Comparative Analysis of Gene Expression Profiles in Ovarian Clear Cell Carcinoma and High-Grade Serous Ovarian Cancer

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ABSTRACT

Objective: To evaluate disparities in gene expression profiles between Ovarian Clear Cell Carcinoma (OCCC) and High-Grade Serous Ovarian Carcinoma (HGSOC).

Study Design: A descriptive study.

Place and Duration of the Study: The Second People's Hospital of Jingdezhen, Jiangxi, China, between 31st December 2017 and December 2023.

Methodology: Basic and clinical diagnostic information, along with genetic test reports, were compiled from all patients within the included groups. Differential gene expression between the two cohorts was scrutinised to elucidate its clinical significance.

Results: Comparative analysis revealed nine differentially expressed genes in OCCC relative to HGSOC, with six exhibiting significant disparities ($p < 0.05$). These genes are implicated in pivotal cellular processes including the cell cycle, apoptosis, DNA damage repair, and the *PI3K* pathway. Notably, aberrant expression patterns, such as overexpression of *MET* and downregulation of *PTEN* and *SMARCA4*, correlated with adverse prognosis and survival outcomes in selected patients.

Conclusion: Distinctive gene expression profiles between OCCC and HGSOC underscore disparate tumorigenic mechanisms, thereby laying a foundation for the tailored therapeutic interventions. Further elucidation of the identified differentially expressed genes is warranted to delineate their role in OCCC pathogenesis and prognostic significance.

Key Words: *Ovarian clear cell carcinoma, High-grade serous ovarian cancer, Gene expression profiles, Homologous recombination repair.*

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INTRODUCTION

Epithelial ovarian carcinoma (EOC) represents the most lethal gynaecological malignancy, characterised by heterogeneous histological subtypes, each bearing unique molecular signatures and clinical behaviours.[1] Among these subtypes, high-grade serous ovarian carcinoma (HGSOC) and ovarian clear cell carcinoma (OCCC) predominate, comprising 71.3% and 10.8% of EOC cases, respectively.[2,3] OCCC poses a particularly formidable challenge as it commonly exhibits resistance to platinum-based chemotherapy and confers a poorer prognosis compared to HGSOC. Moreover, OCCC demonstrates marked racial diversity, with Asians exhibiting a higher prevalence of OCCC compared to other ethnic groups.[4]

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Despite advancements in understanding ovarian carcinogenesis, the molecular underpinnings and mechanisms of chemotherapy resistance in OCCC remain incompletely elucidated. Nonetheless, extensive investigations have revealed distinct genetic alterations in OCCC compared to HGSOC. Notably, OCCC is frequently devoid of *TP53* mutations and exhibits a lower incidence of mutations in *breast cancer susceptibility genes 1/2* (*BRCA1/2*), which are commonly observed in HGSOC.[5,6] Conversely, mutations in *AT-rich interaction domain 1A* (*ARID1A*) and *phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha* (*PI3KCA*) are prevalent in OCCC.[7,8]

Given the imperative to unravel the molecular basis of OCCC pathogenesis and devise effective therapeutic strategies, there is a pressing need to identify novel tumour markers of chemotherapy resistance and therapeutic targets. Accordingly, this study aims to comprehensively characterise genes associated with poly ADP-ribose polymerase (PARP) inhibitors, DNA damage repair pathways, targeted therapies, prognosis, drug-resistance, immunotherapy, and chemotherapy in patients with OCCC and HGSOC. By elucidating changes in gene expression profiles and their correlation with clinical outcomes, this investigation endeavours to provide critical insights into the management of these chal-

lenging malignancies. The aim of this study was to compare the gene expression in OCCC and HGSOC.

METHODOLOGY

In this descriptive study, the genetic test reports were sourced from OCCC and HGSOC patients treated at the Gynaecology Department of the Second People's Hospital of Jingdezhen, between 31st December 2017 and 2023. Specifically, two clinicians independently logged into the Hospital Information System, searched for OCCC and HGSOC cases, set the age range, and reviewed the complete records of each patient. Patients who met the inclusion criteria were subsequently enroled in the study. Prior to participation, all patients provided informed consent for inclusion in the experimental protocol and gene sequencing analysis. Ethical approval for the study was obtained from the Medical Ethics Committee of the Second People's Hospital of Jingdezhen.

