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Comparison of Survival Outcomes According to *BRCA1/2* Variant Type in High-grade Serous Ovarian Cancer

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Abstract. *Background/Aim: Mutations of BRCA1/2 improve cancer prognosis due to their better response to platinum-based chemotherapy. This study evaluated overall survival (OS) and progression-free survival (PFS) under similar conditions of first-line adjuvant chemotherapy within seven years in high-grade serous ovarian cancer (HGSOC). Patients and Methods: A total of 160 patients were enrolled. The pathogenic BRCA1/2 variant group included pathogenic variant and likely-pathogenic variant, while the non-pathogenic group included wild-type and variant of uncertain significance. For first-line chemotherapy, delivered dose intensity, relative dose intensity, and delay of duration were calculated in all patients. Results: Of the tested variants, 108 (67.5%) were non-pathogenic and 52 (32.5%) were pathogenic. No significant difference was found in various clinical factors of cancer stage, surgery, or chemotherapy. There was no significance for OS or PFS within five or seven years. Conclusion: In patients with HGSOC, the OS and PFS for germline BRCA1/2 pathogenic and non-pathogenic variants were not significantly different under similar conditions of first-line adjuvant chemotherapy within seven years.*

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Human DNA is constantly exposed to damage from external or internal factors and is repaired by either a DNA single-strand break repair, a double-strand break (DSB) repair, or a base mismatch repair (1). Of these types of damage, a DSB can be repaired without error by homologous DNA recombination (HR). *BRCA1/2* encodes the BRCA1/2 proteins involved in HR function as tumor-suppressor genes (2-4).

Women with a germline mutation in *BRCA1* or *BRCA2* have an increased risk of developing ovarian or breast cancer (5), although this risk can be vastly different in women with *BRCA1* and *BRCA2* mutations. The mutations of both genes can lead to a significant decrease or loss of function of those proteins and other genetic factors can influence the proteins (6). Because the BRCA1/2 proteins are tumor-suppressors, loss of their function can result in the development of malignant tumors, especially in the ovaries or breast tissue. According to a recent population-based study, germline mutations of *BRCA1* and *BRCA2* are present in approximately 15% of all ovarian cancer cases (7). High-grade serous ovarian cancer (HGSOC) is the most common histologic subtype in epithelial ovarian cancer, representing up to 20% of germline mutations in *BRCA1* and *BRCA2* (8, 9).

Many studies have reported relatively better survival outcomes in ovarian cancer patients with inherited *BRCA1* and *BRCA2* mutations than wild-type or benign variants, which resulted in a higher sensitivity to platinum-based chemotherapy (10-14). However, some studies report an insignificant correlation (15-17). Beyond the presence or absence of pathogenic variants in *BRCA* genes, there is also

a recent study that showed the correlation between mutations in a specific exon of *BRCA1* and the prognosis in epithelial ovarian cancer (18).

To appropriately evaluate the influence of pathogenic *BRCA1/2* mutations on survival outcomes, various clinical factors related to chemotherapy should be controlled because those mutations are correlated with platinum-based chemotherapy agents. However, few previous studies have considered factors, such as delivered dose intensity (DDI) of chemotherapy agents, relative dose intensity (RDI), or treatment delay. We thus evaluated the influence of a germline *BRCA1/2* mutation on the long-term prognosis of HGSOC under a controlled dose intensity and delay of chemotherapy in Korean women.

