Mutational profiles of ovarian cancer in Chinese patients reveal potential therapeutic targets and prognostic markers

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Research Article

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Abstract

Background: Ovarian cancer (OC) is a common and lethal gynaecologic malignancy. The prognosis of OC is variable among different patients treated with standard of care therapies. Herein, we described the mutational profiles of OC to identify underlying therapeutic targets and prognostic markers.

Methods: The study was performed on 38 Chinese patients with high-grade serous ovarian cancer (HGSOC). Most patients (86.8%) had advanced disease (stage III-IV). Tissue samples were subjected to capture-based targeted sequencing using a panel consisting of 520 cancer-related genes. Mutational profiles, including gene mutations and copy number variations (CNVs), were evaluated in each patient. Homologous recombination deficiency (HRD) status was also assessed. Analysis of the mutational profile with platinum-sensitivity, progression-free survival (PFS) and platinum-free interval (PFI) was performed.

Results: Germline BRCA1 and BRCA2 mutations were identified in 5 (13%) and 2 (5%) patients, respectively. Somatic genetic alterations were mainly identified in *TP53* (97%), *BRCA1* (24%), *RB1* (21%), *FGF23* (21%), *CCND2* (18%), *RECQL4* (18%) and *NF1* (16%). CNVs were comprehensively distributed in 242 genes, with 76% (29/38) of patients harbouring at least one CNV. In addition to *BRCA1*, somatic genetic alterations were also present in other homologous recombination repair (HRR) genes, including *CDK12* (5%), *BRCA2* (3%), *ATM* (3%), *BRIP1* (3%), *CHEK1* (3%) and *FANCI* (3%). In total, 22 of 38 (58%) patients had genetic alterations in the HRR pathway.

The prognosis analysis indicated that *BRCA1/2* mutations were significantly associated with improved PFI ($p<0.05$) and marginally associated with improved PFS ($p=0.05$). Patients with R0 resection found positive HRD showing a significant association with better PFI ($p<0.05$) and a marginal association with better PFS ($p=0.06$).

In patients with NF1 mutation, improved PFS and PFI were observed. However, the difference was not ideal (PFS, $p=0.06$, PFI, $p=0.084$). Platinum-sensitivity was significantly associated with *BRCA1/2* mutations ($p<0.01$).

Conclusions: In OC patients, genetic mutations frequently occurred in both HRR and non-HRR genes. CNVs are widely present in many genes and patients. Mutational profiling also identified a number of potential therapeutic targets and prognostic markers at the molecular level that could contribute to the personalised treatment and management of OC.

Introduction

Epithelial ovarian cancer (EOC) affects one in every 60 women in industrialised countries. It remains the leading cause of death from gynaecologic malignancies [1], with HGSOC being the most common histologic subtype [2]. The prognosis for ovarian cancer is poor, with a five-year survival rate of just 30%, and most deaths occurring within two years of diagnosis. The current five-year survival rate for patients

with FIGO stage IIIc–IV EOC is less than 30% and no real improvements have been achieved in recent decades. Following cytoreductive surgery and platinum-based chemotherapy, approximately 70% of patients with HGSOC relapse despite an initial response to therapy [1].

Approximately 50% of HGSOC patients have deficiencies in homologous recombination (HR) pathways, which have been associated with BRCA1 or BRCA2 germline or somatic mutations (20 and 5% of cases, respectively), BRCA1 promoter methylation (10% of cases), additional mutations in HR repair pathway genes and copy number alteration (CNA) in their regulators (PTEN and EMSY) [3]. BRCA1/2-associated ovarian carcinomas show improved OS and sensitivity to both platinum chemotherapy and PARPi [4-7].

As a maintenance therapy agent, the importance of PARPi in the treatment of ovarian cancer has attracted much attention in recent years. PARP inhibitors are active in patients with germline BRCA1/2 mutations and a subset of genes, that play key roles in HR, the primary mechanism that repairs double-strand DNA breaks (DSBs) [3]. although germline detection of BRCA1/2 is currently in extensive genetic testing, this approach does not allow patients with somatic and other HR gene mutations to avail themselves of the opportunity to use DNA-damaging agents.

Herein, we applied high-throughput next-generation sequencing (NGS) technologies covering 520 cancer-related genes to test DNA from 38 HGSOC tissue samples and analysed the relationship between genetic alterations and clinical parameters to pinpoint additional therapeutic targets and prognostic markers.

Methods

Patient collection and follow-up:

Primary tumour tissue and blood samples were obtained from 38 patients with HGSOC treated at Ruijin Hospital. These patients underwent radical surgery between 2017 and 2020. Clinical records, including sex, age, primary tumour size, FIGO stage, family history, date of diagnosis and date of the last contact, were collected by our medical record system.

The end of the follow-up period within this cohort was November 2021. The median follow-up period was 19 months. The study was reviewed and approved by the ethics committee of Ruijin Hospital affiliated to Shanghai Jiaotong University, school of medicine. The patients provided written informed consent to participate in this study.

DNA isolation and capture-based targeted DNA sequencing:

DNA isolation and targeted sequencing were performed in Burning Rock Biotech, a commercial clinical laboratory accredited by the College of American Pathologists (CAP) and certified by the Clinical Laboratory Improvement Amendments (CLIA), according to optimised protocols as described previously [8-9]. Briefly, tissue and blood white cell DNA were extracted from formalin-fixed, paraffin-embedded (FFPE) tumour tissues using a QIAamp DNA kit (Qiagen, Hilden, Germany), according to the manufacturer's

standard protocol (Qiagen, Hilden, Germany). Target capture was performed using a commercial panel consisting of 520 genes (OncoScreen Plus) spanning 1.64 megabases of the human genome. The size and quality of the fragments were assessed by a high sensitivity DNA kit using a Bioanalyzer 2100 (Agilent Technologies, CA, USA). Indexed samples were sequenced on a Nextseq 500 (Illumina, Inc., CA, USA) with paired-end reads and an average sequencing depth of 1,000×.

Sequence data analysis:

Sequence data were mapped to the reference human genome (hg19) using Burrows-Wheeler Aligner version 0.7.10[10]. Local alignment optimisation, duplication marking, and variant calling were performed by Genome Analysis Tool Kit version 3.2 and VarScan version 2.4.3. To identify somatic variants, tissue was compared against their own white blood cell control. Copy number was calculated based on the ratio between the depth of coverage in tumour samples and the average coverage of an adequate number (n>50) of samples without CNVs as references per capture interval. CNV is called if the coverage data of the gene region was quantitatively and statistically significant from its reference control. The limit of detection for CNVs was 1.5 for copy number deletions and 2.64 for copy number amplifications.

Tumour mutation burden (TMB) calculation:

TMB was computed as a ratio between the total number of nonsynonymous mutations detected, and the total coding region size of the panel used using the equation below. The mutation count included nonsynonymous SNVs and Indels detected within the coding region and ±2 bp upstream or downstream region and does not include hot mutation events, CNVs, structural variants (SVs), and germline single nucleotide polymorphisms (SNPs). The total size of the coding region for estimating TMB was 1.003 Mb for the 520-gene OncoScreen Plus panel.

