Research Article

An Investigation of Survival following Ovarian Cancer

Jamil Hasan Karami[1*], Kehui Luo[2], Thomas Fung[2,3], Jonathan Carter[4], Zongqun Ding[4]

[1]Department of Statistics, University of Dhaka, Dhaka 1000, **BANGLADESH**
[2]Department of Statistics, Macquarie University, Sydney, NSW 2109, **AUSTRALIA**
[3]Honorary Associate, University of Sydney, **AUSTRALIA**
[4]Lifehouse Gynaecologic Oncology Group, Sydney Cancer Centre, University of Sydney, **AUSTRALIA**

*Email for Correspondence: karami.stat@du.ac.bd

ABSTRACT

Ovarian cancer is one of the most malignant gynaecological cancer for women. Women with ovarian cancer generally have a poor prognosis with short survival. In our study, an exploratory analysis was carried out using the data routinely collected on patients with ovarian cancer, who were diagnosed and treated in a large hospital in Sydney. Survival following the diagnosis of ovarian cancer was examined in relation to several important prognostic factors, including FIGO stage, age, residual disease and histologic type, aiming to evaluate the effect size of each factor and build up a predictive model for survival. The predicted survival provides valuable information for patients and their families, and is particularly important in helping clinician and hospital with the management of each patient with ovarian cancer.

Key words: Ovarian cancer, prognostic factor, survival analysis, Cox model, Kaplan-Meier curve

BACKGROUND

Ovarian cancer is the leading cause of gynaecological cancer-related deaths in many countries of the world. In general, women with ovarian cancer have a poor prognosis with short survival. Winter et al. (2008) estimated an overall median survival of 29 months among patients with advanced ovarian cancer. The prognosis is worse when the cancer is diagnosed at a late stage, which is quite common for ovarian cancer as there are not many clear symptoms for the cancer until tumour has metastasized. Therefore, it is very essential to investigate and identify key prognostic factors of survival following a diagnosis of ovarian cancer. This may provide doctors with a better understanding of their patients' prognosis and potentially enable doctors to understand patients' survival prospects and thus treat them appropriately.

Ovarian cancer is not a homogeneous disease but rather a group of diseases, each with different morphology and biologic behavior. There have been a large number of studies on ovarian cancer over the last few decades. Many of them aimed to predict or estimate survival rate and identify the prognostic factors associated with the survival for women with ovarian cancer, using various methods of survival analysis such as the Cox proportional hazards model. However, the results from those studies are not all that consistent. According to Colombo et al. (2009), the survival of patients with ovarian cancer at an advanced stage is mainly influenced by a few factors, such as the biology and chemo sensitivity of the tumour, the size of the residual disease as well as the extent of the disease at the time of diagnosis.

Ovarian cancer can be broadly divided into two main types, epithelial and non-epithelial ovarian cancer. Any ovarian cancer that started in the surface layer covering the ovary is called epithelial ovarian cancer, and the rest is non-epithelial. Epithelial accounts for 85%-95% of patients with ovarian cancer (Roett and Evans, 2009).

There are many factors that may be associated with the prognosis of ovarian cancer, including residual disease, histology, and stage of cancer, grade of the tumour, CA125 and age. The detailed definition for each of these variables/factors is given in methodology section.

It is also of interest to identify the possible change in survival prospect over time. Note that a set of covariates with a specified relationship with survival represents the true prognostic importance of each covariate, according to Burton et al. (2006).

A number of previous studies (for example, Polterauer et al., 2012; Tingulstad et al., 2003 etc.) showed that residual disease is one of the most important prognostic factors.

In a study of patients with advanced ovarian cancer, Colombo et al. (2009) found that patients with no residual disease after the debulking procedure, i.e., surgery, had experienced a better prognosis with a greater 5-year survival rate.

There are a number of different histologic types of tumour, including serous, mucinous, endometrioid, clear cell and other epithelial types. Women with mucinous and endometrioid tumours had better 5-year survival than the other histologic types (Barnholtz-Sloan et al., 2003).

Ovarian cancer can also be classified by stages, known as FIGO stages. FIGO stage is another important prognostic factor reported in the previous studies (e.g., Obermair et al., 2013; Kotsopoulos et al., 2012; and Chan et al., 2006, etc.). Different FIGO stages may indicate differing prognoses.

Grade of ovarian cancer was considered as an important prognostic variable for ovarian cancer by Eisenhauer et al. (1999) and also by Seiden (2001). Also, it was reported that older women (age > 60) experienced worse prognosis with a shorter survival following the diagnosis of ovarian cancer (Barnholtz-Sloan et al., 2003; Colombo et al., 2009).