Patients and Methods

Patients. We retrospectively reviewed 374 patients who underwent surgery due to suspected ovarian cancer at Kyungpook National University Hospital and Kyungpook National University Chilgok Hospital (KNUCH) from July 1997 to February 2022. All medical records were collected from KNUCH. We excluded 50 patients because their diagnoses were not primary ovarian cancer on permanent biopsy; alternate diagnoses included endometrial cancer and borderline malignancy. Patients with primary tubal cancer and peritoneal cancer were included. We excluded 75 patients due to their histologic subtype; 11 were sex-cord tumors or germ-cell tumors, and 64 were endometrioid, clear-cell, mucinous, or mixed-type tumors. We excluded 52 patients due to insufficient information; 45 were not tested for germline *BRCA1* or *BRCA2* or both, and seven did not have a medical record for the dose of chemotherapy. Another 15 patients were excluded because they refused to complete standard treatment for epithelial ovarian cancer in our institution; nine refused adjuvant chemotherapy after surgery and six were referred to another medical institution after surgery at the patients' requests. We excluded 22 patients due to insufficient follow-up periods to evaluate survival outcomes, such as platinum resistance. Finally, 160 patients were enrolled, and a flow diagram of the patient selection process is shown in Figure 1. This study was approved by the institutional review board of KNUCH (KNUCH 2022-04-004).

Germline BRCA1/2 test and classification. Genomic DNA extraction was performed using EDTA-treated whole blood by the Chemagic Magnetic Separation Module I method (PerkinElmer Chemagen, Baesweiler, Germany) with the DNA Blood 200 μl Kit and QIAamp DSP DNA Mini Kit (QIAGEN GmbH, Hilden, Germany).

The *BRCA1/2* genetic test was conducted using two methods: next-generation sequencing (NGS) and PCR with a direct sequencing method, as previously described (19). From January 2014 to October 2019, NGS was performed using the Celemics Library Prep Kit (Celemics Co., Ltd., Seoul, Republic of Korea) and Illumina MiseqDx platform (Illumina Co., Ltd., San Diego, CA, USA). The DNA sequence reads were aligned to reference sequences based on the public human genome build GRCh37/UCSC hg19. Starting in November of 2019, NGS was performed using the BRCAaccuTest PLUS (NGeneBio, Seoul, Republic of Korea) and Illumina MiseqDx platform (Illumina Co.). Bioinformatics analysis

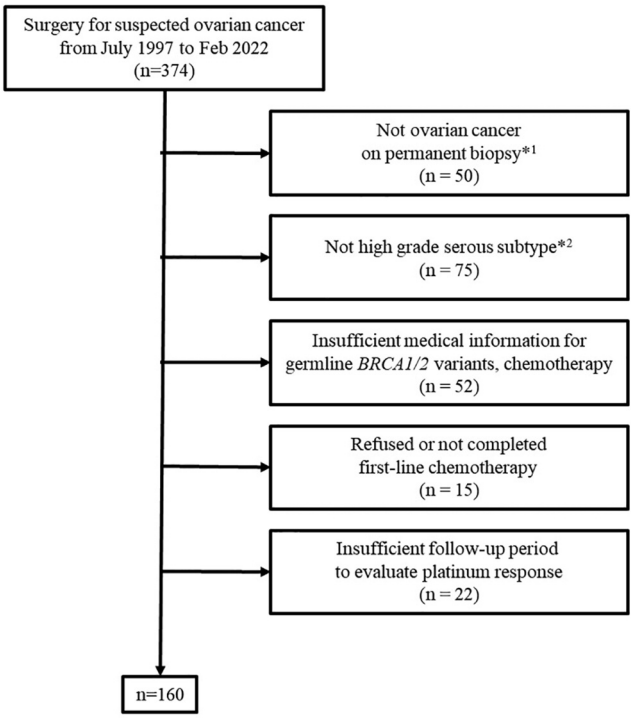

Figure 1. *Flow diagram for patient selection. *1Includes benign, borderline malignancy, and other primary malignancies, such as endometrial cancer or colon cancer; *2Includes endometrioid, clear cell, mucinous, and other histologic types.*

was conducted using the BRCAaccuTest pipeline (version 1.5.0) (NGeneBio). In the PCR with a direct sequencing method, a SimpliAmp Thermal Cycler (Applied BioSystems, Foster City, CA, USA) and QIAGEN Multiplex PCR Plus Kit (QIAGEN) and *Accupower* PCR PreMix (Bioneer Corp., Daejeon, Republic of Korea) were used. The direct sequencing based on Sanger sequencing was conducted using the 3500xL Dx Genetic Analyzer (Applied BioSystems). The detected mutations were interpreted clinically per the 2015 ACMG/AMP guidelines (20). The results of the *BRCA1/2* genetic analysis were reported as wild-type (non-pathogenic variants), a variant of uncertain significance (VUS), likely-pathogenic variant (LPV), and pathogenic variant (PV); benign variants were not reported by laboratory physicians (21).

