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Original Article

Impacts of BRCA mutations and clinical factors on niraparib efficacy in patients with platinum-sensitive recurrent ovarian cancer: a retrospective study

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Abstract: Objective: To investigate the impacts of breast cancer gene (BRCA) mutations, clinical factors such as body mass index (BMI), carbohydrate antigen 125 (CA125), human epididymis protein 4 (HE4), International Federation of Gynecology and Obstetrics (FIGO) staging and platinum sensitivity, and pathological characteristics on progression-free survival (PFS) in platinum-sensitive recurrent ovarian cancer (PSROC) patients treated with niraparib, and to identify independent prognostic factors for treatment outcomes. Methods: A total of 312 patients with ovarian cancer undergoing treatment between Jan. 2020 and Jan. 2022 were selected for the retrospective study. Patients were eligible if they were ≥ 18 years old and diagnosed with epithelial ovarian cancer, fallopian tube cancer, or primary peritoneal cancer. In addition, they received platinum-sensitive treatment (PFS ≥ 6 months) and niraparib as a maintenance therapy. Univariate and multivariate Cox proportional hazards regression models were used to evaluate the influence of clinical and pathological variables on PFS. Time-dependent receiver operating characteristic (ROC) curve analysis was performed to assess the predictive power of significant factors. Results: Univariate Cox regression analysis identified significant associations between patients' PFS and BRCA mutation status, BMI, CA125 levels, FIGO staging, platinum sensitivity, and niraparib usage and timing. Patients with BRCA mutations, BMI ≥ 24 kg/m^2, CA125 level ≤ 500 U/mL, FIGO stage II, or platinum sensitivity demonstrated a significantly longer PFS. Multivariate Cox regression analysis confirmed BRCA mutations (hazard ratio (HR) = 1.754, P = 0.049), BMI ≥ 24 kg/m^2 (HR = 2.317, P = 0.015), CA125 level ≤ 500 U/mL (HR = 2.517, P = 0.005), FIGO stage III/IV (HR = 0.159, P < 0.001; HR = 2.558, P = 0.011), and platinum sensitivity (HR = 2.599, P = 0.043) as independent predictors for PFS. Time-dependent ROC analysis demonstrated that platinum sensitivity and FIGO staging were the most influential prognostic factors to predict the 1-year and 3-year PFS. In addition, it was found that niraparib-associated adverse events occurred in 62.84% of the enrolled patients, primary of which were mild to moderate hematological and gastrointestinal toxicities. Conclusion: BRCA mutations, CA125 levels, FIGO staging, BMI, and platinum sensitivity are critical factors influencing the efficacy of niraparib in PSROC patients. These findings have provided valuable insights into the individualized application of niraparib and the optimization of treatment strategies for PSROC patients.

Keywords: Niraparib, BRCA mutation, platinum-sensitive recurrent ovarian cancer, progression-free survival, FIGO Staging, CA125, predictive factors, maintenance therapy

Introduction

Ovarian cancer, recognized as one of the most lethal malignancies in the female reproductive system, is characterized by high mortality rates, predominantly attributed to persistent challenges in early detection and a consistently high recurrence rate [1]. On a global scale, the 5-year survival rate of ovarian cancer patients remains alarmingly low (40%-50%), with prognosis worsening significantly in advanced-stage cases [2]. This severe situation is largely related to the nonspecific and clinically silent early-stage symptoms of the disease, resulting in over 70% of patients are diagnosed at stage III or IV of the International Federation of

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Gynecology and Obstetrics (FIGO) staging [3]. While the current standard of care - cytoreductive surgery combined with platinum-based chemotherapy - achieves initial remission in most patients, recurrence rates remain exceedingly high. This is particularly pronounced in high-grade serous ovarian cancer, where the majority of patients experience recurrence within 18 months of initial treatment [4, 5]. Therefore, the quest to effectively prolong the progression-free survival (PFS) of recurrent patients has emerged as a critical and pressing issue that demands immediate attention and resolution in the field of ovarian cancer treatment.

Treatment strategies for ovarian cancer are stratified by platinum sensitivity, distinguishing between platinum-sensitive and platinum-resistant disease depending on patient response to platinum-based chemotherapy. Platinum-sensitive recurrent ovarian cancer (PSROC), defined by relapse occurring ≥ 6 months after completing platinum-based chemotherapy, accounts for approximately 70% of recurrent cases [6]. Although PSROC patients typically demonstrate better response to chemotherapy and longer survival compared to platinum-resistant cohorts, recurrence remains nearly universal, with many enduring multiple relapses [7]. Consequently, optimizing maintenance therapy post initial recurrence - aimed at delaying disease progression, extending PSF, and improving long-term outcomes - has become a cornerstone of clinical research in this field. Recent advances in targeted therapies have reshaped maintenance treatment strategies, particularly with the advent of polyadenosine diphosphate ribose polymerase (PARP) inhibitors [8, 9]. PARP enzymes play a critical role in repairing single-strand DNA damage, and their inhibition disrupts DNA damage repair mechanisms, selectively inducing tumor cell apoptosis [10]. This effect is amplified in tumors with homologous recombination repair deficiency (HRD), where PARP inhibitors exploit synthetic lethality to enhance therapeutic efficacy. Niraparib, a broad-spectrum PARP inhibitor, has emerged as a first-line maintenance therapy for PSROC patients irrespective of their breast cancer gene (BRCA) mutation status, demonstrating significant PFS benefits in randomized trials such as the NOVA study [11-13]. Notably, BRCA-mutated subgroups derive the greatest survival advantage, underscoring the biomarker-driven potential of this class. Despite the revolutionary impact of PARP inhibitors on maintenance treatment, their efficacy varies substantially among patients, suggesting that the determinants of their therapeutic success extend beyond BRCA mutation status, implicating additional molecular, clinical, or microenvironmental factors.

BRCA1 and BRCA2 mutations represent the most prevalent pathogenic genetic alterations in ovarian cancer. These mutations serve as key biomarkers of HRD and are strongly associated with enhanced sensitivity to platinum-based chemotherapy and PARP inhibitors [14]. Patients carrying BRCA mutations typically demonstrate superior therapeutic responses to these agents, with extensive studies confirming significantly prolonged PFS compared to BRCA-negative cohorts [15]. However, emerging evidence suggests that apart from patients with BRCA mutations, BRCA-negative patients may also benefit from PARP inhibitor therapy. This indicates that BRCA status alone may not fully predict therapeutic outcomes of PARP inhibitors. Moreover, real-world data reveal low prevalence of BRCA mutations among patients with ovarian cancer, underscoring the urgent need to optimize treatment strategies for the majority of patient without BRCA mutations [16]. Consequently, current research prioritized identifying multifactorial predictors for niraparib efficacy, including patients' baseline characteristics, such as age and body mass index (BMI), tumor burden metrics, including carbohydrate antigen 125 (CA125) and human epididymis protein 4 (HE4) levels, and pathological parameters, such as FIGO staging and pathological type [17].

CA125 and HE4 are clinically validated tumor biomarkers widely utilized to assess tumor burden, with elevated levels correlating with disease progression and treatment response [18]. Moreover, BMI - a metric for metabolic status - exerts influences on niraparib efficacy, potentially mediated by its effects on drug pharmacokinetics, systemic inflammation, and immune function [19, 20]. Besides patients' baseline characteristics and tumor markers, pathological features (such as FIGO stage and pathological type) and platinum sensitivity during first-line therapy hold prognostic significance in

