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Molecular subtype of ovarian clear cell carcinoma: an analysis of 80 Chinese patients using the TCGA molecular classification of endometrial cancer

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Abstract

Background To assess the utility of the TCGA molecular classification of endometrial cancer in a well-annotated, moderately sized, consecutive cohort of Chinese patients with ovarian clear cell carcinoma (OCCC).

Methods We performed DNA sequencing on 80 OCCC patients via a panel that contains 520 cancer-related genes. The TCGA molecular subtyping method was utilized for classification. The clinicopathological features were analysed, and the survival correlation was assessed for each subtype.

Results The most common mutated genes were ARID1A (49%) and PIK3CA (48%). No pathogenic POLE mutations were detected. MSI-high (MSI-H) tumours were observed in 5 (6.3%) patients. A total of 16.3% (13/80) of the patients were classified as the p53 abnormal (p53abn) subtype, and 77.5% (62/80) were classified as the nonspecific molecular profile (NSMP) subtype. All the MSI-H patients had ARID1A mutations, whereas patients with the p53abn subtype had the lowest percentage of ARID1A mutations (27.3%). No significant differences were observed between the molecular subtypes and clinicopathological features. The progression-free survival and overall survival of the entire cohort were closely associated with FIGO stage ($p < 0.01$), the presence of residual tumour ($p < 0.01$), and the platinum response ($p < 0.01$). Molecular classification did not significantly impact prognosis. Univariate analysis revealed that TP53 mutations in advanced-stage (FIGO III-IV) patients were associated with shorter survival.

Conclusions We did not find prognostic significance of TCGA molecular subtyping in OCCC. POLEmuts are extremely rare, and the incidence of MSI-H and p53abn tumours is also quite low. Further subtyping of the NSMP subgroup is warranted.

Keywords Ovarian clear cell carcinoma, Next-generation sequencing, TCGA subtypes, Prognosis, Molecular subclassification, Microsatellite instability

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Background

Ovarian cancer is the most lethal gynaecologic cancer and lacks effective, adequate screening or preventive methods [1]. It consists of different histologic subtypes, which are deemed to be distinct diseases with distinct clinical and molecular features [2, 3]. Ovarian clear cell carcinoma (OCCC) is the second-largest histological subtype of epithelial ovarian cancer, following high-grade serous carcinoma (HGSC) [4]. Presently, its treatment follows the standard therapeutic approaches for HGSC. However, due to its highly invasive nature and chemotherapeutic resistance, advanced-stage OCCC has a significantly poorer prognosis [5, 6]. Given its unique clinical and biological characteristics, the treatment of OCCC remains an unmet need, which emphasizes the urgent need for personalized therapeutic strategies and predictive biomarkers.

Over the years, our research team has characterized the biological behaviour and clinicopathological features of OCCC patients in China to explore distinct subtypes of OCCC at the genomic and transcriptomic levels [7–12]. We found that OCCC patients with mismatch repair protein deficiency (MMRd) had slightly longer progression-free survival (PFS), but the difference was not statistically significant [11]. OCCC often presents with recurrent somatic mutations in the PIK3CA and ARID1A genes [13, 14], distinguishing it from HGSC. Furthermore, OCCC tends to demonstrate fewer structural rearrangements and typically carries wild-type TP53, establishing a distinctive genetic profile for this subtype [15]. Moreover, OCCC is considered to be associated with endometriosis, suggesting molecular similarities with certain subtypes of endometrial cancer (EC) at the molecular level [16]. In addition to the previously mentioned mismatch repair defects, hypermutation phenomena similar to those of the POLE gene have been reported in a subset of OCCCs, akin to what is observed in EC [17]. This shared molecular aberration may lead to similar biological characteristics in tumour cells and prognostic outcomes.

The molecular classification of EC introduced by The Cancer Genome Atlas (TCGA) research network offers a promising tool for stratifying tumours into four prognostic subgroups [18]. These methods include methods to evaluate gene mutations, genomic copy number abnormalities, gene expression patterns, and signalling pathway activities. Some studies have shown its comparable prognostic significance in ovarian endometrioid carcinomas [19–21]. However, in OCCC, which has a similar origin, relevant knowledge is limited [17, 22]. In this study, we applied the TCGA molecular classification to a well-annotated, moderately sized, consecutive cohort of Chinese patients with OCCC to evaluate its practical utility.