The pathogenic *BRCA1/2* variant group included LPV as well as PV, while the non-pathogenic *BRCA1/2* variant group included wild-type and VUS in one or both *BRCA1* and *BRCA2*; thus, it did not include any PV or LPV.

Surgery. All surgeries were performed by four experienced gynecologic oncologists at KNUCH. Optimal surgery included total hysterectomy, bilateral salpingo-oophorectomy, lymphadenectomy from both pelvic sides to infra-renal level, omentectomy, and resection of other metastatic lesions. A surgery was classified as suboptimal when the residual tumor lesion was larger than 1 cm (22).

Chemotherapy. Some patients were treated with neoadjuvant chemotherapy. They underwent at least three additional cycles of

chemotherapy after optimal or suboptimal surgery, except for one patient, who received one more cycle due to her medical condition. All patients were prescribed a combination of taxane and carboplatin.

We reviewed the delivered doses and durations of chemotherapy for all patients. The DDI was defined as the sum of the total ratio of chemotherapy agents administered over the course, including neoadjuvant and adjuvant. The RDI was the ratio of the DDI divided by the planned dose intensity, 100% per cycle. Delay was defined as the number of days beyond the planned duration, 21 days between two cycles.

Additional treatments. We reviewed additional treatments recently introduced, such as hyperthermic intraperitoneal chemotherapy (HIPEC), bevacizumab, poly(adenosine diphosphate-ribose) polymerase (PARP) inhibitor, and pembrolizumab. The HIPEC group included those who underwent HIPEC during the first operation. The bevacizumab group included those who used it during the first-line adjuvant chemotherapy and neoadjuvant chemotherapy. Patients who used PARP inhibitor or pembrolizumab for at least one month were included in the respective groups.

Evaluation of prognostic outcomes. Response to treatment was evaluated by either computed tomography (CT), magnetic resonance imaging, or positron emission tomography/CT. Outcomes included complete or partial resolution, stable disease, progressive disease, or disease recurrence (23). Platinum resistance was defined when the PD or recurrence was confirmed within six months after the last administration of a platinum-based chemo agent (24). OS and PFS were calculated from the first day of chemotherapy for the patient who underwent neoadjuvant chemotherapy and interval debulking surgery. For those who underwent primary debulking surgery, they were calculated from the operation day.

Statistical analysis. Student's *t*-test, chi-square test, and Fisher's exact test were used to compare both groups. The Kaplan-Meier survival and Cox regression analyses were used for survival outcomes, such as the overall survival (OS) and progression-free survival (PFS) and its hazard ratio (HR). All of the statistical analyses were performed with SPSS (version 26; IBM Corp., Armonk, NY, USA) and MedCalc (version 20.026; MedCalc Software Ltd., Ostend, Belgium).

Results

Table I shows the characteristics and clinical factors of the patients. Out of 160 patients, 108 (67.5%) appeared to have non-pathogenic *BRCA1/2* variants and 52 (32.5%) had a *BRCA1/2* variant; 31 (59.6%) were *BRCA1* and 21 (40.4%) were *BRCA2*. There were no significant differences in terms of age, disease stage, preoperative serum level of CA-125, neoadjuvant chemotherapy, or optimal surgery. There were no differences in additional medical interventions, such as HIPEC, bevacizumab, or pembrolizumab. The only difference was in the use of PARP inhibitor (p=0.000). There were no differences for first-line adjuvant chemotherapy in terms of the number of cycles, delivered dose intensity, relative dose intensity, and delayed period (Table I).

