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Genomic and clinical insights into ovarian cancer: subtype-specific alterations and predictors of metastasis and relapse

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Abstract
Ovarian cancer exhibits marked molecular heterogeneity and variable clinical outcomes. Understanding genomic alterations associated with metastasis and relapses may guide personalized management, particularly in high-grade serous carcinoma (HGSC). We performed targeted sequencing of 1021 cancer-related genes in tumor-normal pairs from 99 treatment-naïve ovarian cancer patients. Associations between copy number variations (CNVs), metastatic patterns, tumor mutation burden (TMB), and relapses were assessed. Analyses of relapse predictors were restricted to HGSC patients. Statistical significance was determined with Bonferroni correction for multiple comparisons. *TP53* mutations were frequent in HGSC (96.6%), whereas *PIK3CA*, *ARID1A*, and *ATRX* mutations were enriched in non-HGSC tumors. *FLT3*, *CDH23*, and *EPAS1* mutations were associated with metastasis. TMB-high tumors (≥ 9 mutations/Mb) showed distinct profiles, including *SMARCA4* and *FUBP1* mutations and CNV gains in *CEBPA*. Among HGSC patients, *TBX3* mutations were exclusively observed in those relapsing within six months ($p = 0.028$), while *ARID1B, MAP2K1*, and *FLT4* were enriched in relapse groups. After neoadjuvant chemotherapy and FIGO stage IV were also associated with relapses. This study reveals subtype-specific and metastasis-related genomic alterations in ovarian cancer and identifies potential relapse-associated mutations in HGSC. While exploring, these findings support further investigation into individualized risk stratification and biomarker-driven therapeutic strategies.

Keywords Ovarian cancer · High-grade serous carcinoma · Genomic profiling · Metastasis · Tumor mutation burden · Relapse · Biomarkers · Precision oncology

1 Introduction

Ovarian cancer (OC) ranks as the eighth most prevalent cancer among women worldwide, contributing to approximately 3.7% of all cancer diagnoses and 4.7% of cancer-related deaths in 2020 [1]. In 2022, 325,000 women were newly diagnosed, and 207,000 women died from OC. With regard to the prediction of a 40.4% increase in incidence by 2045, we are facing a global problem [2]. In recent years, incidence rates have shown an upward trend in certain regions, particularly Eastern Europe and parts of Asia, with a notable increase among women under 50 years of age [3]. The

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evolving understanding of high-grade serous carcinomas (HGSCs) as primarily originating in the fallopian tube has prompted changes in cancer classification and reporting practices. This shift, which began around 2010, complicates global statistical comparisons, as cases coded as fallopian tube cancer (ICD-10 C57) are frequently excluded from ovarian cancer (ICD-10 C56) statistics [4]. HGSCs, the most common and aggressive subtype of ovarian cancer, are typically associated with TP53 mutations [5]. Preventive strategies, such as prophylactic removal of the target organ before cancer develops, have been identified as the most effective means of reducing risk [2] (Fig. 1A, C). Recent advancements in genomic sequencing technologies have shed light on key molecular alterations driving ovarian cancer progression, [6], metastasis [7], and therapeutic resistance [8, 9] (Fig. 1B). Tumor mutation burden (TMB), representing the total number of mutations within a tumor genome, has emerged as a potential biomarker for immunotherapy response [10]. Although ovarian cancer cells express immune checkpoint molecules such as PD-1 and PD-L1, and a positive correlation has been observed between tumor-infiltrating lymphocytes and favorable survival outcomes, clinical trials investigating immune checkpoint inhibitors (ICIs) in this cancer type have largely been disappointing. The limited efficacy of ICIs in ovarian cancer is primarily attributed to tumor heterogeneity and the resistance mechanisms associated with the tumor microenvironment (TME), which can be either inherent or acquired [11]. Adding to the challenge, ovarian cancer often presents with limited treatment options and is typically diagnosed at advanced stages, significantly impacting patient outcomes. High relapse rates further complicate management, driven by both natural and acquired resistance mechanisms in cancer cells and their surrounding TME [12–14]. Furthermore, the absence of reliable biomarkers for predicting therapeutic responses hinders personalized treatment strategies, underscoring the urgent need for research into more effective diagnostic and therapeutic approaches [15] (Fig. 1D). Addressing these challenges requires a deeper understanding of tumor immunobiology, the identification of robust biomarkers for patient selection, and the development of

