Factors affecting survival of patients with oesophageal cancer: a study using inverse Gaussian frailty models

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INTRODUCTION Oesophageal cancer is one of the most common causes of cancer mortality in developing countries, including Iran. This study aimed to assess factors affecting survival of patients with oesophageal cancer using parametric analysis with frailty models.

METHODS Data on 359 patients with oesophageal cancer was collected from the Babol Cancer Registry for the period 1990–1991. By 2006, the patients had been followed up for a period of 15 years. Hazard ratio was used to interpret the risk of death. To explore factors affecting the survival of patients, log-normal and log-logistic models with frailty were examined. The Akaike Information Criterion (AIC) was used for selecting the best model(s). Cox regression was not suitable for this patient group, as the proportionality assumption of the Cox model was not satisfied by our data ($p = 0.007$).

RESULTS Multivariate analysis according to parametric models showed that family history of cancer might increase the risk of death from cancer significantly. Based on AIC scores, the log-logistic model with inverse Gaussian frailty seemed more appropriate for our data set, and we propose that the model might prove to be a useful statistical model for the survival analysis of patients with oesophageal cancer. The results suggested that gender and family history of cancer were significant predictors of death from cancer.

CONCLUSION Early preventative care for patients with a family history of cancer may be important to decrease the risk of death in patients with oesophageal cancer. Male gender may be associated with a lower risk of death.

Keywords: AIC, inverse Gaussian frailty, oesophageal cancer, survival analysis
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INTRODUCTION

Cancer is one of the most important causes of disorders, death and disabilities worldwide.[1,2] The disease has become more widely known in recent years and receives a considerable amount of healthcare resources.[3] In fact, cancer is estimated to become the leading cause of death in many developed and developing countries, including Iran.[1,4] Oesophageal, stomach and colorectal cancers are the three most common cancers among Iranian people.[5] Worldwide, oesophageal cancer is one of the ten most common diseases, with a five-year survival rate of 3%–10%.[6,7] Several epidemiological studies have shown that hot drinks, alcohol and tobacco are the main risk factors for oesophageal cancer.[8-13] Despite medical advances, the development of cancer treatment and increase in the number of cancer survivors, cancer is unique in terms of the desperation and deep fear that it creates in individuals.[14-16] There is no doubt that the diagnosis of life-threatening diseases such as cancer affects the quality of life of patients in various ways.[17-19]

Oesophageal cancer in Western countries is relatively rare, but it is the eighth most common cancer and the sixth leading cause of cancer-related deaths worldwide.[20] Oesophageal cancer exhibits a geographical distribution,[21-24] with approximately 80% of all cancer patients hailing from developing countries.[21,24] The highest incidence of oesophageal cancer is seen in China, South Africa and the regions north of Central Asia.[21,24] It is also known to dominate the northern regions of Iran.[22,25] The highest incidence of oesophageal cancer occurs in the age group 50–70 years, and it is more frequently seen in men.[4,23,26] Cancer is the third most common cause of death in Iran, accounting for 14% of all mortality. Overall, gastrointestinal cancers account for approximately half (44.4%) of all cancer-related deaths in Iran.[27,28] Unfortunately, patients with oesophageal cancer often seek medical care when the disease is in advanced stages and therefore, often limited or no effective therapies are available for their treatment.[1,28] Theoretically, oesophageal cancer may be treatable in its early stages; therefore, early detection is vital.

The Cox regression model, the most popular model in survival analysis, is based on a modelling approach to the analysis of survival data. The purpose of the model is to simultaneously explore the effects of several explanatory variables on the survival of a patient.[29,30] Similarly, the status of the hazard function may be of medical interest, as it is directly related to the time course of disease. Baseline hazard rate can therefore help in the conception of the common history of the disease by way of hazard rate changes over time.[29,30] Although Cox's semi-parametric model[31] is the most frequently employed regression tool for survival data, fully parametric models[32,33] may offer some advantages. Based on asymptotic results, Efron[34] and Oakes[35] showed that under certain circumstances, parameter estimates by parametric models are more efficient than the Cox model. Selected parametric models such as the Weibull, log-logistic and log-normal models are alternatives to the Cox model.

