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Original Article

Special computer-aided computed tomography (CT) volume measurement and comparison method for pulmonary tuberculosis (TB)

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Abstract: The computed tomography (CT) manifestations in pulmonary tuberculosis (PTB) patients are complex and could not be quantitatively evaluated. We aimed to establish a new method to objectively measure the lung injury level in PTB by thoracic CT and make quantitative comparisons. In the retrospective study, a total of 360 adults were selected and divided into four groups according to their CT manifestations and medical history: Normal group, PTB group, PTB with diabetes mellitus (DM) group and Death caused by PTB group. Five additional patients who had continuous CT scans were chosen for preliminary longitudinal analysis. We established a new computer-aided CT volume measurement and comparison method for PTB patients (CACTV-PTB) which measured lung volume (LV) and thoracic volume (TV). RLT was calculated as the ratio of LV to TV and comparisons were performed among different groups. Standardized RLT (SRLT) was used in the longitudinal analysis among different patients. In the Normal group, LV and TV were positively correlated in linear regression ($\hat{Y}$=-0.5+0.46X, R^2=0.796, $P<0.01$). RLT values were significantly different among four groups (Normal: 0.40±0.05, PTB: 0.37±0.08, PTB+DM: 0.34±0.06, Death: 0.23±0.04). The curves of SRLT value from different patients shared a same start point and could be compared directly. Utilizing the novel objective method CACTV-PTB makes it possible to compare the severity and dynamic change among different PTB patients. Our early experience also suggested that the lung injury is severer in the PTB+DM group than in the PTB group.

Keywords: Pulmonary tuberculosis, computer-aided computed tomography, volume measurement, lung volume, thoracic volume

Introduction

Tuberculosis remains one of the most important causes of death from infectious diseases. In 2010 there were 8.8 million new cases of tuberculosis (TB) and 1.4 million TB-related deaths worldwide [1]. Besides the chest X-ray examination, computed tomography (CT) is one of the most important diagnostic methods for pulmonary tuberculosis (PTB). Presenting 3D digital data, CT scans can provide additional information than traditional X-ray. However, in nowadays, CT analysis and comparison were often made by radiologists and physicians, which was subjective and greatly relied on individual experience. Several quantitative methods, algorithm and software in analysis of thoracic CT [2, 3] and computer-aided diagnosis (CAD) [4] were previously reported for solid pulmonary lesions, especially for lung cancer. However, due to the complicated pathological manifestations and dynamic changes in PTB [5], no quantitative analysis of CT image in PTB patient has been established.

We hypothesized that there might be a certain liner relationship between lung volume (LV) and thoracic volume (TV) in healthy subjects. After PTB occurs, LV would change during the course, while TV would be relatively stable. Therefore, the normal relationship would be broken and a new relationship would be formed. We further speculated that the change of the relationship between LV and TV could reflect the severity of PTB. To verify our hypothesis and to establish an objective method of evaluating PTB severity,

Table 1. Baseline characteristics among research groups

	Normal	PTB	PTB+DM	Death
Number	264	48	36	7
Male	132	26	30	6
Age (years)	32.2±10.7	38.9±16.6	53.9±12.4	63.7±17.9

Age was presented as mean ± standard deviation.

we developed a computer-aided CT volume measurement and comparison method for PTB patients (CACTV-PTB). In the current report, we introduced this new method and its preliminary applications in quantitative comparison and longitudinal analysis.

Materials and methods

Ethics statement

The current study was approved by the Research Ethics Committee and waiver of informed consents was granted since the data were retrospectively reviewed and analyzed anonymously.

Patients and materials

In the current retrospective study, all PTB patients were chosen from inpatients of Beijing Chest Hospital, Capital Medical University. PTB was diagnosed directly by positive smear or culture of sputum; or indirectly by 1) excluding other types of pneumonia if there was no improvement after two-week treatment with broad-spectrum antibiotic such as cephalosporin; and 2) more than two evidence of chest radiographs, tuberculin skin tests (TSTs), or special tests for Mycobacterium tuberculosis such as polymerase chain reaction (PCR) and interferon-gamma release assays (IGRAs). In the current study, we only included secondary PTB patients, which covers the majority of adult PTB, from inpatients of our hospital between 2010 and 2012. Among them, patients with extra-pulmonary tuberculosis, other respiratory diseases, and heart disease were excluded. We also included healthy subjects as normal controls to obtain the baseline data calculated by CACTV-PTB and to compare with other groups. Healthy subjects were selected from residents who attended health check-up in Beijing Chest Hospital with normal CT manifestation.

