Original Article

Thin-section Computed Tomography Detects Long-term Pulmonary Sequelae 3 Years after Novel Influenza A Virus-associated Pneumonia

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Abstract

Background: The aim of this research was to evaluate long-term pulmonary sequelae on paired inspiration-expiration thin-section computed tomography (CT) scans 3 years after influenza A (H1N1) virus-associated pneumonia, and to analyze the affecting factors on pulmonary fibrosis.

Methods: Twenty-four patients hospitalized with H1N1 virus-associated pneumonia at our hospital between September 2009 and January 2010 were included. The patients underwent thin-section CT 3 years after recovery. Abnormal pulmonary lesion patterns (ground-glass opacity, consolidation, parenchymal bands, air trapping, and reticulation) and evidence of fibrosis (architectural distortion, traction bronchiectasis, or honeycombing) were evaluated on follow-up thin-section CT. Patients were assigned to Group 1 (with CT evidence of fibrosis) and Group 2 (without CT evidence of fibrosis). Demographics, rate of mechanical ventilation therapy, rate of intensive care unit admission, cumulative prednisolone-equivalent dose, laboratory tests results (maximum levels of alanine aminotransferase, aspartate transaminase [AST], lactate dehydrogenase [LDH], and creatine kinase [CK]), and peak radiographic opacification of 24 patients during the course of their illness in the hospital were compared between two groups.

Results: Parenchymal abnormality was present in 17 of 24 (70.8%) patients and fibrosis occurred in 10 of 24 (41.7%) patients. Patients in Group 1 (10/24; 41.7%) had a higher rate of mechanical ventilation therapy ($Z = -2.340$, $P = 0.019$), higher number of doses of cumulative prednisolone-equivalent ($Z = -2.579$, $P = 0.010$), higher maximum level of laboratory tests results (AST [$Z = -2.140$, $P = 0.032$], LDH [$Z = -3.227$, $P = 0.001$], and CK [$Z = -3.345$, $P = 0.019$]), and higher peak opacification on chest radiographs ($Z = -2.743$, $P = 0.006$) than patients in group 2 (14/24; 58.3%).

Conclusions: H1N1 virus-associated pneumonia frequently is followed by long-term pulmonary sequelae, including fibrotic changes, in lung parenchyma. Patients who need more steroid therapy, need more mechanical ventilation therapy, had higher laboratory tests results (maximum levels of AST, LDH, and CK), and had higher peak opacification on chest radiographs during treatment are more likely to develop lung fibrosis.

Key words: Computed Tomography; Influenza A; Pulmonary Infection; Viral Pneumonia

Introduction

In 2009, a novel type A influenza (H1N1) virus was first identified in patients from Mexico and has since, spread globally.[1] During peak periods of seasonal influenza, the pandemic strain of H1N1 virus caused severe illness that included pneumonia, acute respiratory distress syndrome (ARDS), and even death.[2] Chest radiography has been the main technique in the initial investigation of patients with novel H1N1 virus-associated pneumonia.[3] However, thin-section computed tomographic (CT) scanning is more sensitive than chest radiography and provides more detailed radiological features.[4] There has been some research describing the thin-section CT findings of pneumonia in H1N1 virus infection during the acute and recovery phases of the disease,[4-6] but little is known about thin-section CT findings during the subsequent stage after the recovery phase of H1N1 virus-associated pneumonia, especially with respect to long-term pulmonary sequelae.

Access this article online

Quick Response Code:

Website: www.cmj.org

DOI: 10.4103/0366-6999.154285

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In view of the role of thin-section CT scanning in the diagnosis and management of H1N1 infection, our interests lie in determining and evaluating whether thin-section CT demonstrates any residual pulmonary abnormalities in patients discharged from our institution for 3 years. Thus, the purpose of this study was to evaluate the radiological changes on paired inspiration-expiration thin-section chest CT scans in patients 3 years after H1N1 virus-associated pneumonia during the postdischarge period of the illness, and to analyze the affecting factors on pulmonary sequelae.

