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Original Article

Prognostic nomogram for advanced epithelial ovarian cancer in the era of homologous recombination testing and PARP inhibitor therapy

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Abstract: Homologous recombination (HR) status plays a critical role in selecting advanced epithelial ovarian cancer (EOC) patients for poly (ADP-ribose) polymerase inhibitor (PARPi) therapy. This study aimed to develop a novel nomogram to predict prognosis in these patients in the era of precision medicine. We conducted a single-institute retrospective analysis on patients diagnosed with advanced EOC between January 2021 and January 2024. Clinicopathological factors, HR status, and PARPi use were evaluated for their association with survival outcomes. Multivariate Cox regression analysis identified independent predictors of progression-free survival (PFS), and a nomogram was constructed and validated using bootstrap resampling. Among 128 patients, PARPi maintenance therapy was administered after front-line chemotherapy to 43 patients as indicated. Multivariate analysis identified optimal surgery [hazard ratio 0.47, 95% confidence interval (CI) 0.27-0.83], CA-125 > 10.7 U/mL after front-line chemotherapy [hazard ratio 3.41, 95% CI 1.85-6.31], neoadjuvant chemotherapy [hazard ratio 2.55, 95% CI 1.32-4.91], and PARPi use [hazard ratio 0.22, 95% CI 0.12-0.42] as independent predictors of PFS. Patients with all favorable factors had a predicted 3-year PFS of 100%, compared to 0% for those with none. The nomogram demonstrated strong predictive accuracy, with a concordance index of 0.78, and calibration plots showed excellent agreement. Internal validation confirmed the reliability of the nomogram. Our findings indicate that HR-deficient patients who respond well to upfront optimal debulking surgery and chemotherapy (indicated by a post-treatment CA125 level below 10.7 U/mL) may experience excellent PFS when followed by PARPi maintenance. Our nomogram provides a dependable tool for personalized prognosis assessment, enabling clinicians to optimize treatment strategies in the era of precision medicine.

Keywords: Epithelial ovarian cancer, homologous recombination status, PARP inhibitor, prognostic nomogram

Introduction

Ovarian cancer remains one of the most lethal gynecological malignancies, with an estimated 324,000 new cases and 207,000 deaths worldwide annually [1]. It is often diagnosed at an advanced stage due to its nonspecific symptoms and lack of effective screening methods, contributing to its high mortality rate. Epithelial ovarian cancer (EOC) accounts for approximately 90% of all ovarian cancer cases, and its incidence increases with age, peaking in women aged 55-64 years [2]. Despite advances in treatment, the 5-year survival rate for advanced-stage disease remains unsatisfactory, highlighting the need for improved prognostic tools and therapeutic strategies [3].

The cornerstone of advanced EOC treatment has historically been cytoreductive surgery followed by platinum-based chemotherapy. Achieving optimal debulking (residual tumor < 1 cm) and early FIGO (International Federation of Gynecology and Obstetrics) stage are well-established prognostic factors associated with improved survival outcomes [4]. However, the

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introduction of targeted therapies, particularly poly (ADP-ribose) polymerase inhibitors (PARPi), has transformed the treatment landscape for ovarian cancer, especially in patients with *BRCA* mutations or homologous recombination deficiency (HRD) [5-8]. These advancements raise important questions about how traditional prognostic factors have evolved in the era of precision medicine and what the impact of targeted therapies is on survival outcomes in advanced EOC in real-world clinical practice.

To address these questions, we initiated this study. Our goal was to develop a novel nomogram that incorporates traditional clinicopathological factors, HR status, and PARPi use to predict prognosis in patients with advanced EOC. This tool aims to provide a more personalized and accurate prognostic assessment, allowing clinicians to optimize treatment strategies and enhance outcomes in the era of precision medicine.

Materials and methods

Ethical statement

This study complied with relevant ethical guidelines and was approved by the Institutional Review Board of Chang Gung Memorial Hospital (No. 202500242B0).

