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Use of quantitative CT analysis to evaluate the degree of lung destruction in lymphangioleiomyomatosis

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Abstract

Background Lymphangioleiomyomatosis (LAM) is a multisystem disease that mainly presents with cystic damage in the lungs. The purpose of this study was to quantify the degree of pulmonary cystic damage in CT and to evaluate its correlation with pulmonary function tests (PFTs) and serum levels of vascular endothelial growth factor (VEGF-D).

Subjects and methods 21 patients were included and 36 CT scans and PFTs were analyzed. The correlation of serum VEGF-D levels of 17 patients and their 24 CT scans were studied. Cystic areas were identified by the software. The volumetric percentage of cystic regions of the total lung volume was calculated to get a cyst score. A ROC curve was calculated to select the threshold at which the cyst scores could predict the lung impairment best.

Results The cyst scores correlated best with FEV1%pred ($r = -0.72$, $p < 0.01$) and DLCO%pred ($r = -0.82$, $p < 0.01$). The correlation with serum VEGF-D levels ($r = -0.143$, $p = 0.506$) was not obvious. The Youden Index is max (0.667) when cyst score is 15.80%.

Conclusion The pulmonary cyst scores on CT is strongly correlated with FEV1%pred and DLCO%pred. However, the association with serum levels of VEGF-D is not obvious. Cyst score $> 15.80\%$ might indicate an abnormal lung function and patients are recommended a sirolimus treatment.

Keywords: lymphangioleiomyomatosis, cyst scores, pulmonary damage, computer tomography

BACKGROUND

Lymphangioleiomyomatosis (LAM) is a multisystem disease that primarily affects premenopausal women, but several cases are reported in post-menopausal women.[1, 2] LAM occurs sporadically (S-LAM) or is associated with tuberous sclerosis complex (TSC), and the TSC-LAM is heritable.[3] The mutation of TSC genes is involved in the pathogenesis of LAM. The inactive mutation of TSC1 or TSC2 genes results in the abnormal activation of the target of rapamycin complex 1 (mTORC1), affecting the morphology, growth, and survival of cells.[4] Abnormally proliferated smooth muscle-like cells (LAM cells) infiltrate the lungs, resulting in airflow obstruction and diffuse pulmonary cystic changes.[5] The clinical manifestations of LAM patients include progressive dyspnea after activities, recurrent spontaneous pneumothorax, refractory chylothorax and finally lead to respiratory failure.[6]

Methods used to assess the severity and progression of pulmonary involvement in LAM include arterial blood gas (ABG), St. George's Respiratory Questionnaire (SGRQ), six-minute walk test (6MWT), pulmonary function test (PFT), and high-resolution computed tomography (HRCT).[7] Serum levels of vascular endothelial growth factor (VEGF-D) is a diagnostic biomarker of LAM and associated with severity of LAM.[8] Among these methods, PFT is the most frequently used.[9] PFT typically shows obstructive physiology with a progressive reduction in forced expiratory volume in 1-second percentage predicted (FEV1%pred) and reduced diffusion capacity of the lungs for carbon monoxide (DLCO).[10, 11] According to guidelines released by the American Thoracic Society/Japanese Respiratory Society, for patients with LAM with abnormal/declining lung function, sirolimus treatment was strongly recommended.[12] Abnormal lung function is defined as an FEV1 less than 70% predicted.[12] However, the PFT test requires patient cooperation to keep the results credible and it is forbidden to LAM patients whose complications include pneumothorax or massive chylothorax. Characteristic features that thin-wall cystic air sacs evenly distributed in bilateral lobes in HRCT are critical to identifying LAM.[13] CT is a non-invasive test and does not need much cooperation. It directly shows the cystic changes in the lungs. Several studies have used quantitative analysis of CT scan images to evaluate the severity of cystic destruction in LAM and demonstrate the correlation between lung damage and PFT.[9, 14-16] But most of the subjects recruited are from Europe or the US. There is no study focusing on the quantitative CT analysis of LAM patients in Asia. Thus, this study aims to quantify the extent of cystic changes in LAM patients from China and compare the cyst scores with PFT and VEGF-D levels. We also construct a ROC curve to search for a threshold of cyst score which predicts the severity of lung damage.