The entire thoracic CT in the supine position was transferred from the medical imaging center of Beijing Chest Hospital. CT was performed on Light Speed VCT (GE, USA) and Light Speed 16 (GE, USA). The parameters used for evaluation were 3.75-mm or 5-mm thickness section at 10-mm intervals with a 512×512 reconstruction matrix, 120 kV. All images were obtained at window settings appropriate for lung parenchyma (level, -400 Hounsfield units [HU]; width, 1,500 HU) and for thoracic (level, 40 HU; width, 350 HU). Before transmission all patients' information were anonym zed. Two independent radiologists read all CT images and confirmed the final medical reports. According to the CT report and medical record, all subjects were divided into four groups: Normal, PTB, PTB+DM and Death caused by PTB (**Table 1**). Patients in death group were free of comorbidities related to death, such as cardiovascular diseases or tumor. In PTB and PTB+DM groups, the selected CT scans were the first time CT from the onset of PTB. In Death group, the CT scans were the last CT before death, since we want to evaluate the degree of deterioration between PTB onset and death. None of the patients were taken corticosteroids or other immunosuppressant. Five additional patients who were sputum-positive and had continuous thoracic CT scans were chosen for longitudinal analysis, and none of them had co morbidities.

CACTV-PTB

Work flow: The core of CACTV-PTB is to measure LV using lung window CT and TV using media stinum window CT, respectively. First step is to remove external image such as clothes from body image. The algorithm design of this step relies on the difference in image feature. The sum of body pixels in different directions would be larger than a particular value, but external pixels not. A few body pixels under the skin would be removed with external pixel, but would not influence the LV and TV calculation. After the shared first step, LV and TV were computed individually. RLT was calculated as the ratio of LV to TV:

$$RLT = \frac{LV}{TV} \tag{1}$$

RLT can be used as a parameter in longitudinal analysis of intra-person CT. In order to compare

