



CLIP2 is a potential biomarker for platinum resistance and prognosis in ovarian cancer: a bioinformatics analysis

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Background: Ovarian cancer exhibits the highest mortality rate among gynecologic malignancies. Platinum resistance remains a key determinant of poor clinical outcomes. Early prediction of platinum resistance is critical for personalized treatment. This study aimed to identify *CLIP2* as an independent prognostic biomarker and assess its predictive value for platinum resistance and the tumor immune microenvironment in ovarian cancer.

Methods: Through integrated bioinformatics analysis of ovarian cancer cohorts from TCGA and GEO, we performed differential gene expression profiling, survival analysis, and multivariate Cox regression to identify biomarkers associated with platinum resistance and prognosis. A *CLIP2*-based logistic regression model was constructed and evaluated using leave-one-out cross-validation (LOOCV). TCGA patients were stratified by *CLIP2* expression for comparative analyses of overall survival, mutational landscapes, drug sensitivity, and immunogenomic characteristics.

Results: *CLIP2* was identified as an independent predictor of platinum resistance and a significant prognostic biomarker (HR =1.20; 95% CI: 1.05–1.40; P=0.007). The *CLIP2*-based model achieved an AUC of 0.68. The high-*CLIP2* subgroup exhibited significantly poorer overall survival (log-rank p = 0.04) and distinct somatic mutation profiles. Drug sensitivity analysis revealed that high *CLIP2* expression conferred resistance to platinum-based agents, topotecan, and gemcitabine, but heightened sensitivity to olaparib, cediranib, and pictilisib. Immunogenomic profiling further indicated that *CLIP2* overexpression was associated with an immunosuppressive microenvironment, characterized by depleted infiltration of activated dendritic cells, CD8⁺ T cells, M1 macrophages, and helper T cells, alongside positive correlations with inhibitory checkpoints (*CD276*, *ADORA2A*, and *ENTPD1*) and negative correlations with stimulatory checkpoints (*CD48* and *NCR3*).

Conclusions: Through bioinformatic analysis, this study proposes *CLIP2* as a potential biomarker associated with platinum resistance and immune microenvironment patterns in ovarian cancer. These preliminary findings provide a basis for subsequent mechanistic studies and larger validation cohorts to confirm its clinical relevance in guiding immunotherapy and targeted treatment approaches.

Keywords: Ovarian cancer; platinum resistance; platinum sensitive; *CLIP2*; tumor microenvironment (TME); immune checkpoints

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Introduction

Ovarian cancer is the sixth most common malignant tumor in women and exhibits the highest cancer-related mortality rate among female malignancies (1,2). Due to its insidious early symptoms, most ovarian cancer patients are diagnosed at advanced stages (III/IV) (3-5). Moreover, primary treatment consists of cytoreductive surgery followed by platinum-based chemotherapy. Despite undergoing surgical intervention and systemic chemotherapy, 80% of ovarian cancer patients will experience recurrence and eventual treatment resistance, culminating in a poor prognosis (6,7). Based on the differential response to platinum-based agents in ovarian cancer patients, the disease is clinically categorized into three distinct types as follows: Platinum-sensitive: defined as demonstrating objective response to initial chemotherapy with disease progression or recurrence occurring ≥ 6 months after completion of the last platinum-based chemotherapy cycle. Platinum-resistant: refers to patients showing initial chemotherapeutic response but developing disease progression or recurrence < 6 months after completing platinum-based chemotherapy. Platinum-refractory: characterized by absence of objective response to

initial chemotherapy, manifesting as either stable disease or progressive disease during platinum-containing treatment cycles (8,9).

The accurate prediction of platinum-resistant phenotypes and the administration of molecularly tailored therapies play a pivotal role in optimizing clinical outcomes for ovarian cancer patients (10). Nevertheless, the mechanisms underlying platinum resistance in ovarian cancer are highly complex. Current research focuses on the function of multidrug resistance, DNA damage repair, cellular metabolism, oxidative stress, dysregulated cell cycle pathways, cancer stem cell mechanisms, immune regulation, apoptosis, autophagy, and aberrant signaling pathways (11-14). Although multiple mechanisms can lead to intrinsic or acquired platinum resistance in tumor cells, the tumor microenvironment (TME) plays a major role in ovarian cancer platinum resistance through various pathways, including providing a niche for cancer stem cells, promoting tumor cell metabolic reprogramming, reducing chemotherapy drug perfusion, and fostering an immunosuppressive environment. As a potential therapeutic target for platinum resistance in ovarian cancer, TME has become a major research focus in recent years (15-17). TME in ovarian cancer is often a critical factor contributing to platinum resistance. Extensive studies have shown that high infiltration of M2 macrophages, reduced dendritic cell activation, and CD8⁺ T cell dysfunction in the TME are all associated with poor prognosis in ovarian cancer (15,18-20). Immune checkpoints negatively regulate T cell signaling by transmitting immunosuppressive signals, thereby weakening anti-tumor immune responses. Inhibition of immune checkpoints can reverse this immunosuppressive state in the TME. Consequently, immune checkpoint inhibitors (ICIs) have shown significant therapeutic efficacy in solid tumors such as lung cancer and melanoma (21-24). For platinum-resistant patients, earlier studies showed limited benefit of ICIs monotherapy or combination therapy (25-27). However, the landmark phase 3 KEYNOTE-B96 trial published in 2025 demonstrated that pembrolizumab plus paclitaxel with or without bevacizumab significantly improved 12-month progression-free survival (PFS: 35.2% *vs.* 22.6%) and overall survival (OS: 18.2 *vs.* 14.0 months) in patients with PD-L1-positive platinum-resistant ovarian cancer (28). Notably, the benefit was restricted to the PD-L1-positive population, establishing PD-L1 as the first predictive biomarker for immunotherapy in ovarian cancer. This breakthrough highlights the importance of biomarker-guided patient selection and supports continued

Highlight box

Key findings

- This study preliminarily developed a *CLIP2*-based predictive model (leave-one-out cross-validation, area under the curve =0.68) for platinum resistance in ovarian cancer and proposes *CLIP2* as an exploratory biomarker warranting validation in larger cohorts.

What is known and what is new?

- Ovarian cancer has the highest mortality among gynecologic malignancies, with approximately 80% of patients experiencing recurrence and eventual treatment resistance, leading to poor prognosis.
- This study indicates that elevated expression of *CLIP2* is significantly associated with poor prognosis in ovarian cancer. More importantly, multi-omics analyses suggested *CLIP2* as a potential predictive biomarker for platinum resistance, with preliminary implications for immunotherapy and targeted therapy.

