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Original Article

Survey of Patients with Cervical Cancer in Hospital Universiti Sains Malaysia: Survival Data Analysis with Time-Dependent Covariate

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Abstract

Background: Cervical cancer is the third most common cancer among women in Malaysia. The objective of this study was to estimate the effect of explanatory variables on survival time of cervical cancer patients receiving treatment at a hospital in Malaysia.

Methods: In this retrospective record review study, cervical cancer data obtained from Hospital Universiti Sains Malaysia (HUSM) was analysed. The data comprises of 120 patients who had been diagnosed as cervical cancer between 1st July 1995 and 30th June 2007, and obtained treatment from the hospital. The outcome variable was survival time (in months) from cervical cancer diagnosis to death. A stratified Weibull model was applied to study the effect of explanatory variable on survival time when there was time-dependent covariate in the model.

Results: Stage of disease and metastases were important prognostic variables. However, metastasis had been stratified because this variable did not satisfy the proportional hazard assumption. In without metastasis stratum, patients who were diagnosed at stage III & IV are at 2.30 times the risk of death as those in stage I & II. Meanwhile, in with metastasis stratum, patients in stage III & IV group had 3.53 times the hazard faced by patients in stage I & II.

Conclusion: The prognosis of cervical cancer patients was dependent upon the stage at diagnosis, after the stratification of the metastasis variable. A poorer prognosis on survival was observed for patients in stage III & IV than those in stage I & II.

Keywords: Cervical cancer, Prognostic factor, Survival, Time-dependent covariate, Weibull

Introduction

Cervical cancer is the third most common cancer after breast and colorectal cancer and the fourth leading cause of death among women in Malaysia (1-3). It remains to be one of the major cancers that burden worldwide particularly in under-developed and developing countries (4-5). In Malaysia, the incidence rate of 12.2 per 100,000 in 2006 was higher compared to other developed countries such as Australia and USA (6). Cervical cancer incidence rate increased with age after 30 years and has its peak at ages 65-69 years. According to ethnicity in Malaysia, women of Indian ethnic

group have the highest incidence for cervical cancer followed by Chinese and Malay (3). Majority Malays are Muslims, thus lower incidence of this cancer was observed. In Iran, the incidence of cervical cancer is remarkably low since the dominant residents are Muslims. There are almost no extramarital sexual relations and they depend strongly on family-based traditions (7).

The survival rate of cervical cancer patients may vary by country. The five-year survival exceeded 70% in Korea (8-10), 55% in Turkey (11) and it can be as low as 17% which was in Uganda (12). There were various prognostic factors established in many studies such as stage, age, lymph node involvement and tumor size (13-16). In Kentucky, between January 2001 and May 2010, a study of 381 cervical cancer patients who were referred to tertiary care centre found that stage of disease was a significant prognostic factor for overall survival (17). Meanwhile, a study of 44,182 patients diagnosed with cervical cancer between 1993 and 2002 in Korea, found that both stage and histological type of cervical cancer were important factors for survival (18).

To our knowledge, studies on survival of cervical cancer patients in Malaysia are somewhat limited. The analysis from published studies was often limited to the frequently used Cox proportional hazard regression model when examining the relationship of the survival distribution to covariates (17, 19-21). This is perhaps due to the fact that although baseline hazard is not specified in Cox model, the parameter can still be estimated. The objective of this study was to determine the effects of explanatory variables on the survival of cervical cancer patients using parametric regression model. In some cases, parametric models are more informative than the Cox model such as the baseline hazard and survival estimates are known (can be estimated). Several examples of parametric models can be found in the following studies (22-27). Zhu et al. have compared the Cox and Weibull model in modeling the gastric cancer data and found that the Weibull model gave more a precise results in than the Cox model (28). The Weibull model has gained popularity in modeling survival data due to its flexibility in the shape parameter that can accommodate a decreasing, constant and increasing hazard. Furthermore, the suitability of the Weibull model can be easily assessed using a log-cumulative hazard plot.

In this study, a stratified Weibull model was used since there was a time-dependent covariate that caused the proportional hazard assumption violated.

