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Survival Analysis of Ovarian Cancer Patients in Yazd City, Central part of Iran, 1999-2018

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ABSTRACT

Background: Ovarian Cancer (OC) as a common gynecologic cancer according to mortality rate has the seventh rank among women in the world. This study aimed to identify risk factors associated with OC survival in Yazd, Iran.

Methods: In this observational retrospective cohort study, the medical records of 150 patients who were definitively diagnosed with OC from 1999 to 2018 were investigated. The Kaplan–Meier estimator and the Cox proportional hazard model with hazard ratio and the log-rank test were used for data analysis. All statistical analyses were done in R 4.0.5, package survival.

Results: 60.77% (91 people) of patients were under 60 years old. 32.7% (49 people) were in stage III of the disease. 62% (93 people) did not have ascites, 67.3% (101 people) had disease-free survival more than 65 months. 45 (30%) of 150 patients were dead. Median survival time was 96 months (95% CI:57.20 to 134.79), one, three, five-, and ten-year survival rates were 83,73,55 and 33 months; respectively. Log-rank test results showed there was a significant difference between age, stage, ascites, disease-free survival, and Treatment method, CA125 after and before treatment ($p < 0.05$). Cox proportional hazard model result showed ascites (HRadj = 3.89, 95% CI: 1.35 to 11.15, P = 0.01) and DFS (HRadj = 23.52, 95 % CI: 4.21to128.33, p = < 0.001) as significant covariates.

Conclusion: The results of our study showed that disease-free survival and ascites are the main risk factors for OC and paying attention to them will be effective in increasing patient survival.

Keywords: Ovarian cancer, survival, cox proportional hazard, Iran

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Introduction

Cancer is one of the leading causes of death among non-communicable diseases (1). Ovarian Cancer (OC), like other cancers, is on the rise and is of great importance to women (2). According to previous studies, OC is the most common cause of death among women with malignancies (3). Due to asymptomatic development, the disease is often diagnosed in advanced and incurable stages. it is now the seventh most common cancer in women worldwide and the eighth-most common cause of death and morbidity in women under 65 years of age (4). The high mortality rate is the result of late diagnosis, which is one of the reasons for not performing screening tests that can be used in low-risk populations (5). Ovarian malignancies account for about 33% of all invasive female genital malignancies (6).

OC is the most common cause of death from genital cancer, and usually, 90% of women with early-stage disease have symptoms such as premature satiety, unusual pelvic or abdominal pain, urinary problems, and postmenstrual bleeding (6) Wu et al. 2019 in their survival study on 59,763 patients with OC showed the highest and lowest survival rate was related to the age group over 79 years under 20 years.

Ears, respectively found that increasing age is associated with improved patient prognosis (7). Najla et al. 2015 declared that obesity is an important factor in reducing the survival rate in OC patients (8). Among studies related to OC in Iran, Sharifian et al. 2014 in their study on the incidence and mortality of OC in Iran found that OC is one of the leading causes of death among Iranian women, during the time it had an increasing trend also older women had a lower response to treatments (9). Jaleh et al. 2012 in their survival study in the Fars province of Iran, with study 201 women found that the variables of first menstrual age, metastasis to other near and far places, and history of abortion were associated with the survival time of patients (10). OC is still the leading cause of cancer death in women in developed countries. Despite significant progress in the management of OC, the overall 5-year survival rate at all stages of the disease is estimated at 30%, and in Iran 61 % (6, 11). In the United States, in 2018, approximately 22, 240 new cases of OC were diagnosed, of which 14,070 deaths occurred from OC, so the American Cancer Society provides an overview of the incidence of OC and its population-based mortality across the country. In this country, the overall rate of OC from 1985 (6.16 per 100,000) to 2014 (11.8 per 100,000) was 29% and the mortality rate was between 1976 (10.0 per 100,000). And 2015 (7/6 per 100,000) decreased by 33% (12).

