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Short Communication

Establishing the homologous recombination score threshold in metastatic prostate cancer patients to predict the efficacy of PARP inhibitors

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A R T I C L E I N F O

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A B S T R A C T

Background: The homologous recombination deficiency (HRD) score serves as a promising biomarker to identify patients who are eligible for treatment with PARP inhibitors (PARPi). Previous studies have suggested a 3-biomarker Genomic Instability Score (GIS) threshold of ≥ 42 as a valid biomarker to predict response to PARPi in patients with ovarian cancer and breast cancer. However, the GIS threshold for prostate cancer (PCa) is still lacking. Here, we conducted an exploratory analysis to investigate an appropriate HRD score threshold and to evaluate its ability to predict response to PARPi in PCa patients.

Methods: A total of 181 patients with metastatic castration-resistant PCa were included in this study. Tumor tissue specimens were collected for targeted next-generation sequencing for homologous recombination repair (HRR) genes and copy number variation (CNV) analysis. The HRD score was calculated based on over 50,000 single-nucleotide polymorphisms (SNP) distributed across the human genome, incorporating three SNP-based assays: loss of heterozygosity, telomeric allelic imbalance, and large-scale state transition. The HRD score threshold was set at the last 5th percentile of the HRD scores in our cohort of known HRR-deficient tumors. The relationship between the HRD score and the efficacy in 16 patients of our cohort who received PARPi treatment were retrospectively analyzed.

Results: Genomic testing was succeeded in 162 patients. In our cohort, 61 patients (37.7%) had HRR mutations (HRRm). *BRCA* mutations occurred in 15 patients (9.3%). The median HRD score was 4 (ranged from 0 to 57) in the total cohort, which is much lower than that in breast and ovarian cancers. Patients who harbored HRRm and *BRCA* or *TP53* mutations had higher HRD scores. CNV occured more frequently in patients with HRRm. The last 5th percentile of HRD scores was 43 in the HRR-mutant cohort and consequently HRD high was defined as HRD scores ≥ 43. In the 16 patients who received PARPi in our cohort, 4 patients with a high HRD score achieved an objective response rate (ORR) of 100% while 12 patients with a low HRD score achieved an ORR of 8.3%. Progression-free survival (PFS) in HRD high patients was longer compared to HRD low patients, regardless of HRRm.

Conclusions: A HRD score threshold of 43 was established and preliminarily validated to predict the efficacy of PARPi in this study. Future studies are needed to further verify this threshold.

1. Introduction

Prostate cancer (PCa) is the most prevalent genitourinary cancer globally.[1] While treatment options at early stages offer relatively promising prognosis, options become limited and prognosis becomes poor when patients are diagnosed with metastatic PCa, especially at the castration-resistant stage. This necessitates precision screening for appropriate drugs.

Previous studies have shown that patients with biallelic somatic or germline mutations in *BRCA1* and *BRCA2* are most likely to benefit from

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poly adenosine diphosphate–ribose polymerase inhibitor (PARPi) treatment.[2] Recently, Olaparib has been approved for metastatic castration-resistant prostate cancer patients (mCRPC) with homologous recombination repair pathway mutations (HRRm), and Rucaparib has been recommended for patients carrying *BRCA1* or *BRCA2* mutations. However, only about 6–10% of patients carry *BRCA* mutations.[3] Additionally, some patients with *BRCA* mutations do not respond to PARPi, and some patients with other homologous recombination repair (HRR) gene mutations or without HRRm respond to PARPi.[2] Therefore, there is an urgent need to find a new biomarker that can effectively identify the functional status of the homologous recombination, thereby expanding the population that can benefit from PARPi treatment while predicting the efficacy of PARPi precisely.

The homologous recombination deficiency (HRD) score is a novel technique that estimates the genomic scarring caused by HRD. It is calculated as the sum of three individual scores: loss of heterozygosity (LOH), telomeric allelic imbalance (TAI), and large-scale state transition (LST).[4-6] Previous studies have examined the threshold of the HRD score to predict prognosis and treatment response to platinum chemotherapy and PARPi in ovarian cancer and breast cancer,[7-11] whereas in prostate cancer the optimal HRD score threshold as a predictor remains undetermined.

Herein, we retrospectively collected tumor samples from 181 PCa patients and successfully detected the HRRm status and HRD scores in 162 of them. We explored the threshold of the HRD score and found that an HRD score ≥ 43 may be an effective threshold. Additionally, we analyzed the association between the efficacy of PARPi and HRD scores in 16 patients who underwent PARPi treatment.

2. Materials and methods

2.1. Experimental model and subject details

We initiated the study by screening all patients diagnosed with mCRPC at Sun Yat-sen University Cancer Center between 2019 and 2023. Then, we collected the formalin fixed paraffin-embedded (FFPE) tissues of patients who underwent prostate biopsy from a prospectively established sample library. All the patients signed a written informed consent for the collection and analysis of their tissue samples. The samples were obtained before the prescription of PARPi and underwent pathological re-evaluation, and only those with > 30% tumor content were considered eligible for further analysis. Ultimately, our study included a total of 181 PCa patients for whom the HRD scores and genomic alterations were assessed using their FFPE tumor specimens. Patients included in this clinical cohort underwent PARPi treatment under the following circumstances: 1) progressed after first line androgen receptor pathway inhibitors (ARPIs) treatment at mCRPC and genetic testing suggested that they were HRRm carriers, or 2) received at least two lines of ARPIs at mCRPC.

