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A comprehensive prognostic analysis of cause-specific mortality in patients with ovarian serous cystadenocarcinoma using a competing-risks model: a case study of the SEER database

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Abstract. – OBJECTIVE: This retrospective study employed a competing-risks analysis utilizing the Surveillance, Epidemiology, and End Results (SEER) database to identify precise prognostic factors associated with ovarian serous cystadenocarcinoma (OSCC) in patients.

PATIENTS AND METHODS: Patients with OSCC during 2004-2015 were identified in the SEER database, and their clinicopathological, demographic, and survival data were examined. Univariate analysis using Gray's test and the cumulative incidence function was used to evaluate the prognoses of events of interest. The multivariate analysis involved several models, including the Cox proportional hazards, Fine-Gray, and cause-specific (CS) hazard function models, to estimate the hazard functions of competing risks. Hazard ratios were analyzed to identify the reliability of the prognostic factors.

RESULTS: Among the 10,400 individuals diagnosed with OSCC, 5,713 died from the illness, and 1,125 died from other causes. The cumulative incidence rate of events of interest was found to be significant for ethnicity, age at diagnosis, histological grade, American Joint Committee on Cancer (AJCC) stage, chemotherapy and surgery status, tumor size, marital status, and local lymph node metastases ($p<0.05$). The multivariate analysis revealed that ethnicity, histological grade, surgery and chemotherapy status, age at diagnosis, AJCC stage, marital status, and distant metastases were independent prognostic factors in the Cox model ($p<0.05$). Finally, the Fine-Gray and CS models demonstrated that ethnicity, histological grade, surgery and chemotherapy status, age at diagnosis, AJCC stage, tumor size, marital status, and combination summary stage were all identified as independent prognostic factors ($p<0.05$).

CONCLUSIONS: This study determined the risk factors for OSCC using a competing risk analysis model established by the SEER database. The findings can help clinicians understand OSCC better and provide more accurate medical support to affected patients.

Key Words:
Ovarian serous cystadenocarcinoma, SEER, Prognosis, Competing-risk model, Fine-Gray.

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Abbreviations

OSCC: ovarian serous cystadenocarcinoma; AJCC: American Joint Committee on Cancer; SEER: Surveillance, Epidemiology, and End Results; COD: common cause of death; CS: cause-specific; CIF: cumulative incidence function; RNP: regional nodes positive.
N: patient number; ICD-O-3: International Classification of Diseases for Oncology, Third Edition.

Introduction

Ovarian cancer, one of the most aggressive gynecological malignancies worldwide, is the seventh most common malignant tumor in females, accounting for 3% of cases. Among gynecological tumors, it is the second most common cause of death (COD) and the eighth leading cause of death among tumors in females. Annually, there are 239,000 new cases (3.6% of all malignancy cases) and 152,000 deaths (4.3% of all tumor deaths)[1,2]. In accordance with the Surveillance, Epidemiology, and End Results (SEER) program, over-seen by the American National Cancer Institute (NCI), the latest statistical cohort[3] reported an annual incidence of 11.6 cases per 100,000 women, thereby estimating the prevalence of 224,940 women affected by the ailment in the year 2015. Concurrently, within the Canadian context, the Canadian Cancer Society prognosticated an average of 2,800 newly diagnosed cases and an unfortunate 1,800 mortalities per annum during the year 2017[4].

Ovarian serous cystadenocarcinoma (OSCC) is the predominant histological variation of ovarian cancer, accounting for 90% of cases and has a low 5-year survival rate and poor prognosis[5]. Although the incidence rate of ovarian cancer has decreased in the last 20 years, this was only by less than 1%. At the same time, there was no change in the data on death caused by this disease[6]. The onset of ovarian cancer tends to occur after 60 years of age and has a lifetime death rate of 1 in 90 and a lifetime occurrence risk of 1 in 70[7]. The specific etiology of ovarian cancer remains unclear. A significant family history of ovarian or breast cancer has been considered a significant risk factor for OSCC[8].

Previous studies[9-11] have investigated the prognostic factors for OSCC. However, to examine many possible variables, almost all of those studies employed conventional survival analysis techniques, such as the Cox proportional hazards model for comparing Kaplan-Meier marginal regression analysis, log-rank tests, or survival curves. In contrast, the common survival analysis method should be set so that there is no risk of competition; that is, the censoring time is independent of the expiry time. The result would be a single end-point in this situation[12]. Furthermore, there are often many competing outcomes in medical research; that is, the occurrence of one outcome can prevent or greatly reduce the likelihood of another. For example, a person who dies from heart disease cannot subsequently die from cancer[13]. Such conflicting occurrences are frequently censored by conventional incidence analysis approaches, which could lead to an overestimation of the cumulative incidence rate[14]. These properties imply that multiple endpoints need to be managed, which requires the use of a competing-risks model.