CA125 (Cancer Antigen 125) was discovered in early 1980s (Bast et al., 1981).

It has been considered as a biomarker to monitor epithelial ovarian cancer (Felder et al., 2014).

It is usually found in a greater concentration in tumour cells than other part of the body.

The plausibility of CA125 as a prognostic factor for ovarian cancer was evaluated in some previous studies. Markmann et al. (2007) found that the level of CA125 was correlated with overall survival.

According to this study, the level around 100 U/l is an indication of a bad prognosis. Nowadays, CA125 is routinely used to monitor the response to chemotherapy for patients with ovarian cancer (Schmidt, 2011).

Some other prognostic factors of ovarian cancer were also investigated in the literature. Among them, the following prognostic factors are worth noting:

Performance status, physician's specialty, race, estrogen receptor, progesterone receptor, c-erb-B2, epidermal growth factor receptor, p53, mitotic activity index, volume percentage epithelium, morphometric groups, marital status, height, weight, BMI, alkaline phosphatase, albumin, presence or absence of ascites, GST-pi, etc.

When there are many potential prognostic factors of survival following ovarian cancer studied under a statistical method (model), it is likely that only a small subset of them is sufficient in describing or predicting the survival of ovarian cancer. A natural query is which combination of prognostic factors better describes or predicts the survival sufficiently and thus should be included in the model, i.e., the final model.

Here, it is intended to identify important prognostic factors of survival following ovarian cancer, using some well-known survival methods, based on the data obtained from the Royal Prince Alfred (RPA) Hospital, Sydney, Australia. We have also investigated survival pattern of patients following a diagnosis of epithelial ovarian cancer.

METHODOLOGY

Data and prognostic factors

Data used in this article were obtained from Royal Prince Alfred (RPA) Hospital, Sydney. An ethical application was submitted and approved by the people concerned for the acquisition of this data.

Then a formal request was made to get the information on the demographic, clinical and other prognostic factors of the ovarian cancer for patients being treated in the hospital. Unfortunately, not all relevant information was found in its database of the ovarian cancer patients. A total of 1794 cases of ovarian cancer were obtained. Survival time was then defined as the time from diagnosis to death from ovarian cancer or last medical contact, whichever came first. These patients were diagnosed between 11 January 1979 to 18 December 2012. Among 1794 patients, survival times were determined for 1276 patients of which 269 patients belonged to the non-epithelial group. So, we end up with 1007 epithelial ovarian cancer patients.

We considered following prognostic factors: Histologic types of tumour (Six groups), FIGO stage (I – IV), Grade of ovarian cancer (1 – 3), Residual disease (three groups), CA125 (two groups), Age at diagnosis (six groups) and Year of

diagnosis (1983 – 1997 and 1998 – 2012). Ovarian cancer has two broad types as mentioned before: epithelial and non-epithelial. However, with respect to histologic types of tumour, among epithelial ovarian cancer, several subtypes were considered in our study: High-grade serous; Endometrioid; Low-grade serous; Clear cell; Mucinous; Other epithelial types. FIGO stage is an important prognostic factor for ovarian cancer. It describes how advanced the cancer is and how far it has spread at the time of diagnosis. The staging is done based on the location of cancer in the ovary and in other parts of the body. There are four main stages (I-IV), and an unknown group was considered in our analysis. Grade of ovarian cancer describes how similar the cancer cells are to normal cells. There are three grades (1-3) of epithelial ovarian cancer, and an unknown group was considered in our analysis. Residual disease is defined as the size of the residual tumour after surgery (i.e., debulking procedure). It was categorised into the following groups in our analysis: Microscopic (i.e, not visible to naked eyes), $\leq$ 1 cm, > 1 cm and an unknown group. CA125 is considered a tumour marker or biomarker of ovarian cancer. It is usually found in a greater concentration in tumour cells than in other cells of the body. It is classified as Normal, Elevated and an unknown group in our data. In our analysis, age was categorized as: < 40 years, 40 – 49, 50 – 59, 60 – 69, 70 or above and unknown group. Year of diagnosis was divided into two periods of 1983 to 1997 and 1998 to 2012.

Methods

We have considered two different survival analysis techniques, Kaplan-Meier method (Kaplan and Meier, 1958), and Cox proportional hazards model (Cox, 1972). These statistical techniques are special in the sense that they can handle censored observations, which are common in survival data, i.e., time-to-event data. A (right) censored observation occurs if a subject is lost to follow-up or does not experience the event of interest by the end of the study period. Such an observation, therefore, contains only partial information of the time to an event.