Materials and methods

Patients and samples

The research received approval from the Institutional Review Board of Fudan University Shanghai Cancer Centre. As part of our standard procedure, patients scheduled for surgery are routinely approached to inquire about their willingness to contribute blood and/or tumour samples for research conducted within our institution. Written informed consent was obtained from all participating patients. We retrospectively reviewed the surgical pathology records of patients diagnosed with OCCC between November 2014 and June 2023. Clinical information and survival outcomes, including personal and family history of cancer, age at diagnosis of OCCC, date and type of initial surgery, International Federation of Gynecology and Obstetrics (FIGO) stage at initial treatment, presence of concurrent endometriosis, residual disease, platinum-free interval (the time interval from completion of the last platinum-based chemotherapy to disease recurrence), time of disease progression or recurrence, and tumour status at last contact, were collected from the medical records system. Patients were considered platinum resistant if the platinum-free interval was less than 6 months. PFS and overall survival (OS) were defined as the duration from the initial surgical procedure to the occurrence of first recurrence and death or last follow-up, respectively. The slides were reviewed by a specialist in gynaecologic pathology to confirm the diagnosis.

NGS and sequencing data analysis

A total of 80 patients were included in the study, consisting of 61 patients from our previous study [12] and 19 patients who received the genomic test on their own. Formalin-fixed, paraffin-embedded (FFPE) tumour samples and peripheral blood were obtained. Capture-based targeted sequencing was performed at the Burning Rock Biotech Laboratory (Guangzhou, China), which is a College of American Pathologists-accredited and Clinical Laboratory Improvement Amendments-certified clinical laboratory.

The methods used for DNA extraction, targeted sequencing and sequencing data analysis were described in our published articles [10, 12]. DNA fragmentation was carried out using an M220 focused ultrasonicator (Covaris, USA), followed by end repair, phosphorylation, and adaptor ligation. Fragments ranging from 200 to 400 bp were purified via Agencourt AMPure XP beads (Beckman Coulter, USA). These fragments were then hybridized with capture probe baits, subjected to hybrid selection using magnetic beads, and amplified via polymerase chain reaction (PCR). Target enrichment was performed via the OncoScreen Plus panel (Burning Rock Biotech, China), which includes 520 cancer-related genes

that cover 1.6 MB of the human genome. This panel captured the entire exonic regions of 312 genes, as well as key exons, introns, and promoter regions from 208 other genes. DNA integrity and fragment size were evaluated using a Bioanalyzer 2100 (Agilent, USA). Indexed samples were sequenced on an Illumina NextSeq 500 paired-end system (Illumina, Inc., USA). The tumour mutational burden (TMB) was calculated by dividing the number of nonsynonymous mutations by the total size of the coding regions of the gene panel. The microsatellite instability (MSI) status was assessed based on the percentage of unstable loci via a read-count distribution-based method [23].

Stratification into molecular categories

Based on the TCGA molecular classification and an alternative scheme proposed by the World Health Organization (WHO) [18, 24, 25], the OCCCs in our cohort were classified into four subtypes: (1) POLE mutation (POLEmut). POLE exonuclease domain mutations have been well established and described previously [26], including the two most common mutations related to ultramutated endometrial carcinomas [18, 27]; (2) Microsatellite instability high (MSI-H); (3) No specific molecular profile (NSMP), and (4) p53 abnormality (p53abn). The molecular subgroup allocation scheme followed a stepwise diagnostic algorithm commonly used for endometrial carcinoma. Initially, the POLE exonuclease domain was sequenced to classify POLEmut OCCCs. The MSI status of carcinomas lacking a pathogenic POLE exonuclease domain mutation was evaluated to detect the MSI-H subtype. The remaining OCCCs were subsequently classified as p53abn cancers based on TP53 gene mutations.

Statistical analysis

Continuous variables are depicted as either the mean or median, whereas frequencies are used to present categorical variables. Unpaired Wilcoxon's signed-rank tests were applied for contrasting continuous variables, and two-sided Fisher's exact tests were employed for comparing categorical variables, as deemed suitable. A significance threshold of $P<0.05$ indicated statistical significance. We utilized the Kaplan–Meier method for survival rate estimation and the generation of survival curves. To assess the correlation between genomic alterations and both PFS and OS, univariate analysis was performed with the log-rank test.

The Kaplan–Meier curves were plotted via the Python programming language, version 3.9. We utilized Jupyter Notebook as the interactive development environment for Python code and employed various Python libraries for data processing and visualization purposes. Sankey diagrams were generated via OmicShare tools, a free online platform for data analysis (https://www.omicshare.com/tools). Statistical analyses were performed via the Statistical Package for Social Science (SPSS) (Version 24.0, SPSS, Inc., Chicago, IL, USA).

Results

Molecular classification

Somatic POLE Exonuclease Domain Variants.

Among the 80 patients, four had exon mutations in the POLE gene, specifically in exon 8 or exon 15. They are classified as variants of uncertain significance (VUS) because, according to the EC classification method, only mutations in exons 9 to 14 are considered to define the POLE ultramutated subtype. The TMB of POLE-mutant tumours ranges from 2.2 to 7.98 mutations/Mb. During the follow-up period, a recurrence leading to mortality occurred in half of the four patients, with an OS ranging from 11 to 23 months. No pathogenic mutations were detected. Therefore, no patients were categorized into the POLEmut subtype group.

