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Title Page

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HRD in Endometrial Cancer: LST Loss Drives Distinct Genomic Profile and Platinum Response

Abstract

While homologous recombination deficiency (HRD) presents therapeutic opportunities in endometrial cancer (EC), its molecular determinants and clinical implications remain poorly characterized. Through genomic analysis of 688 cancer-related genes combined with genomic scar assessment, we investigated HRD molecular features and clinical relevance of HRD across three cohorts: an EC cohort from Sun Yat-sen University Cancer Center (SYSUCC, n = 114), the Cancer Genome Atlas EC cohort (n = 500), and a high-grade serous ovarian cancer (HGSOC) cohort (n = 118). HRD was identified in 23.7% of SYSUCC EC cases, and HRD tumors paradoxically had fewer short-nucleotide variations in HRR genes than proficient (HRP) tumors (18.52% vs. 48.28%, P = 0.007). Mechanistic analysis revealed large-scale transition (LST) losses as the potential predominant HRD driver in EC, occurring significantly more frequently in HRD versus HRP tumors (74.1% vs 5.7%; P<0.001). Comparative genomics demonstrated enrichment of HRR gene LST losses was EC-specific, contrasting with HGSOC where LST distribution was HRD-independent. Clinically, elevated HRD scores predicted reduced progression-free survival (HR 1.74, 95% CI 1.03-2.94; P = 0.04) yet enhanced platinum sensitivity (HR 0.41, 95% CI 0.18 – 0.94; P = 0.034). Our findings indicate that the HRD phenotype in EC, driven primarily by LST losses rather than short-nucleotide variations, serves as both a prognostic and predictive biomarker.

Keywords:

Endometrial cancer, homologous recombination deficiency, large-scale state transitions, immunotherapy

Introduction

Endometrial cancer (EC) has become the most prevalent gynecologic malignancy in developed nations, presenting significant clinical challenges despite generally favorable outcomes[1]. Although the overall prognosis for EC is favorable, a subset of EC are very aggressive; for instance, uterine serous carcinoma (USC) accounts for around 10% of all endometrial cancers but is responsible for 40% of fatalities[2]. Despite therapeutic advances, effective regimens for recurrent patients remain limited, with response rates to second-line therapies typically below 30%[3-5.] These persistent poor

outcomes underscore the critical need for biomarker-driven therapeutic strategies in endometrial cancer.

Emerging evidence highlights the homologous recombination repair (HRR) pathway as a particularly promising therapeutic target in endometrial cancer. Notably, EC demonstrates a high prevalence of HRR gene alterations across major solid tumor types, with genomic analyses revealing HRR pathway mutations in 31.9 – 36.6% of cases[6-7]. The Cancer Genome Atlas (TCGA) research further strengthened this therapeutic rationale by identifying significant molecular parallels between *TP*53 mutant (*TP*53mut) EC and high-grade serous ovarian carcinoma (HGSOC)[8-9], the latter being a malignancy with well-established HRD prevalence and poly(ADP-ribose) polymerase (PARP) inhibitors sensitivity.

Building on these molecular insights, PARP inhibitors have emerged as promising targeted therapies for endometrial cancer, especially in high-risk subtypes including USC and *TP*53mut tumors. The clinical rationale stems from established success in ovarian and breast cancers, where HRD status predicts sensitivity to both PARP inhibitors and platinum-based chemotherapy[10-11]. However, the translation to EC has proven more complex. Initial clinical trials evaluating PARP inhibitors plus immunotherapy in recurrent/metastatic disease, including the DOMEC study and NCT03016338 demonstrated limited clinical benefit[12-13]. The recent DUO-E/GOG-3041 and RUBY part II trials investigating first-line maintenance strategies demonstrated promising clinical activity in advanced endometrial cancer, particularly in the mismatch repair-proficient (pMMR) population. Both studies showed a consistent trend toward progression-free survival (PFS) benefit when combining PARP inhibitors with immune checkpoint inhibitors[14.] However, none of these trials used predictive triage marker for PARP inhibitors treatment, such as HRD, which may partly interpret the discrepancy between strong preclinical rationale and variable clinical efficacy.

While preclinical and early clinical data suggest therapeutic potential, significant gaps remain in our understanding of HRD in endometrial cancer. Current evidence reveals inconsistent HRD prevalence across subtypes: functional assays identified HRD in 26% (6/23) of high-grade endometrioid carcinomas[15], while genomic analyses reported 52% prevalence in serous subtypes[9]. Crucially, no consensus exists for defining HRD in EC, unlike ovarian cancer (OC) where HRD score composed of loss of heterozygosity (LOH), telomeric allelic imbalance (TAI), and large-scale state transitions (LST) metrics is clinically validated. This study addresses three critical unmet needs: systematic validation of HRD scoring in EC using established genomic scar

algorithms;comprehensive characterization of EC-specific HRD molecular features through comparison with OC and elucidation of the clinical relevance of HRD status for patient stratification and response prediction.

Results

Exploration of EC-specific HRD threshould

To define the HRD score threshold, we investigated its association with genetic features (Figure. S1). We first identified the most HRD-relevant gene mutations. Among these, *TP*53 mutations exhibited the strongest positive association with HRD or homologous repair proficiency (HRP) (85% in HRD vs. 18% in HRP; $P < 0.001$), whereas *PTEN* mutations showed the strongest inverse association (26% in HRD vs. 78% in HRP; $P < 0.001$). Co-mutation analysis further revealed divergent patterns: *TP*53 mutations were largely mutually exclusive with other alterations, where *PTEN* mutations, which frequently co-occurred with them, suggesting distinct phenotypic associations (Figure. S2).

We further performed survival analysis to evaluate the association between HRD scores and PFS. Among the HRD scores showed significant P values across all analyses (Supplementary Data), we proposed cohort-specific thresholds: 0 for the SYSUCC cohort and 10 for the TCGA cohort (Figure. S1). This variation in cutoffs is primarily attributable to differences in HRD assay methodologies between the cohorts. Interestingly, the HRD threshold in endometrial cancer (ranging from 0 to 10) is significantly lower than that observed in ovarian cancer (typically between 30 and 40). This suggests that the genomic scarring caused by potential HRD-related mechanisms in endometrial cancer may be more subtle and less extensive compared to ovarian cancer.

HRD status and clinicopathologic characteristics

Consequently, 24% of the SYSUCC cohort and 34% of the TCGA cohort were classified as HRD. The clinicopathologic data of patients in the SYSUCC cohort are shown in Table 1. The median age of patients was 57.7 ± 9.4 years, with stage distribution as follows: Stage I (48.2%), Stage II (7.0%), Stage III (27.2%), and Stage IV (17.5%). The majority of cases were endometrioid carcinoma (68.4%), with 55.3% of tumors classified as poorly differentiated (Grade 3). 92.6% of patients in the SYSUCC cohort with HRD were microsatellite stable (MSS) and exhibited low tumor mutational burden (TMB) at 100%. (Figure. 1); Compared to patients with HRP, patients

with HRD showed negative prognostic features such as a higher percentage of non-endometrioid type (74.1% vs. 25.9%, P < 0.001), a higher rate of adjuvant treatments (77.8% vs. 63.2%, P = 0.039), and a higher rate of distant recurrence (95.2% vs. 65.9%, P = 0.013) (Table.1).

