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ORIGINAL ARTICLE

Impact of age on clinicopathological features and survival of epithelial ovarian neoplasms in reproductive age

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Abstract

Background Little is known about the effect of age on the prognosis of epithelial ovarian neoplasms. In the reproductive age, fertility-sparing surgery had been widely implemented. This study aimed to elucidate impact of age on the clinicopathologic characteristics and survival of epithelial ovarian neoplasms in the reproductive age.

Methods The clinical records of patients diagnosed as epithelial ovarian cancer or epithelial borderline ovarian tumor at the age of 40 years or younger at multiple institutions in the Tokai Ovarian Tumor Study Group were reviewed retrospectively. All patients were stratified into two age groups: group A (≤ 30 years) and group B (31–40 years). Univariate and multivariate analyses were performed to evaluate overall survival and disease-free survival.

Results A total of 583 patients (325 patients: cancer, 258 patients: borderline) were included. The median follow-up time was 62.0 months (range 1–270 months). Compared with group B, group A had a significantly higher rate of borderline tumor (66.7% vs. 32.7%, $p < 0.001$); stage I disease (85.9% vs. 70.4%, $p < 0.001$); mucinous type (69.2% vs. 35.6%, $p < 0.001$); conservative surgery (83.8% vs. 41.6%, $p < 0.001$); no adjuvant chemotherapy (67.2% vs. 44.7%, $p < 0.001$); and CA125 ≤ 35 U/mL (39.4% vs. 28.8%, $p < 0.05$). There was a significant difference in the overall survival ($p = 0.0051$) and the disease-free survival ($p = 0.0039$) between the two groups. Multivariate analysis revealed that the independent prognostic factors for the overall survival were age, stage, histology, and ascitic fluid cytology.

Conclusion In epithelial ovarian neoplasms, younger patients had a survival advantage over older patients.

Keywords Ovarian neoplasm · Epithelial ovarian cancer · Fertility preservations · Age group · Survival

Introduction

Ovarian neoplasm is the most fatal gynecologic malignancy, and epithelial ovarian neoplasms consist of epithelial ovarian cancer (EOC) and borderline ovarian tumor (BOT) [1]. Every year in Japan, approximately 10,000 patients are diagnosed as EOC; most of them are in the postmenopausal age and only less than 10% are diagnosed at the age of 40 years or less [2]. One of the clinical dilemmas in the treatment of EOC in the reproductive age is fertility preservation. Providing adequate information about the clinical outcome allows these patients to make a satisfying decision on whether to undergo fertility-sparing surgery (FSS) with unilateral oophorectomy or complete staging laparotomy, including hysterectomy, bilateral salpingo-oophorectomy, omentectomy, and cytology of the ascitic fluid. At this point, FSS had been widely accepted for the clinical management of early-stage EOC, but its efficacy and risks had not been thoroughly elucidated by a prospective study [3]. Therefore, to confirm the efficacy and safety of FSS for patients with early-stage EOC, a confirmatory study was started in Japan [4]. Meanwhile, other previous studies demonstrated that the proportion of BOT was approximately 10–20% of all epithelial ovarian neoplasms [5, 6]. BOT is characterized by nuclear atypia, atypical epithelial proliferation, and elevated

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level of mitotic activity, without destructive stromal invasion [7]. Although patients with BOT are frequently diagnosed at an earlier stage and younger age, compared with those with EOC, complete staging laparotomy is the recommended standard surgical procedure [8]. FSS is also accepted for BOT [9]. Considering the current difficulty in diagnosing malignancy before surgery, provision of as much information as possible is desirable so that patients and their family can properly choose the surgical procedure. The lack of exact details on the clinicopathologic features stratified by age in the reproductive age may lead to suboptimal informed decision.

Considering that fertility declines with age, the characteristics of epithelial ovarian neoplasms may be possibly associated with age [10]. Some previous studies showed that compared with the average ovarian cancer population, younger EOC patients had more favorable prognosis because of the higher rate of early stage, low-grade tumors; however, age was not an independent prognostic factor [11, 12]. On the other hand, other several studies identified younger age as a significant favorable prognostic factor [13, 14]. However, most of these previous publications analyzed data from Western countries, and only few data are available on the effect of age on the clinicopathologic profile and survival rate of epithelial ovarian neoplasm in an Asian population. Therefore, age being an independent prognostic factor in an Asian population is unclear.