TMB = (mutation count (except for CNV, SV, SNPs, and hot mutations)) / (1.003 Mb)

HRD status:

The loss of heterozygosity (LOH), telomeric allelic imbalance (TAI), and large-scale state transitions (LST) were calculated as previously described [11-14]. Briefly, LOH was defined as the number of homozygous segments with zero copies of minor alleles longer than 15 Mb and shorter than the whole chromosome. TAI was defined as the number of subchromosomal allelic imbalanced regions with two alleles having uneven copy numbers, which extend to subtelomere and do not cross the centromere and are longer than 11 Mb. LST was defined as the number of break-points between regions longer than 10 Mb after excluding regions shorter than 3 Mb. The bridge score was calculated as the sum of the LOH, TAI and LST scores. HRD positivity was defined as BRCA mutation (Pathogenic or Likely Pathogenic) and/or a bridge score $\geq$ 30.

Statistical Analysis

Wilcoxon rank-sum test was used to compare two groups of continuous variables. Chi-squared test or Fisher's exact test was used to compare categorical variables. Spearman correlation test was applied to evaluate the correlation between sample factors. Kaplan-Meier method was applied for survival analysis and log-rank test was used to estimate statistical significance. Multivariate Cox regression analysis was used to screen potential prognostic factors. The level of significance was set at $P < 0.05$, and all statistical tests were two-sided. All statistical data analyses were implemented using R software, version 4.0.2.

Results

1. Clinicopathological characteristics and overall HRD status

Thirty-eight Chinese women diagnosed with HGSOC were included in this study, and their clinicopathological characteristics are shown in Table 1. The median age of diagnosis was 59.5 years old (range, 35-78). Most patients were advanced-stage (86.8%) and were optimally cytoreduced (92.1%, to <1 cm maximal residual tumour diameter) at the time of primary surgery. All primary carcinomas received platinum-based chemotherapy and most patients were platinum sensitive (73.7%). After a median follow-up period of 19 months, 13 patients suffered a recurrence (52.9%).

Genomic profiling of all the samples was performed using a panel covering 520 cancer-related genes. After analysis, we defined HRD positive as a BRCA mutation and/or bridge score of ≥ 30. As listed in Table 1, 73.7% (28/38) of patients were HRD positive. Among them, 5 subjects (13%) had a germline BRCA1 mutation, and 9 subjects (24%) had a somatic BRCA1 mutation. Two subjects (5%) had a germline BRCA2 mutation, and 1 subject (3%) had a somatic BRCA2 mutation.

Abundant CNVs were oberved in ovarian cancer patients. We found CNVs in 242 genes in total, and 76% (29/38) of patients harboured at least one CNV.

2. Genomic findings

As displayed in Fig. 1, the most frequently mutated HRR genes were BRCA1 (24%), CDK12 (5%), BRCA2 (3%), ATM (3%), BRIP1 (3%), CHEK1 (3%), and FANCI (3%). Meanwhile, the most frequently mutated non-HRR genes were TP53 (97%), RB1 (21%), and FGF23 (21%). Nine subjects (24%) had deleterious germline mutations in 3 HR genes: BRCA1 (13%), BRCA2 (5%), and RAD51D (5%) (Fig. 2). Notably, only 3 of them claimed a family history of malignant tumours.

Genetic alterations were clustered in the HR pathway (BRCA1, BRCA2, ATM, BRIP1, CDK12, CHEK1, FANCL, RAD51D). Fifty-eight percent (22/38) of patients had mutations in the HR pathway. The above results are consistent with previous reports [3, 15]. One patient had mutations in the MMR pathway (PMS2), and 1 patient had mutations in the BER pathway (PARP1). These two patients had HRR gene mutations at the same time and had relatively long PFS and PFI (Fig. 3).

3. Prognosis analysis

As previously reported [6-7], among 38 patients, *BRCA1/2* mutations were significantly associated with improved PFI ($p<0.05$) (Fig. 4A) and marginally associated with improved PFS ($p=0.05$) (Fig. 4B). Although no association was observed between HRD status and patient prognosis (sul Fig. 1), subgroup analysis in patients with R0 resection found positive HRD showing a significant association with better PFI ($p<0.05$) and a marginal association with better PFS ($p=0.06$) (Fig. 5).

In our study, improved PFS and PFI were seen in patients with NF1 mutation. However, the difference was not ideal (PFS, $p=0.06$, PFI, $p=0.084$) (Fig. 6). To verify the relationship between NF1 and prognosis, we further explored in public databases by a prognostic web server OSov [16] (Online consensus Survival analysis for Ovarian cancer, https://bioinfo.henu.edu.cn/OV/OVList.jsp). As seen in Fig.7, in the three cohorts from The Cancer Genome Atlas (TCGA) and Gene Expression Omnibus (GEO) databases, the expressions of NF1 expression were all negatively correlated with overall survival (OS).

We also observed an association between *LRP1B* mutations and *RAD52* amplification with worse PFS ($p<0.05$) in the study (Fig. 8). No association was observed between P53 mutation and patient prognosis (sul Fig. 2).

4. Platinum sensitivity

According to the effectiveness of platinum, there were 10 patients resistant to platinum (with recurrence within 6 months after platinum-based chemotherapy).Platinum sensitivity was significantly associated with BRCA1/2 mutations ($p=0.001$) (Fig. 9), as previously reported [17]. In platinum-resistant patients, 7 of 10 patients harboured genetic alterations of actionable therapeutic targets, such as *PIK3CA, TSC1* and *HER2* alterations. No association was observed between platinum sensitivity and clinicopathologic features, TMB or pathway mutations (sul Fig. 3).

Discussion

EOC is among the most lethal gynaecological malignancies, but little treatment progress has been made for decades. In recent years, molecular characterisation of EOC has already led to the identification of interesting treatments, such as PARP inhibitors. These new drugs bring a glimmer of light to the darkness of OC treatments. However, molecular characterisation, targeted therapy and long-awaited personalised medicine of EOC still have a long way to go. In this research, a high frequency of gene and pathway mutations was found in patients with ovarian cancer. TP53 (97%), BRCA1 (24%), RB1 (21%), and FGF23 (21%) have the highest somatic mutation frequency. Germline mutations were found in 9 subjects (24%), including BRCA1 (13%), BRCA2 (5%), and RAD51D (5%). Mutations in the HRR pathway occurred in 58% of patients, mutations in the BER pathway occurred in 3% of patients, and mutations in the MMR pathway occurred in 3% of patients. All of these have the potential to become new therapeutic targets and prognostic markers.

The HRD status of HGSOC patients is closely related to their prognosis, platinum sensitivity and the choice of maintenance therapy. At present, the representative product that has been approved abroad to detect HRD status is myChoice. myChoice has participated in a number of clinical trials, such as NOVA, QUADRA, PAOLA-1 and PRIMA, and has been well validated clinically. However, for Chinese patients, there is not yet a recognised product for detecting HRD status.

In this paper, the bridge score is applied to HRD state detection for the first time, which is calculated as the sum of LOH, TAI and LST scores. HRD positivity was defined as a BRCA mutation (pathogenic or likely pathogenic) and/or a bridge score ≥ 30. In this way, 73.7% (28/38) of patients were HRD positive. In this paper, the efficiency of the bridge score in detecting the state of HRD was preliminarily explored, and further clinical verification is needed.