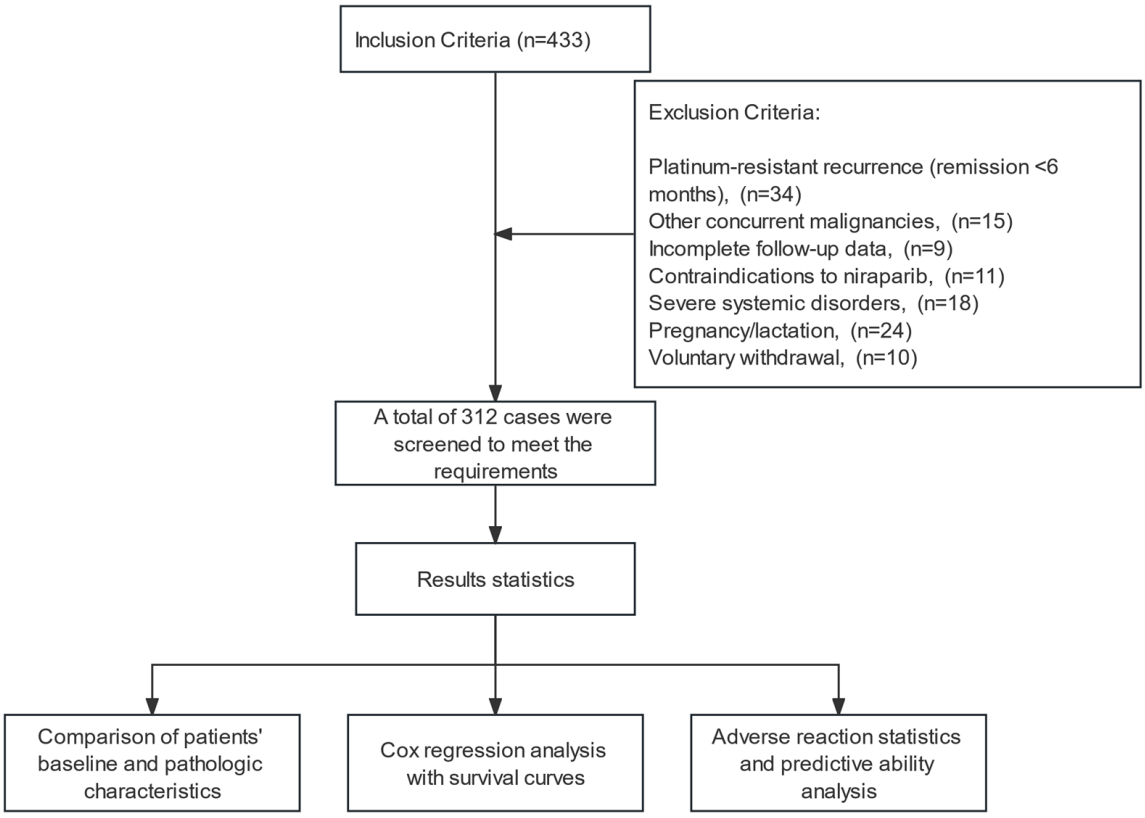


Figure 1. Flow chart of the Study.

maintenance therapy outcomes. Specifically, advanced FIGO stage and platinum-resistant status are associated with shorter PFS, reflecting diminished therapeutic gains from maintenance treatments.

While the efficacy of niraparib as a maintenance therapy for PSROC has been widely recognized, its optimal clinical usage strategy remains controversial. Key unresolved questions include whether niraparib should be universally administered as first-line maintenance treatment for all platinum-sensitive patients or whether its effectiveness can be augmented through combination with other treatment modalities (such as immunotherapy or targeted therapies). To address these uncertainties, this study endeavors to investigate the influence of multiple clinical factors, including BRCA gene mutations, BMI, CA125 and HE4 levels, FIGO staging, and platinum sensitivity, on PFS of patients following niraparib treatment. Through systematic univariate and multivariate analyses, we sought to identify potential prognostic factors and reveal the relationships between these factors and niraparib efficacy. The findings of this research will not only provide crucial evidence for refining niraparib treatment protocols but also offer new insights into individualized treatment for PSROC patients, advancing the paradigm of precision medicine in oncology.

Methods and materials

Sample collection

Retrospectively, a total of 312 patients with ovarian cancer who were treated at the Affiliated Nanhua Hospital, University of South China, from January 2020 and January 2022 were enrolled as the study subjects. This study was approved by the Medical Ethics Committee of Affiliated Nanhua Hospital, University of South China See **Figure 1**.

Inclusion and exclusion criteria

Inclusion criteria: (1) Patients aged 18 years or older, who were diagnosed with epithelial ovar-

ian cancer, fallopian tube cancer, or primary peritoneal cancer. (2) Patients who received treatment for PSROC, with a remission duration of at least 6 months after platinum-based chemotherapy. (3) Patients who received niraparib as first-line maintenance therapy after recurrence. (4) Patients with complete clinical data, including baseline characteristics, treatment information, and follow-up data. (5) Patients classified as FIGO stages II-IV.

Exclusion criteria: (1) Patients with PSROC but whose remission period less than 6 months after platinum-based chemotherapy, or whose treatment proved to be ineffective. (2) Patients with other concomitant malignancies or those who were diagnosed with additional malignancies during the study. (3) Patients with missing follow-up data or incomplete crucial clinical information. (4) Patients with definite contraindications to niraparib treatment, such as hypersensitivity to the drug components, or those who did not receive niraparib treatment. (5) Patients suffering from severe systemic disorders, like severely compromised cardiopulmonary function or active infections, which could potentially impact the evaluation of survival outcomes. (6) Patients who were pregnant or in lactation. (7) Patients who voluntarily withdrew from the study during treatment or failed to complete relevant treatment.

Data sources

The data were sourced from the electronic medical record system and follow-up database of the Affiliated Nanhua Hospital, University of South China. Information regarding patients' baseline characteristics, pathological features, treatment details, and follow-up outcomes was collected. Specifically, this included patients' age, BMI, FIGO staging, pathological type of their tumors, sensitivity to platinum-based chemotherapy in the initial treatment, CA125 and HE4 levels, niraparib use and timing (whether it was used as a first-line maintenance treatment or maintenance treatment after recurrence), as well as PFS and adverse reaction records during follow-ups.

Research variables

Primary research variables: These included patients' baseline characteristics (such as age and BMI), tumor-related variables (FIGO staging, pathological type, CA125 and HE4 levels, etc.), treatment-related variables (such as platinum sensitivity in the initial treatment, niraparib use and timing).

Outcome variables: The primary outcome was PFS, defined as the time from the start of niraparib treatment until disease progression or death. The secondary outcome was the advent of adverse reactions, which included manifestations like leukopenia, thrombocytopenia, nausea, and vomiting.

Data collection and processing

Clinical data of eligible patients were retrospectively collected from the electronic medical record system and follow-up database of the the Affiliated Nanhua Hospital, University of South China. To ensure accuracy, all data were independently verified by two researchers. In the event of uncertainties, the medical records were cross-verified, or the follow-up team was consulted for confirmation. Patient follow-up data were predominantly sourced from outpatient re-examinations, telephone follow-up inquiries, and laboratory test findings. The cut-off date for follow-up was set as January 31, 2024. Specific strategies were employed to manage outliers and missing values while processing these data: Missing value management: Patients were excluded from the study if some crucial data of theirs, such as PFS or baseline characteristics, were absent; Patients with missing secondary variables were either supplemented rationally or analyzed using multiple imputation techniques according to the clinical background. Categorical variable categorization: For instance, BMI was classified into two groups: ≥ 24 kg/m^2 and < 24 kg/m^2. Similarly, CA125 and HE4 levels were grouped based on their respective reference ranges. Data purification: The outliers of continuous variables (such as age and PFS) were identified. Any data points that showed a significant deviation from the expected range were eliminated.

Statistical analysis

In this study, statistical analyses were performed using SPSS 26.0 and R 4.3.3 software packages. When comparing the baseline characteristics and clinicopathological features across different patient groups, the Chi-square test was used for categorical variables, with

results presented as rates or proportions. For categories with expected frequencies greater than or equal to 5, the standard Chi-square test was applied. In cases where some expected frequencies were less than 5, continuity-corrected Chi-square tests (such as Yates' correction) were used to ensure the accuracy of the results. For continuous variables, the normality of the data was first assessed using the Kolmogorov-Smirnov (K-S) test. Data following a normal distribution were analyzed using the independent samples t-test. For data not following a normal distribution, the rank-sum test was used to compare the groups. Survival outcomes were analyzed using the Kaplan-Meier (K-M) approach to estimate the PFS. Log-rank test was utilized to discern differences in survival outcomes among various groups. Univariate and multivariate COX proportional hazards regression models were employed to assess the influence of potential variables on PFS, with results expressed as hazard ratios (HRs) with 95% confidence intervals (95% CIs). Time-dependent receiver operating characteristic (ROC) curves were utilized to evaluate the predictive power of significant variables in the multivariate Cox model for predicting 1-year, 2-year, and 3-year PFS. The area under the curve (AUC) values were compared between groups via the DeLong test in R 4.3.3, thereby determining statistical differences in prediction performance. All statistical analyses adhered to a significance threshold of $P < 0.05$.

Results

Comparisons of baseline characteristics

Demographic and clinical characteristics were compared among patients. Variables, including age, BMI, and pregnancy frequency exhibited no statistically significant differences among groups ($P > 0.05$). In contrast, family history of hereditary breast and ovarian cancer (HBOC) ($P = 0.010$) and CA125 levels ($P = 0.003$) showed statistically significant variations across groups. However, HE4 levels ($P = 0.959$) did not demonstrate any significant differences, indicating that this variable is not related to clinical outcomes. See **Figure 2**.

Comparisons of pathological features

A between-group comparison of patients' pathological features was conducted. Variables including FIGO staging, tumor size, pathological type, and niraparib use did not exhibit statistically significant differences among groups ($P > 0.05$). However, platinum sensitivity of the initial treatment ($P = 0.004$) and the timing of niraparib use ($P < 0.001$) demonstrated statistically significant variances across groups, indicating that these variables might be correlated with clinical outcomes. See **Figure 3**.

