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Association Rule Mining-Based Radiomics in Breast Cancer Diagnosis

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ABSTRACT

Introduction: Breast cancer is the most common cancer among women worldwide. Early detection of breast cancer reduces mortality and morbidity. Acquiring or identifying valuable information in the form of rules is the key to an accurate diagnosis and differentiation between benign and malignant breast cancers. Our goal is to find the hidden but beneficial knowledge in the form of rules from datasets. In this paper, we use association rule mining algorithms to obtain information in the form of data rules for differential diagnosis between benign and malignant breast masses based on radiomic features, extracted from mammography images.

Material and Methods: In this study, 703 patients with both benign and malignant tumors were selected from the Curated Breast Imaging Subset of the Digital Database for Screening Mammography (CBIS-DDSM) database. The embedded method was employed to select the radiomic features of the image and uncover the hidden patterns of data through the Apriori algorithm.

Results: The association rules were generated from separated rules for benign and malignancy classes. The important features of the benign class include mass margins, horizontal long-run emphasis, 135drfraction, WavEnHLs3, vertical short-run emphasis, Teta1, 45dgr run-length with no uniformity, Teta2, and differential entropy2. However, the important features of the malignant class include assessment, correlation4, Teta1, WavEnLHs3, contrast5, vertical short-run emphasis, and differential entropy2.

Conclusion: It can be concluded that the proposed method has been successful in determining specific features for tumor prediction.

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Introduction

The rapid increase in breast cancer worldwide emphasizes the critical importance of early diagnosis. Early detection can significantly reduce both mortality and morbidity rates, ultimately enhancing the chances of survival for patients [1-5]. Mammography is a useful and accessible imaging modality for diagnosis and classification in early-stage breast cancer in two medio-lateral oblique (MLO) and cranio-caudal (CC) views. In the first step, Breast Cancer is diagnosed by using visual variables and a radiologist's knowledge of these parameters in diagnosis. However, it is difficult to differentiate between malignant and benign masses (uncancerous lesions). In fact, there are sometimes different interpretations [6-7].

It is now recommended to employ the quantitative features, extracted from mammographic images by adopting mathematical algorithms. These variables have shown great potential in helping physicians to detect masses and malignancies [8,9]. Radiomics is the procedure of extracting quantitative features from images through mathematical algorithms that are consistent with the visual and inherent characteristics of subjects, extracted from. On the other hand, accurate biological evaluation of breast cancer is essential due to the fact that, each subtype has its own biological and genetic characteristics with different treatment options and final prognosis. Accordingly, biomarkers are crucial in adapting treatment strategies for each patient in personalized precision medicine, and currently, it is possible with tissue samples through surgery or biopsy. Furthermore, a new non-invasive imaging technique will be valuable in the field of Oncology. Radiomics can be a contributory tool in the radiation oncology field by converting standard digital imaging into extractable and quantitative data that expresses different tumor characteristics. Radiomics-derived data can provide valuable information for differentiating benign from malignant lesions, predicting therapeutic response, evaluating the molecular profile of cancer, and

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extracting robust models [10-13]. Data mining uses different algorithms for the analysis of raw and high dimensional data. It helps extract knowledge from any data set and make better decisions for diagnosis and prediction by detecting the correlation between input variables and the target variable [14-20].

One of the applicable and practical methods in data analysis to display the most relevant features with the target feature is the association rule mining method. Association rule mining is a data mining method used for the analysis and interpretation of high-dimensional datasets by uncovering hidden and existing patterns. The goal of this algorithm is to find hidden but valuable knowledge in the form of rules from the data set that can provide potentially important information that is easily understood by clinical users. Association rule learning is aimed at extracting the frequent items of databases based on the user-defined threshold value and ignoring infrequent items [18]. The algorithm extracts rules from frequent items. The extracted rules describe the attributes that are more important than other attributes [19]. The rules extracted from the association rules can demonstrate the importance of the generated rules in the case that all features are placed in the front part of the rules with the same weight. The more features given to the associative rule algorithms, the stronger and more relevant they are to the target features, resulting in better and more reliable rules being produced. Accordingly, the extracted rules describe the presence of some features related to other features.

