

Radiogenomic Analysis of Contrast-Enhanced MRI for Predicting Pathogenic *BRCA* Variants in Ovarian Cancer

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This study evaluated the feasibility of predicting pathogenic *BRCA1/2* variants in ovarian cancer using radiogenomic analysis of contrast-enhanced MRI. Twenty six patients were analyzed, including 14 with pathogenic *BRCA1/2* variants and 12 without. Contrast enhanced MRI was used to generate two dimensional (2D) and three dimensional (3D) tumor segmentations. Radiomic features extracted with PyRadiomics were reduced using least absolute shrinkage and selection operator (LASSO) regression, yielding two selected features. Linear discriminant analysis (LDA) models were trained on 18 patients and tested on 8, with performance assessed using sensitivity, specificity, accuracy, and the area under the receiver operating characteristic (ROC) curve. The DeLong test compared AUCs between segmentation methods. Automated machine learning (AutoML) was performed with a training set of 20 patients and a test set of 6, with multiple performance metrics calculated. LDA achieved approximately 60% accuracy in both 2D and 3D test datasets. AUCs were 0.80 (3D) and 0.77 (2D), with no significant difference ($p=0.85$). AutoML identified CatBoost_BAG_L2_FULL as the optimal model, achieving accuracy above 80%. MRI-based radiogenomic analysis demonstrated moderate classification performance for identifying pathogenic *BRCA1/2* variants in ovarian cancer. These preliminary findings suggest a potential role for noninvasive prediction, warranting further validation in larger cohorts.

Key words: ovarian cancer, *BRCA1/2*, radiogenomics, machine learning, MRI

In 2022, an estimated 324,603 individuals were diagnosed with ovarian cancer worldwide <<https://gco.iarc.fr/today/en>> (last accessed 9.30.2025). Among these, approximately 10–15% were classified as hereditary breast and ovarian cancer (HBOC), caused by pathogenic variants in the *BRCA1/2* genes [1]. Patients with confirmed pathogenic *BRCA1/2* variants can pass these mutations on, increasing familial ovarian cancer risk relative to individuals without such variants [2]. Therefore, determining pathogenic *BRCA1/2* variant

status is crucial for reducing the risk of ovarian cancer and guiding appropriate treatment strategies.

In clinical practice, submitting surgical specimens for genetic testing has become routine, with results guiding treatment decisions. This is particularly important for determining the appropriateness of targeted therapies, such as olaparib, where the test serves as a companion diagnostic tool. Since April 2020, Japan's National Health Insurance has covered *BRCA1/2* genetic testing for patients with suspected HBOC. In March 2021, homologous recombination

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deficiency (HRD) testing of tumor tissue was approved as a companion diagnostic for olaparib in patients with stage III/IV ovarian cancer, with the MyChoice™ diagnostic system from Myriad Genetics [1]. However, these tests are invasive, expensive, and pose significant physical and financial burdens on patients.

Alternatively, radiomics, an imaging analysis technique based on pixel values from computed tomography (CT) and magnetic resonance imaging (MRI), has been explored to determine lesion tissue type and genotype [3]. In radiomic analysis, pixel values from an imaged lesion are used to calculate radiomic features, which are indicators derived from morphological, statistical, and textural information. By evaluating the correlation between these features and pathological findings, tissue type and other pathological characteristics can be inferred from imaging data. Radiogenomics extends radiomics by linking imaging data with genetic information, enabling the detection or prediction of genetic mutations. Notably, MRI enables the acquisition of diverse image contrasts depending on the imaging sequence used, which has promoted numerous MRI-based radiomics studies, particularly in breast cancer, ovarian cancer, soft tissue tumors, and brain tumors [4-7]. Therefore, the successful application of MRI-based radiomics may pave the way for a low-cost, noninvasive diagnostic approach.

Radiomic research on ovarian cancer using MRI has recently expanded across applications, including the

classification of benign and malignant tumors, treatment response, and metastasis risk prediction [8-10]. We hypothesize that pathogenic *BRCA1/2* variants in ovarian cancer can be feasibly predicted using MRI and that such prediction has clinical value. If the presence of pathogenic variants can be inferred from imaging, this approach may support risk stratification and help prioritize genetic testing according to each patient's risk. However, radiogenomic analysis using MRI to identify tumor genotype is still in early stages of development, and no studies have investigated the prediction of pathogenic *BRCA1/2* variants in ovarian cancer using MRI. Therefore, this preliminary study aimed to evaluate the feasibility of identifying pathogenic *BRCA1/2* variants in patients with ovarian cancer using radiogenomic analysis of contrast-enhanced MRI.

