行政院國家科學委員會專題研究計畫　成果報告

（子計畫二）長期追蹤嚴重急性呼吸道症候群病患之肺部機能後遺症

計畫類別：整合型計畫
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計畫主持人：余忠仁
共同主持人：張允中，吳惠東

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行政院國家科學委員會補助專題研究計畫 ■ 成 果 報 告 □期中進度報告

台灣地區「嚴重性呼吸道症候群」之臨床研究－

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計畫參與人員：

成果報告類型(依經費核定清單規定繳交)：□精簡報告　■完整報告

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執行單位：國立台灣大學醫學院內科

中　華　民　國　93　年　12　月　14　日

中文摘要

關鍵字：嚴重急呼吸道症候群、急性呼吸窘迫症候群、高解像力電腦斷層檢查、肺功能檢查、一氧化碳瀰漫量

在 2003 年 2 月至 8 月間，全球共有 8096 位嚴重急呼吸道症候群（SARS）病患，774 位死亡，死亡率為 9.6%。在台灣，346 位病患中，37 位死於 SARS，大多數因發生急性呼吸窘迫症候群（ARDS）而呼吸衰竭。研究顯示，ARDS 的存活者，由於經歷了嚴重的疾病過程，產生了長期在軀體上與神經心理上的後遺症，造成肺部與肺外之病態。本研究計畫以定期之肺功能檢查與高解像力電腦斷層檢查 SARS 病患之肺部變化。由於吾人對於 SARS 的臨床經驗仍在累積中，精確的評估 SARS 的長期肺部機能之變化有助於臨床醫師對於治療此一疾病之思考。

本計畫自 92 年 4 月執行至 93 年 7 月，本院共照顧 76 位嚴重呼吸道症候群之可能病患，15 位死亡。40 位於發病後 51.8±20.2 天接受第一次高解像力電腦斷層檢查，37 位接受肺功能檢查；發病後 140.7±26.7 天，19 位接受第二次高解像力電腦斷層檢查，22 位接受第二次肺功能檢查。第一次高解像力電腦斷層檢查顯示多數病例肺部影像仍有明顯變化（air trapping，92.5%；ground-glass opacity，90%；reticulation，70%；parenchymal band，55%；bronchiectasis，17.5%； consolidation，10%；honeycombing，7.5%）。 發生 ARDS 之 SARS 病患其肺部變化明顯較嚴重，尤其是 ground-glass opacity（GGO）的嚴重度。肺功能檢查有 12 位(37%)病患有囿限性通氣病變，其餘之肺功能檢查為正常。發生 ARDS 之 SARS 病患其肺功能明顯較差。接受第二次檢查之病患，高解像力電腦斷層檢查與肺功能檢查均呈現明顯進步，包括電腦斷層影像之 GGO 嚴重度由 8.68±6.96 分降至 4.42±5.14,（$p < 0.0001$）與纖維化嚴重度由 5.79±6.13 降至 3.05±5.80,（$p < 0.0001$），肺功能檢查 FVC (%預測值) 由 71.3 ± 23.4 上升至 98.1 ± 19.6%,（$p = 0.004$），而 FEV1 (%預測值) 由 73.9 ± 21.0 上升至 96.5 ± 17.9%,（$p = 0.005$）。即使是發生 ARDS 之 SARS 病患其第二次電腦斷層檢查與肺功能檢查也都有明顯進步，但仍有 50%仍有囿限性通氣病變。肺部之一氧化碳瀰漫量（DLco）變化與電腦斷層檢查之纖維化嚴重度成明顯負向相關。本觀察研究顯示嚴重急性呼吸道症候群之肺部傷害之預後可能較原先預期為良好，而肺功能檢查之 DLco 值可作為肺部纖維化嚴重度之參考。

Abstract

Keywords: severe acute respiratory syndrome, acute respiratory distress syndrome, high-resolution computed tomography, pulmonary function test, diffusion capacity

Between Feb to August, 2003, in more than 29 countries, 8096 cases and causing more 774 deaths (fatality rate 9.6%). In Taiwan, 37 out of 346 SARS victims died, most of deaths were attributed to severe acute respiratory distress syndrome (ARDS).