Shah *et al.* [21] distinguished between malignant and benign tumors by identifying frequent items. They used 699 data from the Wisconsin database and extracted their frequent items from 9 features. They also detected benignity and malignancy through neural network methods. The model accuracy was reported 94.4% [22]. Pala *et al.* [23] developed rules to predict breast cancer recurrence by adopting the Apriori algorithm.

Elfarra *et al.* [8] proposed a novel method of extracting mammogram features for Computer-Aided Design (CAD) systems in the diagnosis of benign, malignant, and normal cases through sequential forward features, the genetic algorithm features, the intersection of the selected feature, and the union of the selected features. They employed 410 images of the Digital Database for Screening Mammography (DDSM) database. In the first step, 145 features were extracted, and they were reduced to 31 in the next step. Finally, 18 features were selected. Accuracy, sensitivity, and specificity were reported as 89%, 88.6%, and 93.3%, respectively [6].

Karabatak *et al.* [23] proposed an intelligent diagnostic system for breast cancer based on association rules and neural networks. For this purpose, the Wisconsin database was used, and the Apriori algorithm was then employed to extract effective features, which were given to the neural network. The precision of the neural network was reported as 97.4% [23].

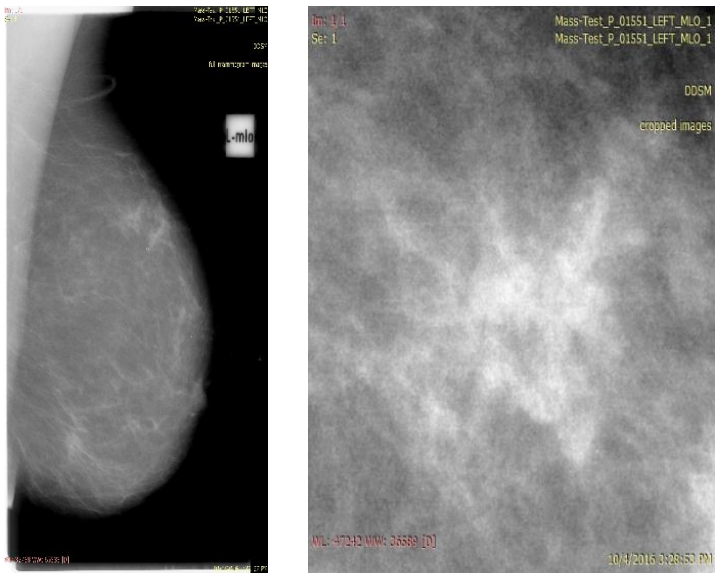
Despite the existence of a valid CAD system in the world, we still do not have enough information about image biomarkers that differentiate benign from malignant tumors. This study aimed to investigate the radiomic features, associated with this differentiation. We extracted quantitative features from mammography images and detected effective attributes for the differentiation of masses based on pathology in order to investigate and develop a powerful rule through the association rule mining algorithms. In other words, the aim of this study was to investigate the important radiomic and clinical characteristics to make rules that help better distinguish between benign and malignant tumors.

Materials and Methods

There are a few mammography databases, one of which is the Digital Database for Screening Mammography (DDSM) containing 2620 scanned films in normal, benign, and malignant mass categories. This study benefited from only benign and malignant mass categories approved by pathology reports. Unfortunately, due to the lack of appropriate mass segmentation, used as the region of interest (ROI), the analysis forced the researchers to employ the Curated Breast Imaging Subset of DDSM (CBIS-DDSM), which is an updated version of DDSM with ROI segmentation [24] (Figure 1).

Moreover, 703 MLO images were utilized to display the whole breast tissues and lymph nodes in this study (366 images were benign, whereas the other 337 images had some malignant mass features) [25] (Tables 1 and 2). The schematic (Figure 2) demonstrates the general process of our study. Image segmentation was done manually by two professional radiologists with more than 10 years of experience in mammography interpretation. Moreover, 2D texture features were extracted in MaZda (developed at the Institute of Electronics, Technical University of Lodz (TUL), Poland).