Table I. *Comparison of patients' characteristics and clinical factors between the pathogenic (including likely-pathogenic) and non-pathogenic (and of uncertain significance) germline BRCA1/2 variants.*

	Non-pathogenic BRCA1/2 variant	Pathogenic BRCA1/2 variant	*p*-Value
Number of patients [n (%)]	108 (67.5%)	52 (32.5%)	
BRCA1 pathogenic variants [n (%)]	0	31 (59.6%)	N/A*
BRCA2 pathogenic variants [n (%)]	0	21 (40.4%)	N/A*
Age (yrs)	58.40±10.73	57.09±11.86	0.486
FIGO stage (n [%])			0.648
I	13 (12.0%)	5 (9.6%)	
II	6 (5.6%)	3 (5.8%)	
III	71 (65.7%)	31 (59.6%)	
IV	18 (11.3%)	13 (25.0%)	
Serum level of CA-125 (U/ml)			
Preoperative	1,001.43±1867.44	828.61±1,266.41	0.555
Neoadjuvant chemotherapy [n (%)]	29 (26.9%)	15 (28.8)	0.851
Residual tumor (n)			0.206
Optimal surgery	83 (76.9%)	45 (86.5%)	
Suboptimal surgery	25 (23.1%)	7 (13.5%)	
Additional medical interventions			
HIPEC (n)	9 (8.3%)	4 (7.7%)	1.000
Bevacizumab (n)	13 (12.0%)	7 (13.5%)	1.000
PARP† inhibitor (n)	11 (10.2%)	23 (44.2%)	<0.001
Pembrolizumab (n)	5 (4.6%)	0 (0.0%)	0.175
For first-line adjuvant chemotherapy			
Regimen [n (%)]			
Taxane and platinum	108 (100.0%)	52 (100.0%)	
Number of cycles (n)	7.47±2.50	7.38±1.93	0.824
Delivered dose intensity (%)†	705.14±227.67	674.27±168.45	0.337
Relative dose intensity (%)‡	98.75±49.54	92.29±10.45	0.354
Delayed period (d)	13.63±20.81	11.92±17.27	0.609

HIPEC: Hyperthermic intraperitoneal chemotherapy; PARP: poly(adenosine diphosphate-ribose) polymerase. Data are shown by mean±SD or number. *not analyzed. †delivered dose over neoadjuvant or first-line adjuvant chemotherapy. ‡Delivered dose/planned dose ×100%.

Clinical outcomes between both groups are shown in Table II. The mean periods of follow-up were 51.14±28.23 months in the non-pathogenic *BRCA1/2* variants group and 52.23±24.33 months in the pathogenic group; this was not significantly different (p=0.811). In this period, the non-pathogenic group showed 68 (63.0%) of PD or recurrence and the pathogenic group showed 33 (63.5%) (p=1.000). Platinum resistance appeared only in the pathogenic group [n=15 (13.9%), p=0.007]. Within three years, the non-pathogenic group showed similar OS and PFS rates

compared with the pathogenic group (89.8% *vs*. 90.4%, *p*=1.000; 43.5% *vs*. 46.2%, *p*=0.865). Within five years, the pathogenic group showed a higher OS rate, although this was not significant (88.5% *vs*. 75.9%, *p*=0.090). The PFS rate was also not significant (38.5% *vs*. 38.9%, *p*=1.000). Within seven years, the pathogenic *BRCA1/2* variant group showed an insignificantly higher OS rate than the non-pathogenic group (84.6% *vs*. 69.4%, *p*=0.053). The PFS rate was also not significantly different between the two groups (38.5% *vs*. 37.0%, *p*=1.000) (Table II).

OS and PFS within five and seven years between both groups are shown with a Kaplan-Meier survival curve analysis in Figure 2. No significant differences were found in OS and PFS. Between both groups within five years, the *p*-Value for the OS was 0.083 and for the PFS was 0.249. Within seven years, the *p*-Value for the OS was 0.071 and for the PFS was 0.557. Univariate Cox-regression analysis was used to evaluate HR for the OS within five and seven years. The non-pathogenic group showed significantly higher HR for death within five and seven years (HR=2.149, 95% CI=0.884-5.223, *p*=0.091; HR=2.006, 95% CI=0.926-4.346, *p*=0.078), although this was not significant for five years (HR=0.265, 95% CI=0.979-5.712, *p*=0.056).

