Correlation Between Quantitative Perfusion Histogram Parameters of DCE-MRI and PTEN, P-Akt and m-TOR in Different Pathological Types of Lung Cancer

Bingqian Zhang
Shaoxing people's Hospital

Zhenhua Zhao (✉ zhao2075@163.com)
Shaoxing people's Hospital  https://orcid.org/0000-0001-8952-8677

Ya'nan Huang
Shaoxing people's Hospital

Haijia Mao
Shaoxing people's Hospital

Mingyue Zou
Shaoxing people's Hospital

Cheng Wang
Shaoxing people's Hospital

Guangmao Yu
Shaoxing People's Hospital

Minming Zhang
the second Affiliated Hospital of Zhejiang University

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Abstract

**Background:** To explore if the quantitative perfusion histogram parameters of dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI) correlates with the PTEN, P-Akt and m-TOR protein in lung cancer.

**Methods:** Thirty-three patients with 33 lesions who had been diagnosed with lung cancer were enrolled in this study. They were divided into three groups: squamous cell carcinoma (SCC, 15 cases), adenocarcinoma (AC, 12 cases) and small cell lung cancer (SCLC, 6 cases). Preoperative imaging (conventional imaging and DCE-MRI) was performed on all patients. The Exchange model was used to measure the pharmacokinetic parameters, including $K_{\text{trans}}$, $V_p$, $K_{\text{ep}}$, $V_e$ and $F_p$, and then the histogram parameters meanvalue, skewness, kurtosis, uniformity, energy, entropy, quantile of above five parameters were analyzed. The expression of PTEN, P-Akt and m-TOR were assessed by immunohistochemistry. Spearman correlation analysis was used to compare the correlation between the quantitative perfusion histogram parameters and PTEN, P-Akt and m-TOR in different pathological subtypes of lung cancer.

**Results:** The expression of m-TOR ($P = 0.013$) and P-Akt ($P = 0.002$) in AC was significantly higher than those in SCC. $V_p$ (uniformity) in SCC group, $K_{\text{trans}}$ (uniformity), $V_e$ (kurtosis, Q10, Q25) in AC group, $F_p$ (skewness, kurtosis, energy), $V_e$ (Q75, Q90, Q95) in SCLC group was positively correlated with PTEN, and $F_p$ (entropy) in the SCLC group was negatively correlated with PTEN ($P < 0.05$); $K_{\text{ep}}$ (Q5, Q10) in the SCLC group was positively correlated with P-Akt, and $K_{\text{ep}}$ (energy) in the SCLC group was negatively correlated with P-Akt ($P < 0.05$); $K_{\text{ep}}$ (Q5) in SCC group and $V_p$ (meanvalue, Q75, Q90, Q95) in SCLC group was positively correlated with m-TOR, and $V_e$ (meanvalue) in SCC group was negatively correlated with m-TOR ($P < 0.05$).

**Conclusions:** The quantitative perfusion histogram parameters of DCE-MRI was correlated with PTEN, P-Akt and m-TOR in different pathological types of lung cancer, which may be used to indirectly evaluate the activation status of P13K / Akt / mTOR signal pathway gene in lung cancer, and provide important reference for clinical treatment.

1. **Background**

Lung cancer is one of the common malignant tumors that seriously threaten the health and life of the population. It is the malignant tumor with the highest morbidity and mortality [1]. Activation of oncogenes and the deletion and mutation of tumor suppressor genes lead to impediments in cell cycle regulation and imbalance of apoptosis regulation, which are the most fundamental causes of tumorigenesis [2]. Phosphatidylinositol 3 kinase (PI3K) / protein kinase B (AKT) / mammalian target of rapamycin (mTOR) signaling pathway plays an important role in the genesis and development of many kinds of tumors. The signaling pathways through PI3K and AKT gene mutation and amplification, oncogene receptor activation, gene expression reduction of phpsphase and tensin homologue deleted on chromosome 10 (PTEN), and regulation of vascular endothelial growth factor (VEGF) expression and other mechanisms to
promote tumor cell growth and angiogenesis [3–5]. Studies have shown that PTEN is a tumor suppressor gene with dual specific phosphatase activity, and its gene mutation and loss of expression can cause the P13K / AKT / mTOR signaling pathway to be activated, leading to abnormal cell proliferation, infiltration and metastasis [6]. P-Akt is the activation state of AKT and is a key signal transduction factor that plays a role in promoting cancer on this signal pathway. m-TOR is the most important downstream signaling molecule of PI3K / AKT [7]. Therefore, the loss of PTEN and the abnormal activation of P-Akt and mTOR is related to tumorigenesis.

