Low FOXJ2 expression is associated with unfavorable postoperative prognosis of patients with epithelial ovarian cancer

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Abstract
The forkhead box (FOX) family is a large and diverse group of transcription factors. Forkhead box J2 (FOXJ2) is a member of the FOX family that is aberrantly expressed in a variety of cancers. However, its role in epithelial ovarian cancer (EOC) remains elusive. The purpose of this study was to evaluate the prognostic value of FOXJ2 expression in patients with epithelial ovarian cancer.

The current study retrospectively included 151 patients with EOC from January 2013 to September 2016. FOXJ2 expression was analyzed by immunohistochemistry based on tissue microarrays. Then, the prognostic value of FOXJ2 expression and clinical outcomes were evaluated by Kaplan–Meier and cox regression analysis.

Low FOXJ2 expression was associated with high International Federation of Gynecology and Obstetrics (FIGO) stage. Kaplan–Meier curves showed that high FOXJ2 expression was associated with improved median overall survival (OS, 57.9 vs 31.9 months; \(P = .037\)) and longer median progression-free survival (PFS, 31.8 vs 18.1 months; \(P = .012\)). Univariate analysis demonstrated that FOXJ2 expression was significantly correlated with OS and PFS in patients with epithelial ovarian cancer. Multivariate analysis revealed FOXJ2 expression as an independent prognostic factor of progression-free survival of epithelial ovarian cancer patients. Low FOXJ2 expression is a novel adverse prognostic factor of clinical outcome in epithelial ovarian cancer.

Abbreviations: Forkhead box, FOX = Forkhead box, FOXJ2 = Forkhead box J2, PBS = phosphate buffered saline, PDS = primary debulking surgery, TMAs = tissue microarrays, WHO = World Health Organization.

Keywords: epithelial ovarian cancer, forkhead box J2, overall survival, prognostic factor, progression-free survival

1. Introduction
Ovarian cancer, one of the most common malignancies affecting the female reproductive system, has the highest mortality rate among malignant gynecological tumors.\(^{1,2}\) The World Health Organization (WHO) estimates that 225,500 individuals are diagnosed with ovarian cancer yearly, with 140,200 patients succumbing to the malignancy; therefore, ovarian cancer is the 7th commonest and the 8th deadliest cancer among women around the world.\(^{3,4}\) Ovarian cancer stages range between I and VI; only approximately 13% of serous ovarian carcinoma cases are detected at stage I or II, with most individuals diagnosed at the stage of distant metastasis.\(^{5}\) Despite complete remission upon initial treatment, 60% of individuals with advanced stage ovarian cancer show relapse within 5 years.\(^{6,7}\) Unfortunately, the pathogenesis of ovarian cancer remains unclear. Thus, it is crucial to investigate the molecular regulatory mechanisms related to the malignant behaviors of epithelial ovarian cancer and identify new therapeutic targets.

Forkhead box (FOX) family factors are transcription factors that share an evolutionarily conserved DNA-binding domain, termed the “fork-head” or “winged-helix” domain.\(^{8}\) Currently, mounting evidence suggests that FOX family members are abnormally expressed in many cancers, and contribute to a variety of cellular processes, such as proliferation, differentiation, adhesion, migration, and invasion.\(^{9-11}\) Forkhead box J2 (FOXJ2), a member of the FOX family, is widely distributed in different organs and tissues, from the fetus to adults.\(^{12}\) Meanwhile, the expression patterns of FOXJ2 have been reported to be aberrant in a variety of cancers, including breast cancer, extra-hepatic cholangiocarcinoma, nasopharyngeal car-
FOXJ2 expression in patients with epithelial ovarian cancer. The results could advance our understanding of the molecular basis of EOC development.

