sex, Esophagectomy surgery, marital status, SES, and radiotherapy are determined as the best subset variables by stepwise selection. This subset fit on the Cox proportional hazards model while the presence of multicollinearity between covariates was considered based on the VIF values. The PH assumption is checked in the Cox regression model and the assumption was rejected ($P=0.035$). Therefore, the Cox proportional hazards model was not appropriate for the dataset. According to the AICs from parametric non-mixture cure rate models, the Weibull non-mixture cure model outperformed other approaches (Weibull: AIC =826.61, Exponential: AIC = 832.96, Log-logistic: AIC=829.16, Lognormal: AIC=832.16).

Table 1. The Esophageal Cancer patients' characteristics and the results of log-rank Test

Variable	N (%)	Death 113 (89%)	Log-Rank Test		
			Mean Survival Time	SE*	P-value
Age**					0.460
≥ 50	113 (89)	101 (89.4)	10.28	0.93	
< 50	14 (11)	12 (85.7)	12.76	2.60	
Gender					0.103
Male	70(55.1)	68(97.1)	9.21	1.03	
Female	57(44.9)	45(78.9)	12.56	1.54	
Education					0.836
Illiterate***	98(77.2)	87(88.8)	10.58	1.05	
Literate	29(22.8)	26(89.7)	10.40	1.46	
Marital Status					0.011
Married	86 (67.7)	35(85.4)	11.88	1.11	
Unmarried****	41 (32.3)	78 (90.7)	7.57	1.24	
Job Status					0.062
Unemployed*****	79 (62.2)	67 (84.8)	11.93	1.21	
Employed	48 (37.8)	46 (95.8)	8.51	1.16	
Smoking Habit					0.181
Yes	42(33.1)	40(95.2)	12.08	1.62	
No	85(66.9)	73(85.9)	9.70	1.01	
NCD affected Status					0.721
No	103 (81.1)	93 (90.3)	10.63	0.98	
Yes	24 (18.9)	20 (83.3)	10.11	1.96	
Esophagectomy Surgery					0.048
Yes	72(56.7)	59(81.9)	12.22	1.34	
No	55(43.3)	54(98.2)	8.71	1.04	
Chemotherapy					0.009
Yes	55(43.3)	51(92.7)	13.18	1.41	
No	72(56.7)	62(86.1)	8.38	1.02	
Radiotherapy					0.052
Yes	43(33.9)	39(90.7)	13.32	1.44	
No	84(66.1)	74(88.1)	9.08	1.06	
SES*****					0.022
High level	66(52)	62(93.9)	12.52	1.52	
Low level	61(48)	51(83.6)	12.55	0.94	

*Standard Error

**Age at diagnosis

*** Illiterate: patients who had no academic education were considered as illiterate.

**** Unmarried: patients who were single, divorced or widow were entered to unmarried group.

*****Unemployed: patients who were retired or had no job were considered as unemployed.

*****SES: socioeconomic status

The results of weibull non-mixture cure rate model with logit link function are demonstrated in Table 2. According to the estimations, odds ratio of males group is reported 0.08 so males had lower odds to be cured of esophageal cancer in comparison to females (OR=0.08, 95%CI: 0.02-0.32, $P<0.001$). Odds of being cured from death in those who underwent Esophagectomy surgery was 6.11 times higher than the other group (OR=6.11; 95%CI: 1.46-25.55, $P=0.013$).

As shown in Figure 2, the Kaplan-Meier curve is stabled at the probability of almost 0.11, which implies that the population cure rate is 11 percent (Standard Deviation=0.01, 95% CI: 0.07-0.19). In addition, the obtained cure fraction was estimated to be 4.9%, which was reasonable compared to population cure rate.

The Kaplan-Meier survival curves of best subset variables is shown in Figure 3. Kaplan-Meier curves for gender, SES, Esophagectomy surgery, marital status and radiotherapy demonstrated that survival odds of cure

among the females group, patients who were in the high level socioeconomic condition, patients with EC who underwent Esophagectomy surgery, married group and patients who received radiotherapy greater than among

the male group, patients who were in the low level socioeconomic condition, no Esophagectomy surgery and unmarried group and people who didn't receive radiotherapy respectively.