This study aimed to identify reliable pro-gnostic factors for OSCC through the application of a competing-risks model utilizing data from the Surveillance, Epidemiology, and End Results (SEER) database. Furthermore, the study aimed to compare and contrast the efficacy of the Cox proportional hazards and competing-risks regression models in determining prognostic factors.

Patients and Methods

Patient Source

The SEER database (version 8.4.0.1) was used to extract the data of patients with OSCC. The SEER database is one of the most representative and important oncology datasets in the Western world. The database collects information on malignancy occurrence and continuation rates and is supported by the National Cancer Institute. It covers 28% of the total United States population and 18 registries and collects relevant data on all malignant tumors identified in the representative population and its subgroups[15-17].

This study followed the principles of the Declaration of Helsinki. No approval was required from an institutional review board or Ethics Committee since the SEER database contains anonymized patient data.

Acquisition and Analysis of Empirical Data

We identified patients with OSCC from the SEER database from 2004 to 2015 by searching for records that contained the site code "C56.9-ovary" under ICD-O-3 "His/behave" code 8441/3 ("Serous cystadenocarcinoma, NOS"). Patients who fulfilled any of the following criteria were not considered for inclusion in the study: (a) diagnosis based solely on autopsy or death certificate,

(b) presence of multiple primary tumors, (c) lack of information on their ethnicity, marital status, laterality, differentiation grade, TNM stage, or COD according to the sixth edition of the AJCC staging system, (d) ovarian cancer with a bilateral origin, or (e) survival time of less than 1 month. We gathered 16 clinicopathological and demographic variables from the SEER database: combined summary stage (local, regional, or distant), age at diagnosis, sex, histological grade, ethnicity, marital status, tumor size, income status, chemotherapy status, surgery status, radiotherapy status, local lymph node metastasis, AJCC stage, life status, survival time, and COD. Patients were categorized by age into 45, 45-65, or >65 years; tumor size was categorized into 1-10, 11-20, and >20 mm; and regional nodes positive (RNP) was classified into two groups: yes and no. Moreover, histological grades were categorized as follows: I, well-differentiated; II, moderately differentiated; III, poorly differentiated; and IV, anaplastic. Marital status was classified as married, unmarried, divorced, or widowed. The study outcomes included patients who succumbed to causes other than OSCC, with the alive or deceased status from OSCC serving as the competing COD outcome indicator.

After performing a thorough and stringent selection procedure, the final analysis was applied to 10,400 eligible patients with OSCC. Figure 1 illustrates the remaining cases that met the inclusion criteria.

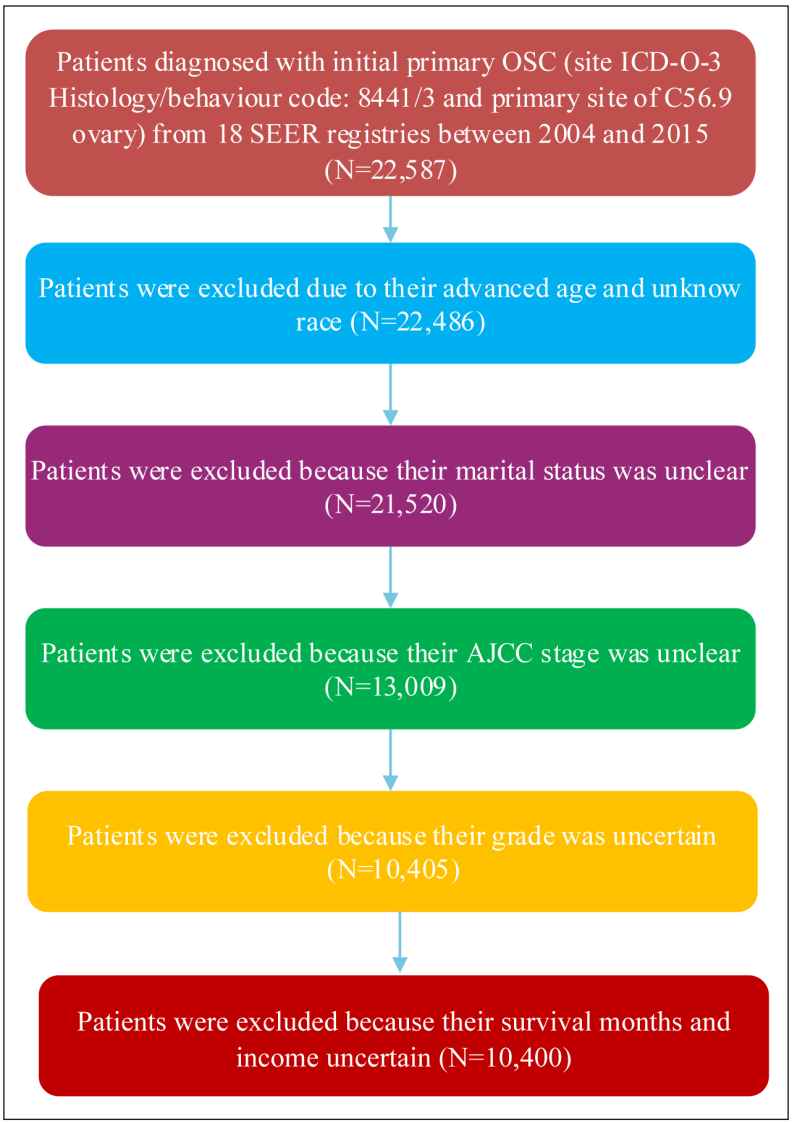

Figure 1. A flowchart depicting the screening procedure in the SEER database.