Table II. *Comparison of clinical outcomes between the pathogenic (including likely-pathogenic) and non-pathogenic (and of uncertain significance) germline BRCA1/2 variants.*

	Non-pathogenic BRCA1/2 variant (N=108)	Pathogenic BRCA1/2 variant (N=52)	*p*-Value
Mean period of follow-up (m)	51.14±28.23	52.23±24.33	0.811
PD or recurrence [n (%)]	68 (63.0%)	33 (63.5%)	1.000†
Platinum resistance [n (%)]	15 (13.9%)	0 (0.0%)	0.007†
Survival outcomes in three years (%)			
Overall survival rate	89.8	90.4	1.000†
Progression-free survival rate	43.5	46.2	0.865†
Survival outcomes in five years (%)			
Overall survival rate	75.9	88.5	0.090†
Progression-free survival rate	38.9	38.5	1.000†
Survival outcomes in seven years (%)			
Overall survival rate	69.4	84.6	0.053†
Progression-free survival rate	37.0	38.5	1.000†

PD: Progression of disease. Data are shown by mean±SD or number. †Evaluated with chi-square test.

Discussion

The group that appeared to have a pathogenic variant of *BRCA1* or *BRCA2* did not show significantly longer OS within five to seven years compared with the non-pathogenic variants in HGSOC. The significance for PFS was much lower during that period.

Although not significant, the longer OS could result from the significantly greater use of PARP inhibitors. The OS will be significantly longer in the pathogenic *BRCA1/2* variant group. Unlike OS, the PFS did not show any trends within seven years. We inferred that this resulted from the similar dose intensity during first-line adjuvant chemotherapy. The higher sensitivity of the pathogenic *BRCA1/2* variant was demonstrated as no platinum resistance in that group; however, it did not result in a significantly longer PFS.

Unlike recent previous studies, we specified the controlled clinical factors related to first-line chemotherapy, including the regimen, the number of cycles, DDI, RDI, and duration delay in the real world. Both groups showed a similar ratio of patients who were prescribed additional intervention or medicines, except PARP inhibitors. This means that the OS or PFS are comparable within seven years between *BRCA1/2* pathogenic and non-pathogenic variant groups under similar surgery and chemotherapy conditions.

We conducted a subgroup analysis to evaluate OS and PFS between the germline *BRCA1* only pathogenic variant group, the germline *BRCA2* only pathogenic group, and both germline *BRCA1/2* non-pathogenic variants group. This was also analyzed by Kaplan-Meier survival curves within five and seven years. There was no significant difference between the three groups in terms of OS and PFS, except between the only *BRCA2* pathogenic group and both non-pathogenic group for OS. Between them, a significantly longer OS was found within five (*p*=0.047) and seven years (*p*=0.041). The *BRCA1* and *BRCA2* pathogenic group did not show significantly different OS and PFS within that period (Figure 3).

We conducted another subgroup analysis with a Kaplan-Meier curve for the advanced stage. In total, 135 patients with stage III and IV were included, and 44 were classified as the germline *BRCA1/2* pathogenic group. The significantly longer OS and PFS were not found in five and seven years; however, a nearly significantly longer OS was found in seven years in the *BRCA1/2* pathogenic group (*p*=0.051). In this subgroup, the non-pathogenic group including wild-type or VUS of both *BRCA1* and *BRCA2* was 91, the only *BRCA1* pathogenic group was 30, and the only *BRCA2* group was 14. We found a significantly longer OS in the *BRCA2* pathogenic group than the non-pathogenic group including wild-type or VUS of both *BRCA1* and *BRCA2* within seven years (*p*=0.048).

