Correlation between PD-L1 expression and radiomic features in early-stage lung adenocarcinomas manifesting as ground-glass nodules

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Background: Immunotherapy might be a promising auxiliary or alternative systemic treatment for early-stage lung adenocarcinomas manifesting as ground-glass nodules (GGNs). This study intended to investigate the PD-L1 expression in these patients, and to explore the non-invasive prediction model of PD-L1 expression based on radiomics.

Methods: We retrospectively analyzed the PD-L1 expression of patients with postoperative pathological diagnosis of lung adenocarcinomas and with imaging manifestation of GGNs, and divided patients into positive group and negative group according to whether PD-L1 expression ≥1%. Then, CT-based radiomic features were extracted semi-automatically, and feature dimensions were reduced by univariate analysis and LASSO in the randomly selected training cohort (70%). Finally, we used logistic regression algorithm to establish the radiomic models and the clinical-radiomic combined models for PD-L1 expression prediction, and evaluated the prediction efficiency of the models with the receiver operating characteristic (ROC) curves.

Results: A total of 839 “GGN-like lung adenocarcinoma” patients were included, of which 226 (26.9%) showed positive PD-L1 expression. 779 radiomic features were extracted, and 9 of them were found to be highly correlated with PD-L1 expression. The area under the curve (AUC) values of the radiomic models were 0.653 and 0.583 in the training cohort and test cohort respectively. After adding clinically significant and statistically significant clinical features, the efficacy of the combined model was slightly improved, and the AUC values were 0.693 and 0.598 respectively.
**Conclusions:** GGN-like lung adenocarcinoma had a fairly high positive PD-L1 expression rate. Radiomics was a hopeful noninvasive method for predicting PD-L1 expression, with better predictive efficacy in combination with clinical features.

**KEYWORDS**

PD-L1, radiomics, prediction model, ground-glass nodules, lung adenocarcinoma

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**Introduction**

Ground-glass nodules (GGNs) refer to the shadows with similar density of ground glass but not covering blood vessels and bronchial structures on computed tomography (CT) images. Lung cancer, tuberculosis, pneumonia and other lung diseases can all present such non-specific imaging manifestations. GGN bears the increased incidence with the popularization of low-dose CT screening and a significantly higher degree of malignancy than solid nodule, and the most common type of malignant GGN is early-stage lung adenocarcinoma (1). It’s reported that 95.5% stage 0/IA lung cancer patients detected by health screening were manifested as GGNs and 98.9% diagnosed as adenocarcinomas (2). Surgery is the main treatment strategy for early-stage lung cancer, whereas the 5-year recurrence-free survival (RFS) rate is about 85.5%-87.6% in these presented as mixed ground-glass nodules (mGGNs); in addition, treatment option for multifocal GGNs is limited in consideration of the nodule characteristics and the patient’s health condition, which lower the feasibility of curative surgery (3–5). Therefore, with a view to reduce recurrence risk in surgery patients and provide more treatment options for inoperable patients, “GGN-like lung adenocarcinoma” requires systemic therapy as an auxiliary or alternative to achieve individualized treatment.

Immune checkpoint inhibitors (ICIs) targeting programmed cell death-1/programmed cell death-ligand 1 (PD-1/PD-L1) pathway have been widely used in advanced non-small cell lung cancer (NSCLC) for the enduring efficacy and better safety, and the PD-L1 expression is approved by the Food and Drug Administration (FDA) as a predictive biomarker of ICI efficacy (6–8). Recently, several clinical trials have demonstrated that early-stage lung adenocarcinoma patients can benefit from neoadjuvant immunotherapy (9–14). Besides, studies also elucidated that PD-L1≥1% was positively associated with the major pathological response (MFR), pathological complete response (PCR), 3-year overall survival (OS) and disease-free survival (DFS) rates in neoadjuvant immunotherapy (15, 16). Therefore, PD-1/PD-L1 inhibitors are expected to be a promising remedy for early-stage lung adenocarcinoma patients and PD-L1 expression is likely to be the best predictive biomarker or one of the best biomarker combinations for predicting efficacy in these patients. Currently, PD-L1 expression in tumor tissues is mainly detected in surgical or biopsy specimens. Nevertheless, for early-stage lung adenocarcinoma patients who have not yet or cannot receive surgical treatment and whose biopsy specimens are difficult to obtain due to the size and location of GGNs, the PD-L1 detection is a bottleneck in the ICI treatment.

Radiomics means the process of manually or automatically extracting hundreds of quantitative features from medical images, reducing the dimensionality of the features, and ultimately using artificial intelligence methods such as machine learning or deep learning to build models relevant to clinical problems. Due to the panoramic analysis and dynamic monitoring of lesions, radiomics is widely used in precision medicine, especially in diagnosis, staging, treatment and prognosis of malignant tumors (17, 18). In the field of lung cancer, radiomics based on CT, positron emission tomography (PET)/CT and even magnetic resonance imaging (MRI) can not only contribute to the detection and identification of pulmonary nodules, the judgment of metastasis, the monitoring of treatment response and adverse events, and the assessment of prognosis, but also make some achievements in the prediction of mutated genes, immune microenvironment and even molecular markers (19–23). These studies indicated that microscopic changes at the histological and even molecular levels were correlated with macroscopic changes in imaging features. PD-1/PD-L1 pathway is an important immune checkpoint in lung adenocarcinoma, and abnormal expression of PD-L1 molecules would affect the tumor microenvironment and then change the overall morphology of the tumor, which can be captured by sophisticated imaging analysis. Several studies have focused on the noninvasive prediction of PD-L1 expression and have developed promising CT or PET/CT radiomic models; however, the sample size of these literatures was small, and most of the subjects were advanced NSCLC patients (24–26). So far, noninvasive prediction of PD-L1 expression in early-stage lung adenocarcinoma remains for further research. Considering chest CT is the most common clinical screening and follow-up tool for lung nodules, this study intends to analyze the PD-L1 expression...
in GGN-like lung adenocarcinomas, and explore the predicting impact of CT-based radiomic features on PD-L1 expression, thus facilitate the immunotherapy for these patients and contribute to precision medicine for early-stage lung adenocarcinoma.