Table 2. Estimation Based on Weibull Non-mixture Cure rate Model with logit link function

Variable	OR*	SE**	95% CI***		P-value
			lower	upper	
Sex (Male)	0.08	0.70	0.02	0.32	<0.001
SES**** (Low level)	2.70	0.58	0.86	8.47	0.089
Esophagectomy Surgery (Yes)	6.11	0.73	1.46	25.55	0.013
Radiotherapy (Yes)	2.14	0.56	0.71	6.46	0.177
Marital status (Unmarried)	0.30	0.65	0.08	1.05	0.060

*Odds Ratio**Standard Error;***95% confidence interval****socioeconomic status

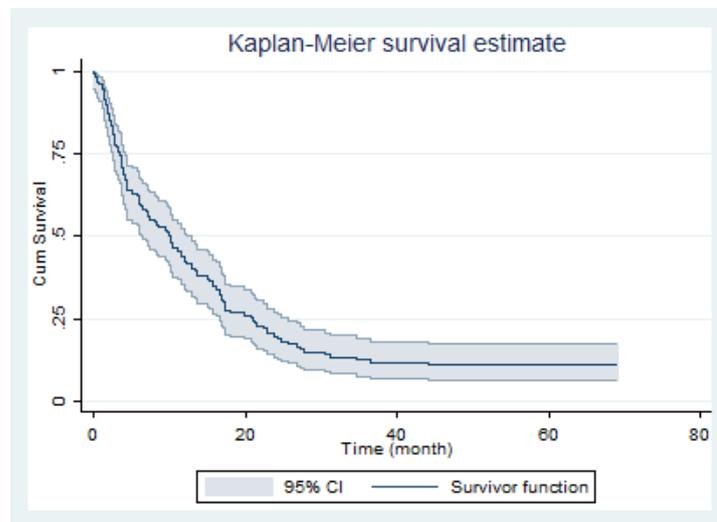


Figure 2. The Kaplan-Meier curve of patients with esophageal cancer

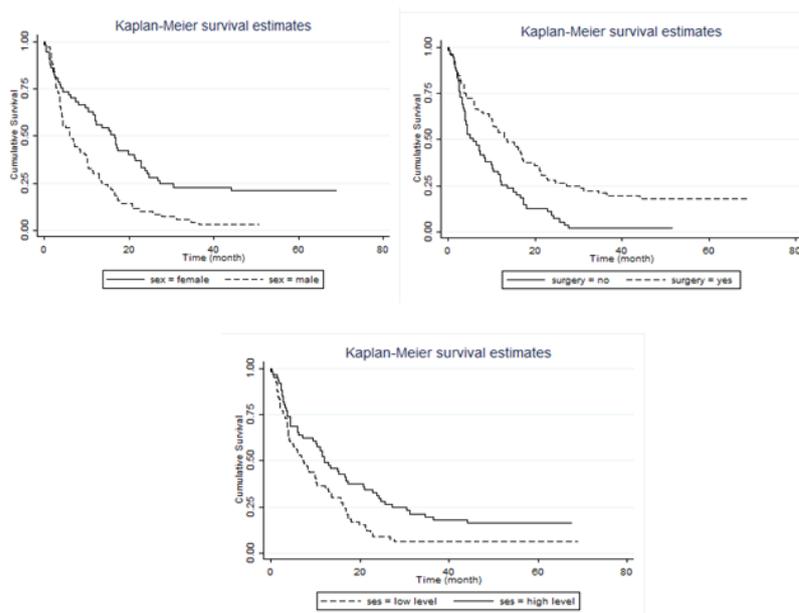


Figure 3. Kaplan-Meier survival curves of best subset variables

Discussion

This study revealed that the survival time after the diagnosis of esophageal cancer is significantly affected by sex, marital status, job status, socioeconomic condition and Esophagectomy surgery. In our sample a high proportion of the patients died by the end of the study. In addition, the mean survival time was less than one year.