Methods

Patients

This study and the use of patient case files were approved by the Institutional Review Board, and informed consent was obtained from the patients.

Ninety patients who received an initial diagnosis of H1N1 virus-associated pneumonia at our institution were included in the study. Oropharyngeal or nasopharyngeal specimens from all patients were evaluated by real-time polymerase chain reaction at the Center for Disease Control and Prevention, China, and were found positive for pandemic novel H1N1.[7] All patients were treated by a team of specialists in the fields of infectious respiratory disease and critical care medicine, assigned during the outbreak of novel H1N1. A standard treatment protocol was arranged and implemented, including combined therapy with antibacterial, antiviral, and corticosteroid agents, as well as ventilation support when necessary. Eight patients died during hospitalization. The remaining 82 patients were discharged after clinical improvement. Although all 82 were scheduled for thin-section CT follow-up study, 24 patients (15 men, 9 women; mean age, 40 years; age range, 22–69 years) who had been discharged from our hospital between September 15, 2009 and January 1, 2010 were enrolled in the study after informed consent was obtained. These patients underwent a thin-section CT examination 3 years after the onset of symptoms. The remaining 58 patients refused to participate in the study after their discharge from the hospital.

Ten of the 24 patients were smokers who on average consumed half a pack of cigarettes per day for more than 16 years. Four patients presented with chronic lung diseases: One had bronchiectasis, the other three patients had chronic obstructive pulmonary disease (This information was provided to the two radiologists to enable differentiation of the nodules and bronchiectasis from the pulmonary sequelae after H1N1-associated pneumonia). Four patients had coronary heart disease. Two patients had cirrhosis, and two patients had diabetes. Follow-up pulmonary function testing was performed in all 24 patients if they had not had a respiratory tract infection for at least 3 weeks before testing. Except for two patients who had a prior history of pulmonary disease, the remaining patients had normal follow-up pulmonary function test results. Although these patients were well enough to perform their daily activities, they complained of exertional dyspnea and/or reduced exercise tolerance at clinical follow-up.

Thin-section computed tomography imaging

All patients underwent thin-section CT examination of the chest in a helical CT scanner (BrightSpeed, GE Medical Systems, Yizhuang, Beijing, China), between 34.3 months and 37.7 months (mean, 35.7 ± 0.8 months) after the onset of symptoms. Thin-section CT was performed from the lung apices to the adrenal glands at full inspiration, and the process was later repeated at full expiration. The CT scanning parameters were: 16 mm × 1.25 mm collimation, 120 kV, 240 mA, 0.5 s gantry rotation time, and a table speed of 13.75 mm per rotation. Images were reconstructed using a lung algorithm, and a standard algorithm was used to obtain contiguous inspiratory and expiratory thin-section CT images with a thickness of 1.25 mm at 1.25 mm intervals. CT scans were interpreted at window settings that are optimal for lung parenchyma (window level, −600 HU; window width, 1500 HU) and soft tissue (window level, 400 HU; window width, 40 HU).

Thin-section CT scans were reviewed by two radiologists using a viewing console, and findings were established by consensus. The thin-section CT findings were described on the basis of the recommendations of the Nomenclature Committee of the Fleischner Society.[8] The observers assessed the presence of ground-glass opacity, consolidation, reticulation (interlobular septal thickening and intralobular lines), parenchymal bands, honeycombing, traction bronchiectasis, air trapping, and architectural distortion. The presence of architectural distortion, traction bronchiectasis, or honeycombing was considered as evidence of fibrosis.[8] Interlobular septal thickening or intralobular lines could not be used as evidence of fibrosis since it may also be present during the acute illness.[9]

Demographics, clinical and radiologic data

The patients' clinical information during the course of their illness in the hospital was retrieved from their records. The data included demographic characteristics (age, sex), presence or absence of intensive care unit admission, with or without mechanical ventilation therapy, and laboratory tests results (maximum levels of alanine aminotransferase [ALT], aspartate transaminase [AST], lactate dehydrogenase [LDH], and creatine kinase [CK]).

