Du *et al.*
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Clinical-genomic characteristics of homologous recombination deficiency (HRD) in breast cancer: application model for practice

Jinsui Du[1], Lizhe Zhu[1], Chenglong Duan[1], Nan Ma[3], Yudong Zhou[1], Danni Li[1], Jianing Zhang[1], Jiaqi Zhang[1], Yalong Wang[1], Xi Liu[2*], Yu Ren[1*] and Bin Wang[1*]

Abstract

Background Homologous recombination deficiency (HRD) affects breast cancer patients. Treatment guided by multigene testing may be particularly beneficial in HRD patients by using platinum-based drugs and poly ADP-ribose polymerase inhibitor (PARPi). However, the optimal method for HRD testing remains undetermined by guidelines or consensus and economic disparities limit the availability of genetic testing. Prioritizing HRD testing by clinical-genomic characteristics is critical for efficient utilization of healthcare resources and improved treatment accuracy.

Methods A total of 93 breast cancer patients who underwent HRD genetic testing were included in the study. According to the machine learning model called genomic scar (GS) HRD was defined as a genomic scar score (GSS) ≥ 50 or with deleterious mutation in the *BRCA*. Multivariate logistic regression analysis was employed to identify the clinical-pathological factors potentially associated with HRD. Suitable variables were selected to construct a predictive model, and the model's efficacy was evaluated using the area under the receiver operating characteristic (ROC) curve. Internal validation was performed using bootstrap resampling (500 replicates).

Results Patients harboring pathogenic mutation in *BRCA* exhibited higher GSS (99.85 vs 36.90). HRD was not detected in 41.75% of patients, and 34.95% had HRD but no *BRCA* pathogenic mutations. HRD risk in human epidermal factor growth receptor 2 (HER2) low or positive was significantly lower compared to HER2 negative (OR: 0.390, 95% CI: 0.159–0.959, $P = 0.040$). High Ki- 67 index was strongly associated with HRD (OR: 28.434, 95% CI: 3.283–246.293, $P = 0.002$). Significant variations in GSS were observed based on estrogen receptor (ER) and progesterone receptor (PR) status, histological grade, and molecular types. The area under the ROC curve (AUC) of the combined prediction model combining HER2 status and Ki- 67 index was 0.749, and the accuracy of the model was further validated using bootstrap resampling (500 replicates), resulting in an AUC of 0.730, indicating a high predictive accuracy for HRD status.

Conclusions *BRCA* mutation status did not fully reflect HRD status. Patients with a negative HER2 status and high Ki- 67 index are more likely to exhibit positive results when undergoing HRD genetic testing. The ER, PR, HER- 2 status, Ki- 67 index, molecular typing, and histological grading may have a strong influence on the HRD status.

*Correspondence:
Xi Liu
xliu83@xjtu.edu.cn
Yu Ren
renyyyyy@126.com
Bin Wang
february111@163.com
Full list of author information is available at the end of the article

Keywords Homologous recombination deficiency, Breast cancer, *BRCA*, Genomic scar score, Clinical-genomic characteristics

Introduction

Breast cancer (BC) is a highly heterogeneous tumour, which greatly increases the complexity and challenges of its treatment and management [1]. Homologous recombination deficiency (HRD) has emerged as a key biomarker in BC. While *BRCA* mutations play a pivotal role in DNA damage repair (DDR) and are strongly associated with HRD, other alterations in the homologous recombination repair (HRR) pathway also contribute to HRD status [2, 3]. This complexity underscores the importance of HRD testing in precision medicine, as it guides the use of platinum-based drugs and poly (ADP-ribose) polymerase inhibitors (PARPis), both of which demonstrate superior efficacy in HRD-positive patients [4–6].

The OlympiAD clinical trial revealed that human epidermal growth factor receptor 2 (HER2)-negative patients with *BRCA* mutations who received the PARPi olaparib had a significantly longer median progression-free survival (PFS) than did those in the standard treatment group (7.0 months vs. 4.2 months; hazard ratio (HR), 0.58; 95% CI, 0.43–0.80; $P < 0.001$)[7]. Studies have also shown that the residual cancer burden (RCB) 0/I ratio and pathologic complete response (pCR) rate can be significantly improved when triple-negative breast cancer (TNBC) patients with HRD receive neoadjuvant treatment with platinum-based drugs (OR = 10.18, $P = 0.0011$; OR = 17.00, $P = 0.0066$) [8]. Approximately 40–60% of TNBC exhibit HRD [9, 10]. In particular, *BRCA* mutations account for 10–20% of TNBC patients [11]. Therefore, in clinical practice, HRD testing is highly recommended for TNBC patients to screen corresponding therapeutic targets. In addition, emerging evidence has shown that HRD is also present in patients with non-TNBC [12].

Despite these advances, critical barriers impede the widespread adoption of HRD testing. Current HRD detection methods are mainly Myriad myChoice CDx and FoundationOne CDx (F1 CDx).The above two methods lack prospective clinical research data on the Chinese population [13]. Moreover, HRD testing is expensive, and the standards for HRD testing and appropriate populations are still controversial.

We expect to be able to screen out people with potential HRDs based on the clinical and genomic characteristics of patients to prioritize high-probability candidates for confirmatory genomic testing. Moreover, we aim to predict the results of HRD testing by establishing clinical models to guide clinical medication and reduce treatment costs.

