Supplementary

Appendix 1

Informed consent process

This study was a retrospective study and the medical records or biological specimens used were obtained from previous clinical treatment. Exemption from informed consent will not adversely affect the rights or health of the subjects.

Appendix 2

Chest CT Scanning and Image Acquisition

Chest high resolution CT scans were obtained during patients' full inspiration using the Somatom Definition AS (Siemens Medical System, Germany) or brilliance 40 (Philips Medical Systems, Netherlands) at 120 KVp tube energy and 200 mAs effective dose. All CT images were reconstructed using a medium sharp reconstruction algorithm with a slice thickness of 1 mm with 0.7 mm increment, and the size of CT images is 512×512 pixels. The identified CT scans were downloaded from the Picture Archiving and Communication Systems. The nodules types were independently assessed by three researchers (S.S., X.M., H.H.). The disagreement was resolved by the group discussion with a senior radiologist (Y.S.).

Appendix 3

Radiomics feature Selection and Radiomics Score Calculation

Totally, 1,317 radiomics features were extracted consisting of 7 classes: (a) first order statistics (n=252); (b) shape (n=14); (c) Gray level co-occurrence matrix (n=336); (d) Gray level dependence matrix (n=197); (e) Gray level run length matrix (n=224); (f) Gray level size zone matrix (n=224); (g) Neighboring gray tone difference matrix (n=70). To ensure stability and reproducibility of the radiomics features, the mRMR method was first applied to rank each feature depending on its relevance with the malignant status of nodules in the training set, and redundancy with other radiomics features. The top 100 most significant features were selected as candidate for LASSO analysis. By introducing a tuning parameter to penalize the coefficient of variables that entered into the regression model, LASSO aimed to reduce the possibility of overfitting. With the increase in the tuning parameter (λ), the absolute values of variable coefficients were reduced toward zero, and less variables were then selected. The area under the curve (AUC) was used as the criteria of model performance, and the model with the maximum AUC was selected. The computing algorithms could be found at www.radiomics.io and the image biomarker standardization initiative (IBSI) presented a document to standardize the nomenclature and definitions of radiomics features. The radiomics score was calculated based on the following formula:

$$\text{Radiomics score} = \sum_{i=1}^{N} coef_i X_i$$

Where N represent the number of the selected feature, $coef_i$ is the value of non-zero coefficient of the i_{th} selected feature, X_i is the value of the i_{th} selected feature.

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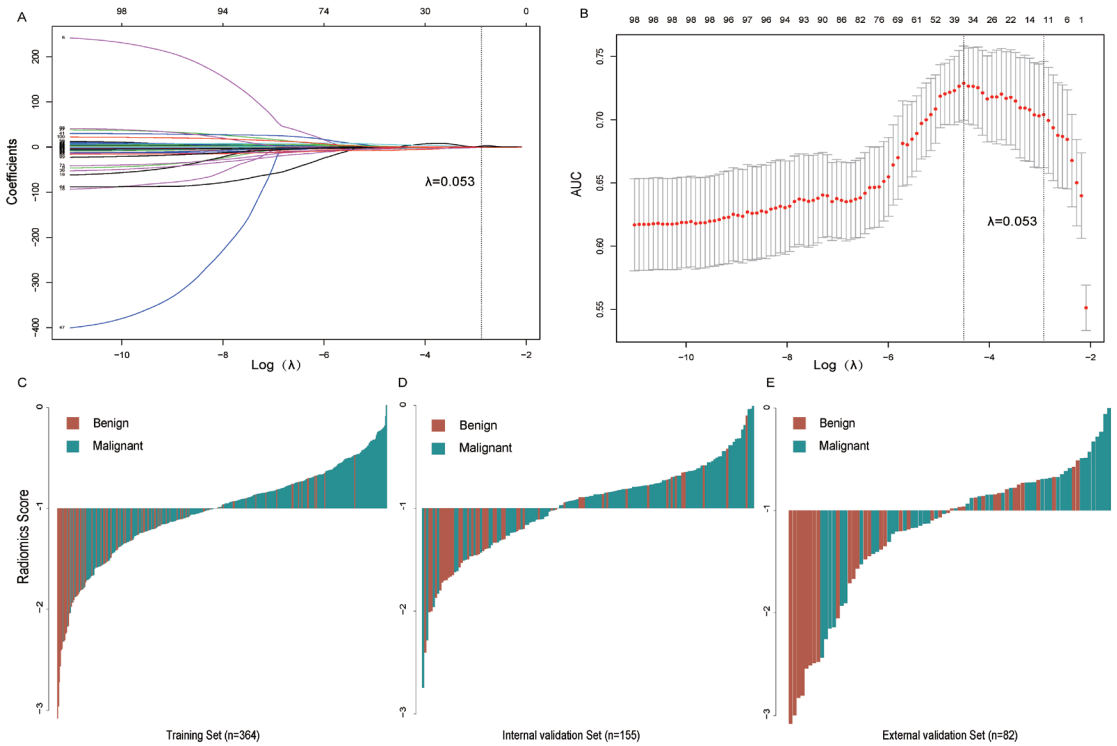