Pulmonary sequelae is especially anticipated in patients developing severe pulmonary infection or acute lung injury. Survivors of the acute respiratory distress syndrome have persistent functional disability one year after discharge from the intensive care unit. As the clinical experience of dealing with SARS is accumulating, studies prospectively evaluating physiological, functional, and morphological measures during the year after diagnosis of SARS will provide valuable information for clinicians to handle patients with this new disease.

From April, 2003 till now, 76 patients with documented SARS were admitted to our hospital,15 died of the disease. Forty of the survivors received first HRCT examination at 51.8±20.2 days after symptom onset, 37 received pulmonary function examination；140.7±26.7 after symptom onset,19 received a second HRCT examination，22 had a second pulmonary function examinations。HRCT of lung parenchymal change revealed air trapping (92.5%), ground-glass opacity (90%), reticulation (70%), parenchymal band (55%), bronchiectasis (17.5%), consolidation (10%), and honeycombing (7.5%) in the first follow-up study. SARS patients who experienced ARDS (n=16) had significantly higher scores than those without ARDS (n=24) in

ground-glass opacity. Twelve of the 37 patients (37%) showed variable degrees of restrictive ventilatory defects in first PFT examiantion and 11 of them had been complicated by ARDS. On the first PFT patients without ARDS had better test results than those complicated by ARDS. Comparison between the first and second follow-up HRCT of 19 cases revealed significant improvement in ground glass opacity (CT scores 8.68±6.96 vs. 4.42±5.14, $p < 0.0001$) and fibrosis (CT scores 5.79±6.13 vs. 3.05±5.80, $p < 0.0001$). All these impairments in PFT improved 2 months later. The FVC (% predicted) values improved from 71.3 ± 23.4 to 98.1 ± 19.6% ($p = 0.004$) and the FEV1 (% predicted) increased from 73.9 ± 21.0 to 96.5 ± 17.9% ($p = 0.005$). Most HRCT and PFT parameters in patients with SARS-ARDS significantly improved on the second examinations, but a restrictive defect was still present in 5 of the 10 patients (50%), probably because of residual pulmonary fibrosis. The DL_{co} (% predicted) was inversely correlated with the total fibrotic scores on the high-resolution computed tomography (HRCT) of the chest. Our observation study revealed that lung damage in SARS patients usually resolve over time. The DLco may be a useful marker to follow-up fibrosis sequelae.

Background information

Severe acute respiratory syndrome (SARS) is a new infectious disease identified since late February, 2003. The disease was first reported among people in Guangdong Province of China, Hanoi of Vietnam, and Hong Kong. It has since then spread worldwide, including North America, Europe, and other Asian countries [1]. The disease was horrible by its high infectivity, rapid progression to respiratory failure and potentially lethal in severe cases. As of April 16, 3293 cases of SARS had been reported in the world, and 159 died of the disease. In Taiwan, 27 probable cases are reported; most of them are imported from affected area, such as Hong Kong or Mainland China, or close contacts (like health care workers or family) of a SARS patient [2].

SARS does not respond to empirical antimicrobial agent for acute community- acquired typical or atypical pneumonia. Bacteriological and virological pathogens known to cause pneumonia were not identified. A new virus belonging to the family Coronaviridae was recently isolated from the body fluids and tissues of SARS victims [3-5]. More evidence supports this novel coronavirus as the causative pathogen of SARS. Yet, so far, laboratory diagnostic tests used to test clinical specimens for evidence of this novel coronavirus are still in development and are not available outside a research setting. Serologic testing for coronavirus antibody consists of indirect fluorescent antibody testing and enzyme-linked immunosorbent assays that are specific for antibody produced after infection [5]. Although some patients have detectable coronavirus antibody within 14 days of illness onset, definitive interpretation of negative coronavirus antibody tests is possible only for specimens obtained >21 days after onset of fever. A reverse transcriptase-polymerase chain reaction (RT-PCR) test specific for RNA from the novel coronavirus has been positive within the first 10 days after fever onset in specimens from some SARS patients, but the duration of detectable viremia or viral shedding is unknown, and RT-PCR tests on samples collected during convalescence might be negative. Viral culture followed by RT-PCR also has been used to detect the novel coronavirus in some specimens [3,4].

