ORIGINAL ARTICLE

Eight-Month Prospective Study of 14 Patients With Hospital-Acquired Severe Acute Respiratory Syndrome

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OBJECTIVE: To define the clinical characteristics and clinical course of hospital-acquired severe acute respiratory syndrome (SARS).

PATIENTS AND METHODS: This 8-month prospective study of 14 patients with hospital-acquired SARS in Taipei, Taiwan, was conducted from April through December 2003.

RESULTS: The most common presenting symptoms in our 14 patients with hospital-acquired SARS were fever, dyspnea, dizziness, malaise, diarrhea, dry cough, muscle pain, and chills. Lymphopenia and elevated serum levels of lactate dehydrogenase (LDH) and C-reactive protein (CRP) were the most common initial laboratory findings. Initial chest radiographs revealed various pattern abnormalities and normal results. Five of the 14 patients required mechanical ventilation. The need for mechanical ventilation was associated with bilateral lung involvement on the initial chest radiograph and higher peak levels of LDH and CRP. Clinical severity of disease varied from mild to severe. At 8 months after disease onset, patients with mild or moderate SARS had normal findings or only focal fibrosis on chest high-resolution computed tomography. However, bilateral fibrotic changes remained in the 4 patients who had recovered from severe SARS, 1 of whom had mild restrictive ventilatory impairment. One patient with severe SARS died; she was elderly and had other comorbidities. Five additional patients had reduced diffusing capacity.

CONCLUSION: The clinical picture of our patients presenting with hospital-acquired SARS revealed atypical pneumonia associated with lymphopenia, elevated serum levels of LDH, rapid clinical deterioration, and lack of response to empirical antibiotic therapy. Substantially elevated levels of LDH and CRP correlated with severe illness requiring mechanical ventilatory support. In those receiving mechanical ventilation, pulmonary function was only mildly reduced at 6 to 8 months after acute illness, consistent with the natural history of acute respiratory distress syndrome due to other causes.

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ALT = alanine aminotransferase; ARDS = acute respiratory distress syndrome; AST = aspartate aminotransferase; CK = creatine kinase; CRP = C-reactive protein; FEV_1 = forced expiratory volume in 1 second; F_{IO_2} = fraction of inspired oxygen; FVC = forced vital capacity; HRCT = high-resolution computed tomography; LDH = lactate dehydrogenase; RT-PCR = reverse transcriptase–polymerase chain reaction; SARS = severe acute respiratory syndrome; TLC = total lung capacity

In November 2002, there were reports from the Guangdong Province in southern China of 305 cases of highly contagious, severe atypical pneumonia of unknown cause.[1,2] On March 13, 2003, as this novel infectious disease spread beyond China's borders, the World Health Organization issued a global alert and initiated worldwide surveillance. By this time, the US Centers for Disease Control and Prevention had named the condition *severe acute respiratory syndrome* (SARS) and had provided a clinical case definition.[3] During an outbreak of atypical pneumonia in Hong Kong, scientists at the Centers for Disease Control and Prevention and in Hong Kong announced that a new coronavirus had been isolated from patients with SARS.[4] Additional cases of suspected SARS were reported worldwide,[5] but China, Hong Kong, Singapore, Toronto (Canada), and Taiwan have borne the brunt of the caseload.

The first case of SARS occurred in Taiwan in February 2003[6]: a merchant was returning to Taipei from the Guangdong Province via Hong Kong. On March 14 and 17, 2003, his wife and son, respectively, presented with probable SARS. Soon thereafter, other Taiwanese citizens returning from mainland China and Hong Kong were diagnosed as having SARS. During the early stages of the additional outbreaks in Taiwan, awareness of this new communicable disease was poor, and stringent infection control procedures had not been implemented in the hospitals, leading to a series of hospital-acquired infections.

Although several case series of SARS have been reported,[7-9] to our knowledge, a prospective clinical study including long-term follow-up assessment by chest radiography, chest high-resolution computed tomography (HRCT), and pulmonary function testing has not been reported, particularly for hospital-acquired cases. This prompted us to study prospectively the presenting manifestations and the eventual clinical outcome of 14 patients with hospital-acquired SARS.

PATIENTS AND METHODS

This study was approved by the ethics committee of the Veterans General Hospital, Taipei, Taiwan.