2. Methods

2.1. Patients and specimens

This was a retrospective study. A total of 151 tumor specimens from EOC patients administered surgical treatment in Nantong Tumor Hospital from January 2013 to September 2016 were enrolled in our study. Tumor specimens were obtained by surgery and selected for tissue microarrays (TMAs). Inclusion criteria were:

1. pathological diagnosis of epithelial ovarian cancer confirmed by 2 experienced pathologists according to the 2014 WHO classification of ovarian tumors;
2. available formalin fixed paraffin embedded specimen of the tumor mass (≥1 cm³);
3. underwent surgical treatment by primary debulking surgery (PDS) or interval debulking surgery after neoadjuvant chemotherapy (NACT+IDS);
4. complete clinical and follow-up data.

Exclusion criteria were:

1. other previous malignant tumors;
2. samples with over 80% necrotic or hemorrhagic area;
3. missing follow-up or clinic data. This study was approved by the ethics committee of Nantong Tumor Hospital.

Informed consent was waived by the committee because of the retrospective nature of the study.

2.2. Data collection

Overall survival was defined as time from cancer diagnosis to death or the date of last contact. Progression-free survival was defined as time from cancer diagnosis to recurrence or progression. Patients were followed up every 2 to 3 months during the first 2 years after the end of the initial treatment and every 4 to 6 months thereafter. Censoring occurred on January 12, 2020. Chemosensitivity was identified by a time interval of ≥6 months between chemotherapy completion and the detection of recurrence. Chemoresistance was defined as disease progression during adjuvant chemotherapy or within a time interval of <6 months between chemotherapy completion and the detection of recurrence.

2.3. Tissue microarray construction and immunohistochemistry

TMAs were obtained with formalin-fixed, paraffin embedded surgical specimens. All samples were assessed histologically by hematoxylin and eosin staining, and representative tumor areas were marked on the paraffin blocks away from necrotic and hemorrhagic regions. Tissue cylinders of 2 mm in diameter containing tumor tissues were punched out from the selected area of each tissue block and transferred into a TMA block using a TMA instrument.

Sections from TMA blocks were sectioned at 4 μm. Paraffin embedded sections were dewaxed in xylene and rehydrated in graded ethanol. After washing with phosphate buffered saline (PBS) for 3 times, citrate buffer (pH=6) was used to restore the product in a pressure cooker at high pressure. The tissue sections were rinsed with PBS and soaked in 3% H₂O₂ for 10 minutes to block endogenous peroxidase. The samples were washed with PBS, and incubated with rabbit anti-FOXJ2 polyclonal primary antibodies (Abcam, ab22857, 1:100) at room temperature for 2 hours. After rinsing with PBS, the slides were incubated with secondary antibodies for 30 minutes, washed with PBS, and developed with DAB solution for about 3 minutes, counter-stained with hematoxylin, dehydrated, and mounted with resin mount. Two independent pathologists evaluated FOXJ2 staining in TMAs, based on a semi-quantitative H-score ranging from 0 to 300, derived from the multiplication of staining intensity (0, negative; 1, weak staining; 2, moderate staining; 3, strong staining) and distribution (0–100%). In brief, H-score was derived as 3% percentage of strongly stained positive cells + 2 × percentage of moderately stained positive cells + 1 × percentage of weakly stained positive cells, with a range of 0 to 300.

2.4. Statistical analysis

Statistical analysis were performed with SPSS 23.0 (IBM, Armonk, NY). The Chi-Squared test was performed to evaluate the associations of FOXJ2 expression with clinicopathological parameters. The Kaplan–Meier method and log-rank test were applied to analyze differences in survival rates between groups. The Cox proportional hazard regression model was used for univariate and multivariate analyses of prognosis. P < .05 was considered statistically significant.

