

Survival Study and Prognostic Factors of Ovarian Cancer Registered in a Teaching Hospital in Malaysia (Kajian Mengenai Kelangsungan Hidup dan Faktor Prognostik bagi Kanser Ovari yang Berdaftar di Hospital Pelatih Perubatan di Malaysia)

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ABSTRACT

Ovarian cancer is one of the highest causes of death among female population in Malaysia. A retrospective cohort study among 127 ovarian cancer patients registered in one of the teaching hospital in Malaysia was conducted from 1st January 2002 until 31st December 2011. The objective of this study was to determine the median survival time, five year survival probability and prognostic factors of ovarian cancer patients. Only ovarian cancer patients were selected with strict inclusion and exclusion criteria. Data was analyzed using Kaplan-Meier Survival analysis and Cox proportional hazard regression analysis. The results showed that the overall five-year survival probability of ovarian cancer was 35.2% (95%CI: 26.3, 44.3) with 38 month (95%CI: 25.7, 50.1) median survival time. After adjustment for potential cofounder, significant prognostic factors of ovarian cancer were observed in FIGO stage (HR: 2.53; 1.44, 4.45), loss of appetite (HR: 1.95; 1.23, 3.11) and presence of pleural effusion (HR: 1.98; 1.19, 3.30). Overall, the survival probabilities of ovarian cancer were low and further actions must be taken to improve the survival among advanced cancer patients

Keywords: Median survival time; ovarian cancer; prognostic factors; survival probability

ABSTRAK

Kanser ovari merupakan salah satu penyebab utama yang membawa kepada kematian dalam kalangan populasi wanita di Malaysia. Satu kajian kohort retrospektif dalam kalangan 127 orang pesakit kanser ovari yang berdaftar di salah sebuah hospital pelatih perubatan di Malaysia telah dijalankan dari 1 Januari 2002 sehingga 31 Disember 2011. Objektif kajian ini adalah untuk mengkaji mengenai tempoh median kelangsungan hidup, keberangkalian kelangsungan hidup untuk lima tahun dan faktor prognostik bagi pesakit kanser ovari. Hanya pesakit kanser ovari dipilih berdasarkan kriteria rangkuman dan penyisihan yang ketat. Data kajian ini dianalisis menggunakan analisis 'Kaplan-Meier Survival' dan analisis regresi bahaya berkadaran Cox. Hasil kajian ini menunjukkan bahawa keseluruhan lima tahun keberangkalian kelangsungan hidup bagi pesakit kanser ovari adalah 35.2% (95%SK: 26.3, 44.3) dengan median kelangsungan hidup selama 38 bulan (95%SK: 25.7, 50.1). Selepas penyesuaian untuk potensi pengasas bersama, faktor prognostik bererti kanser ovari telah diperhatikan pada tahap FIGO (NB: 2.53; 1.44, 4.45), kurang selera makan (HR: 1.95; 1.23, 3.11) dan kehadiran pleural efusi (NB: 1.98; 1.19, 3.30). Secara keseluruhannya, keberangkalian kelangsungan hidup bagi pesakit kanser ovari di Malaysia adalah rendah dan tindakan selanjutnya mesti dilakukan untuk meningkatkan kelangsungan hidup dalam kalangan pesakit kanser kronik.

Kata kunci: Faktor prognostik; kanser ovari; keberangkalian kelangsungan hidup; median kelangsungan hidup

INTRODUCTION

Ovarian cancer is a commonly diagnosed and a deadly gynaecological malignancy worldwide. This type of cancer is ranked as the top ten diagnosed cancer and deadliest cancer among women in the world. It is estimated that a total of 238,700 new cases of ovarian cancer have been reported worldwide in 2012. Based on this 2012 report, 99,800 of new cases were reported in more developed regions, 139,000 of the cases being reported in less developed regions and 111,900 of the cases have been reported in Asia (Ferlay et al. 2015).

In 2007, ovarian cancer is the fourth most common cancer among female in Malaysia with a total of 656 cases

been diagnosed. It ranked as the third most common cancer among female in Kelantan with a total of 40 cases were diagnosed during the same year (Zainal Ariffin & Nor Saleha 2011) (Table 1).

The five year survival rate varies greatly across the country. The patients in developed country reported higher five year survival rate compared with those in developing country. For example, a developed country such as Singapore reported higher five year survival rate (62%) compared to a developing country such as Thailand with 47% five year survival rate. This situation showed that high advancement in medical services and availability of diagnostic facilities may lead to a better survival rate (Wong et al. 2012).