Study design and clinical data collection

This retrospective cohort study attempted to investigate the predictive capabilities of a nomogram for survival outcomes in women with newly diagnosed advanced EOC (included tubal or primary peritoneal cancer) who underwent upfront or interval cytoreductive surgery and platinum-based chemotherapy with or without maintenance PARPi in the era of HR status evaluation. PARPi treatments were suggested according to the latest clinical guidelines. Data were collected from women diagnosed with stage III/IV EOC between January 2021 and January 2024 treated at Kaohsiung Chang Gung Memorial Hospital. Relevant clinical, pathological, and treatment data were retrieved from medical records, including age at diagnosis, histological subtype, FIGO stage, CA-125 levels after front-line chemotherapy, and residual disease after cytoreductive surgery. Patients who did not undergo cytoreductive surgery, lacked complete clinical and treatment data, or who had chemotherapy less than six cycles were excluded. Patients who underwent neoadjuvant chemotherapy (NACT) followed by interval debulking surgery were also eligible for inclusion. Treatment outcomes were retrospectively reviewed using RECIST and Gynecological Cancer Intergroup CA125 related-response criteria [9].

Homologous recombination status evaluation

In the present study, HR status was determined using either ACT or Sofiva Genomics as part of the CareHRD Project in Taiwan. Briefly, ACT Genomics detects HRD status by LOH (loss of heterozygosity) score and 24 HR repair-related genes (including *BRCA* 1/2) to evaluate whether a tumor is HRD or not (ACTHRD™, ACT Genomics, Taipei, Taiwan), while Sofiva Genomics incorporates Illumina's sequencing technology to identify HRD (SOFIVA HRD Testing, Sofiva Genomics, Taipei, Taiwan). The results of HR status were divided into four distinct categories: 1. HRD/*BRCA*m (mutation) (cases with pathogenic *BRCA* 1 or *BRCA* 2 mutations confirmed via genomic sequencing). 2. HRD/*BRCA*wt (wild-type). 3. HRP (HR proficient). 4. Unknown HR/*BRCA*wt.

Statistical analysis

Descriptive statistics were employed to summarize patient characteristics and clinicopathological factors. Receiver operating characteristic (ROC) curve analysis, along with area under the curve (AUC) calculation and Youden's index, was used to determine the optimal cutoff value for CA125 levels in predicting survival outcomes. Univariate and multivariate Cox regression analyses were conducted to identify independent prognostic factors, with hazard ratios (HRs) and 95% confidence intervals (CIs) calculated for each variable. The impact of these factors on progression-free survival (PFS) was assessed using Kaplan-Meier analysis, and differences between groups were evaluated with the log-rank test. PFS was defined as the time from the initiation of PARPi treatment to disease progression or the last follow-up. Overall survival was not selected as an endpoint due to the limited number of events observed at the time of analysis. A nomogram was developed to estimate individualized probabilities of PFS based on signifi-