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For survival analysis, when mortality reaches a peak and then starts to decline, it would be better to use a model with a non-monotonic (hump-shaped) failure rate property. Interestingly, both the log-logistic and log-normal models own this property. On the other hand, the log-logistic distribution achieves a good approximation of log-normal distribution, and is hence preferred to the log-normal model. Furthermore, log-logistic has simpler hazard and survival functions, and thus, when dealing with censored data, it is easier to work with log-logistic than log-normal. Log-logistic also reaches a good approximation of log-normal for all cases except outliers. The aforementioned hazard function pattern was seen in our patient group, where the hazard function increased slowly and then started to decline after a while. For this reason, the Cox, Weibull and exponential models were deemed inappropriate for our data, and the log-logistic model adjudged better, as was verified by the results of our analyses.[36,37]

For the Cox proportional hazard model and the parametric models, individuals with the same values for covariates were assumed to have the same survival function. However, extra heterogeneities that might have existed were not included in the model. It is often important to consider the population as heterogeneous, i.e. a mixture of individuals with different hazards. A frailty model is a random component designed to account for variability due to unobserved individual-level factors, which is otherwise unaccounted for by the other predictors in the model, where the frailty (the random effect) has a multiplicative effect on the baseline hazard function.[37-40] According to Klein and Moeschberger, *"Frailty models are also used in making adjustments for over-dispersion in univariate survival studies. Here, the frailty represents the total effect on survival of the covariates not measured when collecting information on individual subjects. If these effects are ignored, the resulting survival estimates may be misleading. Corrections for this over-dispersion allow for adjustments for other unmeasured important effects. The over-dispersion in this case is indicated by an unobservable multiplicative effect on the hazard, or frailty"*.[37] Since the hazard function cannot be negative, a positive distribution should be considered for frailty distribution. The frailty distributions most often applied are the gamma distribution, inverse Gaussian, log-normal, positive stable distribution, Compound Poisson and a three-parameter distribution (power variance function). Also, due to over-parameterisation and identifiability problems, and because frailty as a random effect indicates the effect of unknown variables, it is necessary to assume that the mean of frailty equals one. This study aimed to estimate the frailty effect of the inverse Gaussian distribution.[29,37-42] We assessed the factors influencing the survival of patients with oesophageal cancer using parametric models with inverse Gaussian frailty.

METHODS

This was a cohort study of 359 patients with oesophageal cancer registered at the Babol Cancer Registry in the period 1990–1991. They had been followed up for a period of 15 years by the year 2006. Pathological diagnosis confirmed that the patients enrolled in the study were at the early stages of the disease. Since all patients were residents of the same region, they were more likely to have availed similar diagnostic and therapeutic facilities during the follow-up period, and therefore, the variable may not have been a significant factor affecting the survival analysis of the patients studied. Due to the special method of analysis used in the study, deaths due to gastrointestinal tract cancer were considered 'events', but deaths due to all other causes were considered 'censored observations'.

Data were sourced mainly from the patient reports of pathology laboratories, hospitals and radiology clinics that also offered samples with cancer progression. Samples were coded under the direct supervision of pathology specialists according to the International Classification of Diseases for Oncology.[43] Sociodemographic and clinical data were obtained through a structured questionnaire and the patients' clinical records. Data on age, gender, ethnicity, marital status, education, occupation, smoking status, place and province of residence, migration status and family history of cancer were entered into parametric regression models (by considering and not considering heterogeneity) for multivariate analysis in order to assess the relationships between the characteristics and prognostic factors for survivors. The study was approved by the Ethics Committee

Table I.Characteristics of patients diagnosed with oesophageal cancer.

