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Follow-up Study on Pulmonary Function and Lung Radiographic Changes in Rehabilitating Severe Acute Respiratory Syndrome Patients After Discharge*

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Objectives: **To follow-up on the changes in lung function and lung radiographic pictures of severe acute respiratory syndrome (SARS) patients discharged from Xiaotangshan Hospital in Beijing (by regularly receiving examination), and to analyze retrospectively the treatment strategy in these patients.**

Methods: **Surviving SARS patients were seen at least twice within 3 months after discharge and underwent SARS-associated coronavirus (SARS-CoV) IgG antibody testing, pulmonary function testing, and chest radiography and/or high-resolution CT (HRCT) examinations at Chinese PLA General Hospital. The treatments received at Xiaotangshan Hospital were analyzed retrospectively and were correlated to later status.**

Results: **Positive SARS-Co virus IgG antibody results were seen in 208 of 258 patients, with 21.3% (55 of 258 patients) still having a pulmonary diffusion abnormality (DLCO < 80% of predicted). By comparing the 155 survivors with positive SARS-CoV IgG antibody results and DLCO ≥ 80% predicted with the 50 patients with negative SARS-CoV IgG results, we found that 53 patients with positive SARS-CoV IgG results and a lung diffusion abnormality had endured a much longer course of fever and received larger doses of glucocorticoid, as well as higher ratios of oxygen inhalation and noninvasive ventilation treatment. For these patients, 51 of 53 patients with positive SARS-CoV IgG results and a lung diffusion abnormality underwent pulmonary function testing after approximately 1 month. DLCO improved in 80.4% of patients (41 of 51 patients). Of the patients with a lung diffusion abnormality, 40 of 51 patients showed lung fibrotic changes in the lung image examination and 22 patients (55%) showed improvement in lung fibrotic changes 1 month later.**

Conclusion: **These findings suggest that lung fibrotic changes caused by SARS disease occurred mostly in severely sick patients and may be self-rehabilitated. DLCO scores might be more sensitive than HRCT when evaluating lung fibrotic changes.**

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Key words: glucocorticoid; high-resolution CT; lung fibrotic changes; lung function; lung radiography; severe acute respiratory syndrome

Abbreviations: ANOVA = analysis of variance; Cor = severe acute respiratory syndrome-associated coronavirus primer sequence; CXR = chest radiography; DLCO = diffusion capacity of the lung for carbon monoxide; DLCO/VA = diffusion capacity of the lung for carbon monoxide constant; HRCT = high-resolution CT; NIPPV = noninvasive positive pressure ventilation; OD = optical density; PCR = polymerase chain reaction; SARS = severe acute respiratory syndrome; SARS-CoV = severe acute respiratory syndrome-associated coronavirus; VC = vital capacity

Severe acute respiratory syndrome (SARS) patients may present with a spectrum of symptoms and signs ranging from relatively asymptomatic to fulminant pneumonitis and death. Lung injury caused by SARS-associated coronavirus (SARS-CoV) is one of the main clinical manifestations in SARS patients, which affects the prognosis. The prognostic factors to be examined are clinical characteristics and laboratory findings. Few studies[1,2] have reported prognosis in relation to the degree of lung injury and

rehabilitation in patients with SARS-CoV. In our study, we observed the changes of lung lesions in discharged but undergoing rehabilitation SARS patients via lung function testing, lung imaging examination, and retrospective analysis of the disease course and therapy.

Materials and Methods

The Record Board of Beijing Xiaotangshan Hospital approved this study and the use of the case files. All patients gave informed consent.

Study Protocol

Our study extended from July 1, 2003, to September 30, 2003, and included 258 SARS patients discharged from Beijing Xiaotangshan Hospital. The individual clinical diagnosis was based on the clinical diagnosis standard for SARS patients issued by Ministry of Chinese Public Health. All patients studied met the specified criteria for discharge.[3] The first follow-up visits for these patients were from July 1, 2003, to August 10, 2003. Although most of these rehabilitating SARS patients were well enough to perform their daily activities in the follow-up study, they complained of limited physical ability from general weakness and/or shortness of breath during the clinical follow-up. Being an entirely new entity, there was no literature to reference for guidance about the course of SARS; therefore, we relied only on performing follow-up pulmonary function testing, frontal chest radiography (CXR), and/or high-resolution CT, and serum SARS-CoV IgG antibody examination in Chinese PLA General Hospital, Beijing.