Figure S1 Radiomics features selection using the LASSO logistic regression model. (A) LASSO coefficient profiles of the 100 candidate radiomics features. Optimal λ was identified used 10-fold cross validation and the minimum criterion, and a λ value of 0.053 was identified with 12 selected radiomics features; (B) AUC from the LASSO regression cross-validation procedure was plotted against log(λ); (C,D) The waterfall plot of the training set (C), internal validation set (D), and external validation set (E) to visualize the distribution of the radiomics score and the benign and malignant state of the IPSNs. LASSO, least absolute shrinkage and selection operator; AUC, area under the curve; IPSNs, indeterminate lung solid nodules.

Table S1 The detailed list of selected radiomics feature in the LASSO regression analysis

Imaging filtering	Feature class	Radiomics feature	Coefficient
Square root	First order	Total energy	3.97E–11
Logarithm	GLCM	Correlation	0.2003277
Wavelet. HLH	GLCM	Imc1	1.846807
Wavelet. LHL	GLCM	MCC	–0.557705
Wavelet. HLH	GLCM	MCC	–0.7074729
Wavelet. LHL	GLCM	Imc2	–0.1703806
Gradient	GLDM	Small dependence high gray level emphasis	–0.006238725
Original	GLDM	Dependence entropy	0.03476835
Wavelet. HHH	GLSZM	Gray level nonuniformity	0.0006610718
Wavelet. LHL	NGTDM	Strength	–0.01518317
Square	NGTDM	Strength	–0.2240264
Gradient	NGTDM	Contrast	–0.6954117

LASSO, least absolute shrinkage and selection operator; GLCM, gray level cooccurrence matrix; GLDM, gray level dependence matrix; GLSZM, gray level size zone matrix; NGTDM, Neighboring gray tone difference matrix.