MSI

MSI-H was observed in five (6.3%) patients. The TMB ranged from 18 to 74 mutations/Mb, with four patients having a TMB ≥ 20 mutations/Mb, whereas the median TMB of the cohort was 3.0 mutations/Mb. As shown in Supplementary Table S1, four patients carried MMR gene mutations. MMR gene mutations were not detected in one patient with synchronous endometrial cancer. However, this patient had MMRd in the pathology report with a loss of MLH1/PMS2 expression. Overall, three patients were diagnosed with synchronous (endometrial or colorectal) or metachronous (endometrial) tumours.

TP53

In our cohort, 14 patients presented with TP53 gene mutations (mutation rate of 17.5%), one of whom was classified into the MSI-H subtype, leading to 16.3% (13/80) of the patients being allocated to the p53abn subtype group.

Others

In line with our previous publication [4], the most common mutated genes were ARID1A (49%) and PIK3CA (48%), accounting for nearly half of the cases. In addition to the aforementioned TP53 mutation, another common gene mutation is ataxia-telangiectasia-mutated (ATM) (11%). ARID1A mutations were significantly different among the three subgroups ($p=0.01$), with all MSI-H patients having ARID1A mutations and the lowest mutation rate being in the p53abn subgroup (27.3%). In one MSI-H patient, simultaneous mutations were observed in three genes: ARID1A, PIK3CA, and TP53. Additionally, in two other patients, mutations were observed either in ARID1A combined with TP53 or in PIK3CA combined

with TP53. Notably, TP53 and ATM mutations did not overlap.

Patient characteristics

The median age of the cohort was 51 years (range: 26–79 years). All 80 patients underwent primary surgery, with 84.2% achieving complete resection (no gross residual disease after surgery). With respect to tumour stage, 54.4% of the patients were classified as FIGO stage I, 15.2% as FIGO stage II, 20.3% as FIGO stage III, and 10.1% as FIGO stage IV. The median follow-up time was 46 months (range, 1–211 months). During the study period, 60.8% and 42.3% of the patients experienced recurrence and death, respectively. Among the recurrences, 63.8% were platinum- sensitive, and 30.0% were platinum-resistant, excluding four patients who did not reach the assessment time.

Based on the selected classification model, five patients were classified as having the MSI-H subtype, 62 as having the NSMP subtype, and 13 as having the p53abn subtype (Fig. 1). As shown in the Sankey diagram (Fig. 2), age, FIGO stage, complete resection rate, platinum sensitivity, recurrence, or mortality rate did not significantly differ by molecular subtype. OCCC patients with MSI-H tumours had the highest rate of platinum sensitivity (80%, 4/5), whereas the overall percentage of patients with platinum sensitivity in the entire cohort was 67.6%. However, the difference was not statistically significant. Table 1 shows the clinicopathological features of the patients in the study cohort.

Survival analyses

Recurrence was more common in the p53abn subgroup (76.9%), whereas it was least common in the MSI-H subgroup (40%), but this difference was not significant. Three patients with MSI-H tumours were progression free at 93, 43, and 101 months after the first diagnosis. Similarly, the death rate was slightly greater in the p53abn subgroup (46.2%) (Table 1).

The Kaplan–Meier curves demonstrated a significant association between PFS and OS in OCCC patients with the following factors: FIGO stage (Fig. 3a, b), residual tumour presence (Fig. 3c, d), and platinum response (Fig. 3e, f), all with p values < 0.01. The TCGA classification did not have a predictive ability for disease recurrence (PFS, $p = 0.278$) or prognosis (OS, $p = 0.917$) in this cohort (Fig. 4a, b). However, as shown in Table 1, the median PFS and OS were not achieved for the five patients with the MSI-H subtype. Patients with the p53abn subtype had worse survival, including both PFS and OS, than their NSMP counterparts did (PFS: 32 months vs. 43 months; OS: 69 months vs. 152 months), although this difference was not significant.

Univariate analysis revealed ATM mutations in FIGO I patients ($p = 0.023$) (Fig. 5a). When we further examined patients with advanced-stage tumours ($n = 24$), we found that patients harbouring TP53 mutations had shorter overall survival ($p = 0.037$) (Fig. 5b) but not progression-free survival ($p = 0.323$).