Due to the lack of a study on OC in recent years in Iran, the present study was conducted to evaluate the survival rate of OC patients in Yazd province, the central part of Iran, from 1999 to 2018 and identify related factors.

Methods

In this observational retrospective cohort study, medical records of 150 OC patients who were referred to Shah Vali Medical Center in Yazd province, (Central part of Iran) between 1999 and 2018 were investigated. The researcher used medical records and also telephone contact for data gathering. Patients who did not consent to participate in this study or whose medical records were incomplete were excluded from the study. The variables of this study include demographic variables such as age at diagnosis (≤ 60, > 60), body mass index (BMI, ≤ 25, 25 to 30, > 30), married (yes, no)and clinical variables such as treatment method (Surgery then chemotherapy, Chemotherapy then surgery, Surgery only, Chemotherapy only), disease stages (I, II, III, IV), metastasis to other parts of the body (yes no), ascites (yes, no), recurrence(yes, no) disease-free survival (DFS, ≤ 65, >65) Oral contraceptive pills (OCP, yes, no), family history of OC(yes, no), other cancers (yes, no) and Cancerantigen1 25 (ca-125, ≤ 11585, > 11585 u/ml) beforehand-125 (≤ 3000, > 3000 u/ml) after treatment.

Patients' survival time was calculated as the time of diagnosis of OC to the time of death (or the last follow-up).

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The Kaplan–Meier estimator was used to estimate survival function in different survival times. To compare and evaluate the difference in patient survival in the subgroups of the study variables, the log-rank test was used. To identify the factors affecting patient survival, a univariate/ multivariable Cox proportional hazard (CPH) model was used and Hazard ratios (HR_{adj}) with 95% CIs were estimated. Assumption of (CPH) such as establishing proportional Hazard assumption (PH assumption)) in each of the variables were checked by Schoenfeld residuals. After performing the univariate model, according to the Hosmer and Lemeshow variable selection process, variables were entered into the multivariable (CPH). All statistical analyses were done in R4.0.5, package survival. A p-value less than 0.05 was considered significant.

Results

out of a total of 150 OC patients, 60.77% (91 people) were age under 60 years, 92.7 % (139 people) had married status, 32.7% (49 people) were in stage number one (I) of the disease, 48% (72 people) underwent dual treatment, first surgery and then chemotherapy, 38% (57 people) had ascites, 78% (117 people) had used OCP. 82.7 % (124 people) had no metastasis and 32.7 % (47 people) had recurrence after treatment. At the end of this study, overall, 45 deaths (30%) of 150 patients were. Using the Kaplan-Meier estimator as a nonparametric method, different survival times were calculated, so that the overall median survival time was 96 months (95%CI :57.20 to 134.79), the overall mean survival rate 84.05 (95% CI: 73.84 to 94.62), and of 1, 3, 5 and 10-year survival rate were obtained 83,73, 55 and 33 percent, respectively. Results of the Log-rank test showed a significant difference in survival rate in age ($p = 0.005$), disease stage ($p = 0.001$), metastasis ($p = 0.018$), and Surgery then chemotherapy ($p = 0.031$), the amount of ca125 after treatment ($p = 0.01$) receiving DFS ($p < 0.001$). pairwise multiple comparisons result in disease stage and treatment method, which had more than two levels, showed that stage one had a significantly different survival rate with stages three and four ($p < 0.001$); stage two had a significantly different survival rate with stage three and four ($p < 0.001$). Also, differences in the survival rate of treatment methods were significant so the method Surgery then chemotherapy and Chemotherapy then surgery ($p < 0.04$), method Surgery then chemotherapy and Surgery only ($p < 0.008$) had significant differences. However, no significant differences were observed in other subgroups ($p > 0.05$) (Table 1).

The Kaplan-Meier survival plot showed Overall Survival Estimates among OC Patients with a 95% Confidence Interval. Age at diagnosis OC patients indicated lower survival in the youngest age group (Figure 1).