3. Results

3.1. FOXJ2 expression and associations with clinicopathological characteristics

A total of 151 epithelial ovarian cancer patients were included in the analysis. Patient characteristics were shown in Table 1. The median age was 58 years (range 20–76). There were 63 (41.72%) patients in the NACT+IDS subgroup, and 88 (58.28%) cases in the PDS group. FOXJ2 expression levels were not compared between tumor and adjacent normal tissue samples, because it is usually hard to define tumor boundaries, which is one of the characteristics of ovarian cancer. Hence, we first evaluated FOXJ2 expression by immunohistochemistry in tumor specimens from 151 epithelial ovarian cancer patients. FOXJ2 expression was detected in tumor cell nuclei and cytoplasm. Immunohistochemical scores (H-scores) of the tumor tissues differed among specimens. Representative photographs under light microscope showing differential FOXJ2 immunohistochemical staining intensities in epithelial ovarian cancer tissues were shown in Figure 1. The average measured H-score was 104.5 (range 0–300). The cut-off point for the high/low expression subgroups was set at 100.0. Consequently, a total of 58 (38.4%) patients...
Table 1
Clinical characteristics of the patients.

| Parameter                          | N      | %     |
|------------------------------------|--------|-------|
| Age, years                         | 58 (20–76) |
| Menopause                          |        |       |
| No                                 | 34     | 22.52%|
| Yes                                | 117    | 77.48%|
| FIGO stage                         |        |       |
| I-II                               | 37     | 24.50%|
| III-IV                             | 114    | 75.50%|
| Histological subtype               |        |       |
| Serous                             | 114    | 75.50%|
| Non-serous                         | 37     | 25.00%|
| Histological grade                 |        |       |
| Low-grade                          | 25     | 16.66%|
| High-grade                         | 126    | 83.34%|
| Ascites (moderate to large volume) |        |       |
| No                                 | 74     | 49.01%|
| Yes                                | 77     | 50.99%|
| CA125 (U/ml)                       |        |       |
| <500                               | 61     | 40.40%|
| ≥500                               | 90     | 59.60%|
| Treatment                          |        |       |
| PDS                                | 88     | 58.28%|
| NACT+IDS                           | 63     | 41.72%|
| Residual disease                   |        |       |
| No                                 | 86     | 56.96%|
| Yes                                | 65     | 43.04%|
| Chemosensitivity                   |        |       |
| Sensitive                          | 107    | 70.86%|
| Resistant                          | 44     | 29.14%|
| Recurrence and progression         |        |       |
| No                                 | 39     | 25.83%|
| Yes                                | 112    | 74.17%|

CA125 = cancer antigen 125, PDS = primary debulking surgery, NACT+IDS = interval debulking surgery after neoadjuvant chemotherapy.

Table 2
Correlations of FOXJ2 expression and clinicopathological characteristics of ovarian cancer patients (n=151).

| Parameter                          | FOXJ2 expression |
|------------------------------------|------------------|
|                                   | High (n=58)      | Low (n=93)   | P value |
| Age, years                         |                  |               |         |
| <58                                | 28               | 46            | .887    |
| ≥58                                | 30               | 47            |         |
| Menopause                          |                  |               |         |
| No                                 | 13               | 21            | .981    |
| Yes                                | 45               | 72            |         |
| FIGO stage                         |                  |               |         |
| I-II                               | 22               | 15            | .002    |
| III-IV                             | 36               | 78            |         |
| Histological subtype               |                  |               |         |
| Serous                             | 45               | 69            | .637    |
| Non-serous                         | 13               | 24            |         |
| Histological grade                 |                  |               |         |
| Low-grade                          | 13               | 12            | .126    |
| High-grade                         | 45               | 81            |         |
| Ascites (moderate to large volume) |                  |               |         |
| No                                 | 30               | 44            | .598    |
| Yes                                | 28               | 49            |         |
| CA125 (U/ml)                       |                  |               |         |
| <500                               | 26               | 35            | .381    |
| ≥500                               | 32               | 58            |         |
| Treatment                          |                  |               | <.001   |
| PDS                                | 45               | 43            |         |
| NACT+IDS                           | 13               | 50            |         |
| Residual disease                   |                  |               | .180    |
| No                                 | 37               | 49            |         |
| Yes                                | 21               | 44            |         |
| Chemosensitivity                   |                  |               | .151    |
| Sensitive                          | 45               | 62            |         |
| Resistant                          | 13               | 31            |         |
| Recurrence and progression         |                  |               | .011    |
| No                                 | 19               | 20            |         |
| Yes                                | 39               | 73            |         |

CA125 = cancer antigen 125, PDS = primary debulking surgery, NACT+IDS = interval debulking surgery after neoadjuvant chemotherapy.