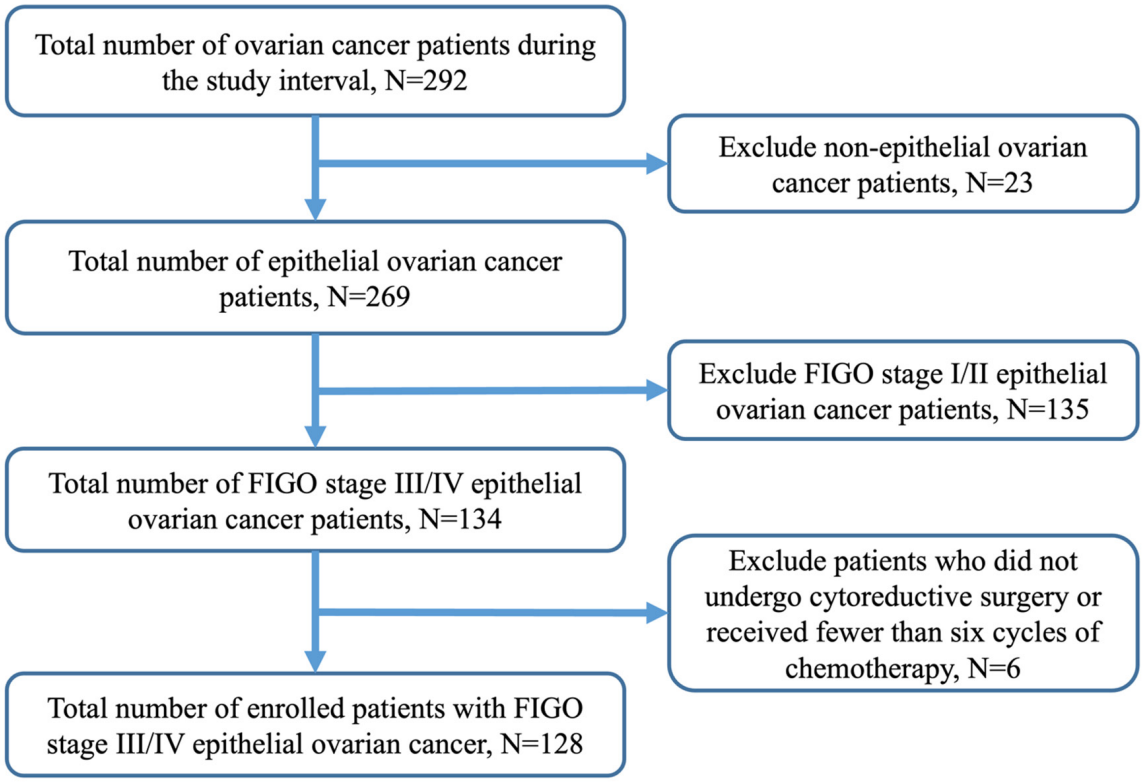

Figure 1. Flowchart illustrating patient enrollment in our study.

cant prognostic factors. Its performance was assessed through calibration, discrimination, and internal validation. Calibration plots were generated to compare predicted probabilities with observed outcomes. Internal validation was conducted using 300 bootstrap resamples to evaluate accuracy and discrimination within the cohort. Discrimination was analyzed by calculating the time-dependent AUC to assess the nomogram's ability to distinguish between progression and progression-free cases. Predictive accuracy was quantified using the concordance index (c-index) for each bootstrap sample. Data management and statistical analyses were performed using SPSS (version 22), SAS (SAS Institute, Cary, NC, USA), and MedCalc (version 22.003), with R 4.1.0 used for nomogram construction and validation. A p-value < 0.05 was considered statistically significant.

Results

Patients' characteristics between those receiving PARP inhibitors and those not receiving PARPi

Figure 1 shows the flowchart of study case enrollment. Initially, a total of 292 patients with newly diagnosed ovarian cancer during the study interval were recruited. After screening these patients, 128 women with FIGO stage III/IV EOC who met the inclusion criteria were finally included in this study. Among them, 43 (33.6%) patients received PARPi (either olaparib or niraparib), with or without concomitant bevacizumab maintenance. This group included 29 patients with *BRCA*m, 12 with HRD/*BRCA*wt, 1 with HRP, and 1 with unknown HR/*BRCA*wt. Detailed comparison of clinical characteristics between patients receiving PARPi and those not receiving PARPi is shown in **Table 1**. The PARPi group exhibited a significantly higher proportion of high-grade serous/endometrioid histologies, *BRCA*m, and HRD status compared to the non-PARPi group, consistent with current evidence supporting the clinical benefits of PARPi in HR-deficient patients. However, no significant differences were observed between the two groups in terms of mean age, stage distribution, NACT or upfront surgery, residual disease following cytoreductive surgery, CA125 level after front-line treatment, or the concomitant use of bevacizumab maintenance.