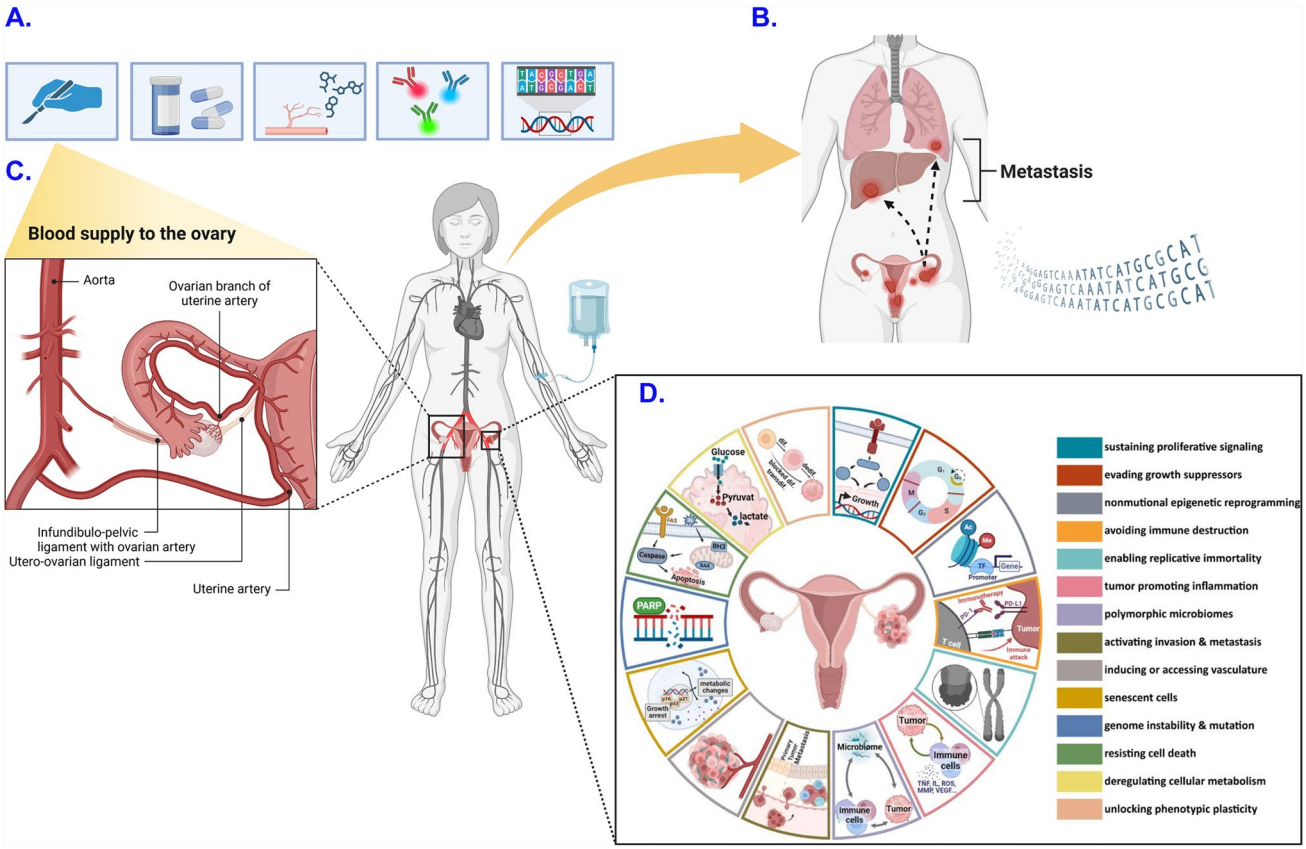

Fig. 1 Overview of ovarian cancer treatment modalities, metastatic pathways, and molecular mechanisms. **A** Current therapeutic approaches for ovarian cancer, including surgery, chemotherapy, immunotherapy, and targeted therapy. **B** Ovarian cancer metastasis, highlighting hematogenous and lymphatic dissemination to distant organs like the lungs. **C** Blood supply to the ovaries, focusing on the ovarian and uterine arteries, which support tumor angiogenesis and growth. **D** Molecular mechanisms and hallmarks of ovarian cancer, including proliferative signaling, evasion of growth suppressors, genome instability, inflammation, and phenotypic plasticity, with therapeutic targets indicated [15]

optimal treatment combinations. These efforts are essential for advancing the use of immunotherapy in ovarian cancer [10]. Despite these advances, the relationship between specific genomic alterations, TMB, and clinical features in ovarian cancer remains poorly understood [16]. To address these gaps, we conducted a comprehensive genomic and clinical analysis of 99 treatment-naïve patients with epithelial ovarian cancer. Using a validated 1021-gene panel We stratified patients by histopathological subtypes, metastatic patterns, and TMB levels to identify molecular drivers and biomarkers relevant to disease progression and treatment outcomes. These findings contribute to a deeper understanding of ovarian cancer heterogeneity and its implications for precision oncology, highlighting new avenues for targeted therapies and patient-specific treatment strategies.

2 Methods

2.1 Patient cohort and sample collection

In total, 99 patients with newly diagnosed epithelial ovarian cancer who received primary treatment at Zhejiang Cancer Hospital between July 2020 and June 2022 were included in the study. Clinical staging was assessed according to the FIGO 2014 criteria, resulting in 1 patient at stage I, 8 at stage II, 45 at stage III, and 45 at stage IV. In terms of treatment strategy, 66 patients underwent primary debulking surgery (PDS), 32 received interval debulking surgery (IDS), and 1 patient received surgery–chemotherapy–surgery. Tumor samples were collected during surgical resection, and clinicopathological data, including histological subtypes, tumor stage, and patterns of metastasis, were recorded for all patients. Patients were classified based on histopathological subtypes, TMB, metastatic patterns (e.g., lymph node metastasis, planting metastasis), and relapse status. Relapses were defined as radiological or clinical evidence of disease recurrence occurring after the completion of initial treatment. Follow-up was completed by telephone follow-up and review of outpatient records. All participants provided written informed consent.

2.2 Sample processing and DNA extraction

Genomic DNA (gDNA) in formalin-fixed, paraffin-embedded (FFPE) tissue samples and peripheral blood lymphocytes (PBL) was extracted by using the QIAamp DNA FFPE Tissue & Blood Mini Kit (Qiagen, Hilden, Germany). DNA concentrations in tissue samples were measured with a Qubit fluorometer and the Qubit dsDNA HS (High Sensitivity) Assay Kit (Invitrogen, Carlsbad, CA USA), while DNA concentrations in PBL was with the Qubit 3.0 fluorometer and the Qubit dsDNA HS (High Sensitivity) Assay Kit (Thermo Fisher Scientific Inc., Carlsbad, CA, USA).

2.3 Target capture and next-generation sequencing

The custom-designed biotinylated oligonucleotide probes (Roche NimbleGen, Madison, WI, USA) covering ~ 1.4 Mbp coding region of genomic sequence of 1021 cancer-related genes (Table S1) was designed. For library construction, 1.0 µg of PBL and tissue DNA were sheared to 300-bp fragments with a Covaris S2 ultrasonicator (Covaris, Woburn, MA, USA). Libraries were constructed using the KAPA DNA Library Preparation Kit (Kapa Biosystems, Wilmington, MA, USA). Captured libraries were measured using an Agilent 2100 Bioanalyzer and an Applied Biosystems 7500 real-time PCR system (Thermo Fisher Scientific Inc., Carlsbad, CA, USA). DNA sequencing was carried out on the Gene-seq 2000 Sequencing System (Suzhou Geneplus, Suzhou, China) with 2×100 bp paired-end reads.

2.4 Next-generation sequencing analysis

From raw sequencing data, terminal adaptor sequences and low-quality reads were removed. The reads were aligned to the human genome build GRCh37 using BWA (a Burrows-Wheeler aligner). To mark PCR duplicates, Picard tools (http://broadinstitute.github.io/picard/) were used. SNVs and Indels were called using MuTect (version 1.1.4) [17] and GATK (version 3.4–46-gbc02625) [18], respectively. PBL sequencing results were used to filter germline variations. All candidate somatic mutations identified by the bioinformatics pipeline were manually reviewed in the Integrative Genomics Viewer

(IGV) (https://igv.org/) through assessing the quality of base calls, the mapping quality of the reads and the overall read depth at each mutation site. Mutations were annotated to genes by ANNOVAR software [19] to identify the mutated protein coding position and filtered intronic and silent changes. Variant allele fraction (VAF) = sequencing read count of altered alleles/ (sequencing read count of reference alleles + sequencing read count of altered alleles) × 100%. For tissue, a mutation was identified according to these standards: VAF ≥ 1.0%, and at least 5 high-quality reads (Phred score ≥ 30, mapping quality ≥ 30, and without paired end reads bias). All tumor samples were sequenced using the Geneplus 1021-gene panel. Based on internal sequencing QC data for this cohort, the mean effective sequencing depth was approximately 812×, with a median of 748×, a minimum of 589×, and a maximum of 1248×. This level of coverage enables confident detection of somatic mutations at ≥ 1% VAF. To measure the TMB value, the total number of somatic mutations within coding regions and with a VAF of no less than 5% is counted, after excluding driver gene mutations that may cause the bias of dataset. Then, TMB is measured as the total number of mutations divided by the length of coding regions covered by our gene panel (1.4 MB) and reported in units of mutations per megabase (mutations/MB). TMB status is classified as either TMB-high or TMB-low based on cut-off values of 9 [20].