Methods

Patient selection

A total of 208 patients who underwent HRD gene testing at the First Affiliated Hospital of Xi'an Jiaotong University between October 2021 and October 2023 were screened. In this study, we initially screened patients diagnosed with breast or ovarian cancer. From the cohort, 103 patients with breast cancer were identified. After excluding those with incomplete clinical information or genetic reports, the final analysis included 93 breast cancer patients. Comprehensive clinical-genomic data, including medical treatment and family history, marital and birth details, menopausal status, body mass index (BMI), and diagnostic reports, including imaging, tumour marker, pathology, and genetics data, were collected for these patients (Fig. 1). Menopausal status was assessed according to the International Menopause Society (IMS) 2016 guidelines [14]. The tumour markers carcinoembryonic antigen (CEA), cancer antigen 15 - 3 (CA- 153) and cancer antigen 12 - 5 (CA- 125) were measured via the chemiluminescent microparticle immunoassay technique on an Abbott I2000 system, which was completed and reported by the laboratory department. Pathological assessments were performed according to the World Health Organization (WHO) classification of breast tumours and the Nottingham classification system for histological grading of the breast [15]. Hormonal receptor (HR) status, including estrogen receptor (ER) and progesterone receptor (PR) expression, along with HER- 2 and Ki- 67 expression, was evaluated based on the guidelines set forth in the National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines for Breast Cancer Oncology (version 4, 2023) for Breast Cancer [16]. The pathological diagnosis was performed via TNM staging in accordance with the eighth edition of the American Joint Committee on Cancer (AJCC) Breast Cancer Staging Manual [17]. The Pathology Department of the First Affiliated Hospital of Xi'an Jiaotong University, with two pathologists independently reading the films, and the final report was reviewed and completed by a senior pathologist. All patients were thoroughly evaluated by their attending physicians based on clinicopathological characteristics, including age, tumour grade, molecular typing and family history. Additionally, some patients actively requested testing based on

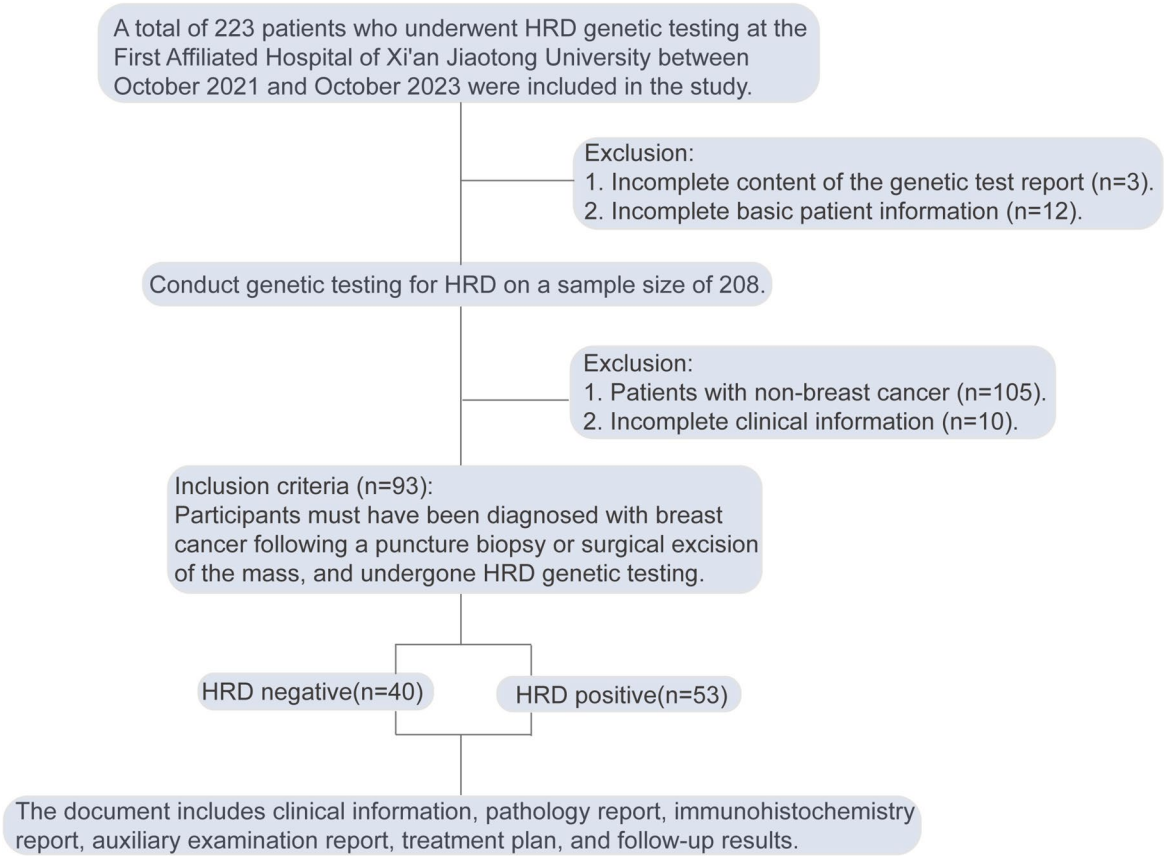

Fig. 1 Flow chart of this study

their understanding of the disease and its genetic implications. After being fully informed of the potential risks and detailed considerations associated with HRD testing, the patients and their families jointly decided whether to proceed with the testing and signed informed consent forms.

HRD detection method

The pathological tissues of breast cancer patients obtained through surgical resection or core needle aspiration were formalin fixed and paraffin embedded (FFPE). The tumour cell content in the pathological tissues submitted for inspection must be > 30%. The HRD Complete Panel provided by AmoyDx (AmoyDx, Xiamen, China) was used to detect the HRD status. This gene covers 1.5 Mb of the human genome, including all exons of *BRCA1/BRCA2*, and targets 24,000 SNPs distributed across the complete human genome. HANDLE technology (Halo-shaped ANnealing and Defer-Ligation Enrichment System) was used to construct amplicon-based DNA libraries [18]. DNA quality and size were assessed through a high-sensitivity DNA assay via a bioanalyzer, and all indexed samples were sequenced via an Illumina NextSeq CN500. The results were jointly interpreted by three qualified pathologists and finally reviewed and reported by a senior pathologist.