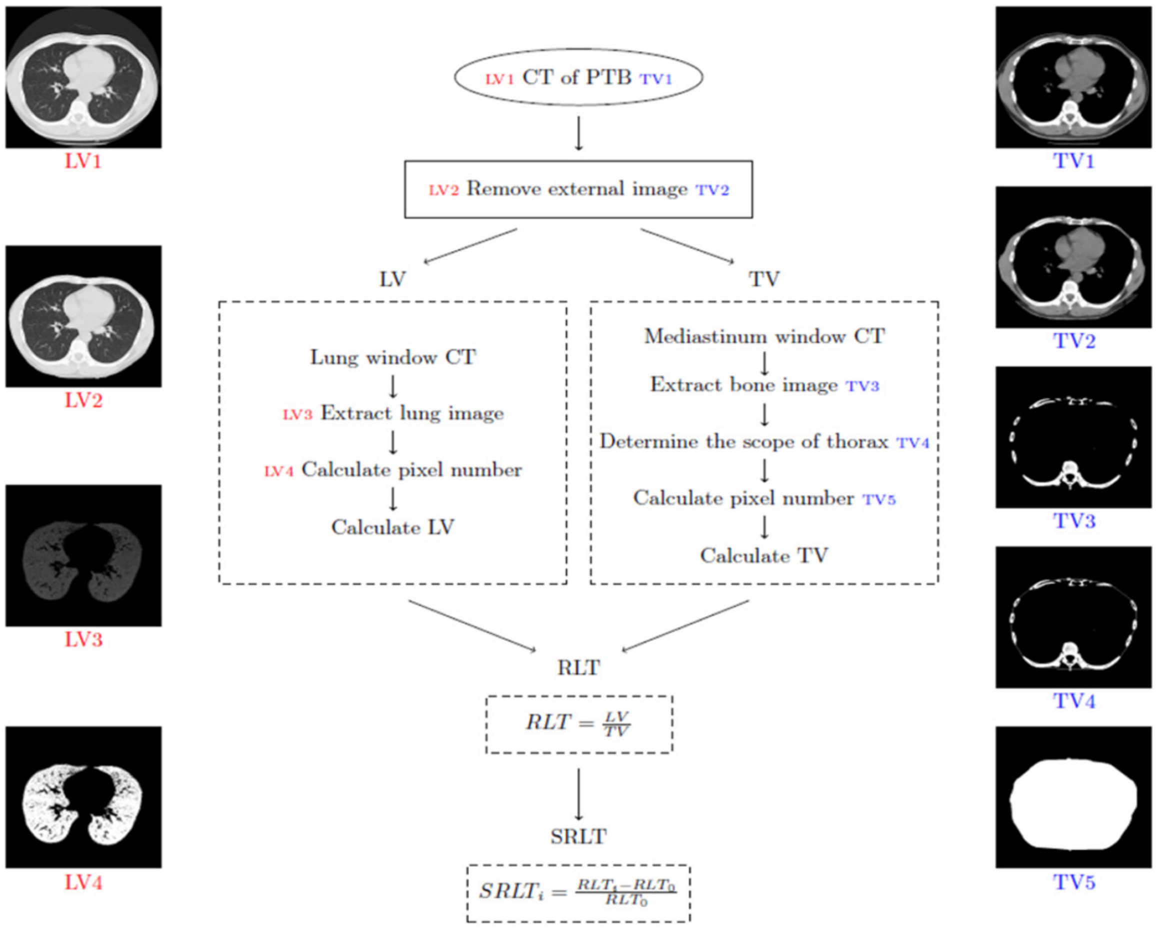

Figure 1. Work flow of CACTV-PTB. Center is the work flow of CACTV-PTB. The series images in the left are different steps of constructing LV. The series images in the right are different steps of constructing TV.

dynamic change among different individuals, we further developed standardized RLT as SRLT:

$$SRLT_i = \frac{RLT_i - RLT_0}{RLT_0} \quad (2)$$

In above equation *I* represents the time sequence number of CT from onset of PTB. The work flow of CACTV-PTB was shown in **Figure 1**.

The calculation of LV: The material of calculating LV is lung window CT. Each image of CT was handled separately. Firstly, we segmented the normal lung image from other body images according to the difference in pixel value, which was significantly lower in the lung image than in the other body images. We analyzed all pixels values of the lung images in normal group. When pixels ranged from 0 to 1, the mean value of lung pixels was 0.26 (standard deviation 0.06). Due to the left skewed distribution, we chose the 95% percentile ($P_{2.5}$=0.16, $P_{97.5}$=0.41) as the boundary values of lung pixels. To maximally remove the image of gas when cavity image existed, the lower boundary value could be increased to 0.2, which would not substantially influence the LV calculation. Notably, the image pixels of surrounding tissue or bones were significantly higher than lung. Therefore, we designed an algorithm which could easily segment the lung image (**Figure 1** LV3). Then we can calculate each layer's lung image pixels as L (**Figure 1** LV4), and summing the values as LV:

$$LV = TR^2 \sum_{i=1}^{n} L_i \quad (3)$$

In the above equation T represents the thickness of each CT layer, R represents the width of each pixel. These two values could be obtained

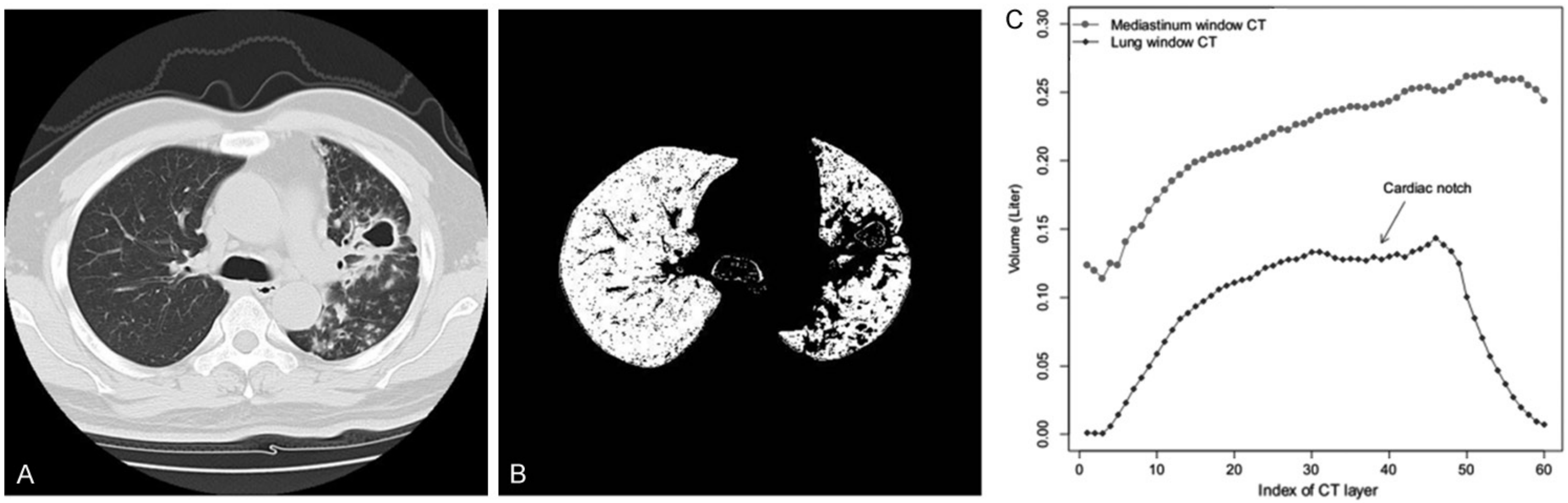

Figure 2. CACTV-PTB. A. An original PTB CT; B. The visualized volume image of A after CACTV-PTB processing; C. The curves of each layer's CT volume. Blue line is LV. Arrow points to the cardiac notch. Red line is TV.

