

# Germline BRCA, Chemotherapy response scores, and survival in the neoadjuvant treatment of ovarian cancer

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## Research article

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# Abstract

**Background** To analyze the effects of BRCA1/2 mutations on chemotherapy response scores (CRS) and survival in a cohort of patients with advanced-stage ovarian cancer who were treated with neoadjuvant chemotherapy (NAC) followed by interval debulking surgery (IDS).

**Methods** We retrospectively reviewed the medical records of 169 high-grade serous ovarian cancer patients who underwent a germline BRCA1/2 test and received three cycles of NAC at the Yonsei Cancer Center from 2006 to 2018. Chemotherapy response scores were compared in patients with and without BRCA1/2 mutations. The effects of BRCA1/2 mutations and CRS on survival were evaluated.

**Results** BRCA1/2 mutations were detected in 47 (28.1%) of the 169 patients. Overall, 16 (34.0%) patients with BRCA1/2 mutations had a CRS 3 to chemotherapy compared to scores of 43 in patients (35.2%) without a mutation. Response scores of 3 in patients with BRCA1/2 mutations were not significantly associated with either improved progression-free survival (PFS) ( $P = 0.949$ ) or overall survival (OS) ( $P = 0.168$ ). However, CRS 3 in patients without BRCA mutations was significantly associated with both improved PFS ( $P = 0.030$ ) and OS ( $P = 0.039$ ). In patients with CRS1/2, carriers of BRCA1/2 mutations had better PFS ( $P = 0.0344$ ) and OS ( $P = 0.043$ ) than wild-type BRCA genotype patients.

**Conclusion** In ovarian cancer patients treated with NAC, CRS did not predict survival for BRCA 1/2 mutation carriers but did for BRCA wild-type patients.

## Background

Several randomized controlled phase III clinical trials with patients with advanced-stage ovarian cancer showed that their survival outcomes and postoperative morbidity and mortality after neoadjuvant chemotherapy (NAC) followed by interval debulking surgery (IDS) were at least as good as the results for patients who primary cytoreductive surgery [1–4]. Therefore, NAC followed by IDS is considered as an alternative treatment for advanced-stage ovarian cancer.

Bohm et al. proposed a simple scoring system for grading the response to NAC based on the histopathological examination of IDS specimens [5]. They reported that in the three-tiered chemotherapy response scores (CRS) of omental tissue sections, approximately 30% of patients who received NAC achieved a CRS 3 (none or very little residual tumor) and that these patients had favorable progression-free survival (PFS). The remaining 70% of CRS 1 or CRS 2 patients, those with residual viable cancer, had higher recurrence rates [5, 6]. As a consequence, an increasing body of research has addressed whether CRS 3 can be used as a surrogate marker, similar to the way the pathologic complete response (pCR) is used in breast cancer, in the prognosis for patients with advanced-stage ovarian cancer treated with NAC followed by IDS. However, platinum-based doublet chemotherapy remains the standard of care for advanced-stage ovarian cancer patients who are treated with NAC followed by IDS, regardless of their response to chemotherapy.

Recently, mutations in BRCA1 and BRCA2 have been recognized as a predictor of advanced-stage ovarian cancer susceptibility and a prognostic factor [7, 8]. Compared with wild-type BRCA genotype patients, patients with advanced-stage ovarian cancer and BRCA1/2 mutations have been reported to have higher clinical response rates to platinum-based chemotherapy [9–11]. Therefore, there are unanswered questions about whether the higher CRS by carriers of the BRCA1/2 germline mutations represents a better prognosis. In triple-negative breast cancers treated with NAC, several studies have tried to identify the relationships between germline BRCA1/2 mutations, response rates, and prognoses [12, 13]. These studies have shown that patients with BRCA1/2 mutations had superior response rates, and response rate was a weaker predictor of disease-free survival rates compared with wild-type BRCA1/2 genotype patients.

In this study, we analyzed the extent to which CRS depended on germline BRCA1/2 mutations, whether CRS correlates with platinum-based chemotherapy, and whether CRS has an impact on survival outcomes in patients with and without germline BRCA1/2 mutations.

## Methods

### Study populations

We retrospectively reviewed the medical records of 326 patients with pathologically confirmed ovarian cancer who from 2006 to 2018 received NAC at the Yonsei Cancer Center, Seoul, South Korea. The patient inclusion criteria included (1) histopathologically confirmed FIGO Stage III or IV high-grade ovarian carcinoma; (2) patients who underwent IDS after NAC; and (3) patients who received three cycles of NAC before IDS.