The current study aimed to clarify clinicopathological differences according to age stratification and to determine whether age was an independent prognostic factor in EOC and BOT patients at the age of 40 years or less.

Materials and methods

Patient enrolment

The clinical records of the Tokai Ovarian Tumor Study Group (TOTSG), from 1986 to 2017 were reviewed. The TOTSG comprised Nagoya University Hospital and 14 collaborating hospitals, including Aichi Cancer Center Hospital, Anjo Kosei Hospital, Toyohashi Municipal Hospital, Toyota Memorial Hospital, Ogaki Municipal Hospital, Nagoya First Red-cross Hospital, Nagoya Second Red-cross Hospital, Nagoya Ekisaikai Hospital, Nagoya Memorial Hospital, Okazaki Municipal Hospital, Handa City Hospital, Komaki City Hospital, and Gifu Prefectural Tajimi Hospital. Patients aged 40 years or less upon the diagnosis of EOC or BOT were enrolled. All histologic slides were pathologically reviewed by one or two pathologists who were blinded to the patients' clinical information. With regard to the histologic types, the World Health Organization classification criteria were adopted [15]. Patients were staged according to the 2014 International Federation of Gynecology and Obstetrics (FIGO) criteria [16, 17]. Patients who were lost to follow-up within a short period after surgery or those with unconfirmed FIGO stage or surgical procedures were excluded from this study. This study was approved by the Nagoya University Hospital's ethics committee. This work was supported in part by the Japan Society for the Promotion of Science (JSPS) KAKENHI Grant number 15H02660 (Grant-in-Aid for Scientific Research A for Fumitaka Kikkawa).

In this study, we divided the whole series of patients into two groups, according to their age at the time of the primary operation: group A (≤ 30 years) and group B (31–40 years).

Treatment

In principle, all patients underwent primary laparotomy to evaluate the abdominal contents and for staging. The standard primary surgical treatment for EOC comprised hysterectomy, bilateral salpingo-oophorectomy, infracolic omentectomy, and retroperitoneal lymphadenectomy or sampling. The standard primary surgical treatment for BOT included hysterectomy, bilateral salpingo-oophorectomy, and infracolic omentectomy. Principally, patients who underwent FSS were eligible if they: (1) had clinically confirmed stage I disease by preoperative CT scan; (2) were less than 40 years of age at primary treatment; (3) had strong desire for fertility preservation at the time of preoperative explanation; (4) were informed of the risk of FSS and signed a consent form; (5) underwent salpingo-oophorectomy on the side of the ovarian tumor, and peritoneal staging including ascitic fluid cytology, careful palpation, and examination over the entire abdominal cavity; and (6) systemic retroperitoneal lymphadenectomy or sampling was optional. In this analysis, we defined as radical surgery, if at least hysterectomy, bilateral salpingo-oophorectomy, and infracolic omentectomy were completed. Conservative surgery was defined as the performance of at least unilateral salpingo-oophorectomy or cystectomy, which includes FSS.

In principle, patients with BOT did not undergo adjuvant chemotherapy except for stage III–IV. Patients in all stage EOC except for IA-IB/Grade 1 tumor were principally treated with 3–6 cycles of adjuvant platinum ± taxane chemotherapy after primary surgery. The chemotherapeutic policy has changed over time. However, as a general rule, the selection criteria for the first regimen was the same among facilities belonging to TOTSG.

Follow-up

After the end of treatment, the patients returned for follow-up evaluation every 2–3 months for the first 2 years, then every 4–6 months for the succeeding 3 years. Computed tomography and/or positron emission tomography

was performed annually to detect radiologic recurrence. Clinical recurrence was defined as elevated CA-125, the development of ascites, or the presence of a palpable mass.