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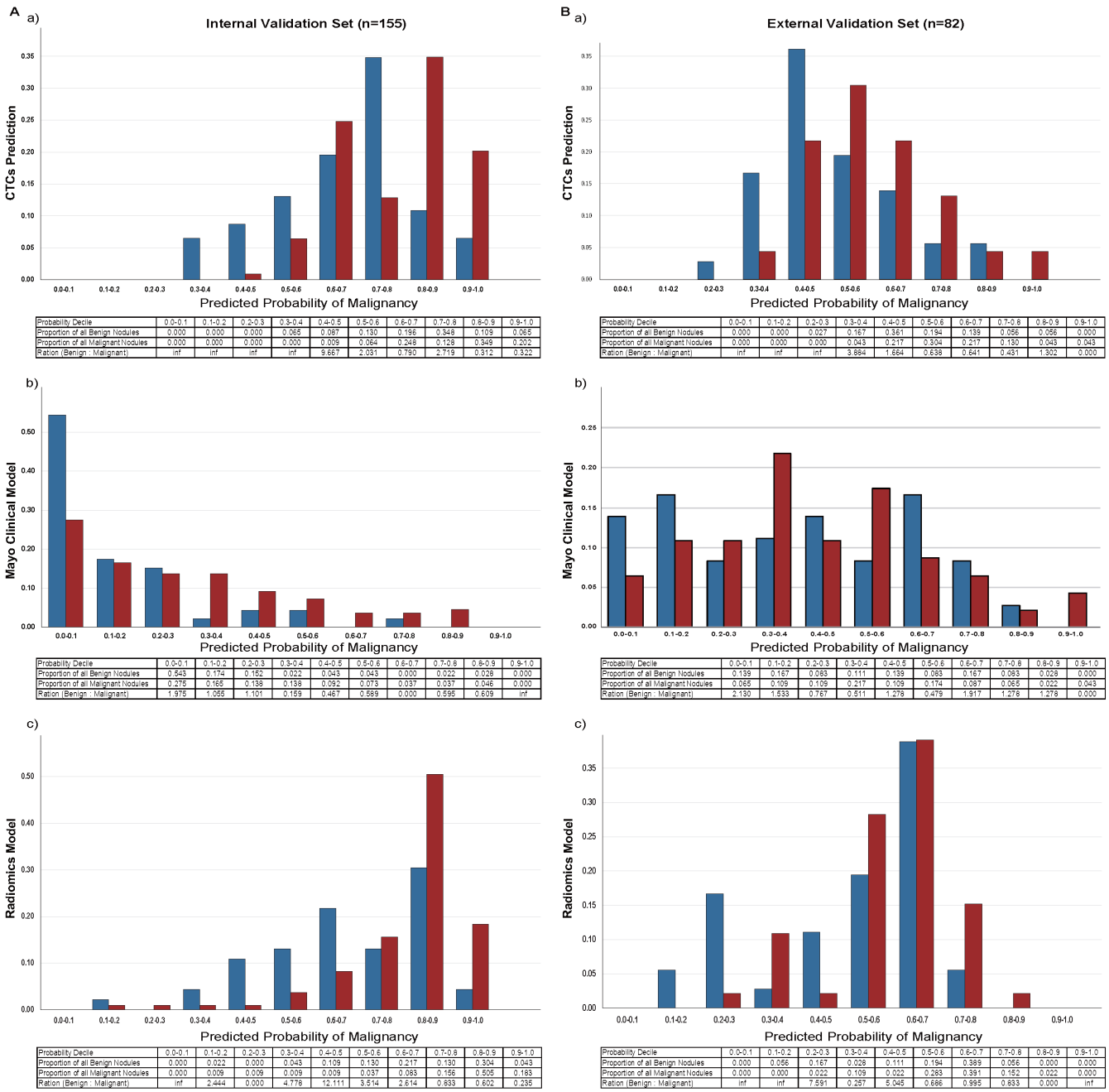

Figure S2 Proportion of malignant and benign nodules at different probability decile by CTCs test prediction (a), Mayo clinical model (b) and radiomics model (c) in the internal validation set (A), in the external validation set (B). CTCs, circulating tumor cells.

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Table S2 Performance metric of integrated risk models in training set and subset with different nodules size