P value for high vs low FOXJ2 expression groups.

Figure 1. Representative micrographs depicting different FOXJ2 expression levels, as assessed by immunohistochemical (IHC) staining of epithelial ovarian cancer tissue samples. Magnifications are 40× (A) and 100× (B).
Kaplan survival rates in all patients were 55.0% and 35.8%, respectively. The 3-year overall survival and progression-free survival (PFS) in all patients were 41.1 months and 20.5 months, respectively. The median follow-up was 64.2 (3.3–80.8) months. Median OS and PFS in all patients were 41.1 months and 20.5 months, respectively. Kaplan–Meier survival analysis was performed to assess OS and PFS according to FOXJ2 expression levels. The high FOXJ2 expression subgroup showed longer median OS (57.9 vs 31.9 months, \( P = .037 \); Fig. 2A) and longer median PFS (31.8 vs 18.1 months, \( P = .012 \); Figure 2B) compared with the low FOXJ2 expression subgroup.

We further performed subgroup analysis according to FIGO stage (I–II or III–IV) (Fig. 3). When the analysis was restricted to the FIGO III-IV subgroup, low FOXJ2 expression correlated with decreased OS and PFS (\( P = .028 \) and \( P = .005 \), respectively; Fig. 3B, 3D). However, in the FIGO I-II subgroup, the difference was not significant in OS or PFS (\( P = .526 \) and \( P = .592 \), respectively; Fig. 3A, 3C).

3.2. Correlations between FOXJ2 expression and prognosis of EOC patients

The median follow-up was 64.2 (3.3–80.8) months. Median OS and PFS in all patients were 41.1 months and 20.5 months, respectively. The 3-year overall survival and progression-free survival rates in all patients were 55.0% and 35.8%, respectively. Kaplan–Meier survival analysis was performed to assess OS and PFS according to FOXJ2 expression levels. The high FOXJ2 expression subgroup showed longer median OS (57.9 vs 31.9 months, \( P = .037 \); Fig. 2A) and longer median PFS (31.8 vs 18.1 months, \( P = .012 \); Figure 2B) compared with the low FOXJ2 expression subgroup.

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3.3. Univariate and multivariate Cox proportional hazard analysis

Univariate analysis was performed for OS and PFS to estimate the clinical significance of FOXJ2 expression in epithelial ovarian cancer (Tables 3 and 4). The results showed that FIGO stage, histological grade, CA125 levels, therapeutic approach, residual disease, chemosensitivity, and FOXJ2 expression were significantly correlated with OS. In addition, FIGO stage, histological grade, CA125 levels, therapeutic approach, residual disease, moderate to large amounts of ascitic fluid and FOXJ2 expression were significantly correlated with PFS.

Next, significant factors (\( P < .05 \)) in univariate analysis were included into multivariate analysis. In the multivariate Cox regression analysis, FIGO stage (HR = 2.025, 95% CI = 1.127–3.605, \( P = .014 \)), histological grade (HR = 3.872, 95% CI = 1.750–8.670, \( P = .001 \)), residual disease (HR = 4.933, 95% CI = 3.055–7.967, \( P < .001 \)) and chemosensitivity (HR = 2.993, 95% CI = 1.823–4.916, \( P < .001 \)) were independent prognostic factors of OS (Table 3). Furthermore, FIGO stage (HR = 2.214, 95% CI = 1.220–4.018, \( P = .009 \)), histological grade (HR = 2.849, 95% CI = 1.407–5.770, \( P = .040 \)), residual disease (HR = 4.046, 95% CI = 2.700–6.062, \( P < .001 \)), FOXJ2 expression (HR = 1.850, 95% CI 1.331–2.408; \( P = .025 \)) were independent prognostic factors of PFS (Table 4). Overall, it illustrated that FOXJ2 expression was an independent prognostic factor of PFS, but not OS, in EOC patients.