2.2. Tissue collection, processing, and genomic DNA extraction

A minimum of 15 FFPE tumor section samples were collected from each patient and the first slide for hematoxylin and eosin (H&E) staining. The H&E slide was reviewed by two independent pathologists to determine the histological type and neoplastic cellularity (30% minimum). Genomic deoxyribonucleic acid (gDNA) was extracted and quantified from the patients' specimen(s) using a standardized methodology.[12]

2.3. Library construction, DNA sequencing, variant calling, and HRD analysis

DNA library construction were using the IDT xGEN Prism DNA Library Prep Kit and the manufacturer's protocol. The Precision Human HRD Assay (OncoDeficiency Pro, Beijing) contains two sets of probes, HRD-score probes (~50 K) and HRR-gene probes, which were used to evaluate HRD scores and genotype 36 HRR genes (*ABRAXAS1, ATM, ATR, BAP1, BARD1, BRCA1, BRCA2, BRIP1, EMSY, CDH1, CDK12, CHEK1, CHEK2, EPCAM, FANCA, FANCC, FANCD2, FANCI, FANCL, MLH1, MRE11, MSH2, MSH6, NBN, PALB2, PMS2, PPP2R2A, PTEN, RAD50, RAD51B, RAD51C, RAD51D, RAD54B, RAD54L, STK11, and TP53*).

Data were sequenced on the NovaSeq platform in PE150 mode by mean depths of 150X (tumor) and 50X (control). The single-nucleotide polymorphisms (SNPs) targeted by the Precision Human HRD Assay were selected based on the following criteria: SNPs on Y chromosome were removed; mitochondrial SNPs were removed; SNPs with minor-allele-frequency (MAF) less than 1% in the European or West African population were removed; SNPs with MAF less than 5% in the East Asian population were removed; SNPs significantly deviated from Hardy-Weinberg Equilibrium (HWE) in any of the three populations mentioned above were removed; SNPs with fixation indices (Fst) < 0.05 in the East Asian population were removed; SNPs with CG-content < 40% or > 60% were removed; SNPs located on short tandem repeats (STRs) were removed; SNPs evenly covered the human genome. We developed in-house HRD score algorithm to assess genomic instability and calculated a score for each of the three features: LOH, TAI, and LST. HRD score was the sum of LOH, TAI, and LST scores.

For genes included in the panel, a custom bioinformatic analysis pipeline was used to detect single nucleotide variants (SNVs) and small insertions and deletions (indels) in protein-coding regions and intron/exon boundaries of the 36 genes. Variants were classified according to the recommendations of the American College of Medical Genetics and Genomics (ACMG) for standards in the interpretation of sequence variations. Copy number variations (CNVs) calling in the 36 target genes were detected using the cnvkit (version v0.9.6).

2.4. Definition of endpoints

The study endpoints included progression-free survival (PFS), defined as the time from inclusion to progression or death from any cause, whichever occurred first; clinical benefit rate, defined according to the Response Evaluation Criteria in Solid Tumours (RECIST)[13] as either complete response, partial response or stable disease (SD) lasting for at least 16 weeks; objective response rate (ORR), defined as proportion of patients in complete remission plus partial remission; and prostate specific antigen (PSA) response rate, defined as proportion of patients with a 50% decrease in PSA from baseline.

2.5. Statistical analysis

The statistical analysis software was R 4.2.1. For descriptive analysis, non-normally distributed data are presented as median with interquartile range (IQR). Qualitative data are depicted as frequencies and percentages. To compare the non-normally distributed continuous variables, the Wilcoxon rank sum test was utilized. Chi-square test was used for comparing categorical variables. PFS estimation was based on the Kaplan-Meier method, and between-group hypothesis testing was based on the log-rank test. Hazard ratios (HR) and corresponding 95% confidence intervals (CIs) were calculated using the CoxPH model. A two-sided *P* value of less than 0.05 was considered statistically significant. Prism 10 and Adobe illustrator 2024 was used to create the graphs and structure the figures.

3. Results

3.1. HRRm status and establishment of a threshold for HRD score

In total, 181 tumor samples were sent for HRD score testing and HRRm detection. Eventually, the HRD score, somatic HRRm, and CNV data were obtained successfully in 162 of 181 patients, with a success rate of 89.5%. The genomic alterations were arranged from left to right

according to the HRD score, with higher scores towards the left (Fig. 1A). HRRm occurred in 61 patients (61/162, 37.7%). Among the entire HRR pathway, *PPP2R2A* (30/162, 18.5%) was the most prevalent mutated gene, followed by *FANCA* (22/162, 13.5%), *CDH1* (16/162, 9.8%), *TP53* (15/162, 9.3%), *BRCA2* (15/162, 9.3%), and *ATM* (10/162, 6.2%) (Fig. 1A). Biallelic mutations only occurred in *TP53, BRCA2, ATM, MSH2, CDK12,* and *PTEN* (Fig. 1A). When patients were divided into HRR mutant and HRR intact groups, HRR mutant patients had higher HRD scores ($P < 0.001$, Fig. 1A and B).