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Table 1. Descriptive statistics of Ovarian cancer risk factors and results of log-rank test

Factors	Levels	N (%)	Log-rank test		
			Median survival times (months) (95% C.I)	p	Pair-wise comparison
Age at diagnosis (yr)	60≤ 60>	91(60.7) 59(39.3)	96 98 (35.341-100.659)	0.005	---
Married	Yes No	139(92.7) 11 (7.3)	96 (63.89-128.10) ---	0.447	---
Stage	I II III IV	47 (31.3) 34 (22.7) 49 (32.7) 20 (13.3)	--- --- 48 (18.58-77.41) 36 (13.39-58.60)	0.001	(1-2) & (1-3) * & (1-*4) (2-3) * (2-4) * (3-4)
Ascites	Yes No	57 (38) 93 (62)	42 (16.47-67.52) ---	0.001	---
Ocp	Yes No	33 (22) 117 (78)	--- 69(43.36-94.63)	0.154	---
Metastatic	Yes No	26 (17.3) 124 (82.7)	69 (21.62-116.38) 120 (48.26-25.39)	0.018	---
Recuarence	Yes No	45 (30) 105 (70)	69 (66.132-71.86) ---	0.178	---
Treatment method	Surgery then chemotherapy Chemotherapy then surgery Surgery only Chemotherapy only	72 (48) 25 (16.7) 40 (26.7) 13 (8.7)	120 68 (25.97-110.02) 96 (22.61-169.38) ---	0.031	(1-2) * & (1-3) * & (1-4) (2-3) & (2-4) (3-4) ---
Othercancer	Yes No	137 (91.3) 2 (1.3)	69 (42.37-95.62) 120 (35.47-189.52)	0.471	---
family history of OC	Yes No	133 (88.7) 17 (11.3)	96 (59.75-132.24) 120 (37.46-202.54)	0.43	---
BMI(kg/m2)	≤ 25 25to30 30>	80 (53.3) 48 (32) 22 (14.7)	120 (27.76-212.24) 96 (66.52-125.47) 96 (66.52-125.47)	0.17	---
Ca-125 (U/ML) before treatment	11585≤ 11585 >	136 (90.7 14 (9.3)	96 (57.26-134-73) 26 (16.16-35.83)	0.02	---
Ca-125 (U/ML) after treatment	3000 ≤ 3000 >	137 (91.3) 13 (8.6)	96 (57.26-134-73) 22	0.01	---
DFS(months)	≤ 65 > 65	133 (88.7) 17 (11.3)	60 (46.82-76.18) ---	0.001 <	---

OC, Ovarian cancer, 95% CI, 95% confidence interval, BMI, body mass index, ca-1251, Cancer antigen 125 before treatment, Ca-1252, Cancer antigen 125 after treatment, Ocp, Oral contraceptive pills, DFS, Disease-Free Survival, p, p-value, *p < 0.05 log-rank test

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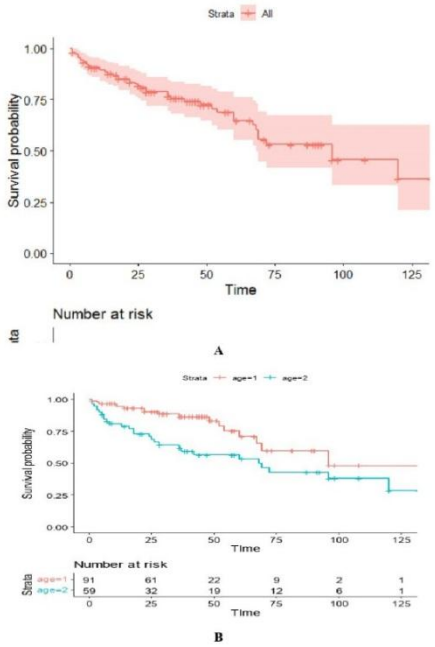

Figure 1. Survival probability of OC patients (A) overall, (B) age at diagnosis (age = 1, <60, age = 2. >60)

Patients in stage number one (I) of the disease had a longer survival estimate than other stages of the disease (II, III.IV) throughout almost the entire study period. The survival curve by treatment method indicated lower survival in the Surgery-only group. Patients who have undergone surgery only had the highest survival estimates (Figure 2).