In the PDS and NACT+IDS subgroups, Cox regression analysis of factors potentially predicting OS and PFS were shown in Tables 5 and 6. Univariate analysis showed that FOXJ2 expression was significantly correlated with OS and PFS in both the PDS and NACT+IDS subgroups. But multivariate analysis showed that FOXJ2 expression (HR=1.762, 95%CI=1.358–2.048, \( P = .010 \)) was an independent prognostic factor of PFS only in the PDS subgroup, but not NACT+IDS group.

4. Discussion

In this study, we assessed FOXJ2 expression levels in EOC specimens and determined the association between FOXJ2 expression and prognosis in epithelial ovarian cancer. The results demonstrated that FOXJ2 expression was negatively correlated to FIGO stage. Moreover, low FOXJ2 expression was correlated with poor prognosis, and FOXJ2 expression was an independent prognostic factor of progression-free survival in epithelial ovarian cancer.

Previous evidence suggests that FOXJ2 actively participated in tumor development and metastasis. It was demonstrated that...
FOXJ2 inhibited metastasis in human breast cancer\cite{13} and glioma\cite{16} by regulating EMT key markers, including E-cadherin and vimentin. Qiang et al identified that FOXJ2 expression was abnormally downregulated in extrahepatic cholangiocarcinoma and its overexpression could markedly inhibit cell proliferation, migration and invasion in vitro, verifying FOXJ2 as a tumor suppressor.\cite{14} In addition, FOXJ2 could also inhibit the proliferation of human hepatocellular carcinoma cells, and reduced expression of FOXJ2 was significantly associated with the poor prognosis of patients with human hepatocellular carcinoma.\cite{20} The present study revealed that low FOXJ2 expression was associated with advanced FIGO stage by assessing 151 epithelial ovarian cancer cases. Besides, FOXJ2 expression was significantly different regarding treatment approaches. Tumor specimens from patients in NACT+IDS subgroups had significantly lower FOXJ2 expression than those in PDS subgroups. Compared with those in PDS subgroup, patients in the NACT+IDS subgroup were mainly advanced FIGO stage III-IV cases. Therefore, FOXJ2 might act as a tumor suppressor in ovarian cancer. Patients with low FOXJ2 expression tended to progress to a higher stage and received NACT+IDS treatment. Another explanation might be the neoadjuvant chemotherapy (Taxol and carboplatin) administered to the NACT+IDS group. FOXJ2 expression might also be involved in the interaction with chemotherapeutic drugs. Cell biology experiments are required to further assess its interaction with chemotherapeutic drugs or its original role in EOC.

