An integrated model of CDCA5 and FOXM1 expression combined with a residual disease that predicts prognosis in ovarian cancer patients

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ABSTRACT

Ovarian cancer (OC) is the most prevalent type of gynecologic cancer, leading to global death. Unfortunately, less than half of patients diagnosed with this cancer survive for up to five years. The factor forkhead box M1 (FOXM1) is a crucial oncoprotein in ovarian cancer and is currently recognized as a potential therapeutic target. The role of the Cell division cycle-associated 5 (CDCA5) is critical for advancing different types of cancers. However, the significance of CDCA5 in OC from a clinical perspective is not well comprehended. This study aimed to build a risk prognosis model and assess the data supporting the prognostic usefulness of CDCA5 and FOXM1 expression in patients with OC. In OC, we found that CDCA5 and FOXM1 were expressed. To establish the existence of variables that were independently related to PFS and OS, Cox regression, data from clinics, and Kaplan-Meier analysis were used. A risk score model and nomogram were created using the independent prognostic parameters. The accuracy of the model's predictions was then evaluated using decision curve analysis (DCA), calibration curve, and receiver operating characteristic (ROC) analysis. Finally, the patients were separated into groups based on their cut-off value, and then the differences in survival were investigated. Significant correlations were found between OC and CDCA5, and FOXM1 expression levels (P<0.0001). Serous ovarian tumors (P=0.025) and even specific subgroups of high-grade serous ovarian tumors were shown to have elevated CDCA5 expression levels. In our database, FOXM1 expression levels were discovered to be related to intestinal metastases (P=0.014). In OC, the expression of FOXM1 was positively correlated with the overexpression of CDCA5 (rs=0.46, P<0.0001). The results of the multivariate analysis indicated that residual disease (RD) (P=0.005), CDCA5 expression level (P=0.028), and FOXM1 expression level (P=0.0001) were identified as independent prognostic factors for PFS. Additionally, RD (P=0.023) and FOXM1 expression level (P<0.0001) were identified as independent prognostic factors for OS. While the prediction model's performance with RD was poor (AUC=0.645 for PFS, AUC=0.650 for OS), the model's performance with tissue biomarkers was enhanced (AUC=0.797 for PFS, AUC=0.741 for OS). The nomogram and risk score method showed a benefit for prognosis prediction. In summary, poor outcomes are predicted by CDCA5, which is overexpressed in OC patients and has a positive correlation with the level of FOXM1 expression. An aid to prognosis prediction in patients with OC and a resource for therapy planning is a risk prognosis model based on CDCA5 and FOXM1 expression with RD.

Introduction

The ovarian organ is located deep in the abdominal cavity, and the symptoms in the early stages of cancer are usually mild or nonspecific, so when detected, they are primarily in an advanced state with a very poor prognosis (1). The standard of care for recurrent ovarian cancer comprises platinum-based chemotherapy, tumor cell annihilation surgery, and maintenance therapy with PARP inhibitors or bevacizumab (2). Even after obtaining standardized treatment regimens, the significant recurrence rate within 3 years is challenging. Patients who experience relapse must receive palliative care, with an approximate 5-year overall survival rate of <50% (3). Therefore, identifying high-risk biomarkers and constructing effective predictive models can influence decisions on clinical treatment options and guide novel drug development.

Altered cell cycle regulation leading to abnormal cell proliferation is a fundamental distinguishing feature of cancer. FOXM1 was found to be a major regulator of the cell cycle by analysis of gene binding sites (4). The maintained forkhead box transcription factor family includes FOXM1. The Cancer Genome Atlas (TCGA) investigation of the ovarian cancer genome and epigenome revealed the FOXM1 pathway as one of the critical pathways affecting ovarian cancer (5). A meta-analysis of gene expression in transcripts related to the cell cycle led to the discovery of CDCA5. Sororin, a sister chromatid in maintaining cell S-phase to late critical conserved protein for cohesion, is a protein that CDCA5 encodes (6). Enriched in intracellular DNA double-strand break sites and promotes recombiant DNA damage repair (7). Recently, researchers have started to investigate CDCA5's potential significance in cancer development. In triple-negative breast cancer cells,

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CDCA5 impacts mitosis (8). It has also been shown that CDCA5 can act as a prognostic indicator and promote the malignant progression of cancer cells in the prostate (9). CDCA5’s predictive function in ovarian cancer has not yet been investigated.

