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Cure mixture model based on hazard modeling non-proportional, application to esophageal cancer

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ABSTRACT

Background & Aim: Esophageal cancer is one of the main common causes of death. The high prevalence of esophageal cancer in northern Iran is an important public health problem. The main aim of this paper was to assess the factors affecting survival of patients with esophageal cancer in neighbor provinces around the Caspian Sea using Weibull mixture cure model and mixture cure model based on a non-proportional hazard.
Methods & Materials: This prospective study was designed to gather data of esophageal cancer from the Babol cancer registry, Iran, registered during 1990 to 1991. The study cases were also followed for a period of 15 years up to 2006. Mixture cure model via non-proportional hazard modeling was used to calculate cure fraction and investigate the factors responsible for the cure probability of patients. Estimates were obtained by maximization of the likelihood via SAS proc NLMIXED.
Results: The median survival time was about 9 months and survival probability in 1, 3, and 5 years following diagnosis were 23%, 15% and 13%, respectively. The family history affected the cured fraction independently of its effect on the early outcome. In addition, it had significant effect on the probability of uncured state in the both models.
Conclusion: The results demonstrated the great potential in cure modeling survival data via non-proportional hazard model compared to Weibull mixture cure model.

Introduction

Cancer has been expected to become the main cause of death in several developed and developing countries including Iran (1-5). Esophageal cancer is the sixth common cause of cancer mortality in the world. The incidence of this disease shows a substantial geographic difference in the world (6).

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Esophageal cancer has a high incidence in areas such as China, Iran, South Africa, Uruguay, France, and Italy (7). Most of the esophageal cancer cases in Iran have been reported from the north and northeast areas of the country. Result from a survey by the Iran Cancer Institution shows 9% of all cancers and 27% of gastrointestinal cancers were esophageal carcinoma. The male to female ratio was 1.7 to 1 (8).

A recent report from Ministry of Health in Iran shows that more than 70% of deaths are caused by cardiovascular diseases, injuries, and cancers so studying the burden of cancers as one

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of the three important causes of death in the country is essential (9).

Esophageal cancer is one of the ten most common diseases worldwide and the five-year survival rate is 3% to 10% (10, 11). Results from several epidemiological studies show that hot drinks, alcohol and tobacco are the main risk factors for esophageal cancer (12-17). Also, geographical distribution is effective in esophageal cancer (18-21).

Highest incidence of esophageal cancer occurs in the age group 50-70 years, also the rate of the disease is higher in men (5, 20, 22). Hypothetically, esophageal cancer may be curable in their primary stages; therefore, early finding is desirable. Survival data are often modeled using a Cox proportional hazards model, which is one of the most popular methods to analyze survival data (23). In short follow-up studies the assumption of a constant risk ratio is very reasonable. However, in long follow-up studies it is more suitable to undertake that time somehow affects the hazard ratios. When the assumption of proportionality is violated then the results from a Cox model are not reliable and other modeling approaches should be considered instead. One approach to model long-term survival studies is through the use of mixture models, known as cure models (24).

In traditional survival analysis, it is assumed that all subjects in the population experience the interested event but in some studies a substantial fraction of the subjects may be long term survivor and never experience the event of interest, if the follow–up period is long enough, thus they can be considered cured. A cure model is a mixed model composed of the cure fraction model and the survival model of non-cured subjects that it estimates both the cure fraction and the survival function for the uncured. Cure model analysis, introduced 50 years ago, is almost better suited to the methodical requirements of clinical research in survival data where cure is attained (25).

In this study a significant fraction of patients was long term survivor or cured and naive use of Cox regression analysis can be misleading in these situations, so cure models were used to analyze our data set. The aim of this paper was to analyze data of a prospective study on cases with esophageal cancer and investigate the proportion of cure patients and to assess the factors influence the survival of the patients with cure models via non-proportional hazard modeling.