At present, Western blot and immunohistochemistry (IHC) are the main methods to monitor these proteins. The disadvantage of these methods is that they need invasive methods to obtain tissue samples, local samples often can't reflect the whole tumor situation, and samples in vitro can't really reflect the metabolism situation in vivo. DCE-MRI quantitative perfusion histogram can detect the metabolic activity inside the tumor from the molecular level based on the gray-scale intensity information of the lesion site and describe the heterogeneity of the lesion [8–10]. Therefore, the purpose of this study is to investigate the correlation between the DCE-MRI histogram parameters and PTEN, P-Akt, and m-TOR of lung cancer, so as to provide a basis for non-invasive prediction of P13K / Akt / mTOR signal pathway gene activation in lung cancer tissue by DCE-MRI histogram parameters.

2. Methods

2.1 Patients

The data of patients with chest MRI examinations in Shaoxing people's Hospital from January 2017 to April 2018 were retrospectively collected. Finally, thirty-three patients with lung cancer were enrolled for this study based on the following: Inclusion criteria: (1) all patients were diagnosed as lung cancer after surgery or biopsy; (2) the diameter of lung lesions was larger than 2 cm; (3) no puncture, surgery, chemoradiotherapy, and drug treatment were performed before MR examination; Exclusion criteria: (1) the interval between operation or puncture time and MR examination time was more than two weeks; (3) the image scanning quality was poor or the tumor boundary could not be clearly delineated. This study was approved by the ethics committee of Shaoxing people's hospital.

2.2 DCE-MRI protocols

The patient was supine and the Siemens Verio 3.0T MRI scanner was used to scan the body with a twelve-element chest phased-array body coil. Routine plain scan: T2WI coronal, T1WI transverse and sagittal; T2WI transverse and sagittal; then multiphase dynamic contrast (DCE-MRI) scans. Dynamic enhancement was performed using a 3D VIBE T1-weighted dynamic perfusion sequence scan, with all sequences using free breathing. Multi-flip angle scan before dynamic enhanced scan, scan parameters: TR 3.25 ms, TE 1.17 ms, Flip Angle: 5°, 10°, 15°, field of view 350 mm × 282 mm, matrix 162 × 288, layer thickness 5 mm, The number of layers was 30, and the time resolution of each period was 6.5 s. Dynamic enhanced scanning sequence parameters: Flip Angle 10°, scanning 35 phases, the remaining parameters were the same as above, the total time of multi-flip angle scanning and dynamic enhanced scanning was
247 s. When the dynamic enhanced scan was in phase 3, a high-pressure syringe was used to inject the contrast agent gadolinium diamine (Omniscan, Ge Healthcare) through the median cubital vein. The injection dose was 0.1 mmol/kg, the injection speed was 3.0 ml/s, followed by a 20 mL saline flush.

### 2.3 MR image analysis

The original DCE data after scanning was imported into Omni.Kinetics (GE Healthcare, China) software. The 3D correction technology of free breathing (no rigid medical image registration algorithm) was used to correct the motion artifacts of dynamic enhancement sequence and check the fitting state of time intensity curve (TIC) before and after registration and check the registration effect. The curve was linear and smooth, which indicated that the fitting was good (Fig. 1). Multi-flip angles of 5 °, 10 °, 15 ° and corrected dynamic enhancement sequence scan were processed by the hemodynamic software Omni.Kinetics, and the perfusion parameters were calculated by the Exchange model of bronchial artery and pulmonary artery double blood supply. Avoiding cystic change, necrosis and normal lung tissue to sketch the region of interest (ROI), 3–5 layers above and below the largest tumor layer were integrated into a 3D ROI for quantitative analysis and calculation. Five quantitative parameters were obtained: $K_{\text{trans}}$ (transfer constant), $V_p$ (fractional volume of plasma), $K_{\text{ep}}$ (rate constant of backflux from extravascular extracellular space [EES] to plasma), $V_e$ (fractional volume of EES) and $F_p$ (tissue plasma perfusion).