To determine whether there is a clinical relationship between FOXM1 and CDCA5 and the clinical importance of CDCA5 in ovarian cancer. In this study, we intended to investigate CDCA5 and FOXM1 expression and prognosis in ovarian cancer. An effort was undertaken to establish a predictive prediction model that could be swiftly utilized in the clinical setting by retrospective analysis of clinical samples. To determine which ovarian cancer patients are more likely to experience a recurrence, the model incorporates clinical characteristics and uses immunohistochemistry techniques to find CDCA5 and FOXM1. Therefore, this study would augment the lack of clinical markers to predict disease relapse or unfavourable outcomes. The present research helps to achieve risk-stratified management at the time of ovarian cancer diagnosis by focusing on treatment planning and monitoring high-risk patients during cancer therapy.

Materials and Methods

Patients and data collection

Between January 2015 and December 2019, we obtained 138 samples from patients with ovarian cancer who underwent primary debulking surgery. Of these samples, 108 were from patients with ovarian cancer, and 30 were normal samples. We followed up with these patients until July 2022. Time from surgery until the incidence of death or progression was used to compute the overall survival (OS) and progression-free survival (PFS), respectively. The First Affiliated Hospital of Bengbu Medical College was the site for collecting all clinical samples. All patients underwent postoperative chemotherapy with a treatment plan including paclitaxel and/or platinum for at least six sessions without radiation, chemotherapy, or immunotherapy before surgery. A gynecologic pathologist extracted information on OC patients’ staging, histology, grading, and residual tumor from pathology and surgical records for correlation analysis. The Bengbu Medical College Ethics Committee provided their approval for this investigation. All patients who took part in the study gave written informed permission.

Immunohistochemical analysis and evaluation

Paraffin specimens were fixed in 4% paraformaldehyde and then serially sectioned at 4 μm. By using H&E staining, representative malignant sections were identified and chosen. The primary antibodies were rabbit anti-CDCA5 and monoclonal antibodies (Abcam, 1:500 dilution). The staining procedure was performed by a fully automated stainer (Bond-Max, Leica, Germany). A combinatorial semiquantitative scoring method was used to quantify IHC results (10). The intensity of nuclear staining is assessed in addition to the numerical data gathered from the measurement of the relative percent of immunopositive cells (0, 10%;1, 10-25%;2, 25-50%;3, 50-75%;4, >75%). The intensity is generally graded from 0 to 3 (0 being negative, 1 being weakly positive, 2 being moderately positive, and 3 being strongly positive). Each score is multiplied to produce the aggregate Immuno score. Without any clinical information, two gynecologic pathologists independently evaluated all tissue samples. When the opinions of the two pathologists differed on an immunohistochemistry assessment, they reviewed the cases and came to a consensus score. The expression of CDCA5 or FOXM1 was categorized into four groups based on their respective IHC scores: Negative (IHC score 0-2), Weak (IHC score 3-4), Moderate (IHC score 5-8), and Strong (IHC score 9-12).

Statistical analysis and development of prediction model

The statistical analysis and data processing were conducted using SPSS 21.0 and R (version 4.2.1), and a significance level of P<0.05 was adopted. The chi-square test was conducted to examine the distinctions between the two groups. The correlation analysis was quantified using Spearman’s rank correlation coefficient (r). In the Kaplan-Meier survival analysis, the log-rank test was used. The impact of various variables on PFS and OS was studied using univariate and multivariate Cox regression analysis. The independent factors identified by multifactor COX regression and the coefficient β were formed into a linear regression equation to construct a risk score model for each patient. The risk score was calculated as follows: risk score =β0+ expression of factor 1 x β1 of factor 1 + expression of factor 2 x β2 of factor 2 +... + expression of factor n x βn of factor n. The accuracy of the risk score and cut-off values was determined using the receiver operating characteristic (ROC). The prediction model’s accuracy was evaluated using various methods, such as the area under the receiver operating characteristic curve (AUC), decision curve analysis (DCA), and calibration curve. Patients were divided into low- and high-risk groups based on the risk score cut-off as a boundary to confirm the ability of the model to differentiate between low- and high-risk patients again. Nomograms and risk factor association plots were created using R version 4.2.1 and the survival and rms packages.