The index patient with SARS visited the emergency department of Hospital A on April 9, 2003, and hospital-acquired infections spread in Hospital A (a community hospital). Subsequently, index patients with SARS seen at

Hospital B (another community hospital) resulted in additional cases of hospital-acquired SARS. Hospitals A and B were closed subsequently. The Taipei Veterans General Hospital (Hospital C), the largest tertiary and national teaching hospital in Taipei City, was ordered by the government to admit the 12 patients with hospital-acquired SARS from Hospitals A and B. Two hospital staff members (a physician and an emergency department nurse) at Taipei Veterans General Hospital also acquired the SARS infection.

We conducted the initial management and data-collecting protocol on April 20, 2003, and enrolled these 14 patients from April 25 to May 7, 2003; follow-up extended through December 2003. All 14 patients met the World Health Organization case definition, established on April 17, 2003, for SARS[1-3]: fever (temperature ≥38°C), cough or shortness of breath, and pulmonary infiltration in the absence of an alternative diagnosis to explain the clinical presentation, combined with a history of direct exposure to SARS or returning from a SARS-infected area. Although the initial chest x-ray films were normal in 3 patients, radiographic abnormalities were noted on films obtained 1 to 2 days later. All 14 of these patients with SARS were admitted to the isolation wards at Taipei Veterans General Hospital. We classified the severity of SARS into 3 groups on the basis of the oxygenation status of the patients at enrollment: *mild* was defined by a normal Pao_2, *moderate* was defined by an abnormally low Pao_2 but a Pao_2/fraction of inspired oxygen (Fio_2) ratio of 200 mm Hg or higher, and *severe* was defined by a Pao_2/Fio_2 ratio lower than 200 mm Hg. (Patients with severe SARS developed adult respiratory distress syndrome [ARDS] and required mechanical ventilation.)

LABORATORY AND RADIOLOGICAL ASSESSMENT

For all patients, hematologic (complete blood cell counts with differential leukocyte count and coagulation profile) and biochemical (electrolytes, liver and renal function, creatine kinase [CK], lactate dehydrogenase [LDH]) tests were performed every 2 days during hospitalization. Chest radiographs were obtained every 2 days during hospitalization and monthly after hospital discharge. Chest HRCT was performed every 3 months.

REVERSE TRANSCRIPTASE–POLYMERASE CHAIN REACTION FOR DIAGNOSIS OF SARS

Blood samples, throat swabs, and/or sputum were collected on the first day of admission. Molecular diagnosis of SARS was performed by extracting the viral RNA according to a viral RNA kit (QIAGEN, Hilden, Germany), followed by the use of a 1-step reverse transcriptase–polymerase chain reaction (RT-PCR) kit with coronavirus-specific primers
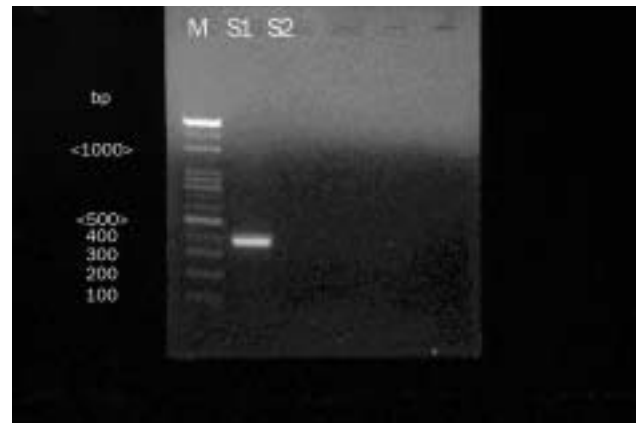

FIGURE 1. Reverse transcriptase–polymerase chain reaction (RT-PCR) was used to diagnose the severe acute respiratory syndrome (SARS) coronavirus in patient 3. The PCR products were observed through 1.5% agarose gel electrophoresis. As shown in the S1 column, RT-PCR was done with the serum from this patient on hospital day 8, and results were positive; product size was 368 base pairs (bp). However, the same procedure was repeated with the serum from this patient on hospital day 50, and results were negative, as shown in the S2 column. This finding indicated that the virus was present in the blood during the initial phase but had disappeared in the late phase of disease.