What is the implication, and what should change now?

- This study reveals potential associations between *CLIP2* expression and platinum resistance, as well as tumor microenvironment remodeling, providing a preliminary foundation for experimental validation and prospective clinical testing. This work aims to facilitate future in-depth exploration of the underlying biological significance of *CLIP2* in platinum resistance and prognosis in ovarian cancer.

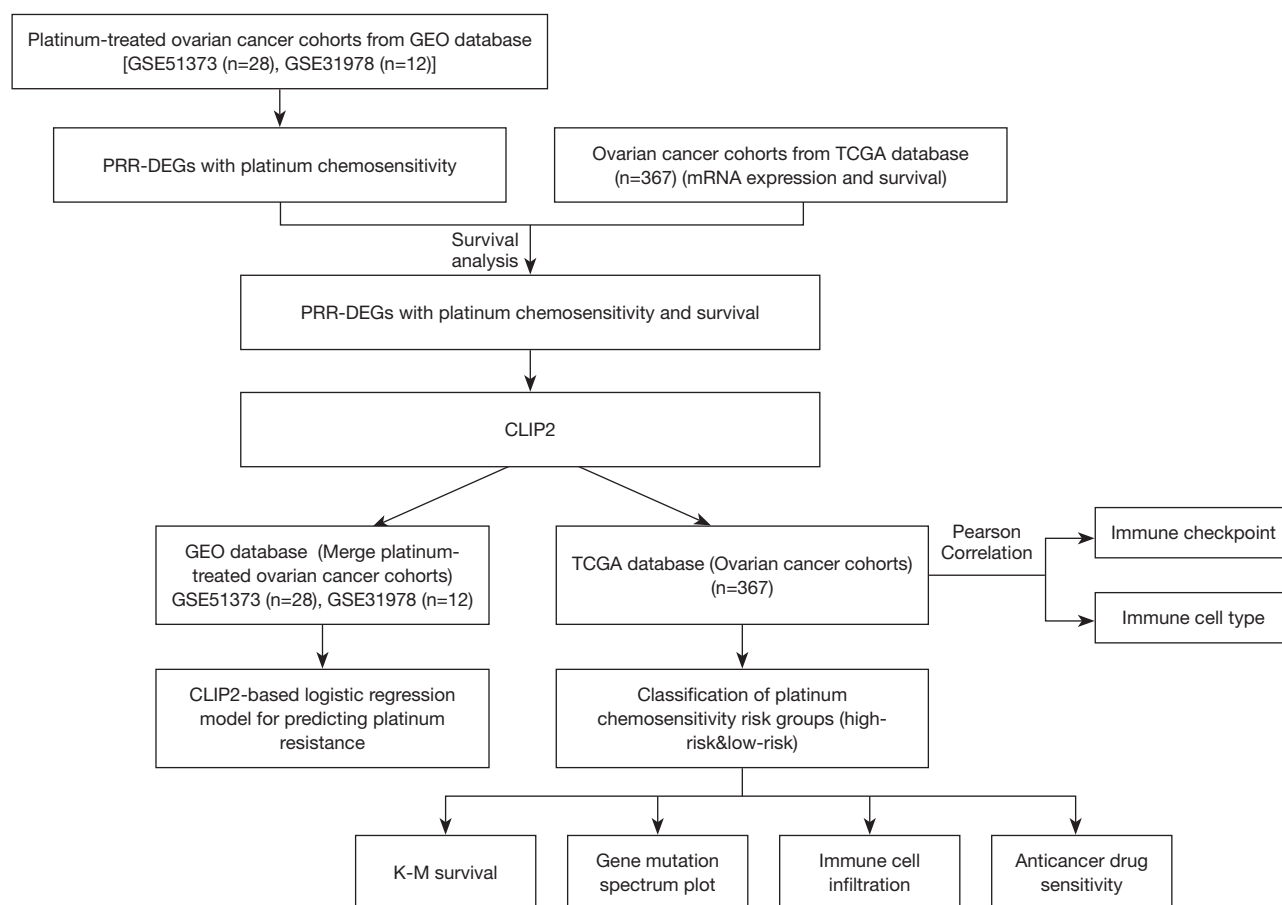


Figure 1 Flowchart for identifying platinum-resistance biomarkers in ovarian cancer. GEO, Gene Expression Omnibus; PRR-DEGs, platinum resistance related differentially expressed genes; TCGA, The Cancer Genome Atlas.

investigation of ICIs in combination strategies, including combinations with PARP inhibitors and anti-angiogenic agents (29).

Bioinformatics serves as a powerful and practical tool for identifying critical genes and pathways in tumorigenesis or pathological processes. In this study, we analyzed microarray data from 19 platinum-resistant ovarian cancer samples and 21 platinum-sensitive controls obtained from the Gene Expression Omnibus (GEO) database. By screening differentially expressed genes (DEGs) and performing enrichment analysis using the Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) databases, we elucidated the functions and regulatory mechanisms of these genes in cellular processes and signaling pathways. Subsequently, we integrated transcriptomic data from 367 ovarian cancer samples in The Cancer Genome Atlas (TCGA) database and employed bioinformatics methods, including

differential gene expression analysis and survival analysis, to identify potential signature genes associated with platinum resistance and prognosis in ovarian cancer. We then constructed a platinum resistance prediction model based on these signature genes and validated its predictive efficacy. Furthermore, we investigated the tumor immune microenvironment and expression differences of immune checkpoints to preliminarily elucidate the mechanisms underlying platinum resistance in ovarian cancer (Figure 1). We present this article in accordance with the TRIPOD reporting checklist (available at <https://tcr.amegroups.com/article/view/10.21037/tcr-2025-aw-2432/rc>).

Methods

Data cases

The microarray expression databases GSE51373 and

Table 1 Summary of GEO datasets used for platinum resistance analysis in ovarian cancer

Datasets	Platforms	Number	Sensitive	Resistance	Tumor histotype
GSE51373	GPL570	28	16	12	High grade serous
GSE131978	GPL570	12	5	7	High grade serous

GEO, Gene Expression Omnibus.