Table 1. Demographic characteristics of participants and comparison between patients receiving PARP inhibitors (PARPi) and those not receiving

Clinical variables	Total N = 128 (%)	PARPi n = 43 (%)	No PARPi n = 85 (%)	*P*-value
Mean age at diagnosis	60.4	59.8	60.7	0.748
FIGO Stage				0.136
III	84 (65.6)	32 (74.4)	52 (61.2)	
IV	44 (34.4)	11 (25.6)	33 (38.3)	
HGSC/HGEC				0.008
Yes	97 (75.8)	39 (90.7)	58 (68.2)	
No	31 (24.2)	4 (9.3)	27 (31.8)	
NACT				0.760
Yes	75 (58.6)	26 (60.5)	49 (57.6)	
No	53 (41.4)	17 (39.5)	36 (42.4)	
Residual disease				0.470
Optimal (< 1 cm)	90 (70.3)	32 (74.4)	58 (68.2)	
Suboptimal (≥ 1 cm)	38 (29.7)	11 (25.6)	27 (31.8)	
CA125 after chemotherapy				0.719
< 10.7 U/mL	50 (39.1)	18 (41.9)	32 (37.6)	
≥ 10.7 U/mL	78 (60.9)	25 (58.1)	53 (62.4)	
Bevacizumab concomitant use				
Yes	75 (58.6)	25 (58.1)	50 (58.8)	0.941
No	53 (41.4)	18 (41.9)	35 (41.2)	
HR status, n (%)				< 0.001
Deficient				
BRCA mutation	30 (23.4)	29 (67.5)	1 (1.2)	
BRCA wild-type	28 (21.9)	12 (27.9)	16 (18.8)	
Proficient	31 (24.2)	1 (2.3)	30 (35.3)	
Unknown HR/*BRCA* wild-type	39 (30.5)	1 (2.3)	38 (44.7)	

HGSC: high-grade serous carcinoma, HGEC: high-grade endometrioid carcinoma, HR: homologous recombination, NACT: neo-adjuvant chemotherapy, PARPi: poly ADP-ribose polymerase inhibitors.

Prognostic factors associated with progression-free survival

We selected the CA125 level after completing front-line chemotherapy as a potential prognostic factor, based on evidence from multiple prior studies [10]. We found that the optimal cutoff value for CA125 was 10.7 U/mL (AUC 0.72) for predicting disease progression. In the Cox regression analysis, HR status was not included due to its strong correlation with PARP inhibitor use. Univariate analysis revealed that NACT, suboptimal debulking with residual disease > 1 cm, CA125 > 10.7 U/mL, and non-PARPi use were significantly associated with poorer PFS (**Figure 2**). Multivariate analysis confirmed these four factors as independent predictors of PFS: optimal surgery (HR 0.47, 95% CI 0.27-0.83), CA125 > 10.7 U/mL (HR 3.41, 95% CI 1.85-6.31), NACT (HR 2.55, 95% CI 1.32-4.91), and PARPi use (HR 0.22, 95% CI 0.12-0.42) (**Table 2**). Kaplan-Meier survival curves demonstrated that patients with all favorable factors had a 3-year PFS rate of 100%, compared to 0% for those without any favorable factors (log-rank $P < 0.001$, **Figure 3**).

Constructed and validated a nomogram to predict progression-free survival

Using these four independent factors, we developed a nomogram to predict the PFS rate at 36 months (**Figure 4A**). The nomogram demonstrated strong predictive accuracy, with a concordance index of 0.785. Time-dependent AUC values were 0.820 (95% CI, 0.768-0.907) at 12 months, 0.818 (95% CI, 0.725-0.901) at 24 months, and 0.785 (95% CI, 0.720-0.830) at 36 months. Notably, our nomogram model showed superior predictive accuracy for PFS

