Comparison of Cox’s Regression Model and Weibull’ Parametric Model in Evaluating Factors Affecting in First Recurrence of Epithelial Ovarian Cancer

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Abstract - Ovarian cancer is one of the most deadly women's gynecological malignancies in the world, and despite the low prevalence, it accounts for about 5% of all cancer deaths in women. Survival analysis is a regression relationship between a set of variables with a specific outcome, which is considered disease survival or recurrence in medical studies. The aim of this study is to determine the important factors in the first recurrence of patients with epithelial ovarian cancer with two statistics methods. In this study, we review medical records of patients with epithelial ovarian cancer who referred to the oncology and radiotherapy department of Imam Hossein Hospital of Tehran from the beginning of 2007 to the end of 2018. Univariate and multivariate Cox regression, as well as the parametric Weibull method, were used to investigate the factors affecting patients' first recurrence. We perform all calculations with Stata Ver14. Of the 141 patients, 58 patients (41%) had a first recurrence during our follow-up. The mean time to the first recurrence was 24.88 months. Univariate Cox regression and univariate Weibull analysis showed that metastatic tumor and tumor stage had highly significant effects in the first recurrence of epithelial ovarian cancer. In multivariate Cox and multivariate Weibull analysis, the metastatic tumor had a significant effect in the first recurrence of epithelial ovarian cancer. One of the causes of ovarian cancer recurrence may be diagnosis happened at late stages. Therefore, screening programs are needed to reduce illness and death from ovarian cancer.

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Keywords: Ovarian cancer; Recurrence; Predictor; Cox regression; Weibull parametric method

Introduction

Ovarian cancer is one of the leading causes of death in the women's gynecological malignancies in the world, and despite improved outcomes from surgery and chemotherapy, most women with ovarian cancer have a recurrence and eventually death in recent decades (1). Epithelial ovarian cancer is one of the leading causes of death in gynecological cancers in the western world (2). Ovarian cancer is a rare disease with a five-year survival rate of almost 47%. These characteristics make it difficult to do retrospectively study (3). It is often diagnosed in an advanced stage due to the lack of specific symptoms (4). While it accounts for 2.5% of all malignancies in women, it accounts for 5% of cancer-related deaths in women (5). There is a need to identify factors that are affected ovarian cancer (6).

Since the diagnosis of CA125 tumor marker, this marker is not only used to evaluate response to treatment widely, but it is used to diagnose ovarian cancer recurrence too (7). The primary treatment for patients with epithelial ovarian cancer is surgery followed by platinum- and taxane-based chemotherapy. Known factors that influence the prognosis of patients with ECO include age, tumor grade, tumor stage, According to “The Federation of Gynecology and Obstetrics” (FIGO), the histology of the tumor, and the outcome of the treatment involving surgery (8).

Survival analysis is a set of statistical methods used to analyze data that our favorite outcome is time to a particular event. One of the most popular survival analyses is Cox regression, as it is semi-parametric, and it can be used to investigate the effect of several variables over time to our event (9). In a study in China that the Cox regression was used to evaluate the prognosis of ovarian cancer patients (10), in the
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univariate and multivariate study, disease stage, disease grade, tumor residual after surgery, and a number of chemotherapy courses were significant.

David Mysona, in his study in 2019, showed that Brain-Derived Neurotrophic Factor and Platelet-Derived Growth Factor molecules were significant in predicting high-grade serous ovarian cancer recurrence in both univariate and multivariate analysis (11). In another study in 2019, Dan Nie showed that Systemic immune-inflammation index is associated with the advanced stage of the disease and lymph node metastasis and tumor recurrence in epithelial ovarian cancer which in both univariate and multivariate Cox method, higher SII predicts less overall survival and less progression-free survival (12).

Objectives
There are many studies that have investigated the factors affecting survival or recurrence of ovarian cancer, but so far, no studies have compared factors affecting the first recurrence of ovarian cancer by two different statistical methods in Iran.

