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Original Article

The effectiveness of CA125 and HE4 as clinical prognostic markers in epithelial ovarian cancer patients with BRCA mutation

Young Joo Lee [1], **Woojin Kim** [2,3], **Soomin Hong** [1], **Yong Jae Lee** [1], **Jung-Yun Lee** [1], **Sang Wun Kim** [1], **Sunghoon Kim** [1], **Young Tae Kim** [1], **Eun Ji Nam** [1]

[1]Department of Obstetrics and Gynecology, Women's Cancer Center, Yonsei Cancer Center, Institute of Women's Life Medical Science, Yonsei University College of Medicine, Seoul, Korea
[2]Department of Preventive Medicine, Yonsei University College of Medicine, Seoul, Korea
[3]Korea Medical Institute, Seoul, Korea

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Correspondence to
Eun Ji Nam
Department of Obstetrics and Gynecology, Women's Cancer Center, Yonsei Cancer Center, Institution of Women's Medical Life Science, Yonsei University College of Medicine, 50-1 Yonsei-ro, Seodaemun-gu, Seoul 03722, Korea.
Email: nahmej6@yuhs.ac

ORCID iDs
Young Joo Lee
https://orcid.org/0000-0003-1945-1090
Woojin Kim
https://orcid.org/0000-0001-5520-4228
Soomin Hong
https://orcid.org/0009-0006-5138-4819
Yong Jae Lee
https://orcid.org/0000-0003-0297-3116
Jung-Yun Lee
https://orcid.org/0000-0001-7948-1350

ABSTRACT

Objective: To investigate the efficacy of cancer antigen 125 (CA125) and human epididymis protein 4 (HE4) in predicting survival outcomes based on breast cancer gene (BRCA) mutational status in epithelial ovarian cancer.
Methods: Medical records of 448 patients diagnosed with epithelial ovarian cancer at a single tertiary institution in Korea were retrospectively analyzed. Area under the curve, sensitivity, specificity, and accuracy were assessed using the CA125 and HE4 values after surgery and 3 cycles of chemotherapy to predict 1-year survival based on the BRCA mutational status. Kaplan–Meier analysis was used to obtain progression-free and overall survival to evaluate CA125 and HE4 effectiveness in predicting survival outcomes.
Results: A total of 423 patients were analyzed, including 180 (42.6%) who underwent interval debulking surgery (IDS) and 243 (57.4%) who underwent primary debulking surgery (PDS). BRCA mutations were observed in 37 (15.2%) and 44 (22.4%) patients in the PDS and IDS groups, respectively. CA125 and HE4 normalization demonstrated the highest specificity in patients with or without BRCA mutations, with specificities of 97.1% and 99.1% in the PDS group and 78.6% and 86.2% in the IDS group, respectively. Normalizing HE4 alone may be an effective prognostic marker, with an area under the curve of 0.774 and specificity of 75.0%, in patients with BRCA mutations.
Conclusion: Normalizing both biomarkers emerged as the most effective predictive marker for the 1-year recurrence rate, regardless of BRCA mutational status. A negative HE4 value can be a useful predictor for 1-year recurrence-free survival in patients with BRCA mutations.

Keywords: CA-125 Antigen; Biomarkers, Tumor; BRCA1 Protein; BRCA2 Protein; Carcinoma, Ovarian Epithelial

Synopsis

This study is the first to assess cancer antigen 125 (CA125) and human epididymis protein 4 (HE4) efficacy in predicting recurrence in patients with breast cancer gene (BRCA) mutation. Normalizing biomarkers is the most predictive for 1-year recurrence rate. Negative HE4 predicts 1-year recurrence-free survival in patients with BRCA mutations.

Sang Wun Kim
https://orcid.org/0000-0002-8342-8701
Sunghoon Kim
https://orcid.org/0000-0002-1645-7473
Young Tae Kim
https://orcid.org/0000-0002-7347-1052
Eun Ji Nam
https://orcid.org/0000-0003-0189-3560

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Conflict of Interest

No potential conflict of interest relevant to this article was reported.

Author Contributions

Conceptualization: L.Y.J., K.Y.T., N.E.J.; Data curation: H.S.; Formal analysis: L.Y.J., H.S., N.E.J.; Funding acquisition: N.E.J.; Investigation: H.S.; Methodology: K.W., K.S.W.; Project administration: K.S.W., K.S.; Resources: L.Y.J., L.J.Y.; Software: K.W.; Supervision: K.S., K.Y.T.; Validation: L.Y.J., K.W.; Writing - original draft: L.Y.J.; Writing - review & editing: N.E.J.