MATERIALS AND METHODS

Population

We retrospectively searched every patient with LAM who visited our hospital and excluded patients who did not perform CT examinations in our hospital. This study finally included 19 female patients with S-LAM and two with TSC-LAM. All patients

visited our hospital between 2012 and 2019. 12 of them are diagnosed by the combination of typical HRCT features, serum VEGF-D levels, and clinical manifestations.[12] Nine patients have renal or abdominal angiomyolipoma or lymphangioliomyomas. five of them have experienced pneumothorax or chylothorax, but none of them was evaluated during an episode of pneumothorax or chylothorax. 18 of them accepted rapamycin for treatment since diagnosed.

CT database

CT scans with no matched PFTs or VEGF-D levels which tested in six months were excluded. Of 21 patients included in this study, 11 performed one CT examination, six patients had two, three patients had three, and only one patient had four CT examinations. In the total 36 CT scans, each was matched with a PFT tested in 6months. Only 24 CT scans which belonged to 17 patients are matched with VEGF-D levels.

The scans contained 40-70 slices whose thickness is 5mm at 5mm intervals. The soft-tissue reconstruction filter was used to emphasize the range of image pixel values for lung tissues. Quantitative analysis of cystic lesions was accomplished by the FACT Medical Imaging System (DEXHIN; Shanxi, China). A threshold value of -950 HU was applied to segment lungs to select areas less than -950 HU, which is defined as the cystic region (**Figure 1**).[7] Then, a cyst score, which is the volumetric percentage of cystic regions of the total lung volume, was calculated automatically.

Pulmonary Function Values and VEGF-D levels

The pulmonary function tests were performed using the Jaeger MasterScreen IOS (Vyaire Medical, Hchberg, Germany) strictly in compliance with the 2005 American Thoracic Society/European Respiratory Society guidelines.[17] FEV1 and DLCO were obtained.

Serum VEGF-D levels were measured using the Quantikine Human VEGF-D Immunoassay (R&D Systems; Minneapolis, MN) according to the manufacturer's instructions by enzyme-linked immunosorbent assay (ELISA). Patients' understanding of the consent form has been checked before taking the blood samples.

Statistical Analysis

All statistical analyses were done using the Statistical Package for the Social Sciences (SPSS) 22.0 software (SPSS for Microsoft Windows, package version 22.0; SPSS Inc., Chicago, IL, USA). Data are reported as the mean $\pm$ SD for variables with normal distribution, as the median (25th–75th percentiles) for variables with non-normal distribution, or as numbers (percentiles). Pearson correlation coefficients were calculated to measure the degrees of association between the cyst score and PFT and levels of VEGF-D. The Receiver Operating Characteristic (ROC) curve was used to select the optimal cutoff point at which the sensitivity and specificity were maximally reached. $P < 0.05$ was considered statistically significant.

RESULTS

21 LAM patients were included in the study. Clinical features are described in Table 1. The mean age of the first symptoms was 38.1 ± 10.2 years, and the mean age of diagnosis was 44.1 ± 6.6 years. Three (14.3 %) patients are presented with TSC, 13 (61.9%) had renal angiomyolipoma, or abdominal angiomyolipoma, one (4.8%) had a

history of pneumothorax and four (19%) had chylothorax history. None of the patients was an ex-smoker. 18 (85.7%) patients were receiving rapamycin treatment (**Table 1**).