After texture features extraction, the dimensions of features should be reduced. It is also essential to select important and specific features, which are related to the target type by using an embedded method consisting of filter and wrapper methods. The filter method is independent of machine learning for feature selection and is sometimes used as a preprocessing level for data analysis. In the filter method, feature selection is based on the score given to each feature after Pearson's chi-squared test. The score corresponds to the first p-value (p-value<0.05). The wrapper is a combination method of machine learning classifiers, aiming to achieve important features. A neural network, a Classification and Regression Tree (CART) decision tree, and a Support Vector Machine (SVM) approach were employed in this study based on forward selection. The lower sum of the square error rate means a higher score and a higher correlation rank in this method [26, 27].



(a) (b)

Figure 1. Mammographic image (a) Mediolateral Oblique (MLO) and (b) Region of interest (ROI) views.

Table 1. Image specification in Digital Database for Screening Mammography (DDSM) Dataset

Image specification	Number of images
MLO View	703
Benign in MLO View	366
Malignant in MLO View	337
Resolution of images	16 BITS per Pixel

Table 2. Tumor and Mass features were reported in The Digital Database for Screening Mammography (DDSM) Dataset for each patient.

Feature	Definition
Density category	Low/High/Iso density/Fat Density
Breast side	Right/Left
Number of abnormalities	
Mass shape	Irregular, Round, Lobulated, Oval, Asymmetric breast tissue
Mass margin	Spiculated, Circumscribed, Indistinct (ILL_Defined), ILL_Defined_Spiculated, Obscured, Micro Lobulated
BI-RADS assessment	0-5
Pathology	Malignant/Benign

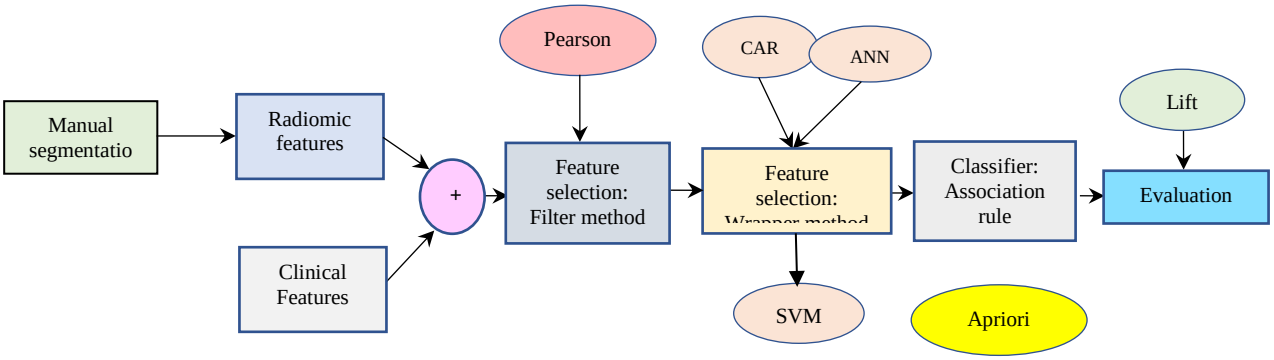


Figure 2. The schematic illustration of our study process.

Abbreviation: SVM: Support Vector Machine, CART: A Classification and Regression Tree, ANN: Artificial Neural Network

The 10-fold method was used to evaluate the classifiers and calculate accuracy. Data were divided into the train and test groups, and the accuracy of each classifier was calculated in two groups of training and testing. Moreover, the Apriori algorithm was used in this study for associate rule mining. This algorithm includes two basic steps, including the identification of frequent features and the generation of rules from frequent features. The first step aims to calculate support amounts through Eq. 1 [29]:

$$\text{Support} = Ni/N \quad (1)$$

Ni: number of records that include frequent features
N: Total of Records

When all frequent attributes are generated, the Apriori algorithm begins extracting rules from frequent features. For algorithm evaluation and calculation of the power of rules, several measurement approaches were suggested. The different aspect of rules is determined by different measurements [28, 29].

Table 3. The extracted features by Mazda.