INTRODUCTION

Despite significant advancements in surgical techniques and medications, ovarian cancer remains one of the most lethal gynecologic malignancies in developed countries. Most ovarian cancers are epithelial ovarian cancers, specifically high-grade serous carcinoma (HGSC). Despite its favorable response to platinum-based chemotherapy agents, HGSC has an overall 5-year survival rate of approximately 40%, with a lifetime recurrence rate of >80% [1-3]. One important contributor to the limited improvement in survival outcomes is that most cases are diagnosed at advanced stages [4].

Therefore, biomarkers such as cancer antigen 125 (CA125) have long been used for diagnosing and predicting disease relapse and predicting platinum sensitivity and the potential for optimal debulking surgery [5,6]. However, the reliability of CA125 has been questioned because it can be influenced by benign conditions, particularly in cases of endometriosis or severe chronic medical conditions [7]. In contrast, human epididymis protein 4 (HE4), which has recently gained attention as a new biomarker in ovarian cancer, is less influenced by chronic underlying conditions or benign endometriosis [8,9]. Moreover, several studies [10-12] have indicated that HE4 outperforms CA125 as an indicator for diagnosing or predicting ovarian cancer relapse in terms of specificity and, in some studies, it even exhibits higher sensitivity. However, HE4 also demonstrates age-related variation and can yield false-positive results in cases of impaired renal or hepatologic function [13,14]. Therefore, recent recommendations suggest using both biomarkers in combination rather than relying on CA125 or HE4 alone, as they have been shown to possess superior predictive abilities than those of imaging studies [15]. The risk of ovarian malignancy algorithm (ROMA), which combines CA125 and HE4, is widely recognized for its enhanced diagnostic accuracy [16].

Despite the effectiveness of biomarkers such as CA125 and HE4, research on the usefulness of breast cancer gene (BRCA) mutations as a major risk factor for ovarian cancer remains insufficient. Approximately 20% of patients with HGSC are affected by BRCA mutations, including somatic BRCA mutations [17-19]. In addition, individuals with BRCA1 and BRCA2 mutations have a significantly higher risk of developing ovarian cancer (approximately 40%–60% and 11%–30%, respectively) than the general population (approximately 1.4%) [20,21]. Moreover, patients with BRCA mutations exhibit better overall survival (OS) and a higher response to chemotherapy than those without BRCA mutations. Hence, owing to the unique clinical characteristics of BRCA mutations, the most efficient biomarker may differ depending on these mutations. However, few studies [18-23] have evaluated the efficacy of CA125 or HE4 based on the BRCA mutational status.

Therefore, this research aimed to estimate the value of biomarkers in predicting the recurrence rate and survival outcomes of ovarian cancer in a patient population. Additionally, it aimed to assess whether CA125 and HE4 can serve as reliable prognostic factors for ovarian cancer in patients with BRCA mutations.

MATERIAL AND METHODS

1. Study population

We retrospectively analyzed the electronic medical records of 448 patients diagnosed with ovarian, fallopian, and primary peritoneal cancers between September 2014 and December 2021 at Severance Hospital, Yonsei University College of Medicine, in Seoul, South Korea.

Inclusion criteria involved patients: 1) with epithelial ovarian cancer, 2) aged between 20 and 80 years, 3) who received a minimum of 3 cycles of standard platinum-based chemotherapy and debulking surgery (3 sessions of neoadjuvant chemotherapy [NAC] followed by interval debulking surgery [IDS] or at least 3 sessions of adjuvant chemotherapy after primary debulking surgery [PDS]), and 4) with a performance status of <2 according to World Health Organization criteria.

Exclusion criteria involved patients: 1) aged ≤20 or ≥80 years (n=3), 2) with abnormal hepatic function (transaminases >2.5 times the upper normal level or bilirubin >1.5 times the upper normal level) (n=6), 3) with abnormal renal function (creatinine clearance of <60 mL/min or serum creatinine level of >0.02 mg/mL) (n=12), 4) with altered hematological function (hemoglobin level of <9 g/dL, platelet count of $<100\times10^9$/L, or absolute neutrophil count of $<1.5\times10^9$/L) (n=4), and 5) with severe or uncontrolled disease (n=2).

The final study population comprised 423 patients, including those who underwent PDS (n=243) and IDS (n=180). All patients received platinum-based neoadjuvant or postoperative adjuvant chemotherapy following standard guidelines.