Ovarian cancer is well known as a ‘silent killer’ disease. The disease is usually asymptomatic during early stage causes more than two third of the patients only been diagnosed during advanced stage where the chances of cure is poorer compared to less advanced stage cancer (Goff et al. 2004; Ozols 2005). One study by Bankhead et al. (2005) found that most patients were facing difficulty to identify the symptoms of ovarian cancer; They had mistakenly assuming the symptoms as a normal changes in the body due to the effect of child bearing, menopause or ageing (Bankhead et al. 2005).

The prognostic factors of ovarian cancer were varies across different study. Some report have found out that younger women with early stage ovarian cancer and better differentiated tumours had higher survival probability compared to older women. However, other study had found out that age was not the independent prognostic factor after adjusting for other variables such as stage and grade of disease (Chan et al. 2008).

Since there is inconsistent prognostic factor of ovarian cancer across different study, this study was conducted to identify the real prognostic factors of ovarian cancer after adjusting for potential cofounders. The aim of this study was to determine the median survival time, five year survival probability and the prognostic factor of ovarian cancer. This study was conducted in Malaysian population, with different ethnic group where the cultural, geographical, belief and lifestyle here are different with other country in the world. Thus, the results from this study were expected to give some positive impact to reduce mortality rate among patients with ovarian cancer in Malaysia.

METHODS

STUDY DESIGN AND PARTICIPANTS

This study was a retrospective cohort study using patient record review. All ovarian cancer patients registered in one of the teaching hospital in Malaysia (Hospital Universiti Sains Malaysia) from 1st January 2002 until 31st December 2011 were recruited in the study. There was an additional one year follow-up period after the recruitment phase to determine patients’ survival status especially for those who were recruited at the end of study.

Sample size was calculated using PS Power software. The reference to calculate the sample size was referred from a study by Tingulstad et al. (2003) using the size of residual disease variable. The calculated sample size in this study was 141 patients. However, only 127 patients were selected after considering the inclusion and exclusion criteria (Figure 1). Since the sample size obtained was less than the calculated sample size, no sampling method was applied. An ethical approval was obtained from the Human Research Ethics Committee Universiti Sains Malaysia and the permission to review patients’ folder was approved by Deputy Chairman, Human Research Ethics Committee from Hospital Universiti Sains Malaysia (reference number : USM/JEPeM/276.3.(8)).

STATISTICAL ANALYSIS

Data was analysed using Descriptive Analysis to summarize, organize and simplify the data. The frequency, percentage, mean and standard deviation for demographic background of the patients were summarized using this analysis.

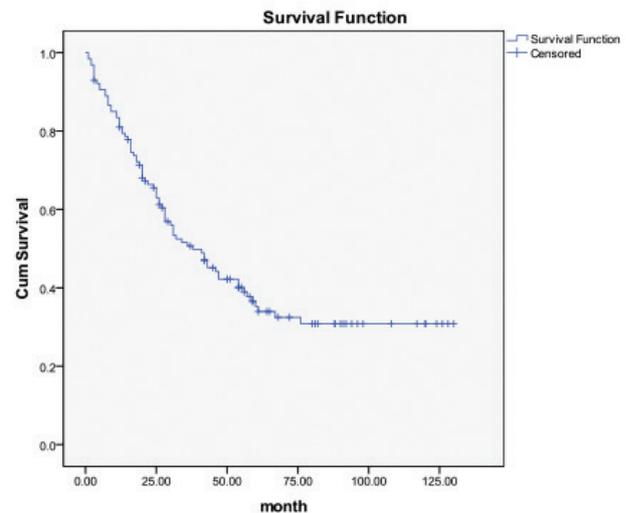


FIGURE 1. Kaplan-Meier survival estimate among ovarian cancer patients in Hospital USM with 49 censored observation ($n=127$)

TABLE 1. Incidence of ovarian cancer

Region	Year	Rank of cancer among female	Number of cases	Age standardized rate per 100,000 women (Incidence)
World	2012	8	238,719	6.1
More developed regions	2012	6	99,752	9.2
Less developed regions	2012	9	138,967	5.0
Asia	2012	9	111,887	5.0
Malaysia	2007	4	656	5.9
Kelantan	2007	3	40	6.6

(Ferlay et al. 2014; Zainal Ariffin & Nor Saleha 2011)

The Kaplan-Meier Survival Analysis was used to determine the overall 5-years survival probability and median survival time of ovarian cancer. The Cox Proportional Hazard Regression analysis was used to identify the prognostic factor of ovarian cancer (Table 2).