Approximately 1 month after the first follow-up, patients underwent pulmonary function testing, lung imaging, and serum SARS-CoV IgG antibody examination to observe the rehabilitative changes in the lung injury, and all examinations performed at the first follow-up visit were repeated at the second visit. The second follow-up was obtained on an average (± SD) of 33 ± 7 days (range, 24 to 50 days) after the first visit.

Pulmonary Function Testing

Each rehabilitating SARS patient underwent standard pulmonary function testing (Model 2200; SensorMedics; Yorba Linda, CA) for FEV_1, vital capacity (VC), FVC, total lung capacity, diffusion capacity of the lung for carbon monoxide (DLCO), and DLCO constant (DLCO/VA) measured by means of the single-breath test. The hemoglobin value was also taken for correcting the DLCO. The results were compared with those of age- and sex-matched control subjects and expressed as a percentage of predicted values. Pulmonary function was regarded as abnormal when DLCO was < 80% of the predicted value.

CXR and Evaluation

CXR was performed at the first follow-up visit for every rehabilitating SARS patient. If CXR abnormalities were found or if the DLCO was < 80% of the predicted value despite a normal CXR, the patients were sent for HRCT scanning (GE LightSpeed; GE Medical Systems; Milwaukee, WI), 1-mm section in thickness with 10-mm gap, supine position, scanning during inspiration, 1 second per scan, 140 kilovolts, 200 mA). Three nonblinded radiologists with a viewing console assessed all CXR and CT images, with the final conclusions established by consensus. Each segment of the lung was reviewed for ground-glass opacification, interstitial thickening, bronchiectasis, and architectural distortion. Abnormalities were magnified by using a zoom function and were examined for intralobular interstitial, interlobular septal, or peribronchovascular interstitial thickening. The presence or absence of nodules or masses, cavitation or calcification, and emphysema was also noted. The presence of parenchymal bands, irregular interfaces (bronchovascular, pleural, or mediastinal), thickened interstitium, and traction bronchiectasis were evidence of fibrotic changes.[4]

SARS-CoV IgG Antibody Test

SARS-CoV IgG antibody present in serum specimens of rehabilitating SARS patients was tested with enzyme-linked immunosorbent assay (No. S20030003; BGI-GBI Biotech Company; Beijing, ROC), and all specimens were tested at BGI-GBI Biotech Company. The wells with polystyrene microplate strips were coated with two recombinant SARS-CoV antigens that are well characterized. The serum was diluted in diluent buffer (1:10), incubated in the coated wells for 30 min at 37°C, and the wells were washed five times with washing buffer. The enzyme-labeled antihuman IgG working dilution (100 μL) was added, incubated for 20 min at 37°C, and washed five times with washing buffer. A tetramethyl-benzidine substrate was then added to each well. The presence of specific antibodies was indicated by the presence of a yellow color after substrate addition. Reaction was terminated by addition of hydrochloric acid. The intensity of the color was measured spectrophotometrically at 450 nm in proportion to the amount of antibodies in the specimen. The optical density (OD) obtained on the y-axis was plotted against the lot-specific standard concentrations on the x-axis, resulting in a linear calibration curve. The OD values of the positive control and negative control were calculated. The cut-off value for IgG was 0.18, which was calculated as the mean + 2 SD of the readings given by 1,000 blood donor control sera. If the OD value was above the cut-off value, it indicated a positive result for SARS-CoV IgG.[5]

Viral RNA Extraction and Reverse Transcriptase-Polymerase Chain Reaction Method

Total RNA from the examining sputum, urine, feces, and whole blood was extracted (QIAamp RNA Blood Mini Kit 52304; QIAGEN; Valencia, CA) according to the instructions of the manufacturer. The RNA was dissolved in 40 μL of diethyl pirocarbonate-treated water containing 1 U of deoxyribonuclease I (Promega; Madison, WI). Nested reverse transcriptase-polymerase chain reaction (PCR) method was primarily used to ensure specificity. The size of the PCR product is 131 base-pairs