Discussion

Due to the histological and molecular similarities between OCCC and EC, we aimed to evaluate the potential applicability of the TCGA classification model derived from EC to OCCC. We observed that NSMP was the most prevalent subgroup among OCCC patients, accounting for 77.5% of the cohort, followed by the p53abn class at 16.3%. Tumours classified as MSI-H are relatively rare, comprising 6.3% of OCCC cases. No tumour with a pathogenic POLEmut was identified. Unfortunately, the prognostic significance of this

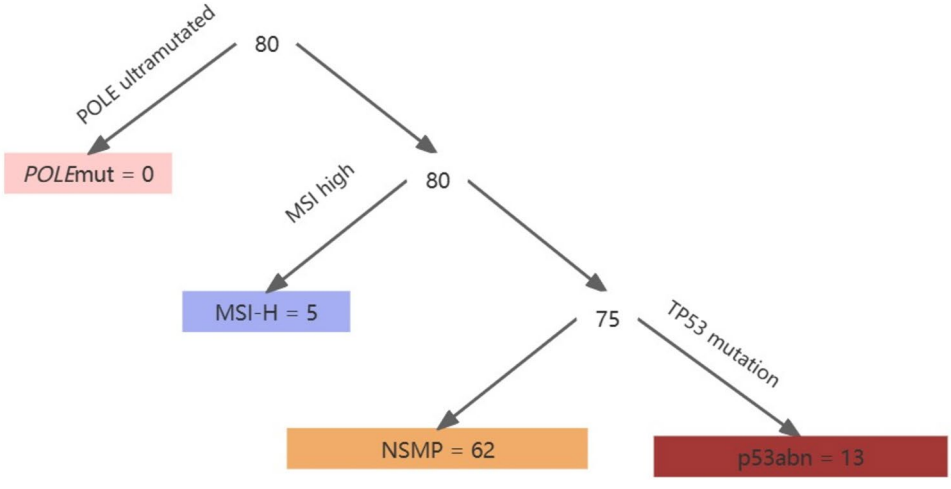

Fig. 1 Molecular classification process

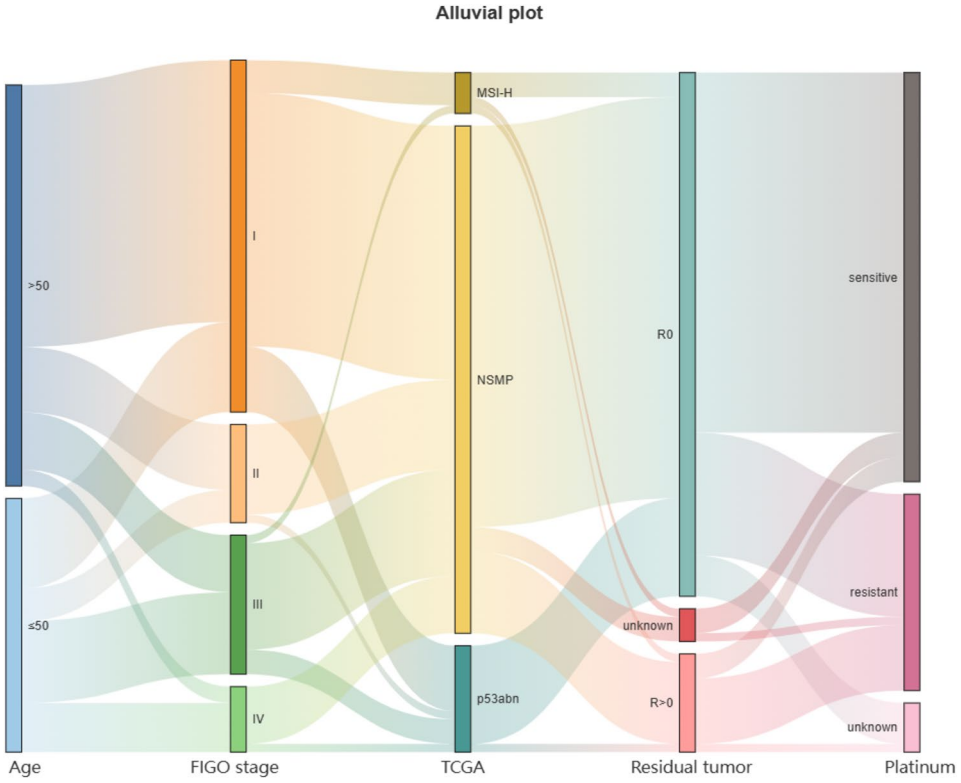

Fig. 2 Alluvial plot showing the distribution of ovarian clear cell carcinoma patients by age, FIGO stage, TCGA classification, residual tumour and response to platinum-based chemotherapy

Table 1 Clinicopathological features of ovarian clear cell carcinoma patients with TCGA classification

	Total	MSI	NSMP	p53abn	*P*
N	80	5(6.3%)	62(77.5%)	13(16.3%)	/
Personal history of cancer (%)	15	60.0	11.3	15.4	0.140*
Endometriosis (%)	30	20	31.5	27.3	0.912*
Age ≥ 50 (%)	61.3	20	62.9	69.2	0.136*
FIGO stage (%)					0.381*
I	54.4	20	55.7	61.5	/
II	15.2	40	14.8	7.7	/
III	20.3	20	19.7	23.1	/
IV	10.1	20	9.8	7.7	/
No residual disease (%)	84.2	100	84.5	76.9	0.253*
Platinum sensitive (%)	68	80	68.4	61.5	0.459*
Recurrence status (%)	57.7	40	55	76.9	0.288*
mPFS(month)	35	NA	43	32	0.247#
Death (%)	39.2	40	37.7	46.2	0.853*
mOS(month)	152	NA	152	69	0.911#
ARID1A mutation (%)	50	100	50	27.3	***0.010****
PIK3CA mutation (%)	47.5	80	50	23.1	0.058*
ATM mutation (%)	11.3	60	9.7	0	***0.003****