A total of 60 patients diagnosed with OCCC (n=30) and HGSOC (n=30) were included, all of whom had undergone surgical resection and received pathological confirmation. The classification of tumour subtypes was meticulously evaluated and validated by multiple pathologists at the institution. Optimal cytoreduction was defined as the absence of visible residual lesions upon completion of cytoreductive surgery. Patients with incomplete data or no genetic testing were not included in the cohort.

All included patients had a comprehensive follow-up evaluation, typically quarterly, during the initial three years post-treatment and semiannually thereafter. The clinicopathological characteristics of the study cohort, encompassing age, International Federation of Obstetrics and Gynaecology (FIGO) staging, treatment modalities, recurrence patterns, and progression-free survival (PFS).

Specimen testing for all patients followed the specifications outlined by 3D Medicines, which had specifically required histological specimens with an effective area greater than 1.5 × 1.5 cm^2, including approximately five paraffin rolls with a thickness of approximately 10μm. For biopsy specimens, the number of wax rolls had been adjusted according to the tissue area. Additionally, 3 mL of venous blood had been collected as a paired sample, and single nucleotide polymorphisms (SNPs) had been used to assess the consistency between the paired samples.

In the part of gene sequencing, it was outsourced to Shanghai Sidi Precision Medicine (3D Medicines), entailing comprehensive detection of genes associated with PARP inhibitors, DNA damage repair pathways, targeted therapies, prognosis, drug-resistance, immunotherapy, and chemotherapy. Detection parameters included *BRCA1/2* mutations, homologous recombination deficiency (HRD) scores, DNA damage repair pathway-related genes, clinically relevant somatic and germline variants, mismatch repair-related genes, microsatellite analysis, and chemotherapy-related markers. Experimental procedures encompassed DNA / RNA extraction, DNA probe design, molecular hybridisation, elution, and purification of hybridisation products, sample plate preparation, quantitative real-time PCR (qRT-PCR), and result output.

In the part of gene comparison and bioinformatics analysis, following gene sequencing, the hs37d5 version of the thousand genome database served as the reference genome, with sequencing data analysed using BWA to identify single data sequences on the genome. Subsequent analysis involved evaluating the uniformity of single-base depth distribution and coverage in the target region. Base quality recalibration was performed using the Genome Analysis Toolkit to enhance accuracy. Mutation databases referenced include TCGA, COSMIC, 1,000 Genomes, and dbSNP.

In the part of statistical analysis, it was conducted using SPSS 26.0. Firstly, the normality of all data was assessed using the Kolmogorov-Smirnov test. Descriptive statistics were presented as mean ± standard deviation or median ± interquartile range, depending on the data distribution. Based on the normality of the data, continuous variables were compared using either an Independent t-test or the Mann-Whitney U test. Categorical variables were expressed as numbers and percentages and were compared using the Chi-square test or Fisher's exact test. Group differences were evaluated using Log-Rank statistics, with data expressed as mean ± standard deviation. A significance threshold of $p < 0.05$ denoted statistical significance.

RESULTS

In this study, the results of the baseline characteristics (age, FIGO stage, chemotherapy regimen, recurrence, PFS, and overall survival) indicated no significant differences between the two groups (Table I).

Also, frameshift mutations resulting from base insertions in the *BRCA1* gene were observed in OCCC patients, indicative of pathogenic variants. Conversely, in HGSOC, mutations in both *BRCA1* and *BRCA2* genes were more prevalent, predominantly characterised by amino acid changes caused by base substitutions, leading to structural alterations or premature protein synthesis termination. The majority of these mutations were classified as pathogenic (Table II).

Table I: Clinical characteristics of sixty patients with OCCC and HGSOC.