Materials and Methods

The workflow of this study is illustrated in Fig. 1. This retrospective study was approved by the Ethics Committee of Okayama University Hospital (Approval No. K2409-039), which waived the requirement for informed consent for inclusion in this retrospective study because existing medical information was used. For the MRI examination, written informed consent had been obtained from all patients before imaging.

Patients. This retrospective study reviewed the medical records of patients treated at our institution.

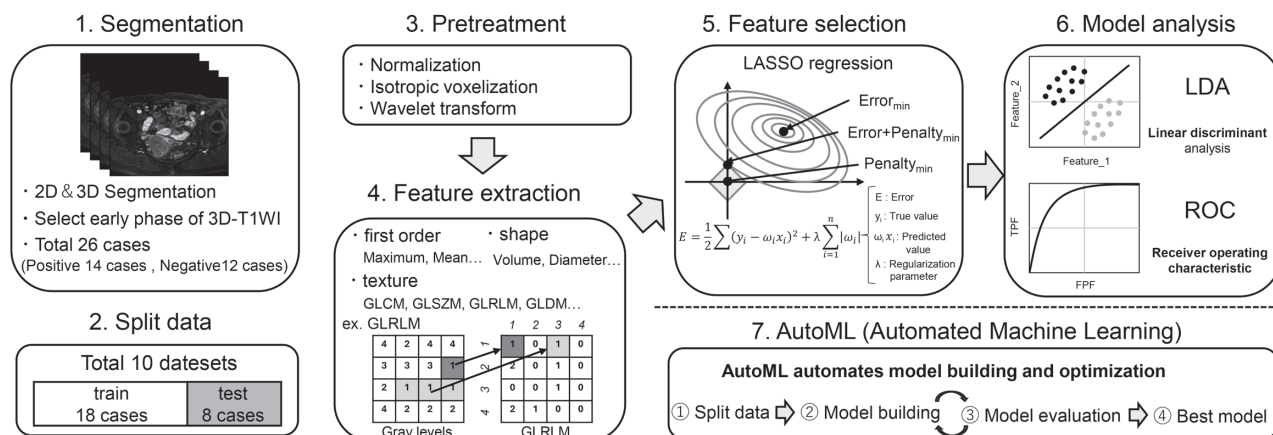


Fig. 1 Radiogenomic analysis workflow. Contrast-enhanced 3D T1-weighted MR images were used for both two-dimensional (2D) and three-dimensional (3D) tumor segmentation. Radiomic features were extracted using PyRadiomics and reduced using LASSO regression with leave-one-out cross-validation (LOOCV). Preliminary model validation was performed using linear discriminant analysis (LDA) and receiver operating characteristic (ROC) analysis. A comprehensive model search was performed using automated machine learning (AutoML).

The inclusion criteria were as follows: (i) diagnosis of unilateral or bilateral ovarian cancer, (ii) contrast-enhanced MRI performed between March 2021 and May 2024 at Okayama University Hospital or Okayama Diagnostic Imaging Center, and (iii) confirmed pathogenic *BRCA1/2* variant status through genetic testing. The exclusion criteria were: (i) MRI images containing artifacts and (ii) images obtained after the initiation of radiation therapy or chemotherapy.

Data preparation. The dataset was divided into training and test sets for model construction and independent evaluation, respectively. Only contrast-enhanced three-dimensional T1-weighted images (3D-T1WI) acquired on 1.5T or 3.0T MRI scanners during the first post-contrast phase, approximately 30 s after contrast injection, were included. Contrast-enhanced images are commonly used in radiogenomics analyses, and the first post contrast phase is considered to better reflect intratumoral microstructural characteristics. Based on these considerations, the present study employed first post contrast images for analysis.

Segmentation. Tumor segmentation was performed using 3D Slicer (version 5.2.2). First, areas of high signal intensity within the tumor were identified using diffusion-weighted imaging (DWI) with a b-value of 800. These areas served as references for manual segmentation on contrast-enhanced 3D-T1WI. Both two-dimensional (2D) and three-dimensional (3D) manual segmentations were performed. In the 2D approach, segmentation was applied to the single axial slice showing the maximum tumor diameter. In the 3D approach, segmentation was applied to multiple slices encompassing the entire tumor volume. All segmentation results were reviewed and confirmed by consensus between two radiologic technologists (H.S. and R.F.) with 2 and 12 years of experience, respectively.