Statistical Analysis

Frequencies and percentages were used to represent qualitative statistics, while means and standard deviations were used for continuous data.

The cumulative incidence function (CIF), which accounts for competing risks, was employed to assess the cumulative probability of each event at 1, 3, and 5 years. The follow-up results for each patient were divided into three categories to complete the model analysis: censored events, competing events, and OSCC-specific deaths. CIF is a representation of the probability of the k-th event occurring prior to time t, along with any subsequent events. It can be expressed as $CIFk(t)=Pr(T\leq t, D=k)$[18]. Gray's test was used to evaluate the cu-mulative incidence rates of the different groups[19].

The univariate analysis employed the CIF to estimate the probability of each event occurring, while Gray's test was utilized to assess differences in CIF between the groups. Multivariate analysis was conducted using the Fine-Gray model to systematically examine the variables that influenced the cumulative incidence rate of OSCC. The Fine-Gray model is a statistical approach primarily used to calculate and analyze the cumulative occurrence of target events[20]. This method can effectively predict and analyze individual risks and plays a positive role in determining the risk and prognosis of a disease[21].

Nelson-Aalen cumulative risk curves were generated to depict the CIF. Gray's test was applied to compare the results of the Cox regression model with those of the Fine-Gray and competing-risk models and to assess the OSCC-specific mortality rates between the two groups. Competing-hazard models were utilized to compare the risk of a specific endpoint of interest and the cumulative hazard, with the aim of developing a prog-nostic clinical model.

Statistical analyses were conducted using R statistical software (https://www.r-project.org; version 4.2.1) and SPSS software (version 25.0, IBM Corp., Armonk, NY, USA). The R package "cmprsk" was utilized to construct the model. A two-sided $p<0.05$ was chosen as the significance threshold in all statistical tests.

Results

Patient Characteristics

Among the eligible 10,400 patients with OSCC, 1,125 (10.82%) died from other causes that were considered competing events, such as other malignancies, accidents, and suicide. Among the population, 5,713 (54.93%) died from OSCC. The most common characteristics of those who died from OSCC were being 45-65 years old (n=2,799, 26.91%), white (n=4,877, 46.89%), having a poorly differentiated histological grade (n=2,969, 28.55%), previously received surgery (n=5,428, 52.19%), AJCC stage III (n=3,384, 32.54%), previously received chemotherapy (n=4,859, 46.72%), tumor larger than 2 cm (n=5,276, 50.73%), never received radio-therapy (n=5,640, 54.23%), regional lymph nodes involved (n=5,639, 54.22%), affluent class income (n=2,087, 20.07%), married (n=3,110, 29.9%), and a predominance of distant organ metastases (n=5,119, 49.22%). Table I provides a comprehensive summary of the detailed information regarding the study outcomes.

Univariate Analysis of Prognostic Factors in OSCC

The CIF and Gray's tests were applied to the univariate analysis. When competing risks were present, Gray's test indicated that the following variables exerted significant effects on the OSCC prognosis in patients: AJCC stage, ethnicity, chemotherapy status, surgery status, marital status, age at diagnosis, and combination summary stage, regional lymph node metastasis, histological grade, and tumor size ($p<0.05$). The CIF demonstrated an increase for nearly all variables at 1, 3, and 5-year follow-ups, with a higher incidence rate observed among individuals older than 65 years, who were black, divorced, or widowed, in AJCC stage IV, with relatively large tumors (1-2 cm), who had never undergone surgery or chemotherapy and had regional lymph node metastasis, a poor differentiation grade, and a higher rate of distant metastases. CIF val-ues for patients with poorly differentiated tumors were 10.6%, 33.3%, and 48.9% at 1, 3, and 5 years, respectively. Table II lists the detailed information on outcomes, while Figure 2 illustrates the CIF curves for cause-specific (CS) mortality.

Multivariate Analysis of Prognostic Factors in OSCC

Variables that were significant in the univariate analysis, while competing events were present, were applied to the Fine-Gray model. Risk variables that independently influenced the prognosis of patients with OSCC were middle-aged or elderly, black or other ethnicity, AJCC stage, no surgery or chemotherapy, distant metastasis, tumor size, histological grade, and single or divorced/widowed.

Table I. Baseline characteristics and demographics of patients.