Table 1. Clinicopathologic characteristics stratified for homologous recombination capacity in SYSUCC cohort (EC)

Characteristics	All patients (*N* = 114)	HRD *n* = 27	HRP *n* = 87	*P*-value[a]
Age,years				0.57
Median (range)	59 (34 - 83)	58 (34 - 83)	62 (37 - 71)	
Mean ±SD	57.7 ± 9.4	58.6 ± 9.8	57.4 ± 9.3	
Family history				0.89
Positive	18 (15.7)	5 (18.5)	13 (14.9)	
Negative	96 (84.2)	22 (81.5)	74 (85.1)	
Stage				0.28
FIGO I-II	63 (55.3)	12 (44.4)	51 (58.6)	
FIGO III-IV	51 (44.7)	15 (55.6)	36 (41.4)	
Histologic subtype				< 0.001
Endometrioid	78 (68.4)	7 (25.9)	71 (81.6)	
Non-endometrioid	36 (31.6)	20 (74.1)	16 (18.4)	
Grade				0.057
1-2	51 (44.7)	7 (25.9)	44 (50.6)	
3	63 (55.3)	20 (74.1)	43 (49.4)	
LVSI				0.88
No	64 (56.1)	16 (59.3)	48 (55.2)	
Yes	50 (43.8)	11 (40.7)	39 (44.8)	
Myometrial invasion				0.87
< 50%	67 (58.7)	15 (55.6)	52 (59.8)	
≥ 50%	47 (41.2)	12 (44.4)	35 (40.2)	
Locoreginal Lymph node				0.16
Negative	78 (68.4)	15 (55.6)	63 (72.4)	
Positive	36 (31.6)	12 (44.4)	24 (27.6)	
Peritoneal cytology				0.06
Negative	91 (79.8)	18 (66.7)	73 (83.9)	
Positive	23 (20.2)	9 (33.3)	14 (16.1)	
Adjuvant treatment				0.039
Chemotherapy	66 (58.9)	12 (44.4)	44 (50.6)	
RT/CTRT	20 (17.5)	9 (33.3)	11 (12.6)	
None	38 (33.3)	6 (22.2)	32 (36.8)	
MS				0.057
MSI-H/dMMR	31 (27.2)	3 (11.1)	28 (32.2)	
MSS/pMMR	83 (72.8)	24 (88.9)	59 (67.8)	
Gene Mutation				
POLE Hotspot[d]	4 (3.5)	0 (0)	4 (4.6)	0.847
TP53 Mutation	39 (34.2)	23 (85.2)	16 (18.4)	<0.001
*POLE/TP53*wt	71(62.3)	4(14.8)	67(77.0)	<0.001
TMB[b]				0.005
TMB-H	30 (28.7)	1 (0)	29 (28.7)	

TMB-L	84 (71.3)	26 (100)	58 (71.3)	
Recurrence pattern[c]				0.013
Locoregional, pelvic	16 (24.6)	1 (4.8)	15 (34.1)	
Extrapelvic, distant	49 (75.4)	20 (95.2)	29 (65.9)	

a Non-parameters test was performed for age. Fisher exact test was used for variables excluding age
b Tumor mutation burden (TMB) were calculated in 94 patients. Median value of 10 mut/MB was used as cut-off value for TMB-H and TMB-L.c: Only recurrent patients were calculated. d: Only hotspot mutation were counted (Table S1).
Aberrations:LVSI: lymphovascular space invasion. HR: Homologous repair; RT: adjuvant radiotherapy alone; CTRT: combined adjuvant chemotherapy and radiotherapy. MS: microsatellite status; dMMR: mismatch repair deficiency; pMMR: mismatch repair proficiency; TMB-H: tumor mutation burden-high; TMB-L: tumor mutation burden low; wt: wild type

Paradoxical distribution and heterozygous nature of HRR gene alterations in EC

In the SYSUCC cohort, 41.2% of samples had alterations in HRR pathway genes. The *BRCA*2 gene exhibited the highest mutation frequency at 9.65%, followed by *FANCM* at 7.89% and *BRCA1* at 7.02%. Paradoxically, the HRR gene mutation rate was significantly lower in patients with HRD compared to those with HRP (18.52% vs. 48.28%, P = 0.007), a trend also observed in the TCGA cohort (20.36% vs. 52.74%, P < 0.001) (Figure. S3B). Extending this pattern, analysis of additional DNA damage repair (DDR) pathways, including MMR, BER, and NHEJ revealed consistently higher alteration rates in HRP patients versus HRD patients in both SYSUCC and TCGA cohorts (Figure. S3A–B).

To address the unusually high rate of DDR-related gene mutations in HRP phenotype with EC, we examined the zygosity of HRR genes, recognizing that biallelic changes are typically required for loss of function. Our methodology defined an HRR gene to be homozygous if it showed LOH positive at single gene level. Intriguingly, our results indicated that all mutations in HRR genes were heterozygous, implying that despite the higher mutation rate in HRP patients, these mutations were potentially non-functional and not associated with HRD in EC .

HRD in EC was characterized by LST loss of HRR genes

Previous studies have reported that large deletion (> 1MB) in HRR genes is a recognized source of HRD[19]. We categorized LST alterations at a single gene level into LST-gain or LST-loss. Typically, LST loss results in LOH-positive and functional loss. Thus, we further classified HRR genes into five types: LOH negative, LOH negative with LST gain, LOH only, LOH with LST gain, and LOH with LST loss (Figure. 2A). LOH with LST loss was observed in all HRR genes except *ATR* in EC with HRD. *MRE11A* had the highest LOH with an LST loss rate of 40.74%, followed by *ATM* (37.04%) and *FANCC* (37.04%) (Figure. 2B).

LOH with LST loss was further analyzed and compared in a chromosomal view in HRD patients from both the SYSUCC EC cohort and the FUDAN HGSOC cohort. Chromosomally, the hotspot regions of LOH with LST loss in EC were generally overlapped with OC (Figure. 2C-D). Notably, we identified specific regions that are particularly susceptible to LST loss in EC, including *MRE11A*, *FANCL*, *XRCC2*, *ATM*, *BRAD1*, and *FANCC* (Figure. 2E). Additionally, *RAD51C* and *BRCA1*, which were core HRR genes involved in OC with HRD, showed a significantly increased rate of LST loss in OC compared to EC (Figure. 2E).

We further compared patients dominated by LOH with LST loss in EC and OC. While LOH with LST loss was strongly associated with HRD in EC (74.1% vs. 5.7% in HRP; $P < 0.001$), it was independent of HRD status in HGSOC (Figure. 3, Table. 2). In EC, patients with the "LOH with LST loss" pattern had significantly higher HRD scores than those in other categories ($P < 0.001$, Figure. 2F). In contrast, in HGSOC, this pattern was not associated with HRD scores (Figure. 2G). Furthermore, Gene Ontology (GO) enrichment analyses showed that genes with "LOH with LST loss" were enriched in pathways involved in DNA binding (Figure. S4) in EC. Taken together, these results hinted that EC had specific hotspot regions of LST loss that encompass a bunch of HRR genes, providing a distinct source of HRD.