Row	Feature	Sub feature description	Abbreviation
1	HISTOGRAM	histogram's mean	Mean
		histogram's variance	Variance
		histogram's skewness	Skewness
		histogram's kurtosis	Kurtosis
		1% percentile	Perc.01%
		10% percentile	Perc.10%
		50% percentile	Perc.50%
		90% percentile	Perc.90%
		99% percentile	Perc.99%
2	GRADIENT	absolute gradient mean	GrMean
		absolute gradient variance	GrVariance
		absolute gradient skewness	GrSkewness
		absolute gradient kurtosis	GrKurtosis
		percentage of pixels with nonzero gradient	GrNonZeros
3	RUN LENGTH MATRIX	run length nonuniformity	RLNonUni
		grey level nonuniformity	GLevNonU
		long run emphasis	LngREmph
		short run emphasis	ShrtREmp
		fraction of image in runs	Fraction
4	COOCURRENCE MATRIX Features are computed for 5 between-pixels distances (1, 2, 3, 4, 5)	angular second moment	AngScMom
		contrast	Contrast
		correlation	Correlat
		sum of squares	SumOfSqs
		inverse difference moment	InvDfMom
		sum average	SumAverg
		sum variance	SumVarnc
		sum entropy	SumEntrp
		entropy	Entropy
		difference variance	DifVarnc
		difference entropy	DifEntrp
5	AUTOREGRESSIVE MODEL	parameter θ1	Teta1
		parameter θ2	Teta2
		parameter θ3	Teta3
		parameter θ4	Teta4
		parameter σ	Sigma
6	HAAR WAVELET Feature is computed at 5 scales within four frequency bands	wavelet energy	WavEn
		Low-pass filtering in both directions (LL) assessed the lowest frequencies	WavEn LL
		Low-pass filtering followed by high-pass filtering (LH) assessed horizontal edges	WavEn LH
		High-pass filtering followed by low-pass filtering (HL) assessed vertical edges;	WavEn HL
		High-pass filtering in both directions (HH) assessed diagonal details	WavEn HH

For each rule in the form X→Y, Support(s), the probability of simultaneous occurrence of X and Y in a transaction Eq. 2 [29].

$$\text{Support}=P(X\cup Y)=\frac{Count\ (X\cup Y)}{N} \quad (2)$$

C (Confidence) is the probability conditional that a transaction with X contains Y Eq. 3.

$$\text{Confidence}(X\rightarrow Y)=P(Y|X)=\frac{Support\ (X\cup Y)}{Support(X)} \quad (3)$$

Lift shows Correlation between items. If the value is greater than 1, the correlation is positive, less than 1 correlation is negative and there is no correlation if the value is 1 Eq. 4 [29].

$$\text{Lift}(X,Y)=\frac{Support\ (X\cup Y)}{Support(X)*Spport(Y)} \quad (4)$$

123 radiomic features, extracted by Mazda, listed in (Table 3). Features selection and rules extraction were done by IBM SPSS Modeler 18.

Results

The analysis of a large number of variables has no clear and direct relationship with the target (independent) variable of the study.

Table 4. Rules on benignity

Row	Rules	Confidence%	Lift
1	Benignity → (massmargins = CIRCUMSCRIBED), (HorzlShrtREmp ≥ 0.5), (135drfraction ≥ 0.5), (Teta2 ≥ 0.5), (Teta1<0.5), (45dgrRLNonUni<0.5), and (WavEnHLs3<0.5)	94.38	1.81
2	Benignity → (BI-RADS assessment = 3.0), (VertlShrtREmp ≥ 0.5), (HorzlShrtREmp ≥ 0.5), (135drfraction ≥ 0.5), (Teta2 ≥ 0.5), and (Teta1<0.5)	93.75	1.8
3	Benignity → (massmargins = CIRCUMSCRIBED), (HorzlShrtREmp ≥ 0.5), (135drfraction ≥ 0.5), (Teta1<0.5), (45dgrRLNonUni<0.5), and (WavEnHLs3<0.5)	93.33	1.79
4	Benignity → (BI-RADS assessment=3.0), (DifEntrp2 ≥ 0.5), (VertlShrtREmp ≥ 0.5), (HorzlShrtREmp ≥ 0.5), and (135drfraction ≥ 0.5)	93.18	1.78
5	Benignity → (massmargins = CIRCUMSCRIBED), (HorzlShrtREmp ≥ 0.5), (135drfraction ≥ 0.5), (Teta2 ≥ 0.5), and (WavEnHLs3<0.5	93.18	1.78