The exclusion criteria were as follows: Patients still receiving chemotherapy at the time of data analysis (N = 19); patients who had not received IDS after NAC (N = 15); patients for whom data was missing (N = 31); and, lastly, patients who had not undergone a germline BRCA test (N = 92). After this review, 169 patients met our criteria. Of these, 122 patients had the wild-type BRCA genotype, and 47 had BRCA1 or BRCA2 mutations (Fig. 1).

### Treatment

Most patients received taxane and platinum combination chemotherapy. Other treatments such as radiation or endocrine therapy were not performed before surgery. Determination of which patients required NAC was based on initial imaging studies that showed high tumor dissemination that was assumed to have occurred under the following conditions [14]: (1) patients had a poor performance status and high operative risk because of medical comorbidities, or (2) optimal debulking surgery (residual disease measuring 1 cm or less) was unsuitable because of a high tumor burden [predictive index value (PIV)  $\geq 8$ ]. For diagnostic laparoscopy, the degree of tumor burden was determined with the PIV [15]. For IDS, all patients underwent surgery with the intent to achieve complete resection with no residual tumor. Standard surgical procedures included the following: sampling of free fluid or peritoneal

washings for cytology; thorough inspection of the abdomen and pelvis, including the upper abdominal viscera, diaphragm, and retroperitoneal spaces; and hysterectomy, bilateral oophorectomy and omentectomy, pelvic/para-aortic lymph node dissection, and appendectomy. Radical surgery included any of following: bowel surgery, cholecystectomy, diaphragm peritonectomy/resection, distal pancreatectomy video-assisted thoracoscopic surgery, splenectomy, liver resection, supraclavicular fossa resection, ureter resection, and others. Subsequently, additional cycles of adjuvant chemotherapy were administered to complete a total of six cycles at the discretion of the treating physician. Surgical complexity was classified as low, intermediate, or high [16].

### Pathologic review

The resected tissues were formalin-fixed and paraffin-embedded according to standard procedures and stained with hematoxylin and eosin (H&E) in the Department of Pathology, Severance Hospital, Yonsei University College of Medicine. All available H&E-stained slides obtained from IDS tissues were reviewed by three experienced gynecologic pathologists who independently scored each slide according to the three-tiered CRS system proposed by Böhm et al. [5] CRS 1 indicated minimal or zero tumor response. CRS 2 indicated appreciable tumor response amid a viable tumor easily identifiable in the omentum. CRS 3 indicated complete or near-complete response with zero or very little residual tumor up to a maximum size of 2 mm.

### BRCA testing

From the whole blood samples, genomic DNA was extracted according to the protocol provided by the manufacturer (QIAamp DNA Blood Mini Kit, QIAGEN, USA). To assess the germline mutations in *BRCA1* and *BRCA2*, the entire coding region and intron-exon boundaries of two genes were amplified using polymerase chain reaction (PCR) amplification. We identified all variants using Sanger sequencing on a 3730 DNA Analyzer with the BigDye Terminator v3.1 Cycle Sequencing Kit (Applied Biosystems, Foster City, CA, USA). Sequencing data were aligned against appropriate reference sequences (accession numbers NM\_007294 and NM\_000059, respectively) and analyzed using the Sequencher 5.3 software (Gene Codes Corp., Ann Arbor, MI, USA). Variations were described following the nomenclature system of the Human Genome Variation Society (<http://www.hgvs.org/mutnomen>) and the conventional nomenclature system from the Breast Cancer Information Core (BIC; <http://research.nhgri.nih.gov/bic/>). Pathogenicity interpretation of the variants were performed according to 2015 American College of Medical Genetics and Genomics guideline by professional medical geneticists, using evidences of variant type assessment, population allele frequency, prediction algorithm results, and database search such as Human Gene Mutation Database, ClinVar, and BIC.

### Statistical Analysis

Descriptive data are reported as the median (range) or frequency (percentage). Categorical variables were compared with the chi-square or Mann-Whitney U test and continuous variables with the Student's t-test. Responses were assessed according to the Response Evaluation Criteria in Solid Tumors criteria, version

1.1. We defined PFS as the time from the date of diagnosis to disease progression or death; overall survival (OS) was measured from the date of diagnosis to death or to the date of the last follow-up. Survival analysis was performed using the Kaplan-Meier method with a log-rank test. For all analyses, the significance level was set at 0.05. The statistical analyses were performed with the SPSS statistical software (version 21.0; IBM Corp., Armonk, NY).