2.5 Statistical analysis

Statistical analyses were performed using Python (v3.8.8) and R (v4.1.2). Continuous variables were compared using the student's *t*-test or the Mann–Whitney *U* test, as appropriate. Categorical variables were analyzed using the chi-square test or Fisher's exact test when expected counts were less than five. Multiple comparisons of gene-level mutation frequencies were corrected using the Bonferroni method. A two-sided *p* value of less than 0.05 after adjustment was considered statistically significant.

3 Results

3.1 Molecular landscape and subtype-specific alterations

A total of 99 primary, treatment-naïve ovarian cancer specimens were analyzed using targeted sequencing of 1021 cancer-related genes. Clinical staging followed FIGO 2014 criteria, and sample classification was based on initial metastatic assessment. The cohort included 89 patients with high-grade serous carcinoma (HGSC) and 10 with non-HGSC subtypes (Table 1). Across the entire cohort, the most frequently mutated genes were *TP53* (92.9%), *ARID1A* and *MLL2*. Copy number variation (CNV) analysis revealed recurrent amplifications in *MYC, TERC, EXT1, RECQL4, SOX2*, and *ZMAT3*, each observed in > 10% of patients. CNV losses were rare (Fig. 2A). All patients underwent germline *BRCA1/2* testing, twenty-nine patients (29.3%) had pathogenic or likely pathogenic variants (22 *BRCA1*, 7 *BRCA2*), consistent with the reported prevalence in Chinese ovarian cancer populations [21]. Subtype-specific analysis revealed distinct mutational profiles (Fig. 2B, F). TP53 mutations were significantly enriched in HGSC (96.6% vs. 60%, $p = 0.0017$, Bonferroni adjusted p-values: p = 0.0102, Fisher's exact test). In contrast, *PIK3CA* and *ARID1A* mutations were more common in non-HGSC tumors (adjusted $p = 0.0004$, 0.0324 respectively; Bonferroni corrected). Other genes, such as *ACIN1* and *NRAS*, showed nominal significance ($p < 0.05$) but did not survive correction.

3.2 Genomic features associated with metastatic patterns

A genomic analysis of ovarian cancer subgroups revealed distinct mutation patterns associated with metastasis and tumor progression. Based on a comprehensive evaluation of preoperative imaging, intraoperative findings, and postoperative pathology, metastatic patterns were categorized as follows: 53 patients had both peritoneal (planting) and lymph node metastases; 46 patients were classified into the "Other" group, which included 39 with only peritoneal metastasis, 5 with only lymph node metastasis, 1 with fallopian tube invasion, and 1 without any detected metastasis. Mutations in *FLT3*, *CDH23*, and *EPAS1* were associated with reduced incidence of LN and Planting metastasis. (*FLT3*: 1.89% vs. 13.04%, $p = 0.0437$; *CDH23*: 0% vs. 8.7%, $p = 0.0433$; *EPAS1*: 0% vs. 8.7%, $p = 0.0433$; all by Fisher's exact test; Fig. 2C–E, G). However, after Bonferroni correction (adjusted p-values: *FLT3* = 0.1892, *CDH23* = 0.1732, *EPAS1* = 0.1732),

Table 1 Clinicopathological characteristics of ovarian cancer across histological subtypes and metastatic patterns

Category	HGSC (N = 89)	Non-HGSC (N = 10)	P-value	LN & Planting (N = 53)	Other (N = 46)	P-value
Age (years)						
Mean (SD)	56.1 (9.97)	46.8 (8.75)	0.115	55.5 (9.75)	54.6 (10.8)	0.474
Median [Min, Max]	56.0 [24.0, 82.0]	48.5 [30.0, 59.0]		56.0 [24.0, 79.0]	53.0 [28.0, 82.0]	
Operation_history						
Direct_surgery	56 (62.9%)	10 (100%)	0.062	29 (54.7%)	37 (80.4%)	0.00856**
Surgery-Chemotherapy-surgery	1 (1.1%)	0 (0%)		0 (0%)	1 (2.2%)	
Surgery_after_neoadjuvant	32 (36.0%)	0 (0%)		24 (45.3%)	8 (17.4%)	
Type						
CCC	0 (0%)	2 (20.0%)	< 0.001***	1 (1.9%)	1 (2.2%)	0.339
EC	0 (0%)	3 (30.0%)		1 (1.9%)	2 (4.3%)	
HGSC	89 (100%)	0 (0%)		48 (90.6%)	41 (89.1%)	
LGSC	0 (0%)	2 (20.0%)		2 (3.8%)	0 (0%)	
MC	0 (0%)	2 (20.0%)		0 (0%)	2 (4.3%)	
Missing	0 (0%)	1 (10.0%)		1 (1.9%)	0 (0%)	
Clinical_stage						
I	0 (0%)	1 (10.0%)	0.00925**	0 (0%)	1 (2.2%)	< 0.001***
II	6 (6.7%)	2 (20.0%)		0 (0%)	8 (17.4%)	
III	42 (47.2%)	3 (30.0%)		19 (35.8%)	26 (56.5%)	
IV	41 (46.1%)	4 (40.0%)		34 (64.2%)	14 (23.9%)	
TMB_group						
High	3 (3.4%)	2 (20.0%)	0.137	3 (5.7%)	2 (4.3%)	1
Low	84 (94.4%)	8 (80.0%)		48 (90.5%)	44 (95.7%)	
Missing	2 (2.2%)	0 (0%)		2 (3.8%)	0 (0%)	
Planting_metastasis						
No	5 (5.6%)	2 (20.0%)	0.302	0 (0%)	7 (15.2%)	0.0107*
Yes	84 (94.4%)	8 (80.0%)		53 (100%)	39 (84.8%)	
Lymph.node_metastasis						
No	36 (40.4%)	5 (50.0%)	0.808	0 (0%)	41 (89.1%)	< 0.001***
Yes	53 (59.6%)	5 (50.0%)		53 (100%)	5 (10.9%)	

*$p < 0.05$, **indicated $p < 0.01$, ***indicated $p < 0.001$; "LN & Planting" refers to patients with both lymphatic and peritoneal dissemination (i.e., multi-site metastasis), while "Other" includes those with single-site or limited metastatic involvement

only the combined mutation profile (*FLT3/CDH23/EPAS1*; raw $p = 9.04 \times 10^{-5}$; adjusted $p = 0.0004$) remained statistically significant.