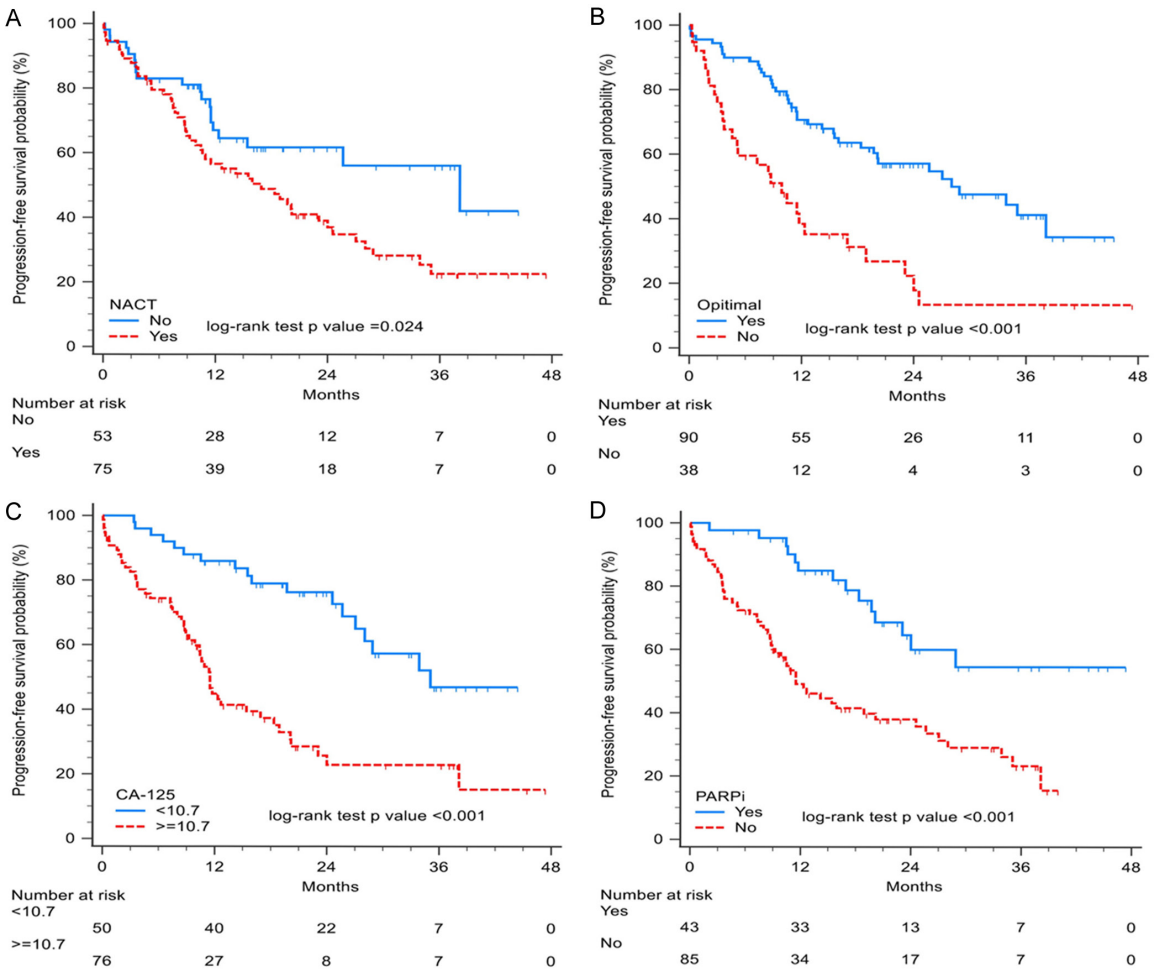

Figure 2. Kaplan-Meier survival curves revealed that patients who underwent NACT (A), had suboptimal debulking surgery (B), exhibited CA125 levels > 10.7 U/mL after front-line chemotherapy (C), or did not receive PARPi maintenance therapy (D) experienced significantly worse PFS.

compared to the individual independent factors (**Figure 4B**). Calibration plots indicated excellent agreement between predicted probabilities and observed outcomes, confirming the nomogram's reliability (**Figure 4C**). Internal validation provided further support for its accuracy in discriminating between progression and progression-free cases. For example, a patient who received NACT (55 points), underwent suboptimal interval debulking surgery (50 points), and had a CA125 level < 10.7 U/mL (0 points) after front-line treatment would accumulate a total of 105 points in the model, despite receiving PARPi treatment (0 points). Projecting 105 points to the risk axis estimates a 3-year PFS probability of 0.62.

Discussion

This study provides real-world evidence supporting the efficacy of PARPi as first-line maintenance therapy. Our findings suggest that patients with HR-deficient tumors who respond well to upfront optimal debulking surgery and adjuvant chemotherapy, characterized by a post-treatment CA125 level below 10.7 U/mL, may achieve excellent PFS when followed by PARPi maintenance. The nomogram developed in this study demonstrated robust predictive performance, reinforcing its value as a reliable tool for individualized risk stratification in advanced EOC patients.