(Roche, Mannheim, Germany) to carry out RT-PCR. The PCR products were observed through 1.5% agarose gel electrophoresis (Figure 1). The primers of RT-PCR were Cor-p-F2 (+) 5′CTAACATGCTTAGGATAATGG3′ and Cor-p-R1 (–) 5′CAGGTAAGCGTAAAACTCATC3′. The product size (Cor-p-F2/Cor-p-R1) was 368 base pairs.[10]

MANAGEMENT PROTOCOL

All patients received oral ribavirin at 2000 mg/d for 10 days, intravenous injection of levofloxacin at 500 mg/d for 7 days, and intravenous immunoglobulin at 1 g/kg per day for 2 days after symptom onset. In cases of acute lung injury (Pao_2/Fio_2 ratio <200 mm Hg), methylprednisolone at 2 mg/kg per day was administered intravenously, and the dosage was tapered subsequently according to clinical response. The criteria for tracheal intubation and mechanical ventilation included an absolute indication, Pao_2/Fio_2 ratio less than 100 mm Hg, and a relative indication, Pao_2/Fio_2 ratio of 100 to 200 mm Hg. Mechanical ventilation was used with a low tidal volume (6-8 mL/kg), plateau pressure lower than 30 to 35 cm H_2O, and adequate positive end-expiratory pressure to lessen the likelihood of barotrauma.[11]

FOLLOW-UP AFTER HOSPITAL DISCHARGE

After discharge from the hospital, patients were followed up as outpatients with chest radiography, HRCT, and pul-

TABLE 1. **Epidemiological Characteristics of the 14 Patients With SARS***

Male	3
Female	11
Mean ± SD age (y)	36.1±13.9
Smoker	
Yes	0
No	14
Occupation (hospital where exposure occurred)	
Clerical staff	1 (A)
Laboratory technician	1 (B)
Physician	1 (C)
Merchant	1 (B)
Nurses	7 (A, 5; B, 1; C, 1)
Patient	1 (B)
X-ray technician	2 (B)
History	
Asthma	1
Diabetes mellitus and congestive heart failure	1
Hepatitis B virus carrier	1
Hyperthyroidism	1
None	10
Travel	
None	14
Exposure to SARS	
Emergency department of Hospital C	2
Patient in Hospital A	1
Patient in Hospital B	5
SARS in Hospital B	6

*SARS = severe acute respiratory syndrome.

monary function tests (Automated Body Plethysmograph 6200 Autobox DL, SensorMedics, Loma Linda, Calif). The impairment of pulmonary function was assessed according to the guidelines of the American Thoracic Society.[12] The pulmonary function test result was interpreted as within normal limits if the total lung capacity (TLC), forced vital capacity (FVC), forced expiratory volume in 1 second (FEV_1), and diffusing capacity were greater than 80% of the predicted normal value and the FEV_1/FVC ratio was greater than 0.70.

DATA ANALYSES
Continuous data are expressed as the mean ± SD or a percentage. The Wilcoxon rank sum test was used to determine whether there was an association between any of the clinical and laboratory variables and mechanical ventilation. The Fisher exact test was used to determine whether there was an association between categorical variables. $P<.05$ was regarded as statistically significant. Statistical analysis was performed with SYSTAT software (Version 7.0, SPSS, Chicago, Ill).

RESULTS

EPIDEMIOLOGICAL CHARACTERISTICS
The mean ± SD age of the 14 patients with hospital-acquired SARS was 36.1±13.9 years (median, 30 years;

range, 25-74 years). Other epidemiological characteristics are shown in Table 1. All patients were Chinese, and all were exposed to SARS in the hospital setting. Twelve of these 14 patients (86%) were health care workers (1 physician, 7 nurses, 2 radiology technicians, 1 clerical staff, and 1 laboratory technician). Most patients had been healthy before exposure to SARS.

INITIAL SYMPTOMS AND PHYSICAL EXAMINATION FINDINGS
The most common symptoms of the patients at presentation were fever (n=14 [100%]), dyspnea (n=12 [86%]), dizziness (n=11 [79%]), diarrhea (n=11 [79%]), malaise (n=11 [79%]), dry cough (n=10 [71%]), muscle pain (n=9 [64%]), and chills (n=8 [57%]). Less common symptoms included sore throat (n=3 [21%]), sputum production (n=4 [29%]), nausea (n=2 [14%]), chest pain (n=2 [14%]), and vomiting (n=2 [14%]). Physical examination at admission revealed fever and inspiratory crackles in all patients. Rash, lymphadenopathy, and purpura were not observed.