Materials and Methods

Eligibility
In this study, we investigate medical records and pathology reports of patients with ovarian cancer who referred to the oncology and radiotherapy department of Imam Hossein Hospital in Tehran for 11 years, from the beginning of 2007 to the end of 2018. Their first recurrence status at the end of 2018 was defined as failure time. In this work, we determine the time to recurrence from the patient’s medical records, and in the absence of a physician’s report, we consider the interval between the end of the first period of treatment and the restart of chemotherapy. The metastatic tumor is generally considered in this work, and the metastatic site is not considered due to a low sample size and incomplete physician's reports. Inclusion criteria are the initial diagnosis of ovarian cancer, and exclusion criteria are benign, borderline ovarian, germ cell and stromal tumors, Metastases to the ovary, and under the age of 18 years. Thus of 176 patients with ovarian cancer, 35 patients are excluded.

Variables
The potential prognostic variables examined in this study are as follows:

A) Patient variables include age, BMI at diagnosis, and ascites at diagnosis.
B) tumor-related variables include tumor stage, tumor grade, tumor histology, CA125 tumor marker at diagnosis, and metastatic tumor.
C) Variables related to the types of treatment include adjuvant or neoadjuvant chemotherapy, weekly or three weeks chemotherapy courses.
D) The patient's blood parameters include hemoglobin, platelet, and white blood cells.

Statistical methods
We first use the Kaplan-Meier survival curve and life table to calculate one, two, three, four, five, and ten years disease-free survival probabilities. In the next step, we use Cox's semi-parametric method and Weibull parametric method for univariate analysis of prognostic factors in the first recurrence of ovarian cancer. In this stage, variables that have a significant impact on recurrence are investigated for the Cox proportional hazards model. Then significant variables enter the multivariate Cox survival model and multivariate Weibull model, and we compare the results. Finally, the cumulative hazard curve is plotted based on variables that are significant in Cox multivariate survival and Weibull multivariate models, then results evaluate.

Results

Descriptive data
Of the 141 patients with epithelial ovarian cancer, 58 patients (41%) recurred during our follow-up period, and the rest was censored (Right Censored). The mean time to the first recurrence was 24.88 months, the number of recurrences and the meantime to the first recurrence were analyzed separately in risk factors (Table 1).

Overall recurrence
Using the life table, disease-free survival was 0.97 in the first seven months after diagnosis, 0.82 in the first year after diagnosis, 0.55 in the first two years, 0.44 in the first three years, 0.42 in the first four years, and 0.39 in the first five years And almost to ten years it was 0.36. Kaplan-Meier survival curves were evaluated for first recurrence strata by metastatic tumor and disease stage (Figure 1). We merged stage I and stage II with respect to the low number of recurrent cases in these two-stage, and we evaluated the Cox proportional hazards.
Table 1. Clinical and demographic characteristics of ovarian cancer patients stratified by recurrence time (N=141)