To further explore the relationship between LN & Planting (N = 53; patients with both lymphatic and peritoneal dissemination, i.e., multi-site metastatic disease) and the Planting-only groups (N = 39), we performed additional analyses (Fig. 3A). These investigations aimed to identify molecular drivers or shared pathways underlying their distinct metastatic behaviors, offering deeper insights into the biological differences and potential overlaps between the two subgroups. Among the top 40 mutated genes, *EPAS1* showed a significantly higher mutation frequency in the Planting-only group ($p = 0.029$, Table S1). No significant differences were observed in CNV gains or losses between the groups. The enrichment of *EPAS1* mutations in the Planting-only subgroup suggests its potential role in driving metastatic progression unique to this pathway, highlighting molecular differences between these transfer types.

3.3 Mutational and clinical correlates of tumor mutation burden

To explore the relationship between TMB and genomic alterations, using a validated method based on coding mutations/Mb (threshold ≥ 9 mut/Mb), ovarian cancer patients were stratified into TMB_low (n = 92) and TMB_high (n = 5) groups. The TMB_low group exhibited significantly higher mutation frequencies in *PIK3CA*, *LRP1B*, *MLL*, *SMARCA4*, and *FUBP1*, with

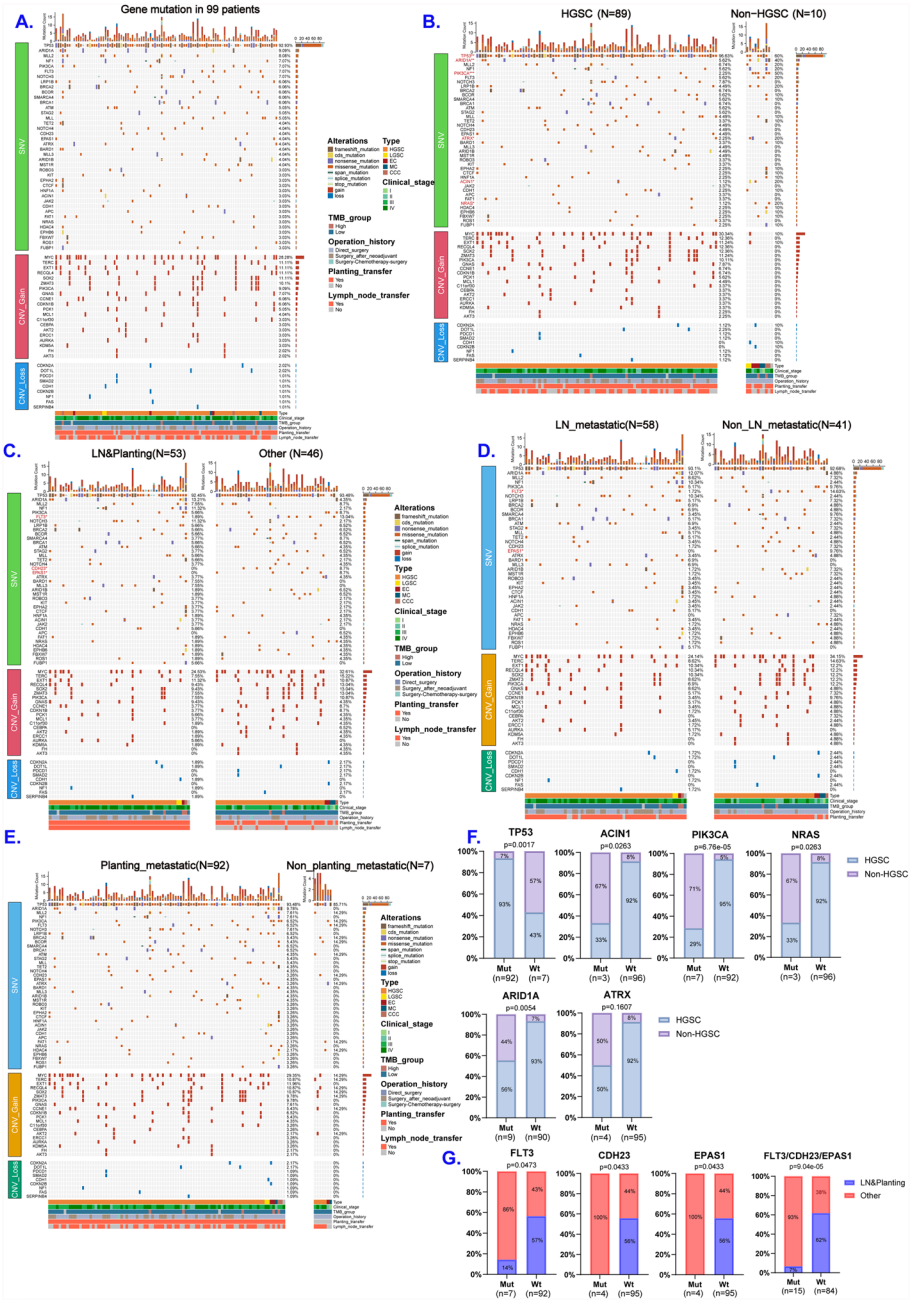

Fig. 2 Genomic alterations and their associations with histologic subtypes and metastatic phenotypes in ovarian cancer. **A** Overview of somatic mutations and copy number variations (CNVs) in 99 patients with ovarian cancer, annotated by histologic subtype, tumor mutation burden (TMB), clinical stage, operation history, lymph node metastasis, and peritoneal seeding status. **B** Comparison of genomic profiles between high-grade serous carcinoma (HGSC, n = 89) and non-HGSC tumors (n = 10) demonstrates distinct mutation patterns, particularly involving TP53, PIK3CA, and ARID1A. **C** Mutational spectrum in patients with both lymph node and planting metastases (LN & Planting, n = 53; "LN & Planting" refers to patients with both lymphatic and peritoneal dissemination (i.e., multi-site metastasis)) versus those with other metastatic patterns (n = 46; "Other" includes those with single-site or limited metastatic involvement). **D** Genomic analysis of lymph node metastasis (LN_metastasis, n = 58) compared to non-lymph