In this research, 14 subjects (37%) had BRCA1 mutations (5/14 were germline mutations). Three subjects (8%) had BRCA2 mutations (2/3 were germline mutations). These subjects were more sensitive to platinum and had a better prognosis. Those results were consistent with previous research [4, 6, 17]. Inherited BRCA1/2-mutation carriers and their close family members could benefit from genetic counselling, body examination and prophylactic risk-reduction treatment under certain indications. However, only 3 out of 7 germline BRCA1/2-mutation carriers had a reported family history of malignant tumours. This means that the proportion of HRD positivity might be underestimated if genetic testing is only performed on patients with a strong family history. Therefore, germline BRCA1/2 testing is currently recommended for all EOC patients regardless of family history by the Society of Gynaecologic Oncology (SGO), the National Comprehensive Cancer Network (NCCN), and other academic societies.

Neurofibromin 1 (NF1) is a negative regulator of the Ras signal transduction pathway that accelerates guanosine triphosphate (GTP) hydrolysis by the RAS protein [18]. Profiles of somatic NF1 aberrations in solid tumours, including breast cancer, lung cancer, and melanoma, have been previously established by various cancer genome sequencing projects [19–21]. In TCGA and GEO cohorts, we can also see NF1 expression was negatively corelated with OS. In our study, improved PFS and PFI were seen in patients with NF1 mutation. However, the difference was not ideal (PFS, $p = 0.06$, PFI, $p = 0.084$). This nonsignificant difference may be due to the limitations of our study, such as the small sample size and the short follow-up period. We also observed an association between *LRP1B* mutations and *RAD52* amplification with worse PFS ($p < 0.05$) in the study. These genes may be potential therapeutic targets and indicators, but further studies are still needed to confirm these findings.

Abbreviations

OC
Ovarian cancer
HGSC
high-grade serous ovarian cancer
CNV

copy number variation
HRD
homologous recombination deficiency
PFS
progression-free survival
PFI
platinum-free interval
BRCA1
Breast Cancer Susceptibility Gene 1
BRCA2
Breast Cancer Susceptibility Gene 1
TP53
tumor protein p53
RB1
transcriptional corepressor 1
FGF23
fibroblast growth factor 23
CCND2
cyclin D2
RECQL4
RecQ like helicase 4
NF1
neurofibromin 1
CDK12
cyclin dependent kinase 12
ATM
ataxia telangiectasia mutated
BRIP1
BRCA1 interacting helicase 1
CHEK1
checkpoint kinase 1
FANCI
FA complementation group I
HRR
homologous recombination repair
EOC
epithelial ovarian cancer
FIGO
The International Federation of Gynecology and Obstetrics
CNA

copy number alterations
PTEN
phosphatase and tensin homolog
EMSY
EMSY transcriptional repressor
BRCA2 interacting
PARPi
poly(ADP-ribose) polymerase inhibitors
NGS
next-generation sequencing
CAP
College of American Pathologists
CLIA
Clinical Laboratory Improvement Amendments
FFPE
formalin-fixed
paraffin-embedded
TMB
tumour mutation burden
SV
structural variant
SNP
single nucleotide polymorphisms
LOH
loss of heterozygosity
TAI
telomeric allelic imbalance
LST
large-scale state transitions
RAD51D
RAD51 paralog D
MMR
mis-match repair
PMS2
PMS1 homolog 2
mismatch repair system component
BER
base excision repair
TCGA
The Cancer Genome Atlas

GEO
Gene Expression Omnibus
OS
overall survival
LRP1B
LDL receptor related protein 1B
RAD52
RAD52 homolog
DNA repair protein
PIK3CA
phosphatidylinositol-4
5-bisphosphate 3-kinase catalytic subunit alpha
TSC1
TSC complex subunit 1
HER2
erb-b2 receptor tyrosine kinase 2
SGO
Society of Gynaecologic Oncology
NCCN
the National Comprehensive Cancer Network
GTP
guanosine triphosphate.

Declarations

Availability of data and materials: The datasets used and/or analyzed in this study are available from the corresponding author on reasonable request.

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Declaration of Competing Interest

The authors report no conflict of interest.

Ethics approval and consent to participate

The study was reviewed and approved by the ethics committee of Ruijin Hospital affiliated to Shanghai Jiaotong University, school of medicine. The patients provided written informed consent to participate in this study.

Consent for publication

All authors agreed to the publication of this data.

Authors' contributions

Weiwei Feng designed of the whole study; Yahui Jiang and Jinyan Ma helped to collect clinicopathological data; Chongying Zhu collected clinical tissue samples; Lifei Shen, Yuhong Shen and Hua Liu helped to enroll patients and follow up; Tianjiao Lyu analysed the data and wrote the manuscript finally.

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Not applicable.

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Tables

Table 1. Clinicopathological features of HGSOC patients.

		Overall (n = 38)
Age (median [IQR])		59.50 [48.00, 65.75]
Platinum sensitivity (%)	1	15 (39.5)
	2	13 (34.2)
	3	10 (26.3)
Debulking surgery (%)	i	16 (42.1)
	p	22 (57.9)
Stage (%)	I	3 (7.9)
	II	2 (5.3)
	III	20 (52.6)
	IV	13 (34.2)
CEA (median [IQR])		1.38 [0.84, 1.88]
HE4 (median [IQR])		452.00 [245.20, 625.65]
CA199 (median [IQR])		6.00 [2.72, 11.53]
CA125_level (%)	<100	5 (13.2)
	>=100	33 (86.8)
BMI status (%)	Normal	23 (60.5)
	Obese	4 (10.5)
	Overweight	11 (28.9)
Primary size (median [IQR])		8.70 [5.00, 12.00]
Metastatic size (median [IQR])		2.50 [1.00, 5.00]
Node size (%)	0	23 (60.5)
	1	15 (39.5)
LDPS (%)	0	9 (23.7)
	2	29 (76.3)
EDPS (%)	0	18 (47.4)
	2	20 (52.6)
Mesenteric root (%)	0	24 (63.2)

	2	14 (36.8)
OGGC (%)	0	25 (65.8)
	2	13 (34.2)
IRILES (%)	0	21 (55.3)
	2	17 (44.7)
Gastric wall (%)	0	37 (97.4)
	2	1 (2.6)
Lesions liver (%)	0	36 (94.7)
	2	2 (5.3)
Fagotti score (median [IQR])		6.00 [2.00, 8.00]
Residual disease (%)	R0	21 (55.3)
	R1	14 (36.8)
	R2	3 (7.9)
bridgeScore status (%)	bridgeScore negative	11 (28.9)
	bridgeScore positive	27 (71.1)
HRD status (%)	HRD negative	10 (26.3)
	HRD positive	28 (73.7)
TMB (median [IQR])		2.99 [1.99, 5.73]

Primary size: Preoperative examination combined with an intraoperative exploration of the maximum primary tumour diameter.

Metastatic size: Preoperative examination combined with an intraoperative exploration of maximum metastatic tumour diameter.

