

ORIGINAL RESEARCH ARTICLE

Clinicopathological characteristics and survival by *BRCA* status in ovarian cancer: A multicenter retrospective cohort study

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Abstract

Introduction: Breast cancer susceptibility gene 1/2 (*BRCA1/2*) mutations are implicated in ovarian cancer biology and may influence tumor phenotype, treatment response, and prognosis.

Objective: To compare clinicopathological characteristics and survival outcomes between *BRCA*-mutated and *BRCA* wild-type ovarian cancer patients in a multicenter cohort.

Methods: This retrospective cohort study included ovarian cancer patients who underwent *BRCA1/2* testing at three hospitals in China from January 2018 to December 2024. Clinicopathological variables were compared between groups. Disease-free survival (DFS) and overall survival (OS) were evaluated using Kaplan–Meier analysis and Cox proportional hazards models.

Results: Among 316 patients, 117 (37.0%) had *BRCA* mutations and 199 (63.0%) were *BRCA* wild-type. *BRCA*-mutated patients had a higher proportion with serous histology (94.9% vs. 87.4%, $p = 0.032$) and a more frequent use of poly(ADP-ribose) polymerase (PARP) inhibitors (47.9% vs. 20.1%, $p < 0.001$). They also had lower crude recurrence (49.6% vs. 73.4%, $p < 0.001$) and mortality rates (28.2% vs. 44.2%, $p = 0.006$). After adjustment, *BRCA* mutation status was not independently associated with DFS or OS. Advanced International Federation of Gynecology and Obstetrics (FIGO) stage, neoadjuvant chemotherapy, bilateral tumors, and residual disease > 1 cm were independently associated with shorter DFS, whereas use of a vascular endothelial growth factor inhibitor was associated with longer DFS. Advanced FIGO stage was associated with worse OS, while PARP inhibitor maintenance therapy was associated with longer OS.

Conclusion: *BRCA*-mutated patients showed better crude outcomes, but the survival

difference was attenuated after multivariable Cox adjustment. *BRCA* testing remains valuable for guiding individualized maintenance therapy.

Keywords: Ovarian cancer; *BRCA1/2*; Clinicopathological features; Prognosis; Poly(ADP-ribose) polymerase inhibitors

1. Introduction

Ovarian cancer remains a difficult gynecologic malignancy to manage because a large proportion of patients are diagnosed only after the disease has extended beyond the ovary. In the GLOBOCAN 2020 estimates, ovarian cancer accounted for 313,959 new cases and 207,252 deaths worldwide, placing it among the major causes of cancer-related death in women.¹ Although the treatment landscape has changed considerably over the past decade, the clinical course of ovarian cancer is still marked by late presentation, frequent relapse after initial response, and substantial differences in outcome between patients who appear similar at diagnosis. These problems are particularly evident in epithelial ovarian cancer, which includes several biologically distinct histological subtypes rather than a single disease entity. High-grade serous carcinoma accounts for most advanced cases and is closely associated with defects in DNA repair pathways, whereas clear cell, endometrioid, mucinous, and low-grade serous tumors have different molecular profiles and treatment sensitivities.^{2,3} Therefore, a purely clinicopathological description is no longer sufficient for understanding prognosis or guiding treatment selection in ovarian cancer.

The discovery of the clinical importance of breast cancer susceptibility gene 1 and 2 (*BRCA1/2*) alterations has substantially changed the management of ovarian cancer. *BRCA1* and *BRCA2* proteins are central components of the homologous recombination repair pathway, which is responsible for accurate repair of DNA double-strand breaks.^{4,5} When this pathway is impaired, tumor cells may become more dependent on alternative DNA repair mechanisms and may be particularly vulnerable to poly(ADP-ribose) polymerase (PARP) inhibitors.^{6,7} On this basis, *BRCA1/2* testing has moved from being mainly a hereditary risk assessment tool to becoming a routine component of therapeutic decision-making. International recommendations now support germline testing for patients with epithelial ovarian cancer, and somatic tumor testing is recommended when germline testing does not identify a pathogenic or likely pathogenic variant.^{8,9} The

result is clinically meaningful for the patient because it may influence maintenance therapy, and for relatives because it may prompt genetic counseling and cascade testing.

Despite the clear predictive value of *BRCA* status for PARP inhibitor benefit, its independent prognostic value in routine practice remains less straightforward. Several studies have reported improved survival among patients with *BRCA*-mutated ovarian cancer, probably because homologous recombination-deficient tumors are more sensitive to platinum-based chemotherapy and because *BRCA*-mutated patients are more likely to receive PARP inhibitor maintenance therapy.¹⁰⁻¹³ However, survival in ovarian cancer is not determined by one molecular marker alone. International Federation of Gynecology and Obstetrics (FIGO) stage, histological subtype, tumor grade, extent of disease, residual tumor after cytoreductive surgery, response to platinum-based treatment, and access to maintenance therapy may all affect recurrence and mortality.¹⁴⁻¹⁶ In addition, the increasing use of PARP inhibitors and antiangiogenic agents has altered the relationship between baseline molecular features and long-term outcomes.¹⁷⁻²⁰ In real-world cohorts, these treatments are not randomly assigned; they are influenced by disease response, financial access, drug approval time, physician preference, and whether the patient survives long enough to receive maintenance therapy. For these reasons, multicenter real-world studies remain important even in an era with strong randomized trial evidence. Randomized trials provide essential efficacy data under defined eligibility criteria, but they cannot fully reflect the variability of routine care, especially across hospitals and over several calendar years.

The present multicenter retrospective cohort study therefore compared clinical features, pathological characteristics, treatment patterns, disease-free survival (DFS), and overall survival (OS) between patients with *BRCA*-mutant and *BRCA* wild-type ovarian cancer treated at three hospitals in China. We further evaluated whether *BRCA* mutation status remained independently associated with DFS and OS after adjustment for clinicopathological variables and treatment-related factors.

2. Materials and methods

2.1. Study design and patient population

This was a multicenter retrospective cohort study of patients with ovarian cancer who underwent *BRCA1/2* testing at three hospitals in Shandong Province, China: Shandong Provincial Hospital, Shandong Maternal and Child Health Hospital, and Dezhou Hospital of Qilu Hospital of Shandong University. The study period was from January 2018 to December 2024. These institutions are tertiary medical centers that provide surgical treatment, systemic therapy, and follow-up care for patients with gynecologic malignancies.

Patients were eligible for inclusion if they met all of the following criteria: histologically confirmed ovarian cancer; available *BRCA1/2* testing result; treatment or follow-up at one of the participating hospitals; and sufficient clinicopathological and follow-up information for survival analysis. Patients were excluded if *BRCA1/2* testing was not performed or the result could not be retrieved, if essential clinical variables were unavailable, if follow-up information was insufficient to determine recurrence or survival status, or if the patient had a previous or synchronous malignant tumor other than ovarian cancer.