Clinical features	OCCC (n = 30)	HGSOC (n = 30)	t/χ^2	p-value
Age (years)	56.1 ± 7.4	45.5 ± 6.5	5.893	< 0.001
FIGO (I / II)	5 (16.7%)	13 (43.3%)	5.079	0.024
FIGO (III / IV)	25 (83.3%)	17 (56.7%)		
Treatment plan	TP	TP	/	/
Recurrence (Yes)	16 (53.3%)	20 (66.7%)	1.111	0.292
Recurrence (No)	14 (46.7%)	10 (33.3%)		
PFS of FIGO I/II (months)	25.0 ± 4.8	26.5 ± 4.4	0.618	0.545
PFS of FIGO III/IV (months)	19.3 ± 4.9	22.6 ± 4.0	2.269	0.029
Survival (Yes)	20 (66.7%)	25 (83.3%)	2.222	0.136
Survival (No)	10 (33.3%)	5 (16.7%)		

OCCC, Ovarian clear cell carcinoma; HGSOC, High-grade serous ovarian cancer; FIGO, Federation International of Gynaecology and Obstetrics; TP; Paclitaxel plus cisplatin; PFS, Progression-free survival.

Table II: *BRCA1/2* gene mutation information in patients with OCCC and HGSOC.

Tumour	Gene	NM No.	Nucleotide	Amino acid	Clinical significance
OCCC	*BRCA1*	NM_007300.3	c.1017_1018insA	p.*Val*340*Argfs*	Pathogenic
	BRCA1	NM_007300.3	c.1421T>G	p.*Leu*474*UGA*	Pathogenic
	BRCA1	NM_007300.3	c.3841C>G	p.*Gln*1281*Glu*	Pathogenic
	BRCA1	NM_007300.3	c.5228C>A	p.*Ser*1743*Tyr*	Likely Pathogenic
	BRCA1	NM_007300.3	c.900A>C	p.*Glu*300*Asp*	Unspecified
HGSOC	*BRCA1*	NM_007300.3	c.4675C>T	p.*Gln*1559*UAG*	Pathogenic
	BRCA1	NM_007300.3	c.2800C>T	p.*Gln*2972*UAG*	Pathogenic
	BRCA2	NM_000059.3	c.2918C>T	p.*Ser*973*Leu*	Unspecified
	BRCA2	NM_000059.3	c.1253C>A	p.*Glu*418*Lys*	Pathogenic
	BRCA2	NM_000059.3	c.7708A>G	p.*Lys*2570*Glu*	Pathogenic

OCCC, Ovarian clear cell carcinoma; HGSOC, High-grade serous ovarian cancer; BRCA1/2, Breast cancer susceptibility genes 1/2.

Table III: The immunotherapy-related gene expression in OCCC and HGSOC.

Gene name	OCCC		HGSOC	
	Up	Down	Up	Down
MLH1	2 (C5, C20)	/	1 (S26)	/
PMSH2	/	/	/	5 (S7, S13, S18, S19, S29)
MSH6	/	/	/	1(S3)
MLH3	1 (C25)	/	2 (S15, S20)	/
POLD1	1 (C14)	/	2 (S3, S18)	/

OCCC, Ovarian clear cell carcinoma; HGSOC, High-grade serous ovarian cancer; Up, Upregulation; Down, Downregulation.