Analysis

Chi square test, Fisher's exact test or Student's *t* test was used to evaluate the differences in the clinicopathologic factors between the two groups. Overall survival (OS) was defined as the period between the day of the primary surgery and the last day of follow-up or death. Disease-free survival (DFS) was defined as the period between the day of the primary surgery and the day that the patient survives without evidence of recurrence. Univariate and multivariate analyses were conducted using the Cox proportional hazards regression model to identify the independent risk factors. The Kaplan–Meier method was performed to calculate the survival rates, which were compared between the two groups using the log-rank test. The threshold for significance was $p < 0.05$. All statistical analyses were conducted using JMP, version 14 (SAS Institution Inc., Cary. NC, USA).

Results

Table 1 shows the clinicopathologic characteristics of the 583 patients included in the study. The median follow-up time was 62.0 months (range 1–270 months) and the median age was 34 years (range 12–40 years). The histological distribution of EOC and BOT is shown in Supplementary Table 1. Table 2 shows the distribution of the clinicopathologic features stratified by age group. The proportion of patients with stage III–IV tumors was 11.1% (22 patients) in group A and 18.7% (72 patients) in group B. Patients in group B had significantly more advanced-stage tumors, compared with patients in group A ($p < 0.001$). Mucinous tumors were significantly more likely to be found in group A than in group B ($p < 0.001$), although this histologic type of tumor was the most represented type in both groups. The incidence of clear cell tumors was 2.5% in group A and 23.4% in group B. The proportion of EOC was significantly lower in group A than in group B. The surgical procedure in groups A and B was conservative surgery in 83.8% and 41.6%, respectively, and radical or other surgery in 16.2% and 58.4%, respectively.

At first, the prognosis between the two groups was compared. Based on Kaplan–Meier analysis, the respective 5- and 10-year OS rates were 90.9% and 86.9% in group A, and 82.6% and 78.8% in group B (Fig. 1). The respective 5- and 10-year DFS rates were 89.9% and 86.7% in group A, and 80.7% and 74.5% in group B (Fig. 2). The OS and DFS were significantly different between the two groups ($p = 0.0051$ and $p = 0.0039$, respectively). On the other hand, the two groups had similar OS, after stratification according to the diagnosis of EOC ($p = 0.495$) or BOT ($p = 0.668$).

Table 1 Patient characteristics

	n	%
Patients	583	
Age, years		
Median (range)	34 (12–40)	
Age		
≤30	198	(34.0)
31–40	385	(66.0)
Period		
1986–1999	168	(28.8)
2000–2017	415	(71.2)
Stage		
I	441	(75.6)
II	48	(8.2)
III	80	(13.7)
IV	14	(2.4)
Ascitic fluid cytology		
Positive	110	(18.9)
Negative	347	(59.5)
NA	126	(21.6)
Histology		
Serous	123	(21.1)
Mucinous	274	(47.0)
Endometrioid	78	(13.4)
Clear cell	95	(16.3)
Others	13	(2.2)
EOC or BOT		
EOC	325	(55.7)
BOT	258	(44.3)
CA125		
≤35 U/mL	189	(32.4)
>35 U/mL	368	(63.1)
NA	26	(4.5)
CA19-9		
≤37 U/mL	277	(47.5)
>37 U/mL	209	(35.8)
NA	97	(16.6)
Surgical procedure		
Conservative	326	(55.9)
Radical	242	(41.5)
Others	15	(2.6)
Adjuvant chemotherapy		
Taxane plus platinum	187	(32.1)
Platinum without taxane	91	(15.6)
No	305	(52.3)

EOC epithelial ovarian cancer, *BOT* borderline ovarian tumor, *NA* not available