Variable	All patients (%)	Concerned (%)	Competition (%)	Censored (%)
N	10,400	5,713	1,125	3,562
Age				
<45	877 (8.43)	375 (3.61)	48 (0.46)	454 (4.37)
45-65	5,324 (51.19)	2,799 (26.91)	448 (4.31)	2,077 (19.97)
>65	4,199 (40.38)	2,539 (24.41)	629 (6.05)	1,031 (9.91)
Ethnicity				
White	8,858 (85.17)	4,877 (46.89)	949 (9.13)	3,032 (29.15)
Black	655 (6.3)	385 (3.7)	76 (0.73)	194 (1.87)
Other	887 (8.53)	451 (4.34)	100 (0.96)	336 (3.23)
AJCC Stage				
I	1,029 (9.89)	173 (1.66)	121 (1.16)	735 (7.07)
II	958 (9.01)	301 (2.89)	112 (1.08)	545 (5.24)
III	5,727 (55.07)	3,384 (32.54)	567 (5.45)	1,776 (17.08)
IV	2,686 (25.83)	1,855 (17.84)	325 (3.13)	506 (4.87)
Differentiation Grade				
Well differentiated	342 (3.29)	94 (0.9)	38 (0.37)	210 (2.02)
Moderately differentiated	937 (9.01)	443 (4.26)	92 (0.88)	402 (3.87)
Poorly differentiated	5,167 (49.68)	2,969 (28.55)	599 (5.76)	1,599 (15.38)
Undifferentiated; anaplastic	3,954 (38.02)	2,207 (21.22)	396 (3.81)	1,351 (12.99)
Surgery				
Yes	10,000 (96.15)	5,428 (52.19)	1,040 (10)	3,532 (33.96)
No/Unknown	400 (3.85)	285 (2.74)	85 (0.82)	30 (0.29)
Chemotherapy				
Yes	8,706 (83.71)	4,859 (46.72)	820 (7.88)	3,027 (29.11)
No/Unknown	1,694 (16.29)	854 (8.21)	305 (2.93)	535 (5.14)
Radiation				
Yes	121 (1.16)	73 (0.7)	21 (0.2)	27 (0.26)
No/Unknown	10,279 (98.84)	5,640 (54.23)	1,104 (10.62)	3,535 (33.99)
Tumor size				
1-10 mm	350 (3.37)	168 (1.62)	52 (0.5)	130 (1.25)
1-20 mm	490 (4.71)	269 (2.59)	54 (0.52)	167 (1.61)
>20 mm	9,560 (91.92)	5,276 (50.73)	1,019 (9.8)	3,265 (31.39)
Regional lymph node metastases				
Yes	10,232 (98.38)	5,639 (54.22)	1,113 (10.7)	3,480 (33.46)
No	168 (1.62)	74 (0.71)	12 (0.12)	82 (0.79)
Combined summary stage				
Local	519 (4.99)	78 (0.75)	65 (0.63)	376 (3.62)
Regional	1,814 (17.44)	516 (4.96)	211 (2.03)	1,087 (10.45)
Distant	8,067 (77.57)	5,119 (49.22)	849 (8.16)	2,099 (20.18)
Income				
<$35,000, $35,000- $44,999	831 (7.99)	449 (4.32)	108 (1.04)	274 (2.63)
$45,000 - $59,999	2,163 (20.8)	1,208 (11.62)	233 (2.24)	722 (6.94)
$60,000 - $74,999	3,848 (37)	2,087 (20.07)	411 (3.95)	1,350 (12.98)
$75,000+	3,558 (34.21)	1,969 (18.93)	373 (3.59)	1,216 (11.69)
Marital status				
Married	5,877 (56.51)	3,110 (29.9)	559 (5.38)	2,208 (21.23)
Unmarried	1,705 (16.39)	915 (8.8)	171 (1.64)	619 (5.95)
Divorced, Widowed	2,818 (27.1)	1,688 (16.23)	395 (3.8)	735 (7.07)

N: patient number; AJCC: American Joint Committee on Cancer.

Variables that demonstrated a significant association in the univariate Cox regression analysis were incorporated into the multivariate Cox analysis ($p<0.05$). The independent risk factors were revealed to be black ethnicity, AJCC stage, distant metastasis, differentiation grade, absence of chemotherapy or surgery, higher age at diagnosis, and being single or divorced/widowed. The outcomes and risk factors of the competing risk model were comparable to those of the Fine-Gray model, except for differences in the point estimation level. Age was an independent risk factor for the prognosis of patients with OSCC. Those aged 45-65 years exhibited a greater risk of unfavorable