SARS is defined by clinical and radiographic categories. Probable SARS includes fever (>38°C), newly developed respiratory symptoms (such as cough, shortness of breath, chest pain), and radiographic evidence of infiltrates consistent with pneumonia or respiratory distress syndrome (RDS) on chest radiograph [1, 6-8]. All SARS patients eventually develop pulmonary complications during the course of the disease. About 25%-40% were admitted to the ICU due to respiratory failure, after a certain period of fever, shortness of breath and hypoxemia. About 4% of all SARS patients eventually die of the disease. The typical finding on chest X-ray and thoracic CT scan is ill-defined, ground-glass opacification in the periphery of the affected lung parenchyma, usually in subpleural location. The characteristic peripheral alveolar opacities are very similar to those found in bronchiolitis obliterans organizing pneumonia. Histologic examination of the lung reveals gross consolidation of the lungs. Both early phase(pulmonary edema with hyaline membrane formation) and organizing phase (cellular fibromyxoid exudates)of diffuse alveolar damage were seen in different parts of the lung. Lymphocytic

inflammatory infiltrate in interstitium, vacuolated and multinucleated pneumocytes were identified, the latter finding suggested viral infection, such as measles, parainfluenzavirus, respiratory syncytial virus and Nipahvirus infection, but not include ordinary human coronavirus [6,8].

Usually, after viral pneumonia, sequelae of respiratory system may persist for certain duration [9]. The pathology of pulmonary sequelae may include bronchiectasis, obliterative bronchiolitis, bronchiolitis obliterans with organizing pneumonia. Pulmonary function testing performed after the convalescence of infection may show either obstructive or restrictive disorder[10,11]. Bronchial hyperreactivity is especially common after RSV infection. Pulmonary sequelae is especially anticipated in patients developing severe pulmonary infection or acute lung injury. Patients who survive the acute respiratory distress syndrome are at risk for physical and neuropsychological complications of the lung injury itself, associated multiorgan dysfunction, and their long stay in the intensive care unit (ICU). Herridge et al had evaluated 109 survivors of the acute respiratory distress syndrome 3, 6, and 12 months after discharge from the intensive care unit. Although lung volume and spirometric measurements were normal by 6 months, carbon monoxide diffusion capacity remained low throughout the 12-month follow-up. Six percent of patients had arterial oxygen saturation values below 88 percent during exercise. The median score for the physical role domain of the Medical Outcomes Study 36-item Short-Form General Health Survey (a health-related quality-of-life measure) increased from 0 at 3 months to 25 at 12 months (score in the normal population, 84). The distance walked in six minutes increased from a median of 281 m at 3 months to 422 m at 12 months; all values were lower than predicted. Survivors of the acute respiratory distress syndrome have persistent functional disability one year after discharge from the intensive care unit. Muscle weakness and fatigue were the reasons for their functional limitation [12].

According to our experience, muscle weakness and functional impairment in SARS patients persists two weeks after weaning from ventilator. Although the general condition improved gradually, pulmonary functional test and thoracic image (chest X-ray and CT scan) performed one month after SARS revealed abnormalities. As the clinical experience of dealing with SARS is accumulating, studies prospectively evaluating physiological, functional, and morphological measures during the year after diagnosis of SARS will provide valuable information for clinicians to handle patients with this new disease. Therefore, the goal of this study was to characterize long-term pulmonary and function in a prospectively identified cohort of patients who survived SARS, especially with ARDS.

Subjects and Methods

Study Population

Seventy-six patients were diagnosed as probable cases in our institution. Fifteen of the 76 cases died in the period of admission. Sixty of the remaining sixty-one cases were discharged after clinical improvement. All patients fulfilled the clinical criteria of SARS according to the definition of the World Health Organization (WHO), with fever of more than 38°C, cough or breathing difficulty, history of exposure within 10 days prior to onset of symptoms, and an abnormal chest radiograph (CXR). All cases should have positive RT-PCR (real-time polymerase chain reaction assay) for SARS-coronavirus (SARS-CoV) in clinical specimens, or positive seroconversion in 28-day convalescent sera.

Testing Procedure

Upon entry into the study, all SARS subjects and control subjects will undergo complete pulmonary function testing and HRCT imaging at 3, 6, 9 and 12months after the initial diagnosis of disease.

Baseline Pulmonary Function Testing

Pulmonary function studies were performed on a Keystone model pulmonary function analyzer (S&M Instrument Co. Inc., Doylestown, PA) or a Sensormedics Series V6200 Autobox (Sensormedics, Inc., Yorba Linda, CA) according to American Thoracic Society (ATS) standards.