The Kaplan-Meier (K-M) method, also known as the product limit method, is often used to estimate the survival function that captures the survival probabilities over time. The survival probability at time t is obtained by multiplying the sequence of conditional survival probabilities estimated up until that time. For a sample of n subjects, let m ($m \leq n$) be the number of unique observed failure times among them $t_{(1)} < t_{(2)} < \cdots < t_{(m)}$. Also let r_i be the number of subjects at risk of experiencing the event, including subjects not yet experienced the event and those censored, and d_i be the observed number of events at each failure time $t_{(i)}$ ($i = 1, 2, \ldots, m$). The Kaplan-Meier estimator of the survival function at any time t (> 0) is expressed as

$$\hat{S}(t) = \prod_{t_{(i)} \leq t} \left(\frac{r_i - d_i}{r_i} \right),$$

where $\hat{S}(t) = 1$ for $0 \leq t < t_{(1)}$.

Based on the Kaplan-Meier estimator, survival curves, which are plots of the estimated survival function over time, can be constructed and used as a graphical display for examining and comparing survival prospects across groups of subjects. These curves are known as the Kaplan-Meier survival curves. These curves can also be used to estimate median survival time (Rochon et al., 2011).

The Cox proportional hazards (PH) model, unlike the Kaplan-Meier method that could only examine one variable at a time, can handle multiple variables. These predictor variables can be continuous and/or categorical. Let $h(t)$ be the hazard function, which specifies the instantaneous risk of an event at time t, given that the individual survives up till that point in time. The Cox model has the following functional form

$$h(t, \boldsymbol{X}, \boldsymbol{\beta}) = h_0(t) exp \left(\sum_{j=1}^{k} x_j \beta_j \right),$$

where $\boldsymbol{X}$ is a vector of covariates and $\boldsymbol{\beta}$ is a vector of regression coefficients. The term $h_0(t)$ is often called the baseline hazard function, and it describes the instantaneous risk of an event at the baseline level of covariates. As $h_0(t)$ is not required to be described explicitly, the Cox proportional hazards model is regarded as a semi parametric model. This model also makes no strict assumption on the distribution of survival times but assumes that the hazard ratio comparing any two groups or individuals is constant over time, which is known as proportional hazards assumption.

RESULTS AND DISCUSSION

Since the distribution of survival times is usually skewed, an appropriate summary measure of survival times is median survival time, which is often of interest in survival analysis. Median survival times can be approximated from Kaplan-Meier survival curves. The Kaplan-Meier survival curves for various prognostic factors are shown in Figure 1 – Figure 7.

From Figure 1, patients with the high-grade serous and other epithelial ovarian cancer had experienced the worse survival among all the histology groups considered. The median survival time for high-grade serous group is approximately four years.

Figure 1: K-M curves by Histologic type
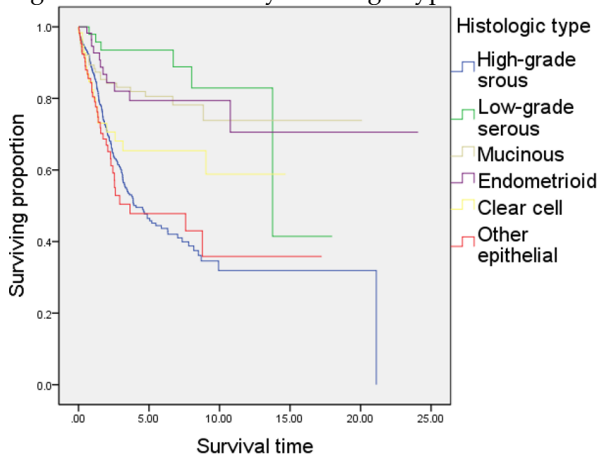
The survival prospect of patients with FIGO stage I is similar to that for those with Stage II and both these two groups have a much better survival than those patients at advanced stages (stages III and IV) as shown in Figure 2. Patients with FIGO stage IV had experienced the worst survival across the four stages with a median survival time of two years approximately.