Materials and methods

Patients

We retrospectively analyzed the clinicopathologic and CT imaging data of lung adenocarcinoma patients pathologically confirmed by resection surgery in the Department of Thoracic Surgery, Chinese PLA General Hospital from December 2018 to December 2020. Inclusion criteria: ① Chest CT examination is performed within 1 month before surgery, and the CT image of the lesion is presented as GGN; ② Postoperative pathological diagnosis is lung adenocarcinoma; ③ PD-L1 test result of surgical specimen is available. Exclusion criteria: ① Solid nodule; ② Preoperative nonsurgical treatment of lung adenocarcinoma or needle biopsy was performed; ③ CT image is unclear. A total of 839 patients were enrolled, including 280 males and 559 females. Their age ranged from 18 to 84 years, with an average of 55.7 ± 10.2 years. All patients were divided into negative group (n=613) and positive group (n=226) based on PD-L1 expression.

PD-L1 expression

PD-L1 expression was detected on formalin-fixed paraffin-embedded surgical specimen, and immunohistochemical test was performed with PD-L1 IHC 22C3 pharmDx Kit (Dako Omnis) (Agilent Cat# GE00621-2, RRID: AB_2833074). PD-L1 expression level was measured by tumor proportion score (TPS) and positive PD-L1 expression was defined as TPS ≥ 1%.

Clinicopathologic information

By searching medical records, the following information was collected: gender, age, body mass index (BMI), malignant tumor history, lung benign disease history (including chronic bronchitis, chronic obstructive pulmonary disease, bronchial asthma, tuberculosis), smoking history, family lung cancer history and other family malignant tumor history. Fasting venous blood was drawn within one week before operation for determination of white blood cell count (WBC), neutrophil percentage (NE), lymphocytes percentage (LP), carcinoembryonic antigen (CEA) and cytokeratin-19 fragment (CYFRA21-1), among which the white blood cell count with its categorical count was taken by the blood analyzer (SysmexXN9000, Sysmex), CEA and CYFRA21-1 level were determined by electrochemiluminescence (Roche, Cobas e602).

According to the World Health Organization (WHO) Classification of Thoracic Neoplasms (Version 5, 2011), the pathological types of lung adenocarcinoma include precursor glandular lesions (PGL) and adenocarcinoma (AC). According to postoperative pathological results, none of the patients had lymph node infiltration, and their pathological staging was stage IA or IB.

CT scanning protocols

Chest CT examination was performed on Brilliance ict (Phillips Medical Systems). Scanning parameters: tube voltage 120kV, tube current 110mA, pitch 1, reconstruction layer thickness 1.00mm, layer spacing 1.00mm, reconstruction kernel iDose 3.

Determination of CT morphological features

CT morphological features were evaluated by a radiologist with 5 years of experience and reviewed by a senior radiologist with 13 years of experience. Following features of GGNs were identified:
① Type: pure ground-glass nodule (pGGN) and mGGN; ② Diameter: the longest diameter of the nodule in the transverse maximum section; ③ Margin: clear or fuzzy; ④ Special signs: lobulation sign, spiculation sign, vacuole sign, pleural pull/indentation sign, vascular cluster sign, abnormal air bronchial sign.

Extraction of radiomic and quantitative features

The entire workflow was done on the FDA-approved FACT Medical Imaging System (Dexin Medical Imaging Technology Company). Firstly, CT images in Digital Imaging and Communications in Medicine (DICOM) format were imported into the workstation, and images with thickness of 1.00mm were selected to enter the automatic processing mode of pulmonary nodules, including nodule recognition and region of interest (ROI) delineation. Then, under a fixed pulmonary window (window width 1500HU, window position -500HU), a respiratory physician with 5 years of clinical experience identified the target nodule and modified the ROI boundary layer by layer without knowing the patient’s pathological diagnosis. The principle of manual segmentation was that the ROI should cover as much of the nodule component area as possible and avoid surrounding vascular and bronchial structures. Next, a senior radiologist confirmed the ROI segmentation results of 50 randomly selected nodules. Eventually, the following parameters were automatically calculated and exported: 779 radiomic features (14 shape features, 24 first order features, 61 texture features and 680 first order texture features, 60 second order texture features, 52 architectural analysis features).
wavelet features) and 15 quantitative features (volume, three-dimensional (3D) maximum diameter, 3D mean diameter, mean density, non-consolidation ratio, mass, surface area, pleural adhesion area, pleural proportion, fat proportion, surface area/volume (SA/V), calcification volume, mean vascular density, irregularity, and void volume ratio). In addition, we calculated inter-class correlation coefficient (ICC) to test the stability of radiomic features. The effect of different physician ROI segmentation levels on the stability of radiomic features was defined as inter-observer consistency, while the effect of ROI segmentation levels of the same physician at different time periods on the stability of radiomic features was defined as intra-observer consistency. Firstly, ROI segmentation was performed on 50 randomly selected CT images by WJS and MHZ; then the radiomic features were extracted for consistency analysis; lastly, radiomic features with ICC less than 0.75 were considered as inter-observer unstable features. After an interval of 1 month, WJS again performed ROI segmentation on previous 50 CT images, extracted radiomic features and performed consistency analysis. Radiomic features with ICC less than 0.75 were also considered as intra-observer unstable features.