Radiomic features. Radiomic features were extracted using PyRadiomics (version 3.0.1) within a Python environment based on Anaconda (version 24.11.1) [11]. PyRadiomics is an open-source library developed in accordance with the Image Biomarker Standardization Initiative (IBSI) guidelines [12]. Prior to extraction, isotropic resampling with B-spline interpolation was applied to standardize voxel size in the x, y, and z directions. Because MR image signal intensity is relative, it cannot be used directly for analysis. Therefore, signal intensity was normalized by scaling the maximum signal intensity for each case to 1.0.

Wavelet transformation was applied to the original images to generate additional images at different spatial frequencies. Morphological, first-order statistical, and textural features (GLCM, GLRLM, GLSZM, and GLDM) were extracted. In the feature names, “Original” and “Wavelet” refer to features extracted directly from unprocessed images and from the wavelet-transformed images, respectively. H and L indicate high- and low-pass filtering in the x-, y-, and z-directions, respectively.

Dimensionality reduction. To mitigate overfitting, feature selection used least absolute shrinkage and selection operator (LASSO) regression [13], implemented in scikit-learn (v1.5.0). LASSO regression applies L1-norm regularization to linear regression model coefficients, yielding sparse coefficients [14].

$$\hat{\beta} = \underset{\beta}{\operatorname{argmin}} \left\{ \frac{1}{2} \sum_{i=1}^N \left(y_i - \beta_0 - \sum_{j=1}^p x_{ij} \beta_j \right)^2 + \lambda \sum_{j=1}^p |\beta_j| \right\} \quad (1)$$

Where $\hat{\beta}$ is the LASSO solution, N is the number of cases, p is the number of features, y_i is the objective variable, x_{ij} is the feature, β_0 is the constant term, β_j is the regression coefficient, and λ is the regularization parameter. λ determines the number of selected features. To prevent overfitting, leave-one-out cross-validation (LOOCV) was used to set λ such that two features were selected for both the 2D and 3D segmentations [15]. Ten datasets were prepared, and the same analysis was performed for each, yielding a total of 20 features.

Radiogenomic model development and statistical evaluation. To assess potential differences in clinical characteristics between the *BRCA*-positive and *BRCA*-negative groups, age and tumor size were compared using the Mann–Whitney U test. Statistical analyses were performed using Python (version 3.11.9) and the SciPy library (version 1.13.1).

To assess the predictive performance of the features selected by LASSO regression, we constructed an LDA model. The training dataset consisted of 18 cases, and the test dataset consisted of 8 cases. LDA was used to determine the decision boundary that best separated the two groups: one with pathogenic *BRCA1/2* variants and the other without. A classification model was developed based on this boundary. Sensitivity, specificity, and accuracy were then calculated using the training and test datasets.

The area under the ROC curve (AUC) was calcu-

lated using the training dataset to assess the model's discriminative ability. To evaluate whether classification performance differed significantly between 2D and 3D segmentations, the DeLong test was applied [16]. The significance level was set at 0.05.

To explore models capable of achieving higher accuracy using the selected features, we used automated machine learning (AutoML) [17] with AutoGluon, an open-source AutoML framework developed by Amazon Web Services. AutoML was conducted using the two most frequently selected features identified by LASSO regression. The dataset was automatically partitioned into 20 samples for training and 6 for validation, and three-fold cross-validation was performed for each machine learning model. Evaluation metrics were calculated from the validation data, including accuracy, balanced accuracy, sensitivity, precision, Matthews correlation coefficient (MCC), F1 score, and training data sensitivity.

Results

The analysis included 26 patients with ovarian cancer (mean age: 65.8 ± 8.1 years; range: 48-78 years). Among these, 14 patients (mean age: 67.5 ± 8.1 years) had pathogenic *BRCA1/2* variants, while 12 patients (mean age: 63.8 ± 7.9 years) did not carry *BRCA1/2* variants. There were no statistically significant differences in age (67.5 vs. 63.8 years, $p=0.267$) or maximum tumor diameter (49.6 vs. 70.7 mm, $p=0.095$) between the *BRCA*-positive and *BRCA*-negative groups (Table 1).