For each patient, cumulative prednisolone-equivalent doses were calculated by adjusting the hydrocortisone or methylprednisolone dose to the cumulative prednisolone-equivalent dose on the basis of antiinflammatory potency.[10] Conversion factors of 0.20 and 1.25 were used to calculate cumulative prednisolone-equivalent doses of hydrocortisone and methylprednisolone, respectively.

Serial chest radiographs obtained during hospitalization were also reviewed for patients. All radiographic examinations were retrospectively reviewed in consensus by two

radiologists without knowledge of the follow-up thin-section CT findings. This system was an adaptation of the method previously applied to assess severe acute respiratory syndrome.[11] For each patient, the radiograph that showed the most extensive disease involvement during the course of illness was chosen for assessment of the percentage involvement of parenchymal abnormalities. Each lung was divided into three zones: Upper, middle, and lower. Each of the three zones spanned one-third of the craniocaudal distance of the lung on a frontal radiograph. The percentage area of parenchyma involved in each zone for each lung was assessed by visual estimation, with the maximum percentage of each zone being 100%. The overall mean percentage (peak radiographic opacification) of lung parenchymal involvement was calculated by averaging the percentage involvement of the six lung zones. The assessments of the two observers were averaged.

We also retrospectively reviewed 20 of the 24 (83.3%) patients who underwent chest CT scans during the course of their illness. The date of symptom onset and the date of CT scans of the 20 patients were recorded. All scans were categorized according to the time between these 2 time points at 1, 2 or 3 weeks after onset of symptoms. Abnormal pulmonary lesion patterns were evaluated, and changes that occurred over time were assessed. The CT findings were described on the basis of the recommendations of the Nomenclature Committee of the Fleischner Society.[8] (Disease history of patients was provided to the two radiologists to enable differentiation of the nodules and bronchiectasis from the H1N1-associated pneumonia).

Statistical analysis

All of the data underwent analysis with statistical software (SPSS, version 18.0; SPSS, Chicago, IL, USA). Patients with evidence of pulmonary fibrosis at thin-section CT were designated as Group 1, and patients without evidence of fibrosis at thin-section CT were designated as Group 2. The Mann–Whitney *U*-test was used to analyze differences between two patient groups. Demographics, rate of mechanical ventilation therapy, rate of intensive care unit admission, cumulative prednisolone-equivalent dose, and laboratory tests results (maximum levels of ALT, AST, LDH, and CK) during the course of illness were compared. The peak opacification on chest radiographs during the hospital stay were also compared. A $P < 0.05$ was considered statistically significant.

Results

Demographics, clinical and radiologic data in the hospital

The demographic data, clinical data, and radiographs of the 24 patients during the course of the illness in the hospital are summarized in Table 1, and the patterns of abnormality of the lesions on the CT in the acute stage at the different weeks after the onset of symptoms are summarized in Table 2. Twenty of the 24 (83.3%) patients underwent 31 chest CT scans between 1 and 3 weeks after the onset of H1N1 symptoms: 12 patients in the 1st week, 11 patients in the 2nd week and 8 patients in the 3rd week. Nine patients had only one chest CT scan and eleven patients had two CT scans within the 3 weeks. The predominant radiographic findings in the 20 patients were unilateral or bilateral multifocal asymmetric ground-glass opacity with or without bilateral consolidation. Ground-glass opacity alone with superimposed consolidation was predominant in the 1st and 2nd week. After the onset of H1N1 symptoms, ground-glass opacity and consolidation were noted in 100% (12/12) and 58.3% (7/12) of patients in the 1st week and in 100% (11/11) and 72.7% (8/11) of patients in the 2nd week. Parenchymal bands, architectural distortion, reticulation, and traction bronchiectasis, which suggested fibrosis, were noted in the 2nd week after onset of symptoms and increased. Four (20%) of the 20 patients had bilateral or unilateral pleural effusions.