Table 2. Genetic features of HRR genes stratified by HRD status in EC and OC

	SYSUCC cohort (EC)			Fudan cohort (OC)		
Genetic signatures	**HRD n = 27 No. (%)**	**HRP n = 87 No. (%)**	**P**	**HRD n=39**	**HRP n=78**	**P**
LOH[a]			<0.001			0.10
Positive	26 (96.3)	22 (25.3)		36 (92.3)	78 (100.0)	
Negative	1 (3.7)	65 (74.7)		3 (7.7)	0 (0.0)	
LST[b]			<0.001			0.08
LST gain	27 (100)	28 (32.2)		33 (84.6)	76 (97.4)	
LST loss	20 (74.1)	5 (5.7)		25 (64.1)	52 (66.7)	
Gene with LOH positive						
LOH positive with LST gain	2 (7.4)	4 (4.6)	0.94	14 (35.9)	44 (56.4)	0.23
LOH positive with LST loss	20 (74.1)	5 (5.7)	<0.001	22 (56.4)	49 (62.8)	0.93
LOH without LST	16 (59.3)	16(18.4)	<0.001	26 (66.7)	70 (89.7)	0.02

a. Loss of heterozygosity; b. Large-scale state transition

The prognostic and predictive value of genomic HRD score

Survival analysis of the overall patient population identified HRD as a negative prognostic indicator in both EC cohorts. In the SYSUCC cohort (median follow-up 77.1 months), HRD patients had significantly shorter PFS compared to HRP patients (HR 1.74, 95%CI 1.032–.94, P = 0.035) (Figure. 4A). This association was even stronger in the TCGA cohort, where the HR was 3.07 (95% CI 2.18–4.33, P < 0.0001) (Figure. 4B). No prognostic significance of HRD was observed in patients who received postoperative platinum-based chemotherapy. This finding implies that the prognostic impact of HRD on survival outcomes is likely modulated by other factors such as clinical stage and pathological subtypes.

The HRD score showed distinct predictive value for treatment response in a recurrent setting. HRD was positively correlated with extended platinum-related PFS in patients undergoing first-line platinum-based chemotherapy (P = 0.034) (Figure. 4C). In contrast, the study identified HRD as a potential negative predictor of response to immunotherapy, as we observed that the presence of any positive LST/LOH/TAI status (LST or LOH or TAI score > 5) tended to shorter PFS in patients who received immunotherapy(Figure. 4D, P = 0.021).

Discussion

Although pan-cancer analyses have consistently reported lower HRD prevalence in endometrial cancer (EC) relative to ovarian, breast, and other high-HRD malignancies HRD is not infrequent, particularly among high-risk subtypes[2,9,15]. Elze, L. et al. and Rempel et al., using genome-wide HRD classifiers (scar-based signatures), placed EC among tumors with modest HRD rates[16-17]. Jonge et al, who reported that 24% (6/25) of EC cases exhibited HRD, as determined by a functional ex vivo RAD51 assay[9]. Tumors harboring HRD exhibit heightened sensitivity to PARP inhibitors and platinum chemotherapy. Contrary to expectations, studies have documented suboptimal and conflicting outcomes of PARP inhibitor (PARPi) therapy in EC[12-14]. Thus, One of the main challenges is identifying tumor-specific biomarkers for HRD with clinical significance to guide clinical decision-making in EC.

Utilizing a clinically validated HRD scoring system and EC-specific cut-offs, our study pioneers the exploration of a clinically applied defination of HRD in EC, with 23.7% and 34% of EC patients classified as HRD in SYSUCC and TCGA cohorts, respectively. The proportion observed in our cohort reflects an EC-specific HRD threshold optimized for LST-dominant scars rather than

pan-cancer cutoffs. Additionally, the relatively high portion of pathological high-risk type and *TP53*mut cases in the SYSUCC cohort may also increase the HRD rate. These factors highlight the critical influence of cohort composition and scoring methodology on reported HRD frequency. It is crucial to note that our study provides only a theoretical estimate of the HRD prevalence in EC. The definitive establishment of an HRD threshold must ultimately be derived from the analysis of prospective clinical trials investigating PARP inhibitors in EC. Notably, the HRD in EC exhibited a much lower genomic scar cut-off value than OC, challenging the well-established BRCA-centric model of HRD in ovarian cancer. These observations collectively suggest that HRD in EC represents a less pronounced or attenuated form relative to OC. This distinction provides a rationale for exploring combination therapies to enhance sensitivity to PARP inhibitors.

To better understand the mechanisms of HRD in EC, we analyzed genetic features of HRD in EC. Although a few studies have documented the high prevalence of HRR gene mutations in EC[6], we observed that HRR mutations occur predominantly in HRD-negative patients. By contrast, the incidence of LST loss in HRR genes was significantly increased in HRD-positive EC, while LST loss event was independent of HRD status in OC. Furthermore, enrichment analysis revealed that in HRD-positive EC, "LOH with LST loss" events are enriched in genes involved in the DNA binding pathway. HRD arises through diverse mechanisms beyond canonical HRR gene mutations, including promoter hypermethylation, large structural variants (SVs), and LOH[18]. While SVs encompassing HRR loci are frequent drivers in high-grade serous ovarian cancer (~20% of cases)[19], they are uncommon in EC. Instead, our data show that HRR gene mutations are predominantly heterozygous and lack a second hit, consistent with non-functional passenger events rather than drivers of HRD. Additional analysis excluding *POLE*-mutated and MSI-H cases, which were expected to have TMB-H and frequent HRR alterations, showed similar enrichment of HRR mutations in HRP phenotype (Figure. S5). In contrast, functional HRD in EC is strongly associated with large-scale structural genomic loss, which frequently results in biallelic inactivation of DNA repair genes, including but not limited to the HRR pathway[20]. Notably, mutations across multiple DNA repair pathways are enriched in HRP tumors, suggesting that compensatory repair mechanisms remain intact in non-HRD cases, whereas LST-mediated broad genomic collapse dominates in HRD EC[21]. This distinguishes EC from ovarian cancer and challenges the sequential, mutation-first model of HRD. To our knowledge, this represents the first comprehensive

mechanistic analysis of HRD etiology in endometrial cancer, establishing LST loss, not HRR SNVs or locus-specific SVs, as the primary driver.

In EC, LST of HRR genes could be a valuable indicators of HRD and was positively corelated with HRD score. Of note, LOH but not LST has been proposed as a valuable indicator for HRD and treatment response in OC[22-23]. To further understand LST events in EC, we compared LST occurence in SYSUCC EC cohort and FUDAN OC cohort. Generally, the hotspots for LST, as well as LOH and TAI are generally congruent between OC and EC (Figure. 2C, Figure. S6). This finding echoed with previous studies which reported common chromosomal fragile sites which are structurally predisposed to generating genomic scars under pressure such as HRD[24-25]. Notably, a small area on chromosome 11 that encompasses both *ATM* and *MRE11A* showed a high incidence of LST loss in EC, which does not exist in OC, highlighting a potential EC-specific pattern of HRD. *ATM* is a pivotal gene in homologous recombination repair and has been identified as a marker of HRD in pancreas cancer[26.] ATM serves as a crucial regulator of *TP53* and *MRE11A*[27]. Interestingly, a significant higher rate of LST loss in *BCRA1* was observed in OC compared with EC in our study. Our results suggest tumor-specific LST loss may be a critical source of HRD and dysfunction in the *ATM/TP53/MRE11A* axis could be a potential driver of HRD in EC.