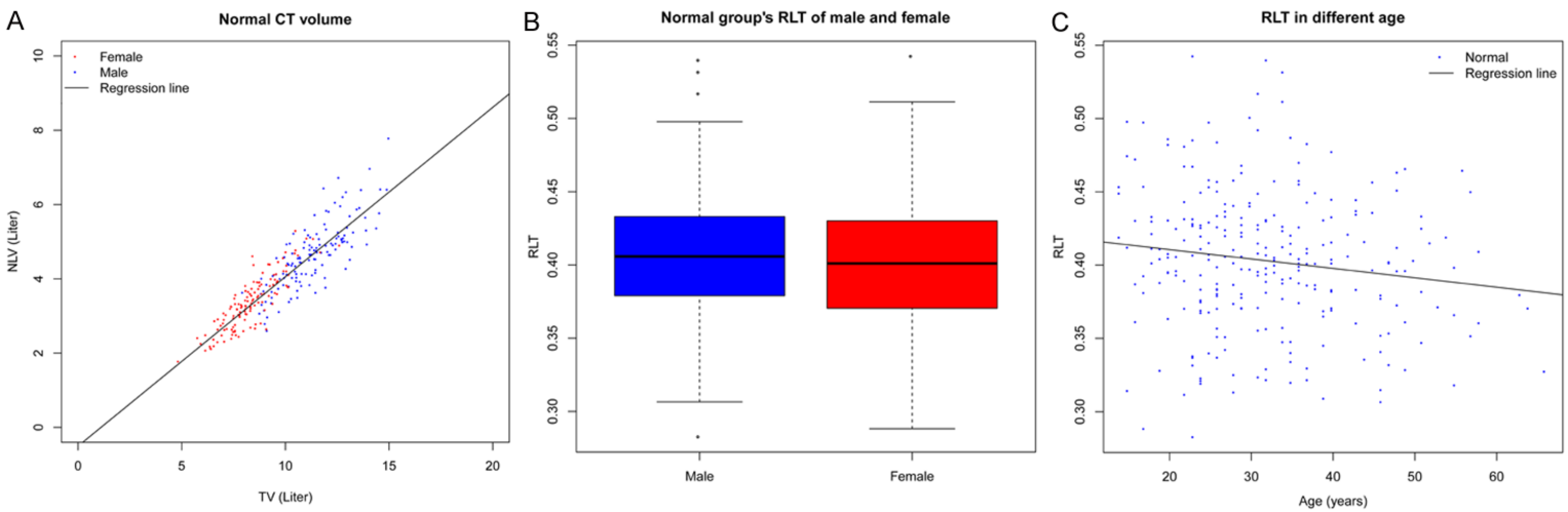

Figure 3. CACTV-PTB in normal thoracic CT. A. The relationship between LV and TV; B. The comparison of RLT values between male and female; C. The distributions of RLT values at different age. RLT was calculated as the ratio of LV to TV.

Table 2. Comparison between male and female in normal thoracic CT

	Male	Female	*P*
LV	4.66±0.90	3.37±0.73	<0.000
TV	11.41±1.49	8.40±1.26	<0.000
RLT	0.41±0.05	0.39±0.05	0.133

RLT was calculated as the ratio of LV to TV.

Table 3. Correlation between LV and TV in different groups of thoracic CT

Groups	LV	TV	R^2	Regression equation	*P*
Normal	4.01±1.04	9.91±2.04	0.796	$\hat{Y}$=-0.5 + 0.46X	<0.000
PTB	3.66±1.26	9.69±2.33	0.626	$\hat{Y}$=-0.48+0.42X	<0.000
PTB+DM	3.75±1.13	10.76±1.93	0.647	$\hat{Y}$=-1.33+0.47X	<0.000
Death	2.22±0.55	9.56±1.21	0.498	$\hat{Y}$=-0.85+0.32X	0.076

from CT outputs. The represents the index of layer, and represents the total number of layers.