Since HRR is the primary pathway of repair when double-strand break of DNA occurs and deficiency in DNA damage repair may cause CNV due to genomic duplication, deletion or structural variation, we analyzed the relationship between HRRm and CNV. In total, 186 CNV events of 32 genes were detected, including 167 events (76 deletions and 91 amplifications) of 32 genes in HRR mutant patients and 19 events (6 deletions and 13 amplifications) of 5 genes in HRR wild-type patients. CNV events including both amplification and deletion were more frequent in HRR mutant patients ($P < 0.001$, Fig. 1A and C). Among the detected genes, *NBN, RAD54B, PPP2R2A, PMS2,* and *ATR* were the top 5 genes that presented with the most CNV events (Fig. 1A). Patients with *BRCA* or *TP53* mutations exhibited higher median HRD scores (3 vs. 24, $P < 0.001$ and 3 vs. 25, $P < 0.001$, respectively. Fig. 1D and E). Additionally, among the patients with biallelic mutations in HRR pathway genes, *BRCA2, ATM,* and *TP53* had the highest HRD scores (median: 55, 36, and 35.5, respectively).

To determine the threshold of the HRD score, the HRD score distribution of 162 PCa patients is presented in Fig. 1F and is grouped by HRRm status, which shows an apparent bimodal distribution. In the entire cohort, the median HRD score was 4 (range from 0 to 57). The median HRD score of HRR intact and HRR mutant patients was 2 (IQR: 1–4) and 15 (IQR: 10–25), respectively. Considering, mutation of any HRR pathway genes may contribute to the dysfunction of HRR. Therefore, to distinguish HRD patients from others more comprehensively, we divided the patients into two groups. To obtain a specificity of at least 95%, the threshold was determined at the last 5th percentile of the HRD scores. Eventually, the threshold of HRD score of PCa patients was set at 43. Patients with a HRD score of ≥ 43 was deemed to be HRD high. At last, 4 of 162 patients were considered to be HRD high, among whom 3 were *BRCA1/2* mutation carriers.

3.2. Clinical characteristics and HRD scores in the clinical cohort

To validate the threshold in the efficacy prediction of PARPi, we collected the clinical data of 16 patients among the entire cohort who underwent PARPi treatment. All patients underwent ARPIs as the first-line treatment in the metastatic castration-resistant stage. The median follow-up of the entire cohort was 5.5 months (range: 4–22 months). Detailed baseline characteristics were presented in Table 1 and Supplementary Table 1. Univariate analysis indicated that patients with higher HRD scores exhibited improved responses in both PSA and radiologic evaluations ($P = 0.003$ and $P < 0.001$, respectively) and longer PFS ($P < 0.001$). No difference was observed in age, HRD score, HRRm status, cT stage, and Gleason score.

3.3. Association of HRD score and HRRm with PSA and radiologic response to PARP inhibitors

The distribution of all HRD scores across different radiologic and PSA response categories is displayed in Fig. 2. Notably, all patients with high HRD scores achieved disease release, including complete response and partial response, and experienced a PSA decline of over 50%.

Fig. 3 shows the clinical benefit rate, ORR, and PSA response rate of our cohorts in tumors stratified by HRD score, HRRm status, or the combination of these two variables. Our findings indicated that patients with higher HRD scores and HRRm status exhibited higher clinical response rates, ORR, and PSA response rates. However, when patients with low HRD scores and HRRm status were considered separately from those with HRRm status, this subgroup of patients exhibited significantly lower clinical response rates, ORR, and PSA response rates compared with patients with high HRD scores and HRRm status (16.7% vs. 100%, 0% vs. 100%, and 16.7% vs. 100%, respectively).

3.4. Association of HRD score and HRRm with survival of PARPi treatment

To evaluate the association between PFS and HRD scores in patients receiving PARPi treatment, we initially stratified the cohort into HRR wild-type (wt) and HRR mutant (mut) subgroups. However, no statistically significant difference in PFS was observed between these two groups ($P = 0.08$, Fig. 4A). Subsequently, we compared PFS between patients with high and low HRD scores. Notably, patients with high HRD scores exhibited significantly longer PFS compared to those with low HRD scores ($P = 0.003$, HR = 0.33 [95% CI, 0.01–0.32], Fig. 4B). To further investigate whether there were differences in PFS among patients with different HRD and HRRm statuses, we separated patients into three groups: HRD low/HRRwt, HRD low/HRRm, and HRD high/HRRm. A statistically significant difference in PFS was observed between HRD low/HRRm and HRD high/HRRm ($P = 0.007$, HR = 0.30 [95% CI, 0.08–1.19], Fig. 4C). No difference was observed between HRD low/HRRwt and HRD low/HRRm ($P = 0.575$, HR = 0.85 [95% CI, 0.27–2.634], Fig. 4C).