Univariate Cox regression analysis and K-M curve results for PFS in ovarian cancer patients

Univariate Cox regression analysis was conducted to evaluate the factors associated with PFS in ovarian cancer patients. The factors included in the analysis were age, BMI, CA125, HE4, FIGO staging, platinum sensitivity of the initial treatment, use of niraparib, and the timing of niraparib administration. The analysis revealed that several factors were significantly associated with PFS ($P < 0.05$). Specifically, patients aged < 65 years exhibited significantly better PFS compared to those aged ≥ 65 years ($P = 0.002$, HR = 0.577). Patients with a BMI ≥ 24 kg/m^2 showed significantly better PFS compared to those with BMI < 24 kg/m^2 ($P = 0.028$, HR = 1.504). Similarly, patients with CA125 ≤ 500 U/mL demonstrated a significantly favorable PFS compared to those with CA125 > 500 U/mL ($P = 0.001$, HR = 1.859). Patients with HE4 ≤ 75 pmol/L exhibited a significantly better PFS compared to those with HE4 > 75 pmol/L ($P = 0.040$, HR = 4.314). On the other hand, patients with FIGO stages III and IV had significantly reduced PFS compared to those with FIGO stage II ($P < 0.001$, HR = 0.289 for stage III and $P < 0.001$, HR = 3.225 for stage IV). Additionally, platinum-resistant patients demonstrated a significantly shorter PFS than platinum-sensitive patients ($P < 0.001$, HR = 3.392). Patients who did not receive niraparib also showed significantly reduced PFS compared to those who received niraparib ($P < 0.001$, HR = 2.026), and those who started niraparib as non-first-line maintenance treatment exhibited significantly reduced PFS compared to those who received it as first-line maintenance ($P < 0.001$, HR = 2.884). These findings were visually supported by Kaplan-Meier (K-M) survival curves, which demonstrated distinct survival differences across the groups, aligning with the results of the univariate regression analysis. In contrast, factors such as mutation sta-

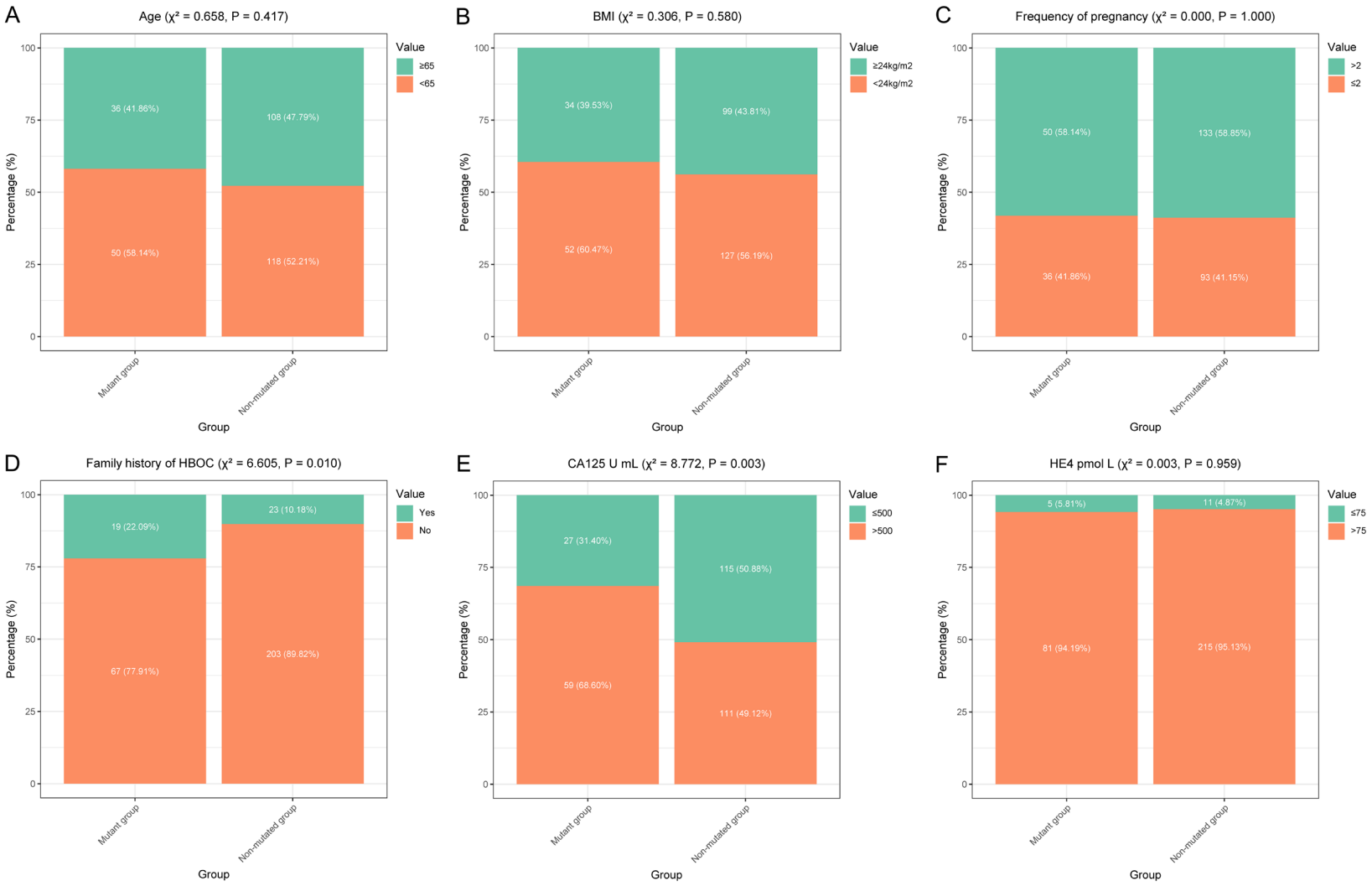


Figure 2. Baseline characteristics of patients grouped by clinical status. A. Distribution of age; B. Distribution of BMI; C. Distribution of pregnancy frequency; D. Distribution of HBOC family history; E. Distribution of CA125 levels; F. Distribution of HE4 levels. Note: BMI, body mass index; HBOC, hereditary breast and ovarian cancer; CA125, carbohydrate Antigen 125; HE4, human epididymis protein 4.