The elevated prevalence of LST loss in EC with HRD has yet to be elucidated, and we hypothesized this may stem from its distinct molecular milieu and endogenous sources of genomic instability. A key vulnerability may arise from the *TP53/ATM/MRE11A* axis, as we observed, where *TP53* mutations disrupt cell-cycle checkpoints, while concurrent *ATM/MRE11A* loss impairs double-strand breaking sensing and resection, synergistically amplifying LST events[28]. Estrogen overexposure—hallmarks of EC etiology—could generate various DNA lesions through genotoxic estrogen metabolites[29]. Endogenous DNA damage, arising from oxidative or metabolic stressors during rapid endometrial cycling, was reported to promote fragility[30]. Certainly, the mechanisms underlying LST occurrence in EC require further mechanistic studies to confirm.

Among the 27 HRD-positive cases in our study, three were concurrently classified as MSI-H/dMMR. Although chromosomal instability and microsatellite instability are generally viewed as mutually exclusive, emerging evidence challenges this paradigm[31]. Specifically, these three patients comprised two cases with a dMMR–*TP*53mut phenotype and one with an MSI-H-*ARID1A*mut genotype. This finding aligns with a prior retrospective study of 3,518 endometrial

cancers, which identified 64 cases (1.8%) with dMMR-p53abn,a subgroup that often retains morphological characteristics typical of dMMR endometrial carcinoma[32]. We hypothesize that these tumors may represent cases where secondary HRD alterations, driven by the functional loss of genome-stabilizing genes such as *TP53* or *ARID1A*, developed within a primary MSI-H/dMMR background. Together, these observations suggest that HRD can arise via mechanisms distinct from impaired homologous recombination repair (e.g.LST loss), underscoring the multifaceted nature of genomic instability in endometrial cancer.

HRD was favorable prognostic markers for OC patients as it provides better responses for chemetherapy and PARP inhibitors. The prognostic significance of HRD in EC is less studed. An HRD score of ≥ 4 is reported to be associated with worse survival in a subset of endometrioid EC[15]. Our analysis further confirmed that HRD is a negative prognostic factor across both EEC and non-EEC patient populations, and it was partly explained by high-risk clinical-pathological factors accompanied in EC with HRD. For predicitve value, HRD is linked to prolonged PFS with first-line platinum-based chemotherapy in recurrent patients.

Tumors with HRD exhibit a richer tumor antigen profile, which theoretically could enhance the efficacy of immunotherapy. Loss of *ATM* function was identified as a potential contributor to HRD in EC in our study and is proposed as a candidate biomarker for immune checkpoint therapy in endometrial cancer[33]. However, in our study patients with HRD, tended to have a shortened PFS with immunotherapy. Although the interpretations of our study should be considered in light of retrospective design and a limited cohort size，similarly, subgroup analyses from NRG-GY018 (NCT03914612) and ENGOT-EN6 (NCT03981796) demonstrated that the additional benefits of immunotherapy were influenced by MMR status but not HRD-related features. MSI-H and POLE mutations in EC were clinically established immunotherapy markers, and most tumors with HRD are mutually exclusive of MSI-H and *POLE*; this biological distinction likely underlies the negative correlation between HRD status and immunotherapy efficacy in EC. However, the intrinsic immunogenic potential of the HRD phenotype may also account for the increased clinical response to immunotherapy observed in *TP53* mutant endometrial cancer,albeit inferior to MSI-H and *POLE*mut tumors[34]. The optimal targeted combination strategy, including immunotherapy in HRD-positive EC patients, should be tailored as we further understand the molecular signatures of HRD EC.

Unlike ovarian cancer, where HRD is often driven by HRR gene mutations, HRD in EC is more closely associated with LST loss. There is still much to learn about the underlying mechanisms and how to best leverage HRD to optimize treatment strategies. The limitations of our study is retrospective nature and lacks futher multi-omics data. The HRD threshold and prevalence estimate in endometrial cancer is preliminary and influenced by sample size, clinical stage, and high-risk histology. Definitive HRD thresholds score must be established through prospective PARP inhibitor trials in EC. Future research should focus on refining therapeutic approaches for HRD-positive EC patients, with particular attention to combination therapies that address the unique molecular features of HRD in EC.

List of abbreviations

Methods

Patients and cohorts

SYSUCC cohort. Patients with a pathological diagnosis of endometrial cancer between 2014 and 2022 at Sun Yat-Sen University Cancer Center were screened for inclusion in this study. Patients were excluded if they had insufficient survival information (follow-up time less than 2 years), a concurrent cancer diagnosis, insufficient tissue samples, or had received non-standard treatment. A total of 114 patients met our inclusion criteria and were included in the SYSUCC cohort.

Detailed information on patient demographics, pathology reports, treatment details, and outcome data were obtained from electronic medical records and telephone follow-up. This retrospective study was approved by the Institutional Review Board and local ethics committees of Sun Yat-sen University Cancer Center (NO. SL–B2021–042–03) and was conducted in accordance with the Declaration of Helsinki. All patients in the cohort provided informed consent for sample collection prior to surgery.

TCGA cohort. The variation data was downloaded from UCSC XENA (cohort name: UCEC; dataset name: MuTect2 Variant Aggregation and Masking). Corresponding clinicopathologic information was downloaded from the TCGA database by aligning the sample ID. HRD scores were downloaded from the literature[35]. Patients with sufficient mutational and clinical information were included in the analysis (n = 500).

FUDAN cohort. Tumor collection for FUDAN cohort was approved by the Institutional Reviewer Board of Fudan University Shanghai Cancer Center (NO. 1703170–15). Informed written consent was obtained from all individual patients. One hundred eighteen patients

with high-grade serous ovarian carcinoma (HGSOC) from Fudan University Shanghai Cancer Center underwent HRD testing (FUDAN cohort). The HRD-related features of these patients were compared with 114 EC patients in the SYSUCC cohort. All the clinicopathologic data for 118 patients in the HGSOC cohort can be found in previous publications[36.]

Mutational profile analysis

Genomic DNA (gDNA) was extracted from formalin-fixed, paraffin-embedded (FFPE)/liquid nitrogen preserved tissue and paired peripheral blood samples by QIAamp DNA TISSUE and paired blood Kit (Qiagen, Hilden, Germany) according to the manufacturer's instructions. Sequencing of 688 key cancer-related genes and HRD-related regions was performed on an MGISEQ-2000 sequencer following the manufacturer's protocols. Raw data was first filtered by SOAPnuke to exclude reads with low quality. The clean reads were then aligned to the reference human genome (UCSC GRCh37/hg19) using the BWA MEM algorithm. Single nucleotide variants (SNV) and insertion and deletion variants (INDEL) were called by the Genome.