Table 2 Clinicopathologic characteristics stratified by age

	Group A (age ≤ 30 years, *n* = 198)		Group B (age 31–40 years, *n* = 385)		*p* value
	n	%	*n*	%	
Period					< 0.05
1986–1999	70	(35.4)	98	(25.5)	
2000–2017	128	(64.6)	287	(74.5)	
Stage					< 0.001
I	170	(85.9)	271	(70.4)	
II	6	(3.0)	42	(10.9)	
III	16	(8.1)	64	(16.6)	
IV	6	(3.0)	8	(2.1)	
Ascitic fluid cytology					0.061
Positive	27	(13.6)	83	(21.6)	
Negative	125	(63.1)	222	(57.7)	
NA	46	(23.2)	80	(20.8)	
Histology					< 0.001
Serous	40	(20.2)	83	(21.6)	
Mucinous	137	(69.2)	137	(35.6)	
Endometrioid	10	(5.1)	68	(17.7)	
Clear cell	5	(2.5)	90	(23.4)	
Others	6	(3.0)	7	(1.8)	
EOC or BOT					< 0.001
EOC	66	(33.3)	259	(67.3)	
BOT	132	(66.7)	126	(32.7)	
CA125					< 0.05
≤ 35 U/mL	78	(39.4)	111	(28.8)	
> 35 U/mL	106	(53.5)	262	(68.1)	
NA	14	(7.1)	12	(3.1)	
CA19-9					0.287
≤ 37 U/mL	88	(44.4)	189	(49.1)	
> 37 U/mL	66	(33.3)	143	(37.1)	
NA	44	(22.2)	53	(13.8)	
Surgical procedure					< 0.001
Conservative	166	(83.8)	160	(41.6)	
Radical	30	(15.2)	212	(55.1)	
Others	2	(1.0)	13	(3.4)	
Adjuvant chemotherapy					< 0.001
Taxane plus platinum	33	(16.7)	154	(40.0)	
Platinum without taxane	32	(16.2)	59	(15.3)	
No	133	(67.2)	172	(44.7)	

EOC epithelial ovarian cancer, *BOT* borderline ovarian tumor, *NA* not available

For univariate analysis, we subsequently categorized patients with EOC and BOT according to age at diagnosis, era at diagnosis, FIGO stage, histologic type, diagnosis of EOC or BOT, preoperative CA-125 value, preoperative CA 19-9 value, surgical procedure, adjuvant chemotherapy, and status of ascitic fluid cytology (Table 3). As a result, age, FIGO stage, histologic type, diagnosis of EOC or BOT, preoperative CA-125 value, surgical procedure, and status of ascitic fluid cytology were identified as the factors associated with short OS. To minimize selection bias and eliminate confounding factors, all of these categories were entered into a multivariate OS analysis system by Cox proportional hazards regression model. Age at diagnosis, FIGO stage, histologic type, diagnosis of EOC or BOT, and status of ascitic fluid cytology retained statistical significance as prognostic factors for OS. Even for EOC alone, multivariate analysis revealed that age at diagnosis, FIGO stage, and histologic type were significant prognostic factors for OS (Table 4).

Discussion

In this study, we analyzed clinicopathological characteristics and the survival outcomes of patients with EOC and BOT in the reproductive age in Japan. We demonstrated a statistically significant inferior survival for patients at the age of 31–40 years than for patients at the age of 30 years or less. We also found significantly different clinicopathologic characteristics between the two groups stratified by age. Our results presented useful information for the treatment selection for patients with both EOC and BOT in the reproductive age.

Our study identified that, in patients with EOC and BOT in the reproductive age, relatively old age, high stage, and positive ascitic fluid cytology were significantly associated with decreased OS. The FIGO stage had been shown to be a prognostic factor for patients with EOC and BOT [18, 19]. Our result on the correlation between advanced FIGO stage and decreased survival in the reproductive age was consistent with the previous findings [20, 21]. Ascitic fluid cytology, which enables detection of occult metastases, is part of the FIGO staging system for early ovarian cancer. Davidson et al. [22] reported that positive ascitic fluid cytology results increased the risk for disease recurrence. In patients with early-stage clear cell carcinoma, Kajiyama et al. [23] reported that stage greater than IC2–IC3 and possible occult metastasis had an increased risk of mortality after complete surgical resection, compared to stage IA–IC1. In agreement with previous studies, our study showed that positive ascitic fluid cytology was significantly associated with short survival time. We also identified age as an independent prognostic factor in our population. Some previous studies analyzed patients of all ages and compared the prognosis between younger and older patients, based on the cutoff age of 40 years [24, 25]. Trillsch et al. [25] reported that increased age (≥ 70 years) was significantly associated with decreased progression-free survival and OS among 275 patients with advanced-stage EOC in Western countries.