## Results

### Patients' characteristics

Table 1 contains a comparison of the clinical characteristics between the BRCA wild

-type genotype group and the BRCA mutation group. Of the 169 patients included, 122 (71.9%) had the wild-type BRCA genotype, and 47 (28.1%) had the BRCA1/2 mutations. There were no significant between-group differences in patient characteristics such as age, CA-125 level, FIGO stage, histologic type, tumor grade, tumor burden, CRS, residual disease, rate of radical surgery, surgical complexity score, chemotherapy regimen, or cycles of NAC.

### CRS relative to BRCA1/2 mutation status

CRS 3 patients were 43 (35.2%) and 16 (34.0%) for patients without and with BRCA1/2 mutations, respectively ( $P = 0.516$ ) (Table 2). Although CRS 3 rates differed between BRCA1 (26.9%), BRCA2 (42.9%) and the wild-type BRCA genotype, these difference did not achieve statistical significance.

Kaplan-Meier curves for OS and PFS stratified by CRS in patients with the BRCA1/2 mutations are shown in Fig. 2. CRS 3 in patients with the BRCA1/2 mutations was not significantly associated with improved PFS ( $P = 0.949$ ) and OS ( $P = 0.168$ ). However, CRS 3 in patients without BRCA mutations was significantly associated with improved PFS ( $P = 0.030$ ) and OS ( $P = 0.039$ ) (Fig. 3).

We also categorized the patients based on BRCA mutations and CRS (BRCA1/2 mutations with CRS 1/2; the wild-type BRCA genotype with CRS 1/2; BRCA 1/2 mutations with CRS 3; and the wild-type BRCA genotype with CRS 3) to evaluate survival according to the relationship of BRCA1/2 mutations in the CRS. In patients with CRS 1/2, the carriers of BRCA1/2 mutations had better PFS ( $P = 0.044$ ) and OS ( $P = 0.043$ ) than the wild-type BRCA genotype patients. However, in patients with CRS 3, there was no significant difference in PFS ( $P = 0.863$ ) and OS ( $P = 0.216$ ) between BRCA1/2 carriers and the wild-type BRCA genotype patients (Fig. 4).

## Discussion

In this study, we evaluated the relationship between BRCA1/2 mutations and CRS and survival outcomes in advanced-stage ovarian cancer patients treated with NAC followed by IDS. The patients with BRCA1/2 mutations did not show higher CRS rates than patients without these mutations. In patients without the

BRCA1/2 mutations, the CRS 3 patients showed superior survival outcomes. In addition, in the CRS 1/2 patient group, the survival outcomes of the BRCA1/2 carriers were superior to those of the wild-type BRCA genotype patients. Because our study showed that patients with BRCA wild-type and CRS 1/2 in advanced-stage ovarian cancer treated with NAC have poor prognoses with platinum-based doublet chemotherapy, these patients need new therapeutic strategies. Patients with the BRCA wild-type should be considered for additional treatments, such as adding a bevacizumab or immune checkpoint inhibitors to conventional chemotherapy to achieve CRS 3 after NAC. To improve the survival of the BRCA wild-type patients with CRS 1/2 who have residual tumors after NAC that may be resistant to platinum-based combination chemotherapy, the genomic profiles of the post-NAC tissues should be evaluated to identify biomarkers and to select targeted therapies.

Response rates to platinum-based NAC predict survival and may be regarded as a surrogate prognostic marker [5, 6]. A three-tiered CRS system showed a significant association with survival outcomes. The CRS system for assessing platinum-based NAC response rates can be a reproducible prognostic tool, and the incorporation of the CRS system after NAC can help determination of adjuvant treatment in advanced-stage ovarian cancer patients. Previous studies [9–11] showed that advanced-stage ovarian cancer patients with BRCA1/2 mutations tend to have higher response rates to platinum-based chemotherapy, longer PFS, and a higher benefit from NAC. The BRCA1/2 mutations are also being considered as specific targets. Recent randomized studies on poly (adenosine diphosphate–ribose) polymerase inhibitors have demonstrated a substantial survival benefit in BRCA1/2 carriers [17–21], hence germline BRCA1/2 testing is becoming a mandatory in treatment decisions in advanced-stage ovarian cancer.