Patient data were retrospectively collected from medical records. The collected information comprised several critical factors, including age, the International Federation of Gynecology and Obstetrics (FIGO) stage, cell type, residual disease, and survival outcomes. The results of germline BRCA1/2 gene testing were used to categorize patients into 2 groups: the BRCA1/2 mutation group and the BRCA wild-type group. Of 423 patients, 345 underwent germline BRCA testing using blood samples, with 81 patients having BRCA1/2 mutations. The Institutional Review Board (IRB) of Yonsei University College of Medicine approved this study (IRB No. 4-2021-1403).

2. Biomarkers assay

Serum CA125 and HE4 values were measured in patients at initial diagnosis and after debulking surgery and the first 3 cycles of chemotherapy. Biomarker levels were measured using the Elecsys CA125 II assay (Roche Diagnostics, Indianapolis, IN, USA) and Elecsys HE4 assay (Roche Diagnostics). These assays employed the electrochemiluminescent immunoassay principle to quantitatively analyze CA125 and HE4 levels in serum. The results were expressed in U/mL for CA125 and pmol/L for HE4. As recommended in the literature, the cut-off values for the 2 assays were established as follows: normal CA125 levels were considered to be <35 U/mL [24], whereas normal HE4 levels were considered to be <70 pmol/L [25].

3. Statistical analysis

Baseline characteristics are described as frequencies with percentages for categorical data, means with standard deviations for continuous data, and medians with interquartile ranges for non-parametric continuous variables. Categorial variables were compared using the χ^2 or

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Fisher's exact test, whereas continuous variables were compared using the Student's t-test or Mann–Whitney U test for parametric/non-parametric variables.

The area under the curve (AUC) was calculated using receiver operating characteristics to predict 1-year survival in the PDS and IDS groups. In the PDS group, biomarker levels after debulking surgery followed by 3 cycles of postoperative adjuvant chemotherapy were used. In contrast, biomarker levels after 3 cycles of NAC followed by debulking surgery were used in the IDS group. Sensitivity, specificity, accuracy, and AUC were assessed, with stratification based on BRCA status. We defined progression-free survival (PFS) as the time from diagnosis to disease progression, and OS was measured from the date of diagnosis to death or the date of the last follow-up. Survival curves were generated for all participants, those with the BRCA wild-type mutation, and those with the BRCA mutation using the Kaplan–Meier method with the log-lank test. We compared the survivals of the following four groups; CA125 <35 U/mL and HE4 <70 pmol/L; CA125 ≥35 U/mL and HE4 <70 pmol/L; CA125 <35 U/mL and HE4 ≥70 pmol/L; and CA125 ≥35 U/mL and HE4 ≥70 pmol/L.

The statistical significance level was set at 0.05. All statistical analyses were performed using the SAS software (version 9.4; SAS Institute Inc., Cary, NC, USA) and R version 4.3.1 (R Project for Statistical Computing, Vienna, Austria).

RESULTS

Our study cohort comprised 423 patients, including 243 patients who underwent PDS and 180 who underwent IDS after 3 cycles of NAC. **Table 1** presents the clinical characteristics of patients in the PDS and IDS groups. The PDS group had a significantly higher number of patients who achieved R0 resection than the IDS group, with 184 (75.7%) and 107 (59.4%) patients, respectively (p=0.001). Moreover, the PDS group had a higher proportion of patients with non-serous type ovarian cancer than the IDS group, with 94 (38.7%) and 16 (8.9%) patients, respectively (p<0.001). Median CA125 and HE4 values for patients who underwent IDS were significantly higher than those for patients who underwent PDS at diagnosis (1,270.4 vs. 211.0 U/mL, p<0.001; 520.0 vs. 130.5 pmol/L, p<0.001, respectively).

Patients were divided into 2 groups based on germline BRCA mutational status, and their clinical characteristics, stratified based on BRCA mutational status, are shown in **Table 2**. Patients with BRCA mutations in the IDS group exhibited a significant improvement in OS than OS of those with BRCA wild-type mutations (42.4 vs. 32.5 months, p=0.016). However, no PFS or OS prolongation was observed for patients with BRCA mutations in the PDS group (p=0.941 and p=0.094, respectively). In addition, patients with BRCA mutations in the PDS group had significantly higher median CA125 values at diagnosis than those with BRCA wild-type mutations (574.3 vs. 208.0 U/mL, p=0.004). However, after PDS followed by 3 cycles of standard chemotherapy, the median CA125 values significantly decreased, particularly for patients with BRCA mutations, compared with those with BRCA wild-type mutations, without observable differences between the 2 groups (10.5 vs. 12.6 U/mL, p=0.941). No significant differences regarding BRCA mutational status were observed in the IDS group and HE4 value.