| Parameter                              | No. of patient | %  | No. of first recurrence | Mean time to the first recurrence |
|----------------------------------------|----------------|----|-------------------------|-----------------------------------|
| **Age at diagnosis (years)**           |                |    |                        |                                   |
| 18–49                                  | 62             | 44 | 30                      | 25.88                             |
| 50–59                                  | 37             | 26 | 16                      | 26.64                             |
| 60–69                                  | 22             | 15.6 | 5                       | 24.76                             |
| 70                                     | 20             | 14.2 | 7                       | 18.66                             |
| **BMI Group (kg/m2)**                  |                |    |                        |                                   |
| Underweight/Normal (BMI < 24.9)        | 28             | 19.9 | 15                      | 19.56                             |
| Overweight (BMI >25)                   | 51             | 36  | 24                      | 26.59                             |
| Missing                                | 62             | 44  | --                      | --                                |
| **Histologic type**                    |                |    |                        |                                   |
| Serous (I)                             | 85             | 60.3 | 44                      | 25.97                             |
| Others (Endometrioid, Clear Cell, Mucinous) | 30         | 21.2 | 6                       | 22.62                             |
| Missing                                | 26             | 18.4 | --                      | --                                |
| **FIGO Stage at diagnosis**            |                |    |                        |                                   |
| Stage I                                | 34             | 24.1 | 5                       | 31.58                             |
| Stage II                               | 16             | 11.3 | 8                       | 25.35                             |
| Stage III                              | 44             | 31.2 | 26                      | 23.7                              |
| Stage IV                               | 14             | 9.9  | 8                       | 12.43                             |
| Missing                                | 33             | 23.4 | --                      | --                                |
| **Tumor Grade at diagnosis**           |                |    |                        |                                   |
| 1                                      | 24             | 17  | 7                       | 28.36                             |
| 2                                      | 32             | 22.2 | 13                      | 27.73                             |
| 3                                      | 37             | 26.2 | 18                      | 26.06                             |
| Missing                                | 48             | 34  | --                      | --                                |
| **Neoadjuvant chemotherapy**           |                |    |                        |                                   |
| Yes                                    | 19             | 13.5 | 9                       | 19.77                             |
| No                                     | 64             | 45.4 | 35                      | 25.6                              |
| Missing                                | 58             | 41.1 | --                      | --                                |
| **Ascites at diagnosis**               |                |    |                        |                                   |
| Yes                                    | 58             | 41.1 | 26                      | 22.59                             |
| No                                     | 78             | 55.3 | 30                      | 26.96                             |
| Missing                                | 5              | 3.5  | --                      | --                                |
| **CA-125 prior to treatment**          |                |    |                        |                                   |
| <1000 (U/mL)                           | 13             | 9    | 9                       | 14.98                             |
| >1000 (U/mL)                           | 42             | 29   | 18                      | 25.38                             |
| Missing                                | 86             | 60   | --                      | --                                |
| **Metastatic tumor**                   |                |    |                        |                                   |
| Yes                                    | 52             | 36.9 | 32                      | 18.47                             |
| No                                     | 80             | 56.7 | 21                      | 30.28                             |
| Missing                                | 9              | 6    | --                      | --                                |
| **Mean White blood cells**             |                |    |                        |                                   |
| <5000                                  | 40             | 28.3 | 27                      | 25.21                             |
| >5000                                  | 36             | 25.5 | 11                      | 23.52                             |
| Missing                                | 65             | 46   | --                      | --                                |
| **Mean Hemoglobin**                    |                |    |                        |                                   |
| <11                                    | 35             | 24.8 | 19                      | 24.61                             |
| >11                                    | 41             | 29   | 19                      | 24.16                             |
| Missing                                | 65             | 46   | --                      | --                                |
| **Maximum Platelet count**             |                |    |                        |                                   |
| <350000                                | 37             | 26.2 | 18                      | 29.73                             |
| >350000                                | 39             | 27.6 | 20                      | 19.36                             |
| Missing                                | 65             | 46   | --                      | --                                |
| **Chemotherapy course**                |                |    |                        |                                   |
| 1week                                  | 37             | 26.2 | 22                      | 21.52                             |
| 3week                                  | 64             | 45.4 | 30                      | 24                                |
| Missing                                | 40             | 28.4 | --                      | --                                |

BMI= body mass index; CA125 = cancer antigen 125; CI = confidence interval.
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![Graph A](image1.png) ![Graph B](image2.png)

Figure 1. First recurrence estimated times strata by A) metastatic tumor B) Figo stage at diagnosis

Main results
In the next step, we first entered each of the variables into the univariate Cox model, and according to the table 2, the metastatic tumor had a hazard ratio (HR=3.617, 95%CI: 2.05_6.35, P<0.001), and the tumor stage had a hazard ratio (HR=1.64, 95%CI: 1.24_2.19, P<0.001). Thus these two variables had highly significant effects in the first recurrence of epithelial ovarian cancer. In addition to these two variables, histologic type, BMI, CA125 tumor marker at diagnosis, ascites, mean white blood cell, and max platelet are entered into the multivariate Cox survival model because they had significantly less than 0.25 (Table 2). According to Cox's results, patients with metastasis are 3.61 times more likely to have a recurrence than those without metastasis, and individuals at the higher stages of the disease are 1.64 times more likely to have a recurrence than those at the lower stages.