Table 2 The clinical information of the ovarian cancer cohort of TCGA

Character	Number
Age, years	
>59	173 (47%)
≤59	194 (53%)
Lymphatic-invasion	
Yes	98 (27%)
No	47 (13%)
NA	222 (60%)
Stage	
I	1 (1%)
II	21 (5%)
III	287 (78%)
IV	55 (15%)
NA	3 (1%)
Tumor histotype	
Serous carcinoma	367 (100%)

TCGA, The Cancer Genome Atlas.

GSE131978 were retrieved from the GEO database via the NCBI website (<https://www.ncbi.nlm.nih.gov/geo/>). The GSE51373 database comprised 28 ovarian cancer patients, including 16 platinum-sensitive and 12 platinum-resistant cases. The GSE131978 database contained 12 ovarian cancer patients, consisting of 5 platinum-sensitive and 7 platinum-resistant cases (*Table 1*). Additionally, transcriptomic profiles and clinical data for 379 ovarian cancer patients were acquired from The TCGA cohort via the UCSC Xena browser (<http://xena.ucsc.edu>). Following exclusion of cases with incomplete survival records or survival durations ≤30 days, 367 eligible samples were retained for subsequent Bioinformatics analyses. This study was conducted in accordance with the Declaration of Helsinki and its subsequent amendments. The details of the

GEO and TCGA databases are shown in *Table 2*.

DEGs associated with platinum resistance

Raw microarray data were standardizedly normalized. Data processing and analysis were performed using RStudio (R version 4.4.1) and relevant R packages (including GEOquery, stringr, dplyr, tinyarray, etc.). Differential gene expression profiling was conducted utilizing the limma package ($|\log FC| > 0.5$ and P value < 0.05). The volcano plot was constructed using ggplot2, while the hierarchical clustering heatmap was rendered with pheatmap. The Venn diagram was constructed using the VennDiagram and ggvenn packages.

KEGG and GO pathway enrichment analysis

DEGs were analyzed using the clusterProfiler R package to calculate the number of DEGs included in each GO term or KEGG pathway and the corresponding p-value for enrichment significance. The enrichment results were filtered to select the top-ranked terms or pathways based on ascending P value order. The dot plot of enriched pathways was visualized using the dotplot function from the enrichplot R package.

Gene set enrichment analysis (GSEA)

Global expressed genes were ranked in descending order according to their $|\log FC|$ values. These values were derived from RNA-seq data of TCGA datasets, comparing high-risk (n=183) and low-risk (n=184) ovarian cancer patient subgroups that were stratified by median CLIP2 expression levels into high and low subgroups, respectively. To ensure compatibility with the Molecular Signatures Database (MSigDB) gene sets, gene symbols were systematically converted to Entrez IDs using the org.Hs.eg.db annotation package (version 3.2.3). For the GSEA, a gene set was considered significantly activated if its Normalized Enrichment Score (NES) > 0 with a FDR

q-value <0.25, while a gene set was considered significantly suppressed if its NES <0 with a FDR q-value <0.25. The results were visually displayed using a faceted bubble plot.

Kaplan-Meier(K-M) survival analysis and multivariate Cox regression analysis

K-M survival analysis was performed using the survival package, with the median gene expression as the cut-off for grouping. Multivariate Cox regression analysis was conducted to evaluate the independent prognostic value of DEGs using the survival and survminer R packages to estimate the hazard ratio (HR) of target genes for survival time. Detailed statistical results were obtained using summary model. The ggforest function was employed to visualize the results in a forest plot.

Binary logistic regression model

To address the risk of overfitting due to the limited sample size, leave-one-out cross-validation (LOOCV) was performed. In this approach, each sample was sequentially held out as the validation set while the remaining n-1 samples were used for model training. This process was repeated 40 times to ensure each sample served as the validation set once.

A binary logistic regression model was developed to predict platinum sensitivity based on the training dataset. Platinum-resistant and platinum-sensitive samples were assigned a value of P=1 and P=0, respectively. The model was fitted using the glm function in R, and parameters were estimated via maximum likelihood. The final predictive model is defined by the equation:

$$\text{Logit}(P) = \beta_0 + \beta_1 X_{g1} + \beta_2 X_{g2} + \dots + \beta_i X_{gi} \quad [1]$$

In this formula, “i” is the total number of selected genes, β_i is the coefficient for gene, and X_{gi} is the expression value of gene. The trained binary logistic regression model was applied to the validation dataset using the predict function to output predicted probabilities of platinum-resistant events. The receiver operating characteristic (ROC) function from the pROC package was utilized to calculate sensitivity and specificity, followed by generation of the ROC curve. The area under the curve (AUC) served as an objective metric to evaluate the model's classification performance.

Gene mutation spectrum analysis

Gene mutation spectrum derived from transcriptomic data of ovarian cancer patients in the TCGA cohort were analyzed using the TCGAmutations R package. Mutation landscape visualization was subsequently constructed via the plotmafSummary package within the R environment.

Human Protein Atlas (HPA)

To further validate *CLIP2* protein expression levels in primary ovarian cancer tissues relative to normal ovarian tissues, immunohistochemistry (IHC) data were retrieved from the HPA (v24.proteinatlas.org) using antibody HPA020430. Specific images were obtained from v24.proteinatlas.org/ENSG00000106665-*CLIP2*/tissue/ovary (Healthy control ovarian tissue, Patient ID: 2004) and v24.proteinatlas.org/ENSG00000106665-*CLIP2*/cancer/ovarian+cancer (Primary ovarian cancer tissue, Patient ID: 3115).

Immune cell infiltration and immune checkpoint correlation analysis

To analyze differences in immune cell expression among ovarian cancer patients using transcriptomic data from TCGA, the LM22 immune cell signature gene set (LM22.txt) from CIBERSORT was downloaded. Additionally, the immune checkpoint-related gene set (checkpoint-genes.txt) was retrieved to assess its correlation with *CLIP2* expression in the same cohort. Data processing and visualization were conducted using R packages, including ggplot2 and dplyr.

Drug sensitivity analysis

The Genomics of Drug Sensitivity in Cancer (GDSC) database was downloaded from the Cancerrxgene website (<https://www.cancerrxgene.org/>), which contains gene mutation profiles, expression data and drug sensitivity information for various cancer cell lines. Drug sensitivity analysis was conducted using the GDSC database as the training set and ovarian cancer patients from the TCGA cohort as the validation set, employing the oncoPredict R package. Subsequent data visualization was conducted utilizing functions draw-boxplot.