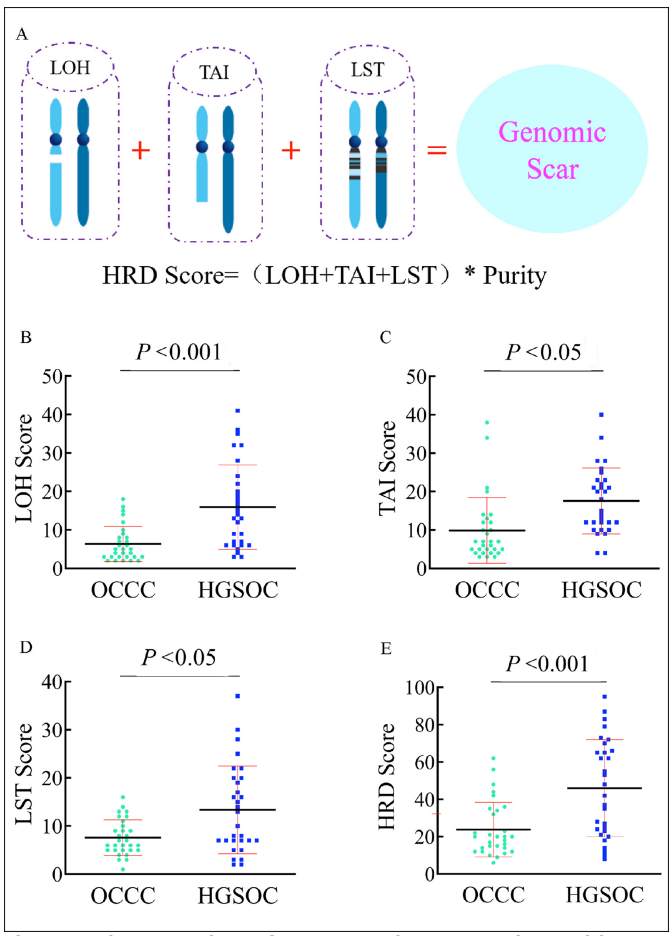

Figure 1: The comparison of HRD scores between patients with OCCC and HGSOC. (A) The calculation formula of HRD score. Purity means the purity of tumour. (B-E) The comparison of LOH, TAI, LST, and HRD scores between patients with OCCC and HGSOC.

OCCC, Ovarian clear cell carcinoma; HGSOC, High-grade serous ovarian cancer. LOH, Loss of heterozygosity; TAI, Telomeric allelic imbalances; LST; Large-scale state transitions; HRD, Homologous recombination deficiency. Data from the B-E were tested by unpaired-samples t-test.

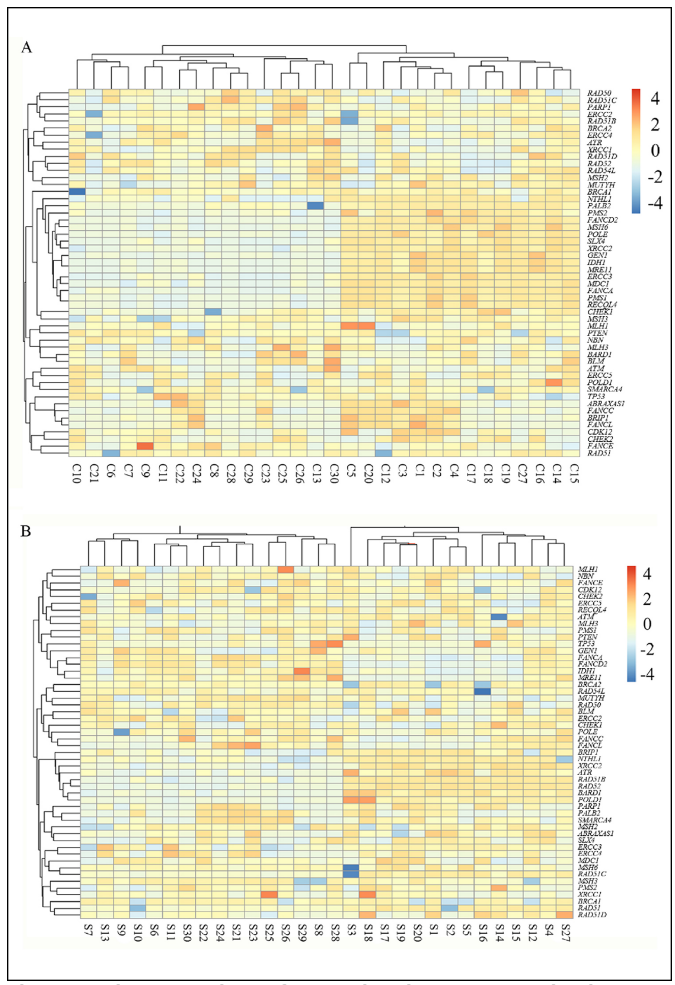

Figure 2: The comparison of HRR-related gene expression between patients with OCCC and HGSOC. (A) HRR-related gene expression of patients with OCCC. (B) HRR-related gene expression of patients with HGSOC.

OCCC, Ovarian clear cell carcinoma; HGSOC, High-grade serous ovarian cancer. C1-C30, the 30 patients of OCCC; S1-S30, the 30 patients of HGSOC. HRR, Homologous recombination repair.