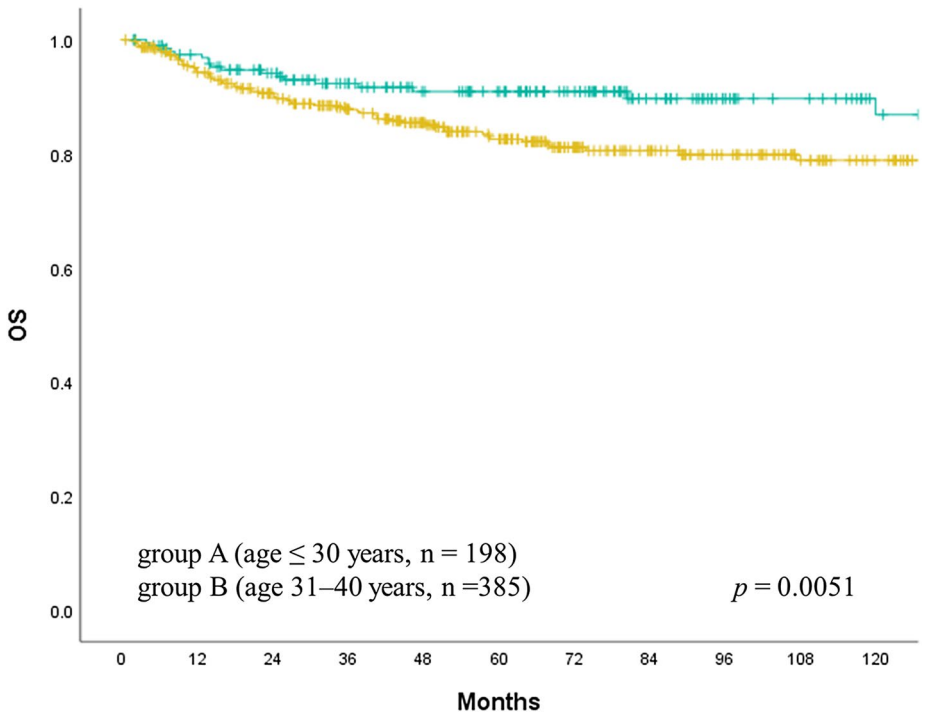

Fig. 1 Estimated overall survival of patients with epithelial ovarian cancer and borderline ovarian tumor stratified by age (group A, age ≤ 30 years; group B, age 31–40 years)