In triple-negative breast cancer, several studies have shown that in the relationships between germline BRCA1/2 mutations, response rates, and prognoses, pCR was not a surrogate marker in BRCA1/2 mutation carriers. However, no such studies have yet been reported for ovarian cancer patients. Hahnen et al. [12] showed that patients without germline BRCA1/2 mutations benefit from the addition of carboplatin and that BRCA1/2 mutation carriers had superior response rates. Fasching et al. [13] showed the effect of BRCA1/2 mutations in the NAC of triple-negative breast cancer. Patients with BRCA1 or BRCA2 mutations had higher pCR rates than patients without a mutation. However, BRCA1/2 mutation patients who receive standard treatment do not benefit as much from a pCR as patients with the wild-type BRCA. These results were similar to our study.

Our study showed that patients with BRCA1/2 mutations enjoyed a good survival outcome regardless of their CRS. In contrast, CRS 3 had a significant survival benefit on PFS and OS for wild-type BRCA genotype patients. In addition, the BRCA1/2 mutations had a significant influence on survival in the CRS 1/2 patient group. One plausible explanation for the absence of the effect of CRS 3 on the prognoses for patients with the BRCA1/2 mutations is the influence of the platinum-based adjuvant treatment after IDS. Although the CRS 1/2 group of patients was expected to have a poor prognosis, their prospects were improved if they had the BRCA1/2 mutations because of their conferred sensitivity to platinum-based adjuvant chemotherapy after IDS. The mechanism of action by platinum drugs is mediated by the

formation of the covalent binding of platinum to DNA. This binding interferes with DNA synthesis and ultimately leads to cell death [22]. It seems likely that partially formed covalent bindings cause replication of fork stalling when it is encountered by the DNA replication machinery during the S phase. These stalled replication forks may degenerate into double-stranded DNA breaks [23] in which tumor cells with defects in their DNA repair pathways achieves increased response rates against platinum drugs, as investigated in previous studies [24–27].

However, unlike in breast cancer studies, the status of BRCA1/2 mutations in our study was unrelated to CRS. In previous studies [28, 29], patients with germline BRCA1/2 mutations were associated with wider disease diffusion than BRCA wild-type patients in terms of peritoneal spread and incidence of bulky lymph nodes. Furthermore, Soslow et al. [30] showed the correlations between the genotype and characteristic morphologic appearance of ovarian cancer. The BRCA1 mutation group had more tumor-infiltrating lymphocytes, thus suggesting that the status of BRCA mutations could influence the immunological microenvironment sufficiently to eventually drive the specific characteristics of disease presentation. Therefore, BRCA 1/2 mutation carriers may have a lower CRS following NAC as compared to BRCA wild-type patients.

The main limitation of our study was its low sample size and the small number of patients with BRCA1/2 mutations. Although 169 patients were genotyped, there were only 47 carriers of these mutations. Another limitation was that NAC was only incorporated into our institution in late 2010; thus, our cohort was limited by the short follow-up period.

In conclusion, in advanced-stage ovarian cancer patients treated with NAC followed by IDS, CRS 3 was not associated with increased survival for BRCA1/2 mutation carriers than for patients without these mutations. Additional studies are needed to elucidate the effect of CRS on prognoses in advanced-stage ovarian cancer patients with and without BRCA1/2 mutations.

## Abbreviations

CRS: Chemotherapy response scores; IDS: Interval debulking surgery; NAC: Neoadjuvant chemotherapy; PCR: Polymerase chain reaction; pCR: Pathologic complete response; PFS: Progression-free survival; PIV: Predictive index value; OS: Overall survival

## Declarations

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### Author contributions

Conceptualization: L.Y.J., L.J.Y., K.S.H.; Methodology: L.Y.J., L.J.Y.; Validation: L.Y.J.; Formal analysis and investigation: L.Y.J.; Resources and data curation: L.Y.J., K.H.S., R.J.H; Writing - original draft preparation: L.Y.J.; Writing - review and editing: L.J.Y., N.E.J.; Supervision: N.E.J., K.S.W., K.Y.T.; Project administration: L.Y.J., L.J.Y.; Funding acquisition: L.J.Y.

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None

## **Availability of data and materials**

The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

## **Ethics approval and consent to participate**

The need for an approval was waived by the 'Institutional Review Board of Severance Hospital at Yonsei University College of Medicine' as the study was retrospective and individual patients were not identifiable.