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covering the nucleotide positions 26, 241–26, 371 base-pairs in SARS-CoV BJ01 strain. Complementary DNA was synthesized by reverse transcription from 6 μL of RNA at 45°C for 50 min in a 20-μL solution containing 50 mM Tris-HCl (pH 8.3), 75 mM KCl, 3 mM $MgCl_2$, 10 mM dithiothreitol, 100 ng of the random hexamer primers, 200 U of Moloney murine leukemia virus (Promega), 25 U of recombinant ribonuclease inhibitor (N2511; Promega) and 0.5 mM deoxynucleoside triphosphate. The primary PCR was carried out in a 25-μL mixture containing 2 μL of complementary DNA, 10 mM Tris–HCl (pH 8.4), 50 mM KCl, 2.5 mM $MgCl_2$, 100 μM deoxynucleoside triphosphate, 1 U of Taq DNA polymerase (Promega), 0.25 μM of forward primer (SARS-Cov primer sequence [Cor] F1: 5′-TCACACTAG CCATCCTTACTG-3′) and 0.25 μM reverse primer (Cor R1: 5′-TATTATGTACAAAAACCTGTTCC-3′). After 35 amplification cycles (94°C for 30 s; 54°C for 30 s; 72°C for 30 s), the secondary PCR was performed in a 25-μL mixture containing 1 μL of the first PCR product, 10 mM Tris-HCl (pH 8.4), 50 mM KCl, 2.5 mM $MgCl_2$, 100 μM deoxynucleoside triphosphate, 1 U of Taq DNA polymerase, 0.25 μM inner forward primer (Cor F2: 5′-CGTGAGTTTAGTAAAACCAA-3′) 0.25 μM reverse primer (Cor R2: 5′-AATGTTAAAGTTCCAAACAGA-3′) and 0.25 μM TaqMan probe (5′FAM-AGAAGATCAGGAACTCCTTCAGA-TAMRA3′) in a fluorometric thermal cycler (iCycler; Bio-Rad Laboratories; Hercules, CA). Forty cycles of amplification (94°C for 15 s; 58°C for 1 min; fluorescence signals were recorded at 58°C) were performed after denaturing at 95°C for 4 min.[5]

Retrospective Analysis for SARS Patients

We retrospectively reviewed and analyzed the data from the records of SARS patients from the onset and throughout the hospital stay, including the duration of persisting fever, total dosage of glucocorticoid, patients requiring supplemental oxygen, and number of noninvasive ventilation treatments.

Statistical Analysis

All data are expressed as mean ± SD unless otherwise indicated. Statistical analyses were done by one-way analysis of variance (ANOVA) and the Student-Newman-Keuls test for multiple comparisons. We used statistical analysis software (STATA 7.0 for Windows; StataCorp; College Station, TX) for evaluating the results of our study. With each statistical test, the level used to determine the significance was considered at a p value < 0.05.

Results

From July 1 to September 30, 2003, a total of 258 SARS patients were followed up at least twice after discharge. There were 107 men and 151 women with a mean age of 37.1 ± 12.9 years (age range, 18 to 74 years). The mean time from discharge to first follow-up was 45.0 ± 20.7 days (range, 11 to 104 days).

Follow-up Findings

Of the rehabilitating SARS patients, as expected, all samples tested negative for the viral RNA. In the serum SARS-CoV IgG antibody examination (each follow-up required serum SARS-CoV IgG antibody testing, and each serum sample was tested at least two times), positive results were seen in 208 patients (80.6%) and negative results were seen in 50 patients (19.4%). Of the patients with positive results, 53 patients (25.5%) had a pulmonary diffusion abnormality (DLCO < 80% predicted), and 2 patients (4%) with negative results had a pulmonary diffusion abnormality (DLCO < 80% predicted with one of them having a history of COPD with pulmonary fibrosis changes, the other with the history of organized pneumonia disease) [p = 0.001; Table 1]. The patients with positive SARS-CoV IgG results and DLCO < 80% predicted were older than the patients with positive SARS-CoV IgG results and DLCO ≥ 80% predicted and the patients with negative SARS-CoV IgG results (p = 0.0088; Table 2).

Table 1—*SARS-CoV IgG Results for SARS Patients*

Variables	Results, No.			χ^2	p Value
	Positive	Negative	Total		
DLCO ≥ 80% predicted	155	48	203		
DLCO < 80% predicted	53	2	55		
Total	208	50	258	11.089	0.001

Of the patients with positive SARS-CoV IgG antibody results and DLCO < 80% predicted, 51 of the 53 patients (96%) underwent pulmonary function testing at least twice, with the second follow-up appointment being on average 33 ± 7 days (range, 24 to 50 days) after the first visit. Table 3 shows the results of pulmonary function testing (VC, FEV_1, DLCO, and DLCO/VA) during the second examination, revealing an improvement in scores compared to the first examination (Table 3).