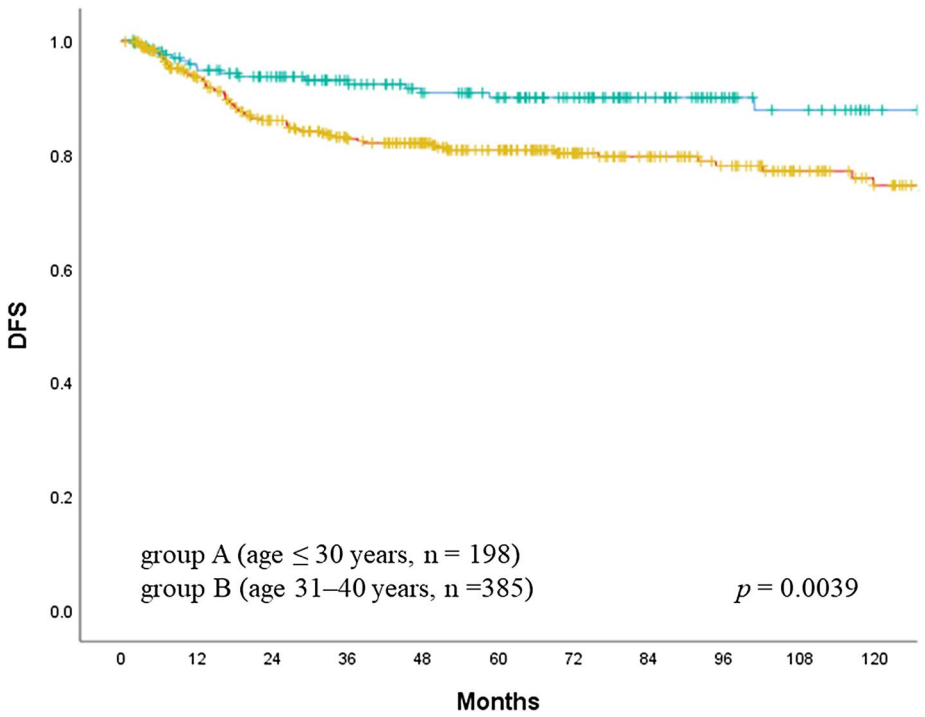

Fig. 2 Estimated disease-free survival of patients with epithelial ovarian cancer and borderline ovarian tumor stratified by age (group A, age ≤ 30 years; group B, age 31–40 years)

Sabatier et al. [26] identified the significant association between age and OS in a French population with EOC. Moreover, by analyzing the SEER database, Chan et al. [13] reported that a relatively young age independently led to a favorable prognosis in a US population. On the other hand, Yoshikawa et al. [24] evaluated 1562 patients with EOC in all stages in Japan, and found that young age (< 40 years) was not an independent prognostic factor for OS. Considering the differences in ethnicity and genetic background among countries, most previous publications suggested that age can be an independent prognostic factor in EOC, and this was consistent with our current findings that younger age was correlated with better prognosis.

Table 3 Uni- and multivariate analyses of clinicopathologic parameters in relation to overall survival of patients with EOC or BOT

	Univariate		Multivariate	
	HR (95% CI)	*p* value	HR (95% CI)	*p* value
Age				
≤30	1		1	
31–40	2.069 (1.259–3.584)	<0.05	2.059 (1.128–3.904)	<0.05
Period				
1986–1999	1		1	
2000–2017	0.942 (0.601–1.508)	0.798	1.149 (0.513–2.495)	0.729
Stage				
I	1		1	
II	4.626 (2.340–8.762)	<0.001	3.713 (1.741–7.609)	<0.05
III	9.758 (5.910–16.334)	<0.001	7.233 (3.849–13.814)	<0.001
IV	19.944 (9.096–40.472)	<0.001	12.737 (5.089–30.140)	<0.001
Ascitic fluid cytology				
Positive	1		1	
Negative or NA	0.220 (0.144–0.336)	<0.001	0.554 (0.341–0.900)	<0.05
Histology				
Serous	1		1	
Mucinous	0.423 (0.239–0.749)	<0.05	2.164 (1.044–4.483)	<0.05
Endometrioid	0.587 (0.280–1.228)	0.144	0.435 (0.191–0.993)	<0.05
Clear cell	1.287 (0.730–2.268)	0.383	1.310 (0.722–2.377)	0.374
Others	2.439 (0.928–6.407)	0.101	2.835 (0.988–8.133)	0.076
EOC or BOT				
EOC	1		1	
BOT	0.045 (0.012–0.126)	<0.001	0.065 (0.015–0.186)	<0.001
CA125				
≤35 U/mL	1		1	
>35 U/mL or NA	4.646 (2.387–10.452)	<0.001	1.906 (0.854–4.735)	0.119
CA19-9				
≤37 U/mL	1		1	
>37 U/mL or NA	1.359 (0.880–2.126)	0.172	1.407 (0.856–2.337)	0.178
Surgical procedure				
Conservative	1		1	
Radical or others	3.051 (1.930–4.982)	<0.001	0.633 (0.365–1.129)	0.120
Adjuvant chemotherapy				
Taxane plus platinum	1		1	
Platinum without taxane	1.097 (0.664–1.781)	0.710	1.924 (0.849–4.113)	0.114
No	0.226 (0.123–0.394)	<0.001	1.134 (0.509–2.414)	0.750

HR hazard ratio, *CI* confidence interval, *EOC* epithelial ovarian cancer, *BOT* borderline ovarian tumor, *NA* not available

The findings in this study of more frequent BOT, mucinous histology, and negative ascitic fluid cytology; decreased value of CA-125 and CA19-9; and earlier stage at presentation in younger patients than in older patients may contribute to better prognosis. Although these findings partly explain the better prognosis, younger age was an independent prognostic factor for increased OS in the multivariate analysis. Although the reason for the correlation between age and prognosis is not clear, unknown differences in the potential immunity or tumor characteristics that promote malignancy, such as DNA ploidy or mutation of TP53, may play a role [27, 28].