Table 1: Demographic data, clinical data, and radiographs in the acute stage

Characteristics	*n* = 24
Age (years)	40.4 ± 12.7
Sex	
Male*	15
Female*	9
Treatment modalities	
Days in hospital (days)	17.8 ± 18.2
Intensive care unit admission*	9
Mechanical ventilation*	6
Cumulative prednisolone-equivalent dose (mg)	745.3 ± 445.9
Blood test results (U/L)	
Maximum ALT level	42.3 ± 20.8
Maximum AST level	52.6 ± 28.9
Maximum LDH level	468.5 ± 289.4
Maximum CK level	429.3 ± 618.7
Chest radiographs	
Peak radiographic opacification (%)	41.3 ± 32.5

Unless otherwise specified, data are the mean ± SD. ALT: Alanine aminotransferase; AST: Aspartate transaminase; LDH: Lactate dehydrogenase; CK: Creatine kinase; SD: Standard deviation. *Data are the numbers of patients.

Table 2: The patterns of abnormality of the lesions on the CT at the different weeks after the onset of symptoms (%)

Parameter	Week 1 (*n* = 12)	Week 2 (*n* = 11)	Week 3 (*n* = 8)
Ground-glass opacity	12 (100.0)	11 (100.0)	8 (100.0)
Consolidation	7 (58.3)	8 (72.7)	8 (100.0)
Parenchymal bands	1 (8.3)	3 (27.3)	4 (50.0)
Architectural distortion	1 (8.3)	1 (9.0)	3 (37.5)
Reticulation	0 (0.0)	0 (0.0)	2 (25.0)
Traction bronchiectasis	0 (0.0)	0 (0.0)	1 (12.5)
Honeycombing	0 (0.0)	0 (0.0)	0 (0.0)
Air trapping	0 (0.0)	0 (0.0)	0 (0.0)

Data are the numbers of patients. The numbers in parentheses are percentages. CT: Computed tomography.

Follow-up thin-section computed tomography findings

The thin-section CT findings at follow-up are summarized in Table 3. Seven of the 24 (29.2%) patients demonstrated no abnormalities on thin-section CT. In the remaining 17 patients (70.8%), the predominant thin-section CT findings included ground-glass opacity in 15/24 (62.5%), architectural distortion in 10/24 (41.7%), and parenchymal bands in 10/24 (41.7%) [Figure 1]. Other CT findings were as follows: Air trapping in 9/24 (37.5%) [Figure 2], reticulation in 8/24 (33.3%), and traction bronchiectasis in 2/24 (8.3%). Among the 17 cases with abnormalities, no thin-section CT evidence of consolidation or honeycombing was found. Ten patients with the CT finding of architectural distortion (two patients with traction bronchiectasis, concomitantly) were designated as Group 1 (10/24; 41.7%), and other fourteen patients without the CT findings of fibrosis were designated as Group 2 (14/24; 58.3%). The most common CT pattern observed was ground-glass opacity along with superimposed architectural distortion in Group 1 patients (100%; 10/10) and ground-glass opacity in Group 2 patients (35.7%; 5/14). In addition to the most common pattern, parenchymal bands (80%; 8/10), air trapping (60%; 6/10), reticulation (70%; 7/10), and traction bronchiectasis (20%; 2/10) were noted in Group 1 and parenchymal bands (14.3%; 2/14), air trapping (21.4%; 3/14), and reticulation (7.1%; 1/14) were noted in Group 2. Besides two patients with mechanical ventilation therapy during the acute phase, the distribution of abnormal follow-up thin-section CT findings of 22 patients was consistent with the same region on previous CT scans. The two patients with mechanical ventilation therapy typically had pulmonary sequelae and were most pronounced in the anterior nondependent portions of the lung, which showed only mild involvement during the acute phase.