[a] *P* values with statistical significance were denoted

* Chi-square or fisher's exact test

Log-rank test

Abbreviations: FIGO, The International Federation of Gynecology and Obstetrics; mPFS, median progression-free survival; mOS, median overall survival

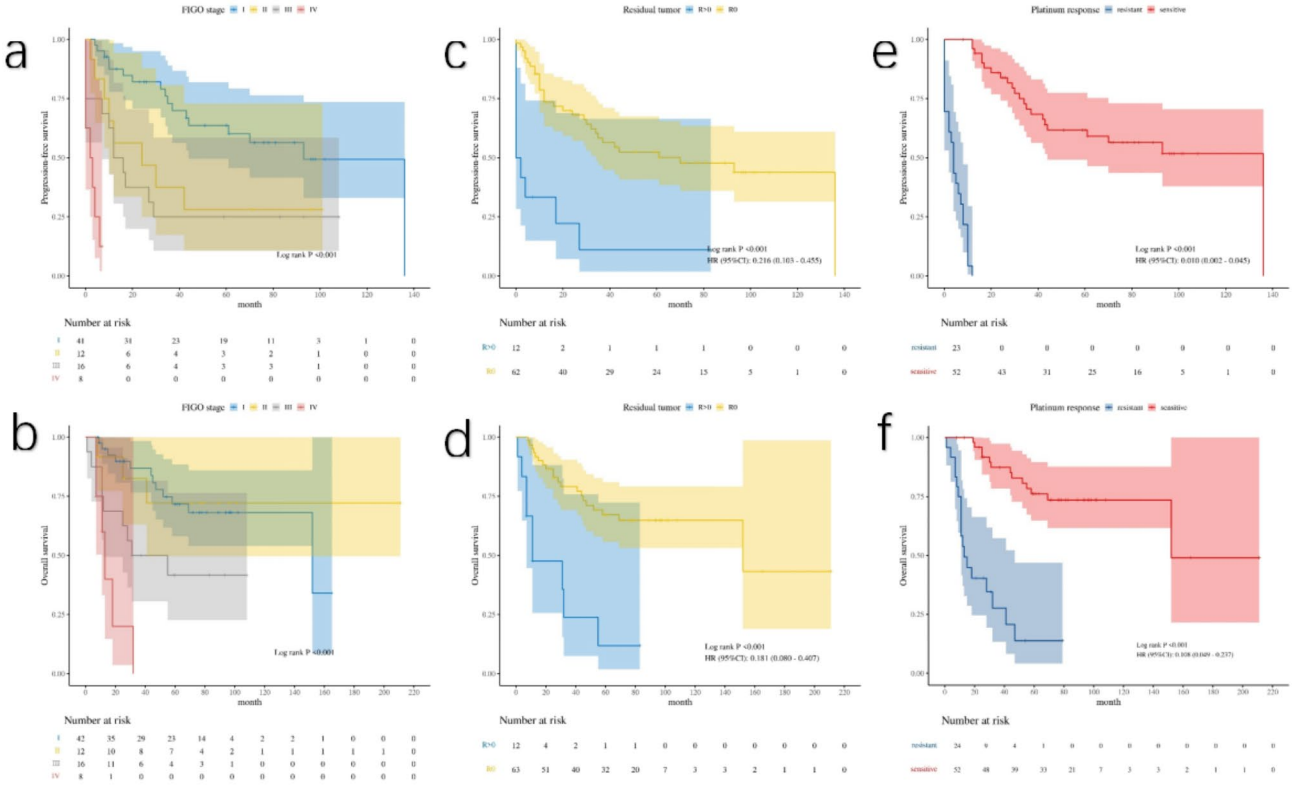

Fig. 3 Kaplan–Meier curves showing overall survival (OS) and progression-free survival (PFS) stratified by FIGO stage (**a**, **b**), residual tumour (**c**, **d**) and response to platinum-based chemotherapy (**e**, **f**). The *p*-values were calculated by the log-rank test. R0 indicates no gross residual disease after surgery