We performed another subgroup analysis to evaluate the influence of the PARP inhibitor in the germline *BRCA1/2*

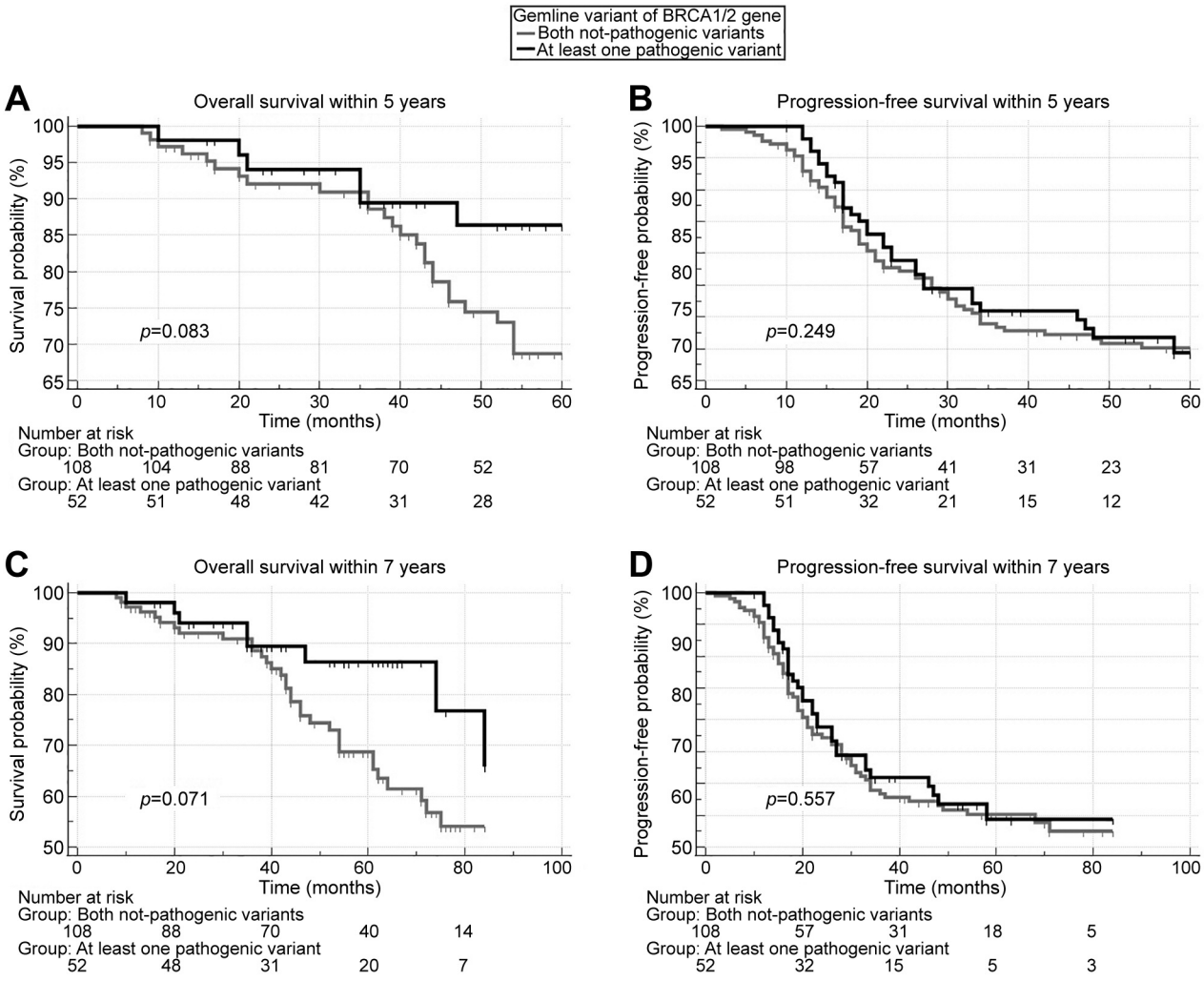

Figure 2. *Comparison of overall survival rate and progression-free survival rate within five and seven years between the pathogenic and non-pathogenic germline BRCA1/2 variants in high-grade serous ovarian cancer. The pathogenic group includes pathogenic and likely-pathogenic variants; the non-pathogenic group includes wild type and variants of uncertain significance.*