The study cohort should be understood as a *BRCA*-tested ovarian cancer population rather than an unselected population of all ovarian cancer patients treated during the same period. In clinical practice, whether a patient undergoes *BRCA* testing may depend on several factors, including age at diagnosis, histological subtype, disease stage, family history, the physician's recommendation, patient preference, affordability, and potential eligibility for targeted maintenance therapy. Therefore, the *BRCA* mutation rate observed in this cohort cannot be interpreted as the true prevalence of *BRCA* mutation among all ovarian cancer patients in the participating hospitals.

The study was conducted in accordance with the principles of the Declaration of Helsinki. Ethical approval was obtained from the Ethics Committee of Shandong Provincial Hospital, with approval number SWYX: 2023-127. Because the study used retrospectively collected clinical data and all patient identifiers were removed before analysis, the requirement for informed consent was waived. The manuscript was prepared with reference to the Strengthening the Reporting of Observational Studies in Epidemiology statement for cohort studies.²¹

2.2. Data collection and variable definitions

Clinical, pathological, genetic, treatment-related, and follow-up data were extracted from electronic medical records by trained investigators using a standardized

data collection form. The collected variables included age at diagnosis, menopausal status, histological type, histological grade, 2014 FIGO stage, serum cancer antigen 125 (CA-125) level, receipt of neoadjuvant chemotherapy, surgical approach, tumor laterality, maximum tumor diameter, postoperative residual tumor size, lymph node pathological status, omental pathological status, ascites cytology, chemotherapy or radiotherapy, PARP inhibitor exposure, vascular endothelial growth factor (VEGF) inhibitor exposure, recurrence or progression, and death.

Age was dichotomized as ≤ 55 years or > 55 years according to the distribution of the cohort and common clinical practice in ovarian cancer studies. Histological type was categorized as serous adenocarcinoma or other histological types. Histological grade was grouped as well or moderately differentiated versus poorly differentiated. FIGO stages were grouped as stage I–II versus stage III–IV, reflecting early- and advanced-stage disease. CA-125 was classified as ≤ 35 U/mL or > 35 U/mL according to the conventional upper limit of normal. Tumor size was dichotomized into ≤ 8 cm and > 8 cm. Postoperative residual tumor size was classified as ≤ 1 cm or > 1 cm because this threshold was consistently recorded in operative notes and postoperative documentation.

Lymph node pathological status was classified as no metastasis, metastasis, or not resected. Omental pathological status was classified as no metastasis, metastasis, or not resected. Ascites cytology was classified as negative, positive, or not submitted for examination. These “not resected” and “not submitted” categories were retained as independent levels rather than being treated as missing data. In a retrospective surgical cohort, these categories may reflect differences in operative strategy, disease distribution, patient condition, or institutional practice and may therefore contain clinically relevant information.

Treatment data were obtained from inpatient records, outpatient prescriptions, chemotherapy records, and follow-up notes. Neoadjuvant chemotherapy was defined as systemic chemotherapy administered before cytoreductive surgery. Chemotherapy or radiotherapy was recorded as a binary variable according to whether the patient received either modality after diagnosis. PARP inhibitor exposure included documented use of PARP inhibitors as maintenance therapy or treatment after ovarian cancer diagnosis. VEGF inhibitor exposure was defined as the use of antiangiogenic therapy, such as bevacizumab, when documented in the medical record. Because PARP inhibitor and VEGF inhibitor exposures occurred after diagnosis and were not randomly assigned, they were treated as treatment-related exposures in the analysis.

2.3. BRCA1/2 testing and classification

BRCA1/2 testing was performed as part of routine clinical molecular assessment. Peripheral blood, tumor tissue, or both were used in accordance with the clinical protocol of the participating hospital and the testing resources available at the time. Testing methods included next-generation sequencing and polymerase chain reaction-based assays performed in certified clinical molecular laboratories. Variant interpretation was based on the clinical reports available in the medical records.

Only pathogenic or likely pathogenic BRCA1/2 variants were classified as BRCA mutations. Patients with no pathogenic or likely pathogenic BRCA1/2 variant were classified as BRCA wild-type. Variants of uncertain significance were not included in the mutation group. Because this study covered multiple centers and several years, testing platforms and specimen sources were not completely uniform. In addition, historical records did not always allow reliable separation between germline and somatic alterations. Therefore, the main analysis classified patients as BRCA-mutant or BRCA wild-type based on available clinical test results.

2.4. Follow-up and study outcomes

The primary time-to-event outcomes were DFS and OS. DFS was defined as the interval from diagnosis to the first documented recurrence or disease progression. Patients without recurrence or progression were censored at the date of last follow-up. OS was defined as the interval from diagnosis to death from any cause. Patients who were alive at the last contact were censored at the date of last follow-up.

Recurrence or progression was determined based on imaging findings, clinical assessment, pathological confirmation when available, serum tumor marker changes when considered clinically relevant, and documentation by the treating physician. Follow-up information was obtained from inpatient records, outpatient visits, imaging reports, and telephone follow-up when necessary. The final follow-up date was January 2025.

The date of diagnosis was used as the starting point for survival analysis because it was the most consistently available time origin across the three hospitals. This approach allowed patients treated with primary surgery and those treated with neoadjuvant chemotherapy to be analyzed using the same time scale.

2.5. Statistical analysis

Categorical variables were presented as frequencies and percentages. Comparisons between the BRCA-mutated

and BRCA wild-type groups were performed using the chi-square test. Fisher's exact test was used when expected cell counts were small. All tests were two-sided, and $p < 0.05$ was considered statistically significant.

Univariable Cox proportional hazards regression analysis was used to evaluate associations between candidate variables and DFS or OS. Candidate variables included BRCA status, age, menopausal status, histological type, histological grade, FIGO stage, CA-125 level, neoadjuvant chemotherapy, surgical approach, tumor laterality, tumor size, postoperative residual tumor size, lymph node pathological status, omental pathological status, ascites cytology, chemotherapy or radiotherapy, PARP inhibitor exposure, and VEGF inhibitor exposure. Variables with $p < 0.20$ in univariable analysis, together with clinically important variables, were considered for entry into multivariable Cox regression analysis.

Before the final multivariable Cox regression analysis, potential collinearity among variables reflecting disease burden and surgical evaluation was assessed, including FIGO stage, neoadjuvant chemotherapy, residual tumor size, lymph node status, omental status, and ascites cytology. Variance inflation factors (VIFs) were calculated for variables retained in the final multivariable models. A VIF below 5 was considered indicative of no substantial multicollinearity. Hazard ratios (HRs) and 95% confidence intervals (CIs) were reported.