The current research demonstrated that a low socioeconomic condition can result in lower probability of survival of esophageal cancer. This might be due to the accessibility to utilities including chemotherapy, hormone therapy, surgery and other treatments. In a study by Louwman *et al.*, the prevalence of life-shortening factors among cancer patients including esophageal with low socioeconomic status was investigated. They showed that cancer patients with a bad SES were more probable to suffer from alternative severe diseases. The negative outcomes after esophageal cancer diagnosis and its link with other diseases are more considerable among those with lower scores of SES (31). Tran *et al.* evaluated the effects of gender, race, socioeconomic status, and treatment on the survival of esophageal cancer patients. They revealed that poor SES is related to less chance of receiving surgery which can lower survival rates (32). In a similar research studies in Iran and India, the relationship between the risk of esophageal squamous cell carcinoma and socioeconomic status was examined and a strong relationship was observed (33, 34).

In our data, males were more likely to die prior to women. This finding can be the result of a more risky lifestyle for men such as smoking and tobacco usage, being an alcoholic, and engaging in poor lifestyle choices. In some studies, it is well discussed that EC is more common among men than women in Asian countries specially in Iran, but in a cross-sectional study Shokri Shrivani *et al.* found that there is no significant difference in gender of patients with esophageal carcinoma (35, 36). Also the impact of gender difference on the survival of patients with esophageal cancer was explored by Bohanes *et al.* it was demonstrated that women have longer survival in both metastatic and locoregional esophageal cancer. The hormonal differences and menopause were the potential reasons for the controversy of the survival rates among the two genders (37). Mathieu *et al.* studied the disparity in esophageal cancer between males and females. Regarding their results, it was established that estrogen is the main preventative factor against the cancer and this protective performance vanishes along with the females approach to Menopause (38).

We showed that Esophagectomy surgery increases the survival time of esophageal cancer. Surgery has been

presented as the best treatment choice for esophageal cancer in early-stage. Moreover, treatments such as chemotherapy and radiation therapy are suggested for the later-stages of cancer in recent studies in Iran (39). In consistence with our result, D'Amico evaluated the consequences after surgery among patients with esophageal cancer. It was shown that chemotherapy after surgery can result in longer survival (40).

In recent years, due to increasing therapies for several types of cancer, the proportion of patients who do not experience the event of interest (cured) are significantly improved (41). The relative survival of patients will reach a plateau for these kinds of disease denoting that the mortality of patients who are cured is the same as expected in the common population (41). Yu *et al.* have proposed that, if there is a proportion of patients who are cured from the event under study, the estimations of classical survival model are biased and failed to converge (42). Since some cancer-related subjects may have long-term survival, cure rate models can be the appropriate method to characterize and study the patients' survival. Mixture and non-mixture are two general forms of cure models and the use of each model depends on the data (43). In order to avoid these potential problems, parametric non-mixture cure model was used in our study.

There were some limitations on the relatively small sample size in our data. Missing data was frequently observed in the patients' records gathered from hospitals and health centers and information about some other potential risk factors were not measured. However, there are lots of other factors related to the lifetime of esophageal cancer such as metastatic status, tumor size, the stage of disease and the certain type of esophageal cancer (adenocarcinoma and squamous). These prognostic factors were not assessed because of the lack of access to the medical records of patients in the East-Azerbaijan cancer registry.

Conclusion

In conclusion, although esophageal cancer is recognized as a malignant disease with a low survival rate, considerable improvement of therapies including surgery and radiotherapy for this cancer have been identified in the recent years. Current study have important clinical and public health implications in Northeastern Iran for monitoring the risk factor and survival time of patient with esophageal cancer. Furthermore, potential risk factors which affect the survival of patients who are not susceptible to the occurrence of the event under study can be determined by clinicians and researchers using appropriate survival analysis. In this study, gender and

Esophagectomy surgery were determined as risk factors that affect both survival and cure fraction of EC patients. Therefore, due to more accurate and more reliable insight into long-term advantages of EC therapy, Weibull Non-mixture cure rate is recommended for analysis of long-term survival of patients with EC. Finally, as a clinical report, this study established 3 risk factor which should be taken into account in the screening, prevention and reduction of esophageal cancer.

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Conflict of Interest

Authors declared no conflict of interests.

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