pathogenic group. Of 52 patients, 23 used PARP inhibitor for maintenance after first-line adjuvant chemotherapy. This group used it after 27.78 months, from the first day of treatment, and the administration period was 383.78±346.81 days (mean±SD). There were no significantly different clinical factors between the group that used PARP inhibitors and those that did not on a non-parametric test and Fisher's exact test. The group that used the PARP inhibitors showed longer OS, but it was not significant within five (p=0.216) and seven years (p=0.104) on Kaplan-Meier survival analysis. Unlike the OS, that group showed significantly shorter PFS within five (p=0.001) and seven years (p=0.001). Because only a few patients had their genetic HRD status examined, we could not analyze that discrepancy appropriately. Linear regression analysis was performed to evaluate the relationship between the PARP inhibitor administration period and OS and PFS within three, five, and seven years. We found a significant relation for OS at five (p=0.033) and seven years (p=0.032), but not for PFS at five (p=0.487) and seven years (p=0.781).

This study has three limitations. First, it was a retrospective study in a single center. Second, the influence of the PARP inhibitors could not be excluded and evaluated appropriately. We could not use that medication for each patient selectively because most patients did not have their HR deficiency examined due to cost. Third, we included 17 patients who underwent an optimal surgery *via* the robotic or laparoscopic method from 2015 to 2020. We evaluated those surgeries as optimal; however, the influence of minimally invasive surgery on survival outcomes in epithelial ovarian cancer remains unclear.