Methods

GTDL regression model

MacKenzie in 1996 introduced a new parametric family of survival models based on the logistic function (23). Three models were introduced the proportional hazard (PH) logistic model, the accelerated life model and the time-dependent logistic (TDL) model. Generalized time-dependent logistic (GTDL) model was first introduced in 1996 as an extension of the logistic function to the time dependent form and its application was confirmed a year later (24). The model has a hazard function defined by:

$$\lambda\,(t|x) = \frac{\lambda \exp(t\alpha + x'\beta)}{1+\exp(t\alpha + x'\beta)} \qquad (1)$$

With the parameter $\lambda > 0$. For ($\lambda(t|x)$, the corresponding survival function is:

$$S(t|x) = \{(1 + \exp(t\alpha + x'\beta))/(1 + \exp(x'\beta))\}^{\frac{-\lambda}{\alpha}} \qquad (2)$$

It should be mentioned that the GTDL model, which is essentially non-PH, can also handle the PH data (24).

The cure mixture model via non-proportional hazard modeling

The hazard function introduced in (1) takes the different behavior, according to the value of α for α = 0 hazard function is constant, for $\alpha > 0$, the hazard function is increasing and for α < 0 the hazard function is decreasing and model takes the cure fraction by

$$p = \{1 + \exp(x'\beta\}^{\frac{\lambda}{\alpha}} \qquad (9)$$

As mentioned above, if the population is a mixture of susceptible and non-susceptible individuals, then a cure model can be used to analyze the survival data.

In this study we wish to investigate the factors responsible for the probability of being cured - via the mixture cure model with the logistic link extension on the time dependent model. Let u be the indicator that indicates an individual who will $(u = 1)$ or will no longer $(u = 0)$ experience the event. Denote $\pi\,(X^*) =$

$P(u = 1|X^*)$, is the fraction of uncured patients which depends on the covariate vector $X = (X_1, \ldots . X_q)'$. The $\pi(X^*)$ is associated with the incidence by the logistic form $\pi\,(X^*) = \exp(b'X^*)/(1 + \exp(b'X^*))$. T is the time to event and defined only when $u = 1$ (i.e. for the uncured patients). The T is defined with conditional survival function $S_u(t|u = 1) = P(T > t|u = 1)$ where X^*, is the covariate vector associated with the latency. Then the marginal survival function is:

$$S(t/X,X^*) = [1 - \pi(X^*)]S_u(T/X) + \pi\,(X^*) \quad (10)$$

Replacing the survival function of the susceptible individuals by the time dependent logistic function model leads to the following cure model via non-proportional hazard modeling:

$$S(t|x,x^*) = 1 - \pi e + \pi(x^*)\left\{\frac{1+\exp(t\alpha+x'\beta)}{1+exp(x'\beta)}\right\}^{\frac{-\lambda}{\alpha}} \quad (11)$$

In this study, we used mixture cure model with the logistic link extension on the time dependent logistic model. The covariates to be included in the models are: sex, age, current job, education, province, ethnicity, place of residence, migration status, family history and cigarette smoking. This data set has been analyzed before calculating cure fraction by Rasouli et al. (26).

Estimates were obtained by maximization of the likelihood via SAS proc NLMIXED. For the purpose of comparisons with standard models, the Weibull mixture cure model was considered as a candidate parametric mixture cure model. The R functions implementing the proposed models were provided by the author upon request.

The study was confirmed by the Ethics Committee of Tehran University of Medical Sciences, Iran.

Results

Patients' characteristics are described in table 1. Estimated survival rates in 1, 3, and 5 years following diagnosis were 23%, 15% and 13%, respectively and the estimated percentiles for the survival times in 25%, 50% and 75% were 21.8, 9 and 4.1 months, respectively. During the follow up time, 310 (86.3%) deaths were observed, that 63.2% were men and 36.8% were women, and 49 (13.6%) were still alive.