Table 3: Follow-up thin-section CT findings (n = 24)

Parameter	n (%)
Normal thin-section CT	7 (29.2)
Abnormal thin-section CT	17 (70.8)
Ground-glass opacity	15 (62.5)
Architectural distortion	10 (41.7)
Parenchymal bands	10 (41.7)
Air trapping	9 (37.5)
Reticulation	8 (33.3)
Traction bronchiectasis	2 (8.3)
Consolidation	0 (0.0)
Honeycombing	0 (0.0)

Data are the numbers of patients. The numbers in parentheses are percentages. CT: Computed tomography.

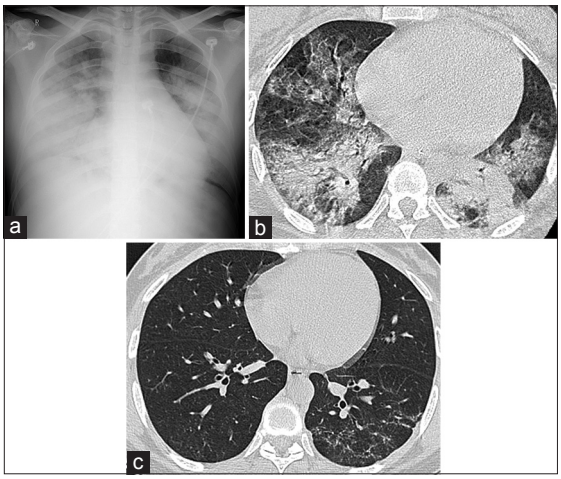

Figure 1: A 35-year-old woman diagnosed with novel influenza A pneumonia without secondary infection. The patient received cumulative prednisolone-equivalent doses of 850 mg and mechanical ventilation therapy. Laboratory investigations showed the maximum levels of alanine aminotransferase, aspartate transaminase, lactate dehydrogenase, and creatine kinase in the acute stage were 32 U/L, 101 U/L, 1160 U/L, and 201 U/L, respectively. (a) A portable chest radiograph obtained 4 days after the onset of clinical symptoms shows widespread consolidation, with central and lower lung zone predominance; (b) Transverse thin-section computed tomography (CT) scans performed 10 days after the onset of clinical symptoms demonstrate consolidations and ground-glass opacities in the lower lung fields; (c) Follow-up transverse inspiration thin-section CT scans obtained 3 years after the onset of clinical symptoms show residual reticular opacity in the lower lobes and ground-glass opacity in the left lower lobe.