Characteristic	No. (%)
Gender	
Men	225 (62.7)
Women	134 (37.3)
Marital status	
Married	340 (94.7)
Single	19 (5.3)
Education	
Literate	35 (9.7)
Illiterate	324 (90.3)
Occupation	
Farmer	186 (51.8)
Employee	3 (0.85)
Others	170 (47.35)
Cigarette smoking	151 (42.1)
Place of residence	
Rural	199 (55.4)
Urban	160 (44.6)
Province	
Mazandaran	188 (52.4)
Golestan	171 (47.6)
Migration status	
Native	327 (91.1)
Non-native	32 (8.9)
Ethnicity	
Aryan	219 (61.0)
Gilak	11 (3.1)
Torkaman	92 (25.6)
Others	37 (10.3)
Family history of cancer	110 (30.6)

Table II. Age-wise survival characteristics of patients with oesophageal cancer.

Group	Mean/Median ± SD (95% CI)	
	Mean* survival rates	Median survival rates
Age group (yrs)		
< 50	33.21 ± 5.18 (23.05–43.38)	9.63 ± 1.46 (6.78–12.49)
51–60	35.09 ± 5.61 (24.10–46.08)	8.13 ± 1.28 (5.63–10.63)
61–70	41.74 ± 6.39 (29.21–54.27)	10.60 ± 1.47 (7.72–13.48)
> 70	13.39 ± 3.32 (6.88–19.91)	4.70 ± 0.95 (2.83–6.57)
Overall	35.10 ± 3.13 (28.97–41.23)	8.97 ± 0.80 (7.39–10.54)

* Estimates were limited to the longest survival time, if it was censored.
SD: standard deviation; CI: confidence interval

Table III. Overview of AIC scores.

Score	Log-likelihood	No. of covariates	AIC	Rank
Without heterogeneity				
Log-normal	−650.33	11	1,326.66	2
Log-logistic	−644.39	11	1,314.78	1
Cox partial likelihood	−1,602.14	11	3,226.29	3
Inverse Gaussian heterogeneity				
Log-normal	−632.99	11	1,293.98	2
Log-logistic	−618.62	11	1,265.24	1
Cox partial likelihood	−1,612.41	11	3,248.82	3

AIC: Akaike Information Criterion

of Tehran University of Medical Sciences, Tehran, Iran. To compare the efficiency of parametric models, the Akaike Information Criterion (AIC),[44] which assesses the goodness of fit of a statistical model, was used. A lower value of AIC suggests a better model, and the AIC of a model may be defined as AIC = − 2 (LL) + 2 (c + a), where, 'LL' is the logarithm of the model likelihood (log-likelihood), 'c' is the number of covariates and 'a', the number of ancillary parameters (e.g. 2 in the case of the log-normal and log-logistic; λ and s).[37] For multivariate analysis, hazard ratio was used to interpret the risk of death in parametric models.[29,37] For statistical analysis, SAS 9.1 (SAS Institue Inc, Cary, NC, USA) and STATA 8.0 (StataCorp, College Station, TX, USA), were used. A p-value < 0.05 was considered to be statistically significant.

RESULTS

Of the 359 patients with oesophageal cancer included in this study, 225 (62.7%) were men and 134 (37.3%), women (Table I). The mean age at diagnosis was 55.23 ± 11.01 years. Table II shows the age-wise survival characteristics of patients with oesophageal cancer. The median survival time reached was about nine months, and estimated survival rates at one, three and five years after diagnosis were 23%, 15% and 13%, respectively. During follow-up, 310 (86.3%) deaths were observed, of which 63.2% were men (n = 196). 49 (13.6%) patients, who were either still alive or detailed as alive (i.e. lost to follow-up), were considered as right-censored observations. Table II shows the mean, median, standard