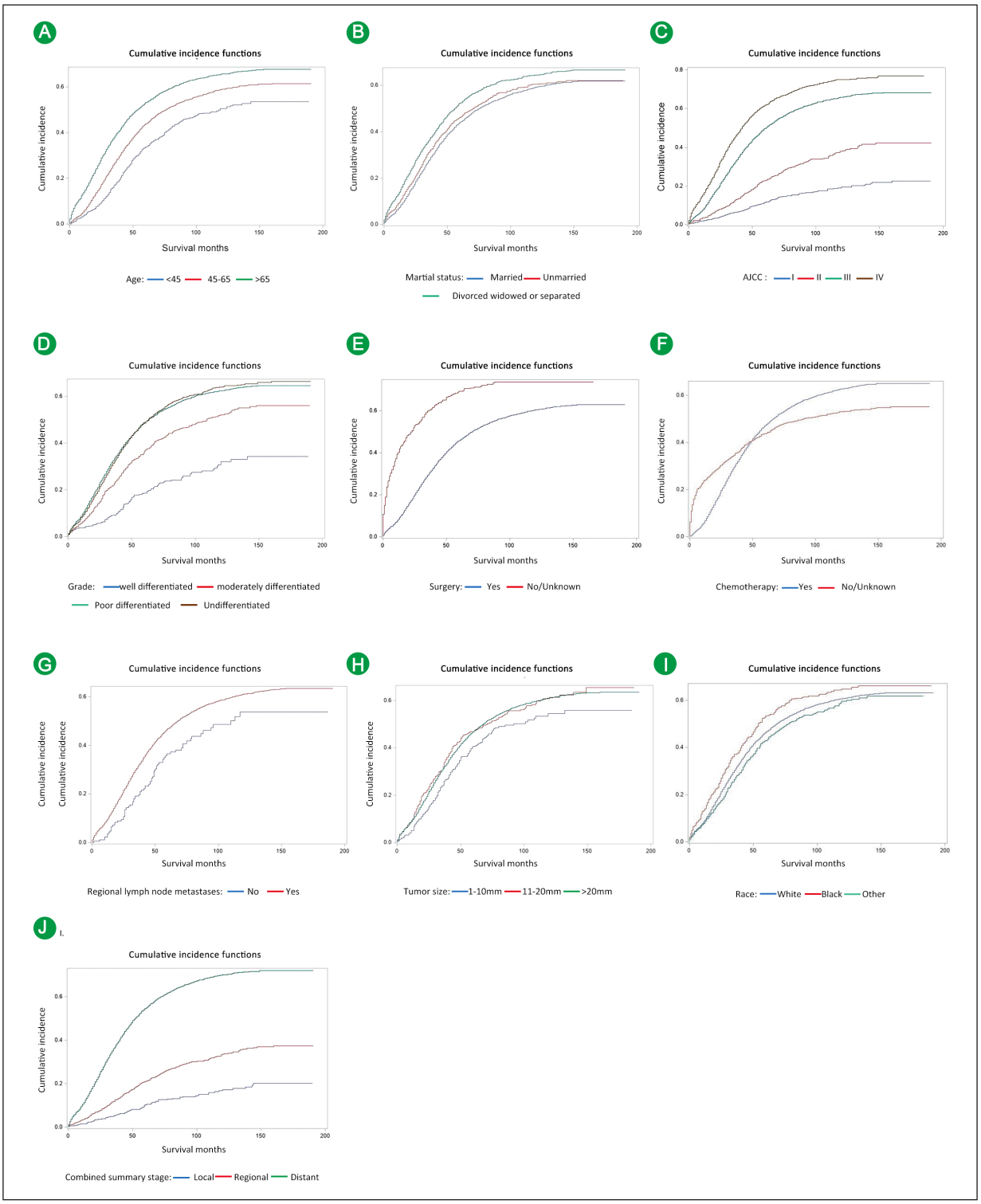

Figure 2. Cumulative incidence curve of ovarian serous cystadenocarcinomas specific mortality. **A**, Cumulative incidence curves of cause-specific death according to age. **B**, Cumulative incidence curves of cause-specific death according to marital status. **C**, Cumulative incidence curves of cause-specific death according to the American Joint Committee on Cancer (AJCC). **D**, Cumulative incidence curves of cause-specific death according to grade. **E**, Cumulative incidence curves of cause-specific death according to surgery. **F**, Cumulative incidence curves of cause-specific death according to chemotherapy. **G**, Cumulative incidence curves of cause-specific death according to regional lymph node metastases. **H**, Cumulative incidence curves of cause-specific death according to tumor size. **I**, Cumulative incidence curves of cause-specific death according to race. **J**, Cumulative incidence curves of cause-specific death according to the combined summary stage.

Table II. Univariate analysis of prognostic factors in patients with ovarian serous cystadenocarcinoma.