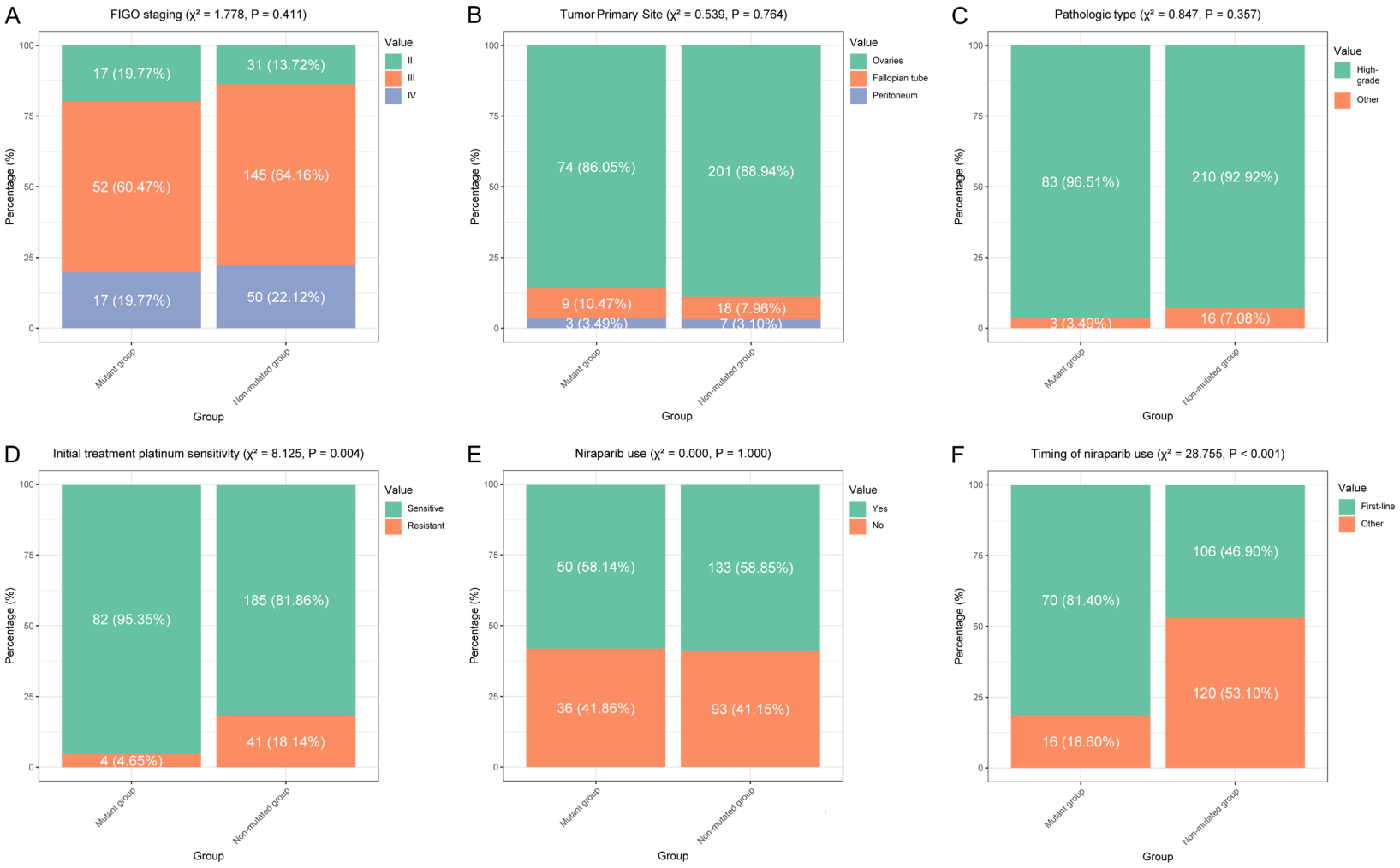


Figure 3. Pathological features of patients grouped by clinical status. A. Distribution of FIGO staging. B. Distribution of tumor/primary tumor size. C. Distribution of pathological type. D. Distribution of platinum sensitivity in the initial treatment. E. Distribution of niraparib use. F. Distribution of the timing of niraparib use. Note: FIGO stands for the International Federation of Gynecology and Obstetrics. “Timing of relapse treatment” refers to the relevant time point. In terms of the timing of niraparib use, “others” includes maintenance treatment for platinum-sensitive recurrence and maintenance treatment for platinum-resistant recurrence.

Table 1. Univariate Cox regression analysis of clinical and pathological factors associated with progression-free survival (PFS) in PSROC patients

Variable	Beta	Std Err	*P*	HR	Lower	Upper
BRCA gene mutation						
Unmutated						
Mutated	0.206	0.191	0.280	1.229	0.845	1.786
Age						
≥ 65						
< 65	-0.550	0.178	0.002	0.577	0.407	0.818
BMI						
≥ 24 kg/m^2						
< 24 kg/m^2	0.408	0.185	0.028	1.504	1.046	2.162
Gravidity						
> 2						
≤ 2	0.023	0.180	0.900	1.023	0.719	1.456
Family history of HBOC						
Yes						
No	0.192	0.275	0.485	1.211	0.707	2.076
CA125 (U/mL)						
≤ 500						
> 500	0.620	0.186	0.001	1.859	1.290	2.678
HE4 (pmol/L)						
≤ 75						
> 75	1.462	0.713	0.040	4.314	1.067	17.443
FIGO staging						
II						
III	-1.241	0.255	< 0.001	0.289	0.175	0.477
IV	1.171	0.237	< 0.001	3.225	2.027	5.133
Primary tumor site						
Ovary						
Oviduct	0.043	0.316	0.891	1.044	0.562	1.941
Peritoneum	0.726	0.390	0.063	2.067	0.962	4.442
Pathological type						
High-grade serous carcinoma						
Others	-0.138	0.389	0.722	0.871	0.406	1.865
Platinum sensitivity in the initial treatment						
Platinum sensitive						
Platinum resistant	1.221	0.206	< 0.001	3.392	2.266	5.075
Niraparib use						
Yes						
No	0.706	0.177	< 0.001	2.026	1.432	2.866
Timing of niraparib use						
First-line maintenance therapy						
Others	1.059	0.182	< 0.001	2.884	2.017	4.123

Note: BRCA, breast cancer gene; BMI, body mass index; HBOC, Hereditary Breast and Ovarian Cancer; CA125, carbohydrate antigen 125; HE4, human epididymis protein 4; FIGO, International Federation of Gynecology and Obstetrics.

tus, parity, family history of HBOC, primary tumor site, and pathological type (HGSC vs. others) did not show significant prognostic effects on PFS (P > 0.05). See **Table 1** and **Figure 4**.

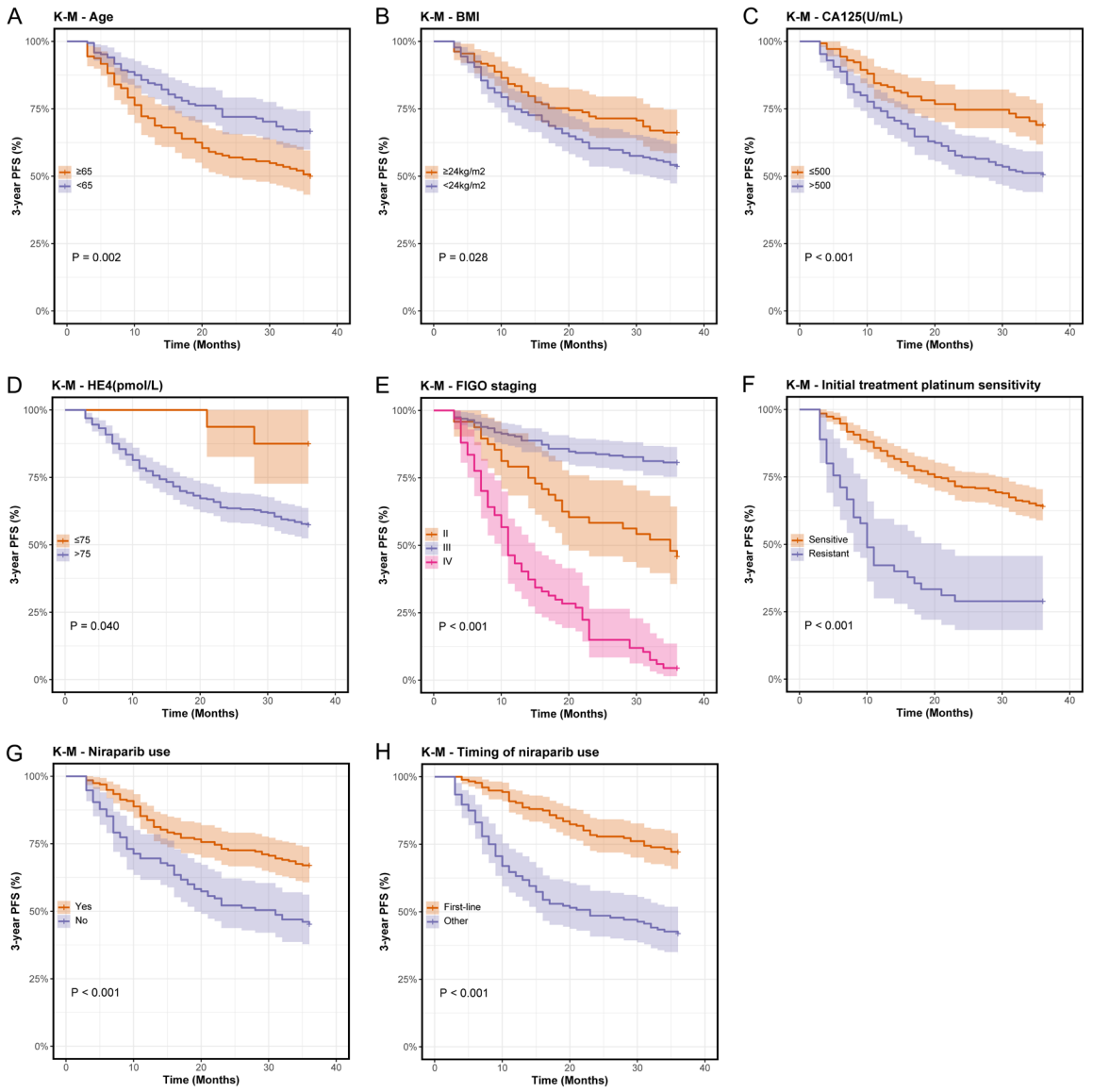


Figure 4. Kaplan-Meier survival curves of significantly associated variables from univariate Cox regression analysis. A. Impact of age on PFS of ovarian cancer patients. B. Impact of BMI on PFS of ovarian cancer patients. C. Impact of CA125 level on PFS of ovarian cancer patients. D. Impact of HE4 level on PFS of ovarian cancer patients. E. Impact of FIGO staging on PFS of ovarian cancer patients. F. Impact of platinum sensitivity in the initial treatment on PFS of ovarian cancer patients. G. Impact of niraparib use on PFS of ovarian cancer patients. H. Impact of the timing of niraparib use on PFS of ovarian cancer patients. Note: PFS, progression-free survival; BMI, body mass index; CA125, carbohydrate antigen 125; HE4, human epididymis protein 4; FIGO, International Federation of Gynecology and Obstetrics.