Histogram analysis of each perfusion parameter includes the following contents: mean value, skewness, kurtosis, uniformity, energy, entropy, Q10, Q25, Q75, Q90, Q95(Fig. 2). The above parameters were also analyzed by Omni.Kinetics. Data processing was measured three times by two senior radiologists with more than five years’ experience in chest imaging diagnosis, and the average value was taken.

### 2.4 Immunohistochemical analysis and evaluation of PTEN, P-Akt, and m-TOR

PTEN, P-Akt, and m-TOR were assessed by immunohistochemistry (IHC) using paraffin-embedded tissue samples which were obtained from surgery or puncture. The process was performed according to the IHC protocol. Briefly, all sections were deparaffinized and rehydrated, and antigen retrieval was performed before immunohistochemical staining. Non-specific binding sites were blocked by serum blocking solution at 37 °C for 10 min (Dako company). The sections were stained with monoclonal mouse anti-human PTEN antibody (Dako company), monoclonal rabbit anti-human P-Akt antibody (Abcam company) or monoclonal rabbit anti-human mTOR antibody (CST company), and 4 °C overnight. The specimens were stained with secondary antibody and were then incubated at 37 °C for 10 min. DBA staining, rinsing, mild counterstaining of hematoxylin. After dehydration, transparency and mounting, the slides were visualized using a microscope. The immunostaining results of specific antibodies were measured semi-quantitatively by immunoreactive score (IRS) method, and the density and distribution of immunostaining were synthesized. The specific calculation method of IRS is as follows: Staining intensity (SI) classification: 0, no staining; 1, light yellow; 2, brown yellow, 3, dark brown; percentage of stained cells (PP): 0, no staining; 1, staining in < 10% of tumor cells; 2, staining in 10–50% of cells; 3, staining in 50–80% of cells; 4, staining in > 80% of cells. IRS = SI × PP.
2.5 Statistical analysis

Shapiro-Wilk test was used to check normality assumption for quantitative variables. The classification variables were analyzed by Fisher exact test. One-way analysis of variance (AVONA) and Least Significant Difference (LSD) were used to compare the expression of PTEN, m-TOR and P-Akt protein among different pathological groups of lung cancer, Kruskal Walls test were used to compare the perfusion histogram parameters among three groups of lung cancer; Nonparametric correlation analysis (Spearman test) was used to analyze the correlation between PTEN, m-TOR and P-Akt and DCE-MRI quantitative perfusion histogram parameters measured by the Exchange model. Statistical analyses were performed using the SPSS (version. 25.0, Chicago, IL, USA). For all the above-mentioned analyses, p < 0.05 was considered statistically significant.

3. Result

3.1 Demographic of patients with lung cancer

Table 1 summarizes the demographic of the three groups of patients with lung cancer subtypes. There were 15 cases of squamous cell carcinoma (SCC), 12 cases of adenocarcinoma (AC) and 6 cases of small cell lung cancer (SCLC). The median age, mean age ± standard deviation (SD) and age range were 66, 66.79 ± 9.24 and 50–85 years, respectively. There was no significant difference in sex, age, BMI and tumor maximum diameter among the three groups (P = 0.059; F = 0.830, P = 0.446; F = 1.459, P = 0.250; F = 0.593, P = 0.559).

| Characteristics          | SCC(n = 15) | AC(n = 12) | SCLC((n = 6) | total     | F value | P value |
|--------------------------|-------------|------------|--------------|-----------|---------|---------|
| Gender                   |             |            |              |           |         |         |
| Male                     | 15(100.0%)  | 9(75.0%)   | 4(66.7%)     | 28(84.8%) | 0.059   |         |
| Female                   | 0(0%)       | 3(25.0%)   | 2(33.3%)     | 5(15.2%)  |         |         |
| Age (years, x ± s)       | 68.3 ± 9.9  | 67.0 ± 10.2| 62.5 ± 3.6   |           | 0.830   | 0.446   |
| Age range                | 51 ~ 85     | 50 ~ 84    | 58 ~ 67      |           |         |         |
| BMI(Kg/m²)               | 21.2 ± 2.6  | 20.9 ± 3.5 | 23.4 ± 2.8   |           | 1.459   | 0.250   |
| Tumor maximum diameter(mm)| 63.4 ± 28.9 | 55.5 ± 26.9| 51.0 ± 11.7  |           | 0.593   | 0.559   |
3.2 Immunohistochemical Expression of PTEN-P-Akt-m-TOR and their Correlations

PTEN-m-TOR-P-Akt expression were identified by immunohistochemical staining (Fig. 3). As shown in Fig. 4, PTEN expression in SCC was lower than that in the other two groups, but not statistically significant (P > 0.05). The expression of m-TOR and P-Akt in AC was higher than that in the other two groups, and significantly higher than that in SCC patients (P = 0.014; P = 0.001).