Results

Study participants and baseline characteristics

The current research found 108 ovarian cancer patients and 30 benign ovarian tissues were chosen as controls. Patients with OC were 56.29 years old on average (IQR: 18-81). 71 OC patients (65.74%) were menopausal in status. 78 of the total number of patients (which is not mentioned) were classified as being in stages III or IV by the FIGO staging criteria, making up 72.22% of the sample. Stage I or II patients comprised 30 or 27.78% of the sample. In sum, 98 patients (90.74% of the total) were categorized as having a high FIGO Grade. Serous histology was present in 76 cases or 70.37%. Some patients who underwent primary debulking surgery (PDS) also undergo complete resection. Residual disease (RO) was divided into three categories. 18 (16.66%) patients had no visible disease (RO), 45 (41.67%) patients had residual disease between 0.1 and 1 cm (R1), and 45 (41.67%) patients had residual disease greater than 1 cm (R 2-1 cm). 44 (40.74%) had no apparent ascites, and 39 (36.11%) patients had moderate or severe ascites. Regarding different transfer locations, 68 (62.92%) patients had intestinal metastasis. 88 (81.48%) patients underwent postoperative chemotherapy with a treatment plan including paclitaxel and/or platinum for at least six sessions without radiation, chemotherapy, or immunotherapy before surgery. A gynecologic pathologist extracted information on OC patients’ staging, histology, grading, and residual tumor from pathology and surgical records for correlation analysis. The Bengbu Medical College Ethics Committee provided their approval for this investigation. All patients who took part in the study gave written informed permission.
the serological indications within a week of surgery (Supplementary Table S1).

Ovarian cancer tissues overexpressed CDCA5 and had a poor prognosis.

The immuno-histochemical findings indicated that CDCA5 was primarily present in the nuclei of ovarian cell carcinomas. Furthermore, the expression of CDCA5 protein became notably higher in ovarian cancer tissues compared to benign control tissues (p<0.001), as shown in Figures 1A and B. Analysis was done on the relationships between 108 OC patients' clinicopathological characteristics and CDCA5 expression (Supplementary Table S1). Serous histology and CDCA5 expression in OC showed a good correlation (p = 0.025). High-grade serous ovarian cancer (HGSOC) and low-grade serous ovarian cancer (LGSOC) CDCA5 expression levels were evaluated to examine whether CDCA5 may further differentiate high-grade from low-grade in serous OC. The Wilcoxon rank sum test results indicated that the expression of CDCA5 was significantly higher in HGSOC tissues than in LGSOC tissues (p=0.0142), as shown in Figure 2A. The KM plotter analysis revealed that patients with high levels of CDCA5 expression experienced more cumulative events for PFS recurrence and had shorter overall survival (as shown in Figures 1C and D). The findings indicate that CDCA5 is a biomarker for an unfavourable prognosis in ovarian cancer.

High FOXM1 expression was positively correlated with CDCA5 expression.

The results of the immunohistochemical analysis indicated that FOXM1 was present in the nuclei of ovarian cancer cells. Furthermore, the expression of FOXM1 protein was notably higher in ovarian cancer tissues compared to benign control tissues (p<0.001), as illustrated in Figures 3A and B. A p-value of 0.014 in Table 1 shows a positive correlation between intestinal metastases and FOXM1 expression in ovarian cancer. Figures 1C and D illustrate how the KM plotter analysis revealed that patients with high levels of FOXM1 expression had higher cumulative recurrence events for PFS and shorter overall survival (OS). Figure 2B shows a positive correlation between the expression of the FOXM1 and CDCA5 proteins (Spearman R = 0.46, p<0.001).