## **Consent for publication**

Not applicable.

## **Competing interests**

The authors declare that they have no conflicts of interest.

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## Tables

Table 1. Patient and clinical characteristics (N = 169)

Characteristics	BRCA wild-type (N = 122)	BRCA mutation (N = 47)	P
Age, median (range), years	57 (32-77)	56 (27-76)	0.610
CA-125 level, median (range), U/mL	1958.7 (94.2.0- 21994.8)	1711.3 (75.0- 23919.0)	0.759
FIGO stage, n (%)			
III	56 (45.9%)	23 (48.9%)	0.734
IV	66 (54.4%)	24 (51.1%)	
Grading			
1	3 (2.5%)	0 (0%)	0.489
2	11 (9.0%)	2 (4.5%)	
3	102 (83.6%)	42 (89.4%)	
Not available	6 (4.9%)	3 (6.4%)	
Tumor burden assessed by diagnostic laparoscopy*			
PIV8	27 (22.1%)	3 (6.4%)	0.097
PIV 10	25 (20.5%)	14 (29.8%)	
PIV 12	10 (8.2%)	4 (8.5%)	
PIV 14	5 (4.1%)	1 (2.1%)	
Not available	55 (45.1%)	25 (53.2%)	
CRS, n (%)			
1-2	90 (63.8%)	28 (63.6%)	0.559
3	51 (36.2%)	16 (36.4%)	
Residual disease, n (%)			
No	62 (50.8%)	18 (38.3%)	0.344
Any residual	58 (47.5%)	28 (59.6%)	
Not available	2 (1.6%)	1 (2.1%)	
Radical surgery <sup>†</sup> , n (%)			
None	59 (48.4%)	19 (40.4%)	0.354
Any radical surgery	63 (51.6%)	28 (59.6%)	
Surgical complexity score groups <sup>‡</sup>			

1-2 (Low/intermediate)	102 (83.6%)	37 (78.7%)	0.457
8 (High)	20 (16.4%)	10 (21.3%)	
Chemotherapy regimen, n (%)			
Paclitaxel + carboplatin	91 (74.6%)	34 (72.3%)	0.576
Docetaxel + carboplatin	8 (6.6%)	6 (12.8%)	
Weekly paclitaxel + carboplatin	15 (12.3%)	5 (10.6%)	
Paclitaxel + carboplatin + bevacizumab	8 (6.6%)	2 (4.3%)	

\* According to Fagotti et al. [15].

† Radical surgery includes any of following: bowel surgery, cholecystectomy, diaphragm peritonectomy/resection, distal pancreatectomy video-assisted thoracoscopic surgery, splenectomy, liver resection, supraclavicular fossa resection, ureter resection, and others.

‡ According to Aletti et al. [19]

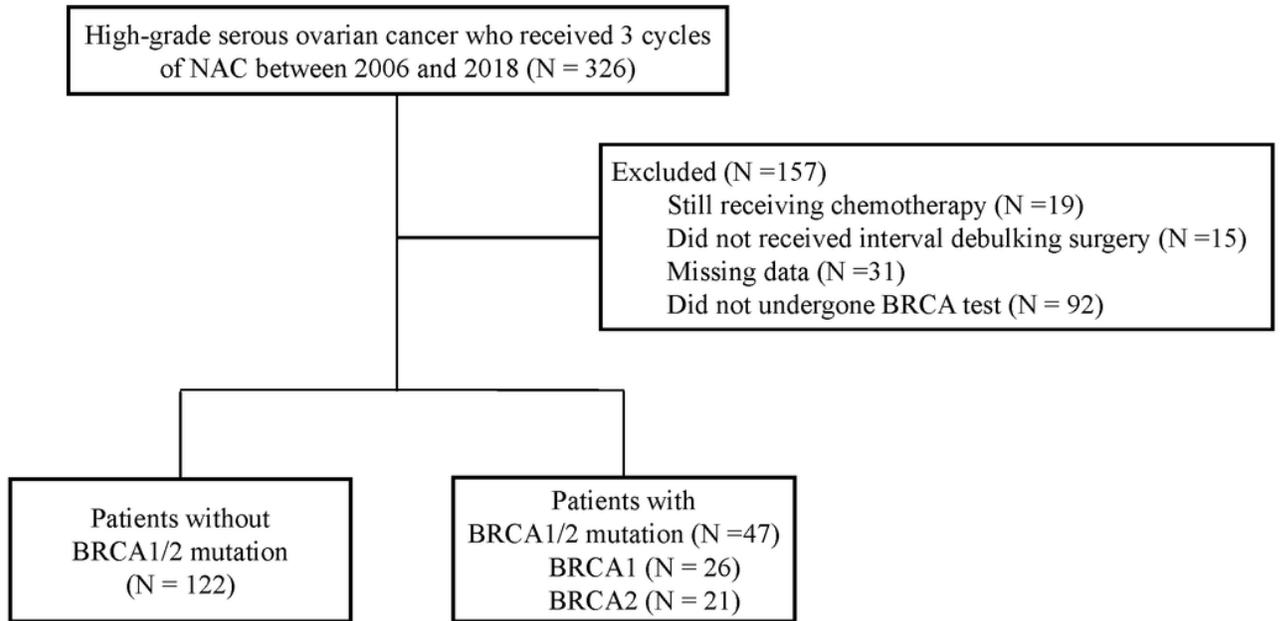
CA-125, cancer antigen 125; FIGO, International Federation of Gynecology and Obstetrics; HGSC, high-grade serous carcinoma; PIV, predictive index value; CRS, chemotherapy response score