There were residual abnormalities on the CXRs and HRCT imaging in 52 of the 258 SARS patients, mainly displaying interstitial thickening,

Table 2—*Characteristics of SARS Patients**

Variables	Male/Female Gender, No.	Age, yr†
SARS-CoV IgG antibody positive and DLCO < 80% predicted	14/39	40.9 ± 12.5
SARS-CoV IgG antibody positive and DLCO ≥ 80% predicted	65/90	37.7 ± 13.0
SARS-CoV IgG antibody negative	28/22	33.0 ± 13.5§
p value	0.010‡	0.0088‖

*Statistical analyses were done by one-way ANOVA and Student-Newman-Keuls test for multiple comparisons.
†Mean ± SD.
‡χ^2 test (females vs males).
§$p < 0.05$ for SARS-CoV IgG antibody negative vs SARS-CoV IgG antibody positive and DLCO < 80% predicted with ANOVA procedures.
‖Separate one-way ANOVA procedures.

Table 3—*Pulmonary Function Test Results for 51 Discharged SARS Patients

Variables	VC, L	FEV_1, L	FEV_1/FVC, %	DLCO, mL/min/mm Hg	DLCO/VA, mL/min/mm Hg/L
First	3.10 ± 0.68	2.47 ± 0.60	79.7 ± 0.09	15.8 ± 2.8	4.12 ± 0.60
Second	3.33 ± 0.63	2.64 ± 0.57	79.8 ± 0.09	17.7 ± 2.9	4.35 ± 0.59
t test	5.7132	5.0470	0.0521	6.8197	3.9212
p value	< 0.00001	< 0.00001	0.9586	< 0.00001	0.0003

*Pairwise *t* test; values are given as mean ± SD.

ground-glass opacification, bronchiectasis, and signs of volume loss. Of the 52 patients, there were 48 patients with positive SARS-CoV IgG results and 4 patients with negative results. In the 48 patients who had a residual abnormality on radiographic examination and positive SARS-CoV IgG results, 40 patients underwent HRCT imaging examination after approximately 1 month. Results showed that 22 of 40 patients had an improvement in the lung abnormality, whereas the remaining 18 patients had an unchanged abnormality (Table 4; Fig 1, 2).

Retrospective Analytic Findings

During the course of SARS disease, the duration of fever in patients with positive SARS-CoV IgG antibody results and DLCO < 80% predicted was longer compared to the patients with positive SARS-CoV IgG results and DLCO ≥ 80% predicted and the patients with negative SARS-CoV IgG results. The doses of glucocorticoid used, the fraction of inspired oxygen concentration, and the number of noninvasive positive pressure ventilation (NIPPV) treatment for patients with positive SARS-CoV IgG results and DLCO < 80% predicted also were higher than for the other patients (Table 5). Of the 258 patients, none were intubated or received invasive mechanical ventilation, but 18 patients received NIPPV (Table 5).

Discussion

SARS caused by SARS-CoV is a unique pneumonia that is contagious and involves multiple organs. SARS-CoV infects the human body through the respiratory tract and replicates in the epithelial cells of the respiratory tract and pneumocytes. The host's immune response to SARS-CoV infection leads to lymphocyte production and to macrophage infiltra-

Table 4—*HRCT Changes for 40 Patients With Positive SARS-CoV IgG Antibody Results and DLCO < 80%

Variables	Improvement	No Change	Total	Rate, %
DLCO ≥ 70%	10	11	21	47.6
DLCO ≥ 60% to < 70%	8	6	14	57.1
DLCO < 60%	4	1	5	80
Total	22	18	40	55

*Values are given as No. unless otherwise indicated.

