Prediction of the progression from mild cognitive impairment to Alzheimer’s disease using a radiomics-integrated model

1. Access to research data
   We obtained T1WI MRI data from the ADNI database, which were acquired with a 1.5 T scanner by a standardized MPRAGE protocol. All T1WI MRI data were obtained with the following parameters: TR/TE/TI, 2400/3/1000 ms, flip angle 8°, 24 cm FOV, 192 × 192 in-plane matrix, and 1.2 mm slice thickness. In addition to MRI measures, non-invasive, inexpensive and easy-to-obtain neuropsychological measures were also employed. All the subjects completed the comprehensive neuropsychological scales, including the Mini-Mental State Examination (MMSE) and Clinical Dementia Rating (CDR), reflecting the overall cognitive status, and the Alzheimer's Disease Assessment Scale (ADAS), reflecting the disease condition. The details of the test procedures and scoring criteria are given in the ADNI General Procedures Manual [1]. In addition, genetic data were included as a demographic variable for further study. To obtain the APOE4 genotype of each subject, blood cells were collected in an EDTA anticoagulant tube (10 ml) and sent to the laboratory at room temperature. The detailed procedure is reported in previous studies where the same standardized procedure was used [2].

2. Image preprocessing
   First, T1WIs were resampled at a single-voxel resolution of 1×1×1 mm³ by linear interpolation. The image greyscale intensity level was then discretized and normalized by downsampling each image into 32 bins to reduce image noise [25]. With such fixed values and numbers of bins, the image grey range was divided into equally spaced intervals. Therefore, the bin size and intensity resolution of the discretized volumes depended on the greyscale value (i.e., four bin sizes for each greyscale) as indicated by Eq. 1

   \[
   \text{BinSize} = \frac{\text{Gray}_{\text{max}} - \text{Gray}_{\text{min}}}{32}
   \]

3. Standardization of data
   Extracted texture features were standardized, which removed the unit limits of the data of each feature and converted it into a dimensionless pure value. This allowed the indexes of different units or orders to be compared and weighted. We used a z-score normalization to make the image intensities fit a standard normal distribution with \(\mu=0\) and \(\sigma=1\), where \(\mu\) is the mean value of the images, and \(\sigma\) is the standard deviation. The normalized values (also called z-scores) of the image intensities (\(x\)) were calculated as follows:
After image z-score normalization, the number of radiomics features arrived at 378 according to QK software. Radiomics features included the histogram (42 features), Haralick (10 features), Formfactor (9 features), Gray-Level Co-occurrence Matrix (126 feature, GLCM), Run length matrix (180 features, RLM) and Gray Level Size Zone Matrix(11 features, GLSZM). The feature details are described in the table below.

| Histogram (42 features) | Haralick (10 features) | Formfactor (9 features) | GLZSM (11 features) | GLCM (126 features) | RLM (180 features) |
|-------------------------|------------------------|------------------------|---------------------|---------------------|-------------------|
| FrequencySize, MaxIntensity, MeanDeviation, MeanValue, MedianIntensity, MinIntensity, RMS, Range, RelativeDeviation, Variance, VolumeCount, VoexValueSum, HistogramEnergy, ImageEntropy, Kurtosis, Skewness, stdDeviation, uniformity, 19 Percentiles, Percentile5-Percetile95 by step 5, Quantile0.025, Quantile0.25, Quantile0.5, Quantile0.75, Quantile0.975 | AngularSecondMoment, HarvEntroy, HaraVariance, contrast, differenceEntropy, differenceVariance, inverseDifferenceMoment, sumAverage, sumEntropy, sumVariance | Compactness1, Compactness2, MaximumDiameter, SphericityDisproportion, Sphericity, SurfaceArea, SurfaceVolumeRatio, VolumeCC, VolumeMM | SizeZoneVariability, HighIntensityEmphasis, HighIntensityLargeAreaEmphasis, HighIntensitySmallAreaEmphasis, IntensityVariability, LargeAreaEmphasis, LowIntensityEmphasis, LowIntensityLargeAreaEmphasis, SmallAreaEmphasis, ZonePercentage, LowIntensitySmallAreaEmphasis | ClusterPraminence, ClusterSize, Correlation, GLCMEntropy, HaralickCorrelation, Inertia, InverseDifferenceMoment, Every feature including 18 Parameters in (0°, 45°, 90° and 135°) directions and (1, 4, 7) displacement vectors | GreyLevelNonuniformity, HighGreyLevelRunEmphasis, LongRunEmphasis, LongRunLowGreyLevelEmphasis, LongRunHighGreyLevelEmphasis, LowGreyLevelRunEmphasis, RunLengthNonuniformity, ShortRunEmphasis, ShortRunHighGreyLevelEmphasis, ShortRunLowGreyLevelEmphasis, Every feature including 18 Parameters in (0°, 45°, 90° and 135°) directions and (1, 4, 7) displacement vectors |

4. Details of Dimension reduction

4.1 The maximum relevance minimum redundancy (mRMR) algorithm

The maximum-relevance selection step aimed to select features that had maximal correlation with the actual disease progression status. The minimum-redundancy step ensured that the selected features had minimal redundancy among one another. By using the mRMR method, the features were ranked according to their relevance-redundancy indexes. Several top-ranking features with high-relevance and low-redundancy were used to select candidate features set.