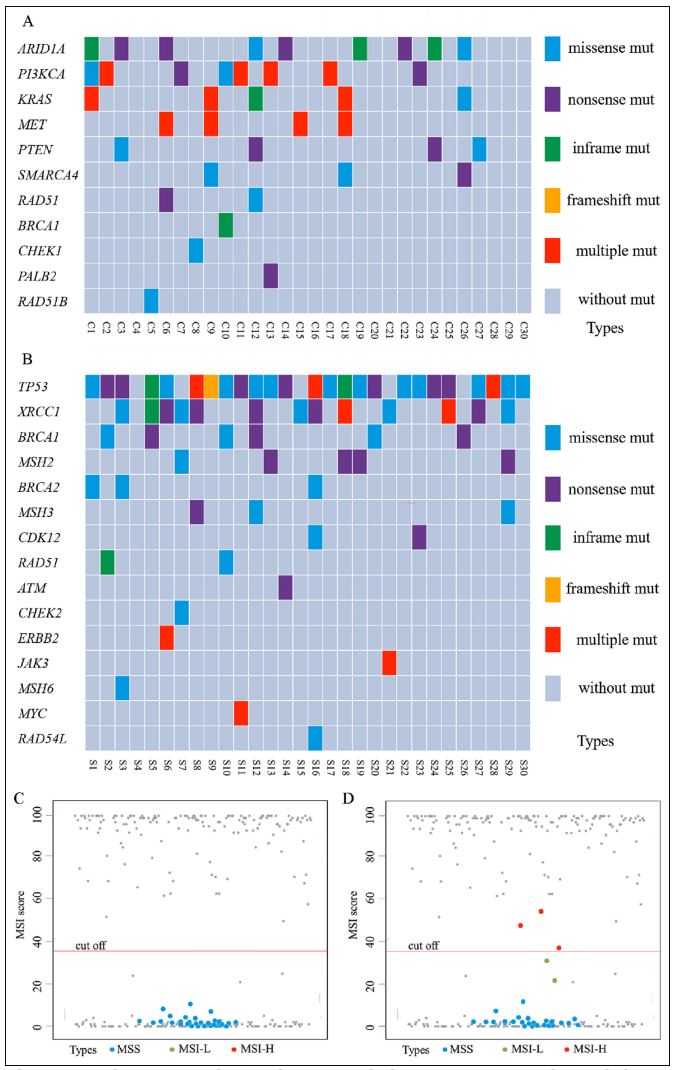

Figure 3: The comparison of targeted therapy, prognosis and drug-resistance related gene expression, microsatellite analysis between the patients with OCCC and HGSOC. (A) The different types of targeted therapy, prognosis and drug-resistance related gene expression of patients with OCCC. (B) The different types of targeted therapy, prognosis and drug-resistance related gene expression of patients with HGSOC. (C) Microsatellite analysis results of patients with OCCC. (D) Microsatellite analysis results of patients with HGSOC.

OCCC, Ovarian clear cell carcinoma; HGSOC, High-grade serous ovarian cancer. C1-C30, the 30 patients of OCCC; S1-S30, the 30 patients of HGSOC. MSS, Microsatellite stability; MSI-L, Low-frequency microsatellite instability, MSI-H, High-frequency microsatellite instability.

Two key outcomes were assessed: HRD status and HRD score. The HRD score was calculated as the sum of three components: Loss of heterozygosity (LOH) score, telomeric allelic imbalances (TAI), and large-scale state transitions (LST), with a requisite tumour cell content of at least 20% (Figure 1A). This study revealed notable discrepancies in both total HRD scores (Figure 1B) and individual component scores (LOH, TAI, and LST, Figure 1C-E) between patients with OCCC and those with HGSOC. Importantly, the positive rate of HRD score among OCCC patients was lower compared to HGSOC patients.

Homologous recombination repair (HRR) serves as a crucial mechanism for rectifying DNA double-strand damage, involving intricate signalling pathways primarily mediated by key proteins such as *BRCA1* and *BRCA2*. In this investigation, OCCC patients exhibited downregulation of *PTEN*, *SMARCA4*, and *ERCC2* genes (Figure 2A). Conversely, in HGSOC patients, downregulation of *BRCA1/2*, *TP53*, *MSH2*, *MSH3*, and *XRCC1* genes was observed (Figure 2B).