Table 1. The characteristics of the patients with diagnosed esophageal cancer

Characteristic		Number (%)
Sex	Male	225 (62.7)
	Female	134 (37.3)
Place of residence	Rural	199 (55.4)
	Urban	160 (44.6)
Province	Mazandaran	188 (52.4)
	Golestan	171 (47.6)
Family history of cancer		110 (30.6)
Education	Literate	35 (9.7)
	Illiterate	324 (90.3)
Job	Farmer	186 (51.8)
	Employee	3 (0.85)
	Others	170 (47.35)
Marital status	Married	340 (94.7)
	Single	19 (5.3)
Cigarette smoking		151 (42.1)
Ethnicity	Persian	219 (61.0)
	Gilak	11 (3.1)
	Torkaman	92 (25.6)
	Others	37 (10.3)
Migration status	Native	327 (91.1)
	Non-native	32 (8.9)

Table 2 shows the results obtained (parameters and coefficients estimated) from Weibull mixture cure model and mixture cure model based on non-proportional hazard model with the logistic link, the average cure fraction was estimated to be 0.10 in Weibull mixture cure model and it was estimated to be 0.12 in model based on non-proportional hazard. Estimates and their standard deviations for long and short-term survivors are given in above and below sections of the table 2, respectively.

In the figure 1, the log-log survival plots indicate the rejection of the proportionality assumption for the covariates: gender (a), family history (b), place (c), province (d), job (e), and ethnicity (f), respectively.

However, there are more factors related to the esophageal cancer lifetime such as certain type of esophageal cancer (adenocarcinoma, squamous), stage of disease, tumor size and metastatic status. These factors were not assessed because of the unavailability of the factors in the Babol Cancer Registry and the lack of the access to the medical records of patients.

The results showed that the Weibull mixture cure model produced the higher standard errors for the parameter estimates compared with the model based non-proportional hazard.

Table 2. Parameter estimates of the Weibull mixture cure model and the cure model based on the non-PH model

Short-term survivors		
Parameters	**Weibull mixture cure model [Estimate (SD)]**	**Mixture cure based on non-PH [Estimate (SD)]**
A	-	-0.001 (0.0002)*
λ	-	0.004 (0.001)
α*	5.58 (0.41)*	-
λ*	1.00 (0.04)*	-
Age (years)	-0.002 (0.005)	-0.02 (0.001)
Sex	0.096 (0.16)	0.23 (0.15)
Province	0.46 (0.16)	1.33 (0.12)
Place	-0.12 (0.12)	-0.10 (0.14)
Positive Family history	0.35 (0.13)*	0.82 (0.11)*
Education	-0.39 (0.21)	-0.99 (0.18)*
Cigarette smoking	-0.02 (0.13)	-0.17 (0.34)
Migration	0.29 (0.69)	0.94 (0.22)
Job (farmer)	0.09 (0.15)	0.26 (0.05)
Job (employee)	-0.02 (0.73)	-0.49 (0.36)
Ethnicity (Persian)	-0.31 (0.76)	-1.48 (0.21)
Ethnicity (Gilak)	-1.02 (0.39)*	-0.30 (0.34)*
Ethnicity (Torkaman)	-0.06 (0.24)	0.21 (0.22)
Long-term survivors		
Parameters	**Weibull mixture cure model [Estimate (SD)]**	**Mixture cure based on non-PH [Estimate (SD)]**
Intercept	1.37 (1.19)	1.36 (1.10)
Age (years)	0.01 (0.01)	0.001 (0.02)
Sex	0.003 (0.46)	0.31 (0.47)
Province	-0.3 (0.41)	-0.70 (0.38)
Place	0.54 (0.34)	0.52 (0.23)
Family history	0.96 (0.42)*	0.41 (0.39)*
Education	-0.63 (0.49)	-0.91 (0.24)
Cigarette smoking	0.73 (0.39)*	1.50 (0.37)*
Migration	-0.35 (0.56)	-1.02 (0.49)
Job (farmer)	-0.03 (0.43)	-0.48 (0.43)
Job (employee)	-0.7 (1.31)	-0.84 (0.65)
Ethnicity (Persian)	-0.30 (0.59)	-0.25 (0.17)
Ethnicity (Gilak)	0.43 (1.26)	1.49 (0.02)
Ethnicity (Torkaman)	0.26 (0.69)	0.35 (0.37)
-2Loglikelihood	4520.0	4505.0
AIC	4578.8	4563.0

* Significant level of less than 0.05

SD: Standard deviation; Non-PH: Proportional hazard; AIC: Akaike's information criterion

The family history had a statistically significant effect by the both parts of the fitted model, although the magnitude of the corresponding standard errors was different. Among the long term survivors, this means that the risk of being uncured (i.e. being at risk of experiencing the interested event) increased significantly for patients having positive family history (vs. patients without positive family history of the cancer).