Reproducibility between the two machines was documented by testing a number of individuals on both systems. Lung volumes were determined using the helium dilution technique (Keystone) or nitrogen washout (Sensormedics); diffusing capacities were determined using the single-breath method and adjusted for hematocrit. The most appropriate reference equations for our laboratory and testing conditions were chosen by applying a number of reference equations to pulmonary function results of normal volunteers.

Diffusion capacity measurement
Subjects performed a total of six diffusing capacity maneuvers, 2 each at low, medium, and high fraction of inspired oxygen (F_{IO2}). Before performance of the D_{LCO} measurements a sample of gas was taken and measured for CO to estimate baseline CO in equilibrium with blood carboxyhemoglobin.

HRCT Technique
Computed tomographic (CT) scanning was performed on all subjects with helical CT scanner (PQ6000, Marconi, USA; High-Speed, General Electric Medical System, Milwaukee, Wis., USA) with 1mm collimation at 10-mm intervals through the chest during suspended inspiration at TLC with the patient in the supine position. Images are reconstructed using the high spatial frequency algorithm and photographed at lung (window width 1,500 Hounsfield units [HU], level −700 HU) and mediastinal (window width 400 HU, level 0 HU) windows. No intravenous contrast will be administered.

HRCT Evaluation
All scans were interpreted by an experienced chest radiologist blinded to SARS/ control status and physiologic data. The HRCT findings were described according to the recommendations of the Nomenclature Committee of the Fleischner Society. The images were viewed at a window/level setting of 1000/600 in standard DICOM (Digital Imaging and Communication in Medicine) viewer. HRCT findings including ground-glass opacity, reticulation, honeycombing, parenchymal band, consolidation, air trapping and bronchiectasis were recorded. Table 1 outlines a modified scoring system used for evaluating HRCT findings. The system has been used to describe idiopathic pulmonary fibrosis and correlated well with the degree of fibrosis manifested by pathologic specimen.(13) As paired inspiration and expiration HRCT were performed in this study, we modified the system to evaluate the extent of hypoattenuation on expiratory HRCT as air trapping (Table 1). For the purpose of analysis, each lobe was scored separately and the sum of all lobes was incorporated into a total score for ground glass attenuation (CT-alv), fibrosis or reticulation (CT-fib), air trapping (CT-air trap) for each study. There was a scale of 0-5 for each lobe and the total score obtained from HRCT ranged from 0 to 25. The scores were obtained with consensus between two chest radiologists.

Results

HRCT findings and score
Forty patients received first HRCT examinations, with about 51.83±20.23 days after onset of symptoms, 16 of them experiencing ARDS. Lung parenchymal change on first HRCT (43.4±9.5 days after the onset of symptoms) including air trapping (92.5%), ground-glass opacity (90%), reticulation (70%), honeycombing (7.5%), parenchymal band (55%), bronchiectasis (17.5%), and consolidation (10%) (Figures 1). Nine patients presented with ground-glass opacity and air trapping, 3 patients presented with only air trapping and one case had only ground glass opacity. The remaining 28 patients had more than two HRCT findings. Among the 19 patients who followed up second HRCT, 4 (24%) presented with ground glass opacity and air trapping, each one case had only ground glass opacity (6%), air trapping (6%), parenchymal band (6%) and bronchiectasis (6%). The remaining 9 (53%) had more than two HRCT findings. CT evidence of small airway change including ground glass opacity, air trapping or both is noted in 13 patients (32%) in the first HRCT study and 5 patients (30%) in the second HRCT study. None of the 40 patients had pleural effusion, cavitation or lymphadenopathy in either the first or second HRCT

study. None of the cases in the first and second HRCT studies was without abnormality. The average HRCT scores in the first evaluation of all these patients were: CT-alv 7.0±6.8, CT-fib 4.93±6.39, CT-air trap 4.68±3.68. The average scores of the second HRCT in 19 patients were: CT-alv 4.42±5.14. CT-fib 3.05±5.80, CT-air trap 5.05±5.17.