The prognostic significance of FOXJ2 varies with the type of malignancy. Studies mentioned above proved that FOXJ2 could suppress carcinogenesis. Nonetheless, Shan et al found that downregulation of FOXJ2 decreased the cell population in the S phase with enhanced G1 cycle arrest in nasopharyngeal carcinoma CNE-2 cells, and confirmed that patients with FOXJ2 overexpression had shorter survival in nasopharyngeal carcinoma.\cite{15} In the current study, Kaplan–Meier survival analysis revealed that the high-FOXJ2 expression group showed longer median OS and PFS compared with the low-FOXJ2 expression group. Similar findings were obtained in the FIGO III-IV subgroup in stratified analysis. In the FIGO I-II subgroup, the difference was not significant, which may be related to the small
| Table 3 | Univariate and multivariate cox regression analyses of factors potentially predicting OS. |
| --- | --- |
| **Univariate** | HR (95% CI) | P | **Multivariate** | HR (95% CI) | P |
| Age, years |  |  |  |  |  |
| <58 | Ref. |  |  |  |  |
| ≥58 | 1.247 (0.830–1.875) | .287 |  |  |  |
| Menopause |  |  |  |  |  |
| No | Ref. |  |  |  |  |
| Yes | 1.442 (0.852–2.438) | .173 |  |  |  |
| FIGO stage |  |  |  |  |  |
| I-II | Ref. |  |  |  |  |
| III-IV | 2.577 (1.479–4.490) | .001 | 2.025 (1.127–3.605) | .014 |
| Histological subtype |  |  |  |  |  |
| Serous | Ref. |  |  |  |  |
| Non-serous | 0.941 (0.587–1.507) | .800 |  |  |  |
| Histological grade |  |  |  |  |  |
| Low-grade | Ref. |  |  |  |  |
| High-grade | 3.705 (1.786–7.684) | <.001 | 3.872 (1.730–8.670) | .001 |
| Ascites (moderate to large volume) |  |  |  |  |  |
| No | Ref. |  |  |  |  |
| Yes | 1.461 (0.970–2.200) | .069 |  |  |  |
| CA125 (U/ml) |  |  |  |  |  |
| <500 | Ref. |  |  |  |  |
| ≥500 | 2.000 (1.285–3.113) | .002 |  |  |  |
| Treatment |  |  |  |  |  |
| PDS | Ref. |  |  |  |  |
| NACT+IDS | 2.243 (1.485–3.387) | <.001 |  |  |  |
| Residual disease |  |  |  |  |  |
| No | Ref. |  |  |  |  |
| Yes | 6.375 (4.124–9.855) | <.001 | 4.933 (3.055–7.967) | <.001 |
| Chemosensitivity |  |  |  |  |  |
| Sensitive | Ref. |  |  |  |  |
| Resistant | 5.084 (3.324–7.776) | <.001 | 2.993 (1.823–4.916) | <.001 |
| FOXJ2 expression |  |  |  |  |  |
| High (>100) | Ref. |  |  |  |  |
| Low (≤100) | 1.577 (1.054–2.429) | .039 | 1.351 (1.058–2.146) | .021 |

Ref. = reference, CA125 = cancer antigen 125, PDS = primary debulking surgery, NACT+IDS = interval debulking surgery after neoadjuvant chemotherapy, OS = overall survival, HR = hazard ratio, CI = confidence interval.

| Table 4 | Univariate and multivariate cox regression analyses of factors potentially predicting PFS. |
| --- | --- |
| **Univariate** | HR (95% CI) | P | **Multivariate** | HR (95% CI) | P |
| Age, years |  |  |  |  |  |
| <58 | Ref. |  |  |  |  |
| ≥58 | 1.140 (0.785–1.655) | .493 |  |  |  |
| Menopause |  |  |  |  |  |
| No | Ref. |  |  |  |  |
| Yes | 1.523 (0.947–2.450) | .083 |  |  |  |
| FIGO stage |  |  |  |  |  |
| I-II | Ref. |  |  |  |  |
| III-IV | 3.280 (1.945–5.530) | <.001 | 2.214 (1.229–4.018) | .009 |
| Histological subtype |  |  |  |  |  |
| Serous | Ref. |  |  |  |  |
| Non-serous | 0.683 (0.434–1.074) | .099 |  |  |  |
| Histological grade |  |  |  |  |  |
| Low-grade | Ref. |  |  |  |  |
| High-grade | 3.490 (1.812–6.270) | <.001 | 2.849 (1.407–5.770) | .004 |
| Ascites (moderate to large volume) |  |  |  |  |  |
| No | Ref. |  |  |  |  |
| Yes | 1.660 (1.138–2.420) | .009 |  |  |  |
| CA125 (U/ml) |  |  |  |  |  |
| <500 | Ref. |  |  |  |  |
| ≥500 | 1.689 (1.140–2.502) | .009 |  |  |  |
| Treatment |  |  |  |  |  |
| PDS | Ref. |  |  |  |  |
| NACT+IDS | 1.643 (1.084–2.467) | .017 |  |  |  |
| Residual disease |  |  |  |  |  |
| No | Ref. |  |  |  |  |
| Yes | 4.266 (2.896–6.284) | <.001 | 4.046 (2.700–6.062) | <.001 |
| FOXJ2 expression |  |  |  |  |  |
| High (>100) | Ref. |  |  |  |  |
| Low (≤100) | 1.962 (1.358–2.808) | .012 | 1.850 (1.331–2.468) | .025 |