Kaplan–Meier survival curves were generated for key variables and compared using the log-rank test. Because treatment exposure variables were recorded retrospectively and did not necessarily occur at diagnosis, the corresponding HRs were interpreted as adjusted associations rather than causal treatment effects.

Statistical analyses were performed using IBM Statistical Package for Social Sciences (version 27.0) and R (version 4.5.1).

3. Results

3.1. Patient selection and BRCA mutation distribution

The patient selection process is shown in [Figure 1](#). During the study period, 758 patients with ovarian cancer were screened across the three participating hospitals. Among them, 442 patients were excluded. The reasons for exclusion were absence of available BRCA1/2 testing results in 401 patients, incomplete clinical information in 22 patients, and history of another malignancy in 19 patients. The final analytic cohort included 316 patients with available BRCA1/2 testing and sufficient follow-up data.

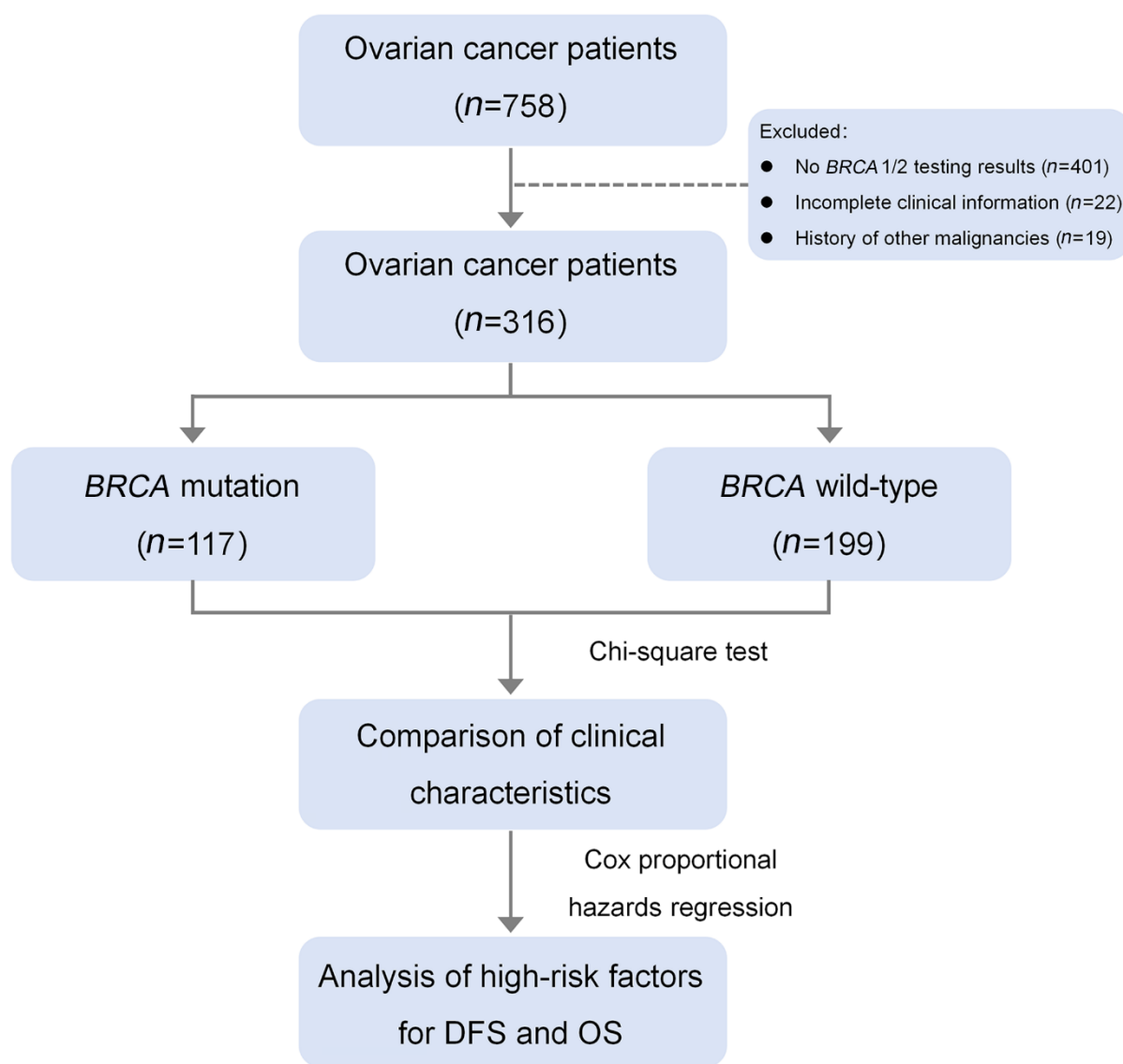


Figure 1. Study flow diagram

Abbreviations: DFS: Disease-free survival; OS: Overall survival.

Of these 316 patients, 117 were classified as *BRCA*-mutated and 199 as *BRCA* wild-type. The observed *BRCA* mutation rate in this tested cohort was 37.0%. Because only patients who underwent *BRCA* testing were included, this percentage reflects the mutation distribution in a clinically selected testing population rather than the background prevalence in all ovarian cancer patients. The median follow-up duration for the overall cohort was 34 months, with a range from 2 to 80 months. During follow-up, 204 patients experienced recurrence or disease progression, and 121 patients died. These event numbers provided the basis for subsequent DFS and OS analyses.

3.2. Baseline clinicopathological characteristics according to *BRCA* status

Baseline clinicopathological characteristics are summarized in Table 1. Among the 316 patients, 117 were classified as *BRCA*-mutated and 199 as *BRCA* wild-type. Patients in the *BRCA*-mutated group were more likely to be aged ≤ 55 years than those in the *BRCA* wild-type group (67.5% vs. 52.3%, $p = 0.009$). Menopausal status did not differ significantly between the two groups ($p = 0.118$).

Serous adenocarcinoma was more common in the *BRCA*-mutated group than in the *BRCA* wild-type group

(94.9% vs. 87.4%, $p = 0.032$). Poor differentiation was also numerically more frequent among BRCA-mutated patients, although the difference was not statistically significant (94.0% vs. 86.9%, $p = 0.056$). Most patients in both groups had advanced-stage disease, and the distribution of FIGO stage III–IV was comparable between groups (82.9% vs. 80.4%, $p = 0.655$). CA-125 level, neoadjuvant chemotherapy, surgical approach, tumor laterality, tumor size, postoperative residual tumor size, lymph node status,

omental status, and ascites cytology were also similar between the two groups.