Comparison of first vs. second follow-up HRCT

Nineteen patients had two serial HRCT studies, at 140.68±26.68 days after symptom onset, 8 were convalescing from ARDS, while the other 11 were non-ARDS. For all the 19 cases receiving second follow-up HRCT, there were significant improvement in CT-alv from 8.68±6.96 to 4.42±5.14 ($p<0.0001$) and in CT-fib from 5.79± 6.13 to 3.05±5.79 ($p< 0.0001$). No difference was found in CT-air trapping (5.37±4.41 vs. 5.05±5.17, $p = 0.45$). (Fig 2) The finding remained significant in subgroup analysis. For ARDS group, CT-alv decreased from 13.12±7.53 to 6.50± 6.65 ($p=0.0078$) and CT-fib decreased from 8.37±7.67 to 4.87± 8.25 ($p=0.0156$). No significant change was noted in the CT-air trap (6.62±1.99 vs. 6.12±4.32, $p = 0.5781$). For non-ARDS group, CT-alv score decreased from 5.45±4.50 to 2.91±3.24 ($p = 0.002$) and CT-fib decreased from 3.91±4.16 to 1.73±2.87 ($p = 0.0039$). No significant change was noted in CT-air trap (4.46±5.48 vs. 4.27±5.78, $p = 0.6875$). (Figure 2).

Pulmonary function tests

Thirty-seven patients received pulmonary function tests at the same time of CT examinations. Twelve of the 37 patients (37%) showed variable degrees of restrictive ventilatory defects, 11 of them had been complicated by ARDS. All these impairments in PFT improved 2 months later except for the DL_{co} (Table 2). The FVC (% predicted) values improved from 71.3 ± 23.4 to 98.1 ± 19.6% ($p = 0.004$) and the FEV1 (% predicted) increased from 73.9 ± 21.0 to 96.5 ± 17.9% ($p = 0.005$). On the first PFT patients without ARDS had better test results than those complicated by ARDS, but these differences did not reach statistical significance 3 months later (Table 3). Most PFT parameters in patients with SARS-ARDS significantly improved on the second PFT, but a restrictive defect was still present in 5 of the 10 patients (50%), probably because of residual pulmonary fibrosis. The DL_{co} (% predicted) was inversely correlated with the total fibrotic scores on the high-resolution computed tomography (HRCT) of the chest (Figure 3A and 3B). The DL_{co} (% predicted) was also associated with the duration of mechanical ventilation in the 7 patients with ventilatory support ($r = - 0.86$, $p = 0.026$).

Table 1. severe acute respiratory syndrome (SARS): HRCT scoring system

Alveolar score (CT-alv)	
0	No alveolar disease
1	Ground glass opacity <5% of the lobe (minimal but not normal)
2	Ground glass opacity involving up to 25% of the lobe
3	Ground glass opacity involving 25-49% of the lobe
4	Ground glass opacity involving 50-75% of the lobe
5	Ground glass opacity involving >75% of the lobe
Fibrotic score (CT-fib)	
0	No interstitial disease
1	Interlobular septal thickening; no discrete honeycombing
2	Honeycombing (+/- septal thickening) involving up to 25% of the lobe
3	Honeycombing (+/- septal thickening) involving 25-49% of the lobe
4	Honeycombing (+/- septal thickening) involving 50-75% of the lobe
5	Honeycombing (+/- septal thickening) involving >75% of the lobe
Air trapping score (CT-air trap)	
0	No bronchiolar disease (no air trapping on expiration)
1	Air trapping involving <5% of the lobe (minimal but not normal)
2	Air trapping involving up to 25% of the lobe
3	Air trapping involving 25-49% of the lobe
4	Air trapping involving 50-75% of the lobe
5	Air trapping involving >75% of the lobe

Table 2. Followed-up PFT in patients with SARS

Timing	First PFT (n = 37)	Second PFT (n = 22)	p
FVC (%)	71.3 ± 23.4	98.1 ± 19.6	0.004
FEV1 (%)	73.9 ± 21.0	96.5 ± 17.9	0.005
FEV1/FVC (%)	91.0 ± 6.8	85.8 ± 8.0	0.16
FRC (%)	95.6 ± 30.7	117.5 ± 30.2	0.04
TLC (%)	86.4 ± 20.3	104.0 ± 14.1	0.03
DL_{co} (%)	88.8 ± 25.7	102.6 ± 16.8	0.19
MVV (%)	80.7 ± 18.9	95.9 ± 14.7	0.03