Based on our results, the prognosis did not differ according to the surgical method. Likewise, previous several reports demonstrated no significant difference in the long-term prognosis of early-stage epithelial neoplasms between FSS and radical surgery [9, 29, 30]. In this context, the current findings suggested that conservative surgery, including FSS, did not affect the survival of patients in the reproductive age. To our best knowledge, there had been only few

Table 4 Uni- and multivariate analyses of clinicopathologic parameters in relation to overall survival of patients with EOC

	Univariate		Multivariate	
	HR	*p* value	HR	*p* value
Age				
≤30	1		1	
31–40	1.124 (0.674–1.984)	0.669	2.008 (1.077–3.895)	<0.05
Period				
1986–1999	1		1	
2000–2017	1.086 (0.688–1.752)	0.728	1.175 (0.512–2.599)	0.697
Stage				
I	1		1	
II	2.859 (1.432–5.490)	<0.05	3.789 (1.766–7.841)	<0.05
III	6.729 (4.011–11.480)	<0.001	7.273 (3.799–14.212)	<0.001
IV	10.650 (4.818–21.890)	<0.001	12.627 (4.998–30.239)	<0.001
Ascitic fluid cytology				
Positive	1		1	
Negative or NA	0.332 (0.215–0.512)	<0.001	0.605 (0.364–1.004)	0.052
Histology				
Serous	1		1	
Mucinous	0.439 (0.242–0.795)	<0.05	1.871 (0.874–4.004)	0.109
Endometrioid	0.276 (0.132–0.578)	<0.001	0.409 (0.179–0.935)	<0.05
Clear cell	0.557 (0.316–0.982)	<0.05	1.259 (0.693–2.288)	0.449
Others	1.670 (0.635–4.391)	0.326	2.725 (0.944–7.865)	0.088
CA125				
≤35 U/mL	1		1	
>35 U/mL or NA	3.259 (1.671–7.340)	<0.05	1.690 (0.743–4.259)	0.218
CA19-9				
≤37 U/mL	1		1	
>37 U/mL or NA	1.371 (0.882–2.163)	0.162	1.467 (0.887–2.455)	0.136
Surgical procedure				
Conservative	1		1	
Radical or others	1.559 (0.973–2.593)	0.066	0.635 (0.361–1.151)	0.132
Adjuvant chemotherapy				
Taxane plus platinum	1		1	
Platinum without taxane	1.239 (0.747–2.019)	0.398	1.932 (0.837–4.185)	0.119
No	0.593 (0.316–1.052)	0.075	1.235 (0.539–2.686)	0.607

HR hazard ratio, *CI* confidence interval, *EOC* epithelial ovarian cancer, *NA* not available

reports that investigated the prognostic factors in a reproductive age population. Age may affect the survival of patients with epithelial ovarian neoplasm as well as female fertility. Even in patients with strong preference for fertility preservation, careful selection of treatment should be made while paying attention to age-dependent changes in fertility and survival.

The strengths of our study were mainly based on the relatively large sample size and the central pathologic review for histology. However, the current study was inconclusive and had several limitations due to its retrospective nature and patient enrolment from multiple hospitals over a long time. The other limitations of this study included heterogeneous follow-up period, varied treatment protocols with various types of surgery for over 30 years, and the different chemotherapy regimens. Moreover, multivariate analysis may not have sufficiently minimized the effects of confounding factors, because some of the variables analyzed in this study are collinear with each other. On this occasion, we merely propose a hypothesis that younger patients (≤ 30 years) suspicious of epithelial ovarian neoplasm may have a better prognosis than older patients (31–40 years). Evaluation of larger populations of ovarian neoplasms in other Asian countries is needed to verify the findings of this study.

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Compliance with ethical standards

Conflict of interest The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Ethical approval The study was approved by the ethics committee of the institution (Approval no.: 2006-0357).

Informed consent For this study, the IRB issued a waiver for written consent because data collection was retrospective.

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