MRI scans were obtained using scanners from Siemens (Germany; 15 patients), Philips (Netherlands; 7 patients), GE Healthcare (USA; 2 patients), and Canon Medical Systems (Japan; 2 patients), as summarized in Table 2.

Overall, 959 radiomic features were extracted from 3D segmentation and 748 from 2D segmentation. LASSO regression with LOOCV retained 20 features. Features selected at least twice are presented in Table 3.

Table 1 Detailed information for each case

Case	Age	Laterality	Maximum Diameter (mm)	BRCA	Tumor histology	Stage
1	67	Both	86.0	Negative	HGSC	IIIC
2	72	Lt	78.0	BRCA1	HGSC	IIIC
3	68	Rt	45.1	Negative	HGSC	IIIC
4	50	Both	30.6	Negative	HGSC	IVB
5	65	Both	56.3	Negative	HGSC	IIIC
6	78	Both	28.7	BRCA2	HGSC	IIIC
7	67	Lt	59.9	Negative	HGSC	IVB
8	76	Both	74.0	Negative	HGSC	IIIC
9	63	Both	34.3	BRCA1	HGSC	IIIB
10	77	Rt	57.6	BRCA2	HGSC	IIB
11	68	Rt	33.6	BRCA2	HGSC	IIIC
12	71	Both	43.3	BRCA2	HGSC	IIIC
13	67	Lt	53.1	Negative	HGSC	IVB
14	69	Both	52.5	Negative	HGSC	IIIC
15	60	Rt	105.6	Negative	HGSC	IVB
16	78	Both	57.0	BRCA1	HGSC	IIIB
17	48	Lt	54.4	BRCA2	HGSC	IIIB
18	62	Both	38.7	BRCA2	HGSC	IIIC
19	69	Lt	143.1	Negative	HGSC	IIIC
20	67	Rt	34.3	BRCA1	HGSC	IVB
21	59	Both	69.5	BRCA1	HGSC	IVB
22	70	Rt	69.6	BRCA2	HGSC	IVB
23	65	Rt	58.4	BRCA2	HGSC	IVB
24	50	Both	96.8	Negative	HGSC	IIIC
25	57	Rt	45.5	Negative	HGSC	IIIA2
26	67	Rt	37.1	BRCA2	HGSC	IIIC

MRI, magnetic resonance imaging; Rt, right; Lt, left

Textural features, particularly those derived from the gray-level run-length matrix (GLRLM) and gray-level size zone matrix (GLSZM), were selected most frequently. Most selected features were derived from wavelet-transformed images, with a greater proportion derived from low-pass-filtered images than from high-pass-filtered ones (Table 3).

LDA performance is summarized in Fig. 2 and Table 4. For the training dataset, accuracy was approximately

80% for the 2D model and 70% for the 3D model. In the validation dataset, accuracy decreased relative to the training dataset, but the 2D model consistently outperformed the 3D model in both datasets. LDA was performed on each of the 10 datasets; the best-performing model is shown in Fig. 2, and the evaluation metrics are reported as mean values across the 10 datasets.

ROC analysis yielded AUCs of 0.77 and 0.80 for the 2D and 3D models, respectively (Fig. 3). The DeLong

Table 2 Examination equipment and acquisition sequences

Case	Manufacturer	Scanner Model	Image Sequence
1	SIEMENS	MAGNETOM_Avanto_Fit	Vibe
2	SIEMENS	MAGNETOM_Skyra_Fit	Vibe
3	SIEMENS	MAGNETOM_Prisma	Vibe
4	PHILIPS	Achieva	e-THRIVE
5	SIEMENS	MAGNETOM_Avanto_Fit	Vibe
6	SIEMENS	MAGNETOM_Avanto_Fit	Vibe
7	SIEMENS	MAGNETOM_Avanto_Fit	Vibe
8	PHILIPS	Ingenia Elition X	e-THRIVE
9	PHILIPS	Ingenia Elition X	e-THRIVE
10	SIEMENS	MAGNETOM_Avanto_Fit	Vibe
11	PHILIPS	Ingenia	e-THRIVE
12	GE	SIGNA Architect	LAVA
13	PHILIPS	Achieva	e-THRIVE
14	SIEMENS	MAGNETOM_Avanto_Fit	Vibe
15	SIEMENS	MAGNETOM_Avanto_Fit	Vibe
16	PHILIPS	Ingenia	e-THRIVE
17	SIEMENS	MAGNETOM_Avanto_Fit	Vibe
18	SIEMENS	MAGNETOM_Avanto_Fit	Vibe
19	SIEMENS	MAGNETOM_Avanto_Fit	Vibe
20	SIEMENS	MAGNETOM_Avanto_Fit	Vibe
21	SIEMENS	MAGNETOM_ESSENZA	Vibe
22	SIEMENS	MAGNETOM_Aera	Vibe
23	PHILIPS	Ingenia	e-THRIVE
24	GE	SIGNA Architect	LAVA
25	CANON	Vantage Gracian	FFE3D
26	CANON	Vantage Gracian	FFE3D