Statistical analysis

All analyses were performed in RStudio (R version

4.4.1). Differential expression was analyzed by limma ($|\log\text{FC}| > 0.5$, $P < 0.05$), and GO/KEGG enrichment by clusterProfiler. GSEA was performed using MSigDB gene sets ($\text{NES} > 0$, $\text{FDR } q\text{-value} < 0.25$). Survival was assessed by Kaplan–Meier and multivariate Cox regression; the logistic regression model was validated by leave-one-out cross-validation and ROC curve. Immune correlations were assessed by Pearson correlation, and drug sensitivity was predicted using the oncoPredict R package. A two-tailed $P < 0.05$ was considered significant.

Results

Identifying DEGs associated with platinum resistance in ovarian cancer

We collected data from 40 patients with high-grade serous ovarian cancer from the GEO database, comprising gene expression profiles and clinical information (Table 1). Differential gene expression analysis of platinum resistant and platinum sensitive ovarian cancer patients revealed 859 DEGs in the GSE51373 database, 1,027 DEGs in the GSE131978 database (Figure 2A–2D). Through Wayne analysis, a total of 40 genes were identified as platinum resistance related DEGs (PRR-DEGs), including 14 up-regulated genes and 26 down-regulated genes (Figure 2E). GO enrichment of the 40 PRR-DEGs showed that they were mainly enriched in biological processes such as cell cycle process regulation, spindle formation, and tubulin movement (Figure 2F).

CLIP2 has been identified as a significant biomarker related to the prognosis and platinum resistance

K–M survival analysis of these 40 PRR-DEGs in 367 ovarian cancer patients of TCGA identified 6 significant prognostic genes. Among these, reduced expression of *CDC7*, *MACROD2*, *MGME1* and *PARP9* correlated with diminished overall survival in ovarian cancer patients ($P < 0.05$). Conversely, elevated expression of *CLIP2* and *GBGT1* predicted poorer overall survival outcomes ($P < 0.05$) (Figure 3A–3F). To assess the independent prognostic value of these 6 candidate genes, multivariate cox regression analysis was used for integrated analysis, with results visualized via forest plots (Figure 3G). Multivariable analysis identified overexpression *CLIP2* as an independent prognostic factor for poor outcomes in ovarian cancer patients [HR = 1.20, 95% confidence interval (CI): 1.05–

1.40, $P = 0.007$]. Conversely, the remaining five candidate genes (*CDC7*, *GBGT1*, *MACROD2*, *MGME1* and *PARP9*) demonstrated non-significant associations in multivariate cox regression analysis, although their hazard ratio directions remained concordant with univariate findings

CLIP2 as a predictor of platinum sensitivity in ovarian cancer

This study implemented standardized integration of GEO microarray databases ($n = 40$). To address the risk of overfitting due to the limited sample size, LOOCV was employed as the primary validation strategy. A univariate logistic regression model based on *CLIP2* expression was constructed within the training set to predict platinum resistance status, defined as $Y = 1$. The model is represented by the equation: $\text{logit}(P(Y=1)) = \beta_0 + \beta_1 \cdot \text{CLIP2}$, where $P(Y=1)$ denotes the probability of platinum resistance. The final regression model was derived as: $\text{logit}(P(Y=1)) = -6.411 + 0.764 \cdot \text{CLIP2}$, with both coefficients exhibiting statistical significance (β_0 : $P = 0.02$; β_1 : $P = 0.02$; $P < 0.05$). Evaluation using LOOCV revealed correct prediction of 12 out of 19 truly resistant cases and 13 out of 21 platinum-sensitive cases (Figure 4A). The model exhibited an overall accuracy of 62.5%, with sensitivity of 63.2%, specificity of 61.9%, positive predictive value of 60.0%, and negative predictive value of 65.0%. The LOOCV approach produced an AUC of 0.68 (95% CI: 0.51–0.85), suggesting the model has modest predictive capability (Figure 4B).

CLIP2 overexpression drives poor prognosis via DNA repair and mutational burden

HPA-based IHC analysis demonstrated *CLIP2* protein overexpression in ovarian cancer tissues compared to normal ovarian tissues (Figure 5A). To validate the predictive model, 367 TCGA patients were stratified into high-risk (predicted platinum-resistant, *CLIP2*-high, $n = 183$) and low-risk (predicted platinum-sensitive, *CLIP2*-low, $n = 184$) groups using the model-derived *CLIP2* expression cutoff (Figure 5B). Survival analysis confirmed that the model-predicted high-risk group exhibited significantly worse overall survival outcomes (Figure 5C, $P < 0.05$), demonstrating the clinical utility of the resistance prediction model. Distinct tumor mutational patterns were observed between high- and low-risk groups. While the high-risk group exhibited higher frequencies of *FLG2* and *MUC16* mutations, and the low-risk group showed more frequent *FLG* and *CSMD3*