Upon scrutinising pertinent targeted and drug-resistant genes within OCCC and HGSOC patient cohorts, it was evident that there was an elevation in the expression levels of *ARID1A*, *PI3KCA*, and *KRAS* genes. Furthermore, within a subset of OCCC patients, a notable upregulation of the *MET* gene accompanied by downregulation of *PTEN* and *SMARCA4* genes was observed (Figure 3A). Conversely, in the realm of HGSOC, amidst the frequently reported alterations in *TP53*, *XRCC1*, and *BRCA1/2* genes, distinct patterns of differential expression emerged for *ATM*, *CHEK2*, *JAK3*, *MSH2*, *MSH3*, and *MSH6* genes (Figure 3B), thereby emphasising the intricate and varied genetic landscape that characterises HGSOC patients in comparison to those with OCCC.

Microsatellite analysis conducted in this study among patients with OCCC and HGSOC revealed microsatellite stability (MSS) in OCCC patients (Figure 3C) and HGSOC patients (Figure 3D). Notably, among HGSOC patients, three exhibited high-frequency microsatellite instability (MSI-H), while two displayed low-frequency MSI (MSI-L). Importantly, all five of these patients exhibited differential expression of the *MSH2* gene. Thus, adjusting treatment strategies in subsequent chemotherapy and immunotherapy regimens based on these findings is imperative to provide tailored therapeutic modalities aimed at enhancing patient prognoses and survival outcomes.

Evaluation of mismatch repair genes in patients with OCCC and HGSOC revealed upregulation of *MLH1*, *MLH3*, and *POLD1* genes in OCCC patients. Conversely, in *HGSOC* patients, besides the upregulation of *MLH1*, *MLH3*, and *POLD1* genes, downregulation of *MSH2* and *MSH6* genes was observed (Table III). These findings suggest the poten-tial utility of adjunctive immunotherapy alongside chemo-therapy or targeted therapy regimens to enhance patient prognoses.

DISCUSSION

Currently, OCCC and HGSOC are managed clinically with similar treatment regimens. However, substantial differences in prog-nosis exist between these two ovarian cancer subtypes due to their distinct origins.[9] Hence, directing research efforts and treatment strategies toward the differential gene expression profiles of these cancers represents a promising avenue for achieving improved clinical outcomes. Given the poor

prognosis and chemotherapy resistance observed in OCCC patients, efficacy monitoring and genomic profiling are imperative in clinical diagnosis and treatment. Genetic diagnosis and targeted therapy offer invaluable insights for guiding treatment decisions in these patients.

In line with existing literature, these findings underscore the prevalence of somatic mutations in key genes among OCCC patients, including *PI3KCA*, *ARID1A*, and *KRAS*.[7,8] This study corroborates previous reports demonstrating the involvement of these genes in OCCC pathogenesis. Additionally, differential gene expression analyses revealed dysregulation in various cancer-related pathways, encompassing cell cycle regulation, apoptosis, chromatin modification, and signalling cascades such as the PI3K/AKT/ mTOR pathway and MET pathway.[10,11]

PI3KCA mutations, identified in approximately 40% of OCCC cases in previous studies,[12] were detected in 26.7% of this cohort. The PI3K pathway plays a pivotal role in tumorigenesis, influencing cell proliferation, survival, and invasion. Aberrant PI3K signalling is associated with disease progression and aggressiveness, making it an attractive therapeutic target.[13] Several PI3K inhibitors have received FDA approval, although none are currently available in China, indicating a gap in treatment options that necessitates further research and development efforts.

The PI3K/AKT/mTOR pathway exerts crucial functions in normal cellular processes, such as growth, motility, metabolism, and angiogenesis, while dysregulation drives malignant transformation, proliferation, and metastasis in various cancers. Overactivation of PI3K/AKT/mTOR pathway not only facilitates tumorigenesis but also fosters drug resistance, making it an attractive therapeutic target across diverse human malignancies.[14] Various inhibitors targeting different components of the PI3K/AKT/mTOR pathway, including PI3K inhibitors, AKT inhibitors, mTORC1 inhibitors, and the dual inhibitor BEZ235, offer promising treatment avenues for OCCC patients facing poor prognosis.[15]