The calculation of TV: The material of calculating TV is mediastinum window CT. Each image of CT was handled separately. Firstly, we segmented the bone image from other body images. Since the bone pixel value was higher than other body images, we determined a cutoff value as 0.8 (**Figure 1** TV3). After this step, the bone image became scatteredly distributed, which was difficult for calculating TV. Therefore, we developed an algorithm which can contour the bone image and form a closed region in each layer of thoracic CT (**Figure 1** TV4). Then we can calculate each layer's thoracic image pixels as B (**Figure 1** TV5), and summing the values as TV:

$$TV = TR^2 \sum_{i=1}^{n} B_i \tag{4}$$

In the above equation T, R, i, and n represent the same meaning as in the LV equation.

Statistical analysis

All values were presented as mean ± standard deviation. Difference between two groups was evaluated by the two-tailed Student's *t* test, while test with Holm adjust method were used for multiple comparisons. The correlation between two parameters was evaluated by linear regression, and the coefficient of determination (R^2) was calculated and tested by *F* test. R version 3.0.1 was used for all statistical analysis [6]. Two sided *P* value <0.05 was considered as statistically significant.

Results

CACTV-PTB

The manifestations of thoracic CT in PTB patients are extremely complicated. We developed CACTV-PTB based on the hypothesis that LV could reflect PTB severity. Therefore, the accuracy of the LV measurement could represent the quality of CACTV-PTB. **Figure 2A** and **2B** showed the CT layer images of a PTB patient before and after CACTV-PTB processing. Most of the lesion image was removed (left lung), while the normal image was maximally retained (right lung). **Figure 2C** showed each layer's LV and TV of a normal thoracic CT. A good continuity was found in both curves, and the cardiac notch could be observed in the LV curve. The area under the curve represented for the summed LV and TV, respectively.

CACTV-PTB in normal thoracic CT

We hypothesized that there was a certain linear relationship between LV and TV in healthy subjects. **Figure 3A** showed that LV and TV were positive correlated, which supported our hypothesis. The regression equation of LV-TV is $\hat{Y}$=-0.5+0.46X, R^2=0.796, P<0.01 (**Table 3**). In addition, we found that the values of LV and TV were significantly different between male and female (**Table 2**). However, none significant gender difference was observed for the RLT value (**Figure 3B**). Therefore, the comparison of RLT value could rule out the gender influence. Age was also associated with RLT value (**Figure 3C**). With increased age, the RLT value declined. Although the linear relationship was statistically significant, the R^2 value was ignorable (0.021). Therefore, we could neglect the age influence in the following comparison of RLT among different groups.

CACTV-PTB in different groups of PTB thoracic CT

The primary aim of CACTV-PTB was to objectively compare the degree of lung injury among