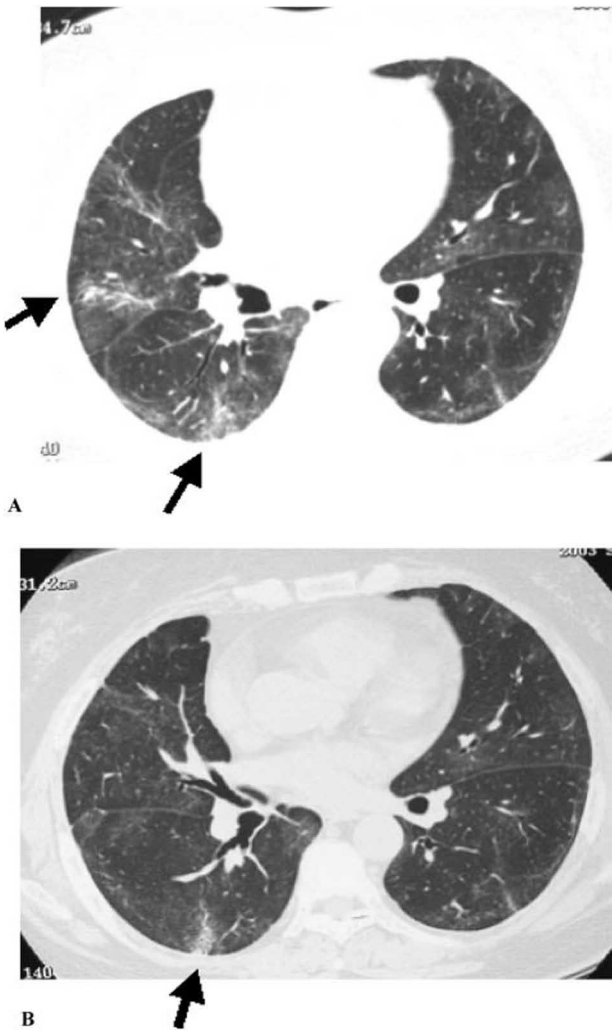

FIGURE 1. *Top*, *A*: HRCT scan of the lung area in a 60-year-old woman with SARS showing interstitial thickening and ground-glass opacification. *Bottom*, *B*: The second CT scan shows improvement of lung abnormalities. The two HRCT images are not from the same anatomic level and are of different attenuation.

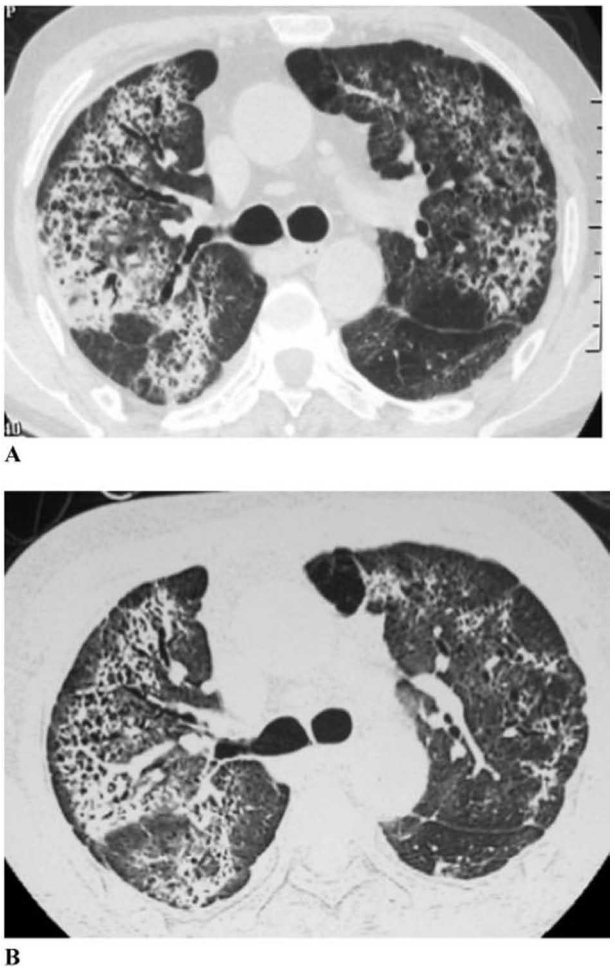

FIGURE 2. *Top*, *A*: HRCT scan of the lung area in a 54-year-old man with SARS showing bronchiectasis and diffusely thickened interlobular septa giving crazy-paving appearance. *Bottom*, *B*: The second CT scan shows no obvious improvement of lung abnormalities.

tion into the alveolar septa and interstitial compartments. In patients with severe SARS, pulmonary lesions may progress into the proliferating and fibrosis phases. In the proliferating phase, cellular components such as myofibroblasts and fibroblasts produce collagen type III and collagen type I.[1,6] In the rehabilitating phase, some patients still have lung fibrotic changes and complain of limited physical function from general weakness and/or shortness of breath affecting their pulmonary functions and life quality.[7,8]