Comparisons between demographics, clinical data, and radiographs

Table 4 lists the results of the comparisons between age,

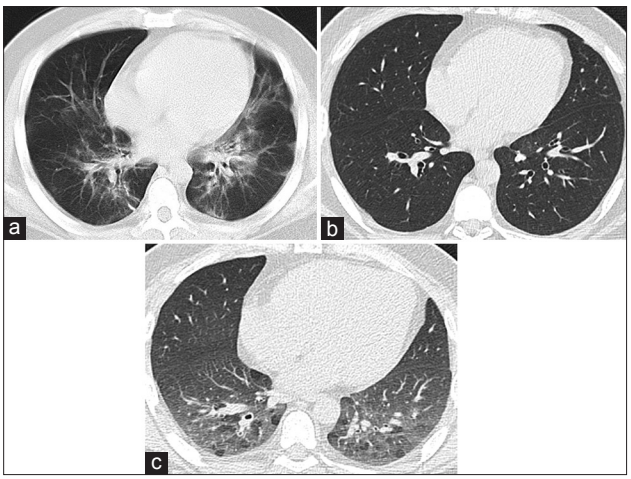

Figure 2: A 24-year-old man diagnosed with novel influenza A pneumonia without secondary infection. The patient without mechanical ventilation therapy received cumulative prednisolone-equivalent doses of 700 mg. Laboratory investigations showed the maximum levels of alanine aminotransferase, aspartate transaminase, lactate dehydrogenase, and creatine kinase in the acute stage were 90 U/L, 69 U/L, 486 U/L, and 1747 U/L, respectively. (a) Transverse computed tomography (CT) scans obtained 18 days after the onset of clinical symptoms through the lower lobes demonstrate ground-glass opacity, parenchymal bands; (b, c) Follow-up transverse thin-section CT scans obtained 3 years after the onset of clinical symptoms; (b) Axial inspiratory image scan demonstrates no clear evidence of lung abnormality; (c) Axial expiratory image shows abnormal low attenuation caused by air trapping, representing failure of the expected increase in lung attenuation.

Table 4: Comparison of demographic data, clinical data, and radiographs between the patient groups

Characteristic	Group 1 (n = 10)	Group 2 (n = 14)	Z	P
Median age (years)	39.0 (22.0-62.0)	35.5 (27.0-69.0)	−0.880	0.379
Male:female ratio*	7:3	8:6	−0.628	0.530
Mechanical ventilation therapy*	5	1	−2.340	0.019
Intensive care unit admission*	6	3	−1.884	0.060
Cumulative prednisolone-equivalent dose (mg)	1000.0 (0.0-1800.0)	537.5 (0.0-1200.0)	−2.579	0.010
Maximum ALT level (U/L)	36.0 (13.0-90.0)	46.0 (16.0-86.0)	−1.469	0.154
Maximum AST level (U/L)	72.5 (15.0-107.0)	40.0 (10.0-78.0)	−2.140	0.032
Maximum LDH level (U/L)	681.0 (292.0-1284.0)	319.0 (208.0-676.0)	−3.227	0.001
Maximum CK level (U/L)	389.0 (58.0-1747.0)	139.0 (38.0-539.0)	−3.345	0.019
Peak radiographic opacification (%)†	90.0 (10.0-90.0)	15.0 (10.0-60.0)	−2.743	0.006

Unless otherwise specified, data are the median. The numbers in parentheses are range. ALT: Alanine aminotransferase; AST: Aspartate transaminase; LDH: Lactate dehydrogenase; CK: Creatine kinase. *Data are number of patients; †Calculated as estimated percentage of area involved.

sex, rate of mechanical ventilation therapy, rate of intensive care unit admission, cumulative prednisolone-equivalent dose, laboratory tests results (maximum levels of ALT, AST, LDH, and CK), and peak radiographic opacification during the course of illness between two groups. The mechanical ventilation therapy rate was higher in Group 1 patients than in Group 2 patients (Z = −2.340, P = 0.019). During their hospital stay, Group 1 patients also received a higher number of doses of cumulative prednisolone-equivalent than did Group 2 patients (Z = −2.579, P = 0.010). The maximum AST level, LDH level, and CK level were also higher in group 1 than in Group 2 patients (Z = −2.140, P = 0.032; Z = −3.227, P = 0.001; Z = −3.345, P = 0.019, respectively). The normal range of AST, LDH, and CK level at our institution is 0–40 U/L, 114–240 U/L, and 0–190 U/L, respectively. The peak opacification on chest radiographs was higher in Group 1 patients compared with that in group 2 patients (Z = −2.743, P = 0.006). With respect to age, sex, rate of intensive care unit admission, and maximum ALT level, there were no significant differences between these two groups.