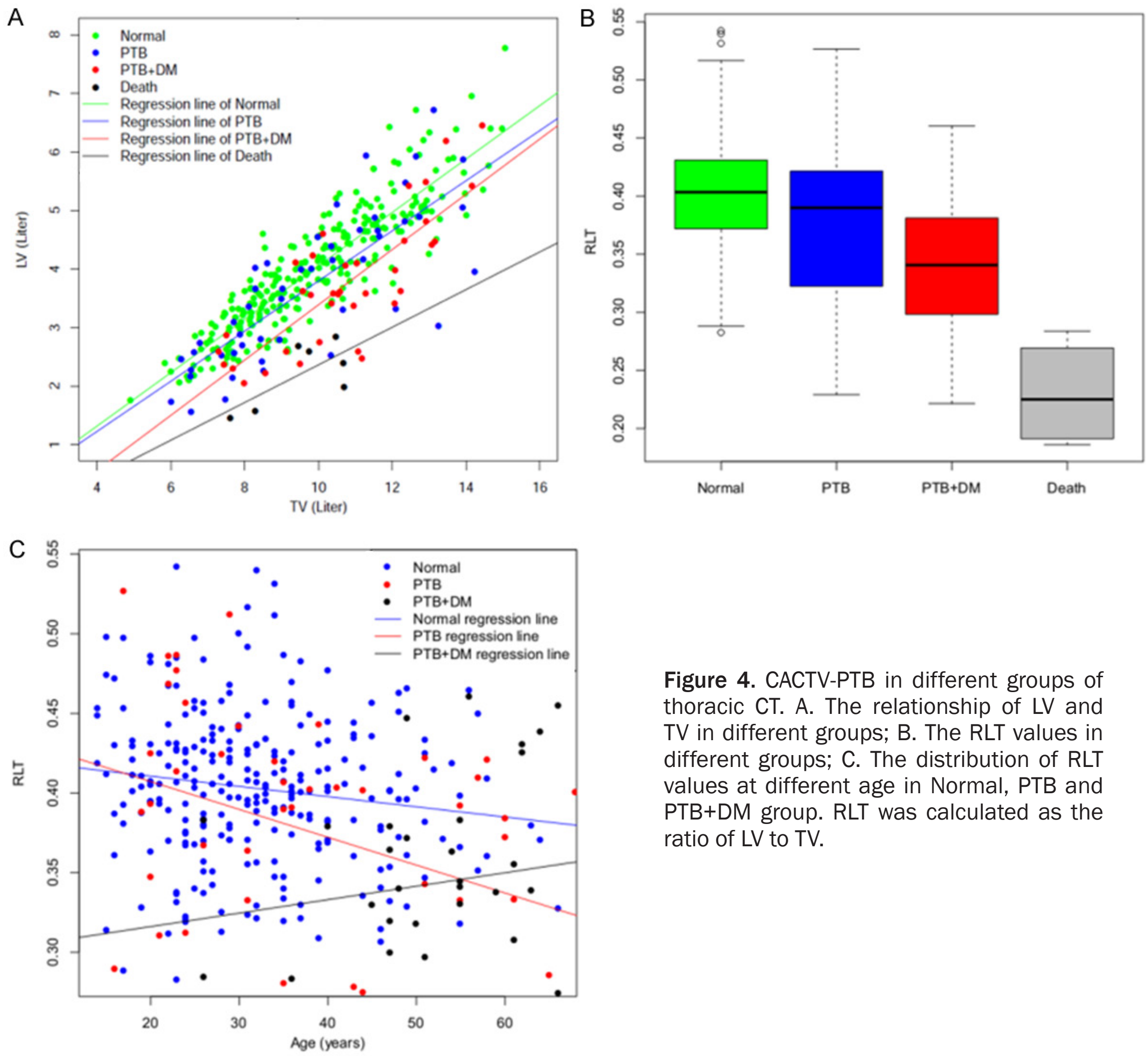

Figure 4. CACTV-PTB in different groups of thoracic CT. A. The relationship of LV and TV in different groups; B. The RLT values in different groups; C. The distribution of RLT values at different age in Normal, PTB and PTB+DM group. RLT was calculated as the ratio of LV to TV.

different groups of PTB. The comparison of LV-TV relationship and RLT values among four groups (Normal, PTB, PTB+DM and Death caused by PTB group) was shown in **Figure 4. Figure 4A** presented the LV-TV relationships in different groups. With the increased disease severity, the LV-TV curve moved towards the bottom of the graph. As in the Normal group, significant positive linear relationships were also found in PTB group and PTB+DM group. Although a similar trend was observed in the Death group, the linear relationship was not statistically significant which might be due to the small sample size (**Table 3**). Comparing the RLT values among different groups, we found a gradually increased severity of lung injury across the groups of PTB, PTB+DM, and Death, which were all higher than the Normal group (**Figure 4B**; **Table 4**). We also evaluated the association between age and RLT in PTB group and PTB+DM group. Interestingly, along with the increased age, the level of lung injurywas aggravated in PTB, but decreased in PTB+DM (**Figure 4C**). However, due to the small sample size, the linear relationship did not reach statistical significance in PTB+DM group, and the R^2 values in both groups were small (**Table 5**).

CACTV-PTB in longitudinal analysis

Another aim of CACTV-PTB was to make intra- and inter-patient longitudinal analysis of PTB severity. As shown in **Figure 3**, RLT value could reflect PTB severity uninfluenced by gender. **Figure 5A** showed RLT longitudinal curve from different patients, which well represented the dynamic changes of PTB severity individually. However due to the discrete of RLT, it could not be directly compared in the longitudinal analysis among individuals. Therefore, SRLT value

Table 4. RLT multiple comparison among different groups of thoracic CT

Groups	RLT	P			
		Normal	PTB	PTB+DM	Death
Normal	0.40±0.05	1	0.002	<0.000	<0.000
PTB	0.37±0.08	0.002	1	0.013	<0.000
PTB+DM	0.34±0.06	<0.000	0.013	1	<0.000
Death	0.23±0.04	<0.000	<0.000	<0.000	1

RLT was calculated as the ratio of LV to TV.

Table 5. Correlation between RLT and age in different groups of thoracic CT

Groups	RLT	Age	R^2	Regression equation	P
Normal	0.40±0.05	32.2±10.7	0.021	$\hat{Y}$=0.42-0.001X	0.018
PTB	0.37±0.08	38.9±16.6	0.147	$\hat{Y}$=0.44-0.002X	0.007
PTB+DM	0.34±0.06	53.9±12.4	0.026	$\hat{Y}$=0.29+0.001X	0.345

RLT was calculated as the ratio of LV to TV.

was computed to eliminate the inter-patient difference unrelated to PTB severity. **Figure 5B** showed the longitudinal curves of same patients as in **Figure 5A** after SRLT conversion. In **Figure 5B**, we found that all curves shared a same start point, therefore could be directly compared among different patients.