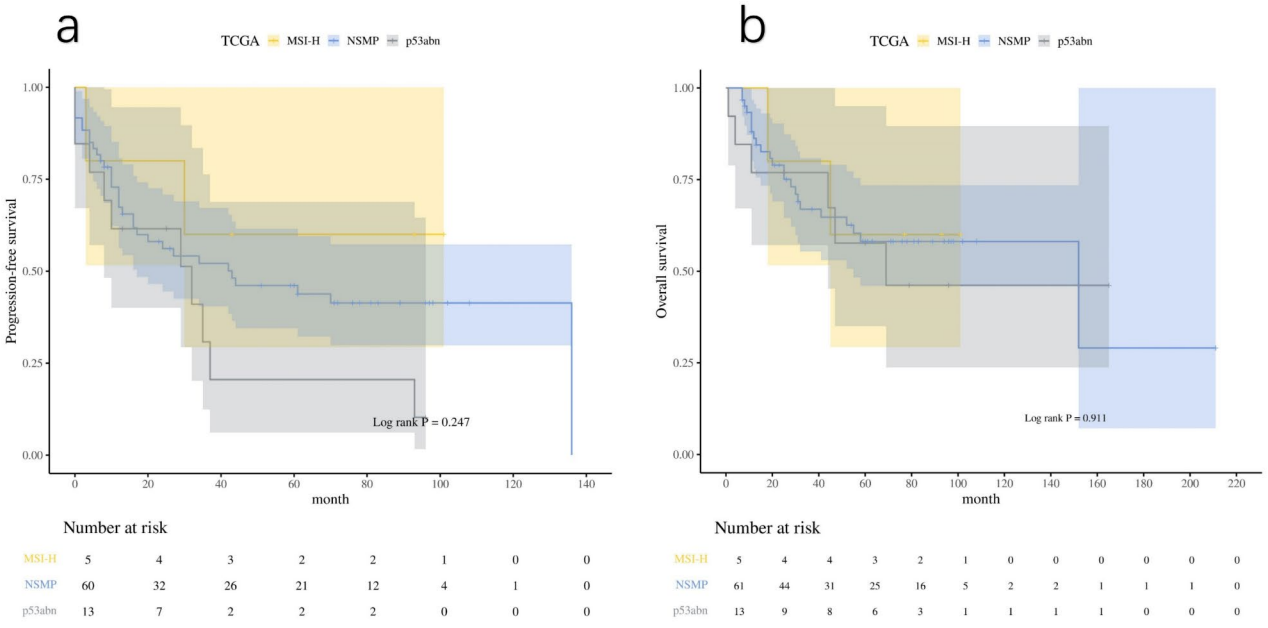

Fig. 4 Kaplan–Meier curves showing OS (**a**) and PFS (**b**) stratified by TCGA classification. The *p*-values were calculated by the log-rank test

molecular classification system for OCCC could not be conclusively established.

To date, the molecular subtypes of OCCC remain largely elusive, although some studies with limited sample sizes have reported prognostic implications for certain classification methods [17, 22, 28–30] (Table 2) or molecular markers [11, 15, 31–37] for OCCC. Most studies of a similar nature have demonstrated that the POLEmut type