Ovarian cancer prognostic factors: univariate and multivariate analysis

A short PFS duration was linked with RD (P=0.003), CDCA5 expression (P=0.001), and FOXM1 expression (P<0.001), according to the results of univariate regression analysis. Multivariate regression analysis was also used for the relevant univariate analysis results. PFS was observed to be correlated with RD (95%CI:1.111-2.286, P=0.011), CCA5 expression (95%CI:1.002-1.781, P=0.048), and FOXM1 expression (95%CI:1.122-1.932, P=0.0005) (Table 1). The univariate and multivariate Cox models were applied to assess OS-related factors (Table 2). The three parameters mentioned above were linked to a brief OS time in the univariate study. In multivariate analysis, RD (95%CI:1.068-2.397, P=0.023) and FOXM1 expression (95%CI:1.296-2.435, P<0.001) were related to OS. However, CDCA5 expression (95%CI:0.799-1.484, P=0.588) was not associated with OS.
analysis. PFS and OS outcomes may be diagnosed with good accuracy using a combination of independent risk variables (AUC=0.846, 95%CI: 0.776-0.916 for PFS and AUC=0.795,95%CI:0.711-0.878 for OS; Figures 4 and 5A). Then, we used the COX regression model's regression coefficient to create a scoring system. Following is how the risk score model was created:

Y1 (for OC-PFS) = 1.797*CDCA5+1.748*FOXM1+1.837*RD1+1.976*RD>1cm-2.941
Y2 (for OC-OS) = 2.087*FOXM1+1.098*RD1+1.700*RD>1cm-2.061.

The AUC of the model Y1 and Y2 were higher than individual predicted indicators (Figures 4 and 5B). The calibration curves demonstrated good agreement between the projected and actual prognosis for 1-year, 3-year, and 5-year PFS and OS (Figures 4 and 5C). The DCA curves show that the risk score models outperformed RD in predicting PFS and OS for the 3-year (Figures 4 and 5D) and 5-year (Figures 4 and 5E) periods. The risk score models are beneficial in clinical practice. We also split patients into high-risk and low-risk groups based on the cut-off value to assess the risk score model's prediction ability.

Regarding PFS, 56 patients were placed in the low-risk category, whereas 52 were placed in the high-risk category. Patients with less risk had a considerably higher PFS, whereas patients in a more significant risk group had a significantly poorer PFS. Figure 4F shows the 5-year PFS rates for the low and high-risk groups, which were 37.50% and 84.62%, respectively (P<0.001). According to the predicted outcomes for overall survival, 43 and 65 cases were categorized as low and high-risk groups, correspondingly. Between several groups, there was a considerable disparity in OS. The 5-year OS rate was 25.58% for low-risk and 67.69% for high-risk groups, respectively (P<0.001) (Figure 5F).

### Table 1. PFS duration exploration utilizing univariate and multivariate Cox regression analyses.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Univariate HR</th>
<th>95% CI</th>
<th>P-Value</th>
<th>Multivariate HR</th>
<th>95% CI</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>1.113</td>
<td>0.682-1.817</td>
<td>0.667</td>
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<td>FIGO stage</td>
<td>1.489</td>
<td>0.836-2.655</td>
<td>0.177</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preoperative CA125</td>
<td>1.436</td>
<td>0.882-2.337</td>
<td>0.145</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Ascites</td>
<td>1.143</td>
<td>0.863-1.514</td>
<td>0.352</td>
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<tr>
<td>Residual disease</td>
<td>1.712</td>
<td>1.200-2.442</td>
<td>0.003</td>
<td>1.594</td>
<td>1.111-2.286</td>
<td>0.011</td>
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<td>CDCA5 expression</td>
<td>1.580</td>
<td>1.198-2.082</td>
<td>0.001</td>
<td>1.336</td>
<td>1.002-1.781</td>
<td>0.048</td>
</tr>
<tr>
<td>FOXM1 expression</td>
<td>1.714</td>
<td>1.327-2.215</td>
<td>0.000</td>
<td>1.472</td>
<td>1.122-1.932</td>
<td>0.005</td>
</tr>
</tbody>
</table>