Table 5. Rules on malignancy

Row	Rules	Confidence%	Lift
1	Malignancy → assessment=5.0, correlat4 ≥ ≥.5, Teta1<0.5, and WavEnLHs3<0.5	98.83	2.06
2	Malignancy → assessment=5.0, correlat4 ≥ 0.5, contrast5<0.5, WavEnLHs3<0.5, and WavEnHLs3<0.5	97.80	2.04
3	Malignancy → assessment=5.0, DifEntrp2<0.5, correlat4>=0.5, contrast5<0.5, and WavEnLHs3<0.5	97.67	2.03
4	Malignancy → massmargins=SPICULATED, VertlShrtREmp<0.5, contrast5<0.5, and WavEnLHs3<0.5	93.02	1.94
5	Malignancy → massmargins=SPICULATED, DifEntrp2<0.5, contrast5<0.5, and WavEnLHs3<0.5	90.10	1.87

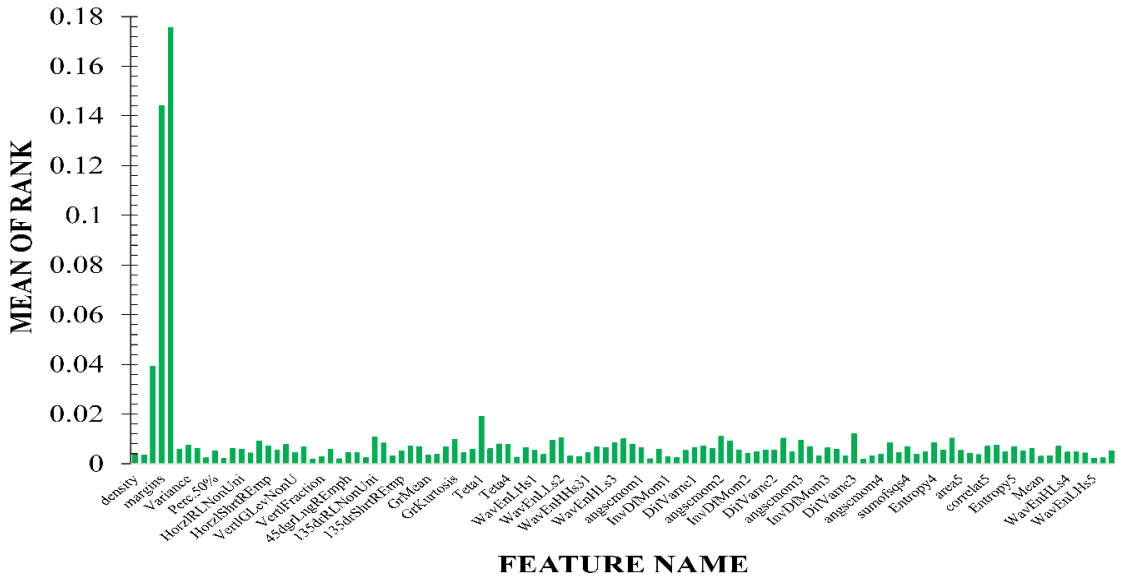


Figure 3. Average importance of features obtained from ANN, SVM and CART algorithms in wrapper method.

Therefore, feature selection methods (i.e. filter and wrapper methods) were adopted to reduce the number of variables and determine the most relevant variables. In total, 123 features were extracted, and 77 of them were selected as important features through the filter method. The average accuracy in the training and test groups of the three methods (SVM, neural network, and CART decision tree) was 97.6%, 96.2% and 95.8%, respectively. The average importance of the variables was then obtained from the three machine learning methods (Figure 3). After using feature selection methods, 14 variables extracted. Finally, 50 rules were extracted by the following mining method for benign and malignant lesions. The rules were evaluated based on lift and confidence values and the opinion of the radiologist.

Discussion

Radiomic features were used in this study to determine the effective rules for differentiating between benign and malignant masses. After extracting the radiomic features and selecting the ones with the highest predictive power of the target variable through various algorithms, 14 extracted features shown in (Figure 3) were considered as specific and effective features for the detection of benign and malignant masses. In total, 10 rules were developed through these features and association rule algorithms for each of the two benign and malignant categories. Out of all the extracted rules, five rules were introduced for each category. In fact, it can be concluded that the tumor margin and Breast Imaging-Reporting and Data System (BI-RADS) assessment, run-length matrix, autoregression, and wavelet are effective and specific features to differentiate between benign and malignant breast masses.