4. Discussion

This study analyzed the tumor samples from 181 PCa patients to obtain HRD scores, somatic HRRm, and CNV data, aiming to establish an HRD score threshold in PCa patients to predict the efficacy of PARPi. We determined the HRD score threshold at 43 by analyzing the distribution of HRD scores among 162 patients. Our results indicated that patients with HRRm mutations had higher CNV frequencyies and HRD scores. We further validated the threshold in a clinical cohort of 16 PCa patients treated with PARPi. Notably, HRD high patients exhibited a significantly better response in both PSA and imaging studies compared with HRD low patients, regardless of HRRm status. These findings suggested that the HRD score may serve as a predictor of response to PARPi treatment in PCa patients.

The frequency of somatic HRRm in our cohort was 37.7% (61/162), which was higher than the PKUFH cohort (3%), TCGA PARD (8.68%) and MSK-IMPACT (9.4%). However, this may be due to the different disease stages.[14,15] In the TOPARP-B study, the frequency of DNA damage repair gene mutations among mCRPC patients was 27%, which was higher than those with localized or metastatic hormone-sensitive patients.[16] Besides, a multi-institutional study revealed a somatic HRRm frequency of 35.7% in Asian patients, which was similar to our cohort and may explain the relatively high frequency of HRRm to some extent.[17] Our cohort showed that *PPP2R2A* was the most prevalent mutant gene, followed by *FANCA, CDH1, TP53, BRCA2,* and *ATM*, which was different from Japanese patients (*CDK12, BRCA2, ATM,* and *CHEK2*), and demonstrated a different mutation landscape between Chinese and Japanese patients. Nevertheless, the prevalence of *BRCA2* and *ATM* mutations was very close (9.3% vs. 12.6% and 6.2% vs. 5.6%, respectively). Previous studies[18] found that patients with *TP53* mutations have higher HRD scores, which is also consistent with our findings (3 vs. 25, $P < 0.001$). Additionally, PCa patients with *BRCA2* mutations had higher HRD scores than those with *ATM* or *CHEK2* mutations, and the median HRD score was lower in patients without HRRm compared with ovarian cancer, which is consistent with our results. Beyond that, we also found that patients with HRRm exhibited more CNV events in both amplification and deletion of HRR genes. Although it has not been well clarified in previous studies of PCa, the amplification and deletion of HRR genes