### Table 2. Overall survival (OS) time assessments using univariate and multivariate Cox regression analyses.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Univariate HR</th>
<th>95% CI</th>
<th>P-Value</th>
<th>Multivariate HR</th>
<th>95% CI</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>1.099</td>
<td>0.646-1.870</td>
<td>0.727</td>
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<td>FIGO stage</td>
<td>1.275</td>
<td>0.684-2.375</td>
<td>0.444</td>
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<td></td>
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<tr>
<td>Preoperative CA125</td>
<td>1.135</td>
<td>0.667-1.930</td>
<td>0.640</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Ascites</td>
<td>1.324</td>
<td>0.973-1.800</td>
<td>0.074</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Residual disease</td>
<td>1.764</td>
<td>1.191-2.613</td>
<td>0.005</td>
<td>1.600</td>
<td>1.068-2.397</td>
<td>0.023</td>
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<tr>
<td>CDCA5 expression</td>
<td>1.401</td>
<td>1.038-1.891</td>
<td>0.028</td>
<td>1.089</td>
<td>0.799-1.484</td>
<td>0.588</td>
</tr>
<tr>
<td>FOXM1 expression</td>
<td>1.949</td>
<td>1.447-2.624</td>
<td>0.000</td>
<td>1.777</td>
<td>1.296-2.435</td>
<td>0.000</td>
</tr>
</tbody>
</table>
Nomogram development and evaluation for predicting PFS and OS

From the above analysis results, it is clear that the combination of independent predictors helps predict patient prognosis. Therefore, based on the multivariate Cox proportional hazards regression models, we created a PFS and an OS nomogram for ease of clinical usage (Figures 4 and 5 G). Finding the point score for each aspect and combining them yielded the total point. The total point value below relates to the chance of survival for each patient. We afterward constructed risk factor association graphs based on the nomogram risk scores, as illustrated in Figures 4H and 5H. All patients were classified into high-risk and low-risk categories based on the median. Patients in the two risk subgroups distributed on both sides of the midline axis with colour-marked survival states showed significant differences in PFS and OS (Figures 4 and 5H).

Discussion

The high recurrence rate of ovarian cancer poses a major obstacle to clinical prognosis. Creating predictive models for ovarian cancer plays a crucial role in clinical significance, risk assessment, and disease management. In a PDS setting, the status of any remaining cancer after the first surgery is a known predictor of how long a woman with advanced ovarian cancer will live generally and without cancer worsening (11-13). The current study found that CDCA5 could affect PFS in ovarian cancer patients, and FOXM1 affected PFS and OS. The model's predictive power was enhanced based on the functional examination of these two proteins. Therefore, this integrated model can predict PFS or OS in ovarian cancer patients better than relying on RD alone.

Ovarian cancer promotes tumor progression by inducing the cell cycle through multiple signaling pathways (14-16). DNA damage repair pathways are also effective therapeutic targets for ovarian cancer today (17). These studies imply that important molecules related to damaged DNA repair and cell cycle regulation may be the target of potential treatment approaches for ovarian cancer. CDCA5 is a crucial molecule in DNA double-strand break repairing and cell cycle phases because it can control sister chromatid cohesion or segregation. Similarly, the current study revealed that CDCA5 is histotype specific for ovarian cancer, and serous ovarian tumors were associated with high CDCA5 expression. After additional differentiation-based categorization, we noticed an intriguing correlation between CDCA5 expression and high-grade serous ovarian cancer (HGSC). The current view is that ovarian cancer is a heterogeneous disease (18). Although HGSC and LGSC evolve via various molecular pathways, their histomorphological characteristics are comparable (19). The low expression of CDCA5 in LGSC is consistent with the clinical feature that LGSC grows slowly. CDCA5 could potentially aid in distinguishing between the two types of tumors based on their clinicopathological characteristics.

Furthermore, it has been observed that a significant increase in the expression of CDCA5 is associated with a higher risk of progression-free survival (PFS) in cases of ovarian cancer. Additionally, this risk factor is considered to be independent of other factors. CDCA5 is an independent factor determining the recurrence of ovarian cancer because a shorter PFS suggests an immediate recurrence of the disease and a quicker advancement of the cancer cell cycle. The fact that various confounding factors, including an individual's personal, social, and economic circumstances, have a more significant impact on overall survival time than CDCA5 expression suggests that CDCA5 expression is not yet an independent factor impacting OS (20).