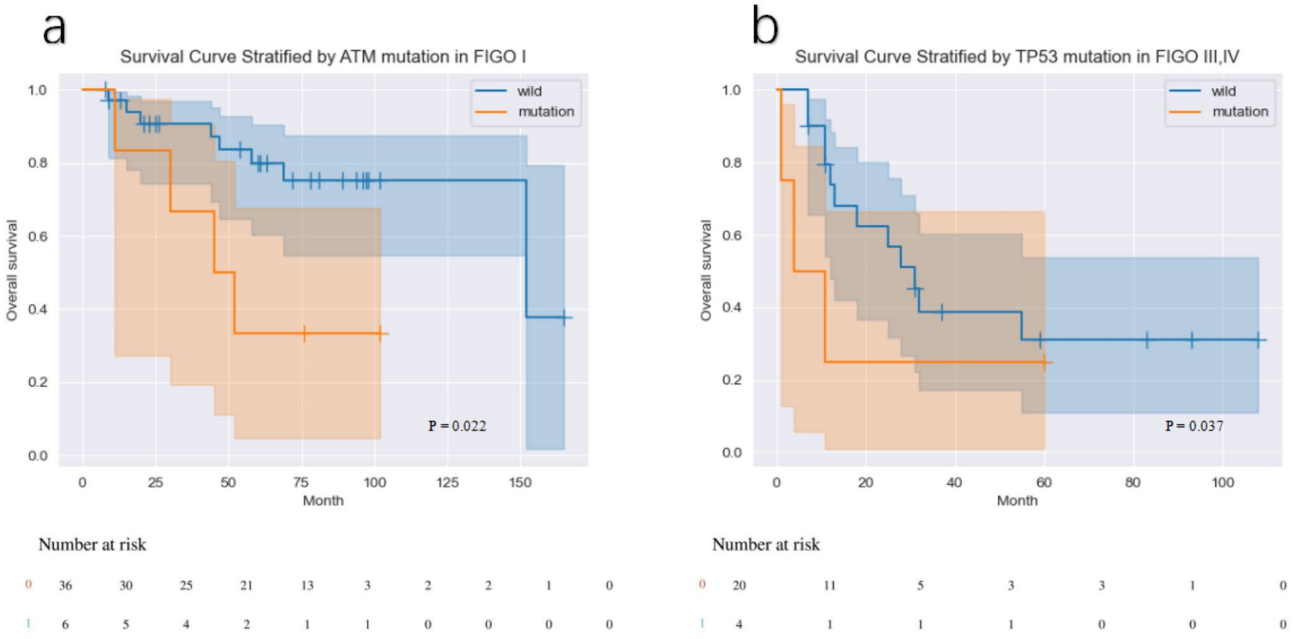

Fig. 5 Kaplan–Meier analysis demonstrated that early-stage (FIGO I) patients with ATM mutations (**a**) and advanced-stage (FIGO III, IV) patients with TP53 mutations (**b**) exhibited worse overall survival

Table 2 A review of studies focusing on molecular classification in ovarian clear cell carcinoma

Author	Year	Method	No. of cases	POLEmut	MSI-H /MMRd	NSMP	p53abn	Others	Result
Carlos Parra-Herran [17]	2019	ProMisE	90	0	2%	91%*	7%	/	P53abn is associated with extrapelvic disease, lymph node metastasis, and recurrence.
Similä-Maarala, J. [22]	2022	ProMisE	115	0.9%	3.5%	76%	20%	/	POLEmut and MMRd OCCCs carried excellent prognosis. The p53abn group was associated with the poorest prognosis.
Liu, H. [28]	2021	NGS	44	0	2.3%	90.9%*	6.8%	/	TP53 mutation was significantly associated with disease-free survival and overall survival.
Irshaid L [29]	2023	NGS	72	2.8%	2.8%	81%	14%	ARID1A (54%), PIK3CA (50%), PTEN (6.9%)	POLE and MSI-H tumors were characterized by an excellent prognosis, and the TP53-mutant subgroup had a worse disease-free survival than NSMP. #
Stružinská I [30]	2023	NGS	113	4%	9%	74%*	13%	ARID1A (51%), PIK3CA (47%), TERTp (27%), KRAS (18%), ATM10(%), PPP2R1A (7%), NF1 (6%), PTEN (6%)	Cases with POLEmut and/or MSI-H had better relapse-free survival.

* This value is estimated by the other three values

The conclusion is targeted towards mullerian clear cell carcinoma rather than OCCC alone

Abbreviations: POLEmut: POLE ultra-mutated; MSI-H: Microsatellite Instability-High; MMRd: Mismatch repair deficiency; NSMP: Non-specific molecular profile; p53abn: p53 abnormal; NGS: Next-Generation Sequencing; ProMisE: Proactive Molecular Risk Classifier for Endometrial Cancer; OCCC: Ovarian clear cell carcinoma

is extremely rare in OCCC [17, 22, 28]. In our research cohort, we also did not identify any OCCC cases with hotspot mutations in POLE, although two patients harboured mutations classified as benign and VUSs. Eleven POLE exonuclease domain mutations, including P286R and V411L, have been identified in EC, eliciting ultra-mutation phenotypes and inert clinical behaviour [18]. However, the biological and clinical significance of other

nonhotspot mutations remain unclear. Similarly, in OCCC, more research and data are needed to determine whether these variations affect the occurrence and development of the disease.

Mismatch repair deficiency, which leads to the accumulation of genomic mutations and microsatellite instability in tumours [38], has emerged as a biomarker indicative of heightened sensitivity to immune checkpoint blockade [39]. The potential clinical significance of the MMRd in OCCC has been evaluated in the literature. A consensus has not been reached due to the rarity of the disease and the low frequency of MMR abnormalities [22, 30, 37]. In our previous work using immunohistochemistry, MMRd accounted for 5.6% of OCCC cases [11]. MMRd patients experienced improved progression-free survival across all patients analysed, but this effect diminished when focusing solely on the early-stage group. In the present study, we reassessed the MSI status of OCCC patients using NGS. No significant associations were found between MSI status and variables such as age, stage, or response to platinum-based treatments. Moreover, MSI-H did not significantly correlate with recurrence/progression or overall survival. Notably, 60% of patients with MSI-H tumours achieved disease-free survival beyond 5 years, indicating a relatively favourable prognosis. However, due to the small number of cases, the results should be interpreted with caution. NGS methods are more sensitive and specific for the detection of MSI than IHC and PCR [40]. However, the spectrum of microsatellite sites may vary by tumour type, and different sites may preferentially mutate in different tumours. Existing studies have focused mostly on unstable sites in gastric cancer, colorectal cancer, and EC [41, 42] but have yet to identify MSI sites with sufficient sensitivity and specificity for ovarian cancer.