Performance	Integrated model	Mayo clinical model	Radiomics	CTCs test
Nodules with size ranging from 5–10 mm				
Training set (n=364)				
Sensitivity (95% CI)	0.92 (0.88–0.95)	0.31 (0.26–0.37)	0.99 (0.96–1.00)	0.99 (0.96–1.00)
Specificity (95% CI)	0.47 (0.36–0.59)	0.86 (0.77–0.93)	0.17 (0.10–0.27)	0.16 (0.09–0.26)
PPV (95% CI)	0.86 (0.82–0.90)	0.89 (0.81–0.94)	0.81 (0.76–0.85)	0.81 (0.76–0.85)
NPV (95% CI)	0.62 (0.49–0.74)	0.27 (0.21–0.32)	0.78 (0.52–0.94)	0.76 (0.50–0.93)
Accuracy (95% CI)	0.82 (0.78–0.86)	0.44 (0.39–0.49)	0.80 (0.76–0.84)	0.80 (0.76–0.84)
Internal validation set (n=155)				
Sensitivity (95% CI)	0.97 (0.92–0.99)	0.85 (0.77–0.91)	0.94 (0.88–0.98)	0.99 (0.95–1.00)
Specificity (95% CI)	0.33 (0.20–0.48)	0.28 (0.16–0.44)	0.26 (0.15–0.41)	0.15 (0.06–0.29)
PPV (95% CI)	0.77 (0.69–0.84)	0.74 (0.65–0.81)	0.75 (0.67–0.82)	0.73 (0.66–0.80)
NPV (95% CI)	0.83 (0.59–0.96)	0.45 (0.27–0.64)	0.67 (0.41–0.86)	0.88 (0.47–1.00)
Accuracy (95% CI)	0.78 (0.71–0.84)	0.70 (0.62–0.77)	0.70 (0.62–0.77)	0.74 (0.67–0.81)
External validation set (n=82)				
Sensitivity (95% CI)	0.74 (0.59–0.86)	0.39 (0.25–0.55)	0.85 (0.71–0.94)	0.74 (0.59–0.86)
Specificity (95% CI)	0.67 (0.49–0.81)	0.64 (0.46–0.79)	0.36 (0.21–0.54)	0.56 (0.38–0.72)
PPV (95% CI)	0.74 (0.59–0.86)	0.58 (0.39–0.75)	0.63 (0.50–0.75)	0.68 (0.53–0.80)
NPV (95% CI)	0.67 (0.49–0.81)	0.45 (0.31–0.60)	0.65 (0.41–0.85)	0.62 (0.44–0.79)
Accuracy (95% CI)	0.71 (0.60–0.80)	0.50 (0.39–0.61)	0.63 (0.52–0.74)	0.66 (0.55–0.76)
Nodules with size ranging from 10–20 mm				
Internal validation set (n=81)				
Sensitivity (95% CI)	0.96 (0.87–1.00)	0.02 (0.00–0.10)	0.96 (0.87–1.00)	0.98 (0.90–1.00)
Specificity (95% CI)	0.34 (0.18–0.54)	1.00 (0.88–1.00)	0.17 (0.06–0.36)	0.07 (0.01–0.23)
PPV (95% CI)	0.72 (0.60–0.83)	1.00 (0.02–1.00)	0.68 (0.56–0.78)	0.65 (0.54–0.76)
NPV (95% CI)	0.83 (0.52–0.98)	0.36 (0.26–0.48)	0.71 (0.29–0.96)	0.67 (0.09–0.99)
Accuracy (95% CI)	0.74 (0.63–0.83)	0.37 (0.27–0.48)	0.68 (0.57–0.78)	0.65 (0.54–0.76)
External validation set (n=34)				
Sensitivity (95% CI)	0.60 (0.36–0.81)	0.05 (0.00–0.25)	0.70 (0.46–0.88)	0.75 (0.51–0.91)
Specificity (95% CI)	0.64 (0.35–0.87)	0.93 (0.66–1.00)	0.57 (0.29–0.82)	0.36 (0.13–0.65)
PPV (95% CI)	0.71 (0.44–0.90)	0.50 (0.01–0.99)	0.70 (0.46–0.88)	0.62 (0.41–0.81)
NPV (95% CI)	0.53 (0.28–0.77)	0.41 (0.24–0.59)	0.57 (0.29–0.82)	0.50 (0.19–0.81)
Accuracy (95% CI)	0.62 (0.44–0.78)	0.41 (0.25–0.59)	0.65 (0.46–0.80)	0.59 (0.41–0.75)