**Statistical analysis and model building**

Data analysis was performed in IBM SPSS Statistics software (V26, RRID: SCR_016479). Continuous variables were compared using Mann-Whitney U test, and categorical variables using Chi-square or Fisher’s exact test. Missing values in laboratory results were supplemented by conditional mean completer. Variables with a P value less than 0.05 were considered statistically significant. R software (version 4.0.3) was used to build the model. The following R packages of psych, pROC, glmnet and e1071 were used during the establishment and evaluation process of models. The establishment process of radiomic model, clinical-radiomic combined model and quantitative model was shown in Figure 1. Radiomic features with ICC ≥ 0.75 were considered stable.

**Results**

**Clinicopathologic characteristics of the patients**

A total of 839 GGN-like lung adenocarcinoma patients were included, of which 226 (26.9%) patients showed positive PD-L1 expression, and 5 (0.6%) patients showed high PD-L1 expression (TPS ≥ 50%). Positive PD-L1 expression rate showed an increasing trend from atypical adenomatous hyperplasia (AAH) to invasive adenocarcinoma (IAC), and all high PD-L1 expression patients were pathologically diagnosed as IACs (Figure 2). In the whole cohort, there was no correlation between PD-L1 expression and pathological type, but the positive PD-L1 expression rate in IB stage was higher than that in IA stage (P < 0.01). The age difference between positive group and negative group was statistically significant (P < 0.05), and patients in the positive group were older. The NE and CEA were positively correlated with PD-L1 expression, while the LP and CYFRA21-1 were negatively correlated with TPS. Other clinical characteristics, including gender, BMI, past history, family history and WBC, showed no statistical difference (Table 1). After randomization, there were statistically significant differences in gender, age, smoking history, pathological stage, CEA and CYFRA21-1 in the training cohort, while only CYFRA21-1 was associated with PD-L1 expression in the test cohort (Table 2).
CT morphological features of the patients

The difference in nodule type between positive group and negative group was statistically significant, and the proportion of mGGN was larger in positive group (P < 0.01). The longer nodule diameter was correlated with the positive PD-L1 expression (P < 0.01). There were no statistically significant differences in nodule margin, peripheral features and internal features between the two groups (Table 1).

Radiomic model

In the training cohort, 762 radiomics features were stable (ICC ≥ 0.75) both inter- intra- observer (Figure 3). 301 features were statistically significant in univariate analysis (P < 0.05). 9 features (Table 3) were eventually selected by least absolute shrinkage and selection operator (LASSO) to establish radiomic model (Figure 4). The area under the curve (AUC) values of the radiomic models in the training cohort and the test cohort were 0.653 and 0.583 respectively (Figures 5, 6), and the negative predictive values were 81.4% and 75.7%, the positive predictive values were 39.1% and 30.2%, the accuracies were 57.4% and 54.8%, the sensitivities were 58.9% and 51.5%, the specificities were 66.2% and 56% in the training cohort and the test cohort.

Quantitative model

In the training cohort, univariate and multivariate analyses identified that SA/V and irregularity were independent risk factors for PD-L1 expression. Smaller SA/V and greater irregularity were correlated with positive PD-L1 expression (P < 0.05) (Table 4). The AUC values of the quantitative models were 0.588 and 0.545 in the training cohort and the test cohort respectively (Figure 5).