Table 3. PFT of patients with SARS: ARDS vs. non-ARDS groups

Timing	First PFT			Second PFT		
	ARDS (n = 11)	Non-ARDS (n = 26)	p	ARDS (n = 10)	Non-ARDS (n = 13)	p
FVC (%)	71.7 ± 22.3	98.3 ± 20.0	0.001	87.4 ± 24.5	93.1 ± 15.0	0.48
FEV_1 (%)	74.7 ± 18.3	96.6 ± 20.4	0.005	90.0 ± 25.8	93.6 ± 16.2	0.52
FEV_1/FVC (%)	91.6 ± 6.1	85.5 ± 8.0	0.03	89.2 ± 5.0	87.7 ± 6.9	0.88
TLC (%)	84.4 ± 16.0	103.3 ± 17.5	0.01	94.3 ± 26.7	100.3 ± 15.8	0.45
DL_{co} (%)	75.8 ± 22.7	103.6 ± 17.2	0.002	90.9 ± 28.9	106.7 ± 19.4	0.21
MVV (%)	83.7 ± 23.6	95.3 ± 15.6	0.08	102.4 ± 29.9	92.8 ± 19.7	0.65

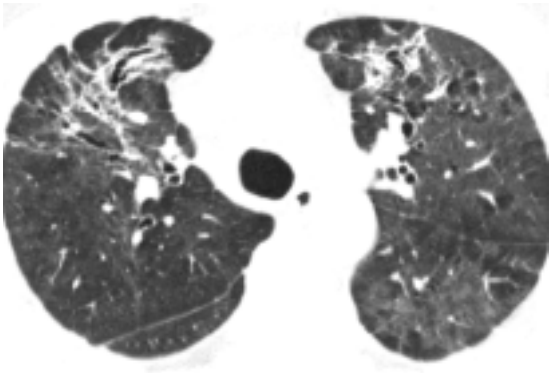
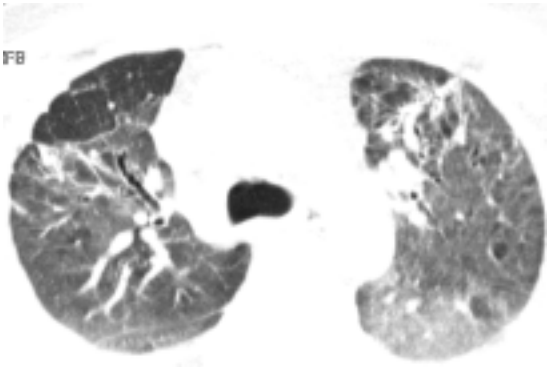


Fig 1A



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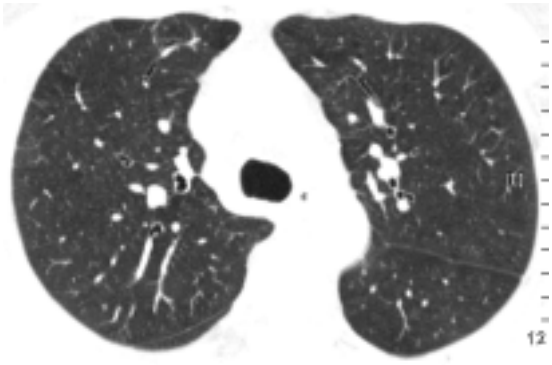

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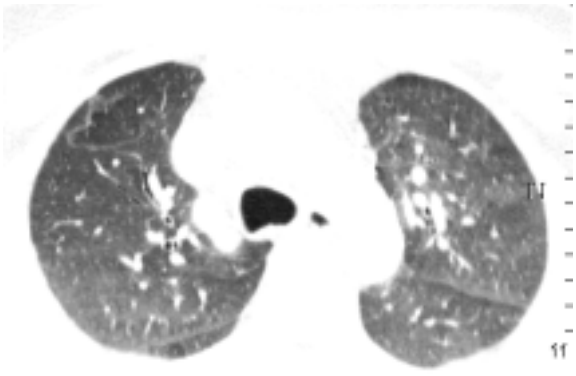


Fig 1D

Fig. 1 HRCT of case 1 (49 days after symptom onset, 26 days after removal of the endotracheal tube) in suspended inspiration (A) demonstrates fibrotic bands, bronchiectasis, ground glass opacities. The expiratory phase (B) demonstrates mosaic attenuation suggesting air trapping. The lung parenchymal change and air trapping at corresponding location on inspiration (C) and expiration status (D) disappeared in the second follow-up CT study (114 days after symptom onset).