Table S2 *(continued)*

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Table S2 *(continued)*

Performance	Integrated model	Mayo clinical model	Radiomics	CTCs test
Nodules with size ranging from 20–30 mm				
Internal validation set (n=62)				
Sensitivity (95% CI)	1.00 (0.93–1.00)	0.38 (0.25–0.53)	0.98 (0.90–1.00)	1.00 (0.93–1.00)
Specificity (95% CI)	0.10 (0.00–0.45)	0.70 (0.35–0.93)	0.00 (0.00–0.31)	0.30 (0.07–0.65)
PPV (95% CI)	0.85 (0.74–0.93)	0.87 (0.66–0.97)	0.84 (0.72–0.92)	0.88 (0.77–0.95)
NPV (95% CI)	1.00 (0.02–1.00)	0.18 (0.08–0.34)	0.00 (0.00–0.97)	1.00 (0.29–1.00)
Accuracy (95% CI)	0.85 (0.74–0.93)	0.44 (0.31–0.57)	0.82 (0.70–0.91)	0.89 (0.78–0.95)
External validation set (n=40)				
Sensitivity (95% CI)	0.91 (0.71–0.99)	0.68 (0.45–0.86)	1.00 (0.85–1.00)	0.73 (0.50–0.89)
Specificity (95% CI)	0.61 (0.36–0.83)	0.39 (0.17–0.64)	0.11 (0.01–0.35)	0.72 (0.47–0.90)
PPV (95% CI)	0.74 (0.54–0.89)	0.58 (0.37–0.77)	0.58 (0.41–0.74)	0.76 (0.53–0.92)
NPV (95% CI)	0.85 (0.55–0.98)	0.50 (0.23–0.77)	1.00 (0.16–1.00)	0.68 (0.43–0.87)
Accuracy (95% CI)	0.78 (0.62–0.89)	0.55 (0.38–0.71)	0.60 (0.43–0.75)	0.72 (0.56–0.85)

PPV, positive predictive value; NPV, negative predictive value; CI, confidence interval.

Table S3 Net reclassification index (NRI) analysis provided by the integrated model in comparison with other three models for different sets

Model	Estimate	Stand Error	Lower	Upper
Internal validation set				
vs. CTCs	0.156	0.086	–0.013	0.324
vs. radiomics	0.161	0.072	0.018	0.303
vs. Mayo clinical model	0.171	0.088	0.003	0.349
External validation set				
vs. CTCs	0.111	0.122	–0.125	0.348
vs. radiomics	0.197	0.108	–0.009	0.411
vs. Mayo clinical model	0.376	0.144	0.095	0.658
Nodules with different size				
Internal validation set				
5–10 mm				
vs. CTCs	0.243	0.096	0.051	0.429
vs. radiomics	0.167	0.091	–0.013	0.350
vs. Mayo clinical model	0.319	0.090	0.141	0.496
10–20 mm				
vs. CTCs	0.257	0.110	0.040	0.469
vs. radiomics	0.172	0.096	–0.009	0.365
vs. Mayo clinical model	0.287	0.095	0.106	0.480

Table S3 *(continued)*

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Table S3 *(continued)*

Model	Estimate	Stand Error	Lower	Upper
20–30 mm				
vs. CTCs	–0.200	0.133	–0.500	0.000
vs. radiomics	0.119	0.102	0.000	0.352
vs. Mayo clinical model	0.015	0.231	–0.397	0.512
External validation set				
5-10 mm				
vs. CTCs	0.171	0.190	–0.201	0.540
vs. radiomics	–0.078	0.155	–0.377	0.231
vs. Mayo clinical model	0.265	0.186	–0.111	0.628
10–20 mm				
vs. CTCs	0.136	0.207	–0.270	0.538
vs. radiomics	–0.029	0.175	–0.361	0.314
vs. Mayo clinical model	0.264	0.211	–0.152	0.673
20–30 mm				
vs. CTCs	0.071	0.138	–0.200	0.341
vs. radiomics	0.409	0.135	0.141	0.667
vs. Mayo clinical model	0.449	0.214	0.027	0.864
Nodules with risk probability ranging from 5% to 65% identified by Mayo clinical model				
Internal validation set				
vs. CTCs	0.082	0.105	–0.124	0.288
vs. radiomics	0.156	0.084	0.000	0.324
vs. Mayo clinical model	0.187	0.106	–0.010	0.409
External validation set				
vs. CTCs	0.115	0.140	–0.158	0.389
vs. radiomics	0.139	0.123	–0.103	0.382
vs. Mayo clinical model	0.365	0.164	0.045	0.690

CTCs, circulating tumor cells.

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