Suboptimal residual disease, particularly in patients undergoing NACT, is a universal poor prognostic factor because NACT is often administered in cases of large-volume, unresectable disease [11-13]. Such extensive tumors may harbor resistant clones and enrich cancer stem cells when treated with initial platinum-based therapy rather than surgery [14, 15]. Recent

Table 2. Univariate and multivariate Cox regression analyses to identify factors associated with progression-free survival (N = 128)

Clinical variables	Univariate			Multivariate		
	HR	95% CI	*p* value	HR	95% CI	*P* value
Age, years (≥ 60 vs. < 60)	1.448	0.892-2.351	0.135	1.026	0.579-1.818	0.930
FIGO stage (IV vs. III)	1.606	0.998-2.587	0.051	0.889	0.523-1.512	0.665
Histology (HGSEC vs. non-HGSEC)	0.740	0.427-1.283	0.284	0.724	0.382-1.374	0.323
NACT (Yes vs. no)	1.808	1.074-3.043	0.026	2.547	1.321-4.911	0.005
Bevacizumab concomitant use (Yes vs. No)	0.823	0.510-1.328	0.425	0.901	0.532-1.526	0.699
Residual disease after cytoreductive surgery (Optimal vs. suboptimal)	0.383	0.236-0.623	< 0.001	0.469	0.265-0.830	0.009
CA125 after front-line C/T, U/mL (≥ 10.7 vs. < 10.7)	3.272	1.890-5.664	< 0.001	3.414	1.846-6.311	< 0.001
PARPi use (Yes vs. No)	0.332	0.184-0.598	< 0.001	0.222	0.117-0.424	< 0.001

CI: confidence interval, C/T: chemotherapy, HGSEC: high-grade serous/endometrioid carcinoma, HR: hazard ratio, NACT: neoadjuvant chemotherapy, PARPi: poly ADP-ribose polymerase inhibitors.

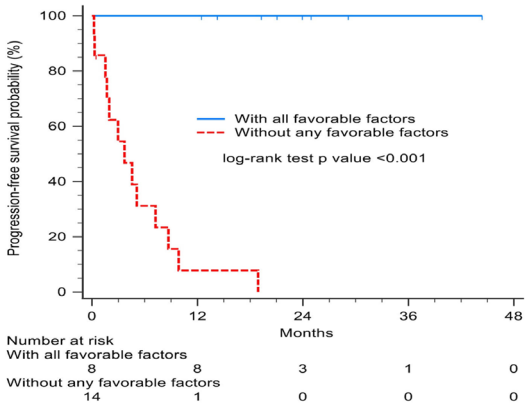

Figure 3. Comparison of Kaplan-Meier survival curves between patients with all favorable prognostic factors and those without any.

advances in targeted therapies raise the question of whether these innovations can mitigate the prognostic impact of traditional factors like suboptimal debulking in advanced EOC. For example, a prospective randomized controlled trial demonstrated that advanced high-risk EOC patients (with residual disease) receiving PARPi plus bevacizumab maintenance had a median PFS of 50.3 months, compared to 44.3 months in low-risk patients (no residual disease) treated with bevacizumab alone [16]. This suggests that PARPi can counteract the adverse effects of residual disease. Similarly, a real-world study from China involving 164 patients in a PARPi first-line maintenance cohort found that R0 resection (no residual disease) was no longer a significant independent prognostic factor [17]. Instead, *BRCA* mutation status and complete/partial response to front-line chemotherapy were the only independent predictors of prolonged PFS. A Korean study of 191 advanced EOC patients receiving PARPi as first-line maintenance (63.4% with *BRCA*m) also found that optimal debulking surgery did not significantly affect disease progression [18]. Independent risk factors for poor PFS included elevated CA125 before PARPi, NACT, non-high-grade serous carcinoma (non-HGSC) histology, and absence of *BRCA*m. While two factors - CA125 and NACT - aligned with our findings, the Korean study used a different CA125 cutoff (23.5 U/mL), likely due to variations in measurement methodologies. Despite this discrepancy, both studies highlight the importance of platinum sensitivity in enhancing PARPi efficacy and improving survival outcomes. Another study from Southeastern Korea involving 96 PARPi-treated patients found that only non-*BRCA* mutations were independently associated with poorer PFS, while NACT was marginally significant [19]. Collectively, these real-world studies highlight that surgical outcomes may lose their prognostic significance when PARPi is used under appropriate indications.