RESULTS

SOCIO-DEMOGRAPHIC OF THE SUBJECTS

There were 127 patients' medical records included in this study after considering the inclusion and exclusion criteria. The main endpoint of this study was death among 78 (61.4%) patients while other 49 (38.6%) patients were censored observations. Censored observations were patients who are still survive at the end of maximum follow up period, died due to other causes and lost to follow-up. The overall mean age was 47.8 (SD 15.5) years with majority of the patients were Malay (89.0%) compared to non-Malay (11.0%). Majority of the patients were married (59.8%), some were divorced/widow (16.5%) and single (23.6%).

MEDIAN SURVIVAL TIME AND FIVE YEAR SURVIVAL PROBABILITY

The cumulative survival probability curve for 127 patients with ovarian cancer registered in Hospital University Sains Malaysia (HUSM) from January 2002 until December 2011 is shown by Kaplan-Meier curve with median survival time was 38 month (95%CI: 25.7,50.1) and five year survival probability was 35.2% (95%CI: 26.3,44.3).

PROGNOSTIC FACTORS OF OVARIAN CANCER

The variables that were selected in this study were categorized into three main categories that are patient-related characteristics, disease-related characteristics and treatment-related characteristics. From Simple Cox Proportional Hazard Regression Analysis, four variables from patient-related characteristics, seventeen variables from disease-related characteristics and three variables from treatment-related characteristics had significant value less than 0.25 and were considered as potential prognostic

factors (Table 3). These variables were then analysed with Multiple Cox Proportional Hazard Regression Analysis to confirm the prognostic factor of the study.

Three significant prognostic factors for ovarian cancer found were stage at diagnosis, loss of appetite and presence of pleural effusion. The findings are as follow: Ovarian cancer patients who were in advanced stage during diagnosis are 2.53 times higher risk (HR: 2.53; 95% CI: 1.44, 4.45) to die from ovarian cancer compared with those in early stage cancer during diagnosis; Ovarian cancer patients who had symptom loss of appetite before the diagnosis of ovarian cancer are 95% higher risk (HR: 1.95; 1.23, 3.11) to die from ovarian cancer compared with those who did not experience loss of appetite; and Ovarian cancer patients who had pleural effusion were 98% higher risk (HR: 1.98; 1.19, 3.30) to die from ovarian cancer compared with those who did not had pleural effusion (Table 4).

The assumption checking was done, showed that there was no possible interaction and correlation present between significant variables. The powerful assumption checking was done by global test showed a non-significant result ($p=0.325$). This showed that the proportional hazard assumption for survival analysis was met. The result from global test showed that hazard is proportional over time and hazard ratio is constant over time.

DISCUSSION

The result from current study showed that the overall five year survival probability was 35.2% with median survival time 38 months. This findings were almost similar with previous study that was conducted among 480 incident cases of ovarian cancer in Norway with five-year survival probability of 39% and another study among 3482 women with epithelial ovarian cancer treated in general hospital in Netherland also showed five-year survival probability of 38% (Tingulstad et al. 2003; Vernooij et al. 2008). Nicholson et al. (1998) concluded that in general the overall five-year survival probability of ovarian cancer was around 30%.

In this study, cancer stage showed a significant value with the hazard ratio of 2.53. As compared with other studies, this study showed a lower hazard ratio. A study from Wong et al. (2012) in Hong Kong found that the hazard ratio increase to 9.7 for stage four ovarian cancer

TABLE 2. Five year survival rate of ovarian cancer patients in some population based series

Population	Period of diagnosis	% 5-year survival rate(95% CI)
Hong Kong	1997-2006	53.1 (60.8,65.5)
Singapore	1993-1997	62
South Korea	1993-2001	59(52-64)
Turkey	1995-1997	60
Thailand	1990-2000	47(45-58)
India	1990-2000	25(19-29)

(Wong et al. 2012)

TABLE 3. Prognostic factors of ovarian cancer in Hospital USM by simple Cox regression