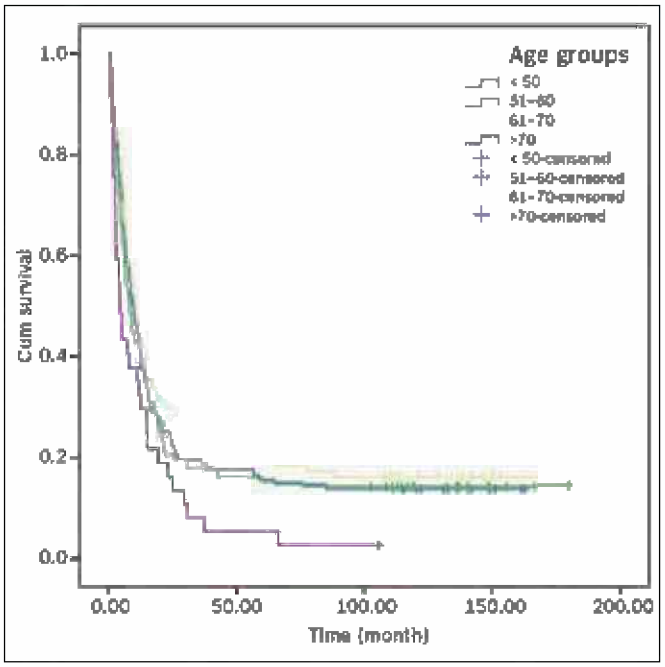

Fig. 1 Comparison of age-wise survival patterns in patients with oesophageal cancer.

deviation and confidence interval for survival time (month) in patients with oesophageal cancer, according to different age groups.

According to the Breslow estimator, the probability value was defined as significant at 0.05 (χ^2 = 8.22, d*f* = 3, p = 0.04) for the various age groups, or that survival functions were different in different age groups (Fig. 1). The AIC, calculated to enable comparison of the various models tested (Table III), showed that the log-logistic model, followed by the log-normal model, attained the best score, indicating that a log-logistic model allowing for inverse Gaussian heterogeneity would be the preferred model for our data set, followed by the log-normal model. Among the parametric models, the log-logistic model with inverse Gaussian frailty fitted data was found to be more appropriate. A review of the residual plots, such as deviance residuals (Fig. 2) and Cox-Snell residuals (Fig. 3), was made to ascertain a better fit of the parametric models. In Fig. 2, the deviance residual was large for short survival times, which then decreased with time. The pattern suggested that the log-logistic model would be better than the log-normal and Cox models. The mean deviance residual of the log-logistic model was also lower than that for the log-normal and Cox models. In Fig. 3, the Cox-Snell residuals (together with their cumulative hazard function) obtained from fitting the various parametric models to our data via maximum likelihood estimation showed that the lines related to the Cox-Snell residuals of the log-normal and log-logistic models with inverse Gaussian frailty were nearest to the line through the origin, again indicating that these models fit the data best. Apart from this, the Cox model did not appear to fit our data well, as the proportional hazards assumption was violated. These results were consistent with our findings based on AIC scores, and consequently, the log-logistic model with inverse Gaussian frailty was deemed more efficient than the log-