Combined model

The clinical-radiomic combined model was constructed from both 9 radiometric features and 7 clinical features, the latter including statistically significant characteristics (age, NE, LP, CEA and CYFRA21-1) in the whole cohort and clinically significant characteristics (sex and smoking history). The AUC values of the combined models were 0.693 and 0.598 in the
|                      | Total                | Negative group (TPS<1%) | Positive group (TPS≥1%) | P value |
|----------------------|----------------------|-------------------------|-------------------------|---------|
| Gender               |                      |                         |                         | 0.081   |
| Male                 | 280 (33.4)           | 194 (31.6)              | 86 (38.1)               |         |
| Female               | 559 (66.6)           | 419 (68.4)              | 140 (61.9)              |         |
| Age (years)          | 56.0 (49.0, 63.0)    | 55.0 (49.0, 62.0)       | 57.0 (51.0, 64.3)       | 0.017   |
| BMI (kg/m²)          | 24.1 (22.0, 26.1)    | 24.1 (22.1, 26.1)       | 24.0 (22.0, 26.1)       | 0.871   |
| Smoking history      |                      |                         |                         | 0.108   |
| Yes                  | 142 (16.9)           | 96 (16.2)               | 46 (20.4)               |         |
| No                   | 697 (83.1)           | 517 (84.3)              | 180 (79.6)              |         |
| Malignant tumor history |                   |                         |                         | 0.790   |
| Yes                  | 49 (5.8)             | 35 (5.7)                | 14 (6.2)                |         |
| No                   | 790 (94.2)           | 578 (94.3)              | 212 (93.8)              |         |
| Lung benign disease history |             |                         |                         | 0.286   |
| Yes                  | 41 (4.9)             | 27 (4.4)                | 14 (6.2)                |         |
| No                   | 798 (95.1)           | 586 (95.6)              | 212 (93.8)              |         |
| Family lung cancer history |             |                         |                         | 0.515   |
| Yes                  | 103 (12.3)           | 78 (12.7)               | 25 (11.1)               |         |
| No                   | 736 (87.7)           | 535 (87.3)              | 201 (88.9)              |         |
| Family malignant tumor history |             |                         |                         | 0.951   |
| Yes                  | 131 (15.6)           | 96 (15.7)               | 35 (15.5)               |         |
| No                   | 708 (84.4)           | 517 (84.3)              | 191 (84.5)              |         |
| Pathological type    |                      |                         |                         | 0.098   |
| PGL                  | 18 (2.1)             | 16 (2.6)                | 2 (0.9)                 |         |
| AC                   | 821 (97.9)           | 597 (97.4)              | 224 (99.1)              |         |
| Pathological stage   |                      |                         |                         | 0.003   |
| IA                   | 167 (19.9)           | 107 (17.5)              | 60 (26.5)               |         |
| IB                   | 672 (80.1)           | 506 (82.5)              | 166 (73.5)              |         |
| WBC (*10³)           | 5.55 (4.76, 6.21)    | 5.57 (4.76, 2.21)       | 5.55 (4.76, 6.10)       | 0.575   |
| NE                   | 0.556 (0.514, 0.609) | 0.556 (0.514, 0.605)    | 0.567 (0.516, 0.623)    | 0.043   |
| LP                   | 0.347 (0.297, 0.390) | 0.347 (0.301, 0.390)    | 0.335 (0.288, 0.390)    | 0.010   |
| CEA (ug/L)           | 1.89 (1.43, 2.18)    | 1.89 (1.39, 1.97)       | 2.18 (1.55, 2.25)       | <0.001  |
| CYFRA21-1 (ng/mL)    | 2.50 (2.03, 2.50)    | 2.50 (2.07, 2.53)       | 2.37 (1.94, 2.37)       | <0.001  |
| Nodule type          |                      |                         |                         | 0.005   |
| pGGN                 | 489(58.3)            | 375(61.2)               | 114(50.4)               |         |
| mGGN                 | 350(41.7)            | 238(38.8)               | 112(49.6)               |         |
| Diameter (mm)        | 13.0(9.7,18.0)       | 12.0(9.0, 17.5)         | 14.0(10.0, 18.0)        | 0.003   |
| Margin               |                      |                         |                         | 0.188   |
| Clear                | 791(94.3)            | 574(93.6)               | 217(96.0)               |         |
| Fuzzy                | 48(5.7)              | 39(6.4)                 | 9(4.0)                  |         |
| Lobulation sign      |                      |                         |                         | 0.745   |
| Yes                  | 227(27.1)            | 164(26.8)               | 63(27.9)                |         |
| No                   | 612(72.9)            | 449(73.2)               | 163(72.1)               |         |
| Spiculation sign     |                      |                         |                         | 0.566   |
| Yes                  | 121(14.4)            | 91(14.8)                | 30(13.3)                |         |
| No                   | 718(85.8)            | 522(85.2)               | 196(86.7)               |         |
| Vacuole sign         |                      |                         |                         | 0.150   |
| Yes                  | 107(12.8)            | 72(11.7)                | 35(15.5)                |         |
| No                   | 732(87.2)            | 541(88.3)               | 191(84.5)               |         |

(Continued)
Table 1 Continued

|                          | Total   | Negative group (TPS<1%) | Positive group (TPS≥1%) | P value |
|--------------------------|---------|-------------------------|-------------------------|---------|
| Pleural pull/indentation sign |         |                         |                         |         |
| Yes                      | 143(17.0) | 99(16.2)                 | 44(19.5)                 | 0.257   |
| No                       | 696(83.0) | 514(83.4)                | 182(80.5)                |         |
| Vascular cluster sign    |         |                         |                         |         |
| Yes                      | 127(15.1) | 97(15.8)                 | 30(13.3)                 | 0.361   |
| No                       | 712(84.9) | 516(84.2)                | 196(86.7)                |         |
| Abnormal air bronchial sign |         |                         |                         | 0.363   |
| Yes                      | 87(10.4)  | 60(9.8)                  | 27(11.9)                 |         |
| No                       | 752(89.6) | 553(90.2)                | 199(88.1)                |         |

TPS: tumor proportion score; BMI: body mass index; PGL: precursor glandular lesions; AC: adenocarcinoma; WBC: white blood cell count; NE: neutrophil percentage; LP: lymphocytes percentage; CEA: carcinoembryonic antigen; CYFRA21-1, cytokeratin-19 fragment; pGGN, pure ground-glass nodule; mGGN, mixed ground-glass nodule.