INITIAL LABORATORY FINDINGS
Initial abnormal laboratory findings included leukopenia (n=4 [29%]), lymphopenia (n=14 [100%]), thrombocytopenia (n=2 [17%]), anemia (n=3 [21%]), and leukocytosis (n=6 [43%]), as well as elevated serum levels of aspartate aminotransferase (AST) (n=4 [29%]), alanine aminotransferase (ALT) (n=4 [29%]), LDH (n=10 [71%]), CK (n=1 [7%]), and C-reactive protein (CRP) (n=11 [79%]). All 14 patients had positive findings on RT-PCR assay of SARS coronavirus.

INITIAL RADIOLOGICAL FINDINGS
In 3 patients (21%), the initial chest radiographs appeared normal, but radiological opacities were noted within 2 days of admission (Table 2). In the other 11 patients with abnormal chest radiographs on admission, the predominant pattern of abnormality was haziness (n=4 [36%]), consolidation (n=3 [27%]), and interstitial infiltrates (n=4 [36%]). The pattern of distribution was unilateral focal opacity (n=6 [55%]), unilateral multifocal opacities (n=4 [36%]), and bilateral opacities (n=1 [9%]).

FOLLOW-UP RADIOLOGICAL FINDINGS
Chest radiographs revealed maximal infiltrates at a mean ± SD of 8.7±3.8 days (range, 3-17 days) after onset of fever. The pattern of radiographic lung involvement varied dramatically among the patients. In 6 patients with only a focal opacity on initial chest radiographs, progression to bilateral lung involvement was seen, including ARDS in 1 patient (Figure 2). In 5 patients presenting with bilateral lung involvement on initial chest radiographs, continued radiological deterioration was seen, with 4 of these patients

developing ARDS (Figure 3). There was a significant association between bilateral lung involvement and development of ARDS (P=.02; Fisher exact test). Thus, patients presenting with bilateral or multifocal involvement on initial chest radiography appeared to be at an increased risk of developing ARDS compared with those presenting with only a focal opacity.

UNIVARIATE ANALYSES CORRELATING CLINICAL AND LABORATORY VARIABLES WITH USE OF MECHANICAL VENTILATION

Initial laboratory findings included leukopenia, lymphopenia, thrombocytopenia, anemia, leukocytosis, and elevated serum levels of AST, ALT, LDH, CK, and CRP. Lymphopenia and elevated CK and LDH levels were the most common. The peak elevation of serum LDH (occurring a mean of 10 days after onset of fever) and CRP (a mean of 8 days after onset of fever), maximal lymphopenia (a mean of 9 days after onset of fever), and maximal infiltrates on chest imaging (a mean of 8.7 days after onset of fever) appeared to coincide within a 48-hour period during the course of illness in 5 patients with severe SARS. Higher peak levels of CRP and LDH were significantly associated with the need for mechanical ventilation (Table 3).

TREATMENT OUTCOME

During hospitalization, 10 of the 14 patients needed supplemental oxygen therapy. Of these 10 patients, 5 (36% of the total 14) had progression to ARDS and required mechanical ventilation. The clinical course of the 14 patients was generally characterized by defervescence and gradual clinical improvement as well as normalization of blood cell counts and diminishing lung infiltrates during a course of 2 weeks of inpatient management. In this cohort of 14 patients, 1 died. This patient was elderly and had comorbidities, including diabetes mellitus and congestive heart failure. Her illness progressed to ARDS and was complicated by bilateral pneumothorax and multiorgan failure (respiratory, heart, and renal failure).

The mean ± SD duration of hospitalization for the entire cohort was 24±5.7 days. In the 4 patients with ARDS who required mechanical ventilation (excluding the 1 patient who died), the duration of hospitalization was 37.2±9.8 days.

At discharge from the hospital, chest imaging showed normal results in 4 patients and residual infiltrates in 9 patients. Only 1 patient had continuing need for supplemental oxygen therapy at the time of hospital discharge.