Node size: Size of retroperitoneal (pelvic/main abdominal) lymph nodes in CT image (0=no, 1=yes, enlarged lymph nodes may be seen, not necessarily clear metastases)

EDPS: Entirely distributed peritoneal seeding (0=no, 2=yes)

LDPS: Locally distributed peritoneal seeding (0=no, 2=yes)

Mesenteric root: Tumour invasion to the mesenteric root (0=no, 2=yes)

OGGC: Omentum with greater gastric curvature (0=no, 2=yes)

IRILES: Small/large intestine resection and/or intestinal loop entirely seeding (0=no, 2=yes)

Gastric wall: Tumour invasion to the stomach wall (0=no, 2=yes)

lesions on the liver: Liver surface lesions >2 cm (0=no, 2=yes)

Figures

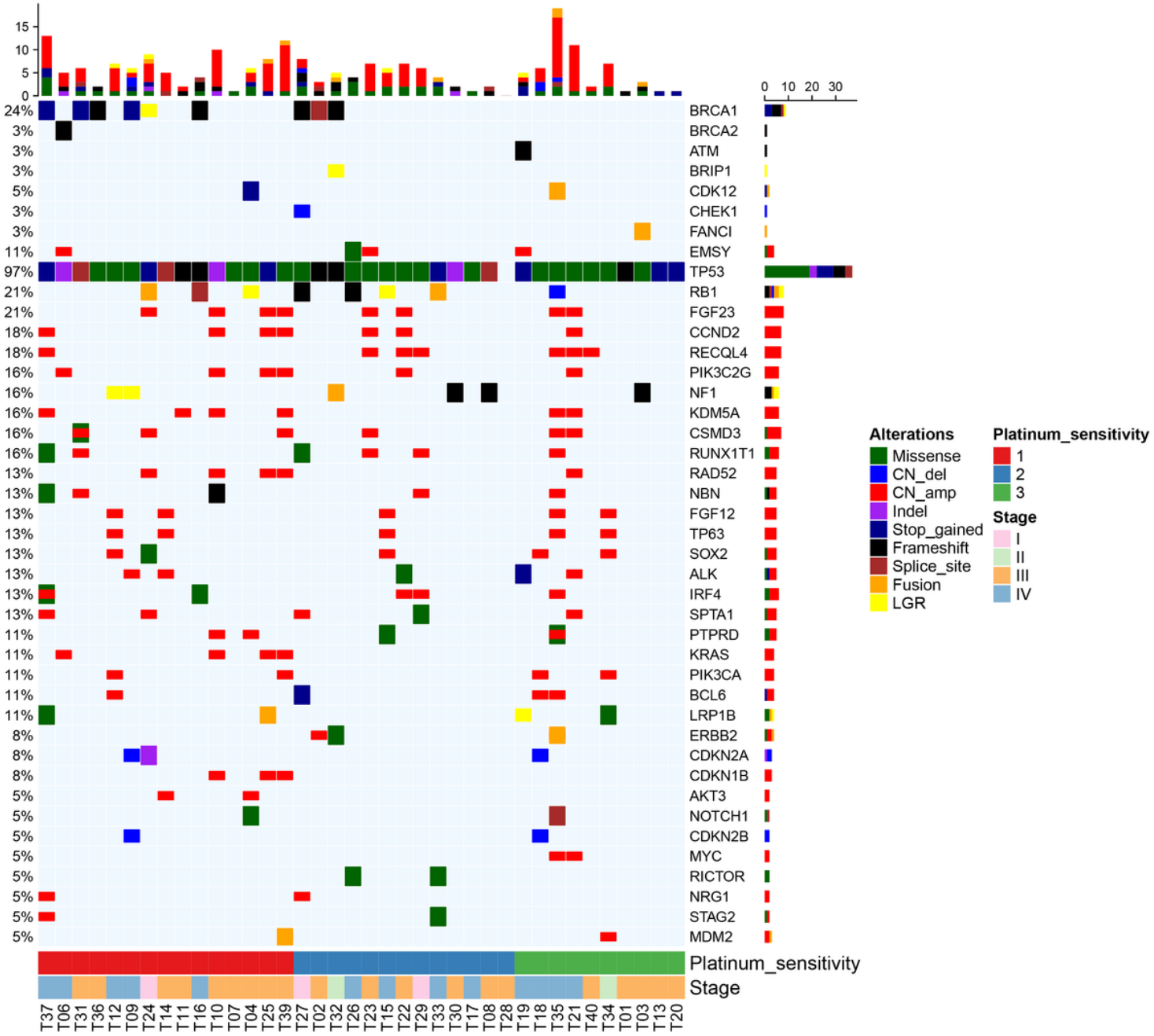

Figure 1

An oncoprint summarising the somatic mutational landscape of HGSOC tumours. The platinum sensitivity and stage of the patients were indicated at the bottom of the oncoprint, wherein red (Group 1) represents patients with platinum-sensitive recurrence, blue (Group 2) represents patients with no recurrence and platinum-free interval of more than 6 months. and green (Group 3) represents patients with platinum resistance recurrence. Each column represents a patient, and each row represents a gene. The numbers on the left represent the percentage of patients with mutations in a specific gene. The top plot represents the overall number of mutations a patient carried. Different colours denote different types of mutations.

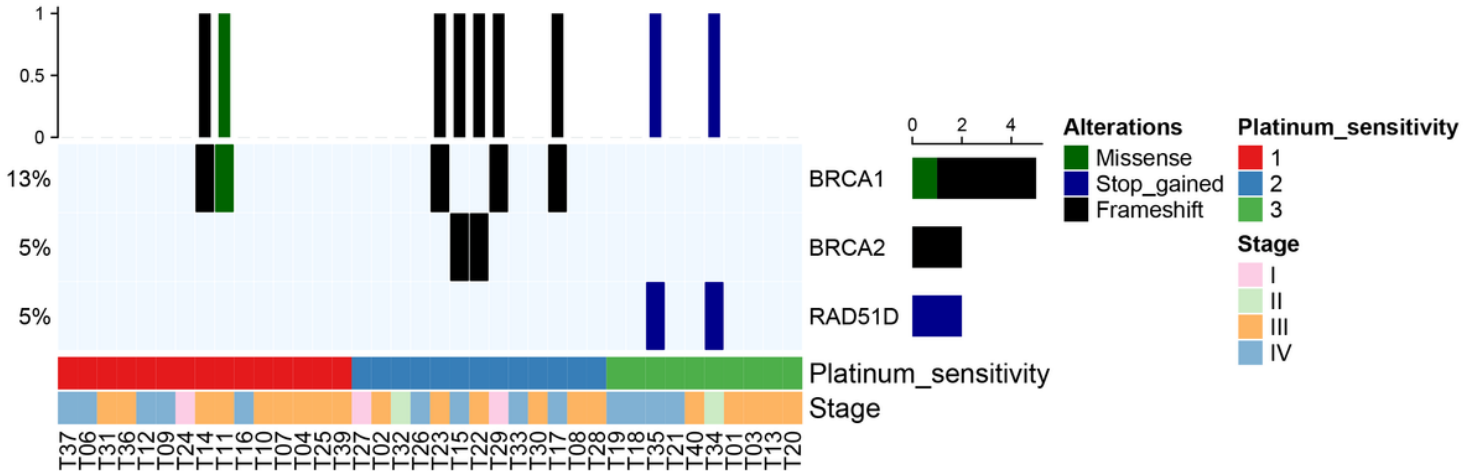

Figure 2

An oncoprint summarising the germline mutational landscape of HGSOC tumours. The platinum sensitivity and stage of the patients was indicated at the bottom of the oncoprint, wherein red (Group 1) represents patients with platinum-sensitive recurrence, blue (Group 2) represents patients with no recurrence and platinum-free interval of more than 6 months. and green (Group 3) represents patients with platinum resistance recurrence. Each column represents a patient, and each row represents a gene. The numbers on the left represent the percentage of patients with mutations in a specific gene. The top plot represents the overall number of mutations a patient carried. Different colours denote different types of mutations.