A retrospective study from the United States (US), reflecting a more real-world treatment setting, analyzed 705 patients with advanced EOC, among whom 166 (23.6%) received PARPi as first-line maintenance therapy [20]. Notably, despite regulatory approval, only 56% of *BRCA*m patients received PARPi during the study period. This balanced distribution allowed for an assessment of PARPi efficacy across different HR statuses. The study found that PARPi maintenance was associated with a significantly reduced risk of disease progression across all biomarker-defined subgroups. Residual disease was a significant prognostic factor in the entire cohort. Interestingly, the prognostic impact of residual disease diminished in the *BRCA*m (P = 0.09) and HRD (P = 0.09) subgroups, where PARPi treatment demonstrated strong efficacy (HR 0.17, 95% CI 0.07-0.41 in *BRCA*m and HR 0.22, 95% CI 0.11-0.44 in HRD). However, in the HRP subgroup, where PARPi was less effective (HR 0.57, 95% CI 0.40-0.81), residual disease status remained a critical prognostic factor (P < 0.01). These findings, in conjunction with data from the above mentioned PARPi-treated cohorts, further support the notion that the greater the benefit of PARPi therapy (particularly in *BRCA*m and HRD patients), the less essential complete cytoreduction becomes in achieving optimal patient outcomes.

We began enrolling advanced EOC patients in our study following the approval of PARPi maintenance therapy by the Taiwan Food and Drug Administration. However, under our National Health Insurance system, reimbursement for PARPi is limited to patients with *BRCA*m due to the strongest clinical evidence supporting its efficacy. As a result, PARPi was predominantly used in *BRCA*m patients, with limited use in HRD/*BRCA*wt cases and only one patient in the HRP subgroup due to financial constraints. Given the strong correlation between PARPi use and biomarker status, we excluded bio-