Multivariate Cox regression analysis of PFS in ovarian cancer patients

Multivariate Cox regression analysis was performed to identify independent prognostic factors for PFS in ovarian cancer patients. Based on the results of the univariate analysis, variables with significant differences ($P < 0.05$) were included in the multivariate model. These variables included age, BMI, CA125 levels, HE4 levels, FIGO staging, platinum sensitivity in the initial treatment, use of niraparib, and the timing of niraparib administration. The analysis revealed that several factors were independently associated with PFS. Patients aged < 65 years exhibited significantly improved PFS compared to those 65 years old or above ($P = 0.003$, HR = 0.560). Conversely, elevated

Table 2. Multivariate Cox regression analysis of independent predictors for progression-free survival (PFS) in PSROC patients

Variable	Beta	Std Err	*P*	HR	Lower	Upper
Age						
≥ 65						
< 65	-0.580	0.195	0.003	0.560	0.382	0.820
BMI						
≥ 24 kg/m^2						
< 24 kg/m^2	0.056	0.197	0.775	1.058	0.719	1.558
CA125 (U/mL)						
≤ 500						
> 500	0.565	0.190	0.003	1.760	1.212	2.554
HE4 (pmol/L)						
≤ 75						
> 75	0.759	0.722	0.294	2.135	0.518	8.798
FIGO staging						
II						
III	-1.098	0.261	< 0.001	0.334	0.200	0.556
IV	1.064	0.252	< 0.001	2.898	1.770	4.745
Platinum sensitivity in the initial treatment						
Platinum sensitive						
Platinum resistant	0.593	0.231	0.010	1.809	1.150	2.845
Niraparib use						
Yes						
No	0.509	0.190	0.007	1.664	1.147	2.413
Timing of niraparib use						
First-line maintenance therapy						
Others	0.580	0.194	0.003	1.786	1.221	2.613

Note: BRCA, breast cancer gene; BMI, body mass index; HBOC, Hereditary Breast and Ovarian Cancer; CA125, carbohydrate antigen 125; HE4, human epididymis protein 4; FIGO, International Federation of Gynecology and Obstetrics.

CA125 levels exceeding 500 U/mL were associated with shorter PFS than those with CA125 levels of 500 U/mL or lower (P = 0.003, HR = 1.760). In comparison to patients at FIGO stage II, those at FIGO stage III demonstrated a significantly longer PFS (P < 0.001, HR = 0.334), whereas patients at FIGO stage IV showed a significantly shorter PFS (P < 0.001, HR = 2.898). Platinum-resistant patients demonstrated markedly a shorter PFS than platinum-sensitive patients (P = 0.010, HR = 1.809). In addition, patients without niraparib use experienced a significantly shorter PFS than those who received niraparib treatment (P = 0.007, HR = 1.664). Moreover, patients with delayed niraparib initiation (non-first-line maintenance) showed a significantly shorter PFS than those otherwise (P = 0.003, HR = 1.786). Notably, this model showed that BMI (P = 0.775) and HE4 levels (P = 0.294) did not demonstrate statistically significant difference. See **Table 2**.

Time-dependent ROC curves and AUC matrices based on variables from multivariate Cox regression analysis

Using variables identified in the multivariate Cox regression analysis, time-dependent ROC curves were generated to evaluate the 1-year, 2-year, and 3-year PFS in ovarian cancer patients (**Figure 5A**, **5C**, **5E**), with AUC matrices developed as well to compare their predictive performance (**Figure 5B**, **5D**, **5F**). Our findings revealed varying predictive strengths among these factors across the different timeframes. FIGO staging demonstrated consistently strong predictive capabilities for PFS, with AUCs of

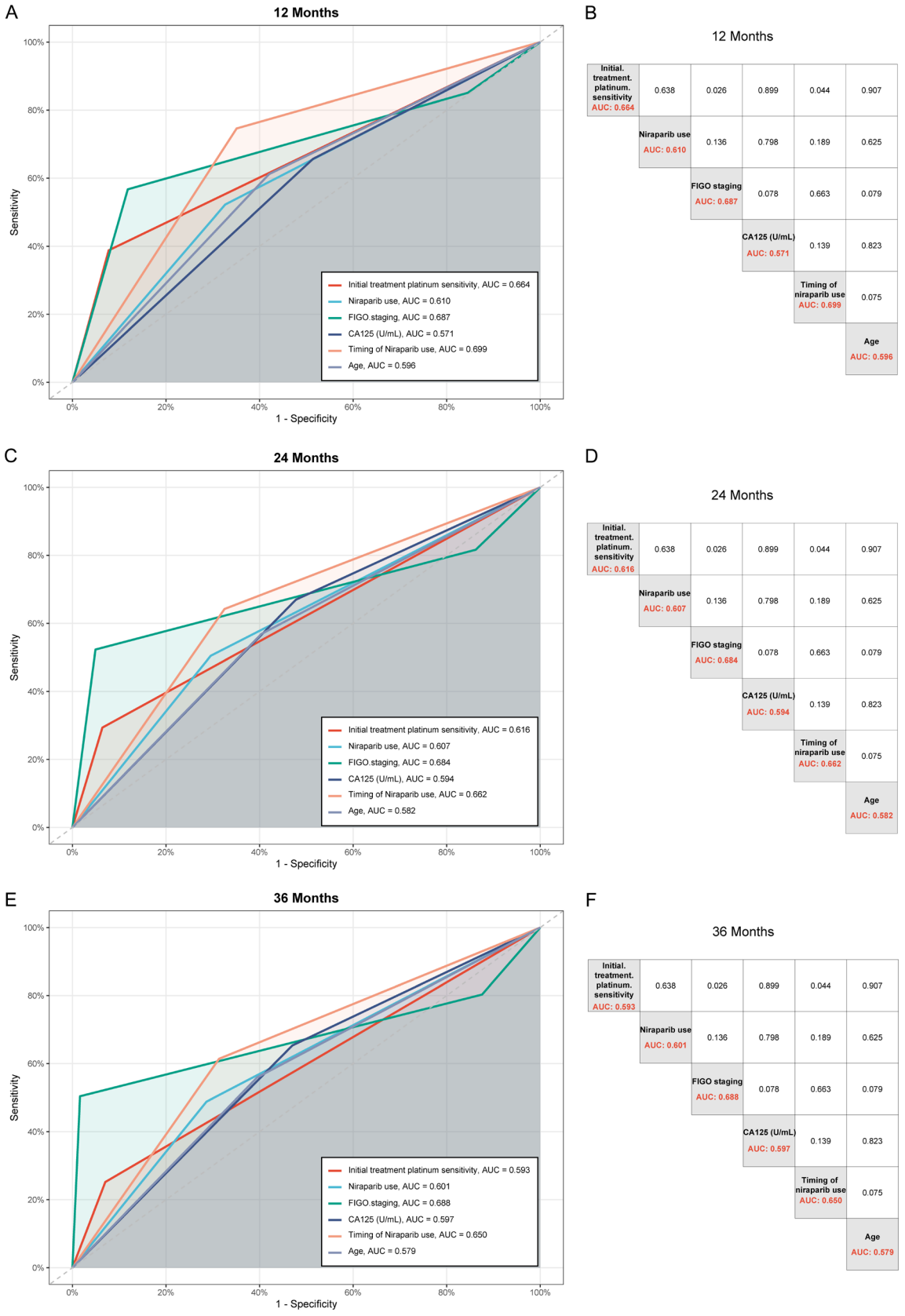


Figure 5. Time-dependent ROC curves and AUC matrices for comparison. A, C, E. Time-dependent ROC curves of variables for the 1-year, 2-year, and 3-year PFS predictions. B, D, F. Comparison of AUC values of each variable for the 1-year, 2-year, and 3-year PFS predictions. Note: ROC, receiver operating characteristic; AUC, area under the curve; FIGO, International Federation of Gynecology and Obstetrics; CA125, carbohydrate antigen 125.