Japanese study showed that the positive PD-L1 rate was 21.9%, and the PD-L1 expression in adenocarcinoma in situ (AIS), microinvasive adenocarcinoma (MIA) and lepidic predominant adenocarcinoma (LPA) was all negative (34). In our study, a larger sample size was included and more optimistic PD-L1 expression results were obtained. The positive PD-L1 rate in PGL was 11.1%, and that in AC was 27.3%. Another European study observed that the positive PD-L1 rate was 30.8%, and the high PD-L1 expression rate was 10.4%. Meanwhile, it uncovered that the PD-L1 expression was correlated with gender and smoking history, and was highly correlated with tumor grade and lymph node invasion (35). In contrast, more GGN-like lung adenocarcinoma patients in our study were female and non-smokers, and all patients had no lymph node infiltration, which may explain the lower positive PD-L1 rate. In general, the positive PD-L1 rate of GGN-like lung adenocarcinomas is comparable to other early-stage lung adenocarcinomas, confirming that immune escape mechanism acted as a super-early event in cancer development (36), thus laying the foundation for the application of ICIs. Immunity, inflammation and their interactions play an important role in the occurrence, development and progression of cancer (37, 38). Studies have shown that both neutrophil-to-lymphocyte ratio (NLR) and absolute lymphocyte count (ALC) can predict the prognosis of nivolumab-treated NSCLC patients (39, 40). Our study also proved that higher NE and lower LP were associated with positive PD-L1 expression. Moreover, we discovered that higher baseline CEA level and lower baseline CYFRA21-1 level might be potential markers of PD-L1 expression, whereas other studies had come to conflicting conclusions (41, 42). The relationship between tumor marker levels and PD-L1 expression in early-stage lung adenocarcinomas has not been extensively studied yet, and more data are needed for further confirmation. Univariate analysis of clinical characteristics in the whole cohort and the training cohort showed that gender, age, smoking history, NE, LP, CEA and CYFRA21-1 might be
associated with the PD-L1 expression, which was also recognized in previous studies. Therefore, above clinical features were added into the clinical-radiomic combined model. It can be seen from Table 2 that few clinical features were statistically different in the test cohort, resulting in a modest improvement in the AUC value of the combined model, which suggested that the correlation between clinical features and PD-L1 expression in GGN-like lung adenocarcinoma needed to be further verified.

PD-L1 expression was associated with nodule type and diameter in this study. In addition to these two CT morphological features, other studies also found that irregular shape, pleural indentation sign, air bronchogram sign, the convergence sign and cavitation sign were correlated with PD-L1 expression (43, 44). These associations of radiological features with PD-L1 expression suggested that pathological and even molecular discrepancy in tumors can be externalized in imaging. The lack of significant CT morphological features in this study might be attributed to the fact that TPS=5% was used as a threshold in above two studies, magnifying the radiological feature difference between groups. Since PD-L1 expression level in early-stage lung adenocarcinoma was relatively low and there were only 9.3% (78/839) GGNs with TPS ≥ 5% in this study, it is statistically difficult to further explore the relationship between CT morphological features and PD-L1 expression by increasing the cut-off value. On the other hand, due to the limitation of volume and density, the internal and peripheral features of GGN