In this study, a total of 1134 texture features were extracted from each patient, and 581 features were retained through the robustness and reproducibility test. Then the maximum relevance minimum redundancy (mRMR) algorithm was used to select the features. Firstly, we selected 64 features which had the greatest correlation with the outcome of disease progression. Secondly, the correlation was analyzed between these features, and 13 features with the least redundancy were selected. The dimension reduction diagram is shown in Figure S1.
Figure S1. Process of heatmap for dimension reduction. A and B figures shows the heatmap of correlation analysis between features and clinical outcomes in training and test sets, respectively. C and D figures shows the heatmap of redundancy analysis between features and features in training and test sets, respectively. Abscissa represents feature ordering, ordinate represents case sequencing, and color represents feature value size.

4.2 The least absolute shrinkage and selection operator (LASSO) algorithm

LASSO is a powerful algorithm for regression analysis with high dimensional predictors. In our study, the LASSO algorithm was combined with the stepwise logistic regression for radiomics development. We used the LASSO logistic regression model to select the most important ten predictive features and construct a radiomics signature in the training set. Details of the ten features can be found in Table S1.

This algorithm minimizes a log partial likelihood subject to the sum of the absolute values of the parameters bounded by a constant:

\[
\hat{\beta} = \text{argmin}_\beta \ell(\beta) \text{ subject to } \sum |\beta_j| \leq t
\]

where \(\hat{\beta}\) is the obtained parameters, \(\ell(\beta)\) is the log partial likelihood of the logistic regression model, and \(t > 0\) is a constant.
The LASSO algorithm shrinks some coefficients and reduces others to exactly 0 via the absolute constraint. Thus, LASSO is an outstanding method for feature selection by retaining the good features of both subset selection and ridge regression. The “glmnet” package in R statistical software version 3.4.1 was used for LASSO logistic regression model analysis, the specific formula is as follows.

**Radiomics signature calculation formula:**

Rad-score = -0.37136856 - 0.23430359 \times \text{ClusterProminence\_AllDirection\_offset4\_SD\_GM} - 0.61560393 \times \text{GLCMEntropy\_angle135\_offset7\_CSF} + 0.49565032 \times \text{Compactness1\_CSF} - 0.44268102 \times \text{ShortRunEmphasis\_angle135\_offset1\_GM} + 0.41446314 \times \text{ClusterShade\_angle135\_offset1\_CSF} - 0.34949258 \times \text{LongRunLowGreyLevelEmphasis\_AllDirection\_offset7\_SD\_CSF} - 0.26706008 \times \text{GLCMEntropy\_AllDirection\_offset7\_SD\_WM} - 0.14906462 \times \text{ClusterShade\_AllDirection\_offset4\_SD\_GM} + 0.10997672 \times \text{ClusterShade\_angle0\_offset7\_WM} - 0.04968291 \times \text{ShortRunHighGreyLevelEmphasis\_angle135\_offset1\_WM}

Note: “SD” indicate the value reflects the standard deviation among the different directions. GM: grey matter, WM: white matter, CSF: Cerebrospinal fluid

Figure S2 shows the rad score of dataset using the LASSO-logistic algorithm

![Figure S2](#)

**Figure S2.** Score diagrams of the radiomics signature in the training set(A) and test set(B). Red represents stable set and blue represents transform set. A score greater than 0 indicates transform set, and a score less than 0 indicates stable set.

| Table S1. The classification and calculation formula of radiomics features |
|-----------------------------|-----------------|-----------------|------------------|
| Category | Feature | Formula | Describe |
|-----------------------------|-----------------|-----------------|------------------|
Cluster Prominence is a measure of asymmetry of a given distribution, high values of this feature indicate that the symmetry of the image is low, in medical imaging low values of cluster prominence represent a smaller peak for the image grey level value and usually the grey level difference between the forms is small.

Cluster Shade in clustered shading, we group similar view samples according to their position and, optionally, normal into clusters.

Entropy is a measure of randomness of intensity image. Entropy shows the amount of information of the image that is needed for the image compression. Entropy measures the loss of information or message in a transmitted signal and also measures the image information.

The grey level run-length matrix (RLM) $\Pr(i, j | \theta)$ is defined as the numbers of runs with pixels of gray level $i$ and run length $j$ for a given direction $\theta$. RLMs is generated for each sample image segment having directions ($0^\circ, 45^\circ, 90^\circ & 135^\circ$).
Form Factor Parameters  Compactness1_CSF

\[ \frac{V}{\sqrt[3]{\pi A^2}} \]

Let in the following definitions \( V \) denote the volume and \( A \) the surface area of the volume of interest

Reference

[1]. ADNI, “ADNI General Procedures Manual,” [Online]. Available: https://adni.loni.usc.edu/wpcontent/uploads/2010/09/ADNI_GeneralProceduresManual.pdf. [Accessed 23 June 2015].

[2]. Saykin AJ, Shen L, Foroud TM, Potkin SG, Swaminathan S, Kim S, et al. “Alzheimer's Disease Neuroimaging Initiative biomarkers as quantitative phenotypes: Genetics core aims, progress, and plans,” *Alzheimer's & dementia : the journal of the Alzheimer's Association*, vol. 6, no. 3, pp. 265-73, May, 2010.