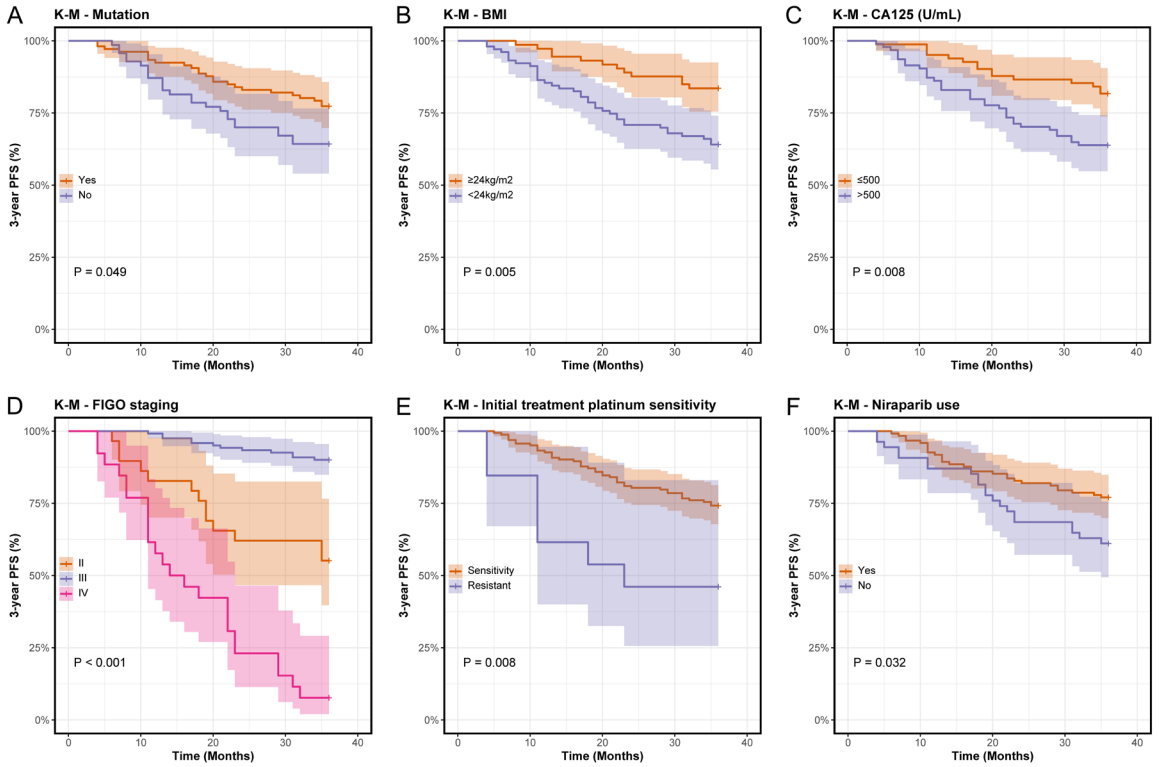


Figure 6. K-M survival curves for patients receiving niraparib as first-line maintenance therapy. A. Influence of gene mutations on patients' PFS. B. Influence of BMI on patients' PFS. C. Influence of CA125 levels on patients' PFS. D. Influence of FIGO staging on patients' PFS. E. Influence of platinum sensitivity in the initial treatment on patients' PFS. F. Influence of niraparib use on patients' PFS. Note: K-M, Kaplan-Meier; PFS, progression-free survival; BMI, body mass index; CA125, carbohydrate antigen 125; FIGO, International Federation of Gynecology and Obstetrics.

0.687 at 1 year, 0.684 at 2 years, and 0.688 at 3 years. The use of niraparib also showed notable predictive performance, registering AUCs of 0.699 at 1 year (the highest among all factors at this point), 0.662 at 2 years, and 0.650 at 3 years. Platinum sensitivity in the initial treatment followed, providing good predictive value with an AUC of 0.664 at 1 year, 0.616 at 2 years, and 0.593 at 3 years. The CA125 level exhibited more moderate predictive power, with AUCs of 0.571 at 1 year, 0.594 at 2 years, and 0.597 at 3 years, indicating its predictive efficacy was comparatively less pronounced but relatively stable or slightly increasing over these periods.

Cox regression analysis and K-M curves for the PFS of patients undergoing niraparib as first-line maintenance treatment

Cox regression analysis identified several significant variables associated with PFS in patients who received niraparib as first-line maintenance treatment ($P < 0.05$). The variables included in the analysis were gene mutations, BMI, CA125 levels, FIGO staging, platinum sensitivity in the initial treatment, and use of niraparib. The analysis revealed that patients with positive gene mutations, a BMI of at least 24 kg/m^2, and a CA125 level of 500 U/mL or lower showed significantly favorable PFS. Conversely, patients with FIGO stages III and IV, those who were platinum-resistant, or those who did not receive niraparib treatment experienced significantly shorter PFS ($P < 0.05$). These findings were corroborated by Kaplan-Meier (K-M) survival curves, which demonstrated significant survival stratification across subgroups, aligning with the results from the Cox regression analysis, as shown in **Figure 6A-F**. However, variables such as age, parity, family history of HBOC, HE4 levels, primary tumor location, and pathological type (high-grade serous carcinoma vs. others) did not show statistically significant effects on PFS ($P > 0.05$). These results are summarized in **Table 3**.

Table 3. Cox regression analysis results for the progression-free survival of patients undergoing niraparib as first-line maintenance treatment

Variable	Beta	Std Err	*P*	HR	Lower	Upper
Mutation						
Mutated						
Unmutated	0.562	0.286	0.049	1.754	1.001	3.072
Age						
≥ 65						
< 65	-0.323	0.286	0.258	0.724	0.413	1.268
BMI						
≥ 24 kg/m^2						
< 24 kg/m^2	0.931	0.332	0.005	2.537	1.322	4.867
Gravidity						
> 2						
≤ 2	-0.309	0.324	0.340	0.734	0.389	1.384
Family history of HBOC						
Yes						
No	-0.090	0.387	0.816	0.914	0.428	1.949
CA125 (U/mL)						
≤ 500						
> 500	0.817	0.310	0.008	2.265	1.233	4.160
HE4 (pmol/L)						
≤ 75						
> 75	1.479	1.010	0.143	4.387	0.606	31.789
FIGO staging						
II						
III	-1.776	0.401	0.000	0.169	0.077	0.371
IV	1.305	0.352	0.000	3.686	1.849	7.349
Primary tumor site						
Ovary						
Oviduct	0.349	0.474	0.462	1.418	0.559	3.592
Peritoneum	0.963	0.525	0.067	2.619	0.936	7.331
Pathological type						
High grade serous carcinoma						
Others	-0.424	0.722	0.557	0.654	0.159	2.694
Platinum sensitivity in the initial treatment						
Platinum sensitive						
Platinum resistant	1.090	0.409	0.008	2.975	1.335	6.630
Niraparib use						
With						
Without	0.620	0.289	0.032	1.859	1.056	3.275

Note: BMI, body mass index; HBOC, Hereditary Breast and Ovarian Cancer; CA125, carbohydrate antigen 125; HE4, human epididymis protein 4; FIGO, International Federation of Gynecology and Obstetrics.

Multivariate Cox regression analysis of PFS in patients undergoing first-line maintenance therapy with niraparib

Multivariate Cox regression analysis identified BMI, CA125 levels, FIGO staging, and platinum sensitivity in the initial treatment as significant predictors of progression-free survival (PFS) in patients receiving niraparib as first-line maintenance therapy ($P < 0.05$). Specifically, patients with a BMI ≥ 24 kg/m^2 exhibited significantly better PFS compared to those with a BMI < 24

Table 4. Multivariate Cox regression analysis of progression-free survival in patients receiving niraparib as first-line maintenance therapy

Variable	Beta	Std Err	*P*	HR	Lower	Upper
Mutation						
Mutated						
Unmutated	0.228	0.346	0.509	1.257	0.638	2.475
BMI						
≥ 24 kg/m^2						
< 24 kg/m^2	0.840	0.344	0.015	2.317	1.181	4.547
CA125 (U/mL)						
≤ 500						
> 500	0.923	0.330	0.005	2.517	1.319	4.802
FIGO staging						
II						
III	-1.840	0.411	0.000	0.159	0.071	0.355
IV	0.939	0.368	0.011	2.558	1.243	5.263
Platinum sensitivity in the initial treatment						
Platinum sensitive						
Platinum resistant	0.955	0.472	0.043	2.599	1.031	6.554
Niraparib use						
Yes						
No	0.561	0.333	0.092	1.752	0.913	3.362

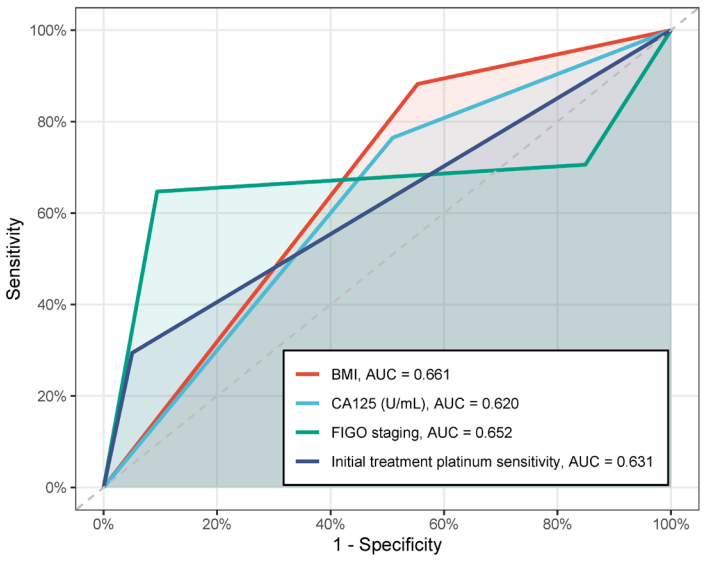
Note: BMI, body mass index; CA125, carbohydrate antigen 125; FIGO, International Federation of Gynecology and Obstetrics.