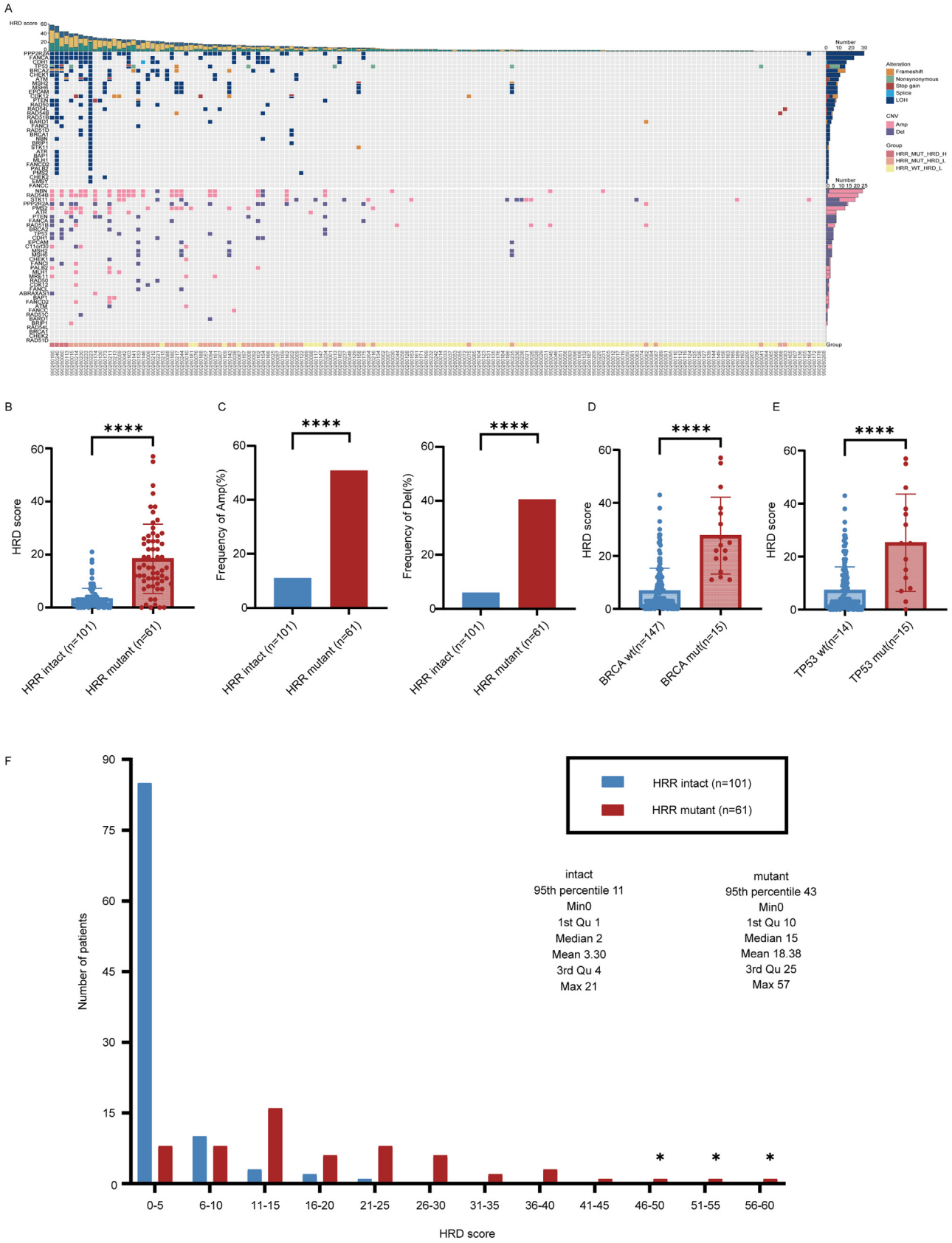

Fig. 1. Establishment of a threshold for HRD score. (A) Heatmap demonstrating the CNV and HRRm status in patients with distinct HRD scores. A HRD score of 43 was used as the threshold of the definition of HRD_L and HRD_H. (B) Histograms displaying the distribution of HRD scores among patients stratified by HRR. (C) Bar plot comparing the frequency of CNV events including amplification and deletion in HRR wt and HRR mut patients. (D-E) Histograms displaying the distribution of HRD scores among patients stratified by *BRCA*, and *TP53* mutation status, respectively. (F) The distribution of HRD scores based on HRRm status in the training set. *, represented where the HRD high patients with *BRCA* mutation located. ****, $P < 0.0001$. Amp, amplification; CNV, copy number variant; Del, deletion; H, high; HRD, homologous recombination deficiency; HRR, homologous recombination repair; L, low; LOH, loss of heterozygosity; Mut, mutant; Wt, wild-type.

Table 1
Baseline characteristics and treatment response of the clinical cohort.

Variables	Entire cohort (n = 16)	HRD high (n = 4)	HRD low (n = 12)	P value
Age, median (IQR), years	64.7 (60.8, 71.8)	69.3 (65.0, 74.3)	63.2 (56.0, 68.0)	0.206
Ethnicity (%)				
Asian	16 (100)	4 (100)	12 (100)	1.000
HRR (%)				
Intact	6 (38)	0 (0)	6 (50)	0.234
Mutant	10 (62)	4 (100)	6 (50)	
cT (%)				1.000
3b	4 (25)	1 (25)	3 (25)	
4	12 (75)	3 (75)	9 (75)	
Gleason score (%)				0.529
7	3 (19)	0 (0)	3 (25)	
8–10	13 (81)	4 (100)	9 (75)	
Baseline PSA (%), ng/mL				1.000
< 15	8 (50)	2 (50)	6 (50)	
≥ 15	8 (50)	2 (50)	6 (50)	
PSA response (%)				0.003
No	11 (69)	0 (0)	11 (92)	
Yes	5 (31)	4 (100)	1 (8)	
Radiologic response (%)				< 0.001
No	12 (75)	0 (0)	12 (100)	
Yes	4 (25)	4 (100)	0 (0)	
PFS (%), months				< 0.001
< 6	12 (75)	0 (0)	12 (100)	
≥ 6	4 (25)	4 (100)	0 (0)	

Abbreviations: HRD, homologous recombination deficiency; HRR, homologous recombination repair; IQR, interquartile range; PFS, progression-free survival; PSA, prostate specific antigen.

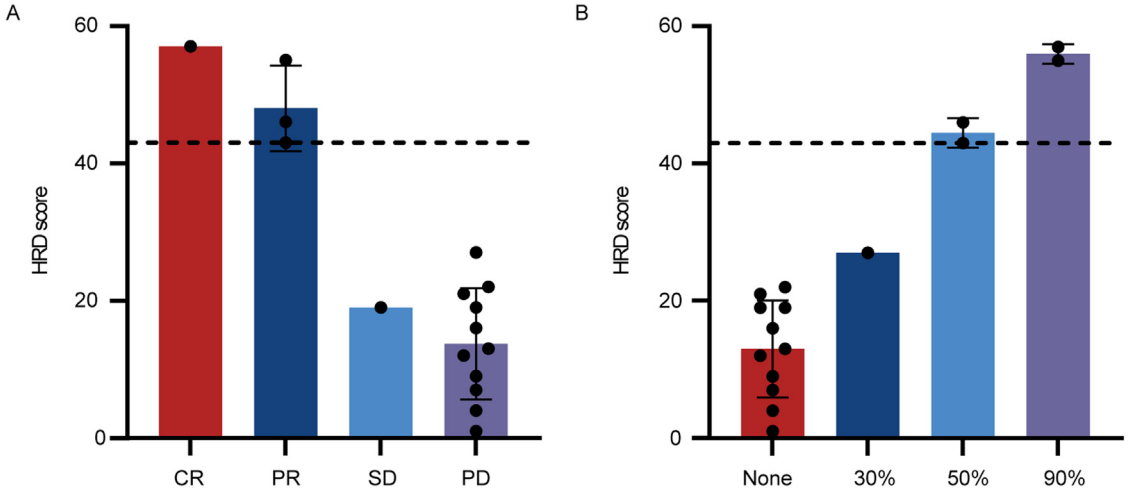

Fig. 2. Box plot showing HRD scores in different (A) radiologic response and (B) PSA response of PARPi treatment. CR, complete release; HRD, homologous recombination deficiency; PD, progression of disease; PR, partial release; SD, stable disease.

may indicate the overexpression and loss of function of genes, contributing to increased genomic instability.