| TABLE 2 | Comparison of clinicopathologic features in training cohort and test cohort. |
|----------|--------------------------------------------------------------------------|
|          | Training cohort                                                                 | Test cohort                                                                 |
|          | Negative group | Positive group | P value | Negative group | Positive group | P value |
| Total    | 429            | 158            | 0.027   | 184            | 68            | 0.870   |
| Gender   | Male           | 127 (29.6)     | 62 (39.2) | 67 (36.4)    | 24 (35.3)   | 0.870   |
|          | Female         | 302 (70.4)     | 96 (60.8) | 117 (63.6)  | 44 (64.7)   | 0.870   |
| Age (years) | 55.0 (49.0, 62.0) | 58.0 (51.0, 65.0) | 0.003  | 57.0 (51.0, 63.0) | 55.5 (50.0, 64.0) | 0.885   |
| BMI (kg/m²) | 23.9 (22.0, 26.0) | 24.2 (22.3, 26.3) | 0.295  | 24.5 (22.3, 26.2) | 23.6 (21.8, 26.0) | 0.203   |
| Smoking history | Yes            | 53 (12.4)     | 32 (20.3) | 43 (23.4)   | 14 (20.6)   | 0.639   |
|          | No             | 376 (87.6)    | 126 (79.7) | 141 (76.6)  | 54 (79.4)   | 0.639   |
| Malignant tumor history | Yes           | 22 (5.1)      | 9 (5.7)   | 13 (7.1)    | 5 (7.4)     | 1.000   |
|          | No             | 407 (94.9)    | 149 (94.3) | 171 (92.9)  | 63 (92.6)   | 0.706   |
| Lung benign disease history | Yes          | 21 (4.9)      | 11 (7.0)  | 6 (3.3)     | 3 (4.4)     | 0.908   |
|          | No             | 408 (95.1)    | 147 (93.0) | 178 (96.7)  | 65 (95.6)   | 0.908   |
| Family lung cancer history | Yes           | 53 (12.4)     | 19 (12.0) | 25 (13.6)   | 6 (8.8)     | 0.307   |
|          | No             | 376 (87.6)    | 139 (88.0) | 159 (86.4)  | 62 (91.2)   | 0.307   |
| Family tumor history | Yes           | 70 (16.3)     | 25 (15.8) | 26 (14.1)   | 10 (14.7)   | 0.195   |
|          | No             | 359 (83.7)    | 133 (84.2) | 158 (85.9)  | 58 (85.3)   | 0.195   |
| Pathological type | PGL           | 10 (2.3)      | 2 (1.3)   | 6 (3.3)     | 0 (0.0)     | 0.007   |
|          | AC             | 419 (97.7)    | 156 (98.7) | 178 (96.7)  | 68 (100.0)  | 0.007   |
| Pathological stage | IA            | 353 (82.3)    | 114 (72.2) | 153 (83.2)  | 52 (76.5)   | 0.227   |
|          | IB             | 76 (17.7)     | 44 (27.8)  | 31 (16.8)   | 16 (23.5)   | 0.665   |
| WBC (×10⁶) | Yes           | 5.44 (4.75, 6.11) | 5.44 (4.70, 6.10) | 0.899 | 5.44 (4.82, 6.35) | 5.44 (4.80, 6.22) | 0.665 |
|          | No             | 0.557 (0.510, 0.601) | 0.557 (0.533, 0.612) | 0.277 | 0.557 (0.517, 0.617) | 0.565 (0.533, 0.636) | 0.313 |
| NE       | Yes           | 0.342 (0.306, 0.394) | 0.342 (0.294, 0.391) | 0.089 | 0.342 (0.294, 0.388) | 0.316 (0.285, 0.364) | 0.450 |
|          | No             | 0.189 (1.36, 1.89) | 2.18 (1.57, 2.40) | <0.001 | 1.89 (1.41, 2.11) | 2.13 (1.51, 2.18) | 0.067 |
| CEA (ug/L) | Yes           | 2.50 (2.09, 2.50) | 2.37 (2.00, 2.44) | <0.001 | 2.50 (2.04, 2.71) | 2.37 (1.82, 2.37) | <0.001 |
|          | No             | 2.50 (2.09, 2.50) | 2.37 (2.00, 2.44) | <0.001 | 2.50 (2.04, 2.71) | 2.37 (1.82, 2.37) | <0.001 |

BMI, body mass index; PGL, precursor glandular lesions; AC, adenocarcinoma; WBC, white blood cell count; NE, neutrophil percentage; LP, lymphocytes percentage; CEA, carcinoembryonic antigen; CYFRA21-1, cytokeratin-19 fragment.

Bold values indicate that the P-value of this feature is less than 0.05, which is statistically significant.
FIGURE 3
Inter-class correlation coefficient (ICC) of inter-observers (A) and intra-observer (B).
were not clear enough to be accurately distinguished by naked eyes. Hence, further evaluation of radiological features in GGN-like lung adenocarcinoma is conducive to the evaluation of PD-L1 expression.

Quantitative CT objectively and quantitatively depict the size, shape and special signs of nodules, which is more dependable than clinician’s determination; it has been applied in the diagnosis, evaluation and prediction of lung diseases (45–47). As shown in Table 4, most quantitative features were correlated with the PD-L1 expression in the training cohort, nevertheless, the quantitative model established by SA/V and irregularity had poor prediction efficiency for PD-L1 expression. It can be concluded that the image information extracted by mere quantitative CT is limited.

Radiomics extracts massive quantitative features from different angles of original images and transformed images, excavating as much image information as possible, thus is more effective than quantitative CT. At present, radiomic method has been fully developed, and its application in lung cancer has progressed from qualitative diagnosis and histological identification to the present level of gene or molecular detection (48–51). Recent studies on noninvasive prediction of PD-L1 expression mainly focus on advanced NSCLC, and the PET/CT-based radiomic model has achieved good prediction effect (52). Due to the low sensitivity of PET/CT in the diagnosis of GGN-like lung adenocarcinomas, thin-layer CT is mostly used for the detection and follow-up of pulmonary nodules. We established a CT-based radiomic model in GGN-like lung adenocarcinoma and found that it had the potential of noninvasive prediction for PD-L1 expression (AUC were 0.653 versus 0.583 in training cohort and test cohort). Several studies have also attempted to establish CT-based PD-L1 expression prediction models in advanced NSCLC, but yielded inconsistent results. Bracci et al. created two radiomic models based on 48 texture features: one model determining whether TPS ≥ 1% achieved AUC values of 0.763 and 0.806 in the training cohort (n=48) and the validation cohort (n=24), and the other for TPS≥50% got AUC values of 0.811 and 0.789 respectively (25). Sun et al. built a radiomic model for PD-L1 expression≥50% on a much larger data set (390 patients, 200 texture features), and achieved the similar predictive effect (AUC: 0.786 and 0.807) (42). The above two favorable results might be attributed to the higher PD-L1 expression level in advanced NSCLC, and the greater differentiation between groups with the TPS cut-off of 50%. However, another study did not seem to support this hypothesis: Yoon et al. extracted 58 radiomic features in 153 advanced adenocarcinoma patients, established a clinical-radiomic combined model for TPS≥50%, and came up with an AUC of 0.667 (24). In fact, the proportion of squamous cell carcinoma in the positive group was higher in the first two studies; since positive PD-L1 expression rate in lung squamous cell carcinoma was significantly higher than that in lung adenocarcinoma (53), better discrimination ability of models could be partly explained by differences in histological types between groups. In addition, due to the smaller sample size and radiomic feature number of the above three studies, the robustness of the models needs to be further verified. Our study focused on the noninvasive prediction of PD-L1 expression in early-stage GGN-like lung adenocarcinoma, and obtained meaningful radiomic models. Firstly, the radiomic features showed good robustness, and 97.8% of them reached the preset ICC. A study revealed that the accuracy of lesion segmentation was less affected by the training level and clinical experience of physicians (54). It might be concluded that regular shape and clear boundary of most GGNs facilitated the ROI segmentation process. Secondly, it is reported that wavelet features have better repeatability and reproducibility (55). Our study covered 680 wavelet features, and over half radiomic features ultimately applied to the prediction model were wavelet features. Thirdly, neither the single radiomic model nor the clinical model had better predictive efficacy than the combined model (24, 56–58), indicating that the combination of radiomic and clinical features was more conducive to accurate prediction of PD-L1 expression. Our study also confirmed that the clinical-radiomic combined model was indeed superior to the radiomic model. Despite this, the prediction performance of either radiomic