kg/m^2 (P = 0.015, HR = 2.317). Patients with CA125 levels exceeding 500 U/mL had a significantly shorter PFS compared to those with CA125 levels ≤ 500 U/mL (P = 0.005, HR = 2.517). Additionally, patients at FIGO stage III demonstrated significantly better PFS than those at stage II (P < 0.001, HR = 0.159), while patients at FIGO stage IV experienced significantly poorer PFS compared to stage II (P = 0.011, HR = 2.558). Furthermore, platinum-resistant patients had significantly shorter PFS compared to platinum-sensitive recurrent ovarian cancer (PSROC) patients (P = 0.043, HR = 2.599). It is noteworthy that variables such as niraparib use (P = 0.092) and gene mutation status (P = 0.509) did not show statistically significant differences in this model (P > 0.05), as detailed in **Table 4**.

Time-dependent ROC curves of variables from multivariate Cox regression analysis for the PFS of patients undergoing niraparib as first-line maintenance therapy

Using variables identified by the multivariate Cox regression analysis, time-dependent ROC curves were generated for the 1-year, 2-year, and 3-year PFS of patients receiving niraparib as first-line maintenance therapy (**Figure 7A**, **7C**, **7E**), with their AUC values calculated for each variable for comparison (**Figure 7B**, **7D**, **7F**). Our findings revealed that BMI presented relatively robust power for predicting the 1-year (AUC = 0.661) and 2-year (AUC = 0.628) PFS; however, this power decreased for predicting the 3-year PFS (AUC = 0.612). FIGO staging demonstrated high-level predictive power throughout all time intervals, with AUCs being 0.652 for 1-year, 0.634 for 2-year, and 0.683 for 3-year PFS, showing the strongest power for the 3-year PFS prediction. The CA125 level, however, showed a moderate predictive capacity, with an AUC of 0.620 for the 1-year and 0.614 for the 2-year PFS predictions, followed by a slight increase to 0.625 for the 3-year PFS prediction. The predictive ability of platinum sensitivity in the initial treatment was at a moderate level, with an AUC of 0.631 for the 1-year PFS prediction, but it gradually declined to 0.570 for the 2-year and 0.551 for the 3-year prediction. Overall, FIGO staging remained to be the variable showing the strongest predictive power across all time points, performing optimally for the 3-year prediction. BMI had a

A

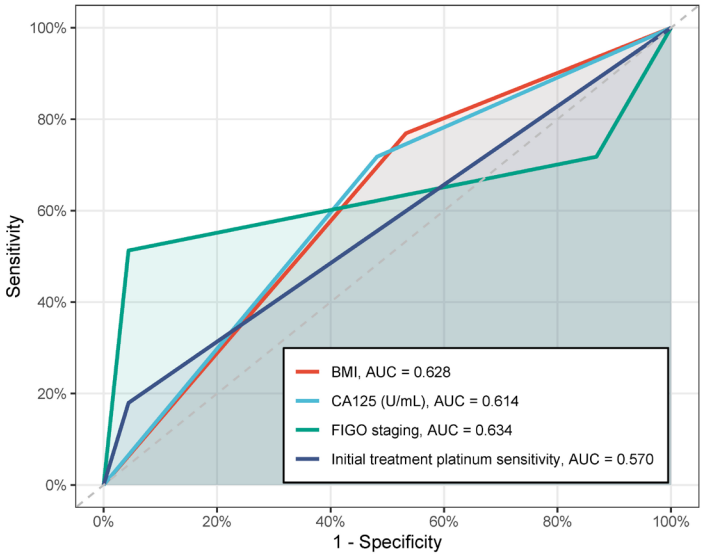


B

12 Months

BMI AUC: 0.661	0.905	0.775	0.119
CA125 (U/mL) AUC: 0.620		0.684	0.248
FIGO staging AUC: 0.652			0.113
Initial treatment platinum sensitivity AUC: 0.631			

C

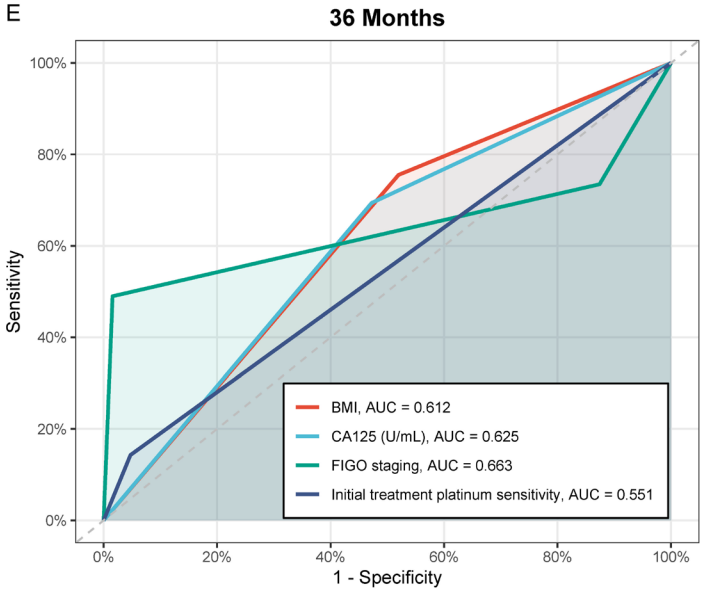


D

24 Months

BMI AUC: 0.628	0.905	0.775	0.119
CA125 (U/mL) AUC: 0.614		0.684	0.248
FIGO staging AUC: 0.634			0.113
Initial treatment platinum sensitivity AUC: 0.570			

E



F

36 Months

BMI AUC: 0.612	0.905	0.775	0.119
CA125 (U/mL) AUC: 0.625		0.684	0.248
FIGO staging AUC: 0.663			0.113
Initial treatment platinum sensitivity AUC: 0.551			

Figure 7. Time-dependent ROC curves and AUC matrices of variables from multivariate Cox regression analysis for predicting PFS of patients administering niraparib as first-line maintenance therapy. A, C, E: Time-dependent ROC curves of BMI, CA125 levels, FIGO staging, and platinum sensitivity in the initial treatment for the 1-year, 2-year, and 3-year PFS predictions. B, D, F: AUC values of the variables for comparing the 1-year, 2-year, and 3-year PFS predictions. Note: ROC, receiver operating characteristic; BMI, body mass index; CA125, carbohydrate antigen 125; FIGO, International Federation of Gynecology and Obstetrics; AUC, area under the curve; PFS, progression-free survival.

relatively strong predictive ability during short-term follow-up. The predictive ability of the CA125 level remained stable, while that of platinum sensitivity in the initial treatment weakened gradually during long-term follow-up.

Adverse reactions associated with niraparib use

In this study, a total of 183 ovarian cancer patients were treated with niraparib, and 129 patients did not receive niraparib. Among the niraparib-treated patients, 115 (62.84%) experienced adverse events. The primary adverse events were hematological and gastrointestinal toxicities. Specifically, thrombocytopenia was observed in 40 niraparib-treated patients (21.86%) and 21 patients (16.28%) in the non-niraparib group (Chi-square = 1.497, P = 0.221), while leukopenia occurred in 40 patients (21.86%) in the niraparib group and 19 patients (14.73%) in the non-niraparib group (Chi-square = 2.508, P = 0.113). Nausea was reported in 34 niraparib-treated patients (18.58%) and 20 non-niraparib patients (15.50%) (Chi-square = 0.500, P = 0.479), and vomiting occurred in 20 patients (10.93%) receiving niraparib and 13 patients (10.08%) not receiving it (Chi-square = 0.058, P = 0.810). Most adverse events in both groups were of grade 1-2, with 29 (15.85%) and 17 (13.18%) patients experiencing adverse events of grade ≥ 3 in the niraparib and non-niraparib groups, respectively.