Table 3 Features selected using LASSO regression

Types of segmentation	Features name	Frequency
2D segmentation	Wavelet-LHL_glrIm_HighGrayLevelRunEmphasis	4
	Wavelet-LHL_glszm_GrayLevelNonUniformityNormalized	2
	Original_shape_MajorAxisLength	2
	Wavelet-LHL_glszm_HighGrayLevelZoneEmphasis	2
3D segmentations	Wavelet-LLL_glszm_LargeAreaHighGrayLevelEmphasis	4
	Wavelet-LHL_glrIm_HighGrayLevelRunEmphasis	2
	Wavelet-LHL_glrIm_LowGrayLevelRunEmphasis	2

2D, two-dimensional; 3D, three-dimensional

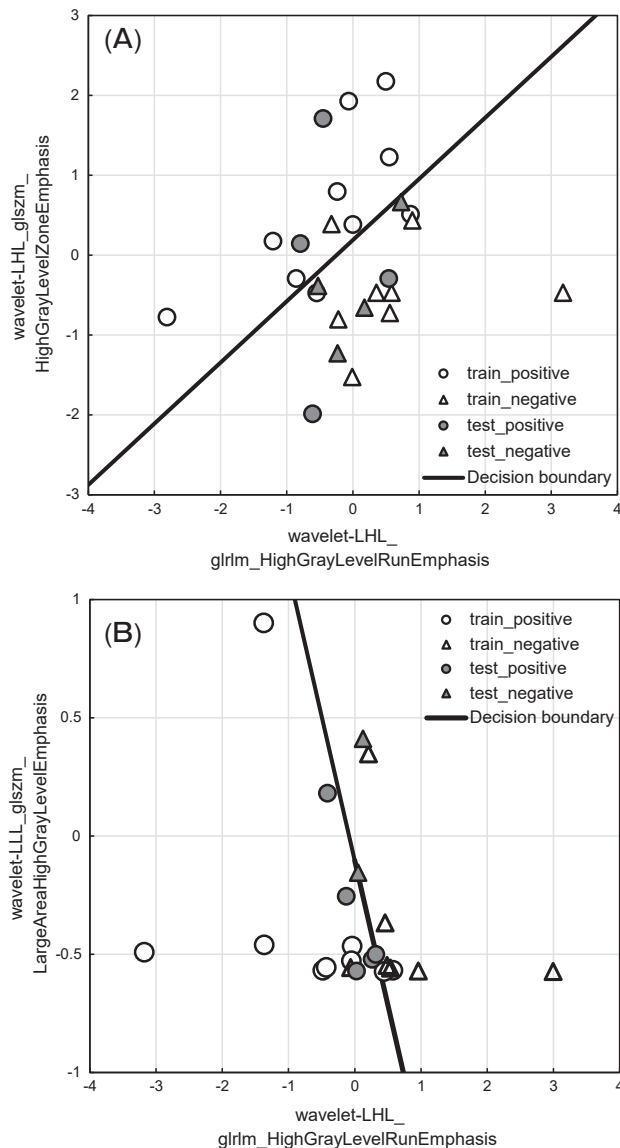


Fig. 2 Linear discriminant analysis (LDA) results for *BRCA* variant classification. LDA results for (A) 2D and (B) 3D segmentation are shown. A decision boundary was used to separate the *BRCA*-positive and *BRCA*-negative groups, and sensitivity, specificity, and accuracy were evaluated accordingly.

test revealed no significant difference in AUC between the two models ($p = 0.85$).