Nearly all patients received chemotherapy or radiotherapy, with no significant difference between groups (99.1% vs. 98.0%, $p = 0.655$). PARP inhibitor use was significantly more frequent in BRCA-mutated patients than in BRCA wild-type patients (47.9% vs. 20.1%, $p < 0.001$). VEGF inhibitor use was numerically higher in the BRCA-mutated group, but the difference was not

Table 1. Baseline clinicopathological characteristics of ovarian cancer patients

Characteristics	Total ($n = 316$)	BRCA mutation ($n = 117$)	BRCA wild-type ($n = 199$)	p
Age, years				0.009
≤55	183 (57.9)	79 (67.5)	104 (52.3)	
>55	133 (42.1)	38 (32.5)	95 (47.7)	
Menopause				0.118
Yes	197 (62.3)	66 (56.4)	131 (65.8)	
No	119 (37.7)	51 (43.6)	68 (34.2)	
Histological type				0.032
Serous adenocarcinoma	285 (90.2)	111 (94.9)	174 (87.4)	
Others	31 (9.8)	6 (5.1)	25 (12.6)	
Histological grade				0.056
Well or moderately	33 (10.4)	7 (6.0)	26 (13.1)	
Poorly	283 (89.6)	110 (94.0)	173 (86.9)	
FIGO (2014)				0.655
I and II	59 (18.7)	20 (17.1)	39 (19.6)	
III and IV	257 (81.3)	97 (82.9)	160 (80.4)	
CA-125, U/mL				0.175
≤35	22 (7.0)	5 (4.3)	17 (8.5)	
>35	294 (93.0)	112 (95.7)	182 (91.5)	
Neoadjuvant chemotherapy				0.416
Yes	77 (24.4)	25 (21.4)	52 (26.1)	
No	239 (75.6)	92 (78.6)	147 (73.9)	
Operation method				1.000
Laparotomy	300 (94.9)	111 (94.9)	189 (95.0)	
Laparoscopy	16 (5.1)	6 (5.1)	10 (5.0)	
Tumor location				1.000
Unilateral	70 (22.2)	26 (22.2)	44 (22.1)	
Bilateral	246 (77.8)	91 (77.8)	155 (77.9)	
Tumor size, cm				0.079
≤8	170 (53.8)	55 (47.0)	115 (57.8)	
>8	146 (46.2)	62 (53.0)	84 (42.2)	

(Cont'd...)

Table 1. (Continued)

Characteristics	Total (n = 316)	BRCA mutation (n = 117)	BRCA wild-type (n = 199)	p
Postoperative residual tumor size, cm				0.133
≤1	241 (76.3)	95 (81.2)	146 (73.4)	
>1	75 (23.7)	22 (18.8)	53 (26.6)	
Lymph node pathological status				0.454
No metastasis	89 (28.2)	32 (27.4)	57 (28.6)	
Metastasis	64 (20.3)	28 (23.9)	36 (18.1)	
Not resected	163 (51.6)	57 (48.7)	106 (53.3)	
Omental pathological status				0.138
No metastasis	110 (34.8)	47 (40.2)	63 (31.7)	
Metastasis	187 (59.2)	61 (52.1)	126 (63.3)	
Not resected	19 (6.0)	9 (7.7)	10 (5.0)	
Cytology of ascitic fluid				0.654
Negative	26 (8.2)	10 (8.5)	16 (8.0)	
Positive	57 (18.0)	24 (20.5)	33 (16.6)	
Not submitted for examination	233 (73.7)	83 (70.9)	150 (75.4)	
Chemotherapy or radiotherapy				0.655
Yes	311 (98.4)	116 (99.1)	195 (98.0)	
No	5 (1.6)	1 (0.9)	4 (2.0)	
PARP inhibitor				<0.001
Yes	96 (30.4)	56 (47.9)	40 (20.1)	
No	220 (69.6)	61 (52.1)	159 (79.9)	
VEGF inhibitor				0.176
Yes	104 (32.9)	44 (37.6)	60 (30.2)	
No	212 (67.1)	73 (62.4)	139 (69.8)	
Recurrence	204 (64.6)	58 (49.6)	146 (73.4)	<0.001
Death	121 (38.3)	33 (28.2)	88 (44.2)	0.006

Note: Values are presented as n (%).

Abbreviations: CA-125: Cancer antigen 125; FIGO: International Federation of Gynecology and Obstetrics; PARP: Poly(ADP-ribose) polymerase; VEGF: Vascular endothelial growth factor.

statistically significant (37.6% vs. 30.2%, $p = 0.176$).

Crude outcome events were less frequent in the BRCA-mutated group. Recurrence or disease progression occurred in 49.6% of BRCA-mutated patients and 73.4% of BRCA wild-type patients ($p < 0.001$). Death occurred in 28.2% and 44.2% of patients, respectively ($p = 0.006$). These unadjusted results suggested better crude outcomes among BRCA-mutated patients, although further survival analyses were needed to account for potential confounding factors.

3.3. Univariate Cox regression analysis for disease-free survival and overall survival

The univariable Cox regression results are presented in Table 2. In the DFS analysis, several variables reflecting disease extent, treatment pathway, and operative findings were associated with shorter time to recurrence or progression. Advanced FIGO stage (III–IV vs. I–II), neoadjuvant chemotherapy, bilateral tumor location, postoperative residual tumor size >1 cm, lymph node metastasis, omental metastasis, and positive ascites

cytology were associated with shorter DFS. Patients whose lymph nodes were not resected also had shorter DFS than those without lymph node metastasis.

BRCA mutation status was not significantly associated with DFS in the univariable model (HR: 0.80, 95% CI: 0.59–1.08; $p = 0.155$). Treatment-related variables showed favorable univariable associations with DFS. PARP inhibitor exposure was associated with longer DFS (HR: 0.48, 95% CI: 0.30–0.75; $p = 0.002$), and VEGF inhibitor exposure was also associated with longer DFS (HR: 0.42, 95% CI: 0.27–0.65; $p < 0.001$). These estimates should be interpreted cautiously because treatment exposure was not randomized and occurred after diagnosis.

For OS, advanced FIGO stage, menopausal status, laparoscopic approach, lymph node pathological status, and omental pathological status were associated with survival in univariable models. BRCA mutation status showed a favorable association with OS (HR: 0.66, 95% CI: 0.44–0.99; $p = 0.046$). Chemotherapy or radiotherapy, PARP inhibitor exposure, and VEGF inhibitor exposure were also associated with longer OS. The estimate for chemotherapy or radiotherapy should be interpreted with caution, as only five patients did not receive such treatment.

3.4. Multivariate Cox regression analysis for disease-free survival and overall survival

The multivariable Cox regression results are summarized in Table 3. After adjustment, BRCA mutation status was not retained in the final DFS or OS model, suggesting that the crude survival differences by BRCA status were partly explained by other clinical, pathological, and treatment-related variables.