PARP inhibitors represent a cornerstone in the targeted therapy arsenal for the ovarian cancer, particularly in high-grade serous ovarian cancer. By interfering with DNA single-strand break repair, PARP inhibitors induce tumour cell apoptosis. Inhibition of the PARP pathway exacerbates DNA damage, leading to double-strand breaks that are lethal in cells with homologous HRD, such as those with BRCA1/2 mutations. OCCC patients, despite exhibiting low *BRCA1/2* mutation rates, may still benefit from PARP inhibitors through HRD assessment.[15-17] Combining PARP inhibitors with PI3K inhibitors offers synergistic benefits, particularly in patients lacking *BRCA1/2* mutations, thereby broadening the therapeutic scope for OCCC management.[16]

In tumour cells, *MET* can undergo ligand-independent activation through mutation, amplification, or overexpression of the *MET* gene. The *MET* signalling pathway orchestrates various tumorigenic processes, including proliferation, apoptotic evasion, angiogenesis, and motility, and reports of patients harbouring these genetic mutations have emerged both regionally, notably in Pakistan, and on a global scale.[18-20] Given the significant chemotherapy resistance and dismal prognosis observed in OCCC compared to other ovarian cancer subtypes, targeting c-MET emerges as a promising therapeutic strategy. Inhibition of c-MET using a c-MET inhibitor such as crizotinib, markedly suppresses OCCC tumour cell proliferation and promotes apoptosis.[21] Moreover, preclinical studies demonstrate the efficacy of c-MET inhibitors in reducing tumour burden in OCCC xenotransplantation models. Considering the high frequency and specificity of *MET* gene alterations in OCCC, targeting *MET* overexpression holds promise as an alternative therapy option.

Additionally, mutations in the *human epidermal growth factor receptor 2* (*HER2*) gene and *KRAS* gene have been identified in OCCC patients.[22,23] Overexpression of *HER2* is associated with poor sensitivity to conventional anticancer drugs in various cancers, including ovarian and breast cancer.[24] Notably, *KRAS* mutations have been linked to highly differentiated and mucinous ovarian cancers, with implications for prognosis.[25] Activation of the RTK/Ras signalling pathway, observed in approximately 15% of OCCC tumour samples, suggests its potential as a prognostic biomarker and therapeutic target. Further studies are warranted to elucidate the prognostic significance and therapeutic implications of RAS pathway activation in OCCC.

In contrast to HGSOC, OCCC exhibits a narrower range of molecular targets. A distinctive gene expression analysis of these ovarian cancer subtypes revealed differential expression of *ARID1A*, *PI3KCA*, *KRAS*, *PTEN*, *MET*, and *SMARCA4* genes in OCCC patients, hinting at their potential roles in tumorigenesis and progression. However, due to the limited follow-up, the full impact on prognosis remains unclear. Nevertheless, these genes emerge as promising biomarkers and therapeutic targets for OCCC.

Further functional exploration and comprehensive gene analyses are crucial to deepen one's understanding of OCCC pathogenesis and pioneer targeted therapeutic approaches. Acknowledging limitations, such as short follow-up, data derived from targeted rather than whole-exome sequencing, and a relatively small, advanced-stage sample, caution is advised in interpreting these findings.

Despite these constraints, this study illuminates gene expression disparities between OCCC and HGSOC, offering genetic insights pivotal for personalised medicine and targeted drug development. It also lays a foundation for future clinical trials exploring targeted therapies for OCCC.

CONCLUSION

The delineation of gene expression profiles among differentially expressed genes in OCCC and HGSOC enhances the understanding of the nuanced mechanisms underlying tumour initiation and progression. However, further longitudinal follow-up and experimental validation are imperative to establish the association between differentially expressed genes and sub-optimal prognosis in OCCC, ultimately facilitating the development of early diagnostic tools and innovative therapeutic interventions for OCCC.

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ETHICAL APPROVAL:
The ethical approval for this study was obtained from the Medical Ethics Committee of the Second People's Hospital of Jingdezhen.

PATIENTS' CONSENT:
All patients provided informed consent for inclusion in the experimental protocol and gene sequencing analysis before participation.

COMPETING INTEREST:
The authors declared no conflict of interest.

AUTHORS' CONTRIBUTION:
CY, GH: Drafting of the work.
XZ, WD: Acquisition, analysis, and interpretation of the data.
KH: Critically revision of the work for important intellectual content.
MF: Substantial contributions to the conception of the work and final approval of the version to be published.
All authors approved the final version of the manuscript to be published.

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