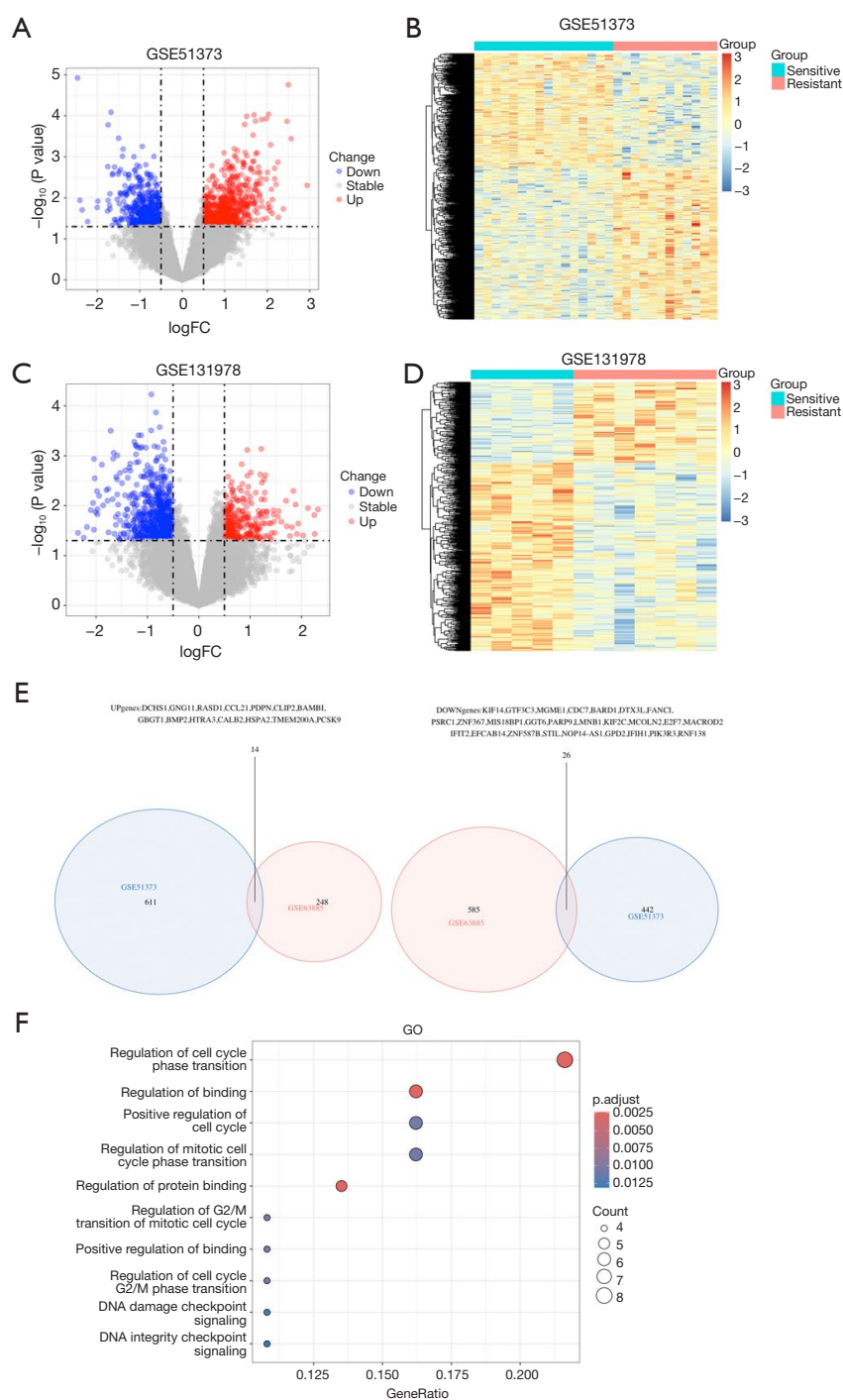


Figure 2 DEGs associated with platinum resistance in ovarian cancer. (A,B) The DEGs of volcano plot and hierarchical clustering heatmap about GSE51373 ($|\log FC| > 0.5$ and $P \text{ value} < 0.05$). (C,D) The DEGs volcano plot and hierarchical clustering heatmap about GSE131978 ($|\log FC| > 0.5$ and $P \text{ value} < 0.05$). (E) The Venn diagram about PRR-DEGs. (F) GO enrichment analysis about PRR-DEGs. DEGs, differentially expressed genes; FC, fold change; PRR-DEGs, platinum resistance related DEGs.