Hair loss and joint pain occurred in patients with severe SARS but resolved within 3 months. Generalized anxiety disorder persisted in 1 patient and required medical attention.

TABLE 2. **Initial and Subsequent Findings on Chest Imaging in 14 Patients With SARS***

Clinical severity of illness	
Mild	4
Moderate	5
Severe	5
Chest radiograph on admission	
Bilateral diffuse interstitial infiltrates	1
Consolidation	
RML	1
RUL, RLL	1
Haziness	
LLL	2
RLL	1
RUL, RLL	1
Interstitial infiltrates	
LLL	1
RLL, LLL	2
Normal	3
Segmental consolidation RUL	1
Chest radiograph at peak illness	
Bilateral diffuse alveolar infiltrates	1
Bilateral diffuse alveolar infiltrates, pneumothorax	1
Bilateral diffuse haziness, pneumothorax	1
Consolidation RLL, haziness RLL	1
Consolidation	
LLL	1
RLL, LLL	5
RLL, RUL, LLL	1
RUL	1
RUL, LLL	1
RUL, RLL	1
6-month follow-up HRCT	
Bilateral basilar fibrosis with ground-glass opacities	1
Focal fibrosis LLL	3
In-hospital death	1
Multifocal fibrosis	1
Multifocal fibrosis with ground-glass opacities	2
Multifocal fibrosis with ground-glass opacities	
RLL, LLL	1
Normal	5

*HRCT = high-resolution computed tomography; LLL = left lower lobe; RLL = right lower lobe; RML = right middle lobe; RUL = right upper lobe; SARS = severe acute respiratory syndrome.

FOLLOW-UP PULMONARY FUNCTION TESTING AND CHEST IMAGING

Of the 13 survivors, 4 refused follow-up assessment of pulmonary function because they had recovered fully and had no residual functional impairment. The 9 patients subjected to follow-up pulmonary function testing 6 months after discharge were 4 who survived ARDS and 5 who did not have ARDS; in 3 of these 9 patients, results were normal (Table 4). Mild restrictive impairment was observed in only 1 patient who had survived ARDS associated with SARS; this patient required 2 episodes of mechanical ventilation. A reduced diffusing capacity was found in 5 additional patients. The mean ± SD diffusing capacity of ARDS survivors who also had SARS was reduced to 51.5%±11.0% of the predicted normal value but was 83.8%±16% of that predicted in SARS patients who did not have ARDS.

FIGURE 2. Images of patient 3 who had severe acute respiratory syndrome complicated by acute respiratory distress syndrome. Left, Chest radiograph on day 8 reveals bilateral consolidation and infiltrates (endotracheal tube was placed for mechanical ventilation). Middle, Chest radiograph performed 6 months after hospital discharge shows residual fibrotic infiltrates in the lower lung zones. Right, High-resolution computed tomography performed 6 months after hospital discharge reveals patchy ground-glass opacities and fibrotic infiltrates. Results of pulmonary function testing showed mild restrictive ventilatory impairment with a total lung capacity of 71%, forced expiratory volume in 1 second of 67%, and diffusing capacity of lung for carbon monoxide of 52%.

In the 13 survivors, chest HRCT performed 6 months after hospital discharge showed normal results in 5, focal fibrosis in 3, multifocal fibrosis in 1, and multifocal fibrosis with ground-glass opacities in 4 with ARDS associated with SARS.

DISCUSSION

Our study population of 14 patients with hospital-acquired SARS included 12 health care workers. In Taiwan, the outbreak of hospital-acquired SARS infection occurred initially in Hospital A and then in Hospital B.[6] These unfortunate events occurred because the health care workers at these 2 hospitals had not been informed of SARS, and infection control measures had not been instituted in these hospitals. Thus, most cases of SARS in Taiwan were related to hospital exposure. Health care workers in the hospitals became infected because of their prolonged exposure to and close contact with patients harboring SARS.