Calculation of GSS

Genomic instability was assessed by analysing different types of copy number events in the genome. Chromosome copy number variation (CNV) includes the length of the copy number (LCN), which can be large (> 15 Mb), moderate (10–15 Mb), or small (5–10 Mb). The type of copy number (TCN) included loss of heterozygosity (LOH), allele-specific CNV, and allele-balanced CNV. Site of copy number (SCN), including telomeres, centromeres and others. The above factors and the number of breakpoints (NB) are combined via a machine learning method to establish a model called the genomic scar (GS) and obtain the GSS [18].

Somatic cell testing of the HRD panel

Detection was confirmed by next-generation sequencing (NGS). An HRD panel was designed based on NCCN guidelines and the genetic characteristics of Chinese

Table 1 Clinical characteristics of breast cancer patients with HRD status

Characteristics	HRD status		*P* value
	Negative, n = 40[1]	Positive, n = 53[1]	
Age (year)			
Median (interquartile range)	44 (37, 52)	40 (34, 48)	0.213[2]
Range	22–86	18–66	
Family history			
No	32 (80.0)	35 (66.0)	0.137[3]
Yes	8 (20.0)	18 (34.0)	
Grade			
1	0 (0.0)	0 (0.0)	* 0.024[4]
2	30 (75.0)	25 (47.2)	
3	9 (22.5)	23 (43.4)	
Others	1 (2.5)	5 (9.4)	
ER			
Negative	19 (47.5)	39 (73.6)	* 0.010[3]
Positive	21 (52.5)	14 (26.4)	
PR			
Negative	22 (55.0)	42 (79.2)	* 0.012[3]
Positive	18 (45.0)	11 (20.8)	
HER2			
Negative	15 (37.5)	33 (62.3)	* 0.039[4]
Low	23 (57.5)	19 (35.8)	
Positive	2 (5.0)	1 (1.9)	
Molecular subtype			
Luminal A	3 (7.5)	1 (1.9)	* 0.018[4]
Luminal B	18 (45.0)	12 (22.6)	
Triple-negative	18 (45.0)	39 (73.6)	
HER2 overexpression	1 (2.5)	1 (1.9)	
Ki- 67	0.45 (0.30, 0.60)	0.65 (0.50, 0.80)	***< 0.001[2]

[1] Median (Interquartile Range, IQR); n (%). [2]Wilcoxon rank sum test. [3]Pearson's Chi-squared test. [4]Fisher's exact test. ER, estrogen receptor; PR, progesterone receptor; HER2, human epidermal growth factor receptor 2; $P < 0.05$ marked as *, $P < 0.01$ marked as **, $P < 0.001$ marked as ***

individuals to detect genes in the HRR pathway. Somatic mutation analysis targeted coding regions and exon–intron junctions of multiple *genes (TP53, ATM, BARD1, BRCA1, BRCA2, BRIP1, CDH1, CHEK1, CHEK2, FANCA, FANCL, HDAC2, PALB2, PPP2R2 A, PTEN, RAD51B, RAD51 C, RAD51D* and *RAD54L*) with variations, including point mutations, insertions, deletions, and amplifications.

Somatic mutation grade and HRD status assessment

Tumour somatic mutations are classified into four levels on the basis of evidence level: level I mutations have strong clinical significance, level II mutations have potential clinical significance, and level III mutations have unknown clinical significance. This is due to the lack of high incidence rates in the population and tumour-related databases, as well as the absence of definitive evidence related to tumours in the literature. Level IV mutations refer to benign or potentially benign mutations [19, 20]. *BRCA* positivity is confidently defined as the discovery of I-II level *BRCA* mutations in somatic mutations. If the test detects a *BRCA* mutation, the patient's peripheral blood should be sampled for germline testing of the *BRCA* gene. Based on the AmoyDx HRD Panel and GS, a positive result on the HRD test was defined as GSS ≥ 50 or GSS < 50 but with the detection of a pathogenic or possibly pathogenic variant in the *BRCA* gene [18].

Data processing and statistical methods

Continuous and categorical variables were analysed separately. Categorical variables are summarized as frequencies (percentages) and were compared via Pearson's χ^2 test or Fisher's exact test. Nonnormally distributed continuous variables were analysed via the Mann–Whitney U test (two groups) or the Kruskal–Wallis test (multiple groups). Binary HRD status was assessed via logistic

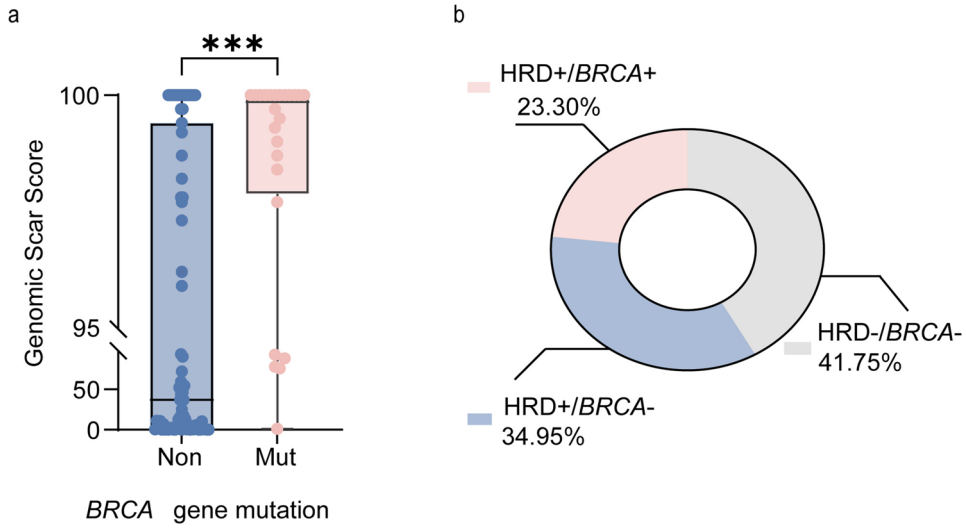

Fig. 2 Relationship between *BRCA* mutations and HRD. **a** Different *BRCA* status and GSS; Mann–Whitney U test. **b** *BRCA* gene mutation status and HRD status and their corresponding proportions in breast cancer patients. HRD, homologous recombination deficiency; *BRCA*, breast cancer susceptibility gene1/2

regression, providing odds ratios (ORs) with 95% confidence intervals (CIs) and *P* values from partial likelihood ratio tests. Backwards stepwise regression identified key predictors for the final model. The receiver operating characteristic (ROC) curve was used to evaluate discriminant validity, and the area under the curve (AUC) was calculated. Internal validation was performed via bootstrap resampling (500 replicates) to obtain bias-corrected AUCs and 95% CIs. A two-tailed $P < 0.05$ was considered statistically significant. Analyses were conducted via SPSS PASW Statistics 18, R software (versions 4.3.3 and 4.2.2), GraphPad Prism 10, and MSTATA (https://www.mstata.com/).

Results

Baseline population characteristics

The baseline characteristics of the 93 patients, stratified by HRD status, are presented in Table 1. Among them, 53 were HRD-positive, and 40 were HRD-negative. The median age was 40 years (range, 18–66) in the HRD-positive group and 44 years (range, 22–86) in the HRD-negative group, with no significant difference ($P = 0.213$). Significant differences in side classification, histological grade, ER/PR/HER2 expression, molecular subtype, and the Ki- 67 index were detected ($P < 0.05$). HRD-positive patients were more likely to have right-sided or bilateral tumours ($P = 0.039$), ER-negative (74% vs. 48%, $P = 0.010$) and PR-negative (79% vs. 55%, $P = 0.012$) statuses, predominantly HER2-negative expression ($P = 0.039$), TNBC molecular subtypes ($P = 0.018$) and elevated Ki-67 indices ($P < 0.001$). Histological grade 3 was also more prevalent in HRD-positive patients (43.4% vs. 22.5%, $P = 0.024$). Comprehensive baseline characteristics for the cohort (n = 93) are systematically detailed in Supplementary Table 1.

Relationship between *BRCA1/2* status and GSS

Among the 103 breast cancer patients who underwent HRD testing, 24 had pathogenic or suspected pathogenic *BRCA* mutations. All 24 of these patients were HRD-positive, with a mean GSS of 99.85 (95% CI: 98.40, 100.00). Among the 79 patients without *BRCA* mutations, 35 were HRD positive, and 44 were HRD negative, with a mean GSS of 36.90 (95% CI: 11.00, 90.00). The difference was statistically significant ($P < 0.001$, Fig. 2a). Overall, 23.3% of patients had *BRCA* mutations, 34.95% had HRD without *BRCA* mutations, and 41.75% were HRD-negative (Fig. 2b).

Possible factors that may affect GSS and HRD status

Univariate analysis revealed significant associations between HRD status and clinicopathological features ($P < 0.05$, Table 2). The median GSS was significantly greater in ER-negative (98.30 vs. 17.40, $P = 0.0054$; Fig. 3a) and PR-negative patients (98.00 vs. 17.40, $P = 0.0089$; Fig. 3b). HER2-negative patients tended to have a greater GSS (97.75 vs. 43.50, $P = 0.0565$; Fig. 3c), but there was no statistically significant difference. Similarly, TNBC patients had a greater GSS than non-TNBC patients did (96.20 vs. 3.20, $P = 0.0028$; Fig. 3d). Patients with a Ki- 67 index ≥ 30% had a significantly greater GSS than those with a Ki- 67 index < 30% (96.20 vs. 3.20, $P = 0.0024$; Fig. 3e).

Table 2 Univariate Analyses Results after missing value removal

Characteristics	HRD status Negative vs positive		*P* value
	Odds ratio	95%CI	
Age(year)	0.97	0.93–1.01	0.176
BMI (kg/m^2)	0.92	0.77–1.10	0.374
Family history			
No	Ref		
Yes	2.06	0.81–5.62	0.141
Marital status			
Unmarried	Ref		
Married	0.43	0.02–3.48	0.469
Menopause			
Premenopausal			
Menopause	1.23	0.44–3.68	0.694
Side classification			
Left	Ref		
Right	2.30	0.99–5.49	0.055
Both	NC	NC	0.990
Pathological type			
Invasive cancer	Ref		
DCIS	NC	NC	0.98
Grade			
1	NC	NC	NC
2	Ref		
3	3.07	1.23–8.12	0.019*
Others	6.00	0.89–119.01	0.112
ER			
Negative	Ref		
Positive	0.32	0.13–0.77	0.011*
PR			
Negative			
Positive	0.32	0.13–0.78	0.014*
HER2			
Negative	Ref		
Low or positive	0.36	0.15–0.84	0.019*
Molecular subtype			
Luminal A	Ref		
Luminal B	2.00	0.22–43.12	0.568
Triple-negative	6.50	0.77–136.50	0.116
HER- 2 overexpression	3.00	0.07–170.77	0.547
T stage			
Tis- 1	Ref		
2–4	1.52	0.63–3.68	0.349
N stage			
0	Ref		
1–3	0.81	0.35–1.85	0.611
M stage			
0	Ref		
1	1.37	0.38–5.57	0.636
Stage			
0–II	Ref		
III–IV	1.20	0.50–2.95	0.686
CEA (ng/ml)	0.90	0.73–1.08	0.271
CA- 125 (U/ml)	1.00	1.00–1.01	0.430
CA153 (U/ml)	1.01	0.99–1.04	0.484
Ki- 67	32.18	4.22–306.29	0.001**

Due to the presence of zero cells or very small numbers in the contingency table, some cell odds ratios are uncalculatable or infinite, which violates the statistical assumptions of OR calculation. HRD, homologous recombination deficiency; Ref, reference; NC, not calculable; BMI, body mass index; DCIS, ductal carcinoma in situ; ER, estrogen receptor; PR, progesterone receptor; HER2, human epidermal growth factor receptor 2; T, tumor size; Tis, tumor in situ; N, lymph node status; M, metastases; CEA, carcinoembryonic antigen; CA- 153, cancer antigen 15–3; CA- 125, antigen 12–5; $P < 0.05$ marked as *, $P < 0.01$ marked as **, $P < 0.001$ marked as ***

The GSS also varied significantly by histological grade ($P = 0.0081$, Fig. 3f).

Multivariate logistic regression analysis revealed that histological grade and the ER, PR, HER2, and Ki- 67 indices were significant predictors of HRD status. HER2-low or HER2-positive patients were less likely to develop HRD (OR: 0.390, 95% CI: 0.159–0.959; $P = 0.040$; Fig. 4), whereas a higher Ki- 67 index was associated with an increased risk of HRD (OR: 28.434, 95% CI: 3.283–246.293; $P = 0.002$; Fig. 4).

Model establishment and verification

Based on multivariate binary logistic analysis, HER2 and Ki- 67 were identified as significant predictors of HRD status. These factors were used to establish a prediction model. The probability of HRD positivity can be estimated via the stepwise nomogram, as described in Fig. 5. We used the ROC curve and obtained an AUC of 0.749 (95% CI: 0.647–0.850) (Fig. 6a). The model's accuracy was further validated via bootstrap resampling (500 replicates), yielding an AUC of 0.730 (95% CI: 0.682–0.779) (Fig. 6b).

Discussion

This study used the GSS to quantify HRD levels. The larger the GSS is, the more likely the patient is to have HRD; this is related to the HRD calculation method. Here, GSS ≥ 50 or *BRCA* pathogenic or suspected pathogenic mutations were considered HRD positive. On this basis, the patients were divided into two different subgroups to further analyse the clinical–genomic characteristics of the patients. Then, we selected appropriate

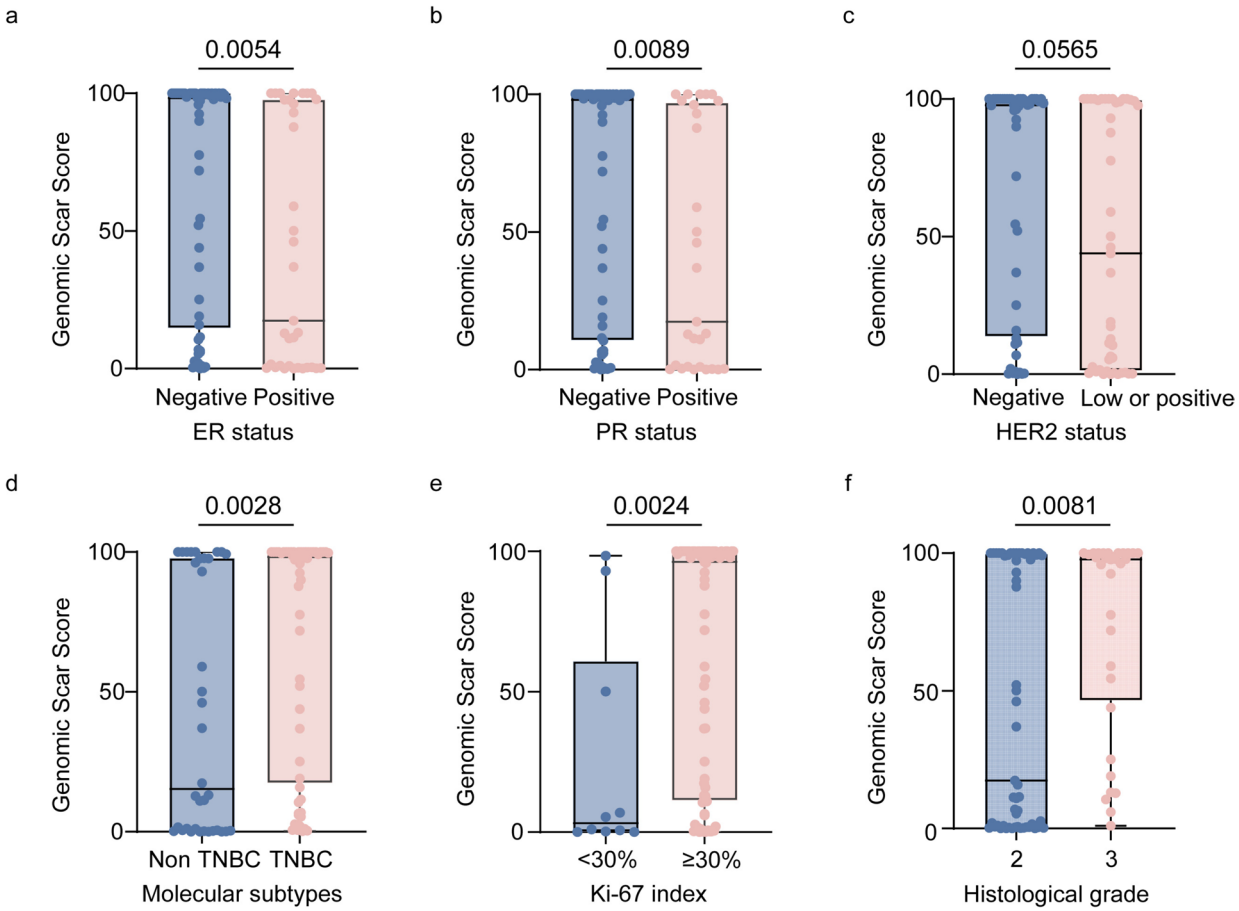

Fig.3 Relationship between clinical characteristics and GSS. **a** ER status vs GSS; Mann–Whitney U test. **b** PR status vs GSS; Mann–Whitney U test. **c** HER2 status vs GSS; Mann–Whitney U test. **d** Molecular subtyping vs GSS; Mann–Whitney U test. **e** Ki- 67 index vs GSS; Mann–Whitney U test. **f** Histopathological grade vs GSS; Mann–Whitney U test. ER, estrogen receptor; PR, progesterone receptor; HER2, human epidermal growth factor receptor 2; TNBC, triple-negative breast cancer

variables to establish a prediction model and provide theoretical support for clinical work.

Our study confirmed that *BRCA* mutations are strongly associated with increased GSS and directly affect HRD status. However, 34.95% of HRD-positive tumours lacked detectable *BRCA* mutations. The TNT clinical trial revealed that people with *BRCA* mutations could benefit from the use of platinum-based drugs, whereas other HRD-related markers did not have the same predictive value [21]. OlympiA study also revealed that adjuvant use of Olaparib significantly improved invasive disease-free survival (IDFS) in patients with high-risk early HER2-negative breast cancer with *BRCA* germline mutations (HR = 0.58, 95% CI: 0.41–0.82; $P < 0.001$) [22]. *BRCA* testing has high guiding value in clinical practice, but increasing evidence has emphasized the necessity of HRD assessment. Wang et al. demonstrated that TNBC patients with HRD could achieve a higher pCR rate after receiving neoadjuvant therapy with platinum-based drugs [23]. Although current guidelines recommend *BRCA* testing for patients at high genetic risk [24], here are no clear guidelines to provide clinical support for HRD testing. However, *BRCA* mutations cannot fully reflect the HRD status [25]. HRD testing reveals that broader patient populations may benefit from targeted therapies and provides mechanistic insights into tumour biology. Therefore, future research should explore the applicable population for HRD testing and clarify its clinical guidance significance to improve screening and diagnostic strategies for HRD.

Furthermore, our study revealed that 39/57 (68.4%) TNBC patients presented HRD characteristics, which is consistent with the conclusions of J. Staaf et al. [9], supporting the high frequency of HRD in TNBC; this may be related to the characteristics of *BRCA* mutations and epigenetic modifications. The proportion of patients with *BRCA* mutations and *BRCA1* promoter methylation is greater in TNBC, which is associated with HRD [26,

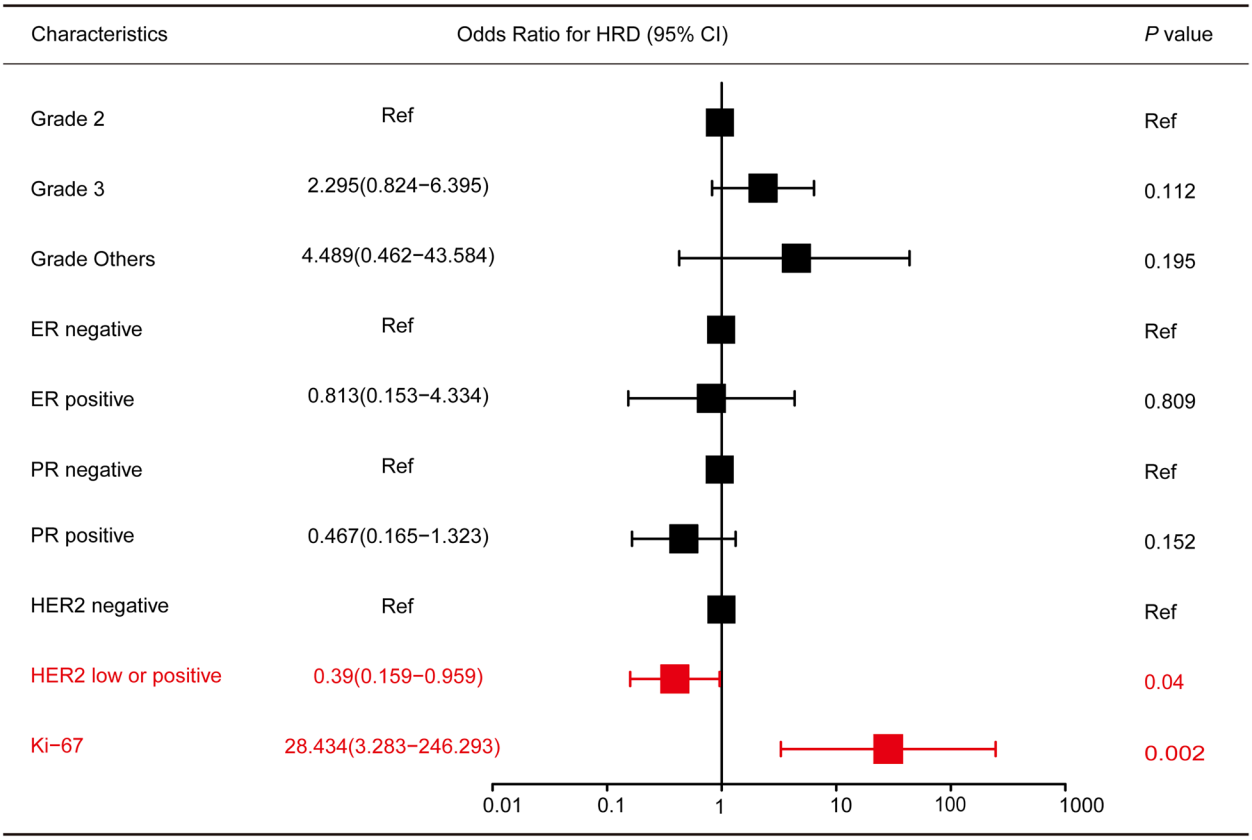

Fig. 4 Forest plot displaying the results of a multivariable logistic regression analysis assessing the impact of various factors on the outcome. Each line represents a different factor with its corresponding odds ratio and 95%CI. The vertical line indicates an odds ratio of 1, where factors to the right are associated with increased odds of the outcome, and factors to the left are associated with decreased odds. CI, confidence intervals; HRD; homologous recombination deficiency; Ref, reference; ER, estrogen receptor; PR, progesterone receptor; HER2, human epidermal growth factor receptor 2; The red font highlights estimate in which $P < 0.05$

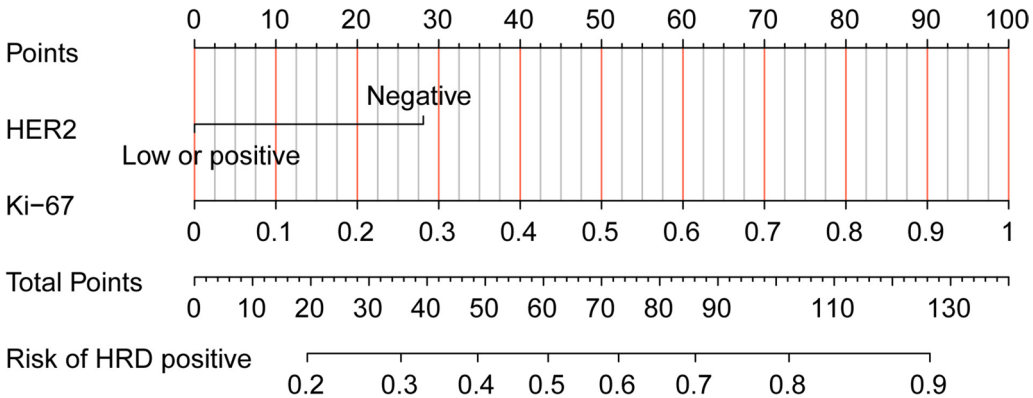

Fig. 5 Nomogram prediction of HRD positive. The steps are: Determine the value of the variable on the corresponding axis, draw a vertical line to the total points axis to determine the points, add the points of each variable, and draw a line from the total point axis to determine the HRD positive probabilities at the lower line of the nomogram. HER2, human epidermal growth factor receptor 2; HRD, homologous recombination deficiency

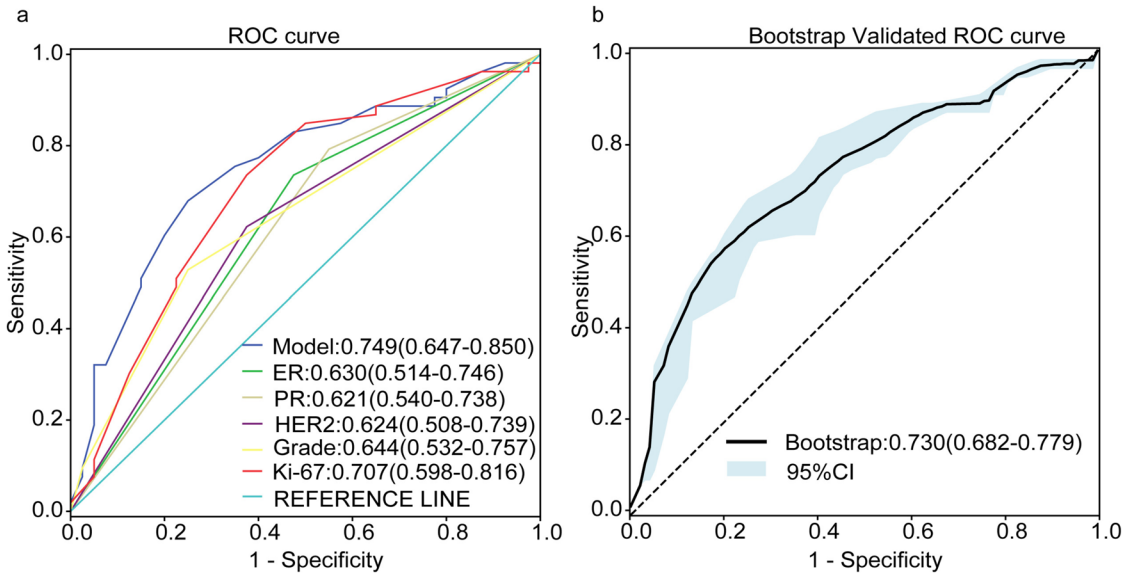

Fig. 6 Receiver operating characteristic curve. **a** ROC curve of the model **b** Bootstrap validated ROC curve. ER, estrogen receptor; PR, progesterone receptor; HER2, human epidermal growth factor receptor 2; AUC; Area under the receiver operating characteristic curve

27]. However, among the Luminal A/B subtypes, 13/34 (38.2%) carried HRD, which was significantly greater than the 10%− 20% reported in previous studies [28, 29]. The heterogeneity in HRD distribution observed in this study may stem from multiple factors. First, the cohort included a greater proportion of young patients with active ovarian function, potentially enriching HR-positive subtypes through hormonal pathways [30]. The sensitivity differences of GSS-based assays in detecting *BRCA* -dependent and *BRCA*-independent HRD mechanisms. Moreover, the unique genetic landscape of Chinese populations is characterized by a relatively high frequency of *BRCA2* mutations [31] strongly associated with HR-positive subtypes [32], whereas *BRCA1* mutations predominantly occur in TNBC [33]. Our study revealed that HRD is not limited to TNBC but also occurs in a certain proportion of patients with the luminal A/B subtype, which may provide new ideas for the treatment of this subtype. Therefore, HRD detection should be extended to a wider range of breast cancer subtypes.

Multivariate analysis identified HER2-negative status and high Ki- 67 expression as independent predictors of HRD. High Ki- 67 reflects cell proliferation [34] and may aggravate HRD-related DNA damage accumulation through replication stress. Based on these findings, this study established an HRD prediction model, which has significantly better predictive performance than a single indicator (AUC =0.749). The model AUC stabilized at 0.730 after internal validation by bootstrap resampling (500 iterations). This model is particularly suitable for primary medical institutions that lack complex molecular testing capabilities; it can assist in the preliminary screening of people who are suitable for HRD testing and save medical resources.

This study has certain limitations. This study is a single-center retrospective study with a relatively small sample size, which may cause certain bias in the research results, and it lacks an external validation set, which may affect the universality of the results. In addition, owing to technical limitations, our study did not include other possible HRD drivers (such as other HRR-related gene mutations and epigenetic modifications), which may limit the comprehensiveness of the model. In the future, multicentre, large-sample prospective studies and the introduction of external validation sets are needed to further verify and optimize the results of this study, establish an accurate prediction model, and assist in clinical decision-making.

This study revealed the relationship between *BRCA* mutations and HRD status and emphasized the potential value of HRD in non-TNBC patients. The HRD prediction model established in this study provides a new tool for clinical practice, which helps to more accurately

identify HRD patients, especially those without *BRCA* mutations but with HRD characteristics. Above all, our findings provide new ideas for the personalized treatment of breast cancer, especially for the application of PARPis and platinum-based drugs. In the future, HRD detection should be extended to a wider range of breast cancer subtypes and combined with multiomics data to further improve the accuracy of HRD screening and treatment.

Conclusions

The *BRCA* mutation status does not fully reflect the HRD status. The ER, PR, and HER2 expression status; molecular type; histological grade; and the Ki- 67 index may be important factors affecting GSS. Patients who were HER2-negative and had a negative Ki- 67 index were more likely to have positive results when undergoing HRD testing. A clinical prediction model was established based on the above factors, and the prediction effect was better. A clinical model was constructed to help predict the HRD test results of breast cancer patients to a certain extent and guide clinical gene testing and treatment.

Abbreviations

HRD	Homologous recombination deficiency
BC	Breast cancer
BRCA1/2	Breast cancer susceptibility gene1/2
GSS	Genomic scar score
ER	Estrogen receptor
PR	Progesterone receptor
HER2	Human epidermal growth factor receptor 2
DCIS	Ductal carcinoma in situ
PARPi	Poly ADP-ribose polymerase inhibitor
CEA	Carcinoembryonic antigen
CA- 153	Cancer antigen 15–3
CA- 125	Cancer antigen 12–5
CNV	Chromosome copy number variation
LCN	Length of copy number
TCN	Type of copy number
SCN	Site of copy number
OR	Odds ratios
CI	Confidence intervals
ROC	Receiver operating characteristic
AUC	Area under the receiver operating characteristic curve

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s40001-025-02520-8.

Additional file 1

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Author contributions

Conceptualization, Jinsui Du and Lizhe Zhu; Data curation, Jinsui Du and Chenglong Duan; Formal analysis, Lizhe Zhu, Jinsui Du, Danni Li and Nan Ma; Funding acquisition, Bin Wang and Yu Ren; Investigation, Jianing Zhang, Nan Ma and Jiaqi Zhang; Methodology, Jinsui Du, Lizhe Zhu and Yudong Zhou; Resources, Xi Liu; Software, Chenglong Duan, Nan Ma, Yudong Zhou and Yalong Wang; Supervision, Bin Wang, Xi Liu and Yu Ren; Validation, Lizhe Zhu and Xi Liu; Visualization, Jinsui Du, Yudong Zhou and Chenglong Duan; Writing-original draft, Jinsui Du; Writing-review & editing, Jinsui Du.

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Availability of data and materials

The datasets used and/or analysed during the current study available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

The study was conducted according to the guidelines of the Declaration of Helsinki and approved by Ethics Committee of the First Affiliated Hospital of Xi'an Jiaotong University.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

Author details

[1]Department of Breast Surgery, First Affiliated Hospital of Xi'an Jiaotong University, No. 277 Yanta West Road, Xi'an 710061, Shaanxi, China. [2]Department of Pathology, First Affiliated Hospital of Xi'an Jiaotong University, No. 277 Yanta West Road, Xi'an 710061, Shaanxi, China. [3]Experimental Pharmacology Mannheim, Medical Faculty Mannheim, Heidelberg University, Heidelberg, Germany.

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