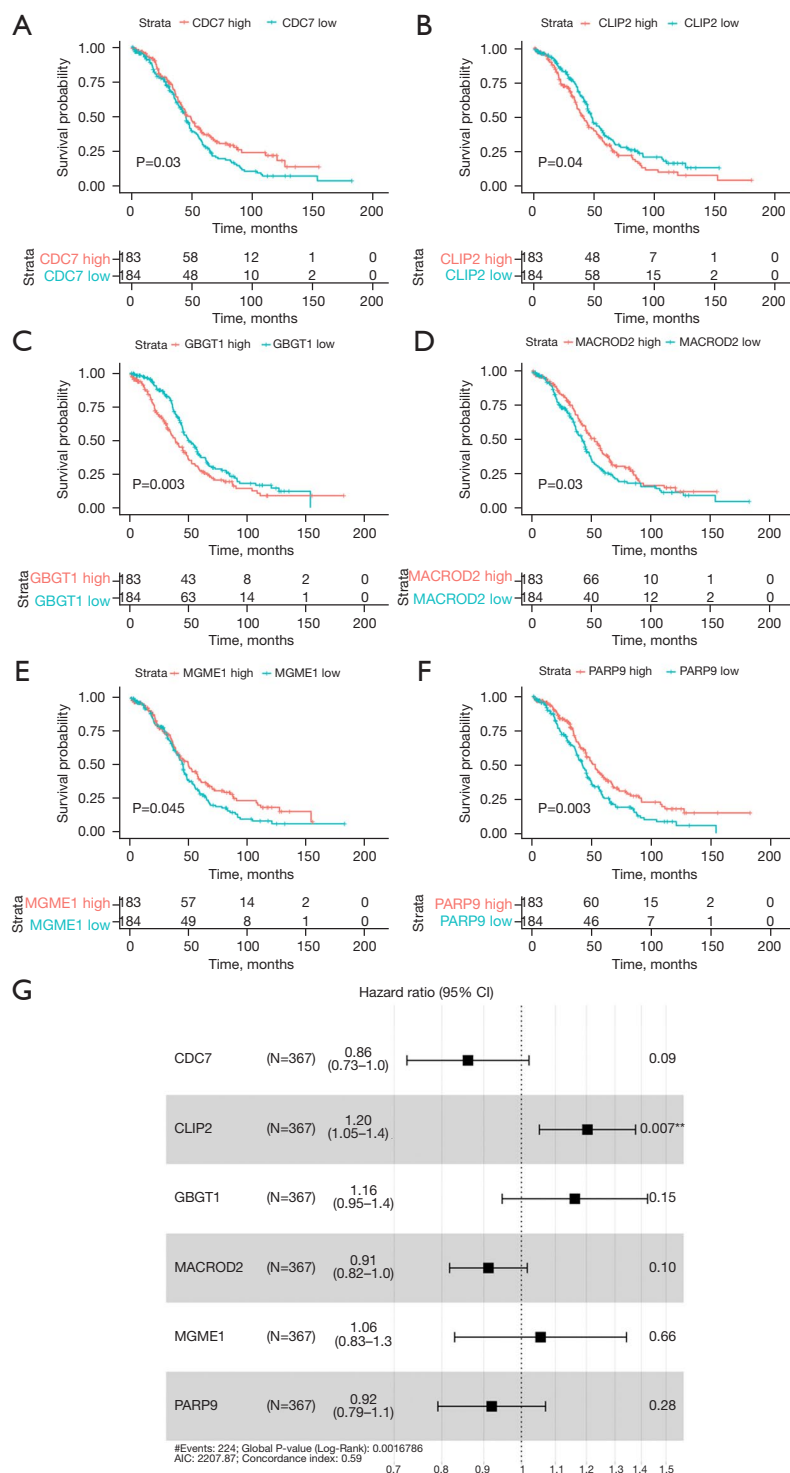


Figure 3 Survival analysis of 40 PRR-DEGs in 367 ovarian cancer patients of TCGA. (A-F) K-M survival analysis of the 40 PRR-DEGs identified six genes (*CDC7*, *CLIP2*, *GBGT1*, *MACROD2*, *MGME1*, and *PARP9*) with statistically significant prognostic value ($P < 0.05$). (G) Forest plot displaying results of multivariate cox regression analysis for six candidate genes (*CDC7*, *CLIP2*, *GBGT1*, *MACROD2*, *MGME1*, and *PARP9*). *CLIP2* was significantly associated with poor prognosis in ovarian cancer patients (HR=1.20, 95% CI: 1.05–1.40, $P=0.007$). CI, confidence interval; HR, hazard ratio; K-M, Kaplan-Meier; PRR-DEGs, platinum resistance related differentially expressed genes; TCGA, The Cancer Genome Atlas.

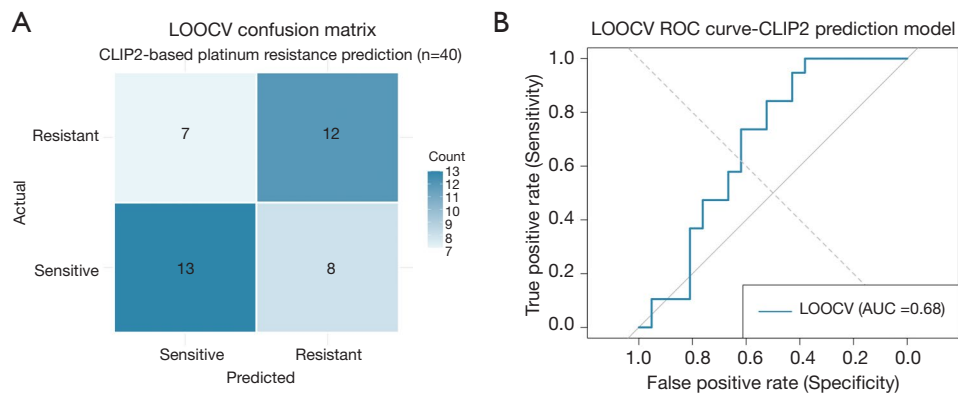


Figure 4 Efficacy of the CLIP2-expression-based logistic regression model in predicting platinum resistance in ovarian cancer using LOOCV. (A) The confusion matrix of the LOOCV evaluation showing correct prediction of 12/19 platinum-resistant and 13/21 platinum-sensitive cases. (B) The ROC curve of the CLIP2-based logistic regression model (AUC =0.68). AUC, area under the curve; LOOCV, leave-one-out cross-validation.

mutations. However, the overall mutation burden (total mutations per sample) did not differ significantly between groups ($P>0.05$). This reflecting divergent mutational spectra between groups, rather than quantitative differences in genomic instability (Figure 5D,5E). Differential gene expression analysis revealed 1,336 significant DEGs, consisting of 610 upregulated and 726 downregulated genes ($|\log FC| > 0.6$ and $P < 0.05$) (Figure 5F). KEGG and GO enrichment analyses of the 1,336 DEGs revealed *CLIP2* was associated with pathways: extracellular matrix reorganization and mitochondrial oxidative phosphorylation (Figure 5G,5H). GSEA analysis revealed that high *CLIP2* expression was associated with upregulation of gene signatures related to Hedgehog signaling, ribosomal biogenesis, and cytochrome P450-mediated xenobiotic metabolism, as well as downregulation of gene sets involved in *de novo* nucleotide biosynthesis, cell cycle progression, DNA damage repair, and homologous recombination-mediated repair (Figure 5I).

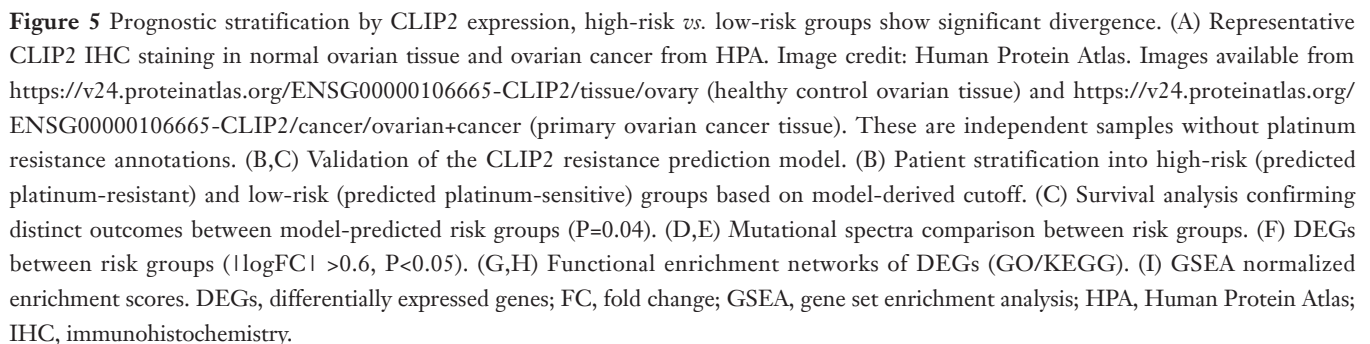
Correlation of *CLIP2* overexpression with anticancer drug sensitivity and immune microenvironment