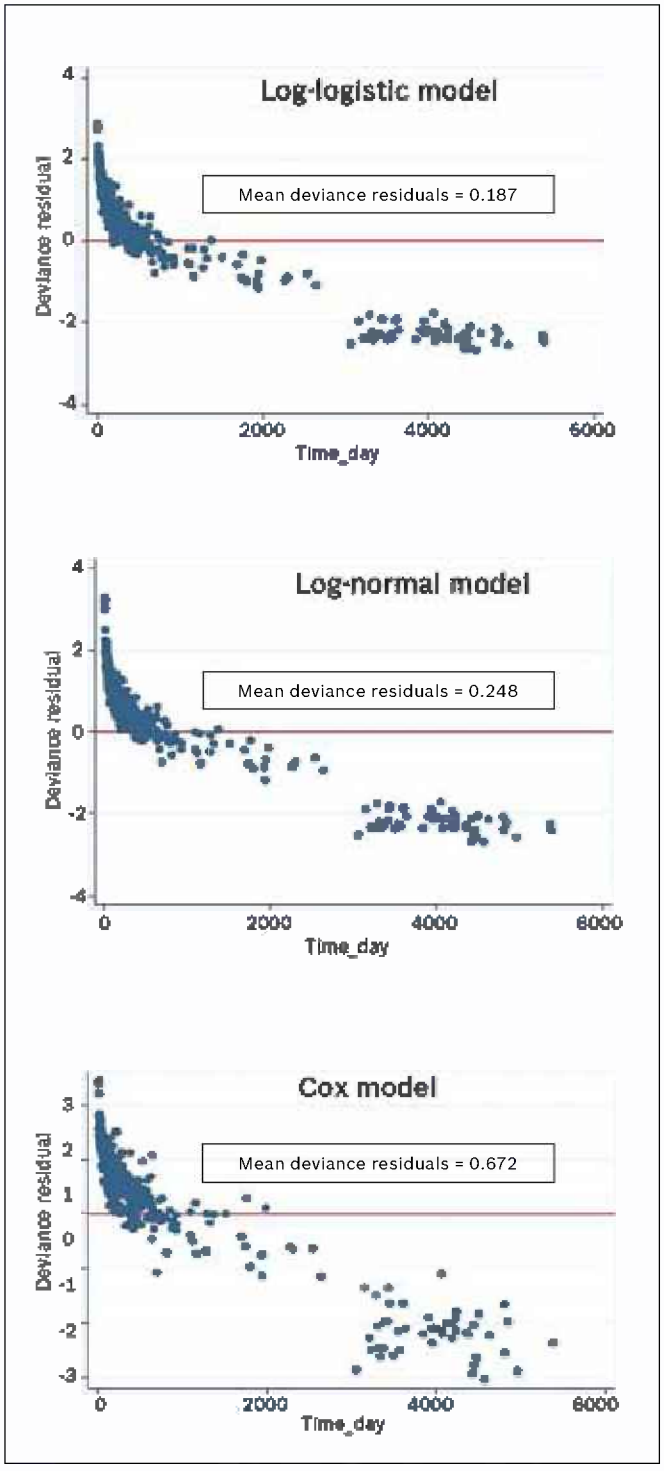

Fig. 2 Deviance residuals to evaluate model fit of parametric models.