Table 2. Univariate and multivariate Cox parametric method for the first recurrence of epithelial ovarian cancer

| Covariate                        | Univariate | Multivariate |
|---------------------------------|------------|--------------|
|                                 | HR         | 95%CI        | P     | Covariate                        | HR         | 95%CI       | P     |
| Age                             | 0.89       | 0.68_1.16    | 0.414 | FIGO Stage at diagnosis          | 1.56       | 0.88_2.76   | 0.12  |
| Metastatic tumor                 | 3.617      | 2.05_6.35    | <0.001| Metastatic tumor                 | 4.06       | 1.2_13.73   | 0.024 |
| Neoadjuvant chemotherapy         | 0.87       | 0.41_1.82    | 0.71  | Histologic type                  | 1.23       | 0.29_5.22   | 0.77  |
| FIGO Stage at diagnosis          | 1.64       | 1.24_2.19    | <0.001| BMI                              | 0.43       | 0.11_1.74   | 0.24  |
| Tumor grade at diagnosis         | 1.22       | 0.82_1.85    | 0.32  | Baseline ascites                 | 1.68       | 0.52_5.48   | 0.38  |
| Histologic type                  | 1.93       | 0.82_4.54    | 0.12  | CA-125 prior to treatment        | 1.64       | 0.29_5.22   | 0.77  |
| Ascites at diagnosis             | 1.36       | 0.8_2.31     | 0.24  | Maximum Platelet count           | 1.36       | 0.41_4.51   | 0.61  |
| CA-125 prior to treatment        | 2.65       | 1.16_6.04    | 0.02  | Mean White blood cells           | 2.62       | 0.78_8.84   | 0.11  |
| Chemotherapy course              | 0.85       | 0.49_1.49    | 0.58  | Floor area                      |            |             |       |
| Mean White blood cells           | 1.77       | 0.87_3.57    | 0.11  | Mean Hemoglobin                 | 1.08       | 0.57_2.05   | 0.71  |
| Maximum Platelet count           | 0.67       | 0.34_1.28    | 0.23  |                                |            |             |       |

P< 0.05 indicating significance, HR indicating hazard ratio

We first tested the Cox proportional hazards assumption for the eight variables selected in the univariate Cox, and the results of the Harell test showed that the Cox proportional hazards assumption was valid for the eight variables. So we imported them into multivariate Cox. Finally, multivariate Cox results showed that the metastatic tumor with a hazard ratio (HR=4.06, 95%CI: 1.2_13.73, P=0.024) had a significant effect in the first recurrence of epithelial ovarian cancer (Table 2). According to our results in multivariate Cox, the hazard ratio in patients with metastasis is four times more recurrence than patients
Again, we entered each of the variables into the univariate Weibull parametric model, and according to table 3, the metastatic tumor (HR=4.62, 95% CI: 2.6_8.19, P<0.001) and tumor stage (HR= 1.87, 95% CI: 1.4_2.5, P<0.001) had highly significant effects in the first recurrence of epithelial ovarian cancer. In addition to these variables, variables histologic type, CA125 tumor marker at diagnosis, mean white blood cell count, and max platelet count also had a significant hazard ratio of less than 0.05. So we entered these six variables into the multivariate Weibull model, and again according to table 3, the metastatic tumor with (HR=3.64, 95%CI: 1.19_11.14, P=0.023) had a highly significant effect in the first recurrence of epithelial ovarian cancer, so that metastatic tumor increases the risk of the first recurrence in epithelial ovarian cancer patients 3.91 times, and the higher stage of the tumor, increases the risk of the first recurrence 2.21 times. So the results were almost the same for both the semi-parametric Cox model and the parametric Weibull model.

| Covariate                        | HR   | 95%CI     | P    |
|----------------------------------|------|-----------|------|
| Age                              | 0.91 | 0.69_1.18 | 0.49 |
| Metastatic tumor                 | 4.62 | 2.6_8.19  | <0.001|
| Neoadjuvant chemotherapy         | 0.83 | 0.39_1.73 | 0.62 |
| FIGO Stage at diagnosis          | 1.87 | 1.4_2.5   | <0.001|
| Tumor grade at diagnosis         | 1.36 | 0.89_2.06 | 0.14 |
| Histologic type                  | 2.3  | 0.98_5.4  | 0.05 |
| FIGO Stage at diagnosis          | 1.55 | 0.91_2.64 | 0.1  |
| CA-125 Prior to treatment        | 2.03 | 0.59_6.98 | 0.26 |
| Mean White blood cells           | 1.71 | 0.54_5.43 | 0.35 |
| Maximum Platelet count           | 1.84 | 0.61_5.56 | 0.27 |