Materials and Methods

The study design was retrospective in nature in which patients' records were reviewed retrospectively to obtain the data. The cervical cancer data was taken from *Hospital Universiti Sains Malaysia* (HUSM). The HUSM, located in Kubang Kerian, Kelantan has been long regarded as the referral centre for the East Coast region of Malaysia. The inclusion criteria were histopathologically and clinically diagnosed with cancer of cervix between 1st July 1995 and 30th June 2007, and received at least one treatment related to cervical cancer in HUSM. Patients who were died due to other competing causes of death (not cervical cancer), or with incomplete data were excluded from this study. One hundred and twenty patients who have fulfilled the inclusion criteria were identified. Ethical clearance was obtained from research and ethics committee of University Sains Malaysia (reference number: USMKK/PPP/JEPeM [205.4 (2.4)]).

The variable of interest was time (in months) which was measured from the patient was diagnosed with cervical cancer up to the time of death. Factors that were considered in the analysis were ethnicity (non Malay, Malay), lymph node involvement (negative, positive), metastasis (with metastasis, without metastasis), histology (squamous cell carcinoma, adeno cell carcinoma), primary treatment (surgery, radiotherapy and/or chemotherapy), age at diagnosis (<40, $40 - 59$, ≥ 60) and stage (stage I & II, stage III & IV). International Federation of Gynecology and Obstetrics (FIGO) system was used in staging patients with cervical cancer. Data analysis was performed using the statistical package TIBCO Spotfire S-Plus ver-

sion 8.1. The suitability of the Weibull model for the data was assessed using a plot of the log of the negative log of the estimated survivor function against log time or log-cumulative hazard plot. Univariate analysis was conducted using the simple Weibull regre-ssion analysis to identify the possible prognostic factors individually. Significant factors from the univariate analysis were further analyzed by the Weibull multivariate analysis to model the prognostic factors. Model selection procedure was based on the forward variable selection method with statistical significance set at $\alpha = 0.10$. The proportionality of the hazards was assessed using the test based on Schoenfeld (29). As the proportional hazard assumption was not satisfied, a stratified model was used instead (30) and in measuring the goodness of fit of the model, deviance residuals were used. Fig. 1 shows a study flow diagram which summarizes the steps of the statistical analysis performed.

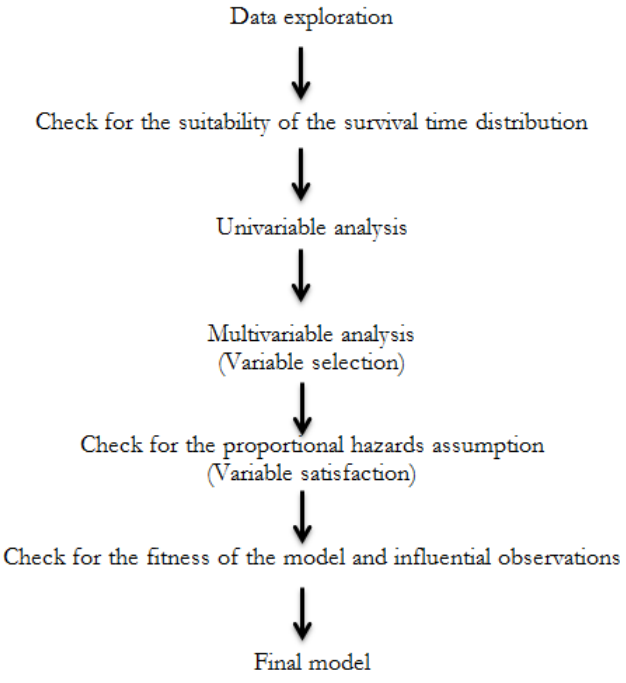

Fig. 1: The study flow diagram

Results

The log-cumulative hazard plot shows a straight line which suggests that the distribution of survival time considered follows Weibull distribution (Fig. 2). Patients' characteristics and the incidence rate ratio were tabulated in Table 1. About 74% of total patients were presented at stage I & II. The ratio of the risk of death for patients who were diagnosed in stage III & IV compared to the risk of death for patients in group stage I & II was 1.44. Meanwhile, the risk of dying of patients in with metastasis group was 1.55, greater than patients who had no metastasis.

The results from the univariate analysis are presented in Table 2. From this analysis, three factors were statistically significant namely, stage, metastasis and primary treatment. Based on the forward selection procedure in multivariate analysis, two variables namely stage and metastasis was found to be significant factors (Table 3). However, it was noted that metastasis (P=0.032) did not satisfy the proportional hazard assumption and a stratified model was then considered. It is worthwhile to note that while the stratification allows separate baseline hazard function to each metastasis group, the coefficient of the predictor variables are assumed to be the same within each metastasis group (29). The first stratum consists of patients without metastasis and the second stratum were patients who do have metastasis. Parameter estimates of the stratified model were performed and the output is given in Table 4.

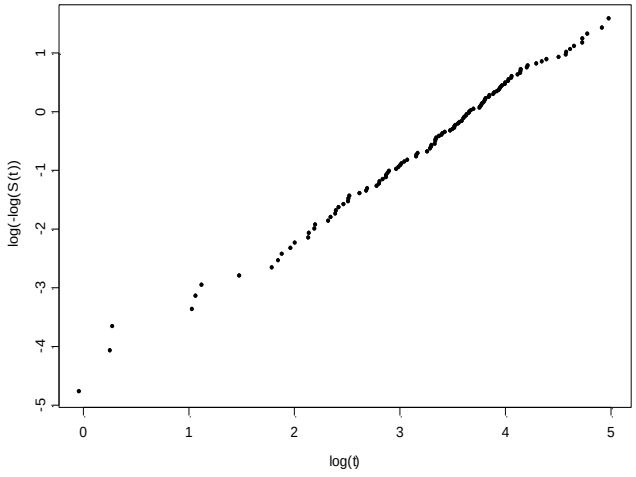

Fig. 2: The log-cumulative hazard plot

Table 1: Characteristics of patients treated in HUSM (n=120)

Variables	No. of patients	Percentage (%)	Incidence rate ratio
Ethnicity			
Non malay	21	17.5	
Malay	99	82.5	1.19
Lymph node involvement			
Negative	89	74.2	
Positive	31	25.8	0.92
Metastasis			
without metastasis	83	69.2	
with metastasis	37	30.8	1.55
Histologic type			
Squamous cell carcinoma	93	77.5	
Adeno cell carcinoma	27	22.5	1.29
Age at diagnosis			
< 40	2	1.7	
40-59	97	80.8	0.56
≥ 60	21	17.5	0.48
Stage			
I & II	89	74.2	
III & IV	31	25.8	1.44
Primary Treatment			
Surgery	40	33.3	
Radiotherapy and/or chemotherapy	80	66.7	1.33

Table 2: Univariate analysis of Weibull model with prognostic factors

Variables	Coefficient (β)	χ^2	Degree of freedom	*P*-value
Ethnicity				
Non malay				
Malay	-0.205	0.34	1	0.560
Lymph node involvement				
Negative				
Positive	-0.130	0.21	1	0.650
Metastasis				
without metastasis				
with metastasis	0.731	7.82	1	0.005
Histologic type				
Squamous cell carcinoma				
Adeno cell carcinoma	0.384	1.81	1	0.180
Stage				
I & II				
III & IV	0.934	10.92	1	<0.001
Primary Treatment				
Surgery				
Radiotherapy and/or chemotherapy	0.827	9.38	1	0.009
Age at diagnosis				
<40				
40-59	-0.810			
≥ 60	-0.831	1.01	2	0.600

Table 3: Multivariate analysis of Weibull model with prognostic factors

Variables	Coefficient (β)	χ^2	Degree of freedom	*P*-value
Metastasis				
without metastasis				
with metastasis	0.892	-	-	-
Stage				
I & II				
III & IV	0.686	17.8	2	<0.001

Table 4: Output of Weibull model under stratification

Variable	Value	Std. Error	z	*P*-value
(Intercept)	4.386	0.158	27.685	<0.0001
Stage	-0.924	0.244	-3.793	0.0002

Table 5: The hazard ratio for variable stage stratified on metastasis

Stratum	Coefficient (β)	Hazard ratio, (ψ)
1 = without metastasis	0.832	2.30
2 = with metastasis	1.261	3.53

The estimated scale parameters (σ) for the first and second stratum were $\sigma_1 = 1.11$ and $\sigma_2 = 0.733$ respectively. The risks of death for cervical cancer patients were estimated by finding the regression coefficient (β_j)

$$\beta_j = -\frac{\alpha}{\sigma_j},$$

and the hazard ratio (ψ_j)

$$\psi_j = exp(\beta_j)$$

where $j = 1, 2$ denotes the stratum. The estimated coefficient α was obtained from the analysis which was equal to -0.924. The result is shown in Table 5. For the first stratum, patients who were diagnosed at stage III & IV are at 2.30 times the risk of death as those in stage I & II. Meanwhile, for the second stratum, patients in stage III & IV group were more likely to die (3.53 times) than patients in stage I & II. The index plot of deviance residuals (r_{D_i}) was performed to identify the presence of subjects who was poorly predicted by the model (31). The plot as given in Fig. 3 shows that the residuals are roughly symmetrically distributed around zero and most of the residuals are between -2 to 2. Outliers and influential observations are not observed in the plot thus implying a good fit of the model.

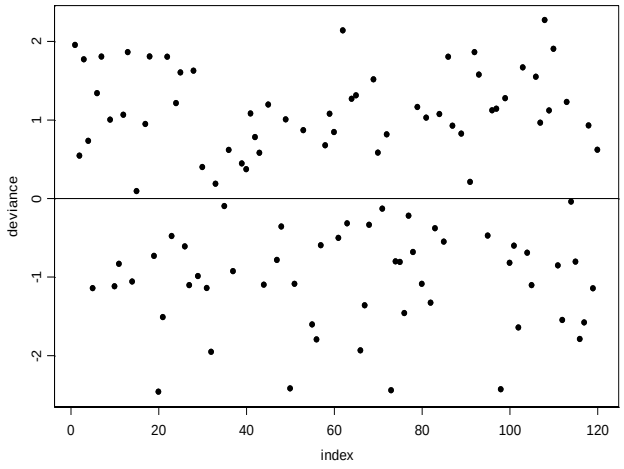

Fig. 3: Deviance residual for the stratified Weibull model

Discussion

In this study, the Weibull model was used instead of the Cox model because the log-cumulative hazard plot has confirmed that the survival time followed the Weibull distribution. Multivariate analysis through forward selection method found that the most feasible model to describe the survival of cervical cancer patients was dependent upon the covariates namely, stage and metastasis. As the metastasis variable did not meet the proportional hazard assumption, the stratified Weibull model was applied. The model was stratified into two strata according to the metastasis variable.

This study found that patients who were diagnosed at stage III & IV have greater risk of death compared to those who were diagnosed at early stage, stage I & II for both stratum, with and without metastasis. It is worthwhile to note that a study of 515 cervical cancer patients by Dueñas-González et al. showed a significant result for advance stage III & IV with adjusted hazard ratio of 1.54 (95% CI= 1.11- 2.14) (16), indicating that patients with advanced stage of disease had a 54% higher risk of progression or death at any time than earlier stage patients. Similar findings were also obtained by other studies (19, 32-34).

Conclusion

After applying the stratified model, this study found that the prognosis of cervical cancer patients was dependent upon the stage at diagnosis. These findings provide useful knowledge on the understanding of the survival of cervical cancer patients. Besides, this study also demonstrates the solution to time-dependent covariates problem, or when the proportional hazards assumption is violated. The limitation of this study was the use of a hospital-based data. Cervical cancer dataset that comprise of the national data may be obtained to give a more general prognosis and a better description of the survival pattern of all cervical cancer patients in Malaysia. Further works can be done to investigate the interaction between covariates, if any.

Ethical considerations

Ethical issues (Including plagiarism, Informed Consent, misconduct, data fabrication and/or falsification, double publication and/or submission, redundancy, etc) have been completely observed by the authors.

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