Subsequently, sensitivities, specificities, and accuracies were assessed based on the normalization of CA125 and HE4 values to predict 1-year survival. The analysis was conducted using biomarker values obtained after a single debulking surgery and 3 cycles of standard

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Table 1. Clinicopathological characteristics of patients based on the primary treatment methods

Characteristics	IDS group (n=180)	PDS group (n=243)	p-value
Mean age (yr)	58.8±10.4	53.1±10.2	<0.001
Stage			<0.001
I–II	9 (5.0)	113 (46.5)	
III	62 (34.4)	80 (32.9)	
IV	109 (60.6)	50 (20.6)	
Cell type			<0.001
Serous	164 (91.1)	149 (61.3)	
Non-serous	16 (8.9)	94 (38.7)	
Grade			<0.001
G1	3 (1.7)	14 (5.8)	
G2	6 (3.3)	35 (14.4)	
G3	162 (90.0)	192 (79.0)	
Unknown	9 (5.0)	2 (0.8)	
gBRCA			0.253
Wild-type	123 (68.3)	141 (5.8)	
Mutation	44 (24.4)	37 (15.2)	
Unknown	13 (7.2)	65 (26.7)	
Residual disease			0.001
R0	107 (59.4)	184 (75.7)	
R ≤1 cm	69 (38.4)	51 (21.0)	
R >1 cm	3 (1.7)	7 (2.9)	
Unknown	1 (0.6)	1 (0.4)	
Recurrence			<0.001
No	52 (28.9)	150 (61.7)	
Yes	128 (71.1)	93 (38.3)	
PFS (mo)	18.6 [13.4]	24.0 [27.3]	<0.001
Death			0.020
No	144 (80.0)	215 (88.5)	
Yes	36 (20.0)	28 (11.5)	
OS (mo)	33.5 [31.1]	41.9 [35.4]	0.108
CA125 (U/mL)			<0.001
At diagnosis	1,270.4 [2,350.0]	211.0 [712.4]	
After operation*	47.4 [73.9]	67.7 [100.1]	
After the third cycle of chemotherapy	30.7 [76.2]	11.4 [12.1]	
HE4 (pmol/L)			<0.001
At diagnosis	520.0 [720.3]	130.5 [307.6]	
After operation†	62.9 [34.7]	52.7 [24.8]	
After the third cycle of chemotherapy	75.7 [52.2]	49.0 [17.7]	

Values are presented as mean ± standard deviation, number (%), or median [IQR].
CA125, cancer antigen 125; gBRCA, germline breast cancer gene; HE4, human epididymis protein 4; IDS, interval debulking surgery; OS, overall survival; PDS, primary debulking surgery; PFS, progression-free survival.
*Missing 4 in the IDS group; †Missing 19 in the IDS group.

chemotherapy for PDS and IDS groups. In the PDS group (**Table 3**), normalizing CA125 or HE4 values alone or in combination yielded high specificity but relatively lower sensitivity. Moreover, normalizing both CA125 and HE4 emerged as the most effective prognostic factor for predicting 1-year survival, with a high specificity of 99.0% (95% confidence interval [CI]=0.965–0.999) and AUC of 0.677 (95% CI=0.579–0.774). In the subgroup analysis based on BRCA mutational status, normalizing CA125 and HE4 demonstrated high specificity in predicting 1-year survival among patients with BRCA mutations. HE4 alone yielded higher specificity in the BRCA mutation group (91.2%) than that in the BRCA wild-type group (89.3%). In the BRCA mutation group, similar to the trend observed in the BRCA wild-type group and overall patient population, the combination of normalized CA125 and HE4 values exhibited a specificity of 97.1% (95% CI=0.847–0.999) and AUC of 0.768 (95% CI=0.382–1.000) for predicting 1-year survival, indicating a higher probability of no recurrence within one year than that in those with either normalized CA125 or HE4 alone.

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Table 2. Differences in clinicopathological characteristics between patients with or without BRCA mutations