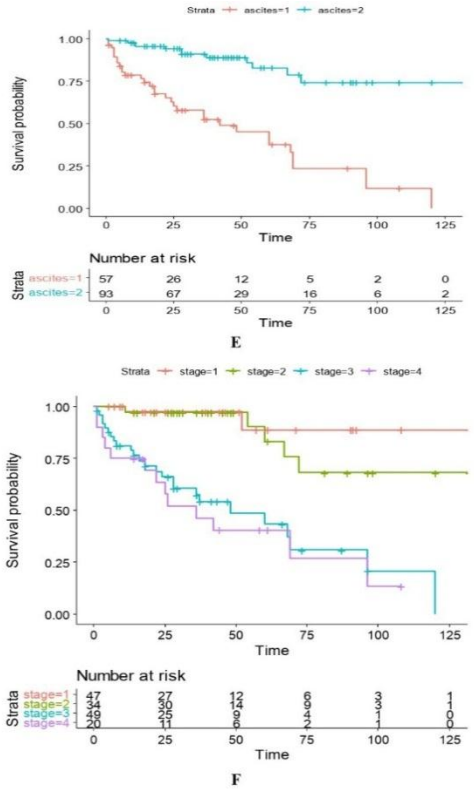

Figure 2. Survival probability of OC patients (C) stage disease (stage = 1, I, Stage2 = II, Stage = 3, III, Stage = 4. IV), (D) treatment method (Surgery then chemotherapy = 1, Chemotherapy then surgery = 2, Surgery only = 3, Chemotherapy only = 4.

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OC patients with ascites and no ascites had the lowest and highest survival probabilities, respectively. Also, Patients with DFS more than 65 months had a longer survival estimate than Patients with DFS less than 65 months (Figure 3).

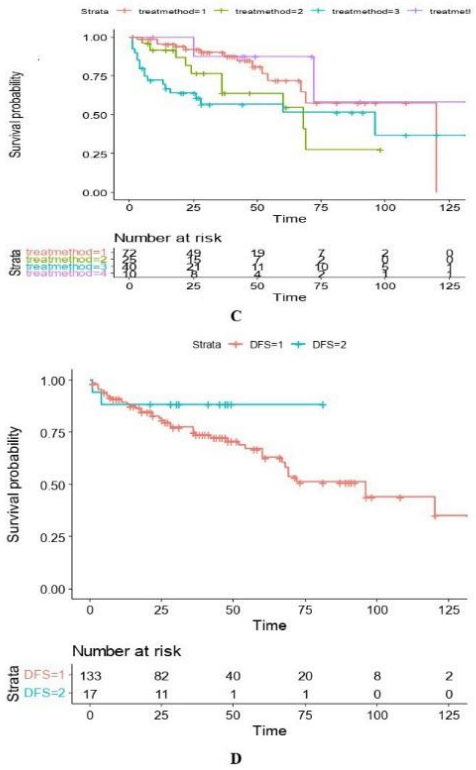

Figure 3. Survival probability of OC patients (E) ascites (ascites = 1, yes, ascites = 2. no), and (F) disease-free survival (dfs = 1, < 65, dfs = 2, > 65), Time (months)

The Schoenfeld residuals test showed no serious violation of the proportional Hazard assumption ($p > 0.05$).

Results of the univariate CPH model showed that the variables of patient age at diagnosis, stage of the disease, metastasis to other parts of the body, ascites, duration of relapse and treatment, ca125 before and after the disease, Recurrence of the disease, and ascites are related to patients' survival ($p < 0.05$).

Results of multivariable with adjusting potential confounders showed ascites and DFS with HR_{adj} =3.89 (95 % CI: 1.35-11.15, p-value = 0.01), HR_{adj} = 23.52 (95 % CI: 4.21-128.33, p-value = < 0.001); respectively as significant variables (Table2).