GDSC-based drug sensitivity analysis suggested that *CLIP2*-high tumors may exhibit differential drug response patterns, including potential resistance to topotecan (topoisomerase I inhibitor) and gemcitabine (DNA synthesis inhibitor), and potential sensitivity to targeted therapies including olaparib (PARP inhibitor), cediranib (anti-angiogenic agent), and pictilisib (PI3K inhibitor) (Figure 6A). TME analysis identified *CLIP2* as a regulator of ECM-

mediated remodeling, evidenced by significant enrichment of ECM-related pathways. Furthermore, *CLIP2*-high tumors exhibited an immunosuppressive phenotype characterized by altered immune cell infiltration patterns (Figure 6B). Using a validated 22-immune-cell signature panel, this study observed distinct immunomodulatory patterns: *CLIP2* expression was positively correlated with immunosuppressive components, including M0 macrophages ($R=0.18$) and resting CD4⁺ memory T cells ($R=0.18$), while showing negative correlations with immunostimulatory populations such as activated dendritic cells ($R=-0.14$), CD8⁺ T cells ($R=-0.17$), M1 macrophages ($R=-0.19$), and helper T cells ($R=-0.19$) (all $P < 0.05$) (Figure 7A). Further characterization of immune checkpoint interactions revealed *CLIP2*'s association with an immunosuppressive signature, demonstrating positive correlations with inhibitory checkpoints *CD276* ($R=0.29$), *ADORA2A* ($R=0.29$) and *ENTPD1* ($R=0.26$), while being negatively associated with activating checkpoints *CD48* ($R=-0.15$) and *NCR3* ($R=-0.18$) (all $P < 0.05$) (Figure 7B). Collectively, these findings suggest that *CLIP2*-high expression was associated with patterns suggestive of an immune-excluded phenotype characterized by ECM remodeling and impaired anti-tumor immunity, whereas *CLIP2*-low expression showed characteristics associated with an immune-permissive microenvironment conducive to effective immune surveillance.

Discussion

Platinum resistance remains a major contributor to poor



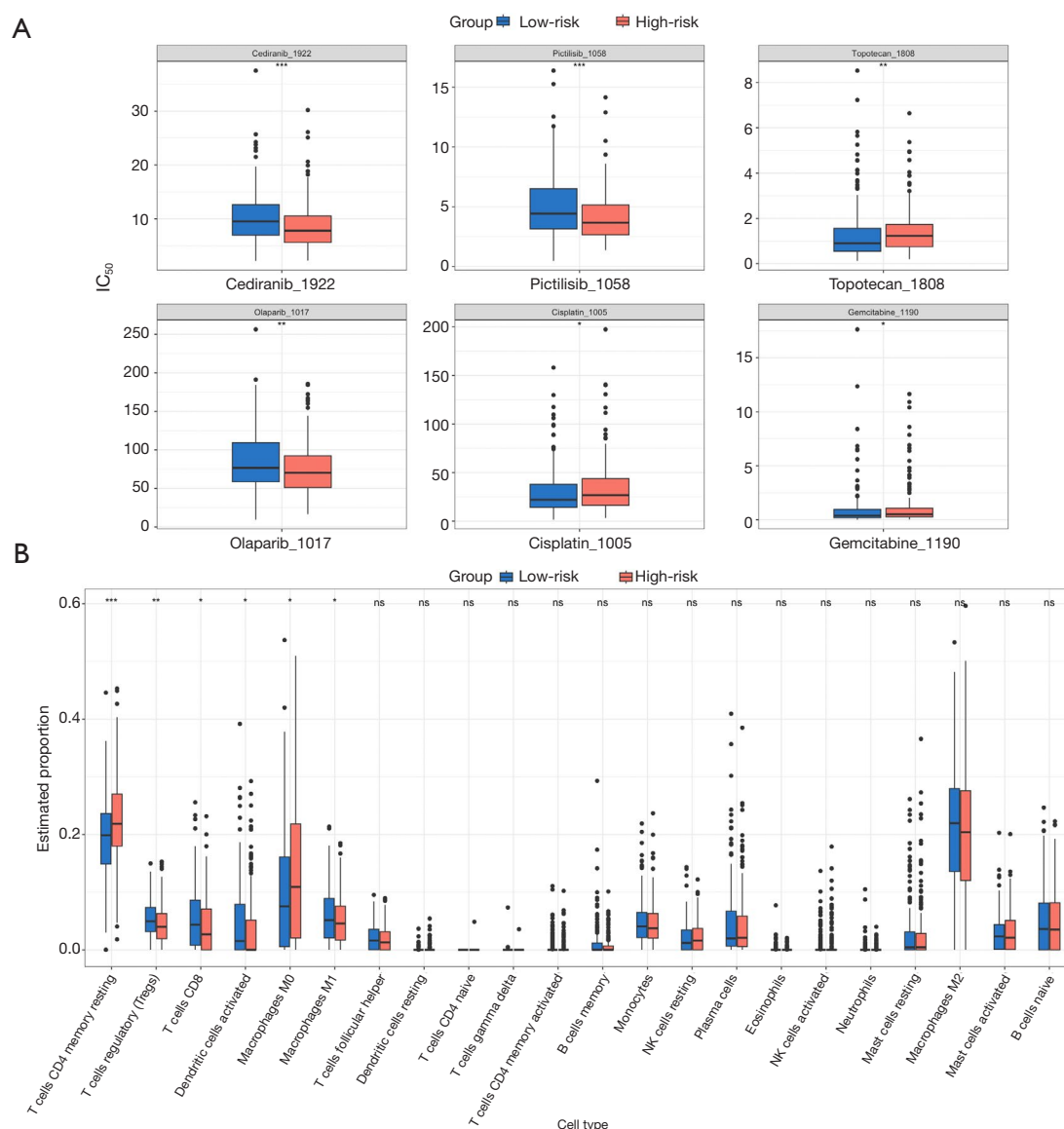


Figure 6 Differential drug sensitivity and immune infiltration landscapes between risk groups. (A) Comparative pharmacosensitivity profiling between risk-stratified cohorts. (B) Immune infiltration landscape analysis stratified by risk groups. ns, no significance; *, P<0.05; **, P<0.01; ***, P<0.001.

prognosis in ovarian cancer. This study identified *CLIP2* as a potential prognostic biomarker associated with platinum resistance through integrated analysis of GEO and TCGA datasets. Multivariate Cox regression demonstrated that high *CLIP2* expression independently predicted shorter overall survival (HR =1.20, 95% CI: 1.05–1.40, P=0.007). The logistic regression model achieved an AUC of 0.68 using LOOCV, suggesting modest predictive potential for platinum resistance.