node metastasis (Non_LN_metastasis, n = 41) identifies key differences linked to metastatic potential. **E** Genomic alterations in patients with planting metastasis (n = 92) compared with non-planting metastatic cases (n = 7). **F** Statistical comparisons of mutation frequencies in six key genes between HGSC and non-HGSC subtypes. TP53 (raw p = 0.0017; Bonferroni-adjusted p = 0.0102), PIK3CA (raw $p = 6.76 \times 10^{-5}$; adjusted p = 0.0004), and ARID1A (raw p = 0.0054; adjusted p = 0.0324) remained significantly enriched after Bonferroni correction. ACIN1, NRAS, and ATRX did not retain significance after adjustment. **G** Mutations in FLT3, CDH23, and EPAS1 were associated with reduced incidence of LN and peritoneal metastasis. However, after Bonferroni correction (adjusted p-values: FLT3 = 0.1892, CDH23 = 0.1732, EPAS1 = 0.1732), only the combined mutation profile (FLT3/CDH23/EPAS1; raw $p = 9.04 \times 10^{-5}$; adjusted p = 0.0004) remained statistically significant

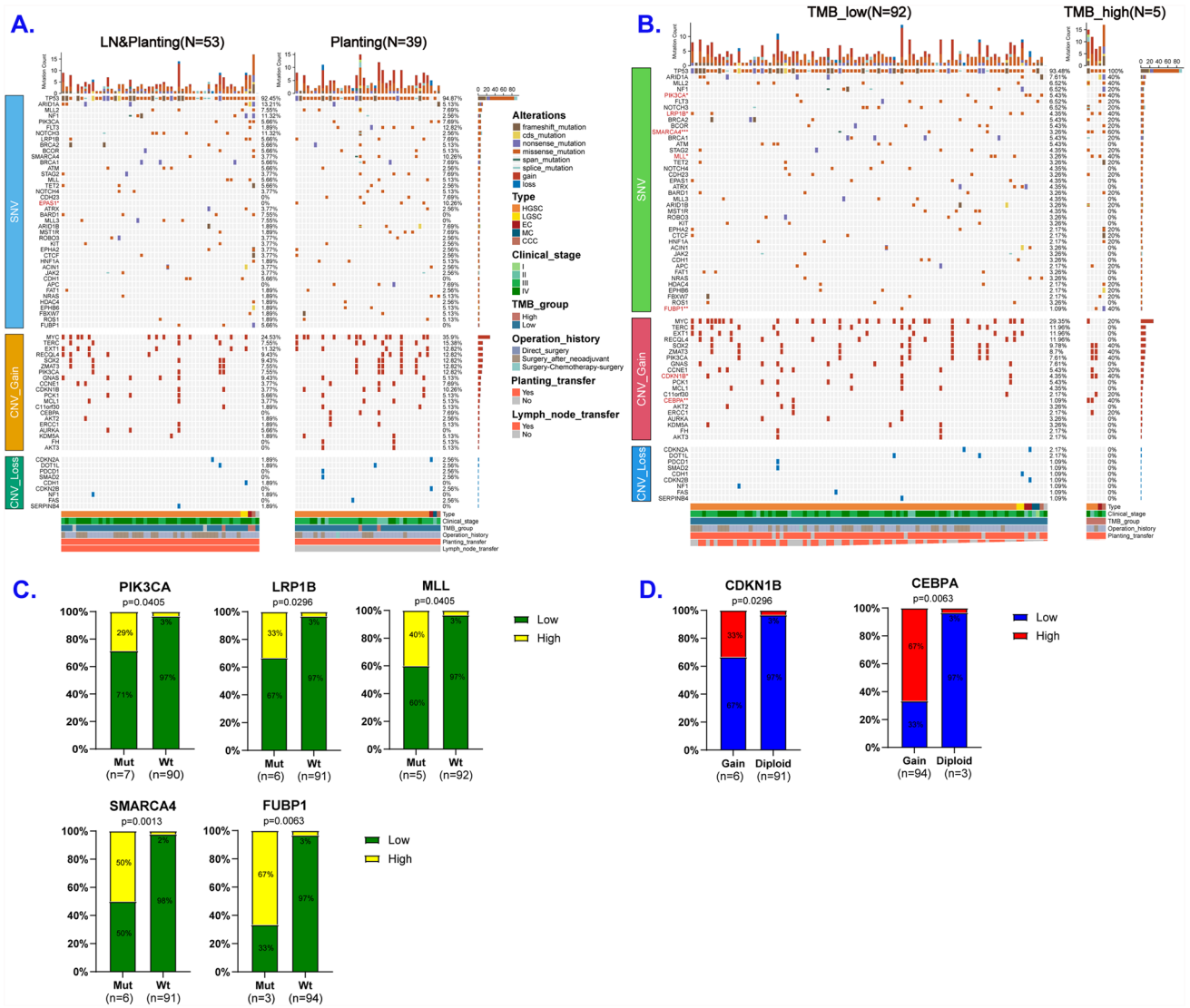

Fig. 3 Genomic landscape and mutation burden stratification in ovarian cancer. **A** Comparison of somatic mutation and copy number variation (CNV) profiles between patients with both lymph node and planting metastasis (LN & Planting, n = 53) and those with planting metastasis only (Planting, n = 39). Distinct genomic alterations were observed across subgroups, annotated by clinical stage, histological subtype, and treatment history. **B** Genomic features of patients with high tumor mutation burden (TMB-High, n = 5) versus those with low TMB (TMB-Low, n = 92). TMB-High cases exhibited a higher prevalence of somatic mutations and CNV gains across multiple genes. **C** Mutation frequencies of selected genes—PIK3CA, LRP1B, MLL, SMARCA4, and FUBP1—were significantly enriched in the TMB-High group. After Bonferroni correction, SMARCA4 (raw p = 0.0013; adjusted p = 0.0065) and FUBP1 (raw p = 0.0063; adjusted p = 0.0315) remained statistically significant, while PIK3CA, LRP1B, and MLL did not retain significance (adjusted p > 0.05). **D** Copy number gains in CDKN1B and CEBPA were more frequent in TMB-High patients. Bonferroni-adjusted p values indicated that only CEBPA remained significantly associated with high TMB status (raw p = 0.0063; adjusted p = 0.0126), while CDKN1B (raw p = 0.0296; adjusted p = 0.0592) did not pass the corrected significance threshold