Figure 2: K-M curves by FIGO stage
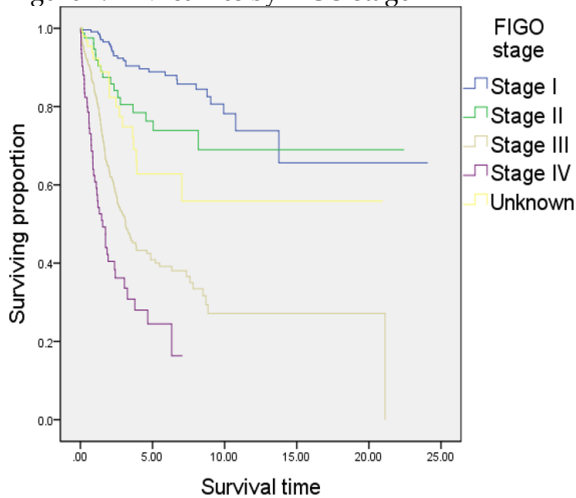
With respect to grade, patients with Grade 3 have experienced the worst survival among the three grades of ovarian cancer for patients included in this study (Figure 3).

Figure 3: K-M survival curves by Grade
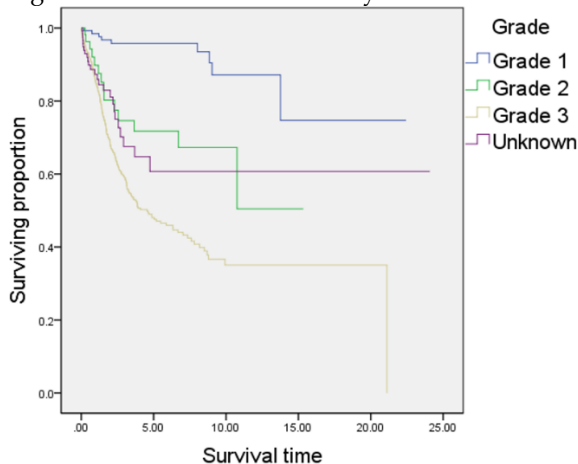
In Figure 4, the survival curve for patients with residual tumour greater than 1 cm falls much sharply compared to the survival curves for patients with smaller sizes of residual tumour. This group of patients has experienced relatively poorer survival with a median survival time of less than two years, while the median survival time for patients with residual tumour size less than or equal to 1 cm is around 2.5 to 3 years. The microscopic group has a much better survival as its survival curve is well above the other two residual disease groups.

Figure 4: K-M curves by Residual disease
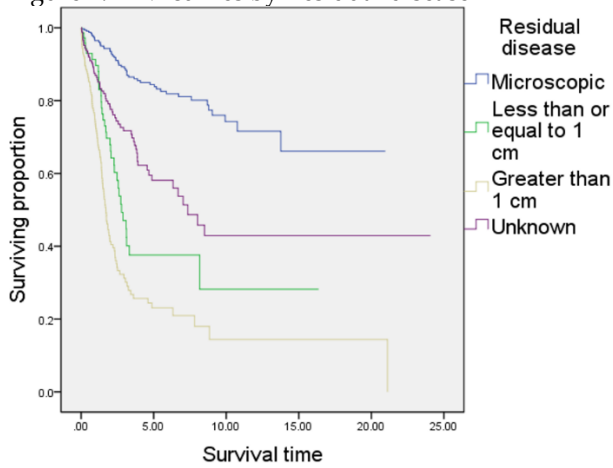
Patients with normal CA125 level had better survival than those whose CA125 level were elevated (see Figure 5) as expected.

Figure 5: K-M survival curves by CA125
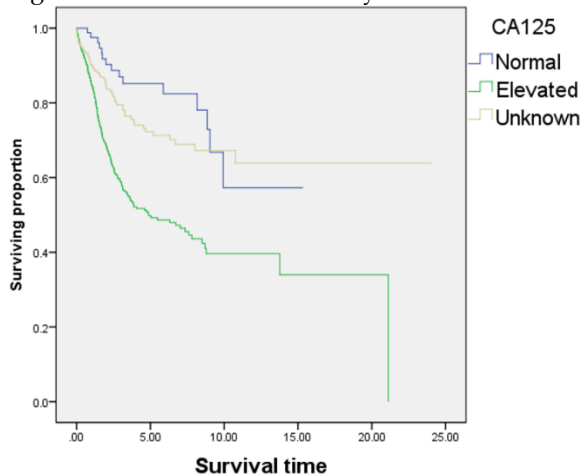
It can be seen from Figure 6 that patients diagnosed relatively younger (below 40 years) had better survival than older patients. Patients who were diagnosed at 70 years or older had experienced the worst survival as expected.