3.3 Correlations of perfusion histogram parameters with PTEN, P-Akt, m-TOR expression

Table 2–4 and Fig. 5 summarizes the perfusion histogram parameters significantly related to PTEN, p-Akt, m-TOR expression.

PTEN was positively correlated with $V_p$ (uniformity) in SCC ($\rho = 0.836, P < 0.001$), $K_{\text{trans}}$ (uniformity) in AC ($\rho = 0.633, P = 0.027$), $V_e$ (kurtosis, Q10, Q25) in AC ($\rho = 0.721, P = 0.008; \rho = 0.590, P = 0.044; \rho = 0.611, P = 0.035$), $F_p$ (skewness, kurtosis, energy) in SCLC ($\rho = 0.941, P = 0.005$) and $V_e$ (Q75, Q90, Q95) in SCLC ($\rho = 0.820, P = 0.046; \rho = 0.942, P = 0.005; \rho = 0.820, P = 0.046$). While PTEN was negatively correlated with $F_p$ (entropy) in the SCLC ($\rho = -0.941, P = 0.005$).
Table 2
Correlation between perfusion histogram parameters and PTEN expression in three types of lung cancer

| Group | Kinetic parameter | Histogram metrics | $\rho$ value | $P$ value |
|-------|-------------------|-------------------|--------------|-----------|
| SCC   | $V_p$             | uniformity        | 0.836        | $0.001$   |
| AC    | $K_{trans}$       | uniformity        | 0.633        | 0.027     |
|       | $V_e$             | kurtosis          | 0.721        | 0.008     |
|       | Q10               |                   | 0.590        | 0.044     |
|       | Q25               |                   | 0.611        | 0.035     |
| SCLC  | $F_p$             | skewness          | 0.941        | 0.005     |
|       | kurtosis          |                   | 0.941        | 0.005     |
|       | energy            |                   | 0.941        | 0.005     |
|       | entropy           |                   | -0.941       | 0.005     |
|       | $V_e$             | Q75               | 0.820        | 0.046     |
|       | Q90               |                   | 0.941        | 0.005     |
|       | Q95               |                   | 0.820        | 0.046     |

P-Akt was positively correlated with $K_{ep}$ (Q5, Q10) in the SCLC ($\rho = 0.841, P = 0.036$). While P-Akt was negatively correlated with $K_{ep}$ (energy) in the SCLC ($\rho = -0.841, P = 0.036$);

Table 3
Correlation between perfusion histogram parameters and P-Akt expression in three types of lung cancer

| Group | Kinetic parameter | Histogram metrics | $\rho$ value | $P$ value |
|-------|-------------------|-------------------|--------------|-----------|
| SCLC  | $K_{ep}$          | energy            | -0.841       | 0.036     |
|       | Q5                |                   | 0.841        | 0.036     |
|       | Q10               |                   | 0.841        | 0.036     |
m-TOR was positively correlated with $K_{ep}$ (Q5) in SCC ($\rho = 0.760, P = 0.001$) and $V_p$ (meanvalue, Q75, Q90, Q95) in SCLC ($\rho = 0.926, P = 0.008$). While m-TOR was negatively correlated with $V_e$ (meanvalue) in SCC ($\rho = -0.619, P = 0.014$).

| Group | Kinetic parameter | Histogram metrics | $\rho$ value | $P$ value |
|-------|------------------|-------------------|--------------|-----------|
| SCC   | $K_{ep}$         | Q5                | 0.760        | 0.001     |
| SCC   | $V_e$            | meanvalue         | -0.619       | 0.014     |
| SCLC  | $V_p$            | meanvalue         | 0.926        | 0.008     |
|       | Q75              |                   | 0.926        | 0.008     |
|       | Q90              |                   | 0.926        | 0.008     |
|       | Q95              |                   | 0.926        | 0.008     |