Although several studies have been conducted on radiomic features or clinical features and association rules, a few studies have been carried out simultaneously in both domains [30-33]. In addition, both clinical and image features were used at the same time, which makes better classification models with higher reliability. Furthermore, we used radiomic features in several groups such as Histogram, Gradient, Run Length Matrix, Autoregressive Model, and Co_occurrence Matrix. Another advantage of this study compared to other studies in this field is that it extracted separate rules from characteristics for both benign and malignant groups. Table 6 listed previous studies on breast cancer and association rules. Shah et al. [21] reported that a significant relationship between the texture features extracted from mammogram images and HER-2 expressions. However, the results of this study verified the ability of radiomics to determine the benign and malignant masses through data mining and association rules.

In some studies, such as Ed-daoudy et al., Karabanak et al., and Keyvanpour et al., association rules were used to select important features and reduce dimensions [23, 30, 31]. As it was shown, the power of these algorithms is effective in making rules for classifying and extracting important features. Data mining algorithms were then employed to classify benign and malignant masses. On the other hand, the tumor microenvironment of benign masses is different from malignant, and this leads to the selection of important features in each group. It can be concluded from the obtained results that most of the important features in the malignant group belong to co_occurrence matrix and run length matrix calsses, and in the benign group belong to the run length matrix class. There are several limitations to our study. First, because contouring of lesion sites was done manually and no automated segmentation algorithm was utilized, errors in boundary detection may occur.

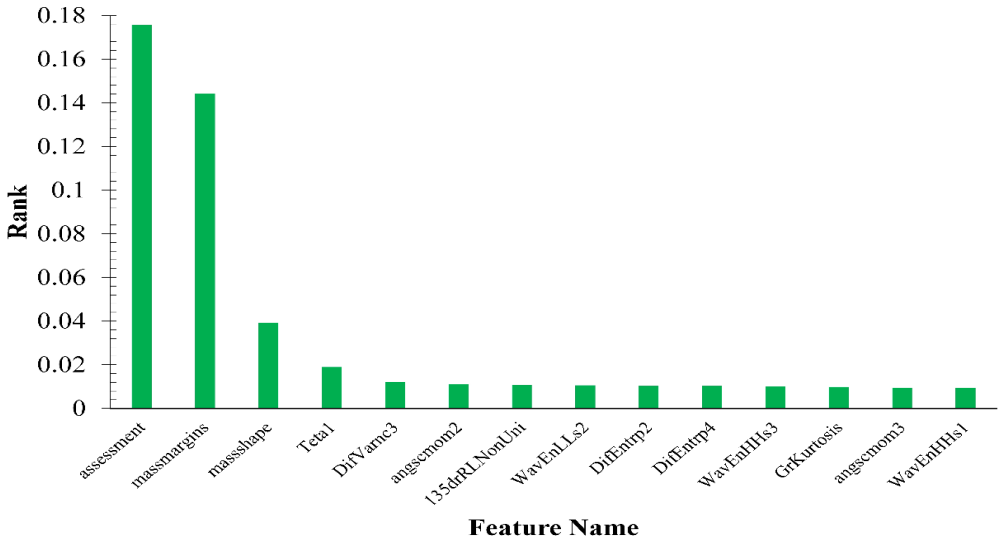


Figure 4. 14 important features after using two stages of feature selection algorithms

Furthermore, we used Mazda software to extract radiomic features, but it attained limited features. If we use other software and applications in future studies, more radiomic features can be obtained and examined. In the end, we employed the DDSM database for feature extraction and modeling, which is recommended to review all the results in local mammography image databases to achieve better outcomes and a modeling generalization. Based on the selection of important features, run length matrix and co_occurrence matrix should be investigated in the studies.

Conclusion

Applied Data mining methods can make a framework to detect a breast cancer in early stage. Also identifying the importance of clinical and imaging features helps physicians make more accurate decisions. The filter and wrapper methods were adopted to select important features (that are essential for rule extraction) in this study. The results helped extract the effective features for distinguishing benign and malignant masses (that can ultimately lead to developing the decision support systems and CAD). Therefore, it is recommended to conduct the following analysis in local databases and compare the outputs with the existing results. In addition, more two-dimensional radiomic features can be used for next projects.

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