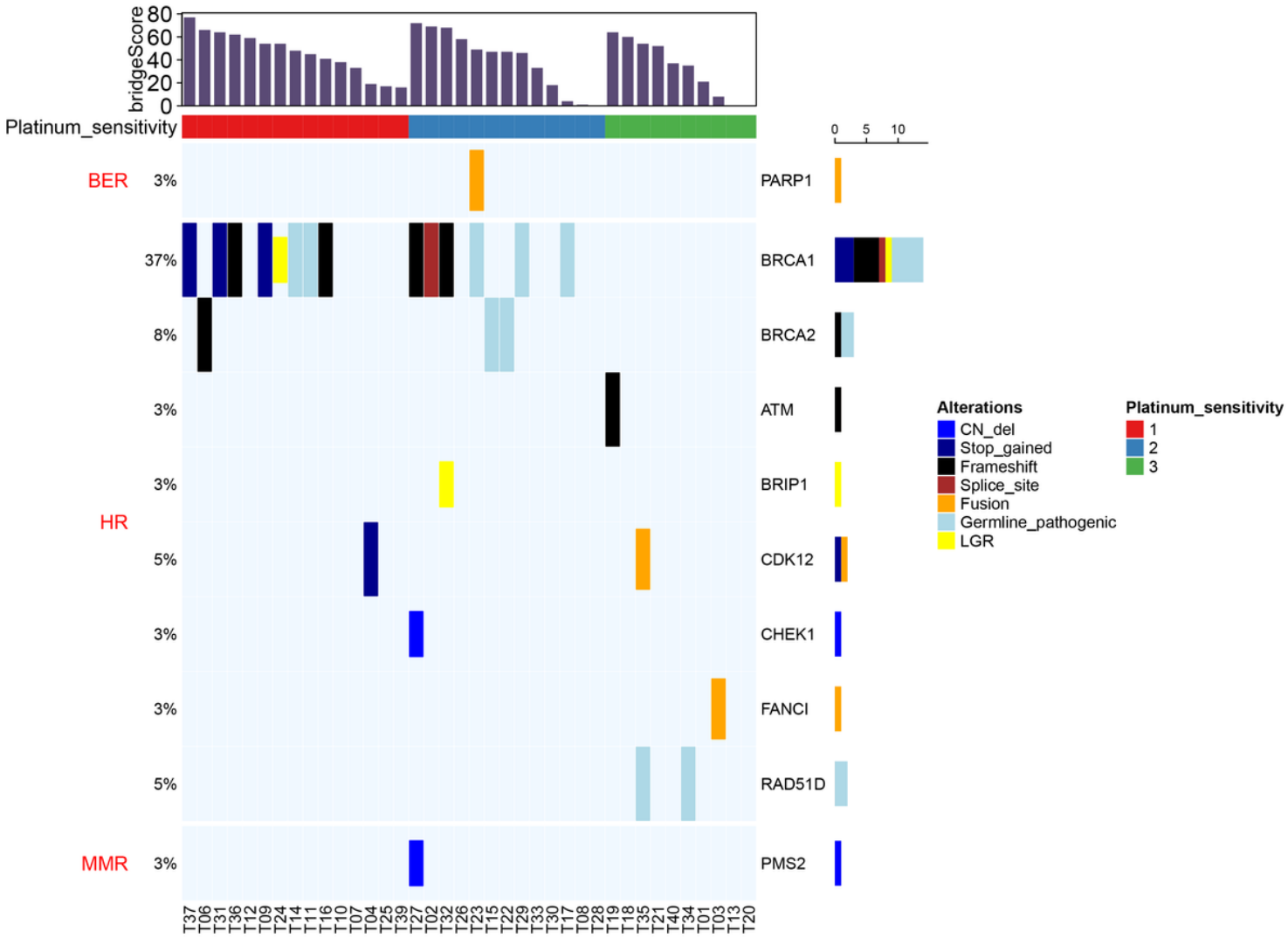

Figure 3

An oncoprint summarising the pathway landscape of HGSOC tumours.

The platinum sensitivity of the patients was indicated at the top of the oncoprint, wherein red (Group 1) represents patients with platinum-sensitive recurrence, blue (Group 2) represents patients with no recurrence and platinum-free interval more than 6 months. and green (Group 3) represents patients with platinum resistance recurrence. The three sets of squares represent the three pathways (BER, HR, MMR) from top to bottom. Each column represents a patient and each row represents a gene. The numbers on the left represent the percentage of patients with mutations in a specific gene. The top plot represents the overall number of mutations a patient carried. Different colours denote different types of mutations.