4. Discussion

In this study, we investigated the associations between the quantitative perfusion histogram parameters of DCE-MRI and the molecular markers PTEN, p-Akt, m-TOR in patients with different pathological subtypes of lung cancer. We observed significant correlations of several quantitative perfusion histogram parameters in different pathological subtypes of lung cancer with PTEN, P-Akt and m-TOR. In addition, we also found P-Akt and m-TOR were more frequently expressed in adenocarcinoma histology than in squamous cell carcinoma, and PTEN was not significantly correlated with pathological type (Fig. 4). It may be suggested that the expression of m-TOR and P-Akt is inconsistent in the development of AC and SCC. Previously, Oh et al. reported that there was more frequent expression of P-Akt and m-TOR in AC compare with SCC [11]. However, Wang et al. discovered that there were no indications of a specific correlation between histologic type and m-TOR or PTEN expression [12]. This conflicting result might be explained because the absence of universally accepted criteria to evaluate the expression of these proteins by immunohistochemistry might lead to different results.

Under physiological conditions, PI3K / Akt / mTOR pathway plays a role in cell survival, proliferation and angiogenesis. The disorder of this pathway will promote the occurrence and development of tumor. Currently, immunohistochemistry and Western blotting are mainly used to detect the expression of PTEN, P-Akt and m-TOR, and the procedures are invasive. Therefore, non-invasive methods are needed to assess tumor characteristics. DCE-MRI has been used as an imaging biomarker to evaluate of tumor heterogeneity, chemotherapy response and prognosis of lung cancer [13, 14]. As a new image analysis method, MRI histogram describes the microcirculation state of tumor tissue in a simple way, which can
better quantify the internal heterogeneity of tumor. Commonly used histogram parameters include: meanvalue, quantile, skewness, kurtosis, uniformity, entropy, energy, etc. Based on the clinical utility of PI3K / Akt / mTOR pathway related proteins, the current study was designed to examine the association between DCE-MRI quantitative perfusion histogram parameters and tumor biomarkers.

PTEN is the first tumor suppressor gene with phosphatase activity. The reduced expression of PTEN in tumor cells will continuously stimulate PI3K Signal Pathway, thereby increasing cell proliferation, invasion and metastasis [15, 16]. In NSCLC, PTEN loss is associated with poor clinical outcomes, and resistance to many anticancer drugs, including gefitinib [17, 18]. In this study, $V_p$ (uniformity) in SCC group, $K_{\text{trans}}$ (uniformity) in AC group was positively correlated with PTEN. $K_{\text{trans}}$ and $V_p$ are closely related to the intravascular plasma flow and vascular wall permeability. Because the tumor grows too fast, it often causes the tumor heterogeneity to be remarkable, namely the uniformity reduces in histogram. The previous study showed that tumor progression appears to be linked to expansion of histograms to the right (decreased skewness) and peak broadening with decreased height (decreased kurtosis) [19, 20]. In the current study, $V_e$ (kurtosis) in AC group, $F_p$ (skewness, kurtosis) in SCLC group was positively correlated with PTEN. The results are in accordance with previous studies. In SCC, PTEN was positively correlated with $F_p$ (energy), while negatively correlated with $F_p$ (entropy). Entropy represents the complexity of texture in image, which is opposite to energy. With the absence of PTEN, the $F_p$ parameter histogram shows a decrease in energy and an increase in entropy value, suggesting that the internal texture features of the tumor are complex. Meng J et al [21] found that as the malignancy of cervical cancer decreases, the ADC entropy value decreases, proving that the entropy value can reflect tumor heterogeneity by reflecting the complexity of the internal texture of the lesion. $V_e$ reflects the size of extracellular space. PTEN loss activates PI3K / Akt / mTOR signaling pathway, tumor proliferation is active, and EES is decreased (decreased $V_e$). In this study, PTEN has no correlation with $V_e$ (meanvalue), but has positive correlation with $V_e$ (Q10, Q 25) in AC group and $V_e$ (Q75, Q90, Q95) in SCLC group. It may be due to the spatial heterogeneity of lung cancer tissue, and the quantile describe the gray distribution of each pixel in the lesion, so the $V_e$ quantile may better reflect the micro physiological structure of tumor tissue.