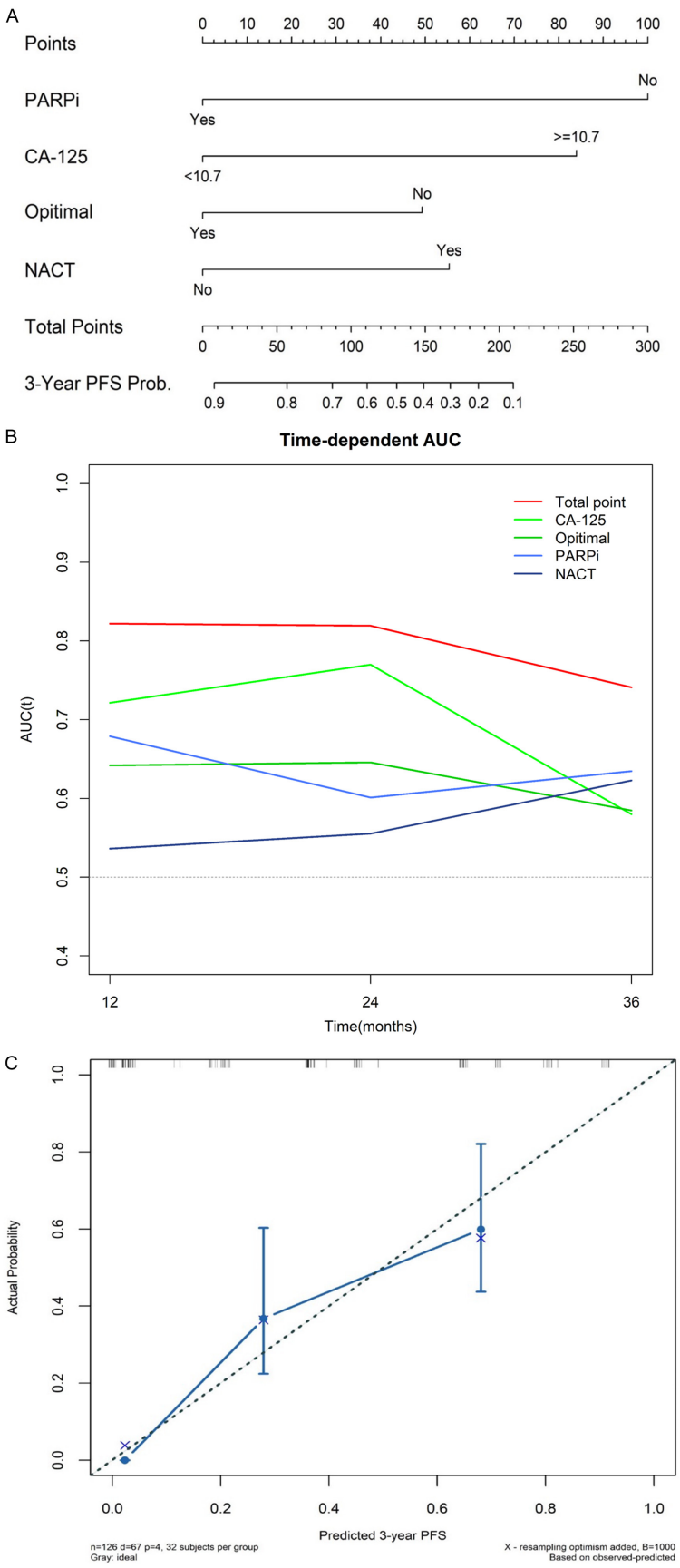

Figure 4. A: A nomogram to predict 3-year PFS. B: Time-dependent AUC at 12, 24, and 36 months, and our nomogram (red line) showed superior predictive accuracy for PFS compared to the individual independent factors. C: Calibration plots of the nomogram to predict 3-year PFS, the dotted line indicates the ideal prediction, and the blue line represents the nomogram's performance. Blue dots with bars represent the nomogram's performance with 95% CI when applied to the observed surviving cohorts.

marker status from our uni- and multivariate Cox regression analyses. Due to the limited proportion of *BRCA*m patients in our cohort (23.4%), similar to the US study [20], we observed comparable findings where traditional prognostic factors - such as NACT, residual disease, and low CA125 levels after front-line chemotherapy (indicative of high chemosensitivity) - remained significant predictors of PFS. Unfortunately, the small number of *BRCA*m cases restricted our ability to conduct a meaningful subgroup analysis. However, our nomogram provides a clearer perspective, demonstrating that when PARPi is used under strict indications, its impact on PFS is the most significant factor, followed by strong chemosensitivity, as reflected by CA125 levels < 10.7 U/mL post-chemotherapy. Although NACT and suboptimal debulking remain important, their influence on PFS is notably less significant compared to PARPi use and post-chemotherapy CA125 levels.

A key strength of our study is the development of a novel prognostic nomogram incorporating traditional factors like NACT, residual disease, and

post-chemotherapy CA125 levels, alongside PARPi use, with strong predictive accuracy confirmed through internal validation. However, its retrospective single-institution design may limit generalizability, and reimbursement constraints restricted PARPi use primarily to *BRCA*m patients, preventing a comprehensive biomarker-based analysis. Additionally, the absence of external validation and the relatively short follow-up period necessitate further studies to confirm long-term applicability.

Conclusions

Our study provides valuable real-world insights into the prognosis of advanced EOC patients in the era of precision medicine. Given the increasing role of HR testing and PARPi therapy in treatment decision-making, our nomogram model provides a clinical tool to optimize personalized management strategies, helping clinicians identify and inform patients who may benefit most from intensified surveillance or therapeutic interventions. Further multi-center real-world study is warranted to confirm the potential role of PARPi to improve outcomes regardless of surgical outcomes. As precision medicine continues to evolve, integrating these novel targeted therapies into clinical practice could reduce the dependency on complete cytoreduction and expand treatment options for patients who are not candidates for optimal debulking.

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Disclosure of conflict of interest

None.

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