Discussion

In this study, we used a retrospective analysis to examine the impact of various clinical variables on the PFS of PSROC patients undergoing niraparib treatment. We systematically assessed the independent predictive capabilities of these variables, and our results revealed that BRCA gene mutations, CA125 levels, FIGO staging, BMI, and platinum sensitivity in the initial treatment were all significant factors influencing PFS. Although HE4 levels and the timing of niraparib administration showed significance in univariate analysis, they did not demonstrate independent effects in multivariate analysis. Specifically, patients under 65 years old, those with a BMI of at least 24 kg/m^2, CA125 levels ≤ 500 U/mL, and platinum-sensitive patients exhibited significantly better PFS compared to their respective controls. The time-dependent ROC analysis further confirmed that platinum sensitivity, FIGO staging, and CA125 levels were powerful predictors for PFS, especially in short-term follow-up (1 and 2 years). In terms of adverse reactions, hematological toxicities (leukopenia and thrombocytopenia) and gastrointestinal issues (nausea and vomiting) were the most common, though most were mild to moderate, with grade 3 or higher adverse events occurring in 15.85%, a manageable rate.

The findings of this study align closely with previous research but also reveal some differences worth exploring. First, our study confirms that BRCA gene mutations play a central role in determining niraparib efficacy, consistent with the findings of González-Martín et al. [11], who observed significantly prolonged PFS in BRCA-positive patients treated with niraparib. This strongly supports the use of BRCA mutations as key biomarkers for PARP inhibitor efficacy. Additionally, research by Monk et al. [21] highlighted an intriguing aspect: even in patients without BRCA mutations, niraparib showed substantial efficacy. This suggests that other homologous recombination deficiency (HRD)-related markers might also contribute to the drug's effectiveness. Our study also supports this notion, indicating that the action of PARP inhibitors may extend beyond BRCA mutations to involve other molecular mechanisms that are yet to be fully understood.

This study highlights the critical role of CA125 as a predictive factor for PFS. CA125, a well-established tumor marker in ovarian cancer, is widely used in diagnosis, treatment monitoring, and prognosis assessment. Our findings indicate that patients with lower CA125 levels (≤ 500 U/mL) experienced longer PFS during niraparib treatment. This may suggest that

patients with a lower tumor burden are more responsive to the treatment. As previous studies [22] have shown, lower levels of tumor markers such as CA125 and HE4 are closely associated with better treatment outcomes. Furthermore, the study by Prueksaritanond et al. [23] reinforced that CA125 was an important marker for predicting ovarian cancer treatment efficacy, supporting individualized treatment strategies. While HE4 demonstrated a significant correlation with PFS in univariate analysis, it did not show an independent impact in multivariate analysis. This aligns with the findings of Kerliu et al. [22], indicating that the role of HE4 may be limited to specific patient subsets. Further research is needed to confirm its predictive value. BMI, a key indicator of metabolic health, was found to significantly impact PFS in this study. Specifically, patients with a BMI of 24 kg/m^2 or higher experienced longer PFS. Valabrega et al. [24] also suggested that BMI could affect cancer treatment efficacy through several mechanisms, including drug metabolism, modulation of the immune microenvironment, and tumor growth. However, the role of BMI in cancer treatment remains debated. Some studies have linked higher BMI with an increased risk of recurrence, while others, including both Valabrega et al. and our research, proposed a potential association between higher BMI and better treatment outcomes. Future studies are needed to better understand the mechanisms by which BMI affects niraparib treatment efficacy.

Regarding the timing of niraparib administration, this study found that patients receiving niraparib as first-line maintenance therapy had significantly longer PFS compared to those starting the maintenance after recurrence. This aligns with the findings of González-Martín et al. [11, 25], which indicate that early use of PARP inhibitors like niraparib can significantly delay disease progression. Additionally, the study by González-Martín et al. [26] proposed an interesting angle, suggesting that combining PARP inhibitors with other treatments, such as immunotherapy, might further enhance treatment efficacy. These findings collectively reinforce the benefits of using niraparib in first-line maintenance therapy.

The findings of this study have significant clinical implications, especially in refining the application strategies of niraparib and patient selection. For patients with BRCA mutations, niraparib is a well-established maintenance treatment that significantly prolongs PFS [21]. Additionally, Li et al. [27] demonstrated that niraparib could also substantially extend PFS in patients with BRCA wild-type, suggesting that the potential benefits of niraparib may extend to a broader range of patients. Our study further indicates that easily measurable factors like CA125 levels and BMI are effective predictors for PFS and could serve as auxiliary reference points to identify patients likely to benefit most from niraparib treatment [23, 24]. In terms of clinical factors, FIGO staging and platinum sensitivity in initial treatment were found to be crucial determinants of niraparib efficacy. González-Martín et al. [26] reported that patients with advanced FIGO stages typically had poorer prognoses, a finding consistent with our results. Additionally, Lee et al. [28] emphasized the impact of platinum sensitivity on ovarian cancer treatment outcomes, which further supports our conclusions. Our time-dependent ROC analysis revealed that platinum sensitivity and CA125 levels offer improved discriminative capabilities for short-term prediction. This finding is valuable for guiding early-stage follow-up and treatment efficacy evaluation. Interestingly, this aligns with the research of Huo et al. [29], who highlighted the importance of dynamic monitoring indicators for personalized treatment strategies.

Taken together, these findings suggest that niraparib's efficacy is influenced by a variety of factors, including BRCA mutations, tumor burden, biomarker levels, and patient characteristics. Future research should focus on exploring the mechanisms behind these influences, particularly how molecular pathways beyond HRD contribute to the effectiveness of PARP inhibitors. Additionally, optimizing maintenance treatment strategies to encompass a wider patient population remains a critical area for investigation.

The results of this study highlight that niraparib exhibits a favorable safety profile, with most adverse reactions being mild to moderate. The incidence of grade 3 or higher adverse events was 15.85%. Hematological toxicity, especially thrombocytopenia, was the most common adverse reaction, which aligns with previous research. For example, Friedlander et al. [30] summarized common side effects of PARP

inhibitors, including anemia, nausea, and fatigue, noting that hematological adverse reactions to niraparib are manageable. Additionally, Guo et al. [31] conducted a pharmacovigilance study based on the FDA's Adverse Event Reporting System (FAERS) and found that hematological toxicities were the predominant adverse events associated with niraparib. They also emphasized the need for intensified monitoring during the early stages of drug administration. Real-world studies have indicated that the incidence of treatment-related adverse events, including grade 3 or higher toxicities, is significantly lower with niraparib compared to platinum-based chemotherapy, particularly for hematological issues like anemia and neutropenia, showcasing niraparib's superior tolerability in clinical practice [32]. Clinically, the incidence of severe adverse reactions can be reduced through dynamic blood monitoring and timely dose adjustments. For instance, Wang et al. [33] demonstrated that implementing an individualized starting dose (ISD) significantly reduced severe hematological adverse events among Chinese patients, highlighting the importance of personalized management to enhance treatment adherence and optimize niraparib's clinical use.

This study has several strengths. First, it incorporates a comprehensive set of clinical and pathological variables affecting PFS, including BRCA gene mutations, baseline characteristics (such as BMI and age), tumor burden indicators (like CA125 and HE4), and pathological features (such as FIGO staging and platinum sensitivity). Univariate and multivariate analyses were conducted to evaluate these variables' roles, providing valuable multi-dimensional insights for individualized treatment with niraparib. Second, by using time-dependent ROC analysis, the study dynamically assesses the predictive power of key variables, reinforcing the reliability of its results. Third, real-world data were utilized to validate niraparib's efficacy and safety in clinical settings.

However, the study has limitations. Being retrospective, it is prone to selection and information biases. For example, baseline patient characteristics may confound the interpretation of the findings. Additionally, the sample size is relatively small, and there may be an imbalance in the distribution of patients receiving first-line versus post-recurrence maintenance therapy, which could influence the statistical significance of some variables. Furthermore, this study did not examine HRD status or other molecular markers like RAD51 or BRIP1 mutations, which could limit a deeper understanding of the mechanisms underlying PARP inhibitor efficacy. Lastly, the study's single-center design means that the results need to be confirmed through multi-center studies to assess their generalizability.

Future research should focus on identifying efficacy-predictive markers for PARP inhibitors, particularly in patients without BRCA mutations, to better understand the role of alternative molecular mechanisms. Prospective multicenter studies are needed to validate the generalizability of these findings and minimize selection bias. Moreover, combining niraparib with other treatment strategies, such as immunotherapy and anti-angiogenic therapies, should be explored to identify optimal treatment plans for patients with different clinical stages and molecular profiles. Extending follow-up periods to assess the impact of niraparib on overall survival would also provide valuable evidence for its long-term efficacy.

Conclusion

In this study, the effects of various clinical variables on patient PFS following niraparib treatment were systematically evaluated. Through meticulous analysis, it has delineated the pivotal significance of elements such as BRCA mutations, CA125 levels, FIGO staging, and platinum sensitivity in predicting the therapeutic efficacy of niraparib. The findings have offered a scientific basis for the individualized application of niraparib and significant guidance for optimizing the treatment strategies for patients with PSROC.

Disclosure of conflict of interest

None.

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