Covariate	b ^a	Crude HR ^b (95%CI)	Wald Statistic	p-value
Age	0.02	1.02(1.00,1.03)	5.02	0.022
Marital status				
Married	0	1		
Divorce/widow	0.35	1.41(0.80,2.50)	1.42	0.234
Single	-3.1	0.74(0.41,1.32)	1.07	0.301
Number of gravida	0.09	1.09(1.02,1.17)	6.18	0.013
Occupation				
Student	0	1		
Employed	1.28	3.61(1.44,9.00)	7.54	0.006
Housewife/unemployed	1.47	4.33(1.57,11.96)	8.00	0.005
Stage at diagnosis				
Early stage	0	1		
Advanced stage	1.2	3.32(1.95,5.66)	19.42	<0.001
Laterality				
Left	0	1		
Right	-0.58	5.60(0.32,0.98)	4.11	0.043
Bilateral	0.12	1.13(0.65,1.98)	0.19	0.666
Unknown	-0.49	0.61(0.14,2.61)	0.44	0.508
Consistency				
Cystic	0	1		
Firm	-0.00	0.99(0.53,1.88)	0	0.992
Hard	0.47	1.60(0.84,3.07)	2.01	0.157
Unknown	-0.20	0.82(0.39,2.74)	0.26	0.610
Ultrasound Findings				
Cystic	0	1		
Solid	0.35	1.42(0.61,3.28)	0.67	0.415
Mixed	0.95	2.58(1.29,5.15)	7.25	0.007
Unknown	1.07	2.92(1.15,7.45)	5.05	0.025
CA125				
Normal	0	1		
Raised	0.93	2.51(1.35,4.66)	8.42	0.004
Lost of appetite				
No	0	1		
Yes	0.90	2.45(1.56,3.84)	15.14	<0.001
Lost of weight				
No	0	1		
Yes	0.60	1.83(1.17,2.85)	7.00	0.008
Lethargy				
No	0	1		
Yes	0.99	2.30(1.33,5.48)	7.53	0.006
Ascites				
No	0	1		
Yes	0.66	1.94(1.22,3.09)	7.87	0.005
Pleural effusion				
No	0	1		
Yes	1.16	3.19(1.98,5.16)	22.55	<0.001
Abdominal mass				
No	0	1		
Yes	-0.53	0.59(0.38,0.92)	5.32	0.021
Uterus				
No	0	1		
Yes	0.50	1.65(0.89,3.05)	2.52	0.113

(continue)

Continued (TABLE 3)

Covariate	b ^a	Crude HR ^b (95%CI)	Wald Statistic	p-value
Rectum				
No	0	1		
Yes	0.57	1.76(1.01,3.06)	4.00	0.045
Omentum				
No	0	1		
Yes	0.76	2.14(1.37,3.36)	11.06	0.001
Colon				
No	0	1		
Yes	0.62	1.87(1.16,2.99)	6.71	0.010
Lung				
No	0	1		
Yes	0.95	2.59(1.18,5.68)	5.63	0.018
Liver				
No	0	1		
Yes	0.86	2.37(1.38,4.07)	9.68	0.002
Surgery type				
Salphingoophorectomy	0	1		
Salphingoophorectomy + omentectomy	-0.40	0.67(0.14,3.31)	0.82	0.622
TAHBSO	0.57	1.78(0.54,5.84)	0.61	0.345
Debulking surgery	1.44	4.21(1.29,13.70)	0.60	0.017
No surgery	1.75	5.76(1.15,28.85)	0.82	0.033
Treatment received				
Surgery only	0	1		
Surgery + chemotherapy	0.88	2.41(1.10,5.28)	4.87	0.027
Surgery + chemotherapy + radiotherapy	1.18	3.24(1.03,10.23)	4.01	0.045
No treatment	1.67	5.32(1.37,20.74)	5.81	0.016
Refuse further treatment				
No	0	1		
Yes	0.41	1.51(0.79,2.87)	1.58	0.209

^aRegression coefficient^bCrude hazard ratio

TABLE 4. Final model of Cox proportional hazard regression for prognostic factor among ovarian cancer patients in Hospital USM (n=127)

Characteristics	n(%)	Crude HR ^a (95%CI)	Adjusted HR ^b (95% CI)	Wald Statistic ^c (df)	p-value ^d
Stage at diagnosis					
Early stage	47(37.0)	0	1		
Advanced stage	80(63.0)	3.32(1.95,5.66)	2.53(1.44,4.45)	10.39(1)	0.001
Lost of appetite					
No	79(62.2)	0	1		
Yes	48(37.8)	2.45(1.56,3.83)	1.95(1.23,3.11)	7.99(1)	0.005
Pleural effusion					
No	97(76.4)	0	1		
Yes	30(23.6)	3.19(1.98,5.16)	1.98(1.19,3.30)	7.00(1)	0.008

Forward stepwise was applied. Two-way interaction and multicollinearity problem were checked and not detected. Proportional hazard assumption were fulfilled (hazard function plot, log-minus-log plot and Schoenfeld residual were checked) Regression diagnostic of Cox-Snell residual, Martingale residuals, deviance residuals and influential analysis were assessed. Remedial measure were perform to identify any influential outliers based on 20% changes of regression coefficients.