Discussion

CT plays an important role in diagnosing PTB of patients whose chest radiograph is normal or inconclusive, as well as in determining active lesions, detecting complication, and managing PTB by providing a roadmap for surgery planning [7]. However, computer-aided thoracic CT measurements are rarely used for the evaluation of PTB patients. Moreover, CT analysis and comparison were often made by radiologists and physicians, which was subjective and greatly relied on individual experience. Therefore, developing an automatic method to quantify the lesions in PTB CT could provide an important complement to the traditional diagnostic value of thoracic CT. The current study has introduced our experience in developing the objective quantitative method of CACTV-PTB and its preliminary application in PTB patients.

Up to now, many volume analytic methods have been developed for solid pulmonary lesions. These analytic methods were initially used for small pulmonary nodules [8], and extended to complex solid pulmonary lesions along with the development of computer-aided technology [2]. However, the CT manifestations are complex in PTB patients, including cavities (single or multiple), infiltration and other phenotypes besides solid lesion. Moreover, the dynamic changes of these manifestations are also complicated. Obviously it is an exceptionally challenging work to the radiologists [9]. Although the performance of lung lesions in PTB thoracic CT are in dynamic change, the status of normal lung tissue is relatively stable. Therefore, the volume of the remaining normal lung could to some extent indirectly reflect the degree of lung injury. However, in such hypothesis the normal lung volume before PTB initiated is needed as a control, which was impractical since some of the patients did not have a previous CT. In order to solve this contradiction, we postulated that there was a certain linear relationship between LV and TV. Owing to the development of multi detector helical CT (MDCT) technology, volumetric data could by obtained easily and rapidly for evaluation [10, 11]. However, existing software and algorithms could not simultaneously compute LV and TV in PTB thoracic CT. Therefore, we developed CACTV-PTB independently, by which LV and TV could be well calculated (**Figure 2**). LV was positively correlated with TV in normal subjects (**Figure 3A**). Moreover, using the concept of RLT and SRLT computed from LV and TV, we could quantitatively compare PTB severity among different individuals and disease groups (**Figure 4B**). Intra-and inter-patient longitudinal analysis could also be made (**Figure 5**).

In our preliminary application of CACTV-PTB approach, we compared the LV-TV relationship and RLT values among four different groups, including Normal, PTB, PTB+DM and Death caused by PTB group. As shown in the results, the four groups can be well distinguished by their LV-TV relationship and RLT values (**Figure 4**). As expected, the RLT value was smallerin PTB group than in Normal group due to the lung injury. Interestingly, a difference in RLT value between PTB group and PTB+DM group was also observed. In 1927, Sosman and Steidl [12] found that a large proportion of diabetic

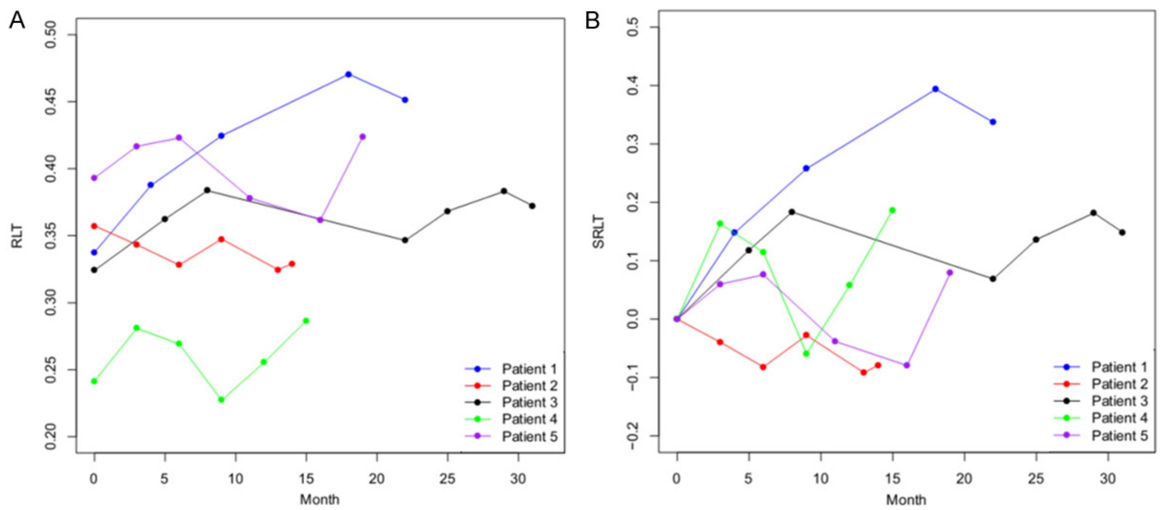

Figure 5. CACTV-PTB in longitudinal analysis of 5 patients. A. Curves of RLT value at different time point in the course of TB; B. Curves of SRLT value at different time point in the course of TB. RLT was calculated as the ratio of LV to TV. SRLT was Standardized RLT.