Figure 6: K-M survival curves by age
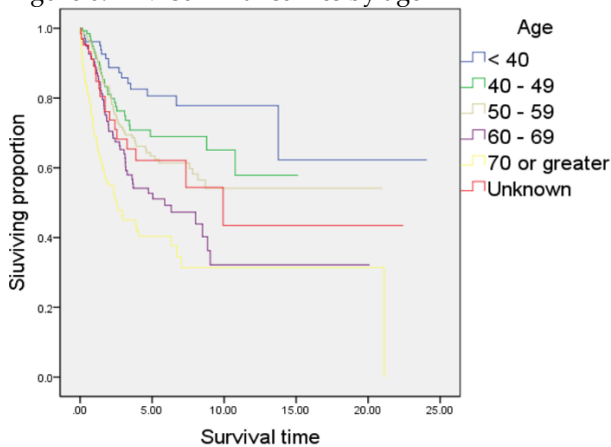
With respect to diagnosis year, patients who were diagnosed after 1997 had experienced better survival than patients who were diagnosed earlier as seen in Figure 7. This may be, at least to some extent, due to the improved treatment (surgery) scheme, and care and quality of treatment following the surgery.

Figure 7: K-M survival curves by year of diagnosis
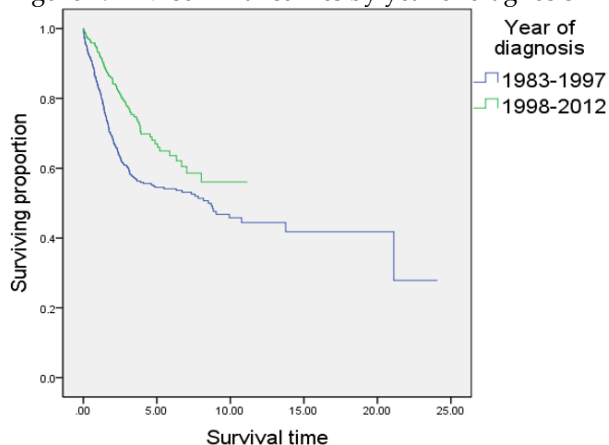
We have used the Cox PH model to evaluate the effects of prognostic factors on survival time, and thus important prognostic factors can be identified. The underlying assumptions of Cox model (PH assumptions) were checked, and they were satisfied. Moreover, histologic types of tumour and grade of ovarian cancer were found strongly associated. So, we dropped the latter from the Cox model that was fitted to the RPA ovarian cancer data. Hazard ratios (HR) for each of the factors considered in the model were reported in Table 1.

Table 1: Estimated Cox model for ovarian cancer data

Factor	Factor levels	HR	95% CI
Histologic types	High-grade serous	1	-
	Low-grade serous	0.55	(0.24, 1.29)
	Mucinous	0.77	(0.48, 1.24)
	Endometrioid	0.90	(0.47, 1.71)
	Clear cell	1.83	(1.07, 3.12)
	Other epithelial	1.75	(1.21, 2.52)
FIGO stage	Stage I	1	-
	Stage II	1.36	(0.74, 2.53)
	Stage III	2.70	(1.64, 4.46)
	Stage IV	5.32	(3.02, 9.37)
	Unknown	1.99	(1.04, 3.82)
Residual disease	Microscopic	1	-
	Less than 1 cm	2.64	(1.62, 4.29)
	Greater than 1 cm	3.20	(2.11, 4.86)
	Unknown	2.73	(1.74, 4.30)
CA125	Normal	1	-
	Elevated	1.78	(1.03, 3.08)
	Unknown	1.46	(0.80, 2.65)
Age	Below 40	1	-
	40 – 49	1.37	(0.75, 2.50)
	50 – 59	1.44	(0.83, 2.51)
	60 – 69	1.89	(1.08, 3.28)
	70 and above	2.77	(1.61, 4.76)
	unknown	1.28	(0.66, 2.51)
Diagnosis year	1983 – 1997	1	
	1998 – 2012	0.48	(0.34, 0.67)

We see that Patients with FIGO stage IV or III was almost five or over two times of the hazard rate, respectively, as those with FIGO stage I ovarian cancer. Patients with 'Greater than 1 cm' or 'Less than 1 cm' residual disease have almost two times higher failure rate compared to those in the microscopic group. The prognostic value of factor CA125 was not significant. Older aged people (60 – 69 and 70+) have significantly higher failure rate than younger patients (age below 40 years). Patients who were diagnosed after 1997 have significantly lower failure rate compared to patients who were diagnosed at or before 1997, as expected.

CONCLUSION

We have investigated survival pattern and effects of prognostic factors through K-M curves and Cox models respectively. We have summarized different prognostic factors of survival following ovarian cancer. Although important prognostic factors have been identified, we could use other parametric model such as accelerated failure time model. However, those models require more stringent assumptions to be met.

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