Characteristics	IDS			PDS		
	gBRCA wild-type (n=141)	gBRCA mutation (n=37)	p-value	gBRCA wild-type (n=141)	gBRCA mutation (n=37)	p-value
Age (yr)	58.9±10.2	56.6±10.8	0.173	53.6±10.5	53.2±8.3	0.173
Stage			0.541			0.019
I–II	7 (5.7)	1 (2.3)		58 (41.1)	6 (16.2)	
III	44 (35.8)	14 (31.8)		52 (36.9)	20 (54.1)	
IV	72 (58.5)	29 (65.9)		31 (22.0)	11 (29.7)	
Cell type			0.037			<0.001
Serous	111 (90.2)	44 (100.0)		91 (64.5)	37 (100.0)	
Non-serous	12 (9.8)	0 (0.0)		50 (35.5)	0 (0.0)	
Grade			0.209			0.058
G1	2 (1.6)	1 (2.3)		9 (6.4)	0 (0.0)	
G2	6 (4.9)	0 (0.0)		21 (14.9)	1 (2.7)	
G3	111 (90.2)	39 (88.6)		110 (78.0)	36 (97.3)	
Unknown	4 (3.3)	4 (9.1)		1 (0.7)	0 (0.0)	
Residual disease			0.703			0.685
R0	74 (60.2)	25 (56.8)		76 (53.9)	21 (56.8)	
R ≤1 cm	46 (37.4)	19 (43.2)		65 (46.1)	16 (43.2)	
R >1 cm	2 (1.6)	0 (0.0)		3 (2.1)	2 (5.4)	
Unknown	1 (0.8)	0 (0.0)		1 (0.7)	0 (0.0)	
Recurrence			0.175			0.853
No	31 (25.2)	16 (36.4)		76 (53.9)	21 (56.8)	
Yes	92 (74.8)	28 (63.6)		65 (46.1)	16 (43.2)	
PFS (mo)	17.5 [13.4]	20.3 [11.6]	0.093	23.4 [28.4]	24.3 [19.3]	0.941
Death			0.024			0.418
No	96 (78.0)	41 (93.2)		120 (85.1)	34 (91.1)	
Yes	27 (22.0)	3 (6.8)		21 (14.9)	3 (8.1)	
OS (mo)	32.5 [30.7]	42.4 [27.0]	0.016	41.7 [30.3]	46.2 [32.2]	0.094
CA125 (U/mL)						
At diagnosis	1,219.0 [2,498.0]	1,462.0 [2,008.0]	0.226	208.0 [855.5]	574.3 [1,945.6]	0.004
After operation*	48.6 [67.5]	37.5 [89.2]	0.984	69.2 [100.2]	92.0 [240.7]	0.162
After the third cycle of chemotherapy	29.0 [65.5]	30.5 [88.6]	0.805	12.6 [11.6]	10.5 [19.9]	0.941
HE4 (pmol/L)						
At diagnosis	532.0 [718.2]	612.6 [753.2]	0.718	153.1 [313.8]	181.3 [374.4]	0.250
After operation†	63.4 [32.9]	58.5 [27.8]	0.145	55.4 [26.1]	55.2 [31.0]	0.602
After the third cycle of chemotherapy	75.6 [61.8]	76.1 [38.2]	0.671	49.0 [18.7]	52.0 [22.8]	0.900
CA125			1.000			0.047
<35 U/mL	50 (40.7)	18 (40.9)		128 (90.8)	29 (78.4)	
≥35 U/mL	71 (57.7)	25 (56.8)		13 (9.2)	8 (21.6)	
HE4			0.453			0.788
<70 pmol/L	96 (78.0)	41 (93.2)		121 (85.8)	33 (89.2)	
≥70 pmol/L	27 (22.0)	3 (6.8)		20 (14.2)	4 (10.8)	
Combined group			0.441			0.164
CA125 <35 U/mL, HE4 <70 pmol/L	29 (23.6)	13 (29.5)		112 (79.4)	27 (73.0)	
CA125 <35 U/mL, HE4 ≥70 pmol/L	17 (13.8)	2 (4.5)		16 (11.3)	2 (5.4)	
CA125 ≥35 U/mL, HE4 <70 pmol/L	33 (26.8)	13 (29.5)		9 (6.4)	6 (16.2)	
CA125 ≥35 U/mL, HE4 ≥70 pmol/L	30 (24.4)	12 (27.3)		4 (2.8)	2 (5.4)	

Values are presented as mean ± standard deviation, number (%), or median [IQR].
CA125, cancer antigen 125; gBRCA, germline breast cancer gene; HE4, human epididymis protein 4; IDS, interval debulking surgery; OS, overall survival; PDS, primary debulking surgery; PFS, progression-free survival.
*Missing 2 in the wild-type group and 1 in the mutation group in the IDS group; †Missing 14 in the wild-type group and 4 in the mutation group in the IDS group.