patients with TB had lower lung involvement, whereas non-diabetic patients usually had upper lobe infiltrates. Similar atypical pattern and distribution were also reported by others studies [13-15]. Junpeilkezoe et al. [16] found that diabetic PTB patients had a higher prevalence of multiple cavities within any given lesion and nonsegmental distribution than non-diabetic PTB patients. However, no previous study had concerned about the comparison of lung injury between PTB group and PTB+DM group, due to lack of suitable quantification method. By applying CACTV-PTB approach, we found that the level of lung injury is severer in PTB+DM group than in PTB group. A possible explanation might be the different immune response to TB in patients with or without DM [17]. Although we found that age was a relatively weak influence factor, RLT was negatively correlated with age in PTB group but positively correlated with age in PTB+DM group. However, we could not reach a conclusion due to the limited sample size. On the other hand, the RLT value in Death group was significantly lower than other groups. Therefore, we assumed that there was a “Death line”, which might indicate poor prognosis when a patient’s RLT value was below a specific value (0.23±0.04 in the current study). To maintain the RLT value above “Death line” would be helpful in improve disease prognosis. Certainly, more studies with larger sample size are needed to confirm our results.

Longitudinal analysis is of great importancein clinic use. It can portray the whole course of disease to provide evidence for the adjustment of treatment in individual patient, and make the comparison possible among different individuals. Nevertheless, the precondition of longitudinal analysis is that continuous or coding discrete variables should be provided. Several scoring method for evaluating [18] or aiding the diagnosis [19] of PTB have been reported. However, most of these methods obtained artificial scores, which were insensitive to the dynamic changes in disease variables. In the CACTV-PTB approach, two objective parameters RLT and SRLT were provided for longitudinal analysis. **Figure 5** showed RLT and SRLT longitudinal data from five different PTB patients. Patient 1 had a moderate level of lung injury at the beginning, but he recovered relatively quickly and had the best outcome. The lung injury of Patient 2 continued to deteriorate. Patient 3 successfully completed the initial treatment with good outcome although the disease recurred after one year, and fortunately after retreatment the outcome was favorable. The lung injury of Patient 4 and 5 were different at the beginning, but they had the similar recovery after treatment. Providing limited number of patients, our results showed an early attempt to comparelongitudinal curves by the CACTV-PTB approach, and more complicated longitudinal analysis could be done while including more patients’ materials.

To the best of our knowledge, our study was the first to develop a computer-aided CT volume measurement for PTB patients. The CACTV-PTB approach could generate quantitative parameters such as RLT and SRLT to represent disease severity and to be compared among individuals. Admittedly, the current study had several limitations. Firstly, there was no standard CT image preprocessing method, which was time-consuming and might introduce bias at the beginning of LV and TV measurement. Secondly, we could not rule out the difference in CT volume measurement caused by the intra- and inter-patient variation of inhaling. Thirdly, due to the limited resources of medical record system, we were unable to select patients with comparable baseline characteristics such as age, gender, history of smoking, occupation and so on. Therefore, we could not exclude the influence of these baseline characteristics on our conclusion. Moreover, due to the small sample size, we could not to stratify our analysis in different subtype of secondary PTB. More studies with larger sample size and better design are needed to confirm our hypothesis that the parameters derived from CACTV-PTB approach could accurately reflect PTB severity irrespective of disease subtype. Fourthly, when selecting the PTB patients, we considered both the result of CT report and the medical records, which might have introduced incorporation bias in the current study. In addition, since ex-pulmonary tuberculosis, other respiratory diseases, and heart diseases were excluded, it was unknown whether these disease conditions would influence the accuracy of RLT and SRLT. Lastly, at the current stage, CACTV-PTB was not a pattern recognition algorithms to distinguish PTB form other respiratory diseases, it could only be used to evaluate the degree of lung damage of PTB patients who has been diagnosed by other criteria.

Conclusions

In conclusion, the current study demonstrated that individual PTB severity could be objectively quantified and compared through measurement of LV and TV, and calculation of RLT and SRLT by CACTV-PTB approach. Our early experience of applying CACTV-PTB approachalso suggested that the lung injury was severer in PTB+DM group than in PTB group.

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Disclosure of conflict of interest

None.

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