Ref. = reference, CA125 = cancer antigen 125, PDS = primary debulking surgery, NACT+IDS = interval debulking surgery after neoadjuvant chemotherapy, OS = overall survival, HR = hazard ratio, CI = confidence interval.
**Table 5**

Cox regression analyses of factors potentially predicting OS in PDS and NACT+IDS subgroups.

|                | PDS |                |                |
|----------------|-----|----------------|----------------|
|                | HR (95% CI) | P       | HR (95% CI) | P |
| Age, years     |       |       |       |       |
| <58            | Ref. | 1.248 (0.686–2.272) | .468 | 1.097 (0.830–1.875) | .745 |
| ≥58            | Ref. | 1.259 (0.604–2.625)  | .540 | 1.546 (0.726–3.194) | .258 |
| Menopause      | No   | Ref. | 1.880 (1.001–3.532) | .046 | NA |
| Yes            | Ref. | 1.039 (0.886–1.217)  | .720 | 0.752 (0.601–0.946) | .022 |
| FIGO stage     | I-II | Ref. | 3.159 (1.323–7.543)  | .010 | 2.511 (0.632–7.068) | .023 |
|                | III-IV | Ref. | 1.043 (0.957–1.240)  | .466 | 1.051 (0.859–1.289) | .626 |
| Histological subtype | Serous | Ref. | 1.542 (0.841–2.287)  | .162 | Ref. | 0.651 (0.257–1.650) | .366 |
|                | Non-serous | Ref. | 1.429 (0.797–2.543)  | .228 | Ref. | 0.747 (0.368–1.519) | .456 |
| Histological grade | Low-grade | Ref. | 0.960 (0.507–1.818)  | .901 | Ref. | 1.318 (0.689–2.520) | .404 |
|                | High-grade | Ref. | 1.842 (0.908–3.403)  | .047 | Ref. | 1.534 (0.782–3.009) | .213 |
| Ascites (moderate to large volume) | No | Ref. | 6.872 (3.595–13.133) | <.001 | Ref. | 6.514 (3.481–12.191) | <.001 |
|                | Yes  | Ref. | 1.088 (0.640–1.851)  | .756 | Ref. | 1.085 (0.636–1.850) | .766 |
| CA125 (U/ml)   | <500 | Ref. | 1.426 (0.794–2.543)  | .228 | Ref. | 0.747 (0.368–1.519) | .456 |
|                | ≥500 | Ref. | 1.900 (1.026–3.532)  | .039 | Ref. | 1.534 (0.782–3.009) | .213 |
| Residual disease | No | Ref. | 4.276 (2.477–7.383)  | <.001 | Ref. | 4.973 (2.742–9.020) | <.001 |
|                | Yes  | Ref. | 1.987 (1.369–2.510)  | .011 | Ref. | 1.762 (1.358–2.406) | .027 |
| Chemosensitivity | Sensitive | Ref. | 6.052 (3.193–11.307) | <.001 | Ref. | 6.052 (3.193–11.307) | <.001 |
|                | Resistant | Ref. | 1.674 (0.992–2.746)  | .040 | Ref. | 1.674 (0.992–2.746) | .040 |

Ref. = reference, CA125 = cancer antigen 125, PDS = primary debulking surgery, NACT+IDS = interval debulking surgery after neoadjuvant chemotherapy, OS = overall survival, HR = hazard ratio, CI = confidence interval.