Analysis Tool kit (GATK) toolkit 3.2, with parameters optimized for HaloPlex-generated sequences. Copy number variants (CNVs) were detected using the CNVnator read-depth algorithm. InterVar was utilized to annotate germline and somatic mutations, which were then interpreted in accordance with the "Genetic Variation Annotation Standards and Guidelines" (2015 Edition) issued by the American College of Medical Genetics (ACMG) for germline mutations and the "Cancer Mutation Interpretation Guidelines and Standards (2017 Edition)" for somatic mutations. CNVs called from NGS data were further validated using quantitative PCR (qPCR) for all reported significant alterations. This two-step approach, initial NGS-based calling followed by independent qPCR confirmation, ensures the high reliability of our CNV findings by effectively filtering out potential technical artifacts. Variants predicted as pathogenic or likely pathogenic were considered deleterious. Microsatellite instability (MSI) and tumor mutation burden (TMB) were calculated using 688 gene panel data. The TMB was generally determined by computing the number of mutations (allele frequency > 1.5%) in non-driver genes per Mb in each sample. MSIsensor and MANTIS were employed to detect the MSI status.

HRD Score Calculation and Threshold Determination

HRD scores for the SYSUCC (EC) and FUDAN (OC) cohorts were computed using ASGAD (Allele-Specific Gene-scar Analysis tool for Diagnosis), a validated genomic scar algorithm. This tool quantifies three key genomic instability markers: LOH,TAI and LST. The algorithm

incorporates tumor purity and ploidy corrections to enhance measurement accuracy. The HRD scores of TCGA EC cohort were downloaded from database.

TO determine HRD threshould, we applied the established gHRD score cut-off of 42 in FUDAN cohort (OC), as previously validated in ovarian cancer[36]. For two endometrial cancer cohorts, we implemented a cancer-type specific approach to determine optimal HRD thresholds as demonstrated in results.

LST/LOH signatures of HRR gene

By aligning the areas of LST events and LOH events in chromosomes with a gene annotation file (GFF file from ENSEMBL), we determined whether an HRR gene was LST-positive or LOH-positive. Each gene with LST positive was subclassified as LST gain and LST loss. LOH of each HRR gene was measured to evaluate the heterozygosity. To better demonstrate, we grouped the HRR gene as "LOH with LST gain," "LOH with LST loss," "LOH only," and "LOH negative with LST gain." As LST loss would inevitably lead to LOH at a single gene level, there is no "LOH negative with LST loss."

Statistical analysis

The t-test, Fisher exact test, and Mann-Whitney test were used to compare clinical-pathological and genetic features between the two groups. Overall PFS was measured from the date of primary surgery until the first relapse or death, whichever occurred first. For recurrent patients in the SYSUCC cohort, the therapeutic effects of first-line platinum-based chemotherapy were measured by the time from initiation of chemotherapy to the second progression, defined as platinum-related progression-free survival (Pt-PFS). Accordingly, we calculated immunotherapy-related PFS (iPFS) in patients treated with immunotherapy. Disease progression was determined by imaging or biopsy. PFS was estimated using the Kaplan-Meier method and compared between subgroups using the log-rank test. Hazard ratios (HR) with a 95% confidence interval (CI) were estimated by Cox proportional hazards model. SPSS software (v.23.0, IBM SPSS Statistics, Armonk, NY, USA) and R software (v4.2.1, http://www.r-project.org) were used for statistical analysis. All P values were two-sided, with $P < 0.05$ indicating statistical significance.

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Data Availability statements

Human DNA data of TCGA cohort (EC) are available via UCSC XENA (cohort name: UCEC; dataset name: MuTect2 Variant Aggregation and Masking; https://xenabrowser.net/datapages/) for interactive use. The HRD scores of TCGA cohort (EC) analysed during this study are included in reference[35] and its supplementary information files. The data of SYSUCC cohort are not publicly available due to but are available from the corresponding author on reasonable request. The data of FUDAN cohort have been deposited into CNGB Sequence Archive(CNSA) of China National GeneBank DataBase (CNGBdb) with accession numberCNP0001456.

Code Availability Statement

The underlying code for this study is not publicly available but may be made available to qualified researchers on reasonable request from the corresponding author.

Competing Interests

All authors declare no financial or non-financial competing interests.

Author Contributions

W.W, Z.M.D and L.J.D: Conceptualization, methodology,draft polish. W.T and Q.Q.L:Provided clinical samples and data collecting.H.W:provided data of FUDAN cohort. Y,X.Analyzied data. M.F.L, B.B,L and D.D: writing-original draft.All the authors have read and approved the final manuscript.

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Figure Legends

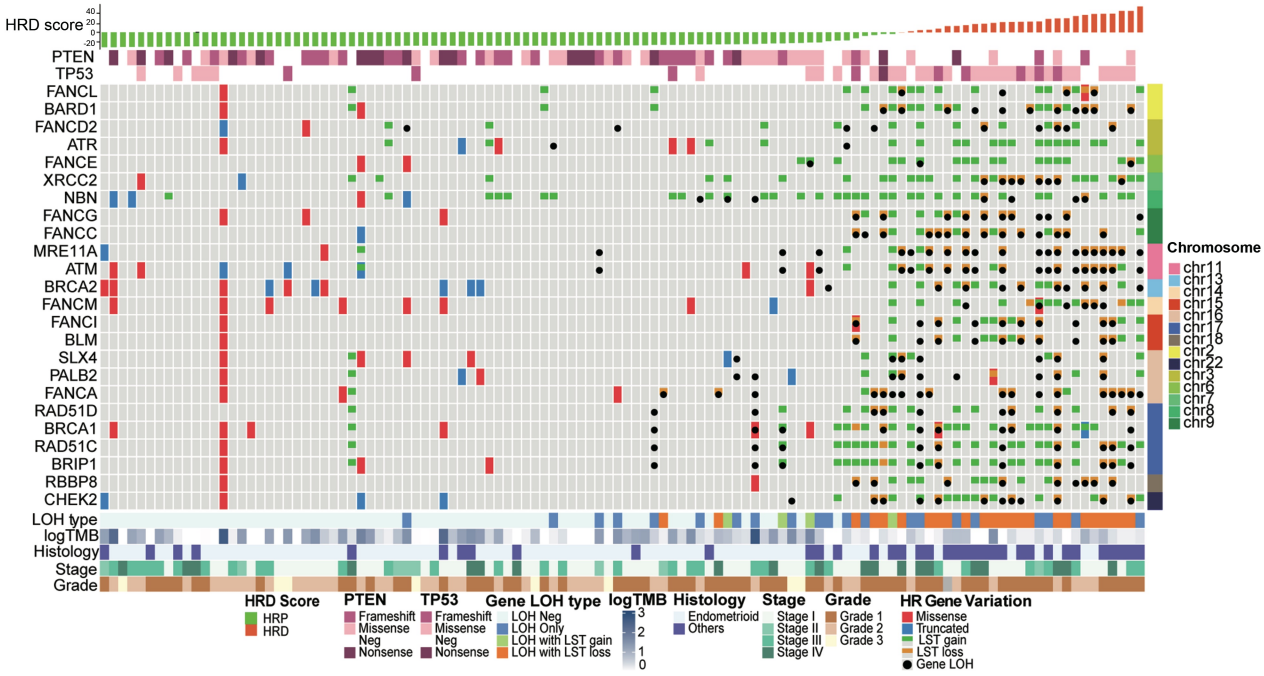
Figure 1. HRR Alterations by HRD Status (SYSUCC EC Cohort) The top panel presents genomic HRD scores, with HRD (red) and HRP (green) distinctly labeled. The second panel depicts the mutation frequencies of TP53 and PTEN. In the third panel, variations in HRR genes are organized by chromosomal location, where LOH positivity at the single gene level is marked by black dots, and LST gain (green) as well as LST loss (orange) are annotated for individual genes. The bottom panels provide a summary of genomic alterations and clinicopathological features. Abbreviations: HRR, homologous recombination repair; HRD, homologous recombination; HRP, homologous recombination proficiency; LOH, loss of heterozygosity; LST, large-scale state transition; Neg, Negative; Chr, chromosome.

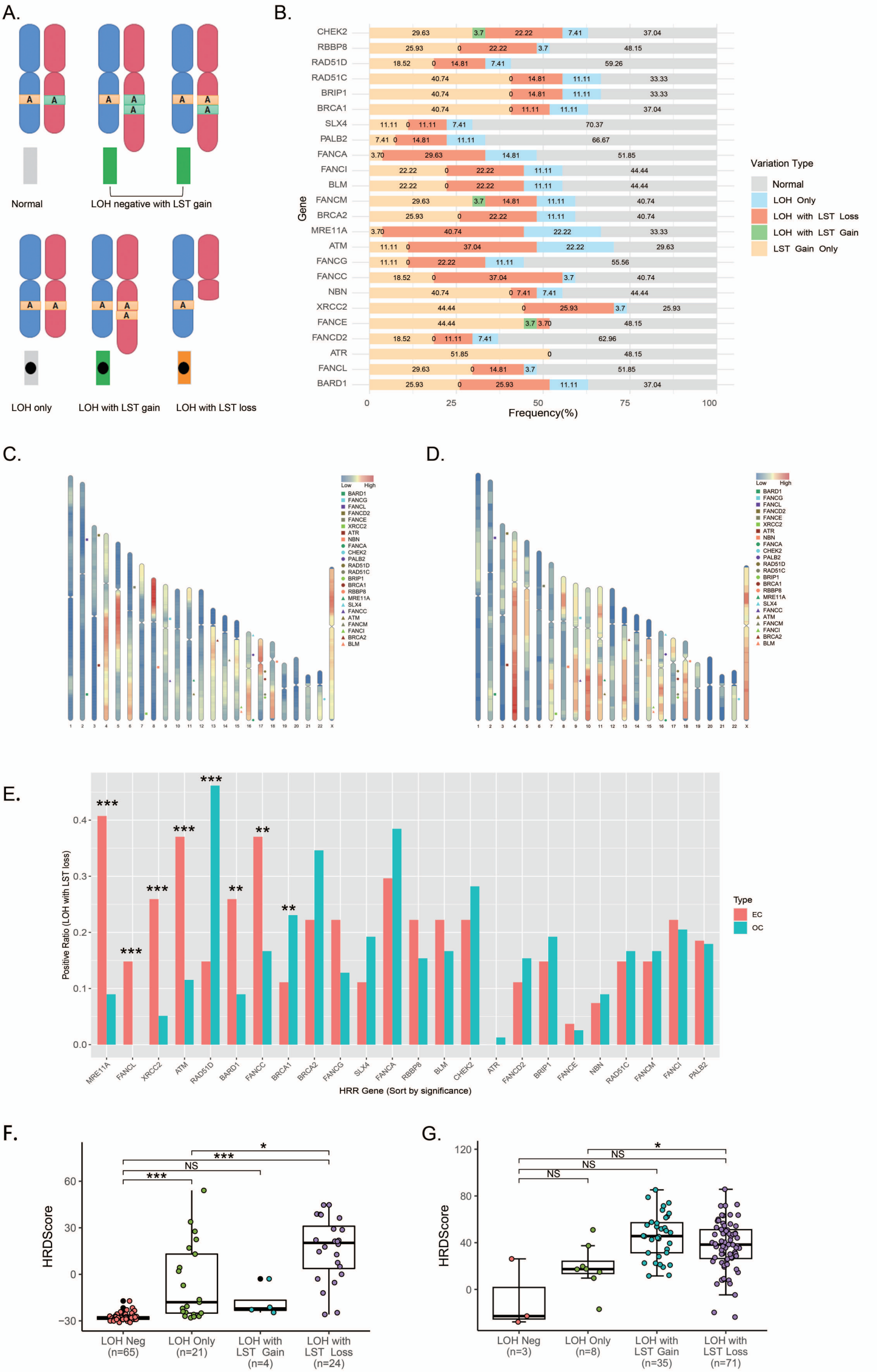
Figure 2. Comparison of HRR Gene LOH and LST Between Endometrial and Ovarian Cancers A) Classification of five types of LOH/LST status at the single gene level. B) Distribution of LOH/LST variations in HRR genes from HRD-positive EC patients. C–D) Chromosomal distribution of LST loss in EC (C) and OC (D). E) Significant differences in the prevalence of LOH with LST gain between the OC and EC for HRR genes. F–G) Association between LOH/LST variations and genomic HRD scores in EC (F) and OC (G). (*$p < 0.01$, **$p < 0.001$, ***$p < 0.0001$, ****$p < 0.00001$). Abbreviations: HRR, homologous recombination repair; LOH, loss of heterozygosity; LST, large-scale state transition; HRD, homologous recombination; EC, endometrial cancer; OC, ovarian cancer; NS, not significant.

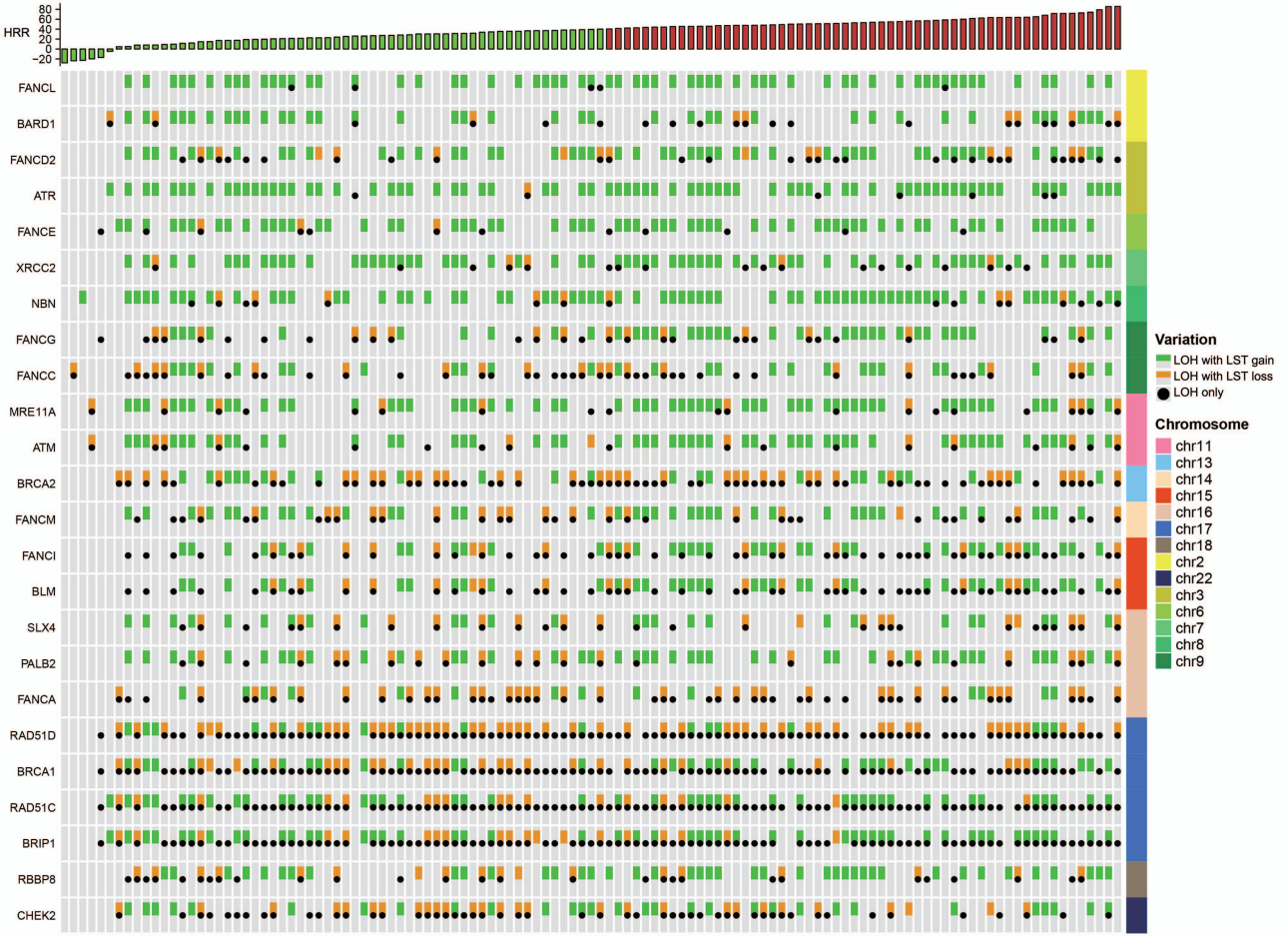
Figure 3. HRR Alterations by HRD Status (FUDAN OC Cohort) The top panel presents genomic HRD scores, with HRD (red) and HRP (green) distinctly labeled. LOH positivity at the single gene level is marked by black dots, and LST gain (green) as well as LST loss (orange) are annotated for individual genes. Abbreviations: HRR, homologous recombination repair; HRD, homologous recombination; HRP, homologous recombination proficiency; LOH, loss of heterozygosity; LST, large-scale state transition; Neg, Negative; Chr, chromosome.

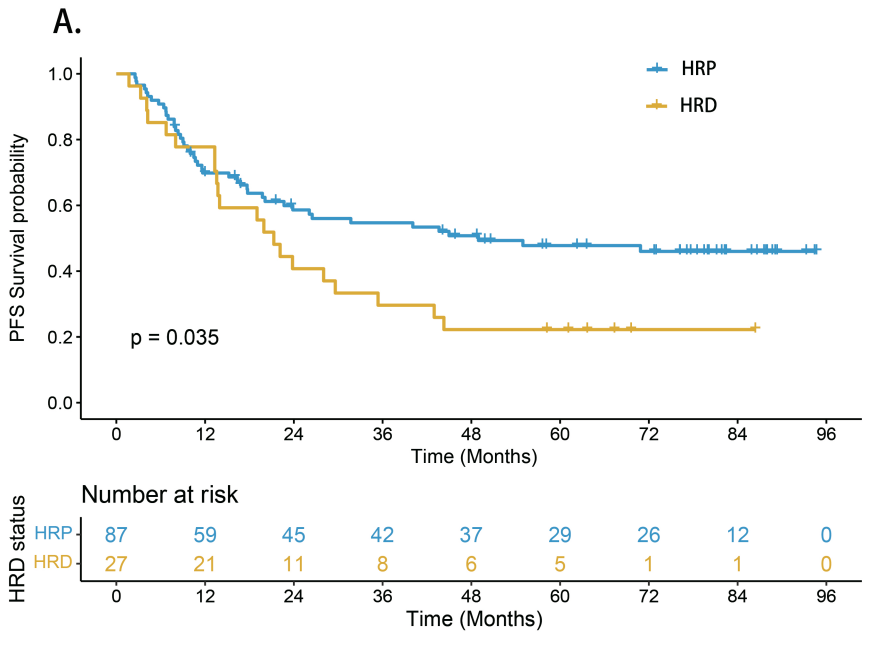
Figure 4. Prognostic and predictive value of genomic HRD score in endometrial cancer

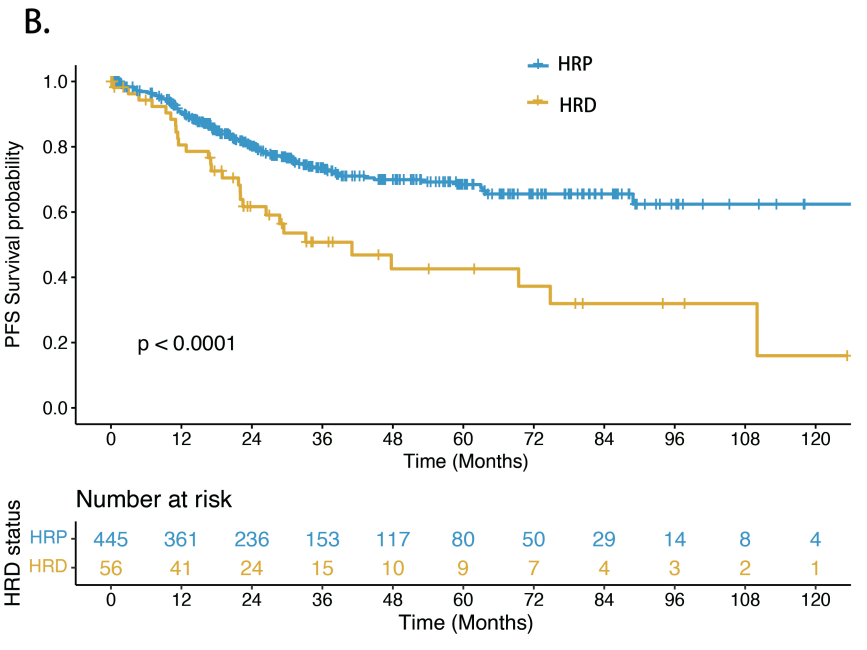
A–B) Patients with HRD exhibit shorter PFS in the SYSUCC cohort (A) and TCGA cohort (B), compared to HRP patients. C) HRD is associated with better PFS in patients receiving platinum-based first-line chemotherapy. D) Recurrent patients receiving immune checkpoint inhibitors showed inferior PFS when exhibiting positivity for any HRD genomic scar signature (LST/LOH/TAI) compared to those without these features. Abbreviations: HRD, homologous recombination; HRP, homologous recombination proficiency;PFS: progression-free survival; LOH, loss of heterozygosity; LST, large-scale state transition; TAI: telomeric allelic imbalance

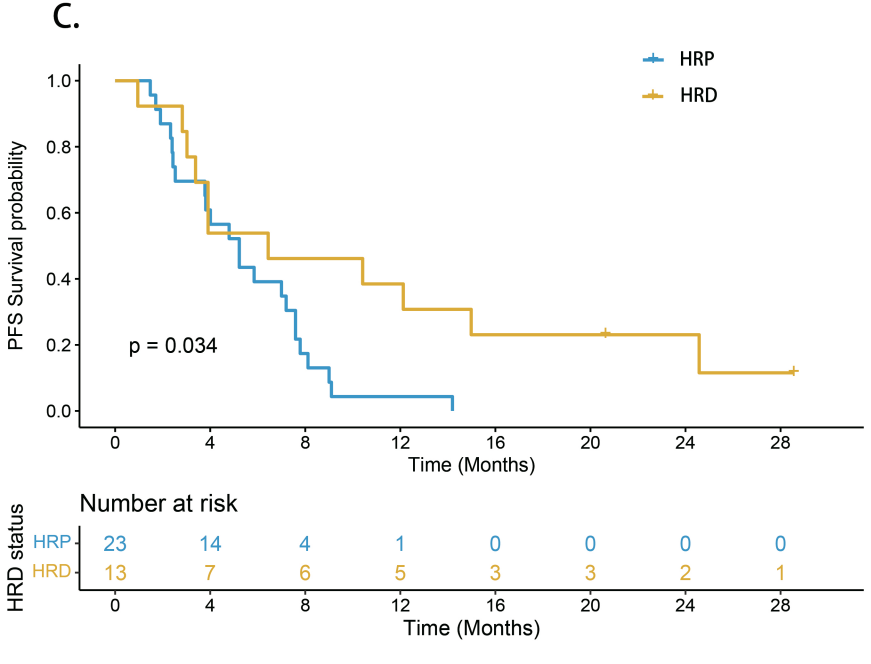

HRD score
40
20
0
-20
PTEN
TP53
FANCL
BARD1
FANCD2
ATR
FANCE
XRCC2
NBN
FANCG
FANCC
MRE11A
ATM
BRCA2
FANCM
FANCI
BLM
SLX4
PALB2
FANCA
RAD51D
BRCA1
RAD51C
BRIP1
RBBP8
CHEK2
LOH type
logTMB
Histology
Stage
Grade
Chromosome
chr11
chr13
chr14
chr15
chr16
chr17
chr18
chr2
chr22
chr3
chr6
chr7
chr8
chr9
HRD Score
HRP
HRD
PTEN
Frameshift
Missense
Neg
Nonsense
TP53
Frameshift
Missense
Neg
Nonsense
Gene LOH type
LOH Neg
LOH Only
LOH with LST gain
LOH with LST loss
logTMB
3
2
1
0
Histology
Endometrioid
Others
Stage
Stage I
Stage II
Stage III
Stage IV
Grade
Grade 1
Grade 2
Grade 3
HR Gene Variation
Missense
Truncated
LST gain
LST loss
Gene LOH

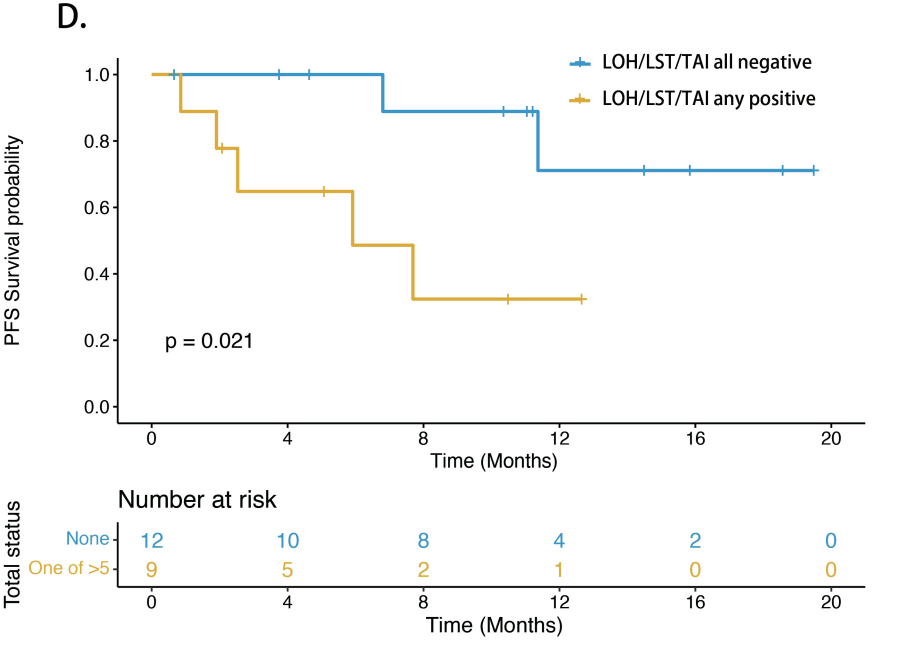

A.
Normal
LOH negative with LST gain
LOH only
LOH with LST gain
LOH with LST loss
B.
Gene
Frequency(%)
Variation Type
Normal
LOH Only
LOH with LST Loss
LOH with LST Gain
LST Gain Only
C.
D.
Low
High
E.
Positive Ratio (LOH with LST loss)
HRR Gene (Sort by significance)
Type
EC
OC
F.
HRDScore
LOH Neg (n=65)
LOH Only (n=21)
LOH with LST Gain (n=4)
LOH with LST Loss (n=24)
G.
HRDScore
LOH Neg (n=3)
LOH Only (n=8)
LOH with LST Gain (n=35)
LOH with LST Loss (n=71)


HRR
80
60
40
20
0
−20
FANCL
BARD1
FANCD2
ATR
FANCE
XRCC2
NBN
FANCG
FANCC
MRE11A
ATM
BRCA2
FANCM
FANCI
BLM
SLX4
PALB2
FANCA
RAD51D
BRCA1
RAD51C
BRIP1
RBBP8
CHEK2
Variation
LOH with LST gain
LOH with LST loss
LOH only
Chromosome
chr11
chr13
chr14
chr15
chr16
chr17
chr18
chr2
chr22
chr3
chr6
chr7
chr8
chr9


A.
HRP
HRD
PFS Survival probability
p = 0.035
Time (Months)
Number at risk
HRD status
HRP 87 59 45 42 37 29 26 12 0
HRD 27 21 11 8 6 5 1 1 0
Time (Months)


B.
HRP
HRD
PFS Survival probability
p < 0.0001
Time (Months)
Number at risk
HRD status
HRP 445 361 236 153 117 80 50 29 14 8 4
HRD 56 41 24 15 10 9 7 4 3 2 1
Time (Months)


C.
HRP
HRD
PFS Survival probability
p = 0.034
Time (Months)
Number at risk
HRD status
HRP 23 14 4 1 0 0 0 0
HRD 13 7 6 5 3 3 2 1
Time (Months)


D.
LOH/LST/TAI all negative
LOH/LST/TAI any positive
PFS Survival probability
p = 0.021
Time (Months)
Number at risk
Total status
None 12 10 8 4 2 0
One of >5 9 5 2 1 0 0
Time (Months)