The Identical analysis was performed in the IDS group (**Table 4**). Similar to the findings of the PDS group, the combined normalization of CA125 and HE4 was shown to be more effective in predicting 1-year survival, compared with the normalization of a single biomarker, regardless of the BRCA mutational status. Therefore, negative values of both CA125 and HE4 indicated a higher probability of recurrence after 12 months for patients with or without BRCA mutations, with rates of 78.6% and 86.2%, respectively. HE4 normalization alone

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Table 3. Sensitivity and specificity of serum HE4 and CA125 (alone and in combination) after the third cycle of chemotherapy followed by PDS, stratified based on BRCA mutational status

Variables	Sensitivity	Specificity	Accuracy	Likelihood ratio +	Likelihood ratio –	AUC
CA125 after the third cycle of chemotherapy						
Total	32.5	93.1	83.1	4.71	0.73	0.725
BRCA wild-type	24.1	94.6	80.1	4.46	0.80	0.700
BRCA mutation	66.7	82.4	81.1	3.79	0.40	0.863
HE4 after the third cycle of chemotherapy						
Total	25.0	89.7	79.0	2.43	0.84	0.602
BRCA wild-type	27.6	89.3	76.6	2.58	0.81	0.706
BRCA mutation	33.3	91.2	86.5	3.78	0.73	0.588
Combined results, either						
Total	45.0	83.7	77.4	2.77	0.66	0.677
BRCA wild-type	41.4	84.8	75.9	2.73	0.69	0.640
BRCA mutation	66.7	76.5	75.7	2.83	0.44	0.768
Combined results, both						
Total	12.5	99.0	84.8	12.63	0.88	0.677
BRCA wild-type	10.3	99.1	80.9	11.62	0.90	0.640
BRCA mutation	33.3	97.1	91.9	11.34	0.69	0.768

AUC, area under curve; BRCA, breast cancer gene; CA125, cancer antigen 125; HE4, human epididymis protein; PDS, primary debulking surgery.

Table 4. Sensitivity and specificity of serum HE4 and CA125 (alone and in combination) after IDS followed by the third cycle of chemotherapy, stratified based on BRCA mutational status

Variables	Sensitivity	Specificity	Accuracy	Likelihood ratio +	Likelihood ratio –	AUC
CA125 after the third cycle of chemotherapy						
Total	73.4	53.6	62.5	1.58	0.50	0.653
BRCA wild-type	77.6	58.7	67.8	1.88	0.38	0.687
BRCA mutation	69.2	46.7	53.5	1.30	0.66	0.582
HE4 after the third cycle of chemotherapy						
Total	60.6	72.2	67.1	2.18	0.55	0.697
BRCA wild-type	58.8	70.7	65.1	2.01	0.58	0.671
BRCA mutation	58.3	75.0	70.0	2.33	0.56	0.774
Combined results, either						
Total	88.7	41.1	62.1	1.51	0.27	0.730
BRCA wild-type	92.2	43.1	66.1	1.62	0.18	0.733
BRCA mutation	83.3	39.3	52.5	1.37	0.42	0.771
Combined results, both						
Total	45.1	83.3	66.5	2.70	0.66	0.730
BRCA wild-type	43.1	86.2	66.1	3.13	0.66	0.733
BRCA mutation	50.0	78.6	70.0	2.33	0.64	0.771

AUC, area under curve; BRCA, breast cancer gene; CA125, cancer antigen 125; HE4, human epididymis protein; PDS, primary debulking surgery.

also displayed good discriminative ability for predicting 1-year survival in patients with BRCA mutations, with an AUC of 0.774 (95% CI=0.596–0.952) and specificity of 75.0% (95% CI=0.551–0.893). Confidence intervals for the sensitivity and specificity of serum CA125 and HE4 are presented in the supplementary material (**Table S1**).

Fig. 1 displays Kaplan–Meier curves for PFS and OS, stratified based on CA125 and/or HE4 normalization after 34 cycles of chemotherapy with debulking surgery. The log-rank test indicated significant differences in the curves for PFS ($p<0.001$) and OS ($p<0.001$) between normalized and non-normalized biomarkers in the overall population. Additionally, subgroup analysis stratified based on BRCA mutational status revealed that patients with BRCA wild-type who achieved normalization of both biomarkers had significantly improved PFS ($p<0.001$) and OS ($p<0.001$) than those who did not achieve normalization of either or both biomarkers. Similarly, patients in the BRCA mutation group who achieved normalization of both biomarkers demonstrated improved PFS and OS than those in patients who did not achieve normalization of both biomarkers ($p=0.045$ and $p=0.005$, respectively).