^a Hazard ratio of Simple Cox Hazard Regression^b Hazard Ratio of Multiple Cox Proportional Hazard Regression^c Wald statistic of Multiple Cox Proportional Hazard Regression^d P-value of Wald statistic in Multiple Cox Proportional Hazard Regression

TABLE 5. The summary of hazard ratio from other study

Author (year)	Country	Stage	Hazard Ratio (95%CI)
Wong et al. (2012)	Hong Kong	1	1.0
		2	2.7(1.9,3.7)
		3	5.9(4.7,7.5)
		4	9.7(7.5,12.7)
O'Malley et al. (2003)	Nothorn California	1	1.0
		2	3.4(1.9,6.0)
		3	8.0(4.8,13.5)
		4	11.8(6.9,20.0)
Tingulstad et al. (2003)	Norway	1	1
		2	4.3(2.51,7.2)
		3	8.03(5.04,12.8)
		4	11.8(7.0,19.8)

(Wong et al. 2012; O'Malley et al. 2003; Tingulstad et al. 2003)

as compared to stage one ovarian cancer. The other study from O'Malley et al. (2003) in Nothorn California and Tingulstad et al. (2003) in Norway also obtained higher hazard ratio of 11.8 for stage four ovarian cancers compared to stage one cancer (Table 5). A possible explanation for a lower hazard ratio in this study compared to other significant studies might happen when the patients from early stage during diagnosis developed to the advance stage throughout the treatment process. This situation will affect the survival probability and lead to the slight difference in hazard ratio between early and advanced stage cancer.

The loss of appetite was found to be a significant prognostic factor of ovarian cancer. It was found that patients that developed this symptom had almost double risk to death compared to the patients who did not presence with this symptom. This finding was supported by a study from Quinten et al. (2009) using 10108 cancer patients in Europe that discovered that loss of appetite was the significant prognostic factor of survival with the hazard ratio of 1.05 (95%CI:1.03,1.06).

This current study identified that patients who had pleural effusion were 3.19 times higher risk to die from ovarian cancer compared with other patients who did not have pleural effusion. This finding seem to be consistent with other research which found out that patients who experienced pleural metastases were 50% more likely to die compared to other patients who experienced lymph node or other site metastases (Bonnefoi et al. 1999). Another retrospective study from Zamboni et al. (2015) from 2000 to 2011 towards 165 malignant pleural effusion in Brazil found that the ovary tumour is the significant prognostic factor among patients with malignant pleural effusions with the median survival time of 21 months.

There are a few strength and limitations in this study. The usage of survival analysis is the best choice in analysing time to event data where the analysis account for censored data, and manage to handle data with subjects entering the study at different time. The survival analysis

also can compare survival between groups and able to assess relationship between covariates and survival time.

However, this study did not fulfil the required number of sample size ($n=144$). After considering the inclusion and exclusion criteria, the researcher only manage to obtain the total number of 127 subjects. However, the number of sample size is still acceptable since the insufficient sample size is less than 30% with the post hoc power of the study is 78.7%.

In this study, some of the potential prognostic factors that have been reported previously in other study such as chemotherapy regime, laboratory findings, weight, duration of treatment and age at menarche were not considered because the data about these variables were vague, incomplete and unavailable in most of the patients' record. Thus, to avoid these missing values from altered the findings of the study, the variables were excluded from the analysis.

CONCLUSION

Overall, the survival of ovarian cancer was worrying with the low percentage. In this study, three significant prognostic factor were found to be significant in this study with the average hazard ratio almost double compared to low risk group. Thus, the prospective cohort study needs to be done to discover more effective and accurate test for early detection of ovarian cancer. Therefore, people are able to come at earlier stage before the symptoms of ovarian cancer such as loss of appetite and pleural effusion arises. This will give a better survival outcome to ovarian cancer patients and reduce mortality rate.

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