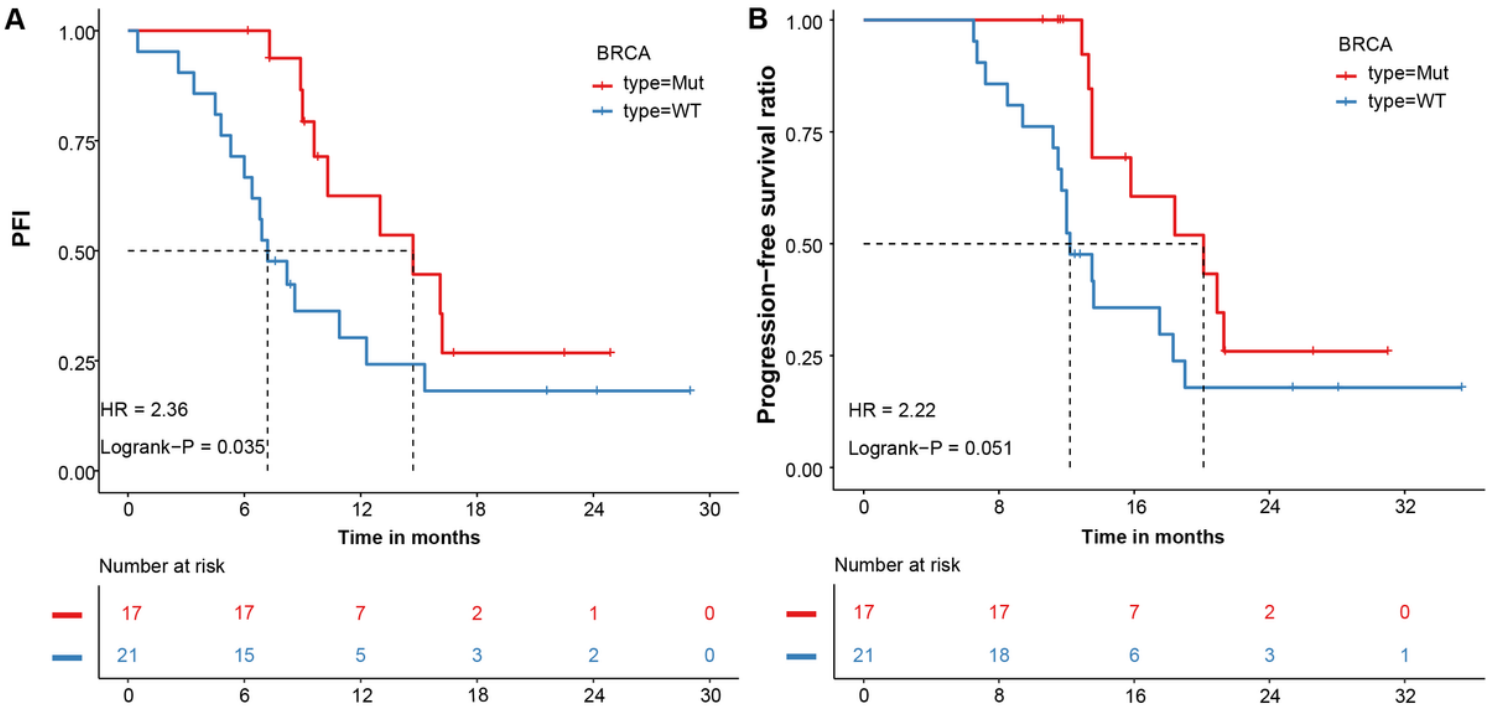

Figure 4

PFI and PFS of HGSOC patients with BRCA and non-BRCA mutations.

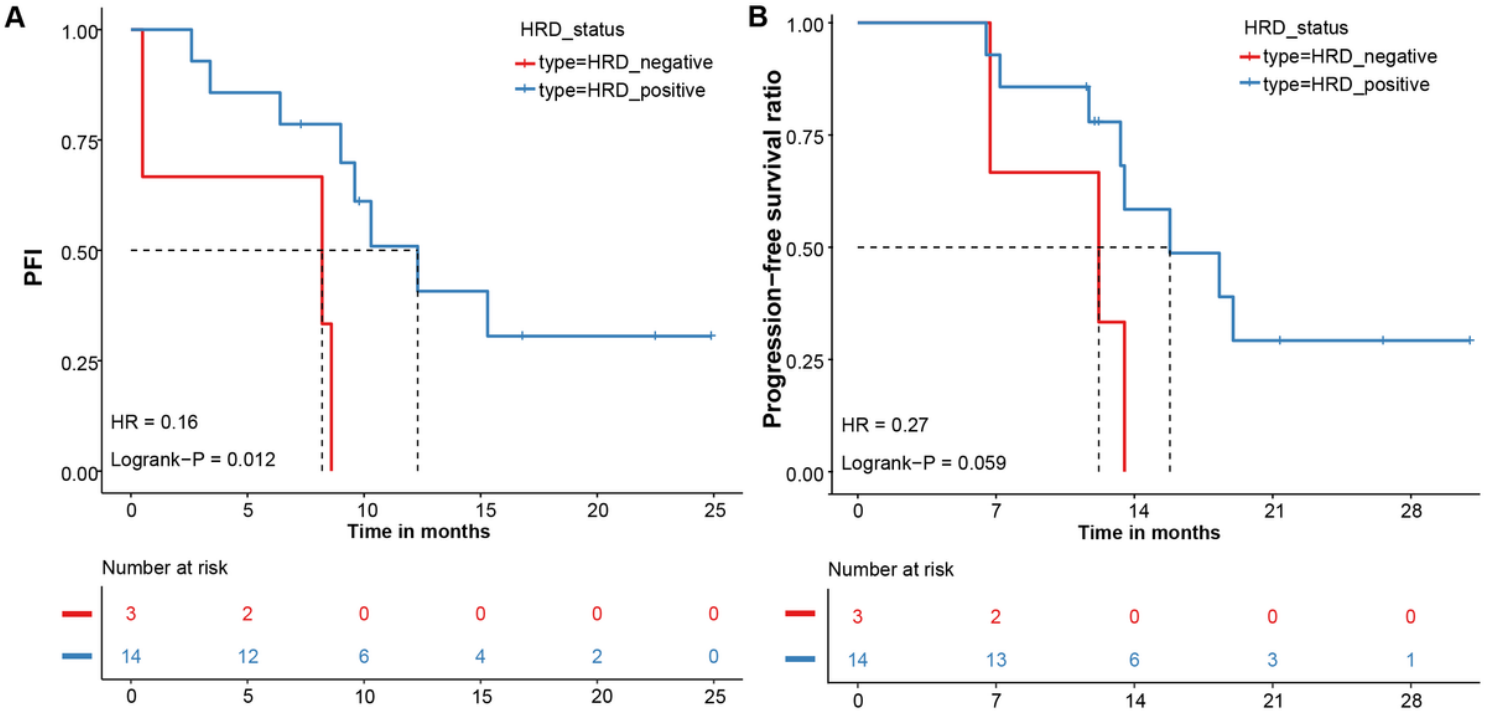

Figure 5

PFI and PFS of R0-resectional HGSOC patients with HRD positivity and HRD negativity.