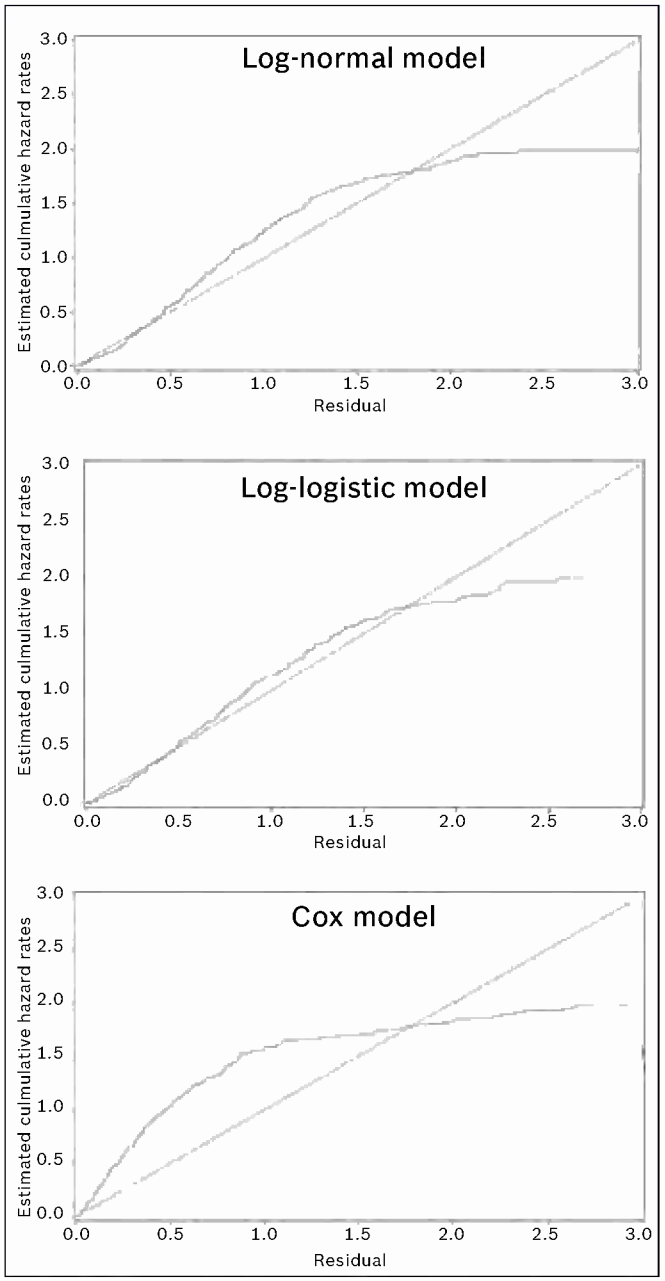

Fig. 3 Cox-Snell residuals obtained from fitting various survival models to the data.

normal model (with and without inverse Gaussian frailty) accordingly.

As was expected, the effects of covariates were biased downwards in the parametric models when not corrected for unobserved heterogeneity in the study population. The inverse Gaussian frailty model was able to account at least in part for this unobserved heterogeneity. Notably, standard deviation also increases in the inverse Gaussian frailty model and the large standard deviation of the frailty variance (σ^2) estimate does not exclude the possibility of no unobserved heterogeneity ($\sigma^2 = 0$).

The results supported our initial assumption that the log-logistic model (with and without inverse Gaussian frailty) represented the estimated parameters and standard deviation better than the log-normal model, and were consistent with our findings based on the analyses of AIC scores and residuals plots earlier. Analyses using both the log-logistic and log-normal with inverse Gaussian frailty models suggested that men were at a higher risk of death due to oesophageal cancer than women. Table IV shows the results of the multivariate analysis of parametric models (with and without frailty) based on HR and confidence intervals for each variable. A significant difference was seen in the results of patients with a family history of cancer in all models.

In this study, gender was a significant factor according to the log-normal and log-logistic with inverse Gaussian frailty models but not the others, which indicates that the risk of death due to oesophageal cancer was significantly reduced for women in

Table IV. Multiple analysis of parametric and Cox regression models with and without inverse Gaussian frailty.