Variable	Gray's test	*p*-value	12-months	36-months	60-months
Age	173.713	<0.001			
<45			0.04118	0.173	0.33704
45-65			0.063	0.271	0.438
>65			0.149	0.389	0.531
Ethnicity	14.751	<0.001			
White			0.093	0.310	0.466
Black			0.141	0.372	0.534
Other			0.087	0.274	0.429
AJCC Stage	1,118.080	<0.001			
I			0.022	0.063	0.116
II			0.037	0.126	0.230
III			0.086	0.320	0.498
IV			0.166	0.451	0.617
Histology Grade	161.669	<0.001			
Well differentiated			0.038	0.091	0.187
Moderately differentiated			0.068	0.228	0.367
Poorly differentiated			0.106	0.333	0.489
Undifferentiated; anaplastic			0.095	0.320	0.486
Surgery	166.373	<0.001			
Yes			0.084	0.299	0.458
No/Unknown			0.403	0.602	0.692
Chemotherapy	5.128	0.0235			
Yes			0.068	0.302	0.473
No/Unknown			0.241	0.353	0.437
Radiation	0.579	0.4467			
Yes			0.107	0.306	0.517
No/Unknown			0.096	0.311	0.466
Tumor size	7.666	0.0216			
1-10 mm			0.052	0.242	0.407
11-20 mm			0.100	0.319	0.469
>20 mm			0.097	0.313	0.469
Regional lymph node positive	9.020	0.0027			
yes			0.097	0.313	0.469
No			0.036	0.191	0.365
Combined summary stage	1,046.960	<0.001			
Local			0.015	0.055	0.103
Regional			0.036	0.124	0.212
Distant			0.114	0.369	0.547
Income	2.738	0.4338			
<$35,000, $35,000 - $44,999			0.116	0.342	0.483
$45,000 - $59,999			0.097	0.322	0.483
$60,000 - $74,999			0.100	0.304	0.457
$75,000+			0.086	0.304	0.465
Marital status	60.219	<0.001			
Married			0.074	0.281	0.441
Unmarried			0.097	0.316	0.461
Divorced, Widowed			0.140	0.369	0.524

AJCC: American Joint Committee on Cancer.

prognosis [*vs.* those aged <45 years: hazard ratio (HR)=1.298, 95% confidence interval (CI)=1.164-1.448], while the elderly (>65 years) had the worst prognoses (*vs.* those aged <45 years: HR=1.704, 95% CI=1.523-1.906). The following factors significantly affected OSCC when the CS model was applied: tumor size of 1.1-2.0 cm (compared with ≤1 cm), undifferentiated grade (compared with relatively high differentiation grade: HR=1.984, 95% CI=1.609-2.46), low differentiation grade (compared with relatively high differentiation grade: HR=1.934, 95% CI=1.571-2.381), medium differentiation grade (compared with high differentiation grade: HR=1.656, 95% CI=1.325-0.71), no surgical treatment (compared with surgical treatment: HR=2.302, 95% CI=2.036-2.602), no

chemotherapy (compared with chemotherapy: HR=1.502, 95% CI=1.393-1.619), AJCC stage II (compared with stage I: HR=1.848, 95% CI=1.467-2.329, $p<0.01$), AJCC stage III (compared with stage I: HR=2.245, 95% CI=1.714-2.940), AJCC stage IV (compared with AJCC stage I: HR=3.11, 95% CI=2.359-4.101; stage IV had the worst prognosis), distant metastasis (compared with local: HR=3.03, 95% CI=2.132-4.306), regional metastasis (compared with local: HR=1.369, 95% CI=0.104-1.848), unmarried (compared with married: HR=1.148, 95% CI=1.065-1.237), black ethnicity (compared with white: HR=1.195, 95% CI=1.075-1.328), and other ethnicity (compared with white: HR=0.892, 95% CI=0.809-0.984). Table III lists the results of the multivariate analysis using the CS and Fine-Gray models, and Cox regression.

Discussion

The purpose of this study was first to analyze the SEER database to identify trustworthy prognostic factors for OSCC-specific mortality using a competing-risks model that considers cumulative death from tumor-related and other causes. Previous studies[22-24] on the prognostic parameters of OSCC patients mostly used the classic Cox proportional-hazards model and Kaplan-Meier analysis, often ignoring competing data that led to inaccurate survival estimates[25].

In previous studies[26,27], it was demonstrated that individuals with cancer had a consistently elevated risk of suicide compared to the general population across all years. The highest risk was observed within the first 6 months after diagnosis, during which these individuals faced more than seven times the suicide risk of the general population. Moreover, when making a direct comparison of suicide and accident injury risk among OSCC patients and the general population, it was evident that individuals with ovarian cancer, as well as those with other types of cancer leading to long-term quality-of-life impairment, also exhibited elevated sui-cide risks. Consequently, excluding suicide from consideration may lead to an underestimation of the indi-rect impact of ovarian cancer.

Our study included 10,400 patients with OSCC who died during 2004-2015, including 1,125 fatalities due to additional causes such as other cancers, suicide, and accidents. Of these, 5,713 deaths were due to OSCC, while 8% of cases were considered censored data.

Competing-risks analysis typically uses the Fine-Gray model to assess disease risk and prognostic factors, while the CS model is commonly used to study etiology[28]. The Fine-Gray model can evaluate various com-peting endpoints and determine the most relevant ones of interest. Our study identified several independent prognostic factors that significantly impacted the mortality risk of patients with OSCC, including ethnicity, AJCC stage, age at diagnosis, differentiation grade, surgery and chemotherapy status, tumor size, combined summary stage, and marital status.