In the DFS model, advanced FIGO stage remained associated with shorter DFS (HR: 1.68, 95% CI: 1.13–2.51; $p = 0.011$). Neoadjuvant chemotherapy (HR: 1.57, 95% CI: 1.12–2.20; $p = 0.009$), bilateral tumor location (HR: 1.63, 95% CI: 1.08–2.48; $p = 0.021$), and postoperative residual tumor size >1 cm (HR: 1.62, 95% CI: 1.17–2.23; $p = 0.004$) were also associated with shorter DFS. VEGF inhibitor exposure was associated with longer DFS in the multivariable model (HR: 0.48, 95% CI: 0.31–0.76; $p = 0.002$). For OS, advanced FIGO stage remained the main adverse factor after adjustment (HR: 3.14, 95% CI: 1.64–6.01; $p < 0.001$). Chemotherapy or radiotherapy was associated with longer OS (HR: 0.17, 95% CI: 0.02–0.33; $p < 0.001$), although this estimate was based on a very small untreated reference group. PARP inhibitor exposure was also associated with longer OS in the multivariable analysis (HR: 0.11, 95% CI: 0.02–0.78; $p = 0.027$). VIF values were low in both final models, suggesting no obvious multicollinearity among the retained variables. Kaplan–

Meier curves stratified by DFS risk factors are shown in Figure 2, and those for OS are shown in Figure 3.

4. Discussion

This multicenter retrospective study evaluated clinicopathological characteristics and survival outcomes by BRCA1/2 mutation status among 316 ovarian cancer patients treated at three Chinese hospitals. The study produced several clinically relevant observations. First, BRCA-mutated patients were more likely to be aged ≤ 55 years and more likely to have serous adenocarcinoma. Second, PARP inhibitor exposure was substantially more frequent among BRCA-mutated patients than among BRCA wild-type patients. Third, BRCA-mutant patients had lower crude rates of recurrence/progression and mortality. Fourth, BRCA mutation status was associated with OS in univariable analysis but was not retained as an independent factor in the final multivariable DFS or OS model. These findings suggest that BRCA status is closely related to tumor phenotype and treatment selection, but its independent prognostic role may be reduced after adjustment for disease stage, surgical factors, and post-diagnosis treatment exposure.

The observed BRCA mutation rate of 37.0% was relatively high compared with many unselected ovarian cancer populations. This finding should be interpreted within the context of the study design. Our cohort included only patients who had undergone BRCA1/2 testing. In daily practice, BRCA testing is more likely to be performed in younger patients, patients with serous or high-grade tumors, patients with advanced disease, patients with a family history suggestive of hereditary cancer, and patients being considered for PARP inhibitor maintenance therapy. These clinical patterns may enrich the tested population for BRCA alterations. Therefore, the mutation rate reported here describes the distribution within a selected BRCA-tested cohort and should not be generalized to all ovarian cancer patients.

The association between BRCA mutation and serous histology is consistent with current understanding of ovarian cancer biology. High-grade serous ovarian carcinoma is the subtype most strongly linked to homologous recombination repair deficiency and is characterized by widespread genomic instability.^{2,3,22} BRCA1/2 alterations represent one important cause of homologous recombination deficiency, although other genes and epigenetic mechanisms may also contribute.^{5,23} In our cohort, serous adenocarcinoma was common in both BRCA-mutated and BRCA wild-type groups, but it was significantly more frequent among BRCA-mutated patients. This finding supports the clinical practice of

Table 2. Univariable Cox proportional hazards regression analysis for disease-free survival and overall survival

Characteristic	DFS		OS	
	HR (95% CI)	P	HR (95% CI)	P
BRCA mutation vs. wild-type	0.80 (0.59–1.08)	0.155	0.66 (0.44–0.99)	0.046
Age > 55 vs. ≤55 years	1.00 (0.75–1.33)	0.993	1.33 (0.92–1.91)	0.128
Menopause	0.90 (0.68–1.19)	0.457	1.46 (1.01–2.11)	0.044
Serous adenocarcinoma vs. others	0.76 (0.47–1.24)	0.267	0.85 (0.47–1.54)	0.584
Poorly vs. well or moderately differentiated	1.13 (0.73–1.74)	0.593	0.93 (0.53–1.62)	0.783
FIGO III and IV vs. I and II (2014)	2.00 (1.36–2.94)	<0.001	2.52 (1.39–4.59)	0.002
CA-125 > 35 vs. ≤35 U/mL	1.09 (0.60–2.01)	0.772	0.63 (0.28–1.44)	0.274
Neoadjuvant chemotherapy	1.61 (1.15–2.25)	0.006	1.10 (0.69–1.74)	0.696
Laparoscopy vs. laparotomy	0.86 (0.32–2.32)	0.765	3.16 (1.15–8.64)	0.025
Bilateral tumor location vs. unilateral	2.09 (1.39–3.14)	<0.001	1.37 (0.78–2.40)	0.269
Tumor size > 8 vs. ≤8 cm	0.87 (0.66–1.15)	0.318	1.00 (0.84–1.20)	0.998
Postoperative residual tumor size > 1 vs. ≤1 cm	2.13 (1.57–2.90)	<0.001	1.25 (0.86–1.82)	0.241
Lymph node pathological status		<0.001		0.010
No metastasis	Reference		Reference	
Metastasis	1.81 (1.17–2.80)	0.008	1.64 (0.87–3.07)	0.125
Not resected	2.10 (1.45–3.03)	<0.001	2.23 (1.30–3.82)	0.003
Omental pathological status		<0.001		0.031
No metastasis	Reference		Reference	
Metastasis	1.96 (1.42–2.72)	<0.001	1.81 (1.16–2.83)	0.009
Not resected	2.27 (1.33–3.90)	0.003	1.77 (0.87–3.60)	0.116
Cytology of ascitic fluid		0.023		0.991
Negative	Reference		Reference	
Positive	3.86 (1.47–10.09)	0.006	1.00 (0.32–3.13)	0.999
Not submitted for examination	3.12 (1.28–7.59)	0.012	1.04 (0.38–2.84)	0.944
Chemotherapy or radiotherapy	0.48 (0.15–1.52)	0.213	0.17 (0.04–0.72)	0.016
PARP inhibitor	0.48 (0.30–0.75)	0.002	0.12 (0.02–0.84)	0.033
VEGF inhibitor	0.42 (0.27–0.65)	<0.001	0.19 (0.05–0.77)	0.020

Abbreviations: CA-125: Cancer antigen 125; CI: Confidence interval; DFS: Disease-free survival; FIGO: International Federation of Gynecology and Obstetrics; HR: Hazard ratio; OS: Overall survival; PARP: Poly(ADP-ribose) polymerase; VEGF: Vascular endothelial growth factor.