Table 2. Chemotherapy response score relative to BRCA1/2 mutation status

	CRS	Wild type	Mutation	Total	P value
BRCA1 or 2	1-2	79 (64.8%)	31 (66.0%)	110 (65.1%)	0.516
	3	43 (35.2%)	16 (34.0%)	59 (34.9%)	
BRCA1	1-2	91 (63.6%)	19 (73.1%)	110 (65.1%)	0.243
	3	52 (36.6%)	7 (26.9%)	59 (34.9%)	
BRCA2	1-2	98 (66.2 %)	12 (57.1%)	110 (65.1%)	0.280
	3	50 (33.8%)	9 (42.9%)	59 (34.9%)	

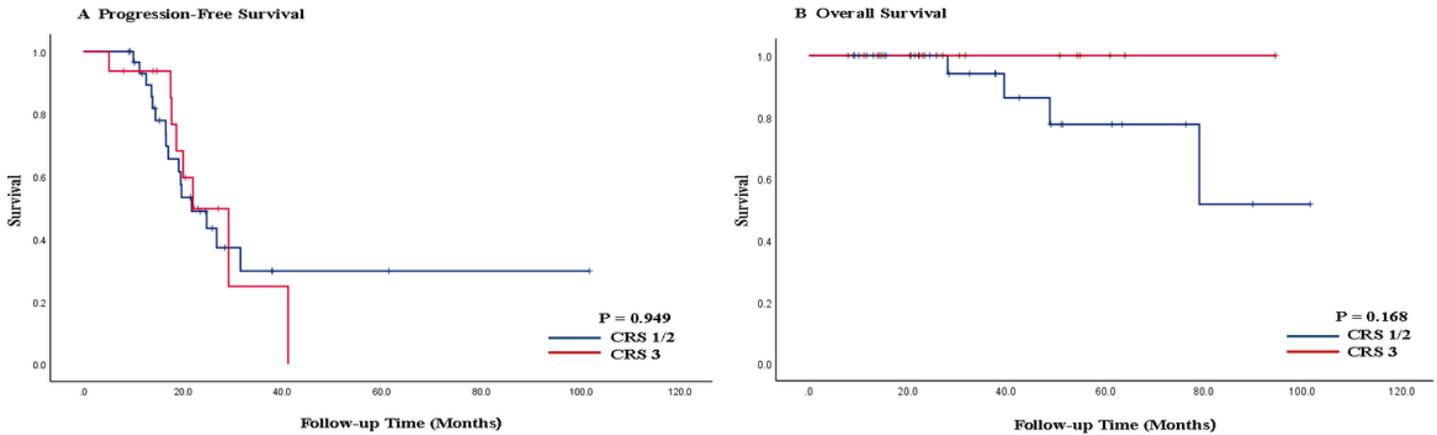
CRS, Chemotherapy response score.