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Table 2. Results of univariate and multivariable Cox proportional hazard model

Factors	Levels	Univariate analysis HR (95%C.I)	p	Multivariable analysis HR_{adj} (95%C.I)	P
Age at diagnosis (yr)	60 < 60 >	Reference 2.3 3(1.26-4.309)	0.007	Reference 0.96 (0.42-2.15)	0.92
Married	yes No	2.12 (0.28-15.56) Reference	0.45	-- ---	---
Stage	I II III IV	Reference 2.24 (0.43-11.62) 13.316 (3.15-56.23) 15.91 (3.58-70.64)	--- 0.33 0.001 0.001	Reference 1.82 (0.30-10.37 4.55 (0.83-24.76) 2.45 (0.28-21.35)	-- 0.507 0.08 0.41
Ascites	Yes No	6.26 (3.22-12.16) Reference	0.001	3.89 (1.35-11.15) Reference	0.01
OCP	Yes No	Reference 1.84(0.78-4.36)	0.16	Reference 2.93(0.89-9.62)	0.07
Metastatic	Yes No	2.12(1.11-3.96) Reference	0.02	1.05(0.22-4.84) Reference	0.94
Recurrence	YES No	1.49(0.82-2.68) Reference	0.18	0.59 (0.27-1.31) Reference	0.19
Ca-1251(U/ML before treatment)	11585 ≤ 11585 >	Reference 4.61 (1.09-19.37)	0.03	Reference 1.84 (0.24-14.10)	0.55
Ca-1252(U/ML) after treatment	3000 ≤ 3000 >	5.03 (1.19-21.29) Reference	0.02	Reference 2.11 (0.26-17.11)	0.48
Dfs(Months)	65 ≤ >65	12.58 (2.89-54.76) Reference	0.001	23.52 (4.21-128.33) Reference	< 0.001
Treatment method	Surgery then chemotherapy Chemotherapy then surgery Surgery only Chemotherapy only	Reference 2.13 (0.94-4.80) 0. 75 (0.17-3.36)	--- 0.01 0.06 0.71	Reference 0.77 (0.26-2.28) 2.55 (0.97-6.73) 2.10 (0.34-12.72)	0.36 0.64 0.58 0.41
Other cancer	Yes No	1.34 (0.59-3.01) Reference	0.47	--- ---	---
family history of OC	Yes No	1.32 (0.65-2.68)	0.43	--- ---	---
BMI (kg/m2)	25 ≤ 25to30 30 >	Reference 0.52 (0.24-1.14) 0.47(0.20-1.11)	--- 0.10 0.08	--- ---	---

HR, Hazard ratio, HRadj, Hazard ratio adjust, p, p-value, Wald statistic

According to the results in Table 2, the risk of death for patients with a recurrence of fewer than 65 months was 23.52 times higher than for patients with a recurrence of more than 65 months. Also, the risk of death for people with ascites was 3.89 times higher for people without ascites.

Discussion

OC has the highest mortality rate of all gynecological cancers worldwide and is frequently (> 75%) diagnosed at an advanced stage (13). At the end of our study, overall, 45 deaths (30%) of 150 patients. Factors such as age at diagnosis BMI,

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married treatment method, disease stages, metastasis, recurrence, DFS, OCP, family history of OC, other cancers, and ca-125 before and after treatment were risk factors for OC. In this study, we found that Ascites and DFS are the most important independent predictors of survival in patients with ovarian cancer in the Yazd region of Iran. Which is compatible with the multivariable CPH model with Eisenkop and et al (14). In addition, DFS in our study was more than 65 months; this may be due to the long study time of our study (19 years). Over time, DFS estimates for patients with ovarian cancer improve dramatically, especially in those with poorer initial prognoses (15).