P-Akt is an important signal transducer in PI3K / Akt / mTOR signaling pathway. Deletion and inactivation of PTEN gene and overexpression of PI3K gene can stimulate Akt activation, and promote tumor growth, invasion and metastasis through a variety of downstream effectors (including mTOR). $K_{\text{ep}}$ describes the rate constant of backflux from EES to plasma, which is closely related to the permeability of blood vessel wall. In this study, $K_{\text{ep}}$ (Q5, Q10) was positively correlated with P-Akt, and $K_{\text{ep}}$ (energy) was negatively correlated with P-Akt, indicating that the quantile and energy of $K_{\text{ep}}$ can reflect the expression of P-Akt by evaluate the heterogeneity and microvascular permeability of lung cancer tissues. A possible explanation is that PI3K/Akt pathway up-regulates the expression of hypoxia-inducible factor-1(HIF-1), thereby activates vascular endothelial growth factor (VEGF) expression to mediate angiogenesis [22].
As the most important downstream signal molecule of PI3K / Akt, mTOR is activated by Akt phosphorylation, and the expression of mTOR is abnormally increased in tumor progression. In this study, we found that $K^{\text{trans}}$ (Q5) in SCC was positively correlated with m-TOR, and $V_e$ (mean) in SCC was negatively correlated with m-TOR in SCC group. The activation of m-TOR promotes tumor proliferation. $V_e$ is related to the size of extracellular space. The more active the tumor proliferation, the smaller $V_e$. With the growth of tumor, the angiogenesis of tumor increases, which shows the decrease of $V_e$ and the increase of $K^{\text{trans}}$ in histogram. $V_p$ reflects the amount of tissue perfusion. The positive correlation between $V_p$ (meanvalue, Q75, Q90, Q95) and mTOR in SCLC also indicated that the activation of downstream signal molecules of this signal pathway increased tumor blood supply.

Our research has several limitations. First of all, the motion artifacts of pulmonary DCE-MRI were common due to respiration. However, we used 3D non rigid correction technology to reduce the impact of motion artifacts on the study. Secondly, due to the limitations of MRI in the use of lung, the sample size of this study was small, especially in small cell lung cancer, which needed to be expanded for further study. Third, the spatial distribution of perfusion parameters is uneven, especially in the peritumoral region, so it is difficult for histopathological samples to accurately match the corresponding ROI delineation regions.

**Conclusions**

In conclusion, DCE-MRI quantitative perfusion histogram can be used as a noninvasive, in vivo and reproducible method to indirectly evaluate the activation of P13K / Akt / mTOR signal pathway gene in lung cancer, and provide a way for MRI to evaluate tumor heterogeneity at the molecular level, which is of great significance to clinical practice.

**Abbreviations**

DCE-MRI: dynamic contrast-enhanced magnetic resonance imaging

SCC: squamous cell carcinoma

AC: adenocarcinoma

SCLC: small cell lung cancer

AKT: protein kinase B

mTOR: mammalian target of rapamycin

PTEN: phpsphase and tensin homologue deleted on chromosome 10

ROI: region of interest
$K_{\text{trans}}$: transfer constant

$V_p$: fractional volume of plasma

$K_{\text{ep}}$: rate constant of backflux from extravascular extracellular space [EES] to plasma

$V_e$: fractional volume of EES

$F_p$: tissue plasma perfusion

**Declarations**

**Ethics approval and consent to participate**

This study was approved by the Institutional Review Board of Shaoxing People's Hospital (approval No. 2020-64). As this study involved a retrospective review of medical records, the requirement for informed consent was waived.

**Consent for publication**

N/A

**Availability of data and material**

All data generated or analysed during this study are included in this published article.

**Competing interests**

The authors declare that they have no competing interests.

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**Authors' contributions**

BZ was involved in study design; analyzed and interpreted the patient data regarding the lung cancer; was the main writer of the manuscript. ZZ was involved in study design; put forward many opinions on the manuscript. YH performed the histological examination of the lung, and was a major contributor in writing the manuscript. HM performed the histological examination of the lung. MZ did some image processing. CW guided and performed the histological examination. GY participated in investigation. MZ reviewed the manuscript. All authors read and approved the final manuscript.
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