**Table 6**

Cox regression analyses of factors potentially predicting PFS in PDS and NACT+IDS subgroups.

|                | PDS |                |                |
|----------------|-----|----------------|----------------|
|                | HR (95% CI) | P       | HR (95% CI) | P |
| Age, years     |       |       |       |       |
| <58            | Ref. | 1.088 (0.640–1.851) | .756 | 1.085 (0.636–1.850) | .766 |
| ≥58            | Ref. | 1.498 (0.773–2.904)  | .231 | 0.977 (0.525–1.819) | .941 |
| Menopause      | No   | Ref. | 2.692 (1.508–4.804)  | .003 | NA |
| Yes            | Ref. | 1.026 (0.588–1.790)  | .927 | 0.920 (0.656–1.064) | .670 |
| FIGO stage     | I-II | Ref. | 3.430 (1.541–7.638)  | .001 | 1.685 (0.580–5.994) | .035 |
|                | III-IV | Ref. | 1.375 (0.796–2.375)  | .254 | 1.670 (1.083–2.204) | .056 |
| Histological subtype | Serous | Ref. | 1.508 (0.884–2.572)  | .132 | 1.529 (1.052–2.221) | .089 |
|                | Non-serous | Ref. | 4.276 (2.477–7.383)  | <.001 | 4.973 (2.742–9.020) | <.001 |
| Histological grade | Low-grade | Ref. | 1.088 (0.640–1.851) | .756 | Ref. | 1.085 (0.636–1.850) | .766 |
|                | High-grade | Ref. | 1.987 (1.369–2.510)  | .011 | Ref. | 1.762 (1.358–2.406) | .027 |
| Ascites (moderate to large volume) | No | Ref. | 1.375 (0.796–2.375)  | .254 | 1.670 (1.083–2.204) | .056 |
|                | Yes  | Ref. | 1.508 (0.884–2.572)  | .132 | 1.529 (1.052–2.221) | .089 |
| CA125 (U/ml)   | <500 | Ref. | 4.276 (2.477–7.383)  | <.001 | 4.973 (2.742–9.020) | <.001 |
|                | ≥500 | Ref. | 1.987 (1.369–2.510)  | .011 | Ref. | 1.762 (1.358–2.406) | .027 |

Ref. = reference, CA125 = cancer antigen 125, PDS = primary debulking surgery, NACT+IDS = interval debulking surgery after neoadjuvant chemotherapy, OS = overall survival, HR = hazard ratio, CI = confidence interval.
sample size. Univariate analysis showed that FOXJ2 expression was significantly correlated with OS and PFS in patients with epithelial ovarian cancer. Similar results were obtained in both the PDS and NACT+IDS subgroups. Multivariate analysis showed that FOXJ2 expression was an independent prognostic factor of progression-free survival in patients with epithelial ovarian cancer, as well as the PDS subgroup. Overall, these findings demonstrated the clinical significance of FOXJ2 expression, which independently predicts progression-free survival in epithelial ovarian cancer.

This study has limitations. It was a single center retrospective analysis, with a limited sample size. In addition, no external validation was performed. Even though this study found the association between FOXJ2 and the prognosis of EOC patients, the underlying pathophysiological mechanisms and causal relationships still remain unclear. Therefore, further studies are needed to investigate the role and mechanism of FOXJ2 at the ovarian cancer cell level.

In conclusion, the present report firstly demonstrated that low FOXJ2 expression is associated with unfavorable prognosis in epithelial ovarian cancer, and FOXJ2 independently predicts EOC progression-free survival. Further studies are required to validate these findings.

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Author contributions

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