High expression of FOXM1 in the present study was associated with intestinal metastasis of ovarian cancer. Most people with primary ovarian cancer have metastases in their intestines. These metastases can cause gut problems and blockages, which is a big reason ovarian cancer patients have a poor quality of life (21). The driving role of FOXM1 in intestinal metastasis of ovarian cancer is a topic that warrants further research. Previous studies on FOXM1 in peritoneal metastasis of ovarian cancer are more common, and intestinal metastases are believed to indicate occult microscopic lesion growth on the intestinal plasma membrane and peritoneum (22).

Interestingly, CDCA5 was significantly and positively correlated with FOXM1 expression in ovarian cancer. No studies have explored the regulatory relationship between CDCA5 and FOXM1. By functioning in the FOXM1 pathway, CDCA5 may influence the cell cycle of cancerous ovarian cells, according to an analysis of its currently understood molecular functions. We will proceed with cellular-level tests to verify this hypothesis.

Figure 5. A risk score model and nomogram development and evaluation for predicting OS. (A): ROC curve analysis for the integrated model of FOXM1 expression combined with residual disease (B): ROC curve for FOXM1 expression, the status of RD, risk score model Y2. (C): Calibration curve of Y2 for predicting 1-, 3-, and 5-year OS. (D): DCA of Y2 and RD at 3-year OS. (E): DCA of Y2 and RD at 5-year OS. (F): Kaplan–Meier curves of OS in two groups divided by Y2. (G): Nomogram for predicting 1-, 3-, and 5-year OS. (H): The OS nomogram analysis shows distributions of risk scores (top), survival statuses of patients in low-risk and high-risk groups (middle), and RD and FOXM1 expression profiles of each patient (bottom).
Regarding clinicopathological indicators, age, clinical stage, and histopathological grading can all influence ovarian cancer prognosis. However, the outcomes of prognostic evaluation in a clinic based only on these parameters appear less trustworthy (23, 24). Age, tumor stage, and tumor grade did not significantly differ from zero in this study’s univariate or multivariate Cox regression coefficients. RD was the only clinical sign in the trial with any actual significance. Postoperative RD status is an important predictive factor in clinical trials and real-world investigations (25, 26). RD means a very satisfactory surgery; RD>1 cm means a high chance of recurrence in the short term (27). Clinical work, clinicians decide whether to add targeted drugs such as bevacizumab in time according to RD status (2). We were intrigued when we observed that adding two prognostic proteins, CDCA5 and FOXM1, improved the accuracy of the assessment of recurrence in ovarian cancer patients. We discovered that RD + FOXM1 detection accuracy in the OS environment was comparable to FOXM1 alone. Similar to the results of earlier studies, patient satisfaction with surgery had minimal effect on their overall survival time. The standard molecular profile determines the patient’s final survival status. Both predictive models based on protein expression patterns and RD status can distinguish between individuals more likely to recur and those with shorter overall survival. This helps clinicians adjust postoperative drug use regimens and follow-up regimes, promoting medical precision.

The identification of CDCA5’s pathogenic role and prognostic correlation in ovarian cancer tissues is the study’s main strength. One potential new biomarker for ovarian cancer is CDCA5. Unlike other research, we need to employ the widely used immunohistochemistry test to determine if two indications have high or low expression levels in postoperative tissues. Clinically speaking, this technique is simple to use, and patients are not economically affected. This study does have some flaws, though. First, this study looks backward, meaning the data collection and follow-up method may be biased. Second, because there were only a few years of follow-up, there weren’t enough cases in the study to make another validation set. This meant an internal study method could only judge the model’s worth. The sample size of the LGSC population in this investigation was modest, and only a few pathological categories have low prevalence rates.

In conclusion, this study is the first to show that CDCA5 expression was abnormally raised in OC tumor tissues and was a risk factor in and of itself for PFS in OC patients. CDCA5 is positively correlated with FOXM1 expression in ovarian cancer tissues. It successfully predicted the survival and recurrence of ovarian patients by integrating gene expression and RD status. Our research suggests a method that could be clinically effective in enhancing the predictive management of ovarian cancer. Therefore, subsequent studies are required to validate and explore the model presented in the current study.

Availability of data and materials
The data supporting the present study findings are available from the corresponding author upon reasonable request.

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Conflict of interest statement
The authors declare that there are no conflicts of interest.

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