Table 3. Multivariable Cox proportional hazards regression analysis for disease-free survival and overall survival

Characteristic	DFS			OS		
	HR (95% CI)	<i>p</i>	VIF	HR (95% CI)	<i>p</i>	VIF
FIGO III and IV vs. I and II (2014)	1.68 (1.13–2.51)	0.011	1.1	3.14 (1.64–6.01)	<0.001	1.2
Neoadjuvant chemotherapy vs. no	1.57 (1.12–2.20)	0.009	1.0	–	–	–
Bilateral tumor location vs. unilateral	1.63 (1.08–2.48)	0.021	1.0	–	–	–
Postoperative residual tumor size > 1 vs. ≤1 cm	1.62 (1.17–2.23)	0.004	1.1	–	–	–
Chemotherapy or radiotherapy vs. no	–	–	–	0.17 (0.02–0.33)	<0.001	1.2
PARP inhibitor vs. no	–	–	–	0.11 (0.02–0.78)	0.027	1.0
VEGF inhibitor vs. no	0.48 (0.31–0.76)	0.002	1.0	–	–	–

Abbreviations: CA-125: Cancer antigen 125; CI: Confidence interval; DFS: Disease-free survival; FIGO: International Federation of Gynecology and Obstetrics; HR: Hazard ratio; OS: Overall survival; PARP: Poly(ADP-ribose) polymerase; VEGF: Vascular endothelial growth factor; VIF: Variance inflation factor.

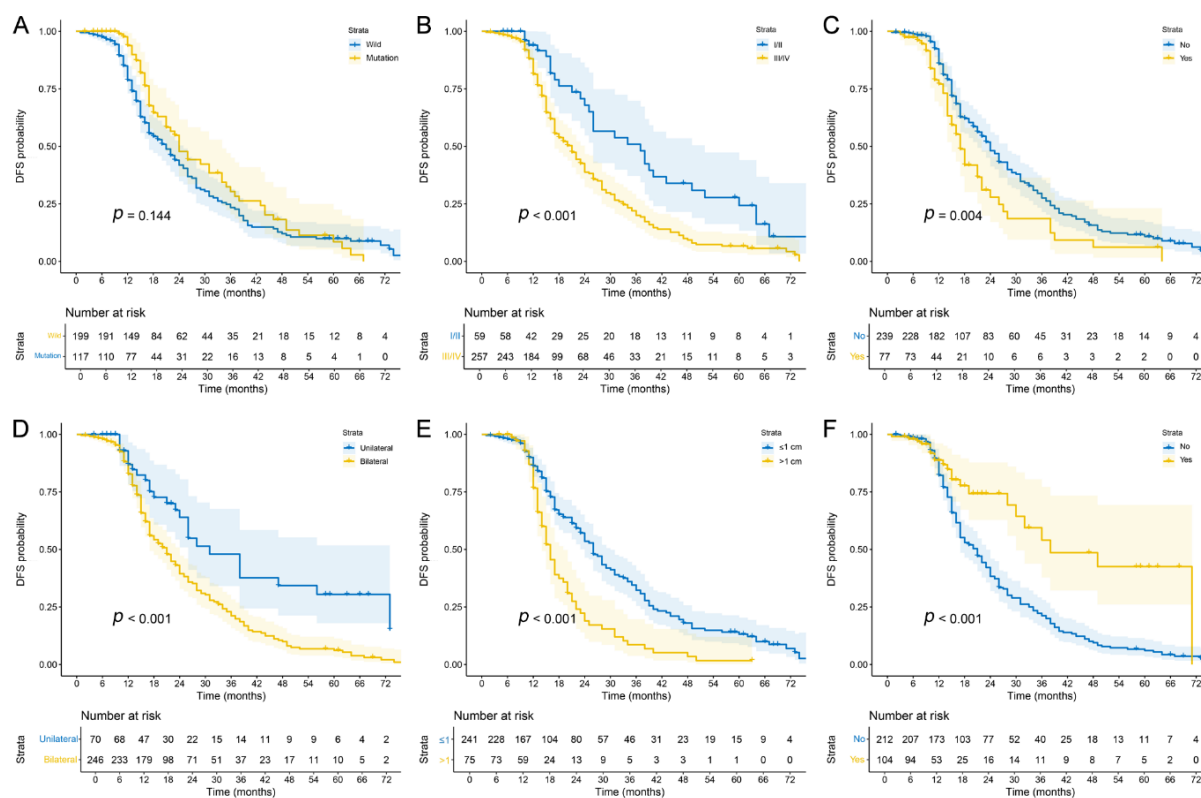


Figure 2. Kaplan-Meier curves for DFS according to selected variables. (A) *BRCA1/2*. (B) FIGO stage. (C) Neoadjuvant chemotherapy. (D) Tumor location. (E) Postoperative residual tumor size. (F) VEGF inhibitor.

Abbreviations: DFS: Disease-free survival; FIGO: International Federation of Gynecology and Obstetrics; VEGF: Vascular endothelial growth factor.

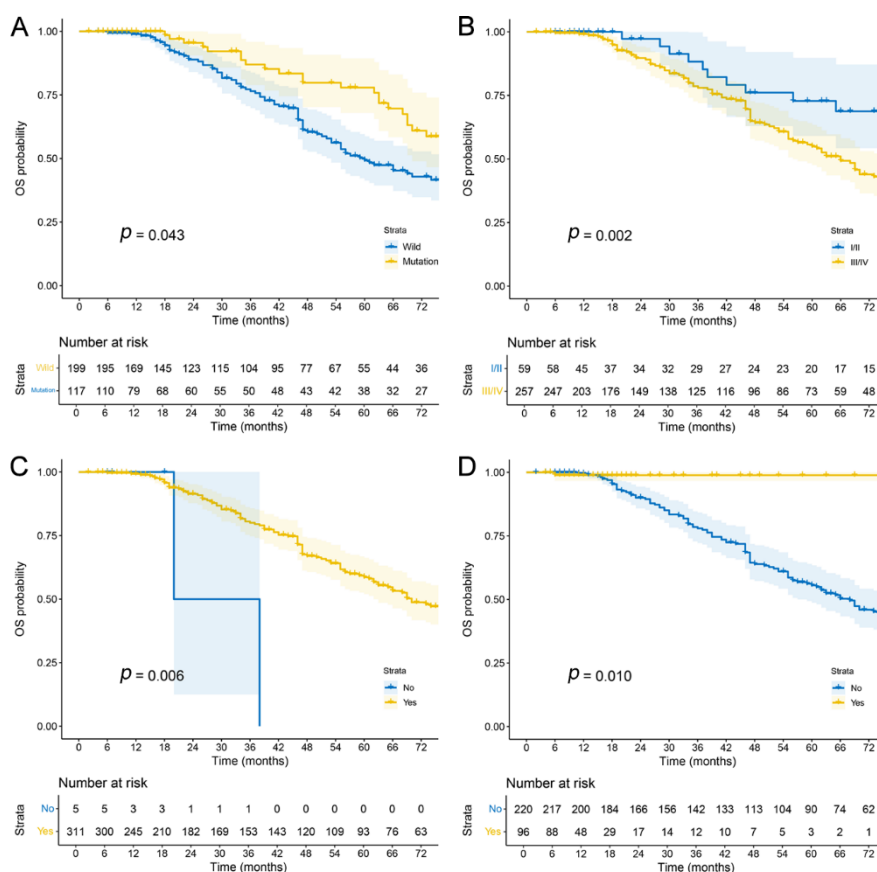


Figure 3. Kaplan–Meier curves for OS according to selected variables. (A) *BRCA1/2*. (B) FIGO stage. (C) Chemotherapy or radiotherapy. (D) PARP inhibitor.