At initial presentation, the main symptoms of SARS in our patients were fever, dyspnea, diarrhea, and dry cough. Our patients experienced diarrhea more commonly than SARS patients reported in other studies.[8,13] However, as many as 66% of the patients in the SARS outbreak in the Amoy Gardens in Hong Kong also had diarrhea, contributing to a significant virus load being discharged in the sewage.[14] In addition, 4 (29%) of our patients had mildly elevated serum aminotransferase levels during hospitalization, and 2 patients experienced nausea and vomiting. Our clinical findings are consistent with those of Zhang,[15] who noted that the SARS virus can involve the digestive system.

Lymphopenia and elevated serum levels of LDH and CRP were the most common laboratory findings in our patients. Some patients had increased levels of AST, ALT, and CK, as well as thrombocytopenia and anemia. Although the symptoms and laboratory findings of SARS are nonspecific, the constellation of these features should alert medical practitioners to the possibility of SARS.

Lymphopenia was an extremely common finding in our patients, as reported in previous studies (69.7%-98.0%).[8,15,16] Depletion of lymphocytes may be secondary to the direct effect of the virus on the lymphocytes, the effect of various cytokines involved in SARS, or a stress response.[17,18] Similar to findings in other reports,[8,15,17] some of our patients with SARS had thrombocytopenia. Wong et al[17] reported evidence of active bone marrow with normal megakaryocytes as part of postmortem findings in patients with thrombocytopenia; these findings favor an immune cause of thrombocytopenia.

Similar to previous reports,[7-9,19] our results show that the primary radiological appearance of SARS is focal airspace shadowing (hazy/ground-glass opacities or consolidation predominantly affecting the lower lobes) or an interstitial pattern. Although the initial radiographic appearance may be normal in some patients, all our patients had radiological abnormalities within 1 or 2 days of presentation, with increasing extent of involvement and consolidation. Radiological opacities progressed from focal to multiple, from unilateral to bilateral, or from focal to bilateral diffuse lung involvement. Abnormalities seen on chest x-ray films were the most severe at a mean of 8.7 days after onset of fever. Compared with patients who had only unilateral focal lung infiltrates, those with bilateral or multifocal pulmonary infiltrates on initial presentation had a higher risk of developing respiratory failure.