mutation rates ranging from 1.09% to 5.43%. Conversely, CNV analysis showed frequent gains in *CDKN1B* and *CEBPA* in the TMB_high group (both 40%) versus 4.35% and 1.09% respectively in the TMB_low group ($p < 0.01$) (Fig. 3B). Mutation frequencies of selected genes—*PIK3CA, LRP1B, MLL, SMARCA4*, and *FUBP1*—were enriched in the TMB-High group. After Bonferroni correction, *SMARCA4* (raw p = 0.0013; adjusted p = 0.0065) and *FUBP1* (raw p = 0.0063; adjusted p = 0.0315) remained statistically significant, while *PIK3CA, LRP1B,* and *MLL* did not retain significance (adjusted $p > 0.05$) (Fig. 3C). Copy number gains in *CDKN1B* and *CEBPA* were more frequent in TMB-High patients. Bonferroni-adjusted p values indicated that only *CEBPA* remained significantly associated with high TMB status (raw p = 0.0063; adjusted p = 0.0126), while *CDKN1B* (raw p = 0.0296; adjusted p = 0.0592) did not pass the corrected significance threshold (Fig. 3D). These findings

indicate that high TMB tumors harbor distinct molecular drivers that may contribute to their aggressive clinical behavior. The integration of genomic and clinical data underscores the heterogeneity of ovarian cancer, revealing subtype-specific and metastatic patterns associated with unique genomic alterations and clinical outcomes.

3.4 Genomic and clinical predictors of six-month relapse in high-grade serous carcinoma (HGSC)

Of the 99 patients, 77 had at least 6 months of follow-up. The genomic profiles of ovarian cancer patients with relapse within six months (Relapse, N = 13) and those without relapse (No_relapse, N = 64) revealed significant genomic alterations associated with relapse (Relapse was defined as radiological or clinical evidence of disease recurrence occurring after the completion of initial treatment.) (Table 2). To minimize confounding from histological subtype and given the significant molecular divergence between HGSC and non-HGSC tumors observed in "Molecular landscape and subtype-specific alterations" section, we restricted the analysis of relapse-associated genomic and clinical features to patients with histologically confirmed high-grade serous carcinoma (HGSC, n = 69). A total of 69 HGSC patients had at least six months of follow-up and were stratified based on relapse status within this period.

Clinically, patients undergoing surgery after neoadjuvant were more likely to relapse early (75.0% vs. 26.3%, $p = 0.0039$). Advanced stage (FIGO IV) was also more prevalent in the relapse group (75.0% vs. 38.6%, $p = 0.066$), though not statistically significant (Table 2). Mutation in *TBX3* was more prevalent in the relapse group, suggesting their potential role in driving early recurrence. Specifically, *TBX3* mutations were observed in 16.67% of relapse cases, but were entirely absent in the no-relapse group (2/12 vs. 0/57; p = 0.028) (Fig. 4A, B and Table S1). These findings suggest that a combination of specific genomic alterations, such as mutations in *TBX3*, and clinical factors like advanced stage and surgical history contribute to the risk of relapse within six months.

3.5 Genomic and clinical insights into relapse within one year

Among 62 HGSC patients with ≥ 12 months of follow-up, 17 (27.4%) experienced a relapse within 1 year. Several genes were exclusively mutated in this group: *ARID1B, TBX3, MAP2K1*, and *FLT4* (Fig. 4C, D and Table S1). While p-values for these genes ranged from 0.059 to 0.072, none remained significant after Bonferroni correction. From a clinical perspective, surgery following neoadjuvant chemotherapy was significantly more common in relapsed patients (58.8% vs. 26.7%, $p = 0.0391$), while FIGO stage IV also showed a higher prevalence (64.7% vs. 40.0%), though the difference did not reach significance ($p > 0.05$) (Table 2). Due to the limited number of events and small sample size, multivariable Cox regression analysis was not feasible. Nonetheless, the observed enrichment of chromatin remodeling and MAPK pathway alterations—alongside established clinical risk factors—highlights a potentially actionable genomic signature. These exploratory findings underscore the need for validation in larger cohorts and may contribute to future strategies for risk-adapted surveillance and treatment optimization in HGSC.

4 Discussion

Advancements in oncology have demonstrated that rare mutations, despite their low prevalence, can redefine treatment paradigms. For instance, microsatellite instability-high (*MSI-H*) colorectal cancer responds robustly to immune checkpoint inhibitors [22, 23], while *ALK* rearrangements [24] and *KRAS-G12C* mutations [25, 26] and *HER2* amplification or overexpression in breast [27] and gastric cancers [28] have revolutionized precision oncology through targeted therapies. Similarly, the introduction of *PARP* inhibitors for *BRCA*-mutant ovarian cancer [29] has transformed the therapeutic landscape, particularly for patients with homologous recombination deficiencies. Beyond the success of *PARP* inhibitors, there is an urgent need to identify additional biomarkers to expand therapeutic options for this heterogeneous disease. These examples collectively highlight the clinical impact of identifying rare but actionable alterations and designing therapies to exploit them.

Our study offers a comprehensive genomic and clinical landscape of epithelial ovarian cancer (OC), emphasizing histological subtype distinctions, metastatic dissemination routes, tumor mutation burden (TMB) profiles, and early relapse predictors. By leveraging targeted sequencing data from a well-annotated Chinese cohort of 99 patients and integrating molecular findings with clinical variables, we identified multiple subtype-specific and metastasis-associated genomic alterations that may inform precision oncology strategies. Our analysis reaffirmed the genomic divergence between

Table 2 Clinical and pathological characteristics of ovarian cancer patients stratified by relapse within 6 months and 1 year