The HRD score is based on genomic scarring to assess the function of the HRR pathway. Compared with detecting mutations in a single gene alone, it provides a more comprehensive evaluation of the function of the HRR pathway. To classify different HRD score patients into HRD and non-HRD, Richardson et al.[7] and Brown et al.[9] initially established two HRD score thresholds of 42 and 33 in breast and ovarian cancers based on the 5th and 1st percentile of the HRD score distribution of *BRCA* mutations in the training set[19-22] and validated in clinical cohorts of neoadjuvant platinum-based chemotherapy. They first established the threshold at the 5th percentile to achieve a sensitivity of 95% in *BRCA* deficient patients. Afterwards, patients with a HRD score of lower than the threshold were found to respond to platinum-based chemotherapy. Therefore, the 1st percentile was further explored. Several subsequent studies further validated these two different thresholds in PARPi treatment cohorts of breast and ovarian cancers.[8,10,11] However, ovarian cancer and breast cancer exhibited higher frequencies of *BRCA* mutations and HRD compared to prostate cancer, resulting in elevated overall HRD scores, and even the *BRCA* intact patients exhibited a higher median HRD score than HRRm patients in our cohort (22 vs. 15).[23] Besides, the landscape of the biallelic mutation type in prostate cancer was different from ovarian and breast cancers. For example, more LOHs were presented in ovarian and breast cancers and more deep deletions in prostate cancer, which may contribute to higher HRD scores in ovarian and breast cancers.[23] Moreover, the HRD score may differ at different disease stages, indicating that the genomic scarring was accumulated without a reversion and it was even not appropriate to use the same threshold at different disease stages in one cancer type.[23,24] Consequently, the threshold values for HRD scores in ovarian and breast cancers may not be applicable to prostate cancer.

A previous study[25] observed that intraductal carcinoma, a rare histology of PCa, displayed a higher HRD score than adenocarcinoma and