Ascites (uh-SIGH-tees) refer to excess fluid in the abdomen. This fluid collects in the space within the wall of the abdomen, between the abdominal organs. It is common in patients with liver disease and cirrhosis, though patients with cancer can also develop ascites (16). Malignant ascites is frequently found in OC, but also in various other solid tumor entities (17-19). According to the National Cancer Institute, malignant ascites is defined by the accumulation of fluid-containing cancer cells in the abdomen (20). Malignant ascites generally resolves when the underlying disease is successfully treated (21).

The adjusted hazard ratio for patients who had DFS lower than 65 months was 23.52 times higher than for patients with DFS more than 65 months. Also, the adjusted hazard ratio for patients with ascites was 3.59 times higher than for patients without ascites.

In our study, most patients were in stage (IV) of the disease, which was consistent with the studies (22, 23) the adjusted Hazard ratio for patients with stage (IV) was 15.91 higher than for patients with stage (I) which was not consistent with the studies (22, 24, 25).

The median survival time was 96 months (95% CI: 57.204-134.79), the overall mean survival rate of 84.05 (95% CI: 73.84- 94.62), and 1, 3, 5, and 10-year survival rates were obtained 83, 73, 55, 33 months, respectively. Which did not in line with the study conducted by Quan-Qing Zheng et al. on survival of ovarian cancer (26); they found that one, three-year, and five-year survival rates were 87.7%, 50.8%, and 31.1%, respectively. This issue may be due to different geographical areas, medical facilities, and disease-related features such as the stage of diagnosis, and marital status.

Most of the patients in our study were less than 60 years old, which was consistent with the studies (23, 26-29). Results of our study in comparing survival in the subgroups of study variables showed age at diagnosis, disease stage, ascites, and treatment methods were significant ($p < 0.05$). The median survival function was 96 months for people under 60 years of age and 98 months for people over 60 years of age, indicating lower survival of young women than middle-aged women, which was consistent with a study conducted by Wang et al. in 2019 (7). Most patients in our study were in the third stage of the disease, and the median survival time for them was 36 months, this finding was consistent with the Lund et al. study, in which most patients were in the same stage, but the median survival time was 16 months (30). Given that this study was conducted in 1991 and our study in 2018, this could be due to the development of treatment methods. Also, the median survival time was 120 months for those without metastasis and 96 months for those with metastases, which was a significant difference in survival time. Also, the median survival time was 120 months for those with a family history of OC and 96 months for those without a family history of cancer, which was a significant difference in survival. This may be because people with a family history go to the doctor sooner to get acquainted with the disease and fear of recurrence and advance the treatment process.

Our results also showed the median survival time for patients with ascites was 48 months, which was inconsistent with a similar study by Wang et al which declared survival time for the same group was 16 months (30). Most of the patients in our study did not have metastases, which may be due to a large number of patients in the first stage. Results of the univariate CPH model showed the variables such as age at diagnosis,

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stage of the disease, ascites, metastasis, ca125 before and after treatment, DFS, Chemotherapy then surgery were significant, this finding was in line with the Eisenkop et al study on OC (11).

In this study in terms, strength should be noted for the long follow-up time of patients as well as the most complete information of patients' medical records. There were limitations to the small sample size and our research was done only on patients of a hospital in Yazd.

Conclusion

OC as a common gynecologic cancer according to mortality rate has the seventh rank among women in the world. The results of the multivariable CPH model of our study showed that the variables DFS and ascites are the main risk factors for OC, and paying attention to them will be effective in increasing patient survival. Contrary to expectations, the age variables of patients at the time of diagnosis and stage of the disease, which were identified as influential variables in most studies, were not significant in this study.

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Conflict of interest

The authors have no conflicts of interest to declare for this study.

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None

Ethical considerations

The study was carried out by the institutional ethical standards and the Helsinki Declaration. Informed consent was taken and the data was de-identified. Permission from the institutional ethical committee was taken before carrying out the study

Code of ethics

IR.SSU.SPH.REC.1399.095

Authors' contribution

M. M., data collection; M.A and F.M, analyzed the data and review of literature and manuscript preparation. The manuscript was reviewed by H.A

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