Category	Not relapse within 6 months (N = 64)	Relapse within 6 months (N = 13)	P-value	HGSC_Not relapse within 6 months (N = 57)	HGSC_Relapse within 6 months (N = 12)	P-value	HGSC_Not relapse within 1 year (N = 45)	HGSC_Relapse within 1 year (N = 17)	P-value
Age (years)									
Mean (SD)	55.0 (9.98)	56.4 (13.4)	0.314	56.3 (9.39)	57.3 (13.5)	0.279	57.0 (8.64)	54.5 (13.0)	0.273
Median [Min, Max]	54.5 [30.0, 82.0]	58.0 [24.0, 79.0]		57.0 [33.0, 82.0]	58.0 [24.0, 79.0]		58.0 [42.0, 73.0]	56.0 [24.0, 79.0]	
Operation_history									
Direct_surgery	49 (76.6%)	4 (30.8%)	0.00348**	42 (73.7%)	3 (25.0%)	0.00392**	33 (73.3%)	7 (41.2%)	0.0391
Surgery-Chemotherapy-surgery				0 (0%)	0 (0%)		0 (0%)	0 (0%)	
Surgery_after_neoadjuvant	15 (23.4%)	9 (69.2%)		15 (26.3%)	9 (75.0%)		12 (26.7%)	10 (58.8%)	
Clinical_stage									
I	1 (1.6%)	0 (0%)	0.0915	0 (0%)	0 (0%)	0.0655	0 (0%)	0 (0%)	0.182
II	4 (6.3%)	0 (0%)		3 (5.3%)	0 (0%)		2 (4.4%)	1 (5.9%)	
III	34 (53.1%)	3 (23.1%)		32 (56.1%)	3 (25.0%)		25 (55.6%)	5 (29.4%)	
IV	25 (39.1%)	10 (76.9%)		22 (38.6%)	9 (75.0%)		18 (40.0%)	11 (64.7%)	
TMB_group									
High	2 (3.1%)	2 (15.4%)	0.266	1 (1.8%)	1 (8.3%)	0.782	1 (2.2%)	1 (5.9%)	1
Low	61 (95.3%)	11 (84.6%)		55 (96.5%)	11 (91.7%)		44 (97.8%)	16 (94.1%)	
Missing	1 (1.6%)	0 (0%)		1 (1.8%)	0 (0%)		0 (0%)	0 (0%)	
Planting_metastasis									
No	5 (7.8%)	1 (7.7%)	1	3 (5.3%)	1 (8.3%)	1	3 (6.7%)	1 (5.9%)	1
Yes	59 (92.2%)	12 (92.3%)		54 (94.7%)	11 (91.7%)		42 (93.3%)	16 (94.1%)	
Lymph.node_metastasis									
No	26 (40.6%)	4 (30.8%)	0.725	23 (40.4%)	4 (33.3%)	0.899	18 (40.0%)	6 (35.3%)	0.962
Yes	38 (59.4%)	9 (69.2%)		34 (59.6%)	8 (66.7%)		27 (60.0%)	11 (64.7%)	
Type_group									
HGSC	57 (89.1%)	12 (92.3%)	1						
Non_HGSC	7 (10.9%)	1 (7.7%)							

* $p < 0.05$, **indicated $p < 0.01$, ***indicated $p < 0.001$. In patients who experienced more than one recurrence, only the first relapse event after completion of primary treatment was used for subgroup classification. Each patient was included only once in the analysis, and no duplication occurred across clinical groups

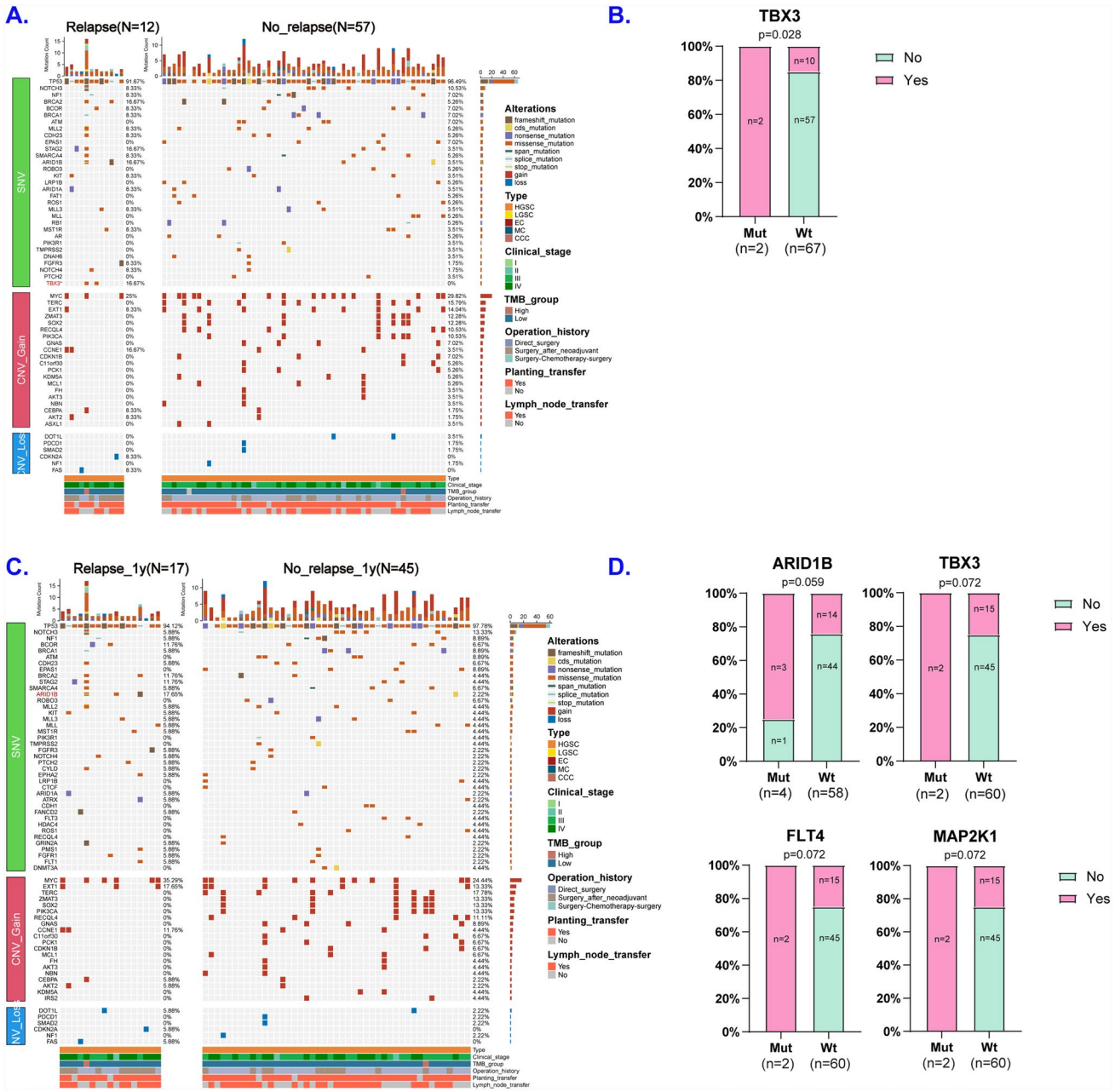

Fig. 4 Genomic profiles and mutation frequencies associated with ovarian cancer relapse. **A** Genomic alterations in high-grade serous carcinoma (HGSC) patients with relapse within 6 months (n = 12) versus those without early relapse (n = 57), highlighting early molecular divergence. **B** TBX3 mutations were more frequent in patients with early relapse (p = 0.028), suggesting a potential role as a biomarker for early disease progression. **C** Comparative mutational landscape in HGSC patients with relapse within 1 year (n = 17) versus those without relapse during the same period (n = 45). **D** Mutations in ARID1B, TBX3, FLT4, and MAP2K1 showed nominal enrichment in the 1-year relapse group (raw p-values 0.059–0.072), but none remained significant after Bonferroni correction (adjusted p > 0.2 for all comparisons)