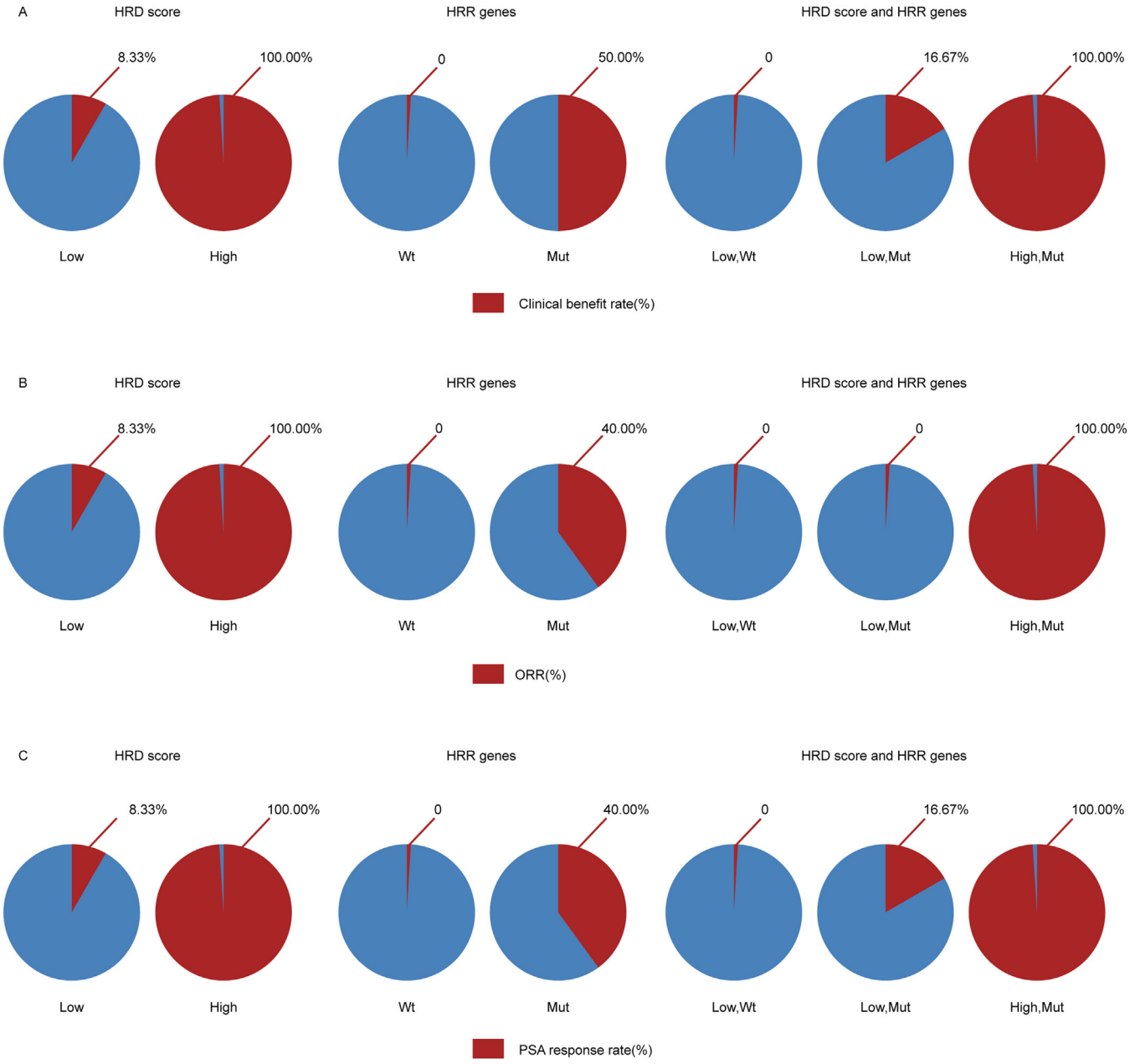

Fig. 3. Pie plot showing (A) clinical benefit rate, (B) ORR, and (C) PSA response rate in the clinical validation cohort stratified by HRD score, HRRm status, and the combination of HRD score and HRR status. HRD, homologous recombination deficiency; HRR, homologous recombination repair; M, mutant; ORR, objective response rate; PSA, prostate specific antigen; WT, wild-type.

a HRD score of ≥ 21 represented a worse prognosis. However, their cohort lacked PARP inhibitor-treated patients. Thus, it was not possible to further determine the threshold value for HRD scores through clinical cohorts. Similar to this study, breast cancer had higher HRD scores in triple-negative breast cancer than in ER+ breast cancer, indicating that different pathological types may require different HRD thresholds to predict the response to PARPi.[11] Another study found that the HRD score was associated with the treatment response to PARPi by setting the cutoff value at 25, the median value of eight *BRCA2* mutant patients.[18] Nonetheless, in their study, they only investigated HRD scores of patients with germline *BRCA1/2* and *CHEK2* and somatic *ATM* mutations and the sample size was relatively smaller than ours. Besides, in their clinical cohort, even the patients with a HRD score < 25 achieved a median PFS of 9.9 months, which was longer than the cohort A in the Profound study (median 7.7 months)[2,18] and indicated a satisfactory treatment response for *BRCA2* mutant patients. Therefore, they failed to conclude a definitive threshold of the HRD score due to the limited samples of their cohort.

Since current clinical guidelines recommend PARPi for HRRm patients, we intended to first establish the threshold by analyzing the HRD score distribution of HRR deficient and HRR intact patients. Since the HRD score of HRRm other than BRCA was lower and a substantial proportion of patients with HRRm may not response to PARPi, we tried to achieve a 95% specificity to ensure the clinical benefit of patients under the clinical trial setting. Therefore, our study firstly determined the threshold of 43 for PCa and analyzed the power as a predictor of the treatment response to PARPi in a small sample population. Consequently, the threshold demonstrated satisfactory efficacy in predicting radiologic and PSA response. We also found that some patients with BRCA or other HRRm but low HRD had poorer response in both PSA