Discussion

The CT findings of patients in the acute stage of H1N1 virus-associated pneumonia were unilateral or bilateral ground-glass opacities with or without focal or multifocal areas of consolidation,[12] which tended to result in short-term residual disease.[13,14] In our study, follow-up thin-section CT scans obtained in discharged patients 3 years after the H1N1 virus-associated pneumonia showed that pulmonary sequelae occurred in 17 of 24 (70.8%) patients, and fibrosis occurred in 10 of 24 (41.7%) patients. These findings of our study revealed that pulmonary sequelae, especially fibrosis, are a frequently long-term complication of H1N1 virus-associated pneumonia. According to reports in the literature, the main pathological change associated with H1N1 virus-associated pneumonia is diffuse alveolar damage (DAD).[13] The histologic appearance of DAD is divided into acute phase, and organizing phase depends on the time from the initial lung injury to lung biopsy. From the initial injury through the 1st week, acute phase DAD is characterized histologically by the presence of hyaline membranes and edema of the alveolar walls. After the 1st week, the organizing phase of DAD predominates and is characterized by organizing fibroblastic tissue and fibrosis.[14] Histologic appearance of DAD can mirror by paired inspiration-expiration thin-section CT scans.[15] In our study, thin-section CT evidence of architectural distortion (10/24; 41.7%) and traction bronchiectasis (2/24; 8.3%) were found. Architectural distortion is characterized by abnormal displacement of bronchi, vessels, fissures, or septa, and traction bronchiectasis represents irregular bronchial and bronchiolar dilatation caused by surrounding pulmonary fibrosis,[8] both of which reflect the pathological findings of lung fibrosis.[16,17]

With the exception of architectural distortion and traction bronchiectasis, the follow-up thin-section CT findings included ground-glass opacity (15/2; 62.5%), parenchymal bands (10/24; 41.7%), air trapping (9/24; 37.5%), and reticulation (8/24; 33.3%). Patients in group 1 had a higher rate of ground-glass opacity (100% [10 of 10] vs. 35.7% [5 of 14]), parenchymal bands (80% [8 of 10] vs. 14.3% [2 of 14]), air trapping (60% [6 of 10] vs. 21.4% [3 of 14]), and reticulation (70% [7 of 10] vs. 7.1% [1 of 14]) than patients in Group 2. Some of these CT findings reflect pulmonary fibrosis but could not be used as evidence of fibrosis, since it may also be present during the acute illness. Ground-glass opacities as nonspecific findings are generally pathologically attributable to the combined effects of diminished intra-alveolar air and increased cellular density, alveolar cuboidal cell hyperplasia, or thickening of the alveolar septa.[18] Persistent ground-glass opacity present on serial inspiration thin-section CT scans suggests the possibility of organizing pneumonia or focal fibrosis.[19] Air trapping is defined as parenchymal areas with less than normal increase in attenuation seen on end-expiration CT scans and lack of volume reduction.[20] Air trapping may be caused by diseases of the small airways.[21] It has been reported that the extent of air trapping assessed by expiratory CT significantly correlates with airflow obstruction.[22] Air trapping observed on thin-section CT in our patients was similar to that observed in the late stages of SARS, such

as in the research of Chang *et al*.[15] in which air trapping was found in 16 of 20 patients at 140.7 ± 26.7 days after symptom onset.

Comparison of the 3 years follow-up thin-section CT findings with clinical data has revealed that differences between patients with CT evidence of fibrosis and those without in terms of rate of mechanical ventilation therapy, cumulative prednisolone-equivalent dose, maximum levels of AST, maximum levels of LDH, maximum levels of CK, and peak radiographic opacification during treatment. These parameters during treatment in patients with H1N1 virus-associated pneumonia are most likely a reflection of the severity of disease. According to former studies, the extents of abnormalities on radiographs during patient treatment are most likely a reflection of the severity of influenza pneumonia. Cho *et al*.[23] found that patient with severe H1N1 virus-associated pneumonia had a significantly greater extent of lung involvement than those nonpatients. LDH, AST, and CK are reliable independent indicators of a worse clinical result. Xi *et al*.[24] found that LDH was independent predictors of hospital mortality in H1N1 virus-associated pneumonia. Patients with increased serum level of AST are at a higher risk of death during hospitalization.[25] CK is also a biomarker of severity in H1N1 infection. Elevation of CK was associated with more complications and increased ICU length of stay.[26] Patients with evidence of fibrosis at thin-section CT also had a higher requirement of steroid therapy during treatment. The need for pulsed steroid therapy may reflect the magnitude of the cytokine "storm" elicited by the viral antigen, which may be the underlying pathogenesis of lung damage and subsequent development of fibrosis.[27]