In addition, among short-term survivors, it indicates that desired event (death) was happening faster for the patients with positive family history of the cancer compared with the reference group. So positive family history increased the probability of being uncured and reduced the survival of those people that are uncured.

The cigarette smoking had a significant positive effect in both models for short-term survivors; so, smokers had the higher risk associated with being uncured compared to the non-smokers.

In the Weibull mixture cure model, p-value was borderline but in the cure model based on

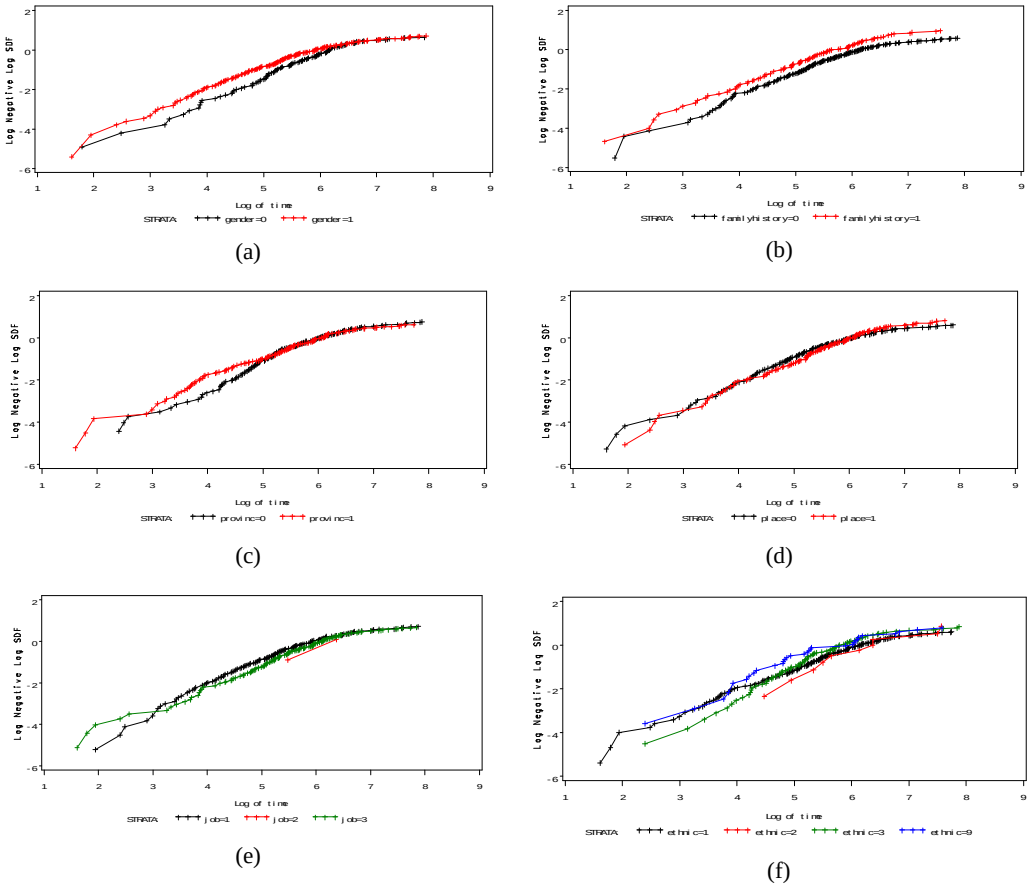

Figure 1. Log-log survival function plots for the covariates: gender (a), family history (b), place (c), province (d), job (e) and ethnicity (f)

non-PH it was nearly 0.01. There was a difference between the ethnicity groups among long term survivors in two models, it is worth mentioning that the risk of being uncured for Gilak patients had the highest odds ratio compared to others and there was evidence of significant effect of this variable.