| Number | Number | Number | Number | Number |
|--------|--------|--------|--------|--------|
| 1      | 0riginal | firstorder | 75 Percentile |
| 2      | 0riginal | Shape | Maximum 2D Diameter Slice |
| 3      | 0riginal | glcm | Correlation |
| 4      | 0riginal | glzsm | Large Area High Gray Level Emphasis |
| 5      | wavelet-LHH | glcm | Maximal correlation coefficient |
| 6      | wavelet-LHH | ngtdm | Busyness |
| 7      | wavelet-HLL | glrlm | Long Run Low Gray Level Emphasis |
| 8      | wavelet-LLL | firstorder | Interquartile Range |
| 9      | wavelet-LLL | glzsm | Large Area Low Gray Level Emphasis |
FIGURE 4
Least absolute shrinkage and selection operator (LASSO) coefficient profiles (A) and determining the parameter Lambda (λ) in the LASSO model with 10-fold cross-validation (B).
FIGURE 5
ROC curves of the radiomic model and quantitative model in the training cohort (A) and the test cohort (B).
FIGURE 6
ROC curves of the combined model and radiomic model in the training cohort (A) and the test cohort (B).
model or combined model remained not ideal and the discrimination error of positive PD-L1 expression were large. The lower PD-L1 expression level in GGN-like lung adenocarcinoma patients and more patients with negative PD-L1 expression included in this study might be one of the reasons. Besides, 1% was used as the cutoff value of PD-L1 expression in this paper, which also resulted in the imperceptible image difference between the negative group and the positive group. Furthermore, the radiomic features included in our and other PD-L1 expression prediction models were different from each other, and these studies lacked external validation data. Though the traditional radiomics method has a relatively mature operation process, there is poor consistency among different studies due to the diversity of original medical image protocols, image segmentation platforms, radiomic feature categories and machine learning algorithms. so we need to expand the patient population and adopt more advanced radiomic methods such as convolutional neural networks to achieve the clinical application of PD-L1 non-invasive prediction. Also, since the predictive efficacy of a single biomarker is limited, PD-L1 could combine genomics, proteomics and so on to construct multi-omics biomarkers.

Our study had several limitations: First, this was a single-center retrospective study with intrinsic bias, patients undergoing thoracic surgery in the hospital were not generally representative and the prediction model was not externally validated; Second, the semi-automatic ROI segmentation was performed by respiratory physicians, though the radiologist confirmed the results of 50 randomly selected nodules the objectivity and reproducibility of the radiomic features still needed to be further verified; Third, the absence of follow-up and prognostic assessment of patients made it impossible to establish an association between radiomic and recurrence or survival for improving the individualized treatment of early-stage lung adenocarcinoma.

In conclusion, early-stage lung adenocarcinomas manifesting as GGNs had a fairly high positive PD-L1 expression rate. Due to the advantages of noninvasiveness and repeatability, the radiomic-based model could better predict the PD-L1 expression of GGNs, thus paves the way of a more accurate diagnosis and treatment scheme for the individualized treatment of early-stage GGN-like lung adenocarcinoma.

**Data availability statement**

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

**Ethics statement**

The studies involving human participants were reviewed and approved by the Medical Ethics Committee of the Chinese People’s Liberation Army General Hospital. The patients/participants provided their written informed consent to participate in this study.

