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Original Research Article

Incidence of homologous recombination deficiency among high grade serous ovarian carcinoma patients from a tertiary care center in India

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ABSTRACT

Background: Ovarian cancer (OC) is the 9th most prevalent cancer overall in India and the 3rd most common among women, following breast and cervical cancers. According to GLOBOCAN 2022, there were 47,333 new OC cases and 32,978 deaths. Epithelial ovarian cancer (EOC) represents 90% of OC cases, of which 70% are high-grade serous ovarian cancer (HGSOC). Unfortunately, most patients are diagnosed at advanced stages III-IV. Homologous recombination deficiency (HRD) is a phenotype that is characterized by the inability of a cell to repair DNA double-strand breaks using the HRR pathway, leading to genomic instability and further malignant transformation. The Cancer Genome Atlas (TCGA) has reported HR deficiency in nearly 50% of HGSOC cases**.**
Methods: This retrospective observational study evaluated 62 HGSOC patients treated at Apollo Cancer Centre Chennai from January 2021 to January 2024. Clinical data were collected from medical records. Formalin-fixed, paraffin-embedded (FFPE) tissue samples were obtained from patients undergoing surgery or biopsy and tested for HRD status. The data was analyzed and represented.
Results: In the study population of 62 patients, 15 patients (24%) had HR deficiency (HRD positive).8 (13%) patients had poor quality FFPE tissue. Out of the 15 HRD-positive patients, six patients were TBRCA1, and four patients were TBRCA2. Five patients had GSS of more than 42.
Conclusions: There is a significant population of HR-deficient HGSOC, comparable with the published literature. Thus, it serves as a predictive biomarker in ovarian cancers with deficiencies in DNA repair mechanisms.

Keywords: Ovarian cancer, Homologous recombination deficiency, BRCA mutation, Genomic scar score

INTRODUCTION

Ovarian cancer (OC) ranks as the 9th most common cancer overall in India and 3rd among women, following breast and cervical cancers.[1] In 2022, GLOBOCAN reported 47,333 new cases and 32,978 OC-related deaths. Epithelial ovarian cancer (EOC) comprises 90% of OC cases, with five main subtypes: high-grade serous ovarian cancer (HGSOC, 70%), low-grade serous ovarian cancer (LGSOC, <5%), endometrioid carcinoma (EC, 10%), clear cell carcinoma (CCC, 10%), and mucinous carcinoma (MC, 3%).[2] The Homologous recombination repair (HRR) pathway is essential for repairing DNA double-strand breaks.

Research by Walsh et al, and Krais JJ et al, has shown that mutations in HRR genes, particularly BRCA1 and BRCA2, significantly contribute to familial EOC.[3,4] HRR repair also involves co-factors like RAD51C, RAD51D, BRIP1, PALB2, and BARD1.[5] Germline and somatic mutations in HRR genes are linked to approximately half of EOC cases with DNA repair defects, including 20-23% involving germline BRCA mutations.[6]

Homologous recombination deficiency (HRD), defined by an impaired ability to repair DNA breaks via HRR, leads to genomic instability and scarring, potentially causing malignancy.[7,8]

The cancer genome atlas (TCGA) reports HRD in about 50% of HGSOC cases.[9] Poly ADP Ribose Polymerase (PARP) 1, which helps repair single-strand DNA, can be inhibited by PARP inhibitors (PARPi), leading to double-strand break accumulation and cell death in HRD-positive or BRCA-mutated cells through synthetic lethality. HRD is considered a predictive biomarker for PARPi in OC treatment.[10]

To calculate the prevalence of homologous recombination deficiency among high-grade serous ovarian carcinoma patients.

METHODS

Study design

The prospective observational study was conducted at Apollo Cancer Centre, Chennai, from January 2021 to January 2024.

A minimum sample of 50 subjects was needed to study the HRR panel and HRD Score among epithelial ovarian carcinomas. Considering the expected proportion was 15.5% (BRCA1 mutations), 10% precision, and 95% confidence interval.[11] The study included all newly diagnosed HGSOC patients.

All histologies other than HGSOC and ovarian metastases from other primary were excluded. After obtaining ethical clearance, A total of 62 patients who met the eligibility criteria were included in the study. Informed consent was obtained from each patient.

Data was collected on demographic and clinical factors, including age, BMI, family history, ECOG status, FIGO stage, histopathology, and HRD status. The molecular testing protocol for somatic HRD Testing included DNA taken from FFPE tissue samples. BRCA1 and BRCA2 testing was done, and genomic scar score (GSS) was calculated via next-generation sequencing, assessing genomic instability through copy number alterations. The typical turnaround for both tests was 14-21 days.

Statistical analysis

MS Excel version 2021 was used to tabulate data. SPSS v28 was used, with a p-value of <0.05 considered statistically significant. The HR deficient status was summarized in terms of frequency (n) and percentages.

Descriptive statistics, Shapiro-Wilk for normality, Chi-square/Fisher's exact for associations, and Student's t-test/Mann-Whitney U for independent groups were applied.

RESULTS

Between January 2021 and January 2024, 62 patients with available demographic, molecular profiling, and clinicopathologic data. Among the 62 patients, 15 patients (24%) were HRD positive, 8 patients (13%) had poor-quality FFPE tissue, preventing testing, and 39 patients (63%) were HR proficient (HRD negative) (Table 1) (Figure 1).

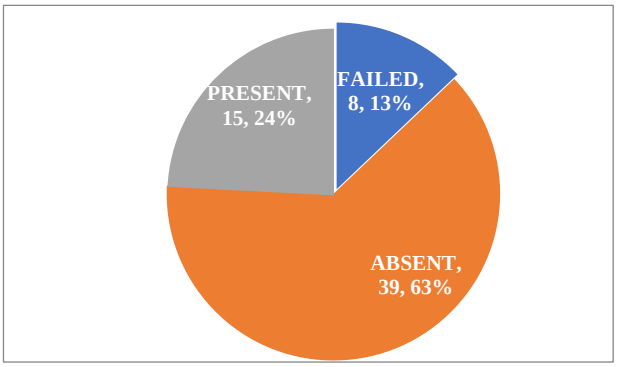

Figure 1: Distribution of patient population based on HRD.

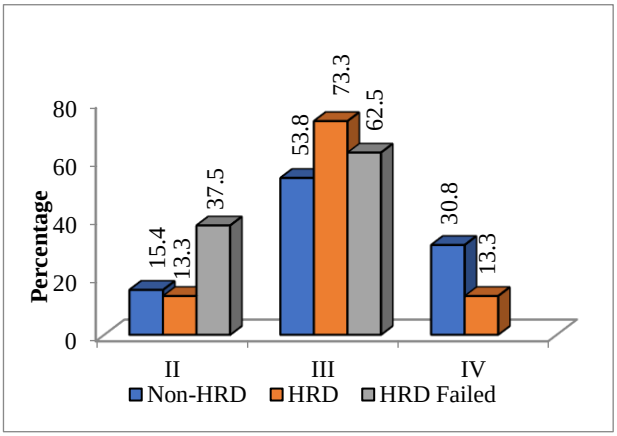

Figure 2: Stage of presentation in the study population.

Out of the 15 HRD-positive patients, six patients were TBRCA1, and four patients were TBRCA2. Five patients had GSS of more than 50 (Table 2).

In our study of 62 patients, the mean age was 54.7+11.7 years, with the minimum age being 28 and the maximum age being 81. In our population, the mean BMI was 25.6+3.9. Only 8 (13%) patients were obese, as per the standardised BMI categorization. One patient was found to be underweight. In our study, hypertension was the most common comorbidity in 13 patients (21%), followed by diabetes mellitus in 8 patients (13%).

10% of the patients (six) had both hypertension and diabetes mellitus. Nine patients (15%) had a history of OCP use, while the rest 53 patients did not. Out of the nine

patients, only two patients had HRD. Thirty-four patients (56%) had an ECOG status of 1 on presentation, and twenty-seven patients (44%) had an ECOG status of 2 or more.

In our study, no patients had FIGO STAGE 1 disease. Thirty-seven patients (56.9%) had stage 3 disease and 17 patients (27.4%) had stage 4 disease (Figure 2). 63% of the patients were non-vegetarians, while the remaining 37% patients were vegetarians. 21% of the study population had a family history of breast, ovary, pancreas, or prostate cancer. The rest, 79%, did not have any family history (Table 3).

The mean age of presentation of the HRD group was 56+11.2 years compared to the overall mean of 54.7+11.7 years. However, the HRD failed group had a lower age of presentation (46.8 + 7.7). 11 out of 15 (73.3%) patients in the HRD group had stage III disease, compared to 21 patients (53.8%) in the non-HRD group. However, only two patients in the HRD group had stage IV disease compared to 12 patients. 5 patients out of 15 had a family history of breast, ovarian, prostate, or pancreatic cancer, out of which 2 had BRCA1, and 3 patients had BRCA2 (Table 3).

7 out of 15 HRD received neoadjuvant chemotherapy (46.7%) compared to 82.1 % of patients in the non-HRD group. On the contrary, 33.3 % of patients in the HRD group underwent primary CRS compared to 25.6% in the non-HRD group. In our study, since fewer patients of stage IV were in the HRD group compared to the non-HRD group, the number of patients receiving neoadjuvant was less in the HRD group (Table 4).

Table 1: Prevalence of HRD in the study population.

HRD status	Frequency	%
HRD absent	39	63.0
HRD present	15	24.0
HRD failed	8	13.0

Table 2: Frequency of HRD in the study population.

HRD subtypes	Frequency	%
BRCA1	6	9.7
BRCA2	4	6.5
GSS	5	7.8

Table 3: Demographic factors in association with HRD.

Parameters	Group, n (%)			Overall (n=62)	P value
	Non-HRD (n=39)	HRD (n=15)	HRD failed (n=8)		
Age (in years)					
Mean±SD	55.8±12.2	56±11.2	46.8±7.7	54.7±11.7	0.121**
Range	28 – 81	37 – 75	34 – 55	28 – 81	
BMI					
Mean±SD	25.8±4.5	25±2.6	25.4±2.3	25.6±3.9	0.780**
Range	18.2 – 39	21.6 – 31.1	22.4 – 29.5	28 – 81	
BMI category					
Underweight	1 (2.6)	0	0	1 (1.6)	
Normal	15 (38.5)	9 (60)	3 (37.5)	27 (43.5)	0.524#
Overweight	16 (41)	5 (33.3)	5 (62.5)	26 (41.9)	
Obese	7 (17.9)	1 (6.7)	0	8 (12.9)	
Comorbidities					
NIL	18 (46.2)	8 (53.3)	4 (50)	30 (48.4)	
HTN	6 (15.4)	4 (26.7)	3 (37.5)	13 (21)	
DM	5 (12.8)	2 (13.3)	1 (12.5)	8 (12.9)	
HTN, DM	5 (12.8)	1 (6.7)	0	6 (9.7)	0.903#
HTN, OTHERS	2 (5.1)	0	0	2 (3.2)	
DM, OTHERS HTN,	2 (5.1)	0	0	2 (3.2)	
DM,others	1 (2.6)	0	0	1 (1.6)	
OCP use					
No	34 (87.2)	13 (86.7)	6 (75)	53 (85.5)	0.665#
Yes	5 (12.8)	2 (13.3)	2 (25)	9 (14.5)	
ECOG					
1	18 (47.4)	9 (60)	7 (87.5)	34 (55.7)	
2	14 (36.8)	4 (26.7)	1 (12.5)	19 (31.1)	0.329#
3	6 (15.8)	2 (13.3)	0	8 (13.1)	

Continued.

Parameters	Group, n (%)			Overall (n=62)	P value
	Non-HRD (n=39)	HRD (n=15)	HRD failed (n=8)		
Diet					
Vegetarian	14 (35.9)	7 (46.7)	2 (25)	23 (37.1)	0.573#
Non-vegetarian	25 (64.1)	8 (53.3)	6 (75)	39 (62.9)	
Stage					
II	6 (15.4)	2 (13.3)	3 (37.5)	11 (17.7)	0.179#
III	21 (53.8)	11 (73.3)	5 (62.5)	37 (59.7)	
IV	12 (30.8)	2 (13.3)	0	14 (22.6)	
Family history					0.378#
Absent	32 (82.1)	10 (66.7)	7 (87.5)	49 (79)	
Present	7 (17.9)	5 (33.3)	1 (12.5)	13 (21)	

**- Anova/ Kruskal Wallis Test, #- Chi square/ Fisher's exact test

Table 4: Clinical factors in association with HRD.

Parameters	Group, N (%)			Overall (n=62)	P value
	Non-HRD (n=39)	HRD (n=15)	HRD Failed (n=8)		
Neo-adjuvant					0.032
Absent	7 (17.9)	8 (53.3)	3 (37.5)	18 (29)	
Present	32 (82.1)	7 (46.7)	5 (62.5)	44 (71)	
Primary CRS					
Absent	29 (74.4)	10 (66.7)	5 (62.5)	39 (62.9)	0.730
Present	10 (25.6)	5 (33.3)	3 (37.5)	23 (37.1)	

DISCUSSION

Ovarian cancer incidence rates increase with age, as seen in our study, with 40% of patients presenting above the age of 55 years. In our study, HR Deficient patients had a similar age group at presentation compared to non-HRD patients and were statistically insignificant. Other demographic factors like BMI, comorbidities, OCP use, ECOG, and diet was also statistically insignificant.

In our cohort, fifteen (24.2%) patients had HRD, compared to Pennington et al, who reported a lower rate of 9%.12 Among them were six patients of BRCA1, four patients of BRCA2, and five patients of GSS above 50. The higher prevalence rate in our study might be due to geographical variation and the usage of different diagnostic assays.

Our reported frequencies of HRD are similar to those of previously published work despite observed variations across different research worldwide. Previous studies have measured HRD using assays measuring loss of heterozygosity, telomere allelic imbalances, large-scale transition scores, BRCA-like genetic signatures, or a combination of these methods. The discrepancies stem from the need for a standardized method. Additionally, differences between whole-exome sequencing and hotspot panels further complicate HRD comparisons, with whole-exome sequencing typically identifying a higher frequency. In Heeke et al.'s study of 9,600 OC patients, using targeted whole-exome sequencing (NGS600) across 592 genes, they evaluated PTEN mutations, leading to potentially higher HRD rates than us.[13]

It is also difficult to compare our HRD data with The Cancer Genome Atlas (TCGA) due to prominent differences in methodology.[14] TCGA reported homologous recombination defects in approximately 50% of high-grade serous cases by including various genomic alterations like BRCA1 hypermethylation, EMSY amplification or mutation, and RAD51C hypermethylation, which aggregated to 22% of their homologous recombination deficiency, which we did not assess. They counted all missense mutations as deleterious and included somatic PTEN mutations as homologous recombination deficient. Therefore, we have likely identified a different subset of ovarian carcinomas to be homologous recombination deficient than those classified by TCGA.

86.6 % of patients in the HRD group had advanced disease with FIGO stage III and IV compared to 84.6 % of patients in the non-HRD group. Pennington et al's study reflected that 83% present with a higher stage, especially with HGSOC. Since the majority of our patients were of stage III and above, Neoadjuvant platinum-based chemotherapy (NACT) was given in 44 patients (71%). However, it was 46.7% and 82.1% in HRD-positive and non-HRD groups respectively. On the contrary, 33.3 % of patients in the HRD group underwent primary CRS compared to 25.6%. In our study, since fewer patients of stage IV were in the HRD group compared to the non-HRD group, the number

of patients receiving neoadjuvant was less in the HRD group. When compared to the Pennington et al. study, the majority of the patients underwent primary CRS, but optimal cytoreduction was achieved in 66.2% of patients. Disparity might be due to small sample size, patient selection, logistics, and delay in surgery due to other comorbidities.

The study population was limited and hence needed careful interpretation and correlation of results with other studies. Comparing our HRD data with other studies was not always appropriate as the testing methodology was different in other studies.

CONCLUSION

This study provides a focused examination of HRD prevalence among HGSOC patients in an Indian tertiary care setting, contributing valuable insights to the growing body of research on ovarian cancer biology in diverse populations. Our findings underscore that HRD is a significant factor in a substantial proportion of HGSOC cases, reflecting trends observed globally and emphasizing the need for targeted genetic profiling. As HRD-positive patients can benefit from therapies like PARP inhibitors, understanding HRD status is crucial for guiding personalized treatment and improving outcomes in this patient population. Future studies with larger cohorts and diverse genetic backgrounds are essential to clarify further HRD's impact on treatment responses and survival outcomes in Indian patients, potentially shaping national guidelines for ovarian cancer management.

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