P<0.05 Indicating significance, HR indicating hazard ratio

The cumulative hazard function was plotted for the two variables that had a significant hazard ratio in the first recurrence of epithelial ovarian cancer (Figure 2). Figure 2(A) shows that during our follow-up period, patients with metastasis had a significantly higher cumulative hazard than patients without metastasis, and for patients without metastasis from month 30 onwards, the cumulative hazard was almost constant. Also, figure 2(B) shows that the higher tumor stage in the first fifty months included a greater cumulative hazard.

**Discussion**

Ovarian cancer is a rare disease in Iran, as well as other areas. The median age of this cancer in our study was 52.5 years; it is lower than the median age of Previs study in the United States in 2014, which was 59 years (13). The one-year disease-free survival rate was 82% in our study. This rate is higher than the Luvero study in
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2019, which reported an 18-month disease-free survival rate of 80% (14).

In our study, it was shown that among the studied variables, metastatic tumor with a hazard ratio of 4.06 is the most important factor in the first recurrence of epithelial ovarian cancer. Further, maximum platelet count, tumor stage, BMI, presence of ascites at diagnosis, CA125 tumor marker, and white blood cell had a hazard ratio higher than 1.3, although they were not statistically significant. In the Previs study in 2014, the presence of ascites had a significant hazard ratio of 2.63 in a multivariate study of factors affecting ovarian cancer recurrence in women treated with chemotherapy and bevacizumab (13). In our study, the presence of ascites at diagnosis in the univariate Cox model had a hazard ratio of 1.36 and in the multivariate Cox model had a hazard ratio of 1.6 in the first recurrence of epithelial ovarian cancer.

Shinagare AB in 2018 showed that a higher rate of CA125 marker tumor increase abdominal recurrence in stage III and IV papillary-serous patients, which was significant in both univariate and multivariate Cox models, but the disease stage was not significant in this study (15). Results of the present study showed the CA125 marker in the univariate Cox model had a significant hazard ratio of 2.65, and in the multivariate Cox, the model had a hazard ratio of 1.64 in the first recurrence of epithelial ovarian cancer. In the Clarke CL study in 2019 that investigated long-term survival predictors of patients with grade III and IV serous ovarian cancer, lower age, lower stage, and depression significantly association with long-term survival (3). In our study, age had no significant effect on the first recurrence, but a higher tumor stage had a significant effect on the first recurrence.

In the Zheng Li study in 2017, who examined the predictors of survival of epithelial ovarian cancer patients using neutrophil-to-lymphocyte ratio and preoperative red cell distribution, in the univariate study, age, stage of the disease, and tumor histology were significant. And in the multivariate study, age and stage of disease were significant (8). In the present study, tumor histology in the univariate Cox model had a hazard ratio of 1.93 with a significance of 0.12, but in the multivariate Cox, the model had a hazard ratio of 1.23.

In the Nagle study in 2015, obesity had a high hazard in ovarian cancer survival (16), and in the same year, the Tran A-Q study showed obesity had a significant hazard on ovarian cancer survival (17). Similar studies have also suggested that obesity is a risk factor for ovarian cancer survival, but in a study (18) in Australia, BMI >25 was less risk than BMI <25 at diagnosis. It is noteworthy, at first recurrence, we found that underweight (BMI <24.9) had an approximate hazard ratio two times then (BMI >25).

One of the limitations of the present study is the percentage increase of right censoring in some variables. Of course, in the variables that were entered into the multivariate Cox analysis, and they were significant in the univariate study, the percentage of right censoring was below 50%, except for the CA125 tumor marker. Another limitation of the present study is the low incidence of ovarian cancer that makes difficult retrospective cohort studies.

Interpretation

According to a high recurrence rate of epithelial ovarian cancer and according to our results that tumor stage and metastatic tumor were identified as two important factors in the first recurrence of this cancer; one of the causes of recurrence may be diagnosis happened at late stages. Therefore, screening programs are needed to reduce illness and death from ovarian cancer.

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