Appendix 1

Data preprocessing and model development

Following the semi-automatic annotation system workflow (41), the model is highly sensitive in detecting nodules in computed tomography (CT) images, which results in multiple lung nodule candidates. These candidates are then reviewed by multiple professional doctors, who annotate the nodules identified as having spread through air spaces (STAS).

For image preprocessing, we resampled the three-dimensional (3D) CT images using a tri-linear interpolation algorithm to achieve a voxel size of 1 mm × 1 mm × 1 mm. Based on the annotated nodule information, we cropped 16×128×128 cubes from the normalized 3D CT images for each patch. To optimize the final receptive field size, we applied both center cropping and random center cropping, reducing it to 64×64 pixels.

The CT values of each scan were normalized to a range of [0, 255] using a window range of [–1,200 HU, 600 HU]. These grayscale values were then mapped to the range of [–1, 1] using the transformation $\frac{I_{3D\_patch}-128}{128}$.

The first branch of the model employed a U-Net (42) segmentation network to separate the solid and ground-glass components into masks. Using these masks, we calculated the mean μ_m and covariance σ_m of the consolidation-to-tumor ratio (CTR) within the patches. Based on the mean and variance, we obtain the variable m as the output of the clinical prior branch through a Gaussian distribution.

The second branch used ResNet-50 (43) as the backbone. To adapt to the variational inference process, the encoder output consisted of two channels: the first channel represented the mean μ_n of the STAS-related feature in the patches, and the second channel represented the covariance σ_n of the relevant features. The variable n for the texture branch was similarly obtained through Gaussian sampling based on the mean and variance.

However, directly computing the united distribution through both the texture branch and the clinical prior branch is computationally expensive. To rectify the weakness, we employed a variational Bayesian framework to model the distribution explicitly. During model training, we minimized the distance between the predicted value pred and the label y using the cross-entropy loss function L_{ce}.

References

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 https://dx.doi.org/10.21037/tlcr-24-890

Table S1 Baseline characteristics of the training, validation, and test cohorts

Variables	Training cohort (n=961)	Validation cohort (n=275)	Test cohort (n=138)	P
Demographic and clinical features				
Age (years)	58.00 [51.00, 66.00]	58.00 [51.00, 66.50]	56.00 [51.00, 65.75]	0.74
Gender				0.54
Male	378 (39.3)	115 (41.8)	50 (36.2)	
Female	583 (60.7)	160 (58.2)	88 (63.8)	
Smoking history				0.33
No	755 (78.6)	219 (79.6)	116 (84.1)	
Yes	206 (21.4)	56 (20.4)	22 (15.9)	
Clinical T stage				0.24
T1a	119 (12.4)	40 (14.5)	16 (11.6)	
T1b	608 (63.3)	174 (63.3)	78 (56.5)	
T1c	234 (24.3)	61 (22.2)	44 (31.9)	
Surgical procedure				0.29
Wedge resection	117 (12.2)	29 (10.5)	9 (6.5)	
Segmentectomy	316 (32.9)	93 (33.8)	43 (31.2)	
Lobectomy	528 (54.9)	153 (55.6)	86 (62.3)	
Tumor location				0.97
Left upper lobe	256 (26.6)	73 (26.5)	38 (27.5)	
Left lower lobe	145 (15.1)	41 (14.9)	18 (13.0)	
Right upper lobe	347 (36.1)	99 (36.0)	46 (33.3)	
Right middle lobe	153 (15.9)	41 (14.9)	25 (18.1)	
Right lower lobe	60 (6.2)	21 (7.6)	11 (8.0)	
CT features				
Tumor size (cm)	1.60 [1.20, 2.00]	1.50 [1.20, 2.00]	1.70 [1.30, 2.20]	0.11
CTR[†]	0.38 [0.20, 0.67]	0.39 [0.20, 0.60]	0.38 [0.21, 0.68]	0.83
Lobulated sign				0.95
Negative	763 (79.4)	217 (78.9)	108 (78.3)	
Positive	198 (20.6)	58 (21.1)	30 (21.7)	
Spicules sign				0.57
Negative	720 (74.9)	208 (75.6)	98 (71.0)	
Positive	241 (25.1)	67 (24.4)	40 (29.0)	
Vessel concentrate sign				0.86
Negative	943 (98.1)	271 (98.5)	136 (98.6)	
Positive	18 (1.9)	4 (1.5)	2 (1.4)	

Table S1 (*continued*)

https://dx.doi.org/10.21037/tlcr-24-890

Table S1 (*continued*)

Variables	Training cohort (n=961)	Validation cohort (n=275)	Test cohort (n=138)	P
Pleural indentation sign				0.98
Negative	781 (81.3)	225 (81.8)	112 (81.2)	
Positive	180 (18.7)	50 (18.2)	26 (18.8)	
Vacuolar sign				0.69
Negative	821 (85.4)	234 (85.1)	114 (82.6)	
Positive	140 (14.6)	41 (14.9)	24 (17.4)	
Air bronchogram				0.35
Negative	906 (94.3)	258 (93.8)	134 (97.1)	
Positive	55 (5.7)	17 (6.2)	4 (2.9)	
Pathological features				
STAS status				0.89
Negative	814 (84.7)	234 (85.1)	119 (86.2)	
Positive	147 (15.3)	41 (14.9)	19 (13.8)	
Predominant subtype				0.42
Lepidic	483 (50.3)	135 (49.1)	67 (48.6)	
Acinar	398 (41.4)	115 (41.8)	56 (40.6)	
Papillary	57 (5.9)	17 (6.2)	12 (8.7)	
Micropapillary	2 (0.2)	2 (0.7)	0 (0.0)	
Solid	19 (2.0)	3 (1.1)	3 (2.2)	
Complex glandular pattern	2 (0.2)	3 (1.1)	0 (0.0)	
High-grade histological type[‡]				0.52
Negative	812 (84.5)	240 (87.3)	117 (84.8)	
Positive	149 (15.5)	35 (12.7)	21 (15.2)	
Differentiation grade				0.85
Poor	87 (9.1)	26 (9.5)	11 (8.0)	
Middle	637 (66.3)	181 (65.8)	98 (71.0)	
High	237 (24.7)	68 (24.7)	29 (21.0)	
Pathologic stage				0.28
IA1	125 (13.0)	41 (14.9)	17 (12.3)	
IA2	602 (62.6)	172 (62.5)	77 (55.8)	
IA3	234 (24.3)	62 (22.5)	44 (31.9)	

Data are presented as median [IQR] or n (%). [†], CTR is calculated by the deep learning method we designed; [‡], high-grade histological type contains at least one of the following histological types: micropapillary, solid, complex glandular pattern, and cribriform pattern. CT, computed tomography; CTR, consolidation-to-tumor ratio; IQR, interquartile range; STAS, spread through air spaces.

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