During follow-up visits, we found that the rehabilitating SARS patients did not express persistence of SARS virus infection, as detected by SARS-CoV RNA examination, and the results showed that the rehabilitating patients did not have infectivity. In our study, 50 of 258 patients (19.4%) showed negative SARS-CoV IgG antibody results in at least two examinations, hinting that they might have been misdiagnosed. Both the Chinese clinical diagnosis standard (2003)[3] and the Centers for Disease Control and Prevention SARS case definition (2003)[9] emphasize the importance of epidemiologic history, clinical manifestation, and CXR changes on clinically diagnosed SARS disease. In the laboratory test, the Centers for Disease Control and Prevention SARS case definition especially emphasizes the importance on confirming SARS through detecting the dynamic changes of titrations of specific antibodies against SARS-CoV and positive detection of SARS-CoV RNA by PCR, but the Chinese clinical diagnosis standard does not mentioned the importance of laboratory SARS-CoV testing in SARS case confirmation. This might cause the existence of misdiagnosed SARS cases. Therefore, in the retrospective and follow-up study, we excluded these cases to ensure data accuracy. In our study, we found that there were 53 of 208 patients (25.5%) whose SARS-CoV IgG antibody results positive and also had a pulmonary diffusion abnormality (DLCO $<$ 80% predicted). Analyzing the results of the second pulmonary function examination and comparing them to the results of the first showed that most of these patients (41 of 51 patients, 80.4%) had improved pulmonary diffusion function ($p = 0.0003$). Of the rehabilitating patients with pulmonary radiologic residue caused by SARS disease presenting as pulmonary fibrotic changes, 22 of 40 patients (55%) showed improvement on the HRCT scan in a month. This suggests that the mechanism of lung injury and lung fibrotic changes caused by SARS-CoV might have a different pathophysiologic process as compared to other diseases in the lung. SARS patients with lung fibrotic changes seem to have the ability of self-rehabilitation, and a pulmonary diffusion test might be more sensitive than HRCT on evaluating lung fibrotic changes (80.4% vs 55%). We think that the radiologic resolution of pneumonic process may lag behind the clinical picture. Although this study was limited to only approximately a 2-month follow-up, the lung function test reflected an earlier resolution of diffusion impairments compared with HRCT.

Through retrospectively analyzing the data of SARS patients including the duration of persistent fever and treatment information, we found that the patients with positive SARS-CoV IgG results and DLCO $<$ 80% predicted were older compared with the patients with positive SARS-CoV IgG results and DLCO $\geq$ 80% predicted and with negative SARS-CoV IgG results. The duration of fever, dosage of glucocorticoid usage, fraction of inspired oxygen, and number of NIPPV treatments in the patients with positive SARS-CoV IgG results and DLCO $<$ 80%

Table 5—*Index of SARS Patients During the Period Having SARS Disease

Variables	SARS-CoV IgG Positive and DLCO < 80% Predicted	SARS-CoV IgG Positive and DLCO ≥ 80% Predicted	SARS-CoV IgG Negative	p Value
Patients	53	155	50	0.010§
Duration of fever presentation, d	9.8 ± 6.2	7.8 ± 6.4	3.1 ± 2.2¶#	< 0.00001
Patients receiving glucocorticoids	53 (100)	129 (83.2)	28 (56)	< 0.00001§
Total dosage of glucocorticoids, mg†	2,446.8 ± 1,775.4	988.3 ± 1,158.1¶	465.6 ± 747.8¶#	< 0.00001
Cases of oxygen treatment‡	47 (88.7)	98 (63.2)	29 (58)	0.001§
Cases of NIPPV	9 (17.0)	9 (5.8)	1 (2.0)	0.007§

*Values are given as No., No. (%), or mean ± SD.
†Total dosage of glucocorticoid means accumulative dosage of glucocorticoid converted to radiosone for SARS patients.
‡Inspiring oxygen via nasal catheter or simple face mask.
§Analyzed with χ^2 test.
‖Analyzed with separate one-way analysis of variance (ANOVA) procedures.
¶$p < 0.05$ vs SARS-CoV IgG positive and DLCO < 80% predicted with ANOVA procedures.
#$p < 0.05$ vs SARS-CoV IgG positive and DLCO ≥ 80% predicted with ANOVA procedures.

predicted were also longer. This may explain why older SARS patients had more severe symptoms than the younger patients. In spite of more aggressive therapy methods, the sequelae rates in the older rehabilitating SARS patients presented higher rates of lung fibrotic changes.[10,11]

In conclusion, SARS is associated with considerable rates of morbidity and mortality in the acute phase. A significant proportion of patients surviving the acute illness have impairment in overall functional capacity and health status in the first few months after discharge from the hospital. However, the long-term effect is still largely unknown. It is necessary to follow-up on these patients for some time with comprehensive assessments for detection and appropriate management, in case any persistent or emerging sequelae exist.

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