Abbreviations: FIGO: International Federation of Gynecology and Obstetrics; OS: Overall survival; PARP: Poly(ADP-ribose) polymerase.

prioritizing genetic and tumor testing in epithelial ovarian cancer, especially in high-grade serous disease.

BRCA-mutated patients in this study had fewer crude recurrence and death events than *BRCA* wild-type patients. This pattern is biologically plausible. *BRCA*-deficient tumors may be more sensitive to DNA-damaging treatments, such as platinum-based chemotherapy, and may also derive greater benefit from PARP inhibition.^{6,7,17,18} Earlier clinical studies have reported improved survival in *BRCA*-associated ovarian cancer, particularly in high-grade serous carcinoma.^{10–12} However, the prognostic effect of *BRCA* status is not uniform across all clinical settings; for example, recent data on early-stage high-grade serous tubo-ovarian carcinoma suggest that *BRCA* status is not clearly prognostic for progression-free survival, although outcomes after relapse may differ by *BRCA* status.¹³ However, not all studies have found an independent survival advantage after adjustment for clinical factors. Some analyses suggest that the favorable

outcomes observed in *BRCA*-mutated disease may be partly mediated by platinum sensitivity, more effective maintenance therapy, and differences in treatment course rather than by *BRCA* status itself.^{24,25}

Our results support this more cautious interpretation. *BRCA* mutation status was not independently associated with DFS or OS in the multivariable models. For DFS, the major independent adverse factors were advanced FIGO stage, neoadjuvant chemotherapy, bilateral tumor location, and residual tumor size > 1 cm, whereas VEGF inhibitor exposure was associated with longer DFS. These findings are consistent with previous evidence that conventional clinical and pathological factors remain valuable for prognostic stratification in ovarian adenocarcinoma. Trifanescu *et al.*²⁶ developed and validated a prognostic score incorporating adverse factors such as impaired performance status, ascites, thrombocytosis, menopausal status, and residual disease after surgery, and demonstrated progressively shorter progression-free survival and OS

with increasing numbers of adverse factors. Together with our findings, this supports the view that postoperative residual disease and other routinely available clinical variables should be interpreted alongside molecular markers when estimating recurrence risk and planning follow-up strategies. For OS, advanced FIGO stage was the main adverse factor, while chemotherapy or radiotherapy and PARP inhibitor exposure were associated with longer OS. These findings suggest that *BRCA* status alone does not fully capture the complexity of survival in ovarian cancer. Instead, prognosis appears to be shaped by a combination of disease extent, surgical result, tumor distribution, systemic therapy, and targeted maintenance treatment.

The absence of an independent association between *BRCA* status and adjusted survival should not be interpreted as evidence against *BRCA* testing. On the contrary, *BRCA* testing remains essential because it provides both predictive and familial information. The American Society for Clinical Oncology guideline recommends that all women diagnosed with epithelial ovarian cancer should be offered germline testing for *BRCA1/2* and other ovarian cancer susceptibility genes, and that somatic tumor testing should be performed if germline testing does not reveal a pathogenic or likely pathogenic *BRCA1/2* variant.⁸ Testing therefore guides PARP inhibitor use, informs genetic counseling, and allows relatives to consider risk assessment and prevention strategies.

The treatment context is particularly important. In SOLO1, maintenance olaparib significantly prolonged progression-free survival in patients with newly diagnosed advanced ovarian cancer and a *BRCA1/2* mutation after response to platinum-based chemotherapy.¹⁷ The seven-year follow-up of SOLO1 further supported durable long-term benefit and suggested an overall survival advantage despite subsequent therapies.¹⁸ In PAOLA-1, olaparib plus bevacizumab as first-line maintenance improved outcomes, with the greatest benefit observed in homologous recombination-deficient tumors.¹⁹ Other trials, including PRIMA, VELIA, and ATHENA-MONO, expanded the evidence base for PARP inhibitor maintenance across broader populations, although the magnitude of benefit varied by *BRCA* and homologous recombination deficiency status.^{20,27,28} These studies have established PARP inhibitors as a major component of modern ovarian cancer treatment.

In our cohort, PARP inhibitor exposure was more frequent in *BRCA*-mutated patients. This is expected because *BRCA* status directly influences treatment eligibility and clinical decision-making. PARP inhibitor exposure was associated with longer OS in multivariable analysis, which is directionally consistent with trial evidence. However,

this association should not be interpreted as an unbiased estimate of treatment efficacy. In real-world retrospective data, patients who receive PARP inhibitors may differ from non-users in multiple ways, including response to platinum therapy, performance status, financial capacity, access to medication, physician preference, and follow-up duration. Moreover, if PARP inhibitor exposure is treated as a fixed baseline variable despite occurring after diagnosis, immortal-time bias may occur. Patients must remain alive and clinically suitable long enough to start the drug, which can artificially favor the exposed group. Because complete treatment initiation dates were not uniformly available, time-dependent Cox modeling and landmark analysis could not be reliably performed in this study.

Vascular endothelial growth factor is a key angiogenic target in cancer and represents the therapeutic target of bevacizumab.²⁹ Bevacizumab has shown benefit in several ovarian cancer settings, including front-line treatment and recurrent disease, particularly with respect to progression-free survival.^{30,31} In our study, exposure to a VEGF inhibitor was independently associated with longer DFS but was not retained in the final OS model. This pattern may reflect the ability of antiangiogenic therapy to delay progression in selected patients, but it may also be influenced by selection factors, contraindications, treatment access, and timing of use. As with PARP inhibitors, the retrospective design prevents causal interpretation.

Advanced FIGO stage remained the most consistent adverse factor in this study. This finding is expected because FIGO stage reflects the anatomical extent of disease and the likelihood of peritoneal, nodal, or distant spread. Most patients in this cohort had stage III–IV disease, which is typical of epithelial ovarian cancer because early symptoms are often vague and no widely effective screening strategy exists for average-risk women. The strong association between advanced stage and OS highlights the continuing need for earlier detection strategies, more effective first-line therapy, and improved maintenance approaches.