Radiologically, SARS may be indistinguishable from bacterial bronchopneumonia or viral infections. Therefore,
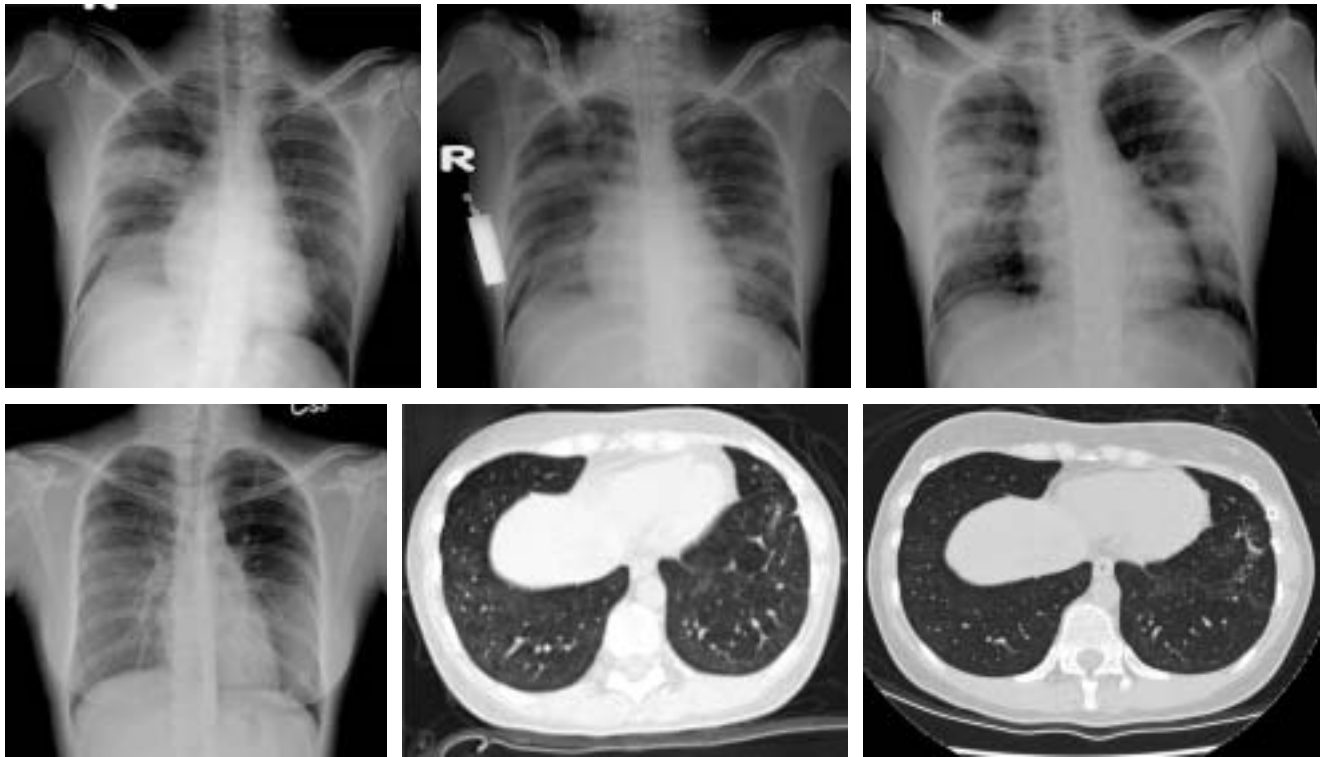
FIGURE 3. Serial radiographic studies of patient 5, a 30-year-old nurse from Hospital B, who had severe acute respiratory syndrome complicated by acute respiratory distress syndrome. Upper Left, Chest radiograph on admission shows bilateral consolidation and infiltrates involving the right upper lung, right lower lung, and left lower lung. Upper Middle, Chest radiograph on hospital day 2 shows progression of infiltration associated with development of severe hypoxia; mechanical ventilation was needed. Upper Right, Chest radiograph on hospital day 25 shows gradual resolution of consolidation and lung fibrotic infiltrates. Lower Left, Chest radiograph 3 months after disease onset shows near-normal findings, except for mild fibrotic lesion in left lower lung. Lower Middle and Lower Right, High-resolution computed tomography performed 3 and 6 months, respectively, after hospital discharge shows ground-glass opacities in the bilateral lower lung and fibrotic infiltrates in the left lower lung. Compared with 3-month scan, the 6-month scan shows that the area of ground glass was smaller but denser and reveals a fibrotic lesion. At 6-month follow-up, results of pulmonary function testing showed a total lung capacity of 82%, forced expiratory volume in 1 second of 53%, and diffusing capacity of lung for carbon monoxide of 39%.

the clinical and radiological characteristics of SARS do not appear to be helpful in differentiating SARS from other pathogens involved in atypical pneumonias. On the basis of the aforementioned findings, we suggest that atypical pneumonia with lymphopenia, elevation of LDH levels, rapid clinical deterioration, and lack of response to empirical antibiotic therapy must raise the suspicion of SARS, especially in the context of suspected exposure.

We evaluated the patients' clinical and laboratory data to determine which factors correlated with a need for mechanical ventilation. High serum LDH levels are often associated with other forms of lung tissue damage. The CRP level generally correlates with the severity of inflammation. Therefore, peak CK and LDH levels might reflect severity of inflammation and damage in the lungs, respectively. Not surprisingly, we found that bilateral lung involvement on the initial chest x-ray film and higher serum peak levels of LDH and CRP were associated with the need

for mechanical ventilation. Our findings are similar to those reported by Lee et al,[8] who noted that high peak serum LDH levels were an independent predictor of an adverse outcome.

Our treatment protocol included an initial regimen of broad-spectrum antibacterial and antiviral therapy. When severe refractory hypoxemia occurred, mechanical ventilation was initiated by using a protective ventilatory strategy, and intravenous methylprednisolone therapy was administered. In our cohort of 14 patients, only 1 patient died. The clinical course of this elderly patient was complicated by ARDS, superimposed bacterial infections, and multiorgan failure. According to previous reports, old age, diabetes mellitus, hepatitis, and other comorbidities (chronic obstructive pulmonary disease, cancer, or cardiac disease) increase the risk of a poor outcome. Our patient who died had 3 risk factors: old age, diabetes mellitus, and congestive heart failure. In previous reports, the overall mortality

TABLE 3. **Univariate Analyses Correlating Clinical and Laboratory Variables With Mechanical Ventilