RESEARCH ARTICLE

Editorial Process: Submission:11/11/2025 Acceptance:06/09/2026 Published:27/09/2026

Clinicopathological Correlation of *BRCA1* Status in High-Grade Serous Ovarian Carcinoma via IHC and NGS

Fathurrahman Muiz[1,2]*, Rina Masadah[1], Berti J. Nelwan[1], Upik A. Miskad[1], Ni Ketut Sungowati[1,3], Cahyono Kaelan[1], Andi Alfian Zainuddin[4], Syahrul Rauf[1,5], Nugraha Utama Pelupessy[1,5], Amalia Yamin[1,3], Amalia Mulia Utami[1]

Abstract

Background: High-grade serous ovarian carcinoma (HGSOC) is the most aggressive subtype of epithelial ovarian cancer and is frequently associated with *BRCA1* dysfunction. This study aimed to evaluate the clinicopathological correlation of *BRCA1* expression and mutation status assessed by immunohistochemistry (IHC) and next-generation sequencing (NGS) with the Whole Exome Sequencing (WES) approach. **Methods:** A retrospective observational study was conducted on thirty-six formalin-fixed paraffin-embedded HGSOC samples. *BRCA1* expression was evaluated by IHC using a 10% nuclear staining cutoff. *BRCA1* mutation profiling was performed using NGS with a whole-exome sequencing (WES) approach. Clinicopathological variables were analyzed using Fisher's exact test. **Result:** Abnormal *BRCA1* expression was observed in 11.1% of cases, while *BRCA1* mutations were detected in 27.8%. Most mutations were somatic (70%) and predominantly loss-of-function variants (90%). A significant association was found between abnormal *BRCA1* expression and younger age ($p = 0.023$), whereas no association was observed with other clinicopathological parameters. **Conclusion:** *BRCA1* expression loss in HGSOC is associated with younger patient age. The discordance between IHC and mutation status highlights the complementary role of protein expression and molecular testing. A combined IHC–NGS approach may improve the identification of *BRCA1* deficiency and support therapeutic decision-making, particularly in the context of targeted therapy.

Keywords: *BRCA1*, High-Grade Serous Ovarian Carcinoma, Immunohistochemistry, Next-Generation Sequencing

Asian Pac J Cancer Prev, **27 (9)**, 3213-3220

Introduction

Ovarian cancer, based on Globocan 2022, has an incidence of 324,603 and a mortality of 206,956, with the Asian continent ranking first in the world, with an incidence of 178,223 and a mortality of 109,547 [1]. In Asia, Indonesia ranks third with 15,130 incidents and 9,673 deaths, after China and India [1]. The very high incidence and mortality need to be addressed in an integrated manner with early detection, morphological diagnostic examination, molecular identification, and clinical treatment, all based on precision medicine.

Ovarian neoplasms originate from three types of ovarian cells; mullerian epithelium, germ cells, and stromal-sex cord cells [2]. These neoplasms were classified according to the 5th edition of the WHO tumor classification [3,4]. These represent distinct tumor types with different molecular pathways and clinical behavior [5]. HGSOC originates from the distal fimbrial tip of the fallopian tube from a previous lesion known as serous tubal intraepithelial carcinoma (STIC), while Low Grade Serous Carcinoma (LGSC) originates from the ovary in the form of a benign, borderline serous tumor [3]. HGSOC cases do not have typical symptoms in the early stages, generally found in the advanced stages which causes high mortality, a high probability of resistance to platinum, and relapse [3,6]. Risk factors include age over 60, having a family history of breast or ovarian cancer, and infertility. On the other hand, breastfeeding, oral contraceptive use, late menarche, early menopause, and multiparity play a protective role against ovarian cancer [3,7].

The genomic landscape of HGSOC, characterized by chromosomal abnormalities, epigenetic modifications, signaling pathway dysregulation, germline and/or somatic

*[1]Department of Anatomical Pathology, Faculty of Medicine, Hasanuddin University, Makassar, South Sulawesi, Indonesia. [2]Department of Anatomical Pathology, Faculty of Medicine, Alkhairaat University, Palu, Central Sulawesi, Indonesia. [3]Pathology Anatomy Laboratory, Dr. Wahidin Sudirohusodo General Hospital, Makassar, South Sulawesi Indonesia. [4]Department of Public Health, Faculty of Medicine, Hasanuddin University, Makassar, South Sulawesi, Indonesia. [5]Department of Obstetrics and Gynecology, Faculty of Medicine, Hasanuddin University, Makassar, South Sulawesi, Indonesia. *For Correspondence: fathurrahman.muiz@gmail.com*

mutations, may be an important factor in treatment response and prognosis [8]. Genomic studies have shown that gene mutations in the homologous recombination pathway in DNA repair occur in approximately 50% of HGSOC cases, including *BRCA1* [9]. *BRCA1* (chromosome 17q21) is a key molecule in DNA repair of double-strand breaks (DSB) through the homologous recombination repair (HRR) mechanism [10,11]. *BRCA1* mutations cause the HRR mechanism to fail at DSBs, thus triggering cancer. Somatic and germline *BRCA1* mutations, methylation, or genomic aberrations in other HRR genes can lead to carcinomas, including HGSOC [3,4,12–14]. The *BRCA1* gene can undergo various forms of mutation, such as frame-shift insertions/deletions, non-synonymous truncations, and splicing site disruptions, resulting in missense mutations or non-functional proteins [15]. *BRCA1* gene mutations are an indication for targeted poly(ADP-ribose) polymerase (PARP) inhibitors (PARPi), therapy, and their expression can be an initial screening tool for PARPi administration [16, 17]. The aim of this study was to analyze the clinicopathological relationships, expressions and mutations of *BRCA1* in HGSOC patients.

Materials and Methods

This retrospective observational study included 36 formalin-fixed paraffin-embedded (FFPE) samples diagnosed as high-grade serous ovarian carcinoma (HGSOC). Samples were collected between March 2019 and June 2023 from the Anatomical Pathology Laboratory of Dr. Wahidin Sudirohusodo General Hospital, Makassar, Indonesia. The samples had not undergone chemotherapy, were not relapse cases, and showed tumor cell foci in at least 10 high-power fields of view (HPFs) at 400x magnification. Histopathological diagnosis was reconfirmed using hematoxylin and eosin staining. This was followed by *BRCA1* expression analysis using immunohistochemistry (IHC), while *BRCA1* gene mutation detection was performed using Next Generation Sequencing (NGS) technology with a Whole Exome Sequencing (WES) approach.

BRCA1 Protein Analysis

FFPE samples were selected and then sectioned at 3 micron thickness for HE staining to ensure suitability for *BRCA1* staining. FFPE samples were sectioned at 3 micron thickness using a microtome to create unstained slides and mounted on poly-L-lysine slides. The slides were then deparaffinized with xylene. Next, the slides were stained with immunohistochemical staining using *BRCA1* Mouse Monoclonal Antibody *BRCA1* antibody [8F7] Cat. GTX70113. Semiquantitative interpretation of *BRCA1* expression status in HGSOC tissue in the form of *BRCA1* loss (<5%), *BRCA1* Equivocal (5-10%) and *BRCA1* Retained (>10%) at 400x magnification [12,14]. *BRCA1* expression scores were expressed in two categories. Tumors with persistent staining, with *BRCA1* nuclear expression ≥10% of the tumor area, were considered "intact." Tumors with absent or equivocal staining, with *BRCA1* nuclear expression <10% of the tumor area, were considered "abnormal" [14,16]. Independent assessment of *BRCA1* expression by two pathologists without knowledge of *BRCA1* genetic status. The stromal cells function as an internal positive control for validity of the staining, as they maintain a normal copy of *BRCA1*, regardless of the tumor cells' status [14].

BRCA1 Gene Analysis

DNA was extracted from FFPE samples and subjected to next-generation sequencing using a whole-exome sequencing (WES) approach on the Illumina platform. Mutations were categorized as truncating or detrimental variants according to their functional impact. The entire coding region (wild type/mutant) was examined, then compared with the reference (GRCh38), so that the entire exome was analyzed. The *BRCA1* mutation on chromosome 17q21.31 consisted of 81,070 base pairs, with a coding sequence region of 5,592 nucleotide(nt) spanning 24 exons [18,19]. The main reference sequence (RefSeq) of *BRCA1* was NM_007294.4, with an mRNA length of 7,088 nt [18,19]. Interpretation of NGS examination results is based on the Standards and Guidelines for the Interpretation and Reporting of Sequence Variants in Cancer, using ClinVar database versions available at the time of analysis (versions 20180225–20201121).

Statistical Methods

Statistical analysis was performed using Statistical Package for the Social Sciences (SPSS) version 26. Fisher's exact test was used to assess associations between categorical variables. Interobserver agreement was evaluated using Cohen's kappa coefficient.

Results

Clinicopathological Characteristics

A total of 36 formalin-fixed paraffin-embedded samples diagnosed as high-grade serous carcinoma (HGSOC) were analyzed. The majority of patients were >50 years old (58.3%), while 41.7% were ≤50 years. Most patients had a normal body mass index (97.2%) and presented with abdominal enlargement (94.4%). Elevated serum CA-125 levels were noted in all cases (100%). Based on International Federation of Gynecology and Obstetrics (FIGO) staging, 83.3% were stage II and 16.7% stage III. Histologically, necrosis was present in all tumors (100%), and high mitotic index (>12/10 HPF) was observed in 94.4% of cases (Table 1), consistent with the high proliferative nature of HGSOC [3,20].

BRCA1 Immunohistochemical Expression

The similarity between the two pathologists in the final *BRCA1* IHC assessment was substantial (kappa coefficient 0.729, P = 0.157; McNemar's test). *BRCA1* nuclear expression was retained (≥10%) in 32 cases (88.9%) and abnormal (<10%) in 4 cases (11.1%) (Table 1). The abnormal category comprised two subcategories: complete loss (<5%) in 3 cases (8.3%) and equivocal expression (5–10%) in 1 case (2.8%). The remaining 32 cases (88.9%) demonstrated intact (retained) nuclear expression (≥10%). Hematoxylin and eosin (HE) and immunohistochemical staining patterns are shown in Figure 1, which depicts

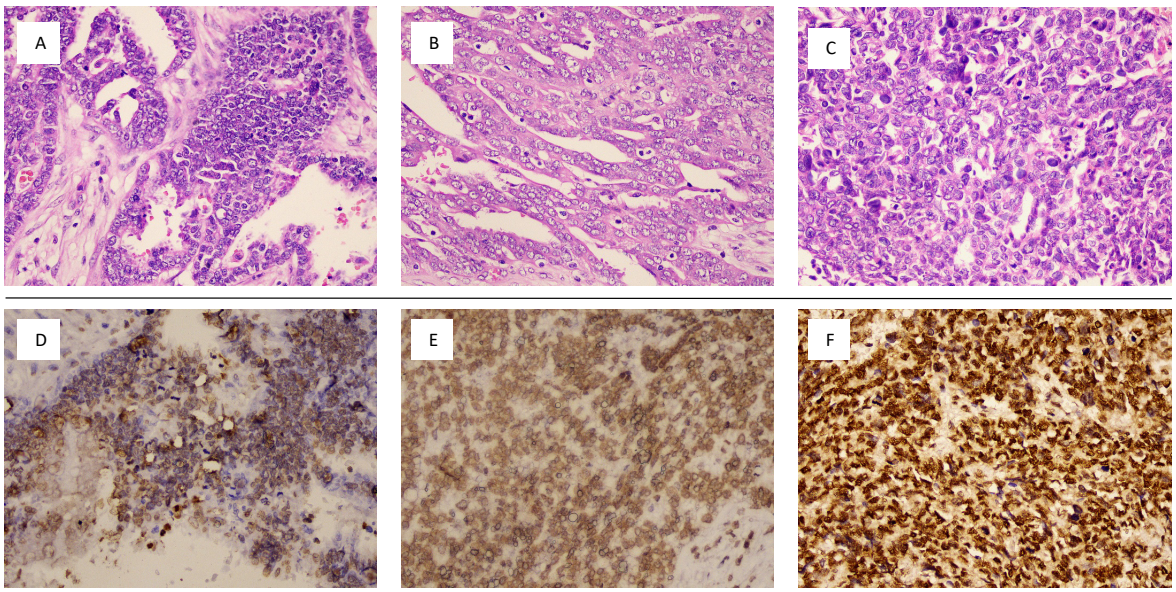

Figure 1. Histopathological and Immunohistochemical Findings of High-Grade Serous Ovarian Carcinoma (HGSOC). (A–C) Hematoxylin and eosin staining. (D–F) Corresponding BRCA1 immunohistochemical staining showing (D) loss of nuclear expression, (E) equivocal expression, and (F) retained nuclear expression (400× magnification).

Table 1. Clinicopathological Characteristics and *BRCA1* Immunohistochemical Expression Profile of Patients with High-Grade Serous Ovarian Carcinoma (HGSOC)

Characteristic	n	(%)
Age (years)		
≤50	15	41.7
>50	21	58.3
Body Mass Index (BMI)		
Underweight	1	2.8
Ideal	35	97.2
Main complaint: Abdominal enlargement		
No	2	5.6
Yes	34	94.4
FIGO Stage		
II	30	83.3
III	6	16.7
CA125 level		
Elevated	36	100.0
Mitotic index		
Low (≤12/10 HPF)	2	5.6
High (>12/10 HPF)	34	94.4
Necrosis		
Present	36	100.0
BRCA1 IHC expression status		
Loss (<5%)	3	8.3
Equivocal (5-10%)	1	2.8
Retained (>10%)	32	88.9
BRCA1 IHC expression score		
Abnormal (<10%)	4	11.1
Intact (≥10%)	32	88.9

BMI, Body Mass Index; FIGO, International Federation of Gynecology and Obstetrics; CA125, Cancer Antigen 125; HPF, high-power field; IHC, Immunohistochemistry.

the histopathological staining of HGSOC, intact nuclear expression, equivocal, and complete absence of staining in *BRCA1* deficiency cases. Loss of *BRCA1* expression was predominantly observed in younger patients (≤50 years). Statistical analysis demonstrated a significant association between patient age and *BRCA1* expression ($p = 0.023$). Other parameters FIGO stage, mitotic index, and necrosis did not show significant correlations ($p > 0.05$).

BRCA1 Mutation Profile

Whole-exome sequencing using the Illumina platform identified *BRCA1* mutations in 10 of 36 cases (27.8%). Among these, 7 (70%) were somatic and 3 (30%) germline (Table 2). Most mutations (90%) were loss-of-function (LOF) variants such as nonsense or frameshift alterations. These mutations were predominantly located in the BRCT domain (exons 16–24), known to mediate transcriptional activation and DNA damage repair [6,18,19]. The complete list of pathogenic *BRCA1* variants identified is provided in Supplementary Table 1.

Association Characteristic Features and BRCA1 Expression

The relationship between *BRCA1* expression and characteristic features was summarized in Table 3. Loss of *BRCA1* expression was significantly associated with younger age ($p = 0.023$), but did not correlate with FIGO stage ($p = 0.61$), mitotic index ($p = 0.73$), or presence of necrosis ($p = 1.00$). These findings suggest that *BRCA1* expression loss in HGSOC was more strongly linked to host-related factors (age) rather than to tumor aggressiveness indicators [4,21].

Association BRCA1 Expression and BRCA1 Mutation

No significant correlation was found between *BRCA1* IHC expression and *BRCA1* mutation status ($p = 1.000$) in Table 2. Among the 10 mutation-positive cases, 9

Table 2. *BRCA1* Mutation Profile Identified by Next-Generation Sequencing and Association with Immunohistochemical Expression

BRCA1 gene	*BRCA1* expression score		Total n (%)	p*
	Abnormal (<10%) n (%)	Intact (≥10%) n (%)		
Mutation Status				
No	3 (8.3)	23 (63.9)	26 (72.2)	1.000*
Yes	1 (2.8)	9 (25.0)	10 (27.8)	
Mutation type				
Somatic	1 (10.0)	6 (60.0)	7 (70.0)	1.000*
Germline	0 (0.0)	3 (100.0)	3 (30.0)	
Oncomine Gene Class				
Loss of Function	1 (10.0)	8 (80.0)	9 (90.0)	1.000*
Missense	0 (0.0)	1 (10.0)	1 (10.0)	
Oncomine Variant Class				
Truncating	1 (10.0)	3 (30.0)	4 (40.0)	0.4000*
Deleterious	0 (0.0)	6 (60.0)	6 (60.0)	

*Fisher's exact test. Mutation classification was based on sequencing results.

retained *BRCA1* nuclear expression, and 1 showed reduced expression. This indicates that *BRCA1* protein loss may not always reflect gene mutation, as expression loss may also be caused by other pathways, such as promoter methylation, post-translational modification, or transcriptional repression [10,16].

Discussion

HGSOC is the most common and aggressive subtype of ovarian epithelial carcinoma with the highest mortality among ovarian carcinomas [3,22]. The study sample predominantly comprised individuals over 50 years of age, aligning with the recognized epidemiological characteristics of HGSOC, which primarily impacts

Table 3. Association between Clinicopathological Characteristics and *BRCA1* Expression (Score and Status) in High-Grade Serous Ovarian Carcinoma

Clinicopathological Feature	Expression Status			Expression Score		Total n (%)	p* (Status)	p* (Score)
	Loss (<5%) n(%)	Equivocal (5-10%) n(%)	Retained (>10%) n(%)	Abnormal (<10%) n(%)	Intact (≥10%) n(%)			
Age (years)								
≤50	3 (8.3)	1 (2.8)	11 (30.6)	4 (11.1)	11 (30.6)	15 (41.7)	-	0.023**
>50	0 (0.0)	0 (0.0)	21 (58.3)	0 (0.0)	21 (58.3)	21 (58.3)		
BMI								
Underweight	1 (2.8)	0 (0.0)	0 (0.0)	1 (2.8)	0 (0.0)	1 (2.8)	-	0.111
Normal	2 (5.6)	1 (2.8)	32 (88.9)	3 (8.3)	32 (88.9)	35 (97.2)		
Abdominal enlargement								
No	0 (0.0)	0 (0.0)	2 (5.6)	0 (0.0)	2 (5.6)	2 (5.6)	-	1.000
Yes	3 (8.3)	1 (2.8)	30 (83.3)	4 (11.1)	30 (83.3)	34 (94.4)		
FIGO Stage								
II	2 (5.6)	1 (2.8)	27 (75.0)	3 (8.3)	27 (75.0)	30 (83.3)	-	0.535
III	1 (2.8)	0 (0.0)	5 (13.9)	1 (2.8)	5 (13.9)	6 (16.7)		
CA125								
Elevated	3 (8.3)	1 (2.8)	32 (88.9)	4 (11.1)	32 (88.9)	36 (100.0)	-	-
Mitotic index								
Low (≤12/10 (HPF)	0 (0.0)	0 (0.0)	2 (5.6)	0 (0.0)	2 (5.6)	2 (5.6)	-	1.000
High (>12/10 HPF)	3 (8.3)	1 (2.8)	30 (83.3)	4 (11.1)	30 (83.3)	34 (94.4)		
Necrosis								
Present	3(8.3)	1 (2.8)	32 (88.9)	4 (11.1)	32 (88.9)	36 (100.0)	-	-

*Fisher's exact test. **Statistically significant (p<0.05). BMI: Body Mass Index; FIGO: International Federation of Gynecology and Obstetrics; CA125: Cancer Antigen 125; HPF: high-power field. '-' indicates p-value cannot be computed (no variation in the variable)

postmenopausal women. A subset of patients in this study were younger than 50 years. The body mass index (BMI) of HGSOC samples was predominantly within the normal range. Obesity does not elevate the risk of HGSOC, so reducing BMI has minimal impact on the prevention. Additional modifiable factors must be explored for a more thorough comprehension of this condition [23].

This study revealed a *BRCA1* mutation prevalence of 27.8% within the sample, characterized by a predominance of stage II malignancies and clinical signs of abdominal pain. This conclusion corresponds with the study of Chao et al. (2016), which indicated a notable prevalence of germline and somatic *BRCA1*/2 mutations in ovarian cancer, with *BRCA1* mutations observed within a comparable prevalence range [24]. Abdominal pain is the predominant complaint reported by HGSOC patients [25]. This study found significantly raised CA125 levels in all samples, consistent with current literature that reports greater CA125 levels in type II ovarian cancer, particularly HGSOC, compared to type I cancer. Such levels can be used as a prognostic indicator [8,26,27]. Numerous investigations have shown contradictory findings concerning *BRCA1* status in epithelial ovarian cancer [28]. The *BRCA1* immunohistochemistry findings in this study revealed that the majority of samples had sufficient *BRCA1* expression, with 32 samples demonstrating above 10% expression and only 4 samples displaying less than 10% expression. A threshold of 10% tumor staining is a standard and prevalent technique employed by pathologists to evaluate *BRCA1* expression [14,16]. An expression of *BRCA1* over 10% in tumor cells is deemed aberrantly positive [14,28,29]. This binary classification approach is consistent with that reported by Manchana et al. (2020), who defined *BRCA1* loss as nuclear staining in fewer than 10% of neoplastic cells and retained expression as staining exceeding 10%, without a separate equivocal subcategory, thereby simplifying interpretation for routine pathological practice [16].

In this study, Abnormal *BRCA1* expression was observed in 11.1% of cases, comparable to the 10–25% loss reported in prior research [12,16]. Notably, a significant association between age and *BRCA1* expression ($p = 0.023$) was observed, where *BRCA1* loss occurred exclusively in patients aged ≤50 years. This finding suggests that younger HGSOC patients may harbor early-onset *BRCA1*-related carcinogenesis, possibly reflecting hereditary predisposition or germline *BRCA1* alterations [4,30]. This finding aligns with the study conducted by Kalachand et al. (2020), which reported a significant association between *BRCA1* methylation and younger age (P=0.005), as well as with the research by Amin et al. (2023), which also showed significant *BRCA1* expression in older age groups [28,31]. These results align with the characteristics of hereditary ovarian cancer, where germline *BRCA1* mutations typically appear at a younger age. Women with *BRCA1* mutations or HRR deficiency have a higher susceptibility to HGSOC. Given that these mutations can also impact other cancer types, such as breast cancer, genetic screening and clinical approaches are crucial for identifying individuals at risk for hereditary ovarian cancer syndromes. However, no significant association was identified between *BRCA1* expression and other clinicopathological factors such as FIGO stage, mitotic index, or necrosis. The *BRCA1* gene encodes a tumor suppressor protein that is crucial for the HRR pathway. Its dysfunction leads to homologous recombination repair deficiency (HRD), genomic instability, and the accumulation of double-stranded DNA breaks [32]. This HRD-driven mutational phenotype forms the biological basis for the high genomic instability characteristic of HGSOC [20].

BRCA1 IHC could serve as a possible biomarker for BRCA1 malfunction in HGSOC [14]. Germline BRCA mutations were the predominant kind of BRCA malfunction; however, somatic BRCA mutations and epigenetic alterations constitute additional pathways [16]. This study identified *BRCA1* mutations in 27.8% of cases by WES, consistent with a prevalence range of 20–30% [9]. Most variants were loss-of-function truncating mutations involving nonsense or frameshift changes, particularly within the BRCT domain (exons 16–24), a critical region responsible for phosphoprotein binding and transcriptional activation during DNA repair [6,18]. Somatic mutations (70%) were more prevalent than germline mutations (30%), indicating that sporadic *BRCA1* inactivation significantly contributes to HRD in this study. This discovery aligns with existing evidence indicating that both germline and somatic *BRCA1* deletions significantly contribute to the HRD phenotype [3,20].

The present study found no significant correlation between *BRCA1* IHC expression and NGS-detected *BRCA1* mutations ($p = 1.000$), indicating that *BRCA1* protein expression does not necessarily reflect underlying genetic alterations. The lack of concordance between *BRCA1* protein expression and mutation status observed in this study highlights the complexity of *BRCA1* regulation in HGSOC. In addition to genetic mutations, *BRCA1* function may be impaired by epigenetic mechanisms, particularly promoter hypermethylation, which can silence gene expression without altering the DNA sequence. This epigenetic inactivation may account for cases showing reduced protein expression in the absence of detectable mutations, as well as retained expression despite underlying genetic alterations. These findings underscore the limitations of relying on a single diagnostic modality and support the integration of both immunohistochemistry and molecular testing in clinical practice. Consistent with Kalachand et al. (2020), who reported an association between *BRCA1* promoter methylation and younger patient age, we similarly observed that loss of *BRCA1* expression predominantly occurred in patients aged ≤50 years [31]. Taken together, these findings suggest that epigenetic silencing may contribute to *BRCA1* dysfunction beyond genetic alterations and support the complementary role of integrating protein expression analysis with molecular testing in a comprehensive *BRCA1* assessment strategy. While *BRCA1* IHC provides a practical and cost-effective initial screening tool, molecular confirmation by NGS remains essential to accurately identify pathogenic *BRCA1* alterations, particularly in cases where protein expression does not reflect underlying genetic status.

Identifying *BRCA1* deficiency has substantial therapeutic and prognostic implications. Tumors with *BRCA1* loss or HRD show increased sensitivity to platinum-based chemotherapy and PARPi, which exploit the concept of synthetic lethality [6,33]. Initial research suggests that *BRCA1* promoter hypermethylation and somatic mutations may exhibit synthetic lethality when combined with PARP inhibitors. *BRCA1* immunohistochemistry can serve as a screening method for *BRCA1* germline mutations and a predictive biomarker for PARPi in patients with wild-type *BRCA1* germline status or aberrant *BRCA1* mutation status [16].

From a therapeutic perspective, the identification of *BRCA1* deficiency has important clinical implications. Tumors with homologous recombination deficiency (HRD), including those with *BRCA1* alterations, are more likely to respond to platinum-based chemotherapy and poly(ADP-ribose) polymerase inhibitors (PARPi) [6,17]. PARPi exploit the concept of synthetic lethality, a well-established therapeutic strategy in BRCA-deficient tumors [33]. Although this study did not directly evaluate treatment outcomes, the combined assessment of *BRCA1* status using immunohistochemistry and next-generation sequencing may provide a more comprehensive framework for identifying patients who could benefit from targeted therapies.

The relationship between *BRCA1* expression and survival after chemotherapy: patients with lower *BRCA1* expression responded better to platinum-based therapy, while patients with higher *BRCA1* expression responded more effectively to taxanes [28,34]. Integrating *BRCA1* IHC with NGS-based mutation testing provides a comprehensive approach. This dual strategy allows pathologists to screen for *BRCA1* dysfunction efficiently while ensuring accurate genetic confirmation in eligible cases. Future follow-up studies necessitate larger multicenter cohorts, the application of whole genome sequencing to investigate potential methylation profiles, epigenetic and other determinants affecting BRCA mutations and expression, as well as survival analysis, to ascertain the prognostic and predictive relevance of *BRCA1* in Indonesian HGSOC patients.

This study has several limitations. The relatively small sample size may limit statistical power and reduce the generalizability of the findings. In addition, the retrospective design may introduce selection bias. Furthermore, epigenetic analyses, such as *BRCA1* promoter methylation status, were not performed, which could have provided additional insight into the observed discordance. Therefore, future studies incorporating larger cohorts and integrated molecular approaches are warranted.

In conclusion, *BRCA1* expression loss in high-grade serous ovarian carcinoma is associated with younger patient age and may reflect underlying hereditary predisposition or early-onset tumorigenesis. The observed discordance between IHC and NGS findings highlights the multifactorial regulation of *BRCA1*, including both genetic and potential epigenetic mechanisms. A combined diagnostic approach integrating protein expression and genomic profiling provides a more comprehensive assessment of *BRCA1* status and may improve patient stratification for targeted therapies.

Author Contribution Statement

All authors contributed equally in this study.

Acknowledgements

We would like to thank the Department of Anatomical Pathology, Faculty of Medicine, Hasanuddin University; the Anatomical Pathology Laboratory of Dr. Wahidin Sudirohusodo General Hospital; the Anatomical Pathology Laboratory of Siloam Hospital Makassar; the Anatomical Pathology Laboratory of Hasanuddin University Hospital; the Faculty of Medicine, Alkhairaat University; and KALGen Innolab for all the support and help in this study.

Funding Statement

This research was supported by the Faculty of Medicine, Hasanuddin University, in the collaborative research grants program 2024 (08831/UN4.6/PT/2024).

Approval

This study is part of an approved student thesis.

Conflict of Interest

The authors declare no conflict of interest. The funders had no role in the design of the study; in the collection, analyses, or interpretation of data; in the writing of the manuscript, or in the decision to publish the results.

Ethical Declaration

This study was approved by the Health Research Ethics Committee, Faculty of Medicine, Hasanuddin University, Makassar, Indonesia in 2024 with approval number 612/UN4.6.4.5.31/PP36/2024. All procedures adhered to the Declaration of Helsinki, with written informed consent obtained prior to data collection.

References

1. Ferlay J, Colombet M, Soerjomataram I, Parkin DM, Piñeros M, Znaor A, Bray F. Global Cancer Observatory: Cancer Today (version 1.1) [Internet]. Lyon: International Agency for Research on Cancer; 2022 [cited 2024 Mar 16]. Available from: https://gco.iarc.who.int/today/en/dataviz
2. Kumar V, Abbas AK, Aster JC. Robbins & Cotran pathologic basis of disease. 10th ed. Philadelphia: Elsevier; 2020.
3. Soslow RA, Soerjomataram I, Campbell I, Malpica A. High-grade serous carcinoma of the ovary. In: WHO Classification of Tumours Editorial Board, editors. Female genital tumours [Internet]. 5th ed. Lyon: International Agency for Research on Cancer; 2020 [cited 2024 Mar 16]. Available from: https://tumourclassification.iarc.who.int/
4. Soslow RA, Han G, Park KJ, Garg K, Olvera N, Spriggs DR, Kauff ND, et al. Morphologic patterns associated with *BRCA1* and *BRCA2* genotype in ovarian carcinoma. Mod Pathol. 2012;25(4):625-636. https://doi.org/10.1038/modpathol.2011.183
5. Singer G, Kurman RJ, Chang HW, Cho SKR, Shih IM. Diverse

tumorigenic pathways in ovarian serous carcinoma. Am J Pathol. 2002;160(4):1223-1228. https://doi.org/10.1016/S0002-9440(10)62549-7
6. Testa U, Petrucci E, Pasquini L, Castelli G, Pelosi E. Ovarian cancers: genetic abnormalities, tumor heterogeneity and progression, clonal evolution and cancer stem cells. Medicines (Basel). 2018;5(1):16. https://doi.org/10.3390/medicines5010016
7. Otsuka I. Mechanisms of high-grade serous carcinogenesis in the fallopian tube and ovary: current hypotheses, etiologic factors, and molecular alterations. Int J Mol Sci. 2021;22(9):4409. https://doi.org/10.3390/ijms22094409
8. Punzón-Jiménez P, Lago V, Domingo S, Simón C, Mas A. Molecular management of high-grade serous ovarian carcinoma. Int J Mol Sci. 2022;23(22):13777. https://doi.org/10.3390/ijms232213777
9. Kroeger PT, Drapkin R. Pathogenesis and heterogeneity of ovarian cancer. Curr Opin Obstet Gynecol. 2017;29(1):26-34. https://doi.org/10.1097/GCO.0000000000000340
10. van der Groep P, van der Wall E, van Diest PJ. Pathology of hereditary breast cancer. Cell Oncol (Dordr). 2011;34(2):71-88. https://doi.org/10.1007/s13402-011-0010-3
11. Turashvili G, Lazaro C, Ying S, Charames G, Wong A, Hamilton K, Yee D, et al. Tumor BRCA testing in high grade serous carcinoma: mutation rates and optimal tissue requirements. Cancers (Basel). 2020;12(11):3468. https://doi.org/10.3390/cancers12113468
12. Garg K, Levine DA, Olvera N, Dao F, Bisogna M, Secord AA, Berchuck A, et al. *BRCA1* immunohistochemistry in a molecularly characterized cohort of ovarian high-grade serous carcinomas. Am J Surg Pathol. 2013;37(1):138-146. https://doi.org/10.1097/PAS.0b013e31826cabbd
13. Sugino K, Tamura R, Nakaoka H, Yachida N, Yamaguchi M, Mori Y, Kashima K, et al. Germline and somatic mutations of homologous recombination-associated genes in Japanese ovarian cancer patients. Sci Rep. 2019;9(1):17808. https://doi.org/10.1038/s41598-019-54116-y
14. Meisel JL, Hyman DM, Garg K, Zhou Q, Dao F, Bisogna M, Gao J, et al. The performance of *BRCA1* immunohistochemistry for detecting germline, somatic, and epigenetic *BRCA1* loss in high-grade serous ovarian cancer. Ann Oncol. 2014;25(12):2372-2378. https://doi.org/10.1093/annonc/mdu461
15. Sharma B, Kaur RP, Raut S, Munshi A. *BRCA1* mutation spectrum, functions, and therapeutic strategies: the story so far. Curr Probl Cancer. 2018;42(2):189-207. https://doi.org/10.1016/j.currproblcancer.2018.01.001
16. Manchana T, Tantbirojn P, Pohthipornthawat N. BRCA immunohistochemistry for screening of BRCA mutation in epithelial ovarian cancer patients. Gynecol Oncol Rep. 2020;33:100582. https://doi.org/10.1016/j.gore.2020.100582
17. Mittica G, Ghisoni E, Giannone G, Genta S, Aglietta M, Sapino A, Valabrega G. PARP inhibitors in ovarian cancer. Recent Pat Anticancer Drug Discov. 2018;13(4):392-410. https://doi.org/10.2174/1574892813666180305165256
18. Brzovic PS, Rajagopal P, Hoyt DW, King MC, Klevit RE. Structure of a *BRCA1*-BARD1 heterodimeric RING-RING complex. Nat Struct Biol. 2001;8(10):833-837. https://doi.org/10.1038/nsb1001-833
19. VarSome. Transcript details *BRCA1* [Internet]. Lausanne: Saphetor SA; 2025 [cited 2025 Aug 29]. Available from: https://varsome.com/gene/hg38/*BRCA1*
20. De Leo A, Santini D, Ceccarelli C, Santandrea G, Palicelli A, Acquaviva G, et al. What is new on ovarian carcinoma: integrated morphologic and molecular analysis following the new 2020 World Health Organization classification of female genital tumors. Diagnostics (Basel). 2021;11(4):697. https://doi.org/10.3390/diagnostics11040697
21. Kurman RJ, Shih IM. The dualistic model of ovarian carcinogenesis: revisited, revised, and expanded. Am J Pathol. 2016;186(4):733-747. https://doi.org/10.1016/j.ajpath.2015.11.011
22. Lisio MA, Fu L, Goyeneche A, Gao ZH, Telleria C. High-grade serous ovarian cancer: basic sciences, clinical and therapeutic standpoints. Int J Mol Sci. 2019;20(4):952. https://doi.org/10.3390/ijms20040952
23. Olsen CM, Nagle CM, Whiteman DC, Ness R, Pearce CL, Pike MC, Rossing MA, et al. Obesity and risk of ovarian cancer subtypes: evidence from the Ovarian Cancer Association Consortium. Endocr Relat Cancer. 2013;20(2):251-262. https://doi.org/10.1530/ERC-12-0395
24. Chao A, Chang TC, Lapke N, Jung SM, Chi P, Chen CH, Yang LY, et al. Prevalence and clinical significance of *BRCA1*/2 germline and somatic mutations in Taiwanese patients with ovarian cancer. Oncotarget. 2016;7(51):85529-85541. https://doi.org/10.18632/oncotarget.13456
25. Sindiani A, Obeidat B, Hamadeh L, Alghazo S, Al-Mohtaseb A, Alshdaifat E. A descriptive study of the clinico-pathological and surgical characteristics of patients with primary epithelial ovarian cancer: a cross sectional study. Ann Med Surg (Lond). 2020;59:254-257. https://doi.org/10.1016/j.amsu.2020.09.043
26. Morales-Vásquez F, Pedernera E, Reynaga-Obregón J, López-Basave HN, Gómora MJ, Carlón E, Cárdenas S, et al. High levels of pretreatment CA125 are associated to improved survival in high grade serous ovarian carcinoma. J Ovarian Res. 2016;9(1):41. https://doi.org/10.1186/s13048-016-0247-6
27. Charkhchi P, Cybulski C, Gronwald J, Wong FO, Narod SA, Akbari MR. CA125 and ovarian cancer: a comprehensive review. Cancers (Basel). 2020;12(12):3730. https://doi.org/10.3390/cancers12123730
28. Amin NH, Ahmed BA, Abou-Bakr AA, Eissa SS, Nassar HR, Gad M, Eissa M. The impact of *BRCA1* expression on survival status in ovarian serous carcinoma of Egyptian patients. Asian Pac J Cancer Prev. 2023;24(10):3613-3620. https://doi.org/10.31557/APJCP.2023.24.10.3613
29. Lesnock J, Darcy K, Tian C, DeLoia J, Thrall M, Zahn C, et al. *BRCA1* expression and improved survival in ovarian cancer patients treated with intraperitoneal cisplatin and paclitaxel: a Gynecologic Oncology Group Study. Br J Cancer. 2013;108(6):1231-1237. https://doi.org/10.1038/bjc.2013.70
30. Guo T, Dong X, Xie S, Zhang L, Zeng P, Zhang L. Cellular mechanism of gene mutations and potential therapeutic targets in ovarian cancer. Cancer Manag Res. 2021;13:3081-3100. https://doi.org/10.2147/CMAR.S292992
31. Kalachand RD, Stordal B, Madden S, Chandler B, Cunningham J, Goode EL, et al. *BRCA1* promoter methylation and clinical outcomes in ovarian cancer: an individual patient data meta-analysis. J Natl Cancer Inst. 2020;112(12):1190-1203. https://doi.org/10.1093/jnci/djaa070
32. Tarsounas M, Sung P. The antitumorigenic roles of *BRCA1*-BARD1 in DNA repair and replication. Nat Rev Mol Cell Biol. 2020;21(5):284-299. https://doi.org/10.1038/s41580-020-0218-z
33. Lord CJ, Ashworth A. PARP inhibitors: synthetic lethality in the clinic. Science. 2017;355(6330):1152-1158. https://doi.org/10.1126/science.aam7344
34. Menghi F, Banda K, Kumar P, Straub R, Dobrolecki L, Rodriguez IV, Yost SE, et al. Genomic and epigenomic BRCA alterations predict adaptive resistance and

response to platinum-based therapy in patients with triple-negative breast and ovarian carcinomas. Sci Transl Med. 2022;14(652):eabn1926. https://doi.org/10.1126/scitranslmed.abn1926