Surgical factors were also important, especially for DFS. Residual tumor size > 1 cm was independently associated with shorter DFS. The prognostic relevance of residual disease after cytoreductive surgery has been repeatedly demonstrated in ovarian cancer.^{14–16} Complete gross resection or minimal residual disease is associated with better outcomes, although achieving optimal cytoreduction depends on tumor distribution, surgical expertise, patient condition, and institutional resources. In this study, the residual disease variable remained significant even after adjustment, emphasizing that surgical outcome continues to matter in the molecular treatment era.

Neoadjuvant chemotherapy was associated with

shorter DFS in the multivariable model. This should not be interpreted as proof that neoadjuvant chemotherapy is inferior or harmful. In real-world practice, neoadjuvant chemotherapy is often selected for patients with extensive tumor burden, poor performance status, medical comorbidities, or disease distribution judged unlikely to be optimally cytoreduced at primary surgery. Large randomized trials have shown that neoadjuvant chemotherapy followed by interval debulking surgery can be a reasonable alternative to primary debulking surgery in selected patients with advanced ovarian cancer.^{32,33} Therefore, the association observed in our study is more likely to reflect baseline disease severity and clinical selection rather than the direct effect of neoadjuvant treatment.

Bilateral tumor location was independently associated with shorter DFS. Bilateral ovarian involvement may be a marker of more extensive disease spread, especially in high-grade serous carcinoma, which often presents with diffuse peritoneal involvement. Although laterality is not always emphasized in modern prognostic models, it may capture part of the anatomical burden of disease in retrospective cohorts. In the present study, bilateral disease remained significant even after adjustment, suggesting that it may provide additional information regarding recurrence risk.

The categories of lymph node not resected, omentum not resected, and ascites not submitted for examination deserve comment. In prospective trials, such categories might be minimized through standardized surgical and pathological protocols. In retrospective clinical practice, however, they are common. We retained these categories because excluding them would have reduced sample size and could have introduced additional bias. The “not resected” category may reflect early-stage disease, extensive unresectable disease, patient frailty, incomplete operative staging, or institutional variation. Therefore, these categories should not be interpreted in the same way as negative pathological findings. Their inclusion improves transparency but limits direct comparison with studies using fully standardized staging procedures.

Histological heterogeneity is another limitation but also an important clinical issue. Most patients in our cohort had serous adenocarcinoma, and non-serous tumors were grouped together because of limited numbers. This approach was necessary for statistical stability, but it may have obscured subtype-specific patterns. Low-grade serous carcinoma, clear cell carcinoma, endometrioid carcinoma, and mucinous carcinoma differ substantially in their molecular profiles and therapeutic vulnerabilities.^{2,3,34} For example, low-grade serous ovarian cancer is biologically distinct from high-grade serous carcinoma and is less

commonly associated with *BRCA1/2* mutations.^{35,36} Future studies with larger sample sizes should evaluate *BRCA* status and survival separately within each histological subtype.

A further issue is the distinction between germline and somatic *BRCA* mutations. Germline mutations have implications for hereditary cancer risk, family counseling, and preventive strategies, whereas somatic mutations are limited to the tumor but may still predict sensitivity to PARP inhibitors. Because our historical medical records did not consistently separate germline and somatic status, these categories were combined. This approach reflects the information available in routine practice but reduces biological precision. Future prospective studies should separate germline *BRCA1*, germline *BRCA2*, somatic *BRCA1*, and somatic *BRCA2* alterations, and should also incorporate broader homologous recombination deficiency testing.

This study has several strengths. It used data from three hospitals and reflects real-world management during a period when *BRCA* testing and maintenance therapy were increasingly incorporated into ovarian cancer care in China. The cohort included genetic information, detailed clinicopathological variables, treatment exposure, recurrence or progression, and mortality. The analysis also considered surgical variables and disease distribution, rather than focusing only on *BRCA* status. In addition, collinearity was assessed in the multivariable models, and clinically meaningful retrospective categories were retained rather than discarded.

Several limitations must be acknowledged. First, the retrospective design makes selection bias and information bias unavoidable. Second, only patients who underwent *BRCA* testing were included, which may have enriched the cohort for younger patients, patients with serous histology, and those considered suitable for targeted therapy. Therefore, the *BRCA* mutation rate of 37.0% should not be treated as a population prevalence estimate. Third, germline and somatic *BRCA* alterations were analyzed together because documentation was incomplete in some records. Fourth, *BRCA* testing platforms, specimen sources, and reporting practices were not fully standardized across centers and calendar years. Although only pathogenic or likely pathogenic variants were classified as mutations, testing heterogeneity may still have influenced variant detection and classification. Fifth, treatment exposure variables were vulnerable to treatment-selection bias and immortal-time bias because PARP inhibitors and VEGF inhibitors were initiated after diagnosis and not assigned by protocol. Sixth, follow-up duration was relatively short for some patients, which may limit assessment of

long-term OS. Finally, the chemotherapy or radiotherapy variable was highly imbalanced because only five patients did not receive such treatment, making its HR statistically unstable and clinically difficult to interpret.

Future studies should be prospective, use standardized BRCA and homologous recombination deficiency testing, precisely record treatment initiation dates, and distinguish germline from somatic alterations. Time-dependent Cox models, landmark analyses, and analyses restricted to patients who are eligible for maintenance therapy would help reduce bias when evaluating PARP inhibitor and VEGF inhibitor exposure. Larger cohorts are also needed to assess BRCA1 and BRCA2 separately, evaluate non-serous histological subtypes, and explore how homologous recombination deficiency beyond BRCA mutations affects treatment response and survival.

5. Conclusion

In this multicenter retrospective cohort of BRCA-tested ovarian cancer patients, BRCA1/2-mutated disease was associated with younger age, serous histology, more frequent PARP inhibitor exposure, and better crude recurrence/progression and mortality outcomes. However, BRCA mutation status was not retained as an independent factor for DFS or OS after adjustment for clinicopathological and treatment-related variables. Survival outcomes appeared to be influenced by disease extent, surgical factors, and post-diagnosis treatment exposures rather than BRCA status alone. These findings support the clinical value of BRCA testing for treatment selection, hereditary risk assessment, and precision management, while suggesting that BRCA status should not be interpreted as an isolated prognostic marker. Prospective studies with standardized molecular testing, separate assessment of germline and somatic alterations, and time-dependent or landmark analyses of targeted therapy are needed to further clarify the prognostic and therapeutic implications of BRCA status in ovarian cancer.

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Conflict of interest

The authors declare they have no competing interests.

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Ethics approval and consent to participate

This study was conducted in accordance with the Declaration of Helsinki and was approved by the Ethics Committee of Shandong Provincial Hospital (Approval No. SWYX: 2023-127). The requirement for informed consent was waived because of the retrospective study design. All patient data were anonymized before analysis.

Consent for publication

Not applicable.

Availability of data

The datasets generated and analyzed during the present study can be obtained from the corresponding author.

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