Variable	Cox regression, HR (95% CI)		Log-normal, RR (95% CI)		Log-logistic, RR (95% CI)	
	Without frailty	Inverse Gaussian frailty	Without frailty	Inverse Gaussian frailty	Without frailty	Inverse Gaussian frailty
Age (yrs)	1.003 (0.99–1.01)	1.004 (0.99–1.02)	1.004 (0.99–1.02)	1.001 (0.99–1.02)	1.002 (0.99–1.02)	1.001 (0.99–1.01)
Gender – male	1.15 (0.83–1.60)	1.48 (0.86–2.53)	1.40 (0.86–2.29)	1.69 (1.07–2.64)*	1.40 (0.87–2.25)	1.67 (1.10–2.53)*
Marital status – married	1.15 (0.68–1.95)	1.23 (0.52–2.88)	1.21 (0.55–2.64)	1.06 (0.51–2.21)	1.19 (0.55–2.56)	1.08 (0.57–2.05)
Education – literate	0.75 (0.50–1.11)	0.62 (0.33–1.17)	0.62 (0.34–1.11)	0.68 (0.39–1.17)	0.59 (0.33–1.06)	0.71 (0.42–1.17)
Occupation						
Employee	0.59 (0.14–2.39)	0.28 (0.02–3.18)	0.35 (0.05–2.44)	0.33 (0.06–1.80)	0.39 (0.06–2.77)	0.43 (0.09–1.97)
Others	0.98 (0.73–1.32)	1.07 (0.61–1.88)	1.07 (0.69–1.67)	1.13 (0.75–1.68)	1.04 (0.68–1.58)	1.10 (0.76–1.58)
Smoking status – smoker	1.17 (0.91–1.51)	1.18 (0.78–1.79)	1.17 (0.79–1.73)	0.95 (0.66–1.36)	1.14 (0.78–1.65)	0.94 (0.68–1.31)
Residence – urban	1.05 (0.84–1.33)	1.02 (0.70–1.48)	1.09 (0.77–1.54)	0.95 (0.69–1.31)	1.04 (0.74–1.44)	0.88 (0.66–1.17)
Province – Mazandaran	0.94 (0.74–1.19)	1.04 (0.70–1.54)	1.04 (0.72–1.49)	1.27 (0.91–1.79)	1.06 (0.75–1.50)	1.28 (0.95–1.72)
Migration status – native	0.83 (0.56–1.25)	0.83 (0.42–1.62)	0.90 (0.49–1.65)	1.07 (0.60–1.92)	0.87 (0.48–1.58)	1.00 (0.59–1.70)
Ethnicity						
Gilak	0.89 (0.47–1.70)	0.51 (0.14–1.78)	0.61 (0.21–1.67)	0.41 (0.17–1.03)	0.58 (0.23–1.46)	0.44 (0.20–1.03)
Torkaman	1.40 (0.98–1.99)	1.82 (0.94–3.51)	1.52 (0.90–2.56)	1.30 (0.80–2.10)	1.55 (0.95–2.53)	1.36 (0.92–2.05)
Others	1.38 (0.93–2.05)	1.85 (0.88–3.87)	1.46 (0.82–2.64)	1.32 (0.79–2.25)	1.54 (0.89–2.69)	1.49 (0.94–2.36)
Family history of cancer – positive	1.49 (1.16–1.91)*	1.91 (1.27–2.86)*	1.84 (1.26–2.66)*	1.60 (1.13–2.25)*	1.72 (1.21–2.44)*	1.43 (1.05–1.93)*
σ^2	-	1.74 (0.87)	-	1.16 (0.39)	-	1.36 (0.37)

* $p < 0.05$ was statistically significant.
HR: hazard ratio; RR: relative risk: CI: confidence interval

the study during the follow-up period. Also, the relative risk of 1.67 for gender according to the log-logistic model indicates that events or patient deaths were 67% more frequent in men than in women. Age, place of residence and province, education levels, smoking, occupation, marital status, ethnicity and migration status were not prognostic factors in any of the parametric models.

DISCUSSION

Oesophageal cancer is one of the most common cancers in Iran.[27] It is a particularly devastating cancer, with a relatively low survival rate. The five-year survival rate in this study was 13%, which is lower than that in many other countries.[45-48] This may be due to the fact that Iranian patients generally seek medical treatment late, when the disease has reached an advanced stage, resulting in a delay in diagnosis.

Various studies have reported a number of prognostic factors for oesophageal cancer.[49-58] This study aimed to determine the relationship between the survival of patients with oesophageal cancer and prognostic factors such as age at diagnosis, gender, ethnicity, marital status, education, occupation, smoking status, place and province of residence, migration status and family history of cancer. Gender was a strong and independent prognostic factor on multivariate analysis, similar to other studies that have reported better survival in women, indicating that women with oesophageal cancer had a slightly higher survival rate than men in Northern Iran. Similar findings were also found for patients with oesophageal cancer in European countries.[1,59-61] Family history of cancer was another important prognostic factor for oesophageal cancer in our study. This is similar to other studies that have shown that patient survival is dependent on the presence of family history of cancer.[62,63]

Although there are numerous studies on cancer in the literature, most have examined the effects of covariates on patient survival using the Cox regression model instead of parametric ones. A systematic review of articles in cancer-related journals by Altman et al found that only 5% of studies on cancer that used the Cox regression model had investigated the assumptions of the model.[64] This is significant given that the results of Cox regression are questionable if the presumptions are not met. Parametric models such as log-normal, log-logistic, Weibull and exponential models can be employed as an alternative in such cases. The only assumption of parametric models is that the variable time follows a specific distribution.[30,37] As the proportionality assumption of the Cox model was not satisfied by our data ($p = 0.007$), using Cox regression was deemed unsuitable for this study, especially as the proportionality assumption remained violated even on adding frailty (with inverse Gaussian) to the model.

Statistical assessment of the considered models using AIC scores revealed that the log-logistic model with inverse Gaussian frailty was most appropriate for predicting survival of patients with oesophageal cancer in this study when compared to the other models. Parametric models should preferably be used for good discrimination provided that the censoring percentage does not exceed 40%–50%.[65] The results of parametric models were considered acceptable for our data set, as the above condition was satisfied at a censoring rate of near 14%.

Nardi and Schemper[65] compared the Cox model with alternative parametric models from three clinical studies using normal-deviate residuals[66] for evaluating the assumptions of parametric models. They also studied the Weibull model based on the estimated variation of parameter rate criteria and showed that it was better than the other models.[65] In our study, the same result was established using the log-logistic model with inverse Gaussian frailty. Orbe et al, in a simulation study, compared Cox regression with accelerated failure time (AFT) models[67] using the method proposed by Stute[68] for fitting linear regression models with right-censored data. Their results showed that when the proportional hazards assumption is violated or such an assumption is established, the log-logistic, log-normal and Stute models are more efficient than the Cox model.[67] Bradburn et al evaluated the adequacy type of parametric models and the Cox proportional hazard model using residuals and AIC.[69] In this study on patients with ovarian and lung cancer, a generalised gamma model reached a higher log-likelihood and lower AIC compared to Cox and other parametric models and was therefore deemed as more efficient.[69]

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.[38,70] 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.[38,41,70-72] Vaupel et al were the first to propose frailty in order to describe the consequences of the existence of multiple variation sources for univariate lifetime data.[73]

Random effects models are called frailty models in survival analysis. These models, which are relatively new in survival studies, were widely studied in the 1990s and are now the subject of various investigations. Technical problems in estimating the parameters using the Cox model have caused the model to be used less frequently. Henderson and Oman revealed theoretically that the non-use of frailty models, when there is a frailty effect, may give rise to bias in estimates of regression coefficients.[74] Schumacher et al showed that the deletion of an important factor could reduce RR estimates.[75] Similarly, a report by Keiding et al showed that the removal of one of the two explanatory variables may increase the hazard variance function and cause bias in estimating the other variable in the model. The authors also suggested that in order to account for the effect of unknown variables in univariate survival data, it may be better to use AFT models.[76]

The study was, however, not without limitations. A key limitation of the survey was the absence of clinical variables, including information on the type of oesophageal cancer and stage of disease. Such clinical data was not available in the Babol Cancer Registry and the authors were unable to access the medical records of the patients. Future studies with a larger sample size and a more complete data set are therefore called for to address the gaps in the current know-how on factors affecting survival in patients with oesophageal cancer.

In conclusion, we found that gender and family history of cancer were significant factors for survival in patients with oesophageal cancer. Early recognition of family history of cancer and awareness among family members regarding family screening may help to decrease death rates due to oesophageal cancer. Regular public and professional education is required to increase the awareness of hereditary oesophageal cancer and the importance of family screening, as well as to promote early diagnosis and treatment. We also recommend the institution of psychosocial support for such at-risk patients and their families as well as the promotion of preventive lifestyle and dietary intervention. A comparison of parametric models for our data set also indicated that the log-logistic model with inverse Gaussian frailty could be a useful tool for the statistical analysis of prognostic factors in patients with oesophageal cancer.

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