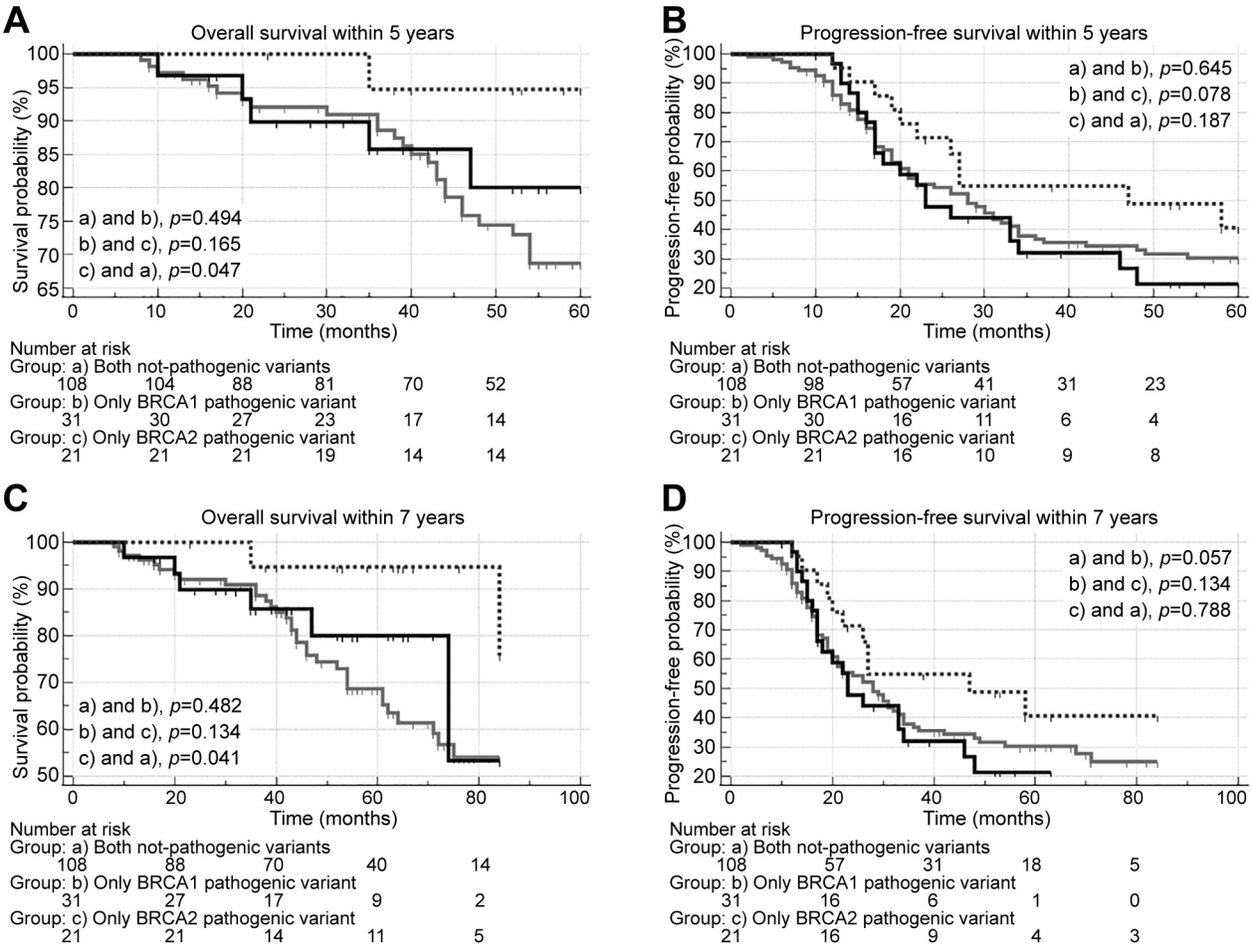

Figure 3. *Comparison of overall survival rate and progression-free survival rate within five and seven years among different variant groups in high-grade serous ovarian cancer. Groups include the germline BRCA1/2 non-pathogenic variant (wild type and variants of uncertain significance), the BRCA1 pathogenic (and likely pathogenic) variants, and the BRCA2 pathogenic (and likely-pathogenic) variants.*

In recent studies, some authors reported reversion of germline *BRCA1/2* mutations and the examination for its detection in HGSOC (25, 26). According to the authors, secondary intragenic mutations sometimes occur, and it can restore the damaged protein function; this phenomenon is called reversion. The restored function of BRCA1/2 proteins can result in poor response to platinum-based chemotherapy, which leads to poor prognosis. The reversion could have occurred in patients in this study; however, we did not consider it as well as the limitations of this study.

There were two previous studies indicating that *BRCA1/2* mutation status was not related to survival outcomes. The R0 surgery was the strongest, or one significant, factor impacting long-term survival (16, 17). We conducted a multivariate linear regression analysis to evaluate the influence of surgery on the OS and PFS; however, the optimal surgery was applied because the R0 surgery was not a clinical factor reviewed in this study. In our data, the optimal surgery was significantly correlated with five ($p<0.001$) and seven-year OS ($p<0.001$). It was also a significant factor for five ($p=0.003$) and seven-year PFS ($p=0.001$). The *BRCA1/2* pathogenic variant was not a significant factor for five ($p=0.811$) and seven-year OS ($p=0.946$). For PFS, it was significant within five years ($p=0.026$) but not within seven years ($p=0.097$).

Conclusion

Many previous studies have reported better survival outcomes of pathogenic variants of germline *BRCA1/2* than non-pathogenic variants in HGSOC. In this study, OS and PFS within seven years between germline *BRCA1/2* pathogenic and non-pathogenic variants were not significantly different under similar first-line adjuvant chemotherapy conditions. Although both OS and PFS were not significant within 7 years, the OS appeared to be longer

in *BRCA1/2* pathogenic variants. Like previous studies, a significantly better response to platinum chemotherapeutic agent was demonstrated in germline *BRCA1/2* pathogenic variants. When a patient with HGSOC has non-pathogenic variants of germline *BRCA1/2*, OS or PFS will be comparable within seven years, as long as they receive appropriate debulking surgery and chemotherapy.

Conflicts of Interest

The Authors have no conflicts of interest to declare.

Authors' Contributions

DG Hong and GO Chong supervised the study. J Lee conceived of the study and performed analytic calculations. DG Hong, J Lee, NY Lee, and IH Lee drafted the manuscript. JM Kim and JY Park processed the clinical data. YH Lee designed the figures and revised the tables. All Authors discussed the results and contributed to the final manuscript.

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