Besides the severity of disease, barotrauma or oxygen toxicity maybe also a major cause of lung fibrosis. Nöbauer-Huhmann *et al*.[28] found that ARDS frequently is followed by fibrosis in lung, and the distribution pattern of fibrotic changes are predominantly located in the ventral zones of the lung. They confirm that the anterior location of the fibrosis may be related to barotrauma due to mechanical ventilation or oxygen toxicity, whereas the dependent lung is protected by collapse. In our study, 2 of 6 patients (33.3%) with mechanical ventilation therapy were predominantly located in the ventral zones of the lung [Figure 3], and we speculate that the barotrauma due to mechanical ventilation or oxygen toxicity was one of the causes of long-term pulmonary sequelae and fibrosis.

This study had several limitations. First, because of the small sample size in each patient group, the results of our comparisons in this study may be biased. Second, these patients have not been followed-up in the recovery phases of the disease. It is difficult to compare the changes in serial thin-section CT from patients with novel swine-origin H1N1 infection between short-term and long-term follow-up.

In conclusion, on thin-section CT scans, pulmonary sequelae occurred in 17 of 24 (70.8%) patients and fibrosis occurred in 10 of 24 (41.7%) patients 3 years after the H1N1 virus-associated pneumonia. There is a difference between patients with evidence of fibrosis at thin-section CT and those without in terms of rate of mechanical ventilation therapy, cumulative prednisolone-equivalent dose, maximum levels of AST, maximum levels of LDH, maximum levels of CK, and peak radiographic opacification during treatment, which suggests that fibrosis is more likely to develop in patients with more severe disease, and barotrauma due to mechanical ventilation or oxygen toxicity was also one of causes of lung fibrosis. However, we wish to clearly state that our findings are only preliminary, and larger studies will be necessary to better determine the long-term outcome for patients with H1N1 virus-associated pneumonia.

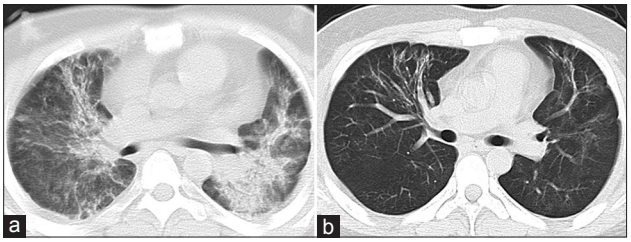

Figure 3: A 22-year-old man diagnosed with novel influenza A pneumonia without secondary infection, and received mechanical ventilation therapy. The patient received cumulative prednisolone-equivalent doses of 1150 mg. Laboratory investigations showed the maximum levels of alanine aminotransferase, aspartate transaminase, lactate dehydrogenase, and creatine kinase in the acute stage were 39 U/L, 124 U/L, 900 U/L, and 876 U/L, respectively. (a) Transverse computed tomography (CT) image obtained 6 days after the onset of clinical symptoms shows diffuse ground-glass opacity (GGO) and dependent consolidation; (b) Follow-up transverse inspiration thin-section CT image obtained 3 years after the onset of clinical symptoms shows resolution of the GGO and dependent consolidation. However, fibrosis has developed in the anterior portion of the lungs, which showed only mild involvement during the acute phase.

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Received: 24-12-2014 **Edited by:** De Wang
How to cite this article: Xing ZH, Sun X, Xu L, Wu Q, Li L, Wu XJ, Shao XG, Zhao XQ, Wang JH, Ma LY, Wang K. Thin-section Computed Tomography Detects Long-term Pulmonary Sequelae 3 Years after Novel Influenza A Virus-associated Pneumonia. Chin Med J 2015;128:902-8.

Source of Support: Nil. **Conflict of Interest:** None declared.