AutoML results are presented in Table 5. AutoML trained 45 machine-learning models in parallel, among which CatBoost_BAG_L2_FULLL yielded the best performance for both the 2D and 3D analyses. All calculated metrics were high, with accuracy exceeding 80% for both the 2D and 3D models. Notably, the 2D model achieved a sensitivity of 1.00, indicating that all cases with pathogenic *BRCA* variants were correctly identified.

Discussion

Using contrast-enhanced MRI, this study evaluated the classification performance of radiogenomic models

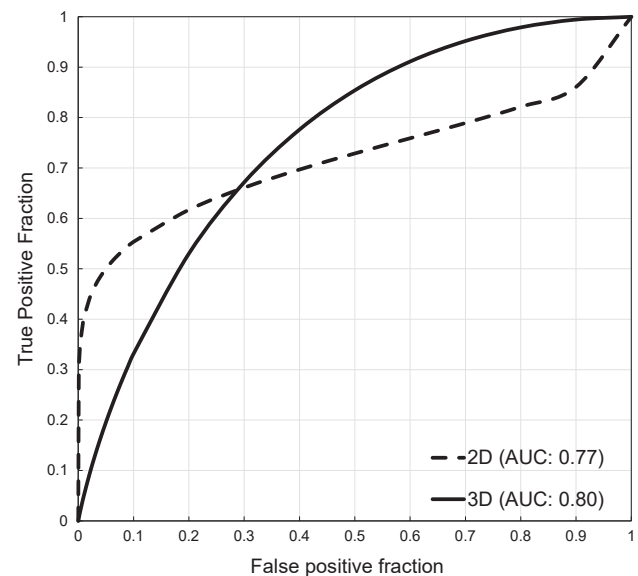


Fig. 3 Receiver operating characteristic (ROC) curves comparing the classification performance of the 2D and 3D segmentation models. The solid line represents the 2D model, and the dotted line represents the 3D model. Values in parentheses indicate the corresponding area under the curve (AUC) scores.

Table 4 LDA results

Type		Sensitivity	Specificity	Accuracy
2D segmentation	Training	0.83	0.79	0.81
	Test	0.50	0.67	0.60
3D segmentation	Training	0.75	0.63	0.69
	Test	0.70	0.45	0.55

2D, two-dimensional; 3D, three-dimensional

Table 5 AutoML results

Type	2D segmentation	3D segmentation
Best model name	CatBoost_BAG_L2_FULL	CatBoost_BAG_L2_FULL
Accuracy	0.83	0.83
Balanced accuracy	0.83	0.83
MCC	0.71	0.71
F1	0.86	0.80
Precision	0.75	1.00
Sensitivity	1.00	0.67
Accuracy(train)	0.90	0.90

2D, two-dimensional; 3D, three-dimensional; MCC, matthews correlation coefficient

for predicting pathogenic *BRCA1/2* variants in ovarian cancer. In both the 2D and 3D analyses, models constructed using image-derived features achieved classification accuracies exceeding 80% with AutoML, whereas those constructed with LDA achieved accuracies of approximately 60%. Prior CT based radiomics studies have constructed 2D, 3D, and combined 2D-3D models, with reported accuracies of approximately 70% for predicting pathogenic BRCA variants [18]. Although this was a preliminary study with a very limited dataset, the accuracies obtained here were comparable to those reported previously. The non-invasive approach employed in this study may therefore be useful for risk stratification.

To address the risk of overfitting associated with the large number of extracted features, a constrained feature selection approach was used, limiting the number of features to two. In general, machine learning models require an events-per-variable (EPV) ratio of at least 10 to minimize the risk of overfitting [19-21]. For classification models, the EPV is based on the number of cases in the smaller class. Because the training dataset contained only nine cases per group, the ideal number of features was one. However, using only one feature would have hindered meaningful model construction and evaluation. Therefore, the number of features was set to two, the minimum deemed necessary for a meaningful analysis.