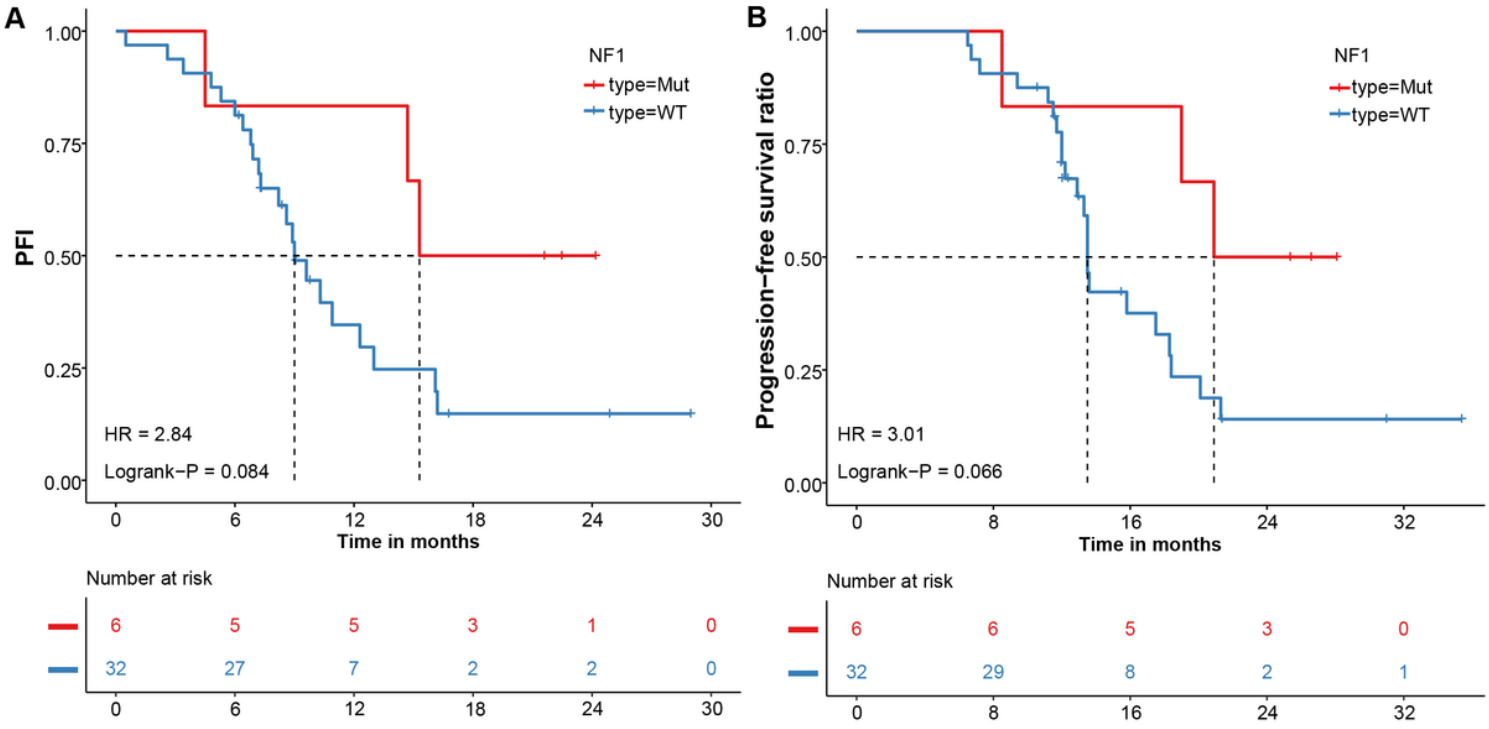

Figure 6

PFI and PFS of HGSOC patients with NF1 and non-NF1 mutation.

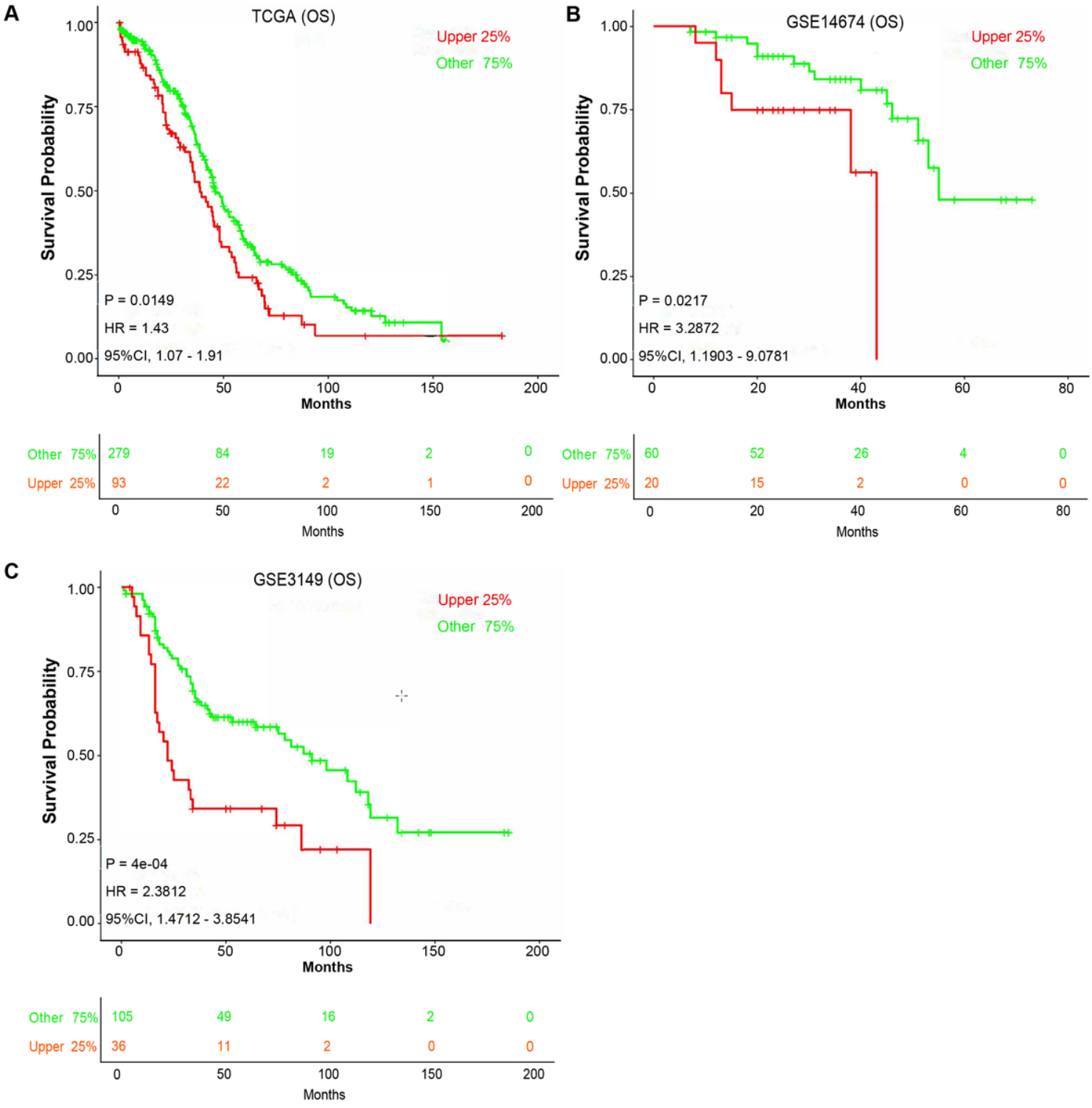

Figure 7

Survival analyses of NF1 expression in TCGA and GEO cohorts. Kaplan–Meier analysis demonstrated that patients with higher NF1 expression exhibited worse overall survival in cohorts from TCGA (A) and GEO (B-C) database.