Previous studies using p53 immunostaining as a surrogate for high copy number have reported that abnormal p53 expression ranging from 0 to 34% is associated with recurrence and shorter overall survival [17, 22, 31, 36, 37]. In our cohort, a TP53 gene mutation rate of 17.5% (14/80) was observed, which is consistent with previous studies that have reported a range from 6 to 20% [15, 28–30]. Most studies indicate an association between abnormal p53 status and shorter disease-specific survival, even within subgroups of stage I and I/II OCCC patients [22, 36, 43, 44]. According to these studies, p53 abnormalities are significantly correlated with more advanced disease stages [15]. Notably, in our cohort, 54.4% of patients had stage I disease, and among those with the TP53 subtype, 61.4% had stage I disease, which is greater than the overall percentage. In the overall population, we did not observe any impact of TP53 mutations on disease stage, recurrence, or survival. However, in late-stage patients, univariate analysis suggested that TP53 mutations are a negative prognostic factor for overall survival. The differences in the results could stem from variations in the distribution of patients across the different cohorts studied. Like our study, Irshaid et al. utilized NGS in their research [29]. They conducted targeted sequencing on 72 samples and reported no significant associations between TCGA subtypes and overall survival in OCCC patients.

NSMP was the most common subgroup in our OCCC cohort, accounting for 77.5% of the cases, which is consistent with the literature [22, 29]. Demographic characteristics, disease stage distribution, or other common genetic mutations did not significantly differ between this subgroup and the overall population. Colleagues from Memorial Sloan Kettering Cancer Centre identified a total of 472 NSMP endometrial cancer cases [45]. Somatic mutation and copy number alteration were subjected to unsupervised hierarchical clustering. Three genomic clusters were ultimately identified via random sampling, with 80 cases in each cluster. The three clusters presented different gene alterations and were associated with different clinicopathological features, such as grade, stage and ER/PR expression. These findings suggest that the potential molecular drivers of NSMP OCCCs remain unidentified, and more data are needed to better characterize this subgroup. We examined a total of 80 patients, including 62 NSMP OCCC patients. Due to the limited sample size, we were unable to further subclassify the NSMP group based on other genetic alterations. The accumulation of additional published data may facilitate the categorization of the NSMP group into distinct molecular subtypes.

This study was subject to several limitations. First, the rarity of the disease resulted in a small sample size for this study; thus, some differences did not reach statistical significance. This lack of significance underscores the need for larger cohorts to comprehensively validate the research findings. Second, the cohort might be constrained by selection and surveillance biases typically associated with studies conducted at a single institution. Finally, this study did not assess specific treatment regimens, potentially serving as a confounding factor in survival outcomes.

Conclusion

The present study investigated the prognostic significance of molecular subtyping in ovarian clear cell carcinoma using TCGA data. POLEmuts are extremely rare, and the incidence of MSI-H and p53abn tumours is also quite low. ATM mutations in early-stage patients and TP53 mutations in advanced-stage patients are potential predictors of poor survival. Further subtyping of the NSMP subgroup is warranted. More multicentre studies are needed to provide insights for clinical management.

Abbreviations

OCCC	Ovarian clear cell carcinoma
HGSC	High-grade serous carcinoma
MMRd	Mismatch repair deficiency
PFS	Progression-free survival
EC	Endometrial cancer
TCGA	The Cancer Genome Atlas
FIGO	International Federation of Gynaecology and Obstetrics
OS	Overall survival
FFPE	Formalin-fixed paraffin-embedded
PCR	Polymerase chain reaction
TMB	Tumor mutation burden
MSI	Microsatellite instability
WHO	World Health Organization
POLEmut	POLE ultra mutated
MSI-H	Microsatellite instability high
MMRd	Mismatch repair deficiency
NSMP	Nonspecific molecular profile
p53abn	p53 abnormal
SPSS	Statistical Package for Social Science
VUS	Variants of uncertain significance
ATM	Ataxia-telangiectasia-mutated gene

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12885-024-13389-x.

Supplementary Material 1

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Not applicable.

Author contributions
All the authors were involved in the study design. SY, QL, SZ and TH carried out the experiments. SY, WC, LY, QL and SZ conceived the experiments and analyzed the data. LY, SY, TH and HY interpreted the data. WC, LY, HY and SY searched the literature. SY and WC were involved in generating the figures. WC, LY, SY and HY were involved in drafting and writing the paper and all authors reviewed and revised the manuscript. All authors provided final approval for the submitted and published versions of the manuscript.

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Data availability
The variation data reported in this paper have been deposited in the Genome Variation Map (GVM) [46] in National Genomics Data Center, Beijing Institute of Genomics, Chinese Academy of Sciences and China National Center for Bioinformation [47], under accession number GVM000847. The dataset supporting the conclusions of this article is available upon request. Please contact Dr. Shuang Ye (mendy_ye@126.com).

Declarations

Ethics approval and consent to participate
The study was conducted in accordance with the Declaration of Helsinki, and approved by the Institutional Review Board of Fudan University Shanghai Cancer Center (050432-4-1212B). Informed consent was obtained from all subjects involved in the study.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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