high-grade serous carcinoma (HGSC) and non-HGSC subtypes. As expected, TP53 mutations were nearly universal in HGSC, while *PIK3CA, ARID1A*, and *ATRX* mutations were enriched in non-HGSC cases—echoing findings from previous large-scale studies (Fig. 2A, B, F) [30–32]. *PIK3CA*, a driver of the *PI3K/AKT/mTOR* pathway, was more frequently mutated in non-HGSC tumors [33]. These distinctions highlight the need to stratify patients by histology in both research and therapeutic development. The study also delineated distinct mutation patterns associated with metastatic phenotypes. Mutations in *FLT3* [34], *CDH23* [35], and *EPAS1* [36] were significantly enriched in patients without dual (lymph node and planting) metastases (Fig. 2C–E), and *EPAS1* was further associated with planting-only spread (Fig. 3A). For instance, *FLT3*, a tyrosine kinase involved in cell proliferation, has been linked to poor prognosis in hematological malignancies and may

play a similar role in metastatic ovarian cancer [37]. Although these findings are exploratory, they suggest that distinct molecular drivers may underlie different metastatic trajectories in ovarian cancer, consistent with emerging concepts of molecularly defined dissemination pathways [38].

TMB is an established biomarker for immunotherapy response in several cancer types [39]. However, in the subgroup of TMB-high tumors (≥ 9 mutations/Mb), rare but potentially targetable alterations were identified, including copy number gains in *CEBPA* and *CDKN1B* [40], and mutations in *SMARCA4* and *FUBP1* (Fig. 3B-C) two genes involved in chromatin remodeling and genomic stability [41]. While TMB has shown prognostic and predictive relevance in other cancers, its role in OC remains poorly defined. Our findings highlight that TMB-high OC represents a distinct molecular subgroup with possible vulnerabilities, warranting further investigation.

Relapse prediction remains a major clinical challenge in OC. By restricting relapse analyses to treatment-naïve HGSC patients. Notably, we identified *TBX3* ($p = 0.028$) mutation as enriched in patients who relapsed within six months (Fig. 4B), and *MAP2K1* and *FLT4* in those who relapsed within one year (Fig. 4D). *MAP2K1*, a kinase within the *MAPK* signaling cascade, further highlights the therapeutic relevance of targeting upstream regulators in RAS-driven pathways [42]. *FLT4*, encoding a *VEGF* receptor, participates in the Hippo and *mTOR* pathways, underscoring its role in angiogenesis and metastasis [43]. These genes are involved in *MAPK*, *EMT*, and chromatin remodeling pathways, which are widely implicated in chemoresistance and disease progression [44, 45].

Clinically, our observation that relapse was more frequent among patients who received neoadjuvant chemotherapy and those with advanced FIGO stage is consistent with previous large-scale studies. Both the EORTC 55971 and CHORUS trials showed that while neoadjuvant chemotherapy is non-inferior to primary debulking in survival, it is often applied in patients with higher tumor burden, leading to increased relapse risk, especially in FIGO stage IV disease. Furthermore, advanced stage at diagnosis remains a well-established predictor of poor prognosis and early recurrence, as emphasized in recent reviews [46–48].

Importantly, all samples used for sequencing were obtained before chemotherapy, ensuring that observed mutations were not treatment-induced—a key strength that aligns with biomarker discovery standards. Several limitations should be acknowledged. First, sample sizes for relapse subgroups were small, and some statistically suggestive findings (e.g., *TBX3* in relapse, $n = 2$ cases) may reflect stochastic variation. These analyses are therefore hypothesis-generating and should not be interpreted as definitive biomarkers without validation in larger, prospective cohorts. Second, while multiple testing correction was applied using the Bonferroni method, some associations may have been missed due to limited power. Despite these limitations, our study provides a valuable integrative resource for understanding the genomic underpinnings of metastasis and recurrence in ovarian cancer. The identification of rare but potentially actionable alterations—such as mutations in *TBX3, EPHA5, MAP2K1*, and *FLT3*—echoes successful precision oncology approaches, where even low-frequency events (e.g., *MSI-H* in colorectal cancer [22, 23] or *KRAS-G*^{12}*C* in lung cancer [25, 26]) have led to paradigm-shifting therapies. Looking ahead, future research should focus on validating relapse-associated genes in larger HGSC cohorts, functionally characterizing *FLT3, CDH23*, and *EPAS1* in metastasis models, and performing clinical annotation of TMB-high OC cases to inform immunotherapy selection. Integrating transcriptomic and epigenomic data will also be essential to contextualize genomic alterations and uncover additional therapeutic vulnerabilities. Altogether, our findings provide a foundation for refining risk stratification and tailoring personalized treatment strategies in ovarian cancer.

5 Conclusion

In this study, we comprehensively profiled the genomic and clinical landscape of epithelial ovarian cancer using a Chinese cohort, revealing subtype-specific alterations, metastasis-associated mutation patterns, and potential predictors of early relapse. Our findings underscore the biological heterogeneity of ovarian cancer, particularly between HGSC and non-HGSC subtypes, and suggest that distinct genomic signatures—such as mutations in *FLT3, CDH23*, *TBX3*, and *ARID1B*—may be associated with metastatic behavior and recurrence risk. The identification of TMB-high tumors and alterations in chromatin remodeling and MAPK pathways further highlights possible therapeutic targets. While these results are exploratory and require validation in larger cohorts, they offer novel insights into the molecular drivers of disease progression and lay the groundwork for developing precision oncology strategies in ovarian cancer.

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Author contributions Feng Cheng contributed to the conceptualization, methodology, data acquisition, and drafting of the manuscript. Feng Shao was responsible for data analysis, interpretation of results, and critical revision of the manuscript. Yiping Tian conducted the pathological examination, validated results, and provided technical support. Shujun Chen supervised the project, managed funding acquisition, and gave final approval of the manuscript.

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Data availability All data generated or analyzed during this study are included in this published article and its supplementary information files.

Declarations

Ethics approval and consent to participate This study was conducted in accordance with the ethical standards of the Declaration of Helsinki and was approved by the Ethics Committee of Zhejiang Cancer Hospital (approval number: IRB-2024–1236).

Competing interests The authors declare no competing interests.

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