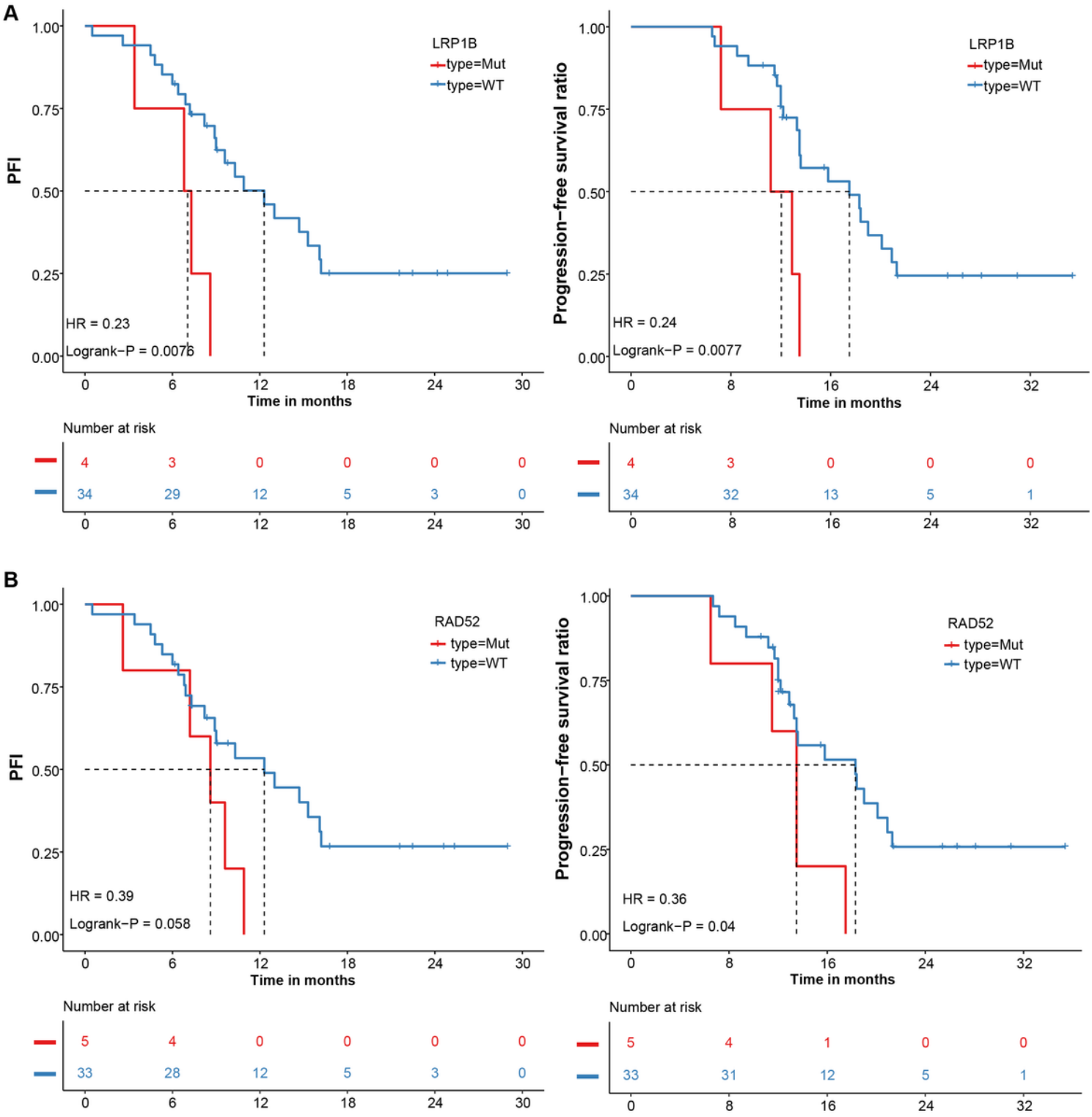

Figure 8

PFI and PFS of HGSOC patients with LRP1B and non-LRP1B mutations (A) and RAD52 and non-RAD52 mutations (B).

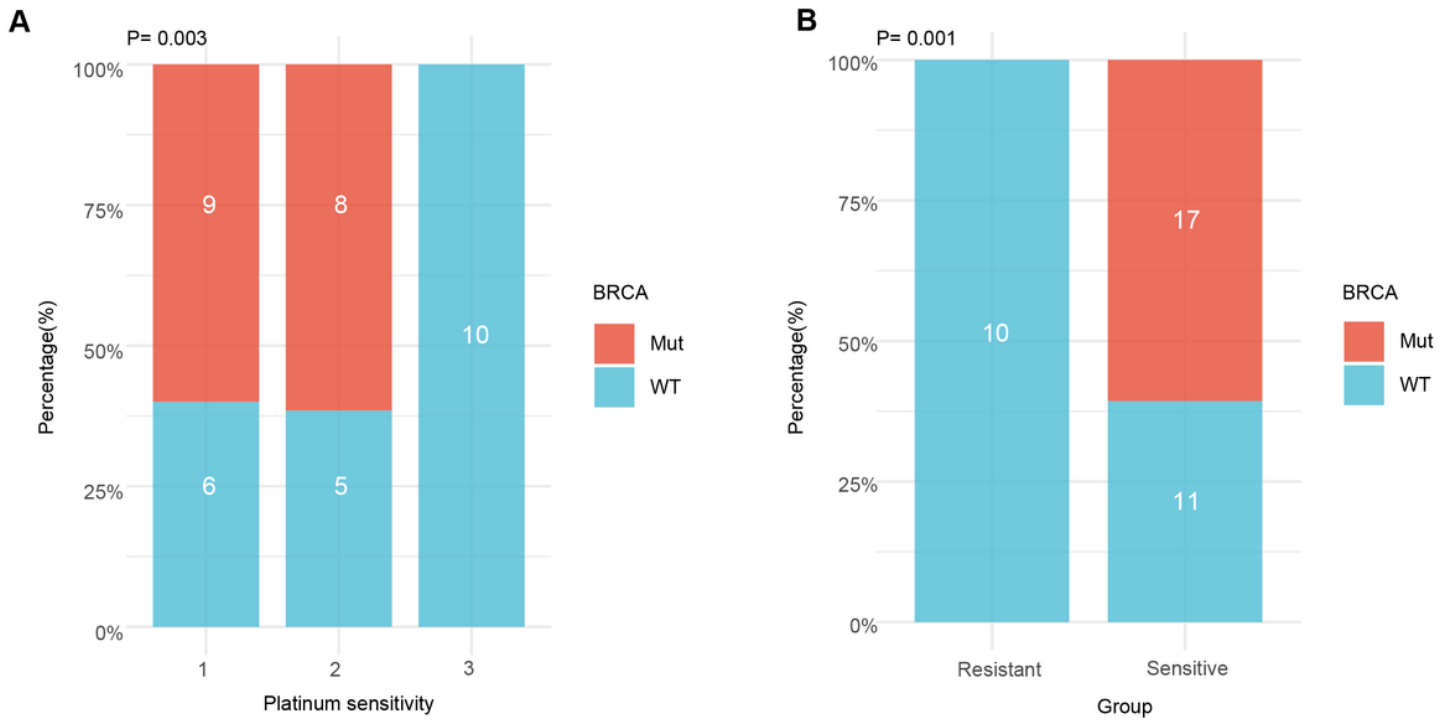

Figure 9

The association between BRCA mutation and platinum sensitivity. The red column represents the BRCA mutation, and the blue column represents BRCA mutation wild type. Group 1 represents patients with platinum-sensitive recurrence, Group 2 represents patients with no recurrence and platinum-free interval of more than 6 months, and Group 3 represents patients with platinum resistant recurrence (A). the left column represents platinum resistance (Group 3), and the right column represents platinum sensitivity (Group 1 plus Group 2) (B).

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- sulfig1.pdf
- sulfig2.pdf
- sulfig3.pdf