Table 1 clinical features of 21 patients

	n=21
Age at first symptoms, years	38.1±10.2
Age at diagnosis, years	44.1±6.6
TSC-LAM	2 (9.5%)
Renal/abdominal angiomyolipoma	9 (42.86%)
History of pneumothorax	1 (4.8%)
History of chylothorax	4 (19.0%)
Ex-smokers	0 (0%)
sirolimus users	18 (85.7%)

Computed Tomography

The CT image from a LAM patient with characteristic lung damage is shown in Figure 1. As is illustrated, 23% of the total lung area was occupied with cysts that are colored. The mean score of cystic lesions on CT compared with PFT was 18.1%±11.2%, and the median score of cysts compared with VEGF-D was 19.66% ± 12.26% (

Table 2,

Table 3).

Table 2 correlations between cyst scores and FEV1%pred and DLCO%pred (n=36)

	Scores (%)	FEV1%pred	DLCO%pred
mean±SD	18.13±11.167	70.37±18.136	61.10±26.674
r		-.716**	-.821**
p		<0.01	<0.01

**P < 0.01 (compared with cyst scores)

Table 3 correlations between cyst scores and VEGF-D (n=24)

	Scores (%)	VEGF-D (pg/mL)
median ± IQR	19.66 ± 12.26	1077 ± 1050
r		-.143
p		.506

Pulmonary Function Tests and serum VEGF-D levels

Mean FEV1%pred and DLCO%pred were 70.4%±18.1% and 60.5%±26.3% respectively. Median serum VEGF-D levels was 1077(727.0-1777) pg/mL (**Table 2,**

Table 3).

Associations Between the Cyst and Other Variables

The cyst scores correlated best with FEV1%pred (r = -0.72, p<0.01) and DLCO%pred (r = -0.82, p<0.01). The correlation with serum VEGF-D levels (r = -

0.143, $p = 0.506$) was not obvious. ROC curve was computed and drawn in Figure 2. FEV1%pred <70% was defined as impaired lung function (state variable = 1). The Youden Index is max (0.667) with a 94% sensitivity and a 72% specificity when the cyst score is 15.80% (**Figure 2**).

DISCUSSION

This study investigated the extent of pulmonary cystic damage in LAM and examined the correlation between cyst scores and PFT and VEGF-D levels. The main findings of this study are as follows: (1) the extent of pulmonary cystic damage is correlated with FEV1%pred and DLCO%pred; (2) there was a no obvious association between VEGF-D levels and cystic damage of lung in LAM patients. (3) the cyst score may be the new indicator of the degree of lung impairment with 15.80% to be the threshold of rapamycin treatment or not.

Previous studies have shown that quantitative analysis of HRCT may be used to evaluate disease severity in LAM patients.[16] Our study tested and verified the correlation between the cyst scores and FEV1%pred and DLCO%pred. Though HRCT is an important follow-up examination that directly shows the change of the lung cysts, the progress on CT scan could be very slight especially in patients taking sirolimus. With the quantitative analysis of CT scans, the slight changes of lung cysts can also be identified and quantified. The results indicate the potential of quantitative CT analysis to assess the pulmonary function and the extent of lung damage in LAM patients. Our study used ordinary CT scans to calculate the cyst scores which also showed a strong correlation with the PFT. It suggests that when the diagnosis has been decided, the follow-up HRCT examination to evaluated lung damage may be replaced by the CT.

For the first time, we evaluated the possibility of cyst scores to determine treatment. ATS/JRS suggested that LAM patients with FEV1%pred<70% are strongly recommended to use sirolimus.[12] Our study found that when the cyst score is >15.80%, the sensitivity and specificity to predict a PFT of which FEV1%pre is <70% is 94% and 72%. The sensitivity is 27.8% when specificity is 100%. Thus, the cyst score >15.80% might indicate an abnormal lung function. For LAM patients with a risk of recurrent pneumothorax, PFT is forbidden. The cyst score may help evaluate the degree of lung damage and decide whether the patient should receive sirolimus treatment. But in our study, the sample size is not large enough and the Youden Index is only 0.667, so evidence with stronger quality is still necessary to study.