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**TABLE 4** Data analysis of quantitative features in training cohort.

| Features                          | Negative group  | Positive group  | P value | P value | \( \beta \) | OR (95%CI) |
|-----------------------------------|-----------------|-----------------|---------|---------|------------|------------|
| Volume (ml)                       | 0.88 (0.42, 2.31) | 1.31 (0.61, 2.94) | 0.001   | 0.419   |            |            |
| 3D maximum diameter (mm)         | 1.60 (1.19, 2.32) | 1.93 (1.30, 2.43) | 0.005   | 0.268   |            |            |
| 3D mean diameter (mm)            | 1.16 (0.91, 1.62) | 1.30 (1.04, 1.72) | 0.003   | 0.764   |            |            |
| Mean density (HU)                | 566.57 (480.53, 641.61) | 541.19 (443.40, 637.90) | 0.101   |            |            |            |
| Non-consolidation ratio          | 0.37 (0.24, 0.51) | 0.36 (0.22, 0.54) | 0.815   |            |            |            |
| Mass (g)                         | 0.21 (0.09, 0.55) | 0.33 (0.13, 0.74) | 0.003   | 0.507   |            |            |
| Pleural adhesion area (cm²)      | 5.56 (3.20, 12.28) | 7.76 (4.05, 14.19) | 0.002   | 0.276   |            |            |
| Pleural proportion               | 0.05 (0.04, 0.07) | 0.05 (0.04, 0.07) | 0.947   |            |            |            |
| Fat proportion                   | 0.02 (0.01, 0.04) | 0.02 (0.01, 0.05) | 0.051   |            |            |            |
| Surface area/volume ratio        | 6.36 (5.22, 7.58) | 5.87 (4.90, 7.07) | 0.002   | 0.009   | -0.348     | 0.706 (0.544, 0.917) |
| Calcification volume (mm³)       | 14.65 (4.27, 32.09) | 16.66 (6.83, 44.98) | 0.001   | 0.078   |            |            |
| Mean vascular density (HU)       | 0.20 (0.09, 0.53) | 0.30 (0.13, 0.72) | 0.002   | 0.508   |            |            |
| Irregularity                      | 0.58 (0.34, 0.82) | 0.68 (0.42, 0.92) | 0.008   | 0.015   | 1.864      | 6.449 (1.438, 28.915) |
| Void volume ratio                | 0.09 (0.05, 0.14) | 0.09 (0.05, 0.16) | 0.395   |            |            |            |

TPS, tumor proportion score; 3D, three-dimensional. Bold values indicate that the P-value of this feature is less than 0.05, which is statistically significant.
Author contributions

LC and WZ designed the study. WS and ZY reviewed literature, interpreted the data and wrote manuscripts. WS, MZ, JL, MW, HY and CZ collected data. WS, MZ, YW, BY and ZW segmented the ROIs. ZY, MZ, CZ and ZL processed the data and analyzed the statistics. LC, WZ, JL and CL revised the manuscript. All authors contributed to the article and approved the submitted version.

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The clinical relevance of PD-L1 expression in lung cancer has been well recognized for many years.

PD-L1 expression in non-small cell lung cancer (NSCLC) is a significant biomarker for determining the efficacy of anti-PD-1/PD-L1 therapy. This review article provides an up-to-date overview of PD-L1 expression in NSCLC, including its relationship with clinicopathological features and the outcomes of patients treated with anti-PD-1/PD-L1 therapy. The article highlights the importance of PD-L1 expression in predicting the response to immunotherapy and identifying potential candidates for personalized treatment strategies.

PD-L1 expression has been shown to correlate with stages of NSCLC and is associated with increased tumor-infiltrating lymphocytes (TILs) and immune checkpoints. The presence of PD-L1-positive tumors has also been linked to improved overall survival and better progression-free survival rates in patients receiving PD-1/PD-L1 inhibitors. However, the effectiveness of anti-PD-1/PD-L1 therapy can be significantly influenced by the level of PD-L1 expression, with lower expression levels being associated with a more favorable prognosis.

Furthermore, PD-L1 expression has been shown to be influenced by various clinicopathological factors such as smoking status, tumor histology, and stage of disease. These factors can impact the efficacy of immunotherapy and should be considered when planning treatment strategies for patients with NSCLC.

In conclusion, PD-L1 expression is a valuable biomarker in NSCLC, with implications for both treatment selection and patient prognosis. Further research is needed to explore the clinical significance of PD-L1 expression in different subtypes of NSCLC and to develop more accurate diagnostic tools for predicting treatment response.

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GGN
CT
RFS
mGGN
ICI
PD-1/PD-L1
NSCLC
FDA
MPR
PCR
OS
DFS
PET
MRI
TPS
BMI
WBC
CEA
CYFRA21-1
WHO
PGL
AC
pGGN
DICOM
ROI
3D
SA/V
ICC
AAH
AIS
MIA
IAC
NE
LP
LASSO
AUC
NLR
ALC
ORR
LPA
ROC
Ground-glass nodule
computed tomography
recurrence-free survival
mixed ground-glass nodule
immune checkpoint inhibitor
programmed cell death-1/programmed cell death-ligand 1
non-small cell lung cancer
Food and Drug Administration
major pathological response
pathological complete response
overall survival
disease-free survival
positron emission tomography
magnetic resonance imaging
tumor proportion score
body mass index
white blood cell count
carcinoembryonic antigen
cytokeratin-19 fragment
World Health Organization
precursor glandular lesions
adenocarcinoma
pure ground-glass nodule
Digital Imaging and Communications in Medicine
region of interest
three-dimensional
surface area/volume
inter-class correlation coefficient
atypical adenomatous hyperplasia
adenocarcinoma <italic>in situ</italic>
microinvasive adenocarcinoma
invasive adenocarcinomas
neutrophil percentage
lymphocytes percentage
least absolute shrinkage and selection operator
Area under the curve
neutrophil-to-lymphocyte ratio
absolute lymphocyte count
overall radiological response
lepidic predominant adenocarcinoma
receiver operating characteristic