## Figures



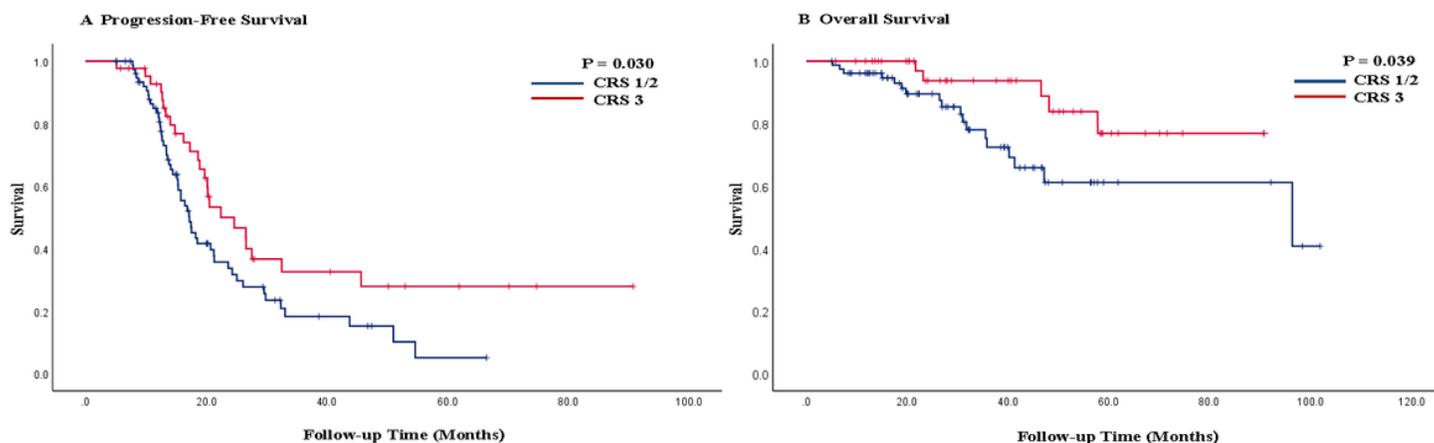
**Figure 1**

Flow diagram of the study population. NAC, neoadjuvant chemotherapy



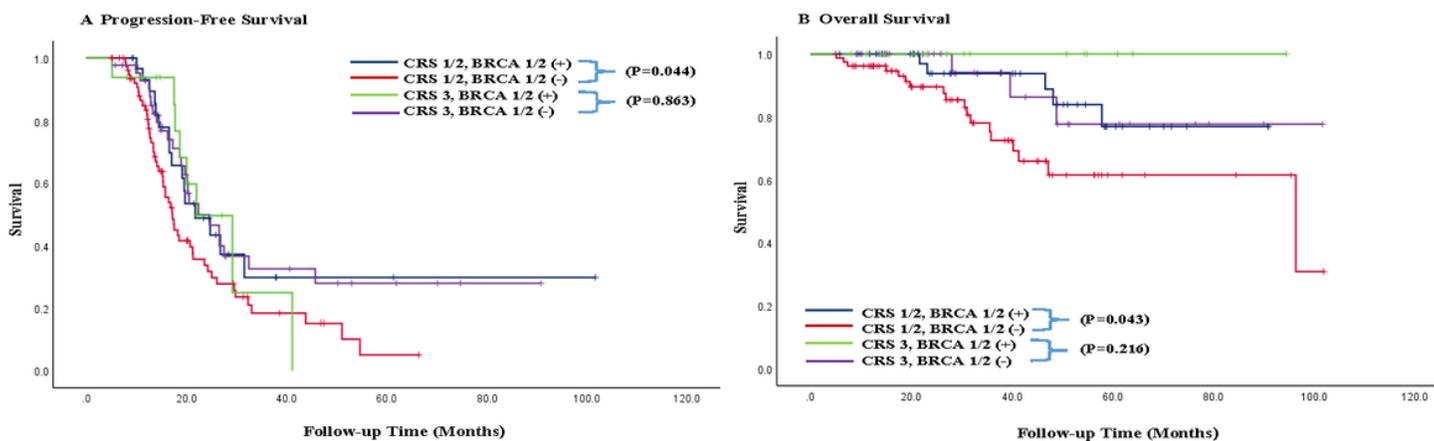
**Figure 2**

Kaplan-Meier curves of progression-free survival (A) and overall survival (B) stratified by CRS in patients with BRCA1/2 mutations. CRS, chemotherapy response score



**Figure 3**

Kaplan-Meier curves of progression-free survival (A) and overall survival (B) stratified by CRS in patients without BRCA mutations. CRS, chemotherapy response score



**Figure 4**

Kaplan-Meier curves of progression-free survival (A) and overall survival (B) stratified by BRCA mutations and CRS. CRS, chemotherapy response score