Our study found no correlation between VEGF-D and the cyst score. Though it might be due to the small size of the sample, it indicated that this important marker for diagnosis is not an appropriate tool to access the degree of cystic damage in LAM. Besides, the association between serum VEGF-D levels and PFT parameters including FEV1%pred and DLCO%pred was not proved in previous researches.[8, 18, 19] Previous research has found that VEGF-D is increased especially in those with lymphatic involvement.[8, 18] In our study, patients included with lymphatic involvement like chylothorax or lymphangioleiomyomas were only 7 (33.3%). That may also explain why the correlation of cyst score with VEGF-D is not obvious. However, a study reported that serum VEGF-D levels are higher in patients with greater

cystic damage on semiquantitative CT.[20] Therefore, more studies are still needed to study the role of VEGF-D in assessing disease severity in all aspects.

Our study has limitations that need to be pointed out. The small sample size which decreases the credibility of results has been addressed. Although we found a strong correlation between the cyst scores and PFT parameters, we didn't compare the cyst scores with other common ways to evaluate lung function and activity endurance, such as ABG, 6MWD, and SGRQ. Another limitation of our study is that we used ordinary CT scans to reconstruct the pulmonary and analyze the ratio of cysts to lung volume. More ideal CT data would be thin-section CT scans which have more than 200 layers.

CONCLUSIONS

In summary, in this study, we found that the pulmonary cyst scores on CT are strongly correlated with FEV1%pred and DLCO%pred. However, we have not found an association with serum levels of VEGF-D, which suggests that it is not an appropriate marker to access the degree of cystic damage in LAM. The expansion of the sample size is necessary to test and verify the results. In the future, the cyst scores are needed to compare with other commonly used ways to evaluate lung function. To improve the accuracy of the calculation results of cyst scores, enough HRCT scans are needed.

ABBREVIATIONS

ABG: arterial blood gas; AML: Angiomyolipoma; CT: computer tomography; DLCO: The diffusing capacity of the lung for carbon monoxide; ELISA: enzyme-linked immunosorbent assay; FEV1: Forced expiratory volume in 1 s; FVC: Forced vital capacity; HRCT: High resolution computer tomography; LAM: Lymphangioliomyomatosis; mTORC1: Mammalian target of the rapamycin complex 1; PFT: pulmonary function tests; ROC: Receiver Operating Characteristic; SD: Standard deviation; SGRQ: St. George's Respiratory Questionnaire; 6MWD: six minute walk distance; SPSS: Statistical Package for the Social Sciences; TSC: Tuberous sclerosis complex; VEGF-D: vascular endothelial growth factor;

DECLARATIONS

Ethics approval and consent to participate

The study was part of LAM registry study of Peking Union Medical College Hospital (S-379). All subjects included in this study signed informed consent documents.

Consent for publication

Consent for publication was obtained from all participants.

Availability of data and materials

The datasets used and analyzed during the current study are available from the corresponding author.

Competing interests

The authors declare that they have no competing interests.

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Authors contribution

LY and MJ contributed conception and design of the study. XS and JW are joint first authors. XS and JW took full responsibility for the content of this manuscript, including its database and analysis. LY and MJ drafted the initial manuscript. All authors contributed to manuscript revision, read, and approved the submitted version.

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Figure 1 CT images with data segmentation. The percentage of the total lung area colored with an attenuation <-950 HU (depicted) is 23%.[_](#)

Figure 2 ROC curve of cyst scores when FEV1%pred $<70\%$ was defined as impaired lung function (state variable = 1). The area under the ROC curve is 0.877 ± 0.061 (95%CI, 0.758-0.995). The max Youden Index is 0.667 when the cyst score is 15.80% with a 94% sensitivity and a 72% specificity.

Figures

Figure 1

CT images with data segmentation. The percentage of the total lung area colored with an attenuation <-950 HU (depicted) is 23%.

Figure 2

ROC curve of cyst scores when FEV1%pred <70% was defined as impaired lung function (state variable = 1). The area under the ROC curve is 0.877 ± 0.061 (95%CI, 0.758-0.995). The max Youden Index is 0.667 when the cyst score is 15.80% with a 94% sensitivity and a 72% specificity.