Assessing the effect of the education among short-term survivors in the cure model based on non-ph showed that the illiterate patients had a higher risk associated with being uncured compared to the literacy patients but this result was not seen in the Weibull mixture cure model.

In the cure model based on non-PH model, the constant coefficient $\hat{\alpha}$ was negative and significant. So, the trend in the hazard was decreasing with the time. According to the Akaike's information criterion (AIC), our results showed that the cure model based on the non-PH model allowing for the time effect was the preferred model. It followed by the mixture Weibull cure model.

Discussion

Most studies have shown that family history for esophageal cancer has a strong association with the disease (27). Result of early study in Iran showed that 47% of 427 Turkmen with esophageal cancer had a positive family history for esophageal cancer. The age of onset for 40% of those with positive family history was younger than 50 years (28, 29). In several case-control studies in Iran done in the high-risk region, odd ratios were reported from 1.8 to 7 for a positive family history (27, 30, 31).

Two recent studies of familial risk in the high-risk area, one of them based on a case

parent study and other based on a cohort study, have estimated more than two-fold increased risk of esophageal cancer among first degree relatives (30, 31).

Compatible with the finding in Iran, studies addressing the familial aggregation in the other areas of the Asian esophageal cancer belt have reported a higher frequency of a positive family history of esophageal cancer among patients living in high-risk regions compared to low-risk regions (32, 33).

Several earlier case-control studies have shown that estimates of the association between smoking and adenocarcinomas of the esophagus and gastric cardia are varied (34-44).

In four case-control studies (34-37) of a combination of adenocarcinomas of the esophagus and gastric cardia, all identified a statistically significant association between cigarette smoking and the disease.

In the literature, there are many studies on the field of cancer that researchers tend to examine the effects of covariates on patients survival using Cox regression model. The Cox model is a very powerful and useful tool for survival analysis. However, if the assumption of proportionality does not hold, the results might be misleading. In a data set with large follow-up period as this one, it is natural to assume that the assumption of proportionality will not hold.

A systematic study on cancer journals showed that only in 5% of studies of cancer in which Cox regression model was used the assumptions of the model have been investigated (45). If the assumptions are not met, results of Cox model are seriously under question. As an alternative, parametric cure model can be employed.

The main aim of the work presented in this paper has been to compare Weibull mixture cure model and mixture cure model based on a non-proportional hazard, and to apply them to esophageal cancer data set. Very little research has been done on non-PH modeling and it is hoped that this model will present for analysis of a wide range of survival data.

Focus was placed on cure mixture model with the non-proportional hazard for survival part of model. Basic properties of the generalized time dependent logistic model have been given by MacKenzie (23, 24) and Blagojevic (46), its key feature being the presence of a time effect measuring parameter.

It appears from the results that the Weibull mixture cure model produced higher standard errors for parameter estimates than the model based on non-proportional hazard. A finding which is perhaps most important for the purposes of this study is that cure model via non-proportional hazard modeling showed much better results, in terms of standard errors, than the Weibull mixture cure model.

One advantage of two models is that they provide a coherent statistical approach to investigate the effect of covariates on the time to failure separately from their effect on ultimate outcome.

As mentioned above $\hat{\alpha}$ is significant and negative, which is a sign of presence cure fraction. The estimated standard errors in the cure models based on non-PH were all increased suggesting that the Weibull mixture cure models under-estimate the dispersion in the data and give over-optimistic results.

Moreover, the cure model based on non-PH had a smaller AIC so appears to be the best model. AIC is one of the most popular and well-studied methods of model information criteria.

In conclusion, if the assumption of proportionality is violated, analysis using a non-PH model is preferred and mixture cure models are useful to investing at the effect of covariates on the time to failure separately from their effect on ultimate outcome.

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