Our univariate and multivariate analyses demonstrated that age was a significant influencing factor. High tumor grade, suboptimal performance, and under-treatment were often associated with the lowest survival rates for patients older than 65 years and the highest risk of cancer-specific mortality in this study. Elevated levels of 8-hydroxy-2'-deoxyguanosine in leukocyte DNA were significantly associated with higher age and unfavorable prognosis in patients with OSCC[29].

This study found that black females with OSCC had lower survival rates than white females in all three models, possibly due to the reduced access to healthcare among minority communities[30]. Previous research[31-33] has suggested that survival rates are higher in other ethnicities than in white females, which may be associated with long-term survival and higher socioeconomic status[34]. However, other ethnicity was not significant in the Cox model, possibly due to false negatives in competing risk events. Despite this, competition was still considered an independent risk factor for OSCC using the same classification criteria.

The analysis using all three models revealed that patients with advanced AJCC stages and undifferentiated histological grade had a higher risk of mortality. The risk of mortality in those patients was substantially underestimated in the Cox regression models. The results of the Fine-Gray model analysis revealed that AJCC stage II (HR=1.754, 95% CI=1.398-2.200, $p<0.001$) and AJCC stage III (HR=2.050, 95% CI=1.566-2.680, $p<0.05$) were significant risk factors for mortality in patients with OSCC when compared with AJCC stage I. The HR of AJCC stage IV was consistently higher than 1 in the Fine-Gray, CS, and Cox regression models. The poor prognosis of undifferentiated-grade OSCC may be attributable to insensitivity to chemotherapy, and patients have higher risks of cancer recurrence and cancer-attributable mortality, particularly in the advanced stages of the illness[35]. Although there were only

Table III. Multivariate analysis of 3 models of prognostic factors in patients with ovarian serous cystadenocarcinoma.

Prognostic factors	Cox model			Fine-gray model			CS model		
	p-value	HR	95% CI	*p*-value	HR	95% CI	*p*-value	HR	95% CI
Age									
<45		reference			reference			reference	
45-65	<0.001	1.341	1.21-1.486	<0.001	1.249	1.128-1.383	<0.001	1.298	1.164-1.448
>65	<0.001	1.878	1.691-2.086	<0.001	1.517	1.364-1.687	<0.001	1.704	1.523-1.906
Ethnicity									
White		reference			reference			reference	
Black	<0.001	1.200	1.09-1.321	0.047	1.121	1.002-1.255	0.001	1.195	1.075-1.328
Other	0.082	0.925	0.846-1.01	0.024	0.894	0.811-0.985	0.0219	0.892	0.809-0.984
AJCC Stage									
I		reference			reference			reference	
II	<0.001	1.614	1.339-1.945	<0.001	1.754	1.398-2.2	<0.001	1.848	1.467-2.329
III	<0.001	1.953	1.564-2.439	<0.001	2.05	1.566-2.682	<0.001	2.245	1.714-2.940
IV	<0.001	2.723	2.166-3.424	<0.001	2.624	1.991-3.459	<0.001	3.11	2.359-4.101
Differentiation Grade									
Well differentiated		reference			reference			reference	
Moderately differentiated	<0.001	1.503	1.241-1.82	<0.001	1.626	1.307-2.022	<0.001	1.656	1.325-2.071
Poorly differentiated	<0.001	1.78	1.492-2.124	<0.001	1.816	1.480-2.227	<0.001	1.934	1.571-2.381
Undifferentiated; anaplastic	<0.001	1.824	1.526-2.18	<0.001	1.816	1.478-2.231	<0.001	1.984	1.609-2.446
Surgery									
Yes		reference			reference			reference	
No/Unknown	<0.001	2.455	2.204-2.736	<0.001	1.386	1.176-1.634	<0.001	2.302	2.036-2.602
Chemotherapy									
Yes		reference			reference			reference	
No/Unknown	<0.001	1.64	1.536-1.751	<0.001	1.177	1.077-1.285	<0.001	1.502	1.393-1.619
Radiation									
Yes		reference			reference			reference	
No/Unknown	0.004	0.741	0.604-0.908	0.3645	0.897	0.709-1.135	0.065	0.805	0.638-1.014

(Table continued)

Table III. ***(Continued).*** Multivariate analysis of 3 models of prognostic factors in patients with ovarian serous cystadenocarcinoma.