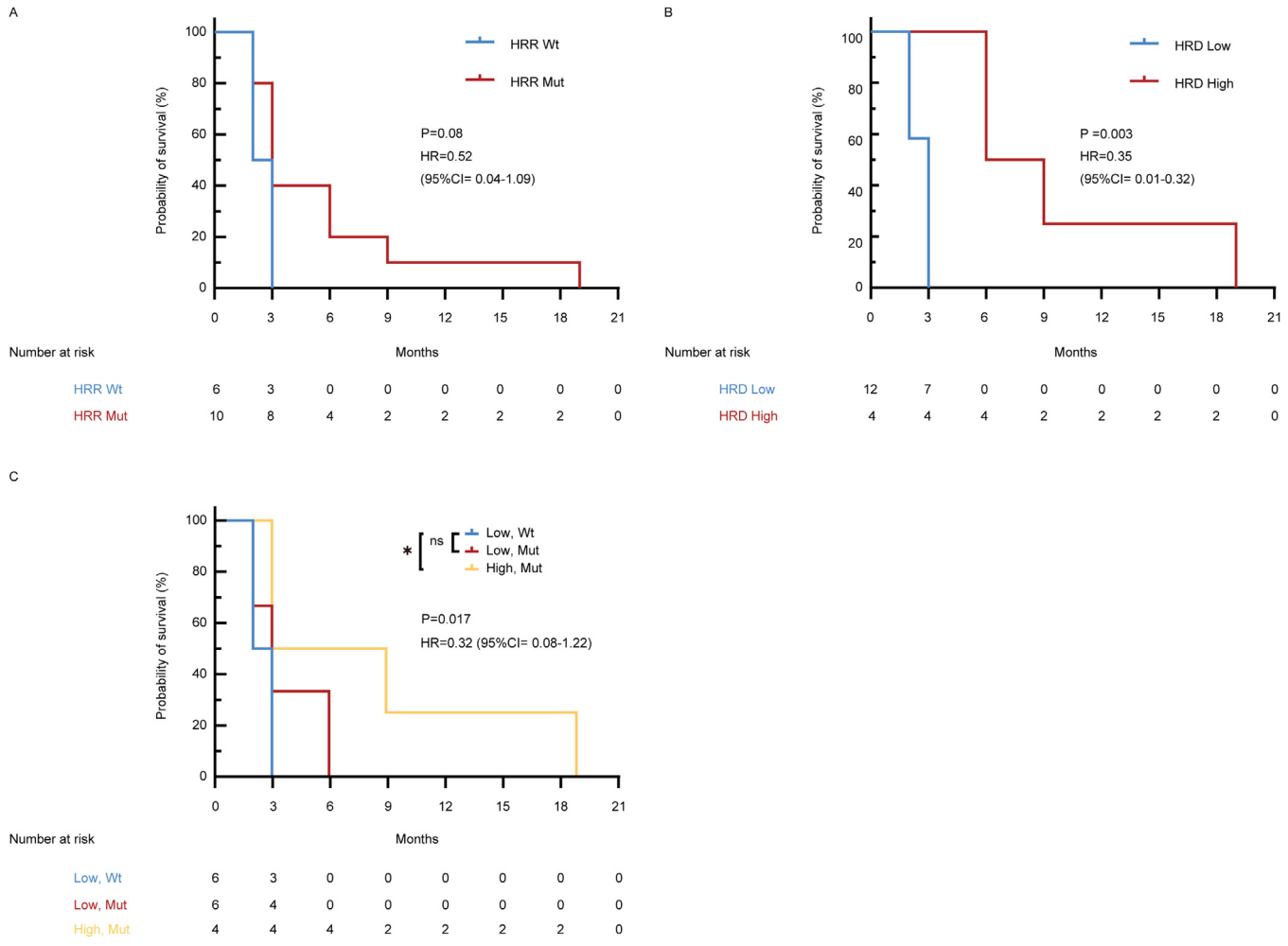

Fig. 4. Association of HRD score and HRR with survival of PARPi treatment. PFS of clinical validation cohort stratified by (A) HRR status, (B) HRD score, and (C) the combination of HRD score and HRR status.
**, $P < 0.001$.
CI, confidential interval; HR, hazard ratio; HRD, homologous recombination deficiency; HRR, homologous recombination repair; PFS, progression-free survival; Mut, mutant; WT, wild-type.

and imaging studies and survival benefits to PARPi treatment compared to patients with high HRD ($P = 0.007$). This suggested that the threshold we set had good specificity for predicting PARPi treatment response. To sum up, a HRD score with an appropriate threshold may broaden the indication of PARPi in future clinical practice, in addition to genetic testing on HRRm. We anticipate that further large clinical trials will confirm the efficacy of this threshold.

Despite these findings, there are some limitations in our study. Firstly, we did not assess the germline mutations due to the lack of paired blood samples and methylation levels at the promoter region of *BRCA1*, which has been reported to be associated with HRD in a previous study.[24] Secondly, genomic mutation detection was based on genes related to the HRR pathway, so other gene mutations that may affect HRD scores, such as *MYC*,[26-29] could not be evaluated. Additionally, our study was lack of analysis on the association between HRD scores and prognosis. Moreover, although preliminary results indicated that the threshold we set had good specificity, the sample size in the clinical cohort was limited and could not achieve the required number for statistical significance. Besides, the clinical analysis was based on the clinical data of a cohort from the training set and lack of internal and external validation for both efficacy and sensitivity in a large population. Therefore, further prospective clinical trials for internal and external validation are needed.

Declaration of competing interest

Dong Yu and Zhao Yi are full-time employees of Precision Scientific Ltd. Other authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Ethics statement

This study was conducted in compliance with the principles of the Declaration of Helsinki and approved by the Institutional Review Board of Sun Yat-sen University Cancer Center (approval number: B2021-288-01). Written informed consent was obtained from all the participants.

Data availability

Further information and requests for resources and reagents generated in this study, the somatic DNA sequencing data and any additional information required to reanalyze the data reported in this paper should be available from the lead contact with a completed materials transfer agreement.

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Author contributions

J.W., D.Z. and Y.H.L. designed the study; D.Z., A.W., Y.W.L., J.Z, T.Z. and X.C. collected samples; D.Z, Y.Z and Y.D. performed sequencing; D.Z., Y.W.L, A.W. and X.C. analyzed the data; J.W. and Y.D. reviewed pathology; J.W., Y.H.L. and F.Z supervised and performed critical review; all authors provided discussion, participated in revising the manuscript, and agreed to the final version.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jncc.2024.05.005.

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