Cytoplasmic linker proteins (CLIPs) bind to

microtubules and bridge the cytoskeletal network with other intracellular structures. Genes of this family primarily regulate cytoskeletal reorganization, cell migration, and intercellular interactions (30,31). The *CLIP2* gene, located at chromosome 7q11.23, encodes a microtubule-binding protein that participates in the dynamic regulation of the cytoskeleton (32). Relevant studies have demonstrated that *CLIP2* overexpression correlates with poor prognosis in lung, breast, prostate, and thyroid cancers (33–35). In ovarian cancer prior research suggests that *CLIP2* may serve

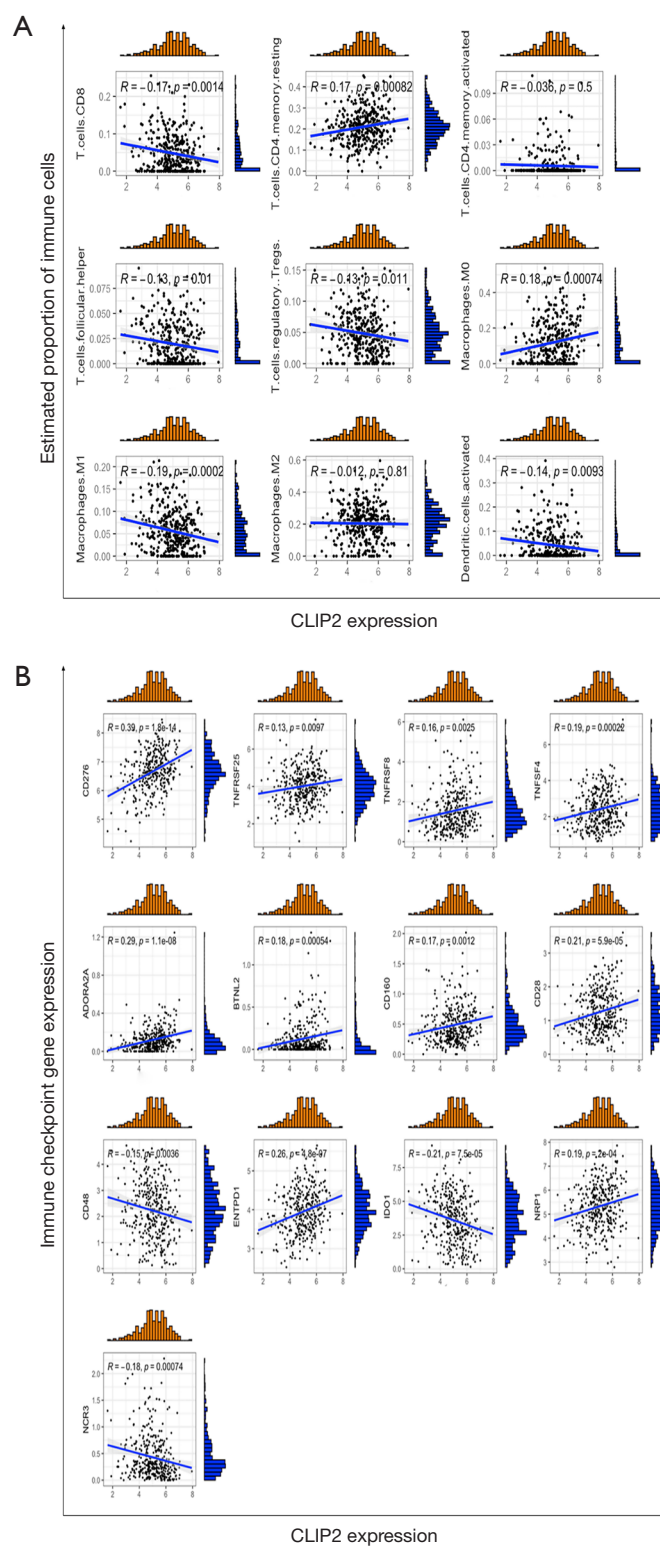


Figure 7 Association between *CLIP2* expression and immune characteristics. (A) Pearson correlation analysis of *CLIP2* expression with immune cell infiltration levels. (B) Association profiling between *CLIP2* expression and immune checkpoint molecules.

as a prognostic marker and is associated with immune cell infiltration, particularly NK cells (36).

In this study, GSEA analysis revealed that high *CLIP2* expression was associated with downregulation of gene signatures related to nucleotide synthesis, cell cycle progression, DNA repair, and homologous recombination repair pathways. Notably, we acknowledge an apparent contradiction in *CLIP2*-high tumors: downregulation of DNA damage repair pathways would classically be associated with increased platinum sensitivity (due to defective repair capacity) (37,38), yet this subgroup exhibited platinum resistance. We hypothesize that TME-mediated mechanisms may override intrinsic tumor cell DNA repair capacity in determining platinum response.

As a cytoskeleton-associated protein, *CLIP2* may modulate cell migration and intercellular interactions, thereby influencing immune cell recruitment and function within the TME. Specifically, the immunosuppressive microenvironment—characterized by ECM remodeling and impaired immune cell infiltration (depleted CD8⁺ T cells and M1 macrophages)—may protect tumor cells from platinum-induced cytotoxicity via immune evasion (39), regardless of DNA repair competence, thereby compensating for the expected platinum sensitivity associated with DNA repair deficiency. Correlated with infiltration of immunosuppressive components (M0 macrophages and resting CD4⁺ memory T cells), while exhibiting negative associations with immunostimulatory populations (activated dendritic cells, CD8⁺ T cells, and M1 macrophages). This altered immune landscape may foster an immunosuppressive TME, enabling tumor cells to evade immune surveillance and cytotoxic killing, thereby enhancing platinum resistance (40–42).

Limitations

This study has several limitations. First, the discovery cohort was small (n=40), and the *CLIP2*-based prediction model exhibited modest discriminative ability (AUC =0.68), constraining its generalizability and immediate clinical utility. Second, functional and mechanistic validation of *CLIP2* in ovarian cancer experimental models is absent, precluding causal inference regarding its role in platinum resistance. Third, GDSC-based drug sensitivity predictions are hypothesis-generating given the limitations of extrapolating cell line IC50 data to clinical tumors. Finally, bulk transcriptomic immune profiling may not fully capture tumor microenvironment spatial heterogeneity. Future studies should validate these findings in prospective

multicenter cohorts and experimental models.

Conclusions

Through multi-omics analysis, this study suggests *CLIP2* as a potential biomarker associated with poor prognosis and platinum resistance in ovarian cancer, with preliminary implications for immunotherapy and targeted therapy.

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Footnote

Reporting Checklist: The authors have completed the TRIPOD reporting checklist. Available at <https://tcr.amegroups.com/article/view/10.21037/tcr-2025-aw-2432/rc>

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. This study was conducted in accordance with the Declaration of Helsinki and its subsequent amendments.

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