Prognostic factors	Cox model			Fine-gray model			CS model		
	p-value	HR	95% CI	*p*-value	HR	95% CI	*p*-value	HR	95% CI
Tumor size									
1-10 mm		reference			reference			reference	
11-20 mm	0.147	1.135	0.956-1.348	0.017	1.271	1.045-1.546	0.031	1.237	1.020-1.500
>20 mm	0.515	1.046	0.914-1.197	0.020	1.203	1.029-1.406	0.093	1.141	0.978-1.331
Regional lymph node positive		reference			reference			reference	
Yes	0.1228	1.183	0.956-1.464	0.547	1.066	0.865-1.315	0.312	1.126	0.895-1.417
No									
Combined summary stage									
Local		reference			reference			reference	
Regional	0.088	1.221	0.971-1.536	0.077	1.304	0.971-1.752	0.040	1.369	1.014-1.848
Distant	<0.001	2.328	1.762-3.074	<0.001	2.812	1.985-3.985	<0.001	3.03	2.132-4.306
Income									
<$35,000, $35,000 - $44,999		reference			reference			reference	
$45,000 - $59,999	0.0965	0.920	0.834-1.015	0.857	1.011	0.901-1.133	0.430	0.957	0.859-1.067
$60,000 - $74,999	<0.001	0.84	0.766-0.922	0.259	0.939	0.843-1.047	0.0096	0.873	0.788-0.968
$75,000+	0.005	0.875	0.797-0.961	0.572	0.969	0.869-1.081	0.066	0.907	0.818-1.006
Marital status									
Married		reference			reference			reference	
Unmarried	<0.001	1.156	1.079-1.239	0.0034	1.12	1.038-1.209	<0.001	1.148	1.065-1.237
Divorced, Widowed	<0.001	1.27	1.201-1.342	<0.001	1.177	1.105-1.254	<0.001	1.246	1.172-1.324

HR: hazard ratio; CI: confidence interval; AJCC: American Joint Committee on Cancer.

differences in point estimates, the analysis data of the competing-risks model was the most accurate.

Tumor size was not significant in the Cox regression model, while it was in the Fine-Gray and CS models for tumor sizes of 1.1-2.0 cm and of >2 cm. However, additional research is needed to elucidate the complex relationships among the model-involved factors. Competing-risks models were more accurate than the other models.

The Cox regression model overestimated risks related to lack of treatment options, including not receiving surgery (HR=2.455, $p<0.001$) or chemotherapy (HR=1.64, $p<0.001$). These findings were consistent with previous research[36,37,] indicating that no surgery and chemotherapy are significant risk factors for CS mortality. The study recommends debulking surgery and platinum-based chemotherapy as standard treatments for OSCC to increase survival rates. The analysis of correctly reviewed data revealed that the impact provided by independent risk factors was the most common and might have been overestimated by the Cox model because it only evaluated the results at a single endpoint.

The important risk variables of distant metastasis are lymph node involvement, grade, and stage[38]. Longer survival time in individuals with distant metastasis likely reflects the abnormal physiological course of such malignancies. Our analysis indicated that patients with developing metastasis have a negative prognosis[39]. While the Cox model underestimated the risk of poor prognosis associated with distant metastasis, the Fine-Gray model provided more accurate results by treating distant metastasis as a competing risk factor that can affect patient survival.

Regional metastasis was found to be significant only in the CS model, and not in the Cox or Fine-Gray model, which we attributed to false positives caused by competing-risks events. This may be explained by the less aggressive nature of lymphatic spread compared with direct pleural invasion or hematogenous spread[40]. Regional metastasis cannot be considered an independent risk factor for OSCC.

All three models demonstrated that being unmarried (including divorced or widowed) was an independent risk factor in patients with OSCC. The risk of death increased dramatically after an OSCC diagnosis. We attributed this finding to an association of being unmarried with a loss of social support, including companionship and mental and economic assistance, both of which should be considered during therapeutic decision-making[41].

Limitations

The limitations of this study included incomplete patient data in the SEER database, limited evaluations of prospective predictive factors, and potential inaccuracies in COD information. Common prognostic markers were not recorded, such as specific doses of chemotherapy or radiotherapy, and hormone treatment history. Furthermore, the applicability of the study to other populations or countries may be limited.

Conclusions

This study first established a competing risk analysis model using the SEER database to assess prognostic factors for OSCC. When compared with the COX model, our competing risk model proved to be more accurate in estimating the effect value after evaluating and modeling the cumulative incidence rates of cause-specific death in OSCC patients within a competing risk analysis. Our research unveiled that various factors, including ethnicity, histological grade, surgery and chemotherapy status, age at diagnosis, AJCC stage, tumor size, marital status, and combination summary stage, are independent risk factors for the prognosis of patients with OSCC in the presence of competing risks. These findings may allow patients to receive more suitable treatment and guide physicians to improve their knowledge of OSCC, thereby improving prognoses.

Availability of Data and Materials

Publicly available datasets were analyzed in this study. This data can be found here: https://seer.cancer.gov/.

Informed Consent

Since cancer is a reportable disease in every state in the USA, informed patient consent is not required. When the data usage agreement was signed, data on cancer research became available to the public.

Conflict of Interests

The authors declare that they have no competing interests.

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Ethics Approval

No ethics approval was required from an institutional review board or Ethics Committee since the SEER database contains anonymized patient data.

Authors' Contributions

JL and SMC designed the study; YH, SCH, and WKM collected and analyzed the data; YJL and SMC drafted the initial manuscript; WHC and CDH revised the article critically; QQZ and NCL reviewed the article; SMC and YJL are co-first authors; JL and LHD are the correspondence authors. All authors approved the final manuscript.

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