Fig. 2 Changes of HRCT scores in 19 SARS patients receiving two HRCT examinations. See text for description and results of statistical analysis between HRCT examinations. 1st: first HRCT study; 2nd: second HRCT study; Alveolar= CT-alv, Fibrosis= CT-fib, Air-trap= CT-air trap.

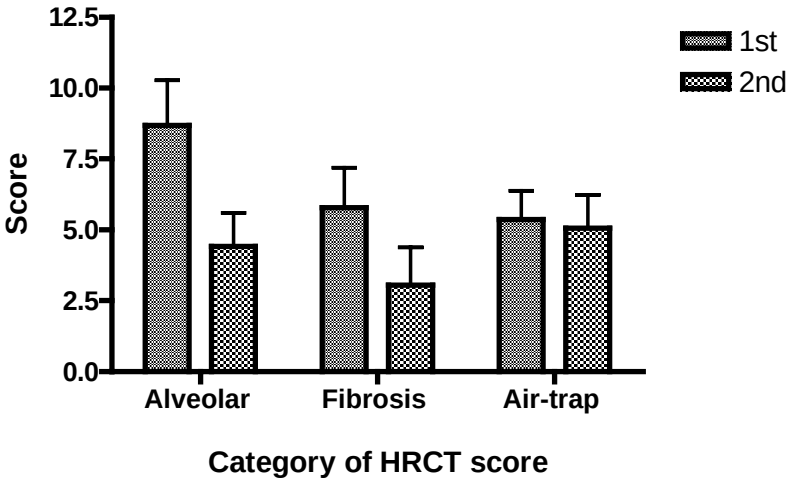
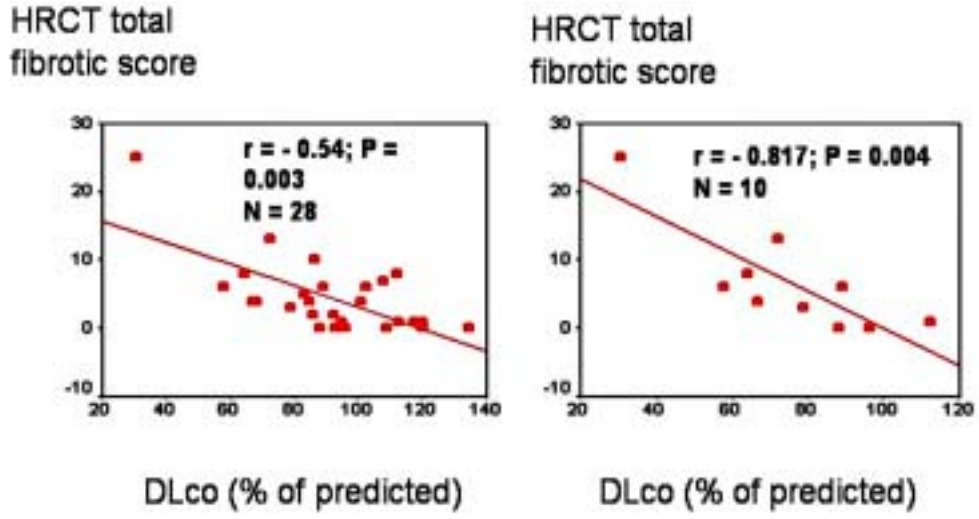


Figure 3. DLco(%) vs. HRCT fibrotic scores. (A) Total study population; (B) SARS-ARDS patients.

(A) (B)



Conclusion

HRCT evidence of ground-glass opacity and fibrosis in lung parenchyma of convalescent SARS patients usually resolve over time. However, air trapping persists. Subclinical airway damage should be considered as a potential complication in patients recovering from SARS, whatever the severity of the clinical disease. All patients with ARDS complicating SARS had restrictive ventilatory defects within 1 month after discharge, and these impairment still persisted in 50% of them 2 months later. The DLco correlated inversely with the fibrotic scores on HRCT in these patients, suggesting that it may be a useful marker to follow-up pulmonary fibrosis.

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