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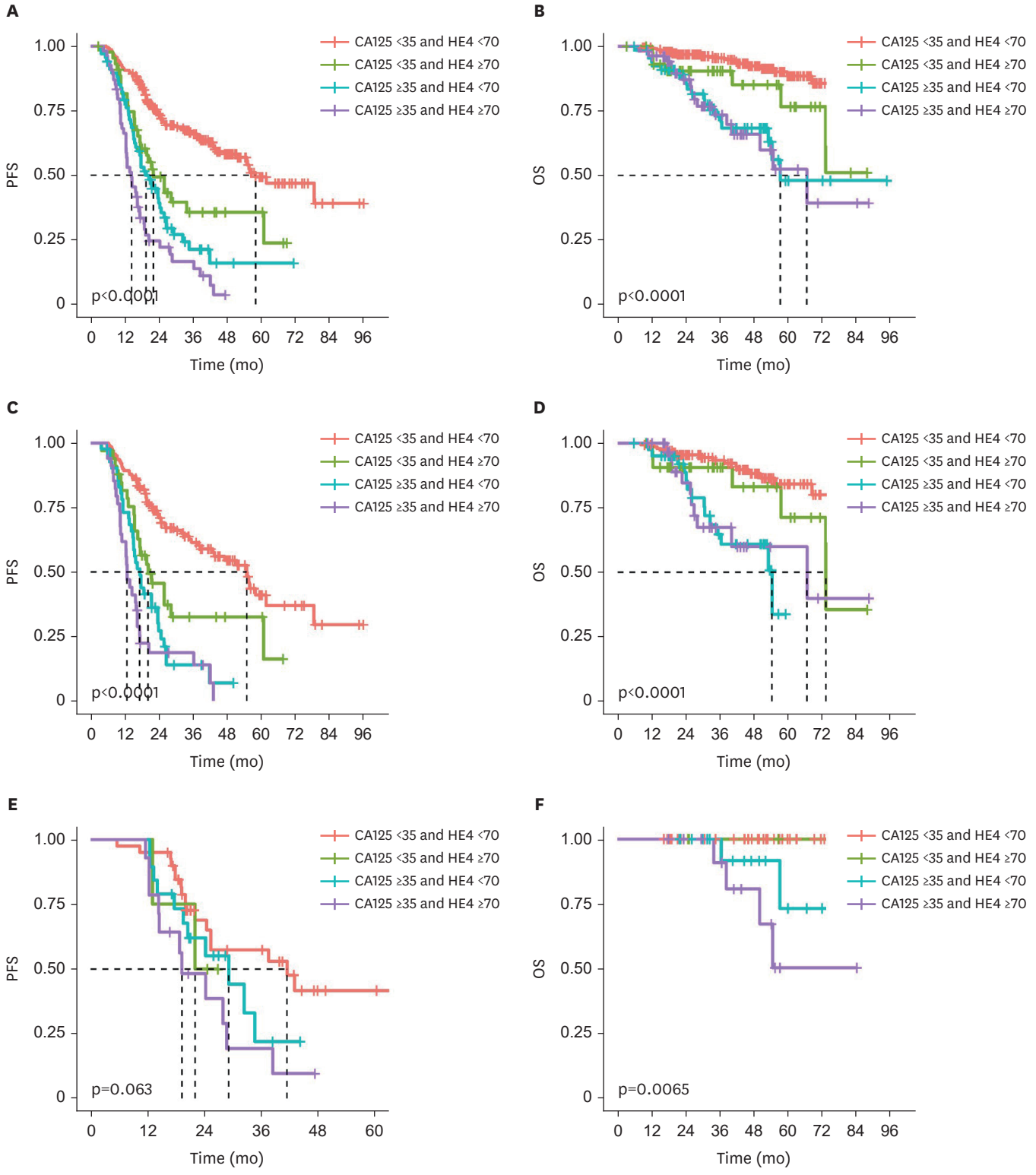

Fig. 1. PFS and OS in patients based on CA125 and/or HE4 normalization. (A) PFS in overall population, (B) OS in overall population, (C) PFS in BRCA wild-type patients group, (D) OS in BRCA wild-type patients group, (E) PFS in BRCA mutational group, and (F) OS in BRCA mutational group.
BRCA, breast cancer gene; CA125, cancer antigen 125; HE4, human epididymis protein 4; OS, overall survival; PFS, progression-free survival.

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Overall, the normalization of both biomarkers is significantly associated with better PFS and OS, regardless of BRCA mutational status.

DISCUSSION

This study demonstrated that normalizing CA125 and HE4 yielded the best prognostic value for PDS and IDS groups. Specifically, we discovered a significant correlation between the normalization of both biomarkers and reduced recurrence risk within 1 year in the PDS and IDS groups, regardless of BRCA mutational status. Moreover, negative values of CA125 and HE4 were strongly associated with improved PFS and OS in patients with or without BRCA mutations. This finding highlights the effective utilization of these biomarkers in accurately predicting a higher probability of recurrence after 12 months. When assessing only one biomarker, HE4 normalization showed higher specificity than CA125 normalization among patients with BRCA mutations in the PDS and IDS groups. Moreover, our findings revealed that the specificity of HE4 alone was comparable to that of both biomarkers in patients with BRCA mutations in the PDS and IDS groups.

In this study, we confirmed that patients with BRCA mutations tended to have higher CA125 and HE4 values at diagnosis. This finding is consistent with those of previous research [26]. However, while most studies have observed elevated CA125 and HE4 values in patients with BRCA mutations, the differences were insignificant. In our study, we observed a significant increase in CA125 values among patients with BRCA mutations who underwent PDS than those in patients with BRCA wild-type. This finding could be ascribed to the fact that patients with BRCA mutations might have higher tumor loads than those with BRCA wild-type. However, the significant increase in initial CA125 values in patients with BRCA mutations who underwent PDS could be attributed to a higher proportion of patients with type 2 epithelial ovarian cancer in the BRCA wild-type group. Kristjansdottir et al. [27] reported that the diagnostic performance of CA125 was lower in type 1 ovarian cancer than that in type 2 ovarian cancer. Additionally, the lower specificity of CA125, compared with that of HE4, may have influenced the results [10,16].

In contrast to HE4, the lower specificity observed in CA125 for patients with BRCA mutations may be attributed to distinct tumor characteristics, compared with those of patients without BRCA mutations. Tjokrowidjaja et al. [23] reported that approximately half of the patients with BRCA mutations who experienced recurrence during poly (ADP-ribose) polymerase (PARP) inhibitor maintenance therapy showed progression only on response evaluation criteria in solid tumors (RECIST), without CA125 elevation. Patients with peritoneal recurrence demonstrated a higher concordance between CA125 elevation and progressive disease on RECIST than those with solid organ recurrence without peritoneal recurrence. This finding could be attributed to a higher prevalence of oligometastasis rather than peritoneal seeding in patients treated with PARP inhibitors [28]. With the increasing use of PARP inhibitors as standard maintenance therapy in patients with BRCA mutations, the effect on tumor molecular biology might be more direct than that on BRCA wild-type. However, further studies are needed owing to the limited research on HE4. Nevertheless, our findings revealed that the combination of CA125 and HE4 may be the most effective prognostic marker, even in patients with BRCA mutations.

This study is the first and largest to evaluate the efficacy of both CA125 and HE4 in predicting recurrence in patients with BRCA mutation. Additionally, it compared the 2 biomarkers

alone or in combination and evaluated them based on BRCA mutational status. With the expanded use of PARP inhibitors, treatment strategies have evolved based on the presence of BRCA mutations [29], and chemotherapy responses may differ with BRCA mutational status. Therefore, investigating the efficacy of CA125 and HE4 in patients with BRCA mutations is necessary. However, only a few studies have examined the effectiveness of these biomarkers in this patient group. Plotti et al. [18] confirmed that normalizing HE4 reflects platinum sensitivity in patients with BRCA mutations, but no difference was observed when compared with those without BRCA mutations. Additionally, they did not analyze the correlation between BRCA mutations and CA125 values. Thus, the present study is of great significance as it validates, for the first time, the efficacy of CA125 and HE4 biomarkers in patients with BRCA mutations. Moreover, our study underscores the consistency of trends when employing normal cut-off values for analysis, irrespective of treatment methods. This suggests the feasibility and versatility of these findings in a clinical setting.

This study has some limitations. First, the study involved a retrospective collection of data and a small sample size of the BRCA mutation group. Second, we only analyzed patients with germline BRCA mutations. Therefore, an additional multi-center prospective study is needed to investigate the efficacy of biomarkers in patients with BRCA mutations, including somatic BRCA mutations.

In conclusion, the normalization of CA125 and HE4 is the most effective predictive factor for 1-year survival in patients with epithelial ovarian cancer, regardless of BRCA mutations. Additionally, among patients with BRCA mutations who underwent PDS or IDS, normalizing HE4 alone demonstrated a higher specificity for maintaining a recurrence-free status within one year than normalizing CA125 alone. Therefore, identifying the appropriate biomarker based on each patient's BRCA mutational status is important when following up on patients with ovarian cancer.

SUPPLEMENTARY MATERIAL

Table S1

Confidence intervals for the sensitivity and specificity of serum CA125 and HE4 (alone and in combination) after PDS followed by the third cycle of chemotherapy and IDS stratified based on BRCA mutational status

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