Many of the features selected through LASSO regression and LOOCV were textural, particularly GLRLM and GLSZM features. The GLRLM represents the number of consecutive pixels with the same intensity value along a given direction, whereas the GLSZM characterizes the size of connected regions with identical intensity values. HighGrayLevelRunEmphasis reflects the

frequency of high gray-level pixel values and increases when multiple high-intensity regions are present within the ROI. In contrast, HighGrayLevelZoneEmphasis characterizes the extent to which high gray-level pixels form broader zones, thereby capturing the spatial continuity of high-intensity regions. LargeAreaHighGrayLevelEmphasis indicates the presence of larger high-intensity regions compared with HighGrayLevelZoneEmphasis [22]. These textural features may reflect biological differences between *BRCA1/2*-mutated and non-mutated tumors. *BRCA1/2*-associated ovarian cancer, particularly high-grade serous carcinoma, often exhibits rapid proliferation, extensive necrosis, and abnormal angiogenesis. These pathological characteristics may appear on MRI as heterogeneous enhancement and disorganized internal structures, which may be reflected in features such as HighGrayLevelRunEmphasis, LargeAreaHighGrayLevelEmphasis, and HighGrayLevelZoneEmphasis. Moreover, the predominance of wavelet-derived features, especially those from low-pass filtering, may indicate that larger-scale structural heterogeneity, such as solid-cystic composition or necrosis, contributes to the radiomic patterns associated with *BRCA* mutations.

This predominance of low-pass-filtered wavelet features may be attributable to the superior contrast resolution of MR images, because low-pass filters may better capture relevant textural characteristics. All MR images were normalized to their maximum intensity to minimize signal bias. Finally, given the variability in imaging equipment and acquisition parameters, features that are robust to these differences, such as textural features, may have been preferentially selected.

LDA achieved a classification accuracy of approximately 70% in the training dataset and approximately

60% in the validation dataset. Compared with AutoML, LDA showed lower accuracy and poorer generalization, suggesting that gradient boosting models may be more appropriate than LDA for identifying pathogenic BRCA variants.

In ROC curve analysis, models based on the 2D and 3D segmentation methods showed similar performance. The AUC values were nearly identical, and the DeLong test revealed no statistically significant difference between the models. In the 2D analysis, a hook appeared at the terminal portion of the ROC curve, indicating an increase in false negatives and a corresponding decline in sensitivity. Consistent with this observation, the LDA model also showed reduced sensitivity in the validation dataset, highlighting an important limitation of this model.

In AutoML, CatBoost_BAG_L2_FULL was selected as the best-performing model. CatBoost is a gradient boosting algorithm developed by Yandex that efficiently handles categorical variables, processes data rapidly, and generates highly accurate predictive models. BAG denotes bagging (bootstrap aggregation), an ensemble method in which similar models are trained independently and their predictions averaged, which improves stability and generalization performance. L2 indicates that the model was retrained based on features derived from independently trained models, while FULL indicates that the model was refit using all available training and validation data. The model constructed with CatBoost_BAG_L2_FULL achieved accuracies exceeding 80% in both the 2D and 3D validation datasets, indicating robust generalization. These findings indicate that 2D and 3D analyses can achieve comparable classification performance. Thus, in preliminary radiogenomic analysis of pathogenic *BRCA1/2* variants in ovarian cancer, a simplified 2D approach may offer a practical alternative, particularly under resource or segmentation time limitations.

This study has several limitations. First, the sample size was small. Because only 26 cases were analyzed, the selected features may have limited reproducibility, and different features may be selected in a larger dataset. The small sample size also limited assessment of the model's generalizability; the test dataset included only eight cases, which was insufficient for robust validation. To address these issues, future studies should use multi-institutional cohorts that expand the dataset. Image augmentation techniques, such as generative

adversarial networks, may also help increase training data [23]. Second, differences in imaging equipment and acquisition protocols among cases may have influenced the radiomic features. Whenever feasible, imaging parameters and equipment should be standardized to minimize this variability. Third, this study did not incorporate clinical information such as ascites or peritoneal dissemination. Including these clinical factors may further improve model performance. Finally, manual segmentation may have introduced subjective variability. Future studies should incorporate semiautomated or automated segmentation methods to improve reproducibility and reduce observer bias.

This study shows that radiogenomic analysis can be used to construct predictive models for identifying pathogenic *BRCA1/2* variants in ovarian cancer. Both 2D and 3D models achieved moderate classification accuracy, supporting the feasibility of noninvasive prediction in a pilot setting. Given the comparable performance of both approaches, a simplified 2D analysis may represent a practical option for clinical applications. This approach may also help prioritize genetic testing according to each patient's risk and thereby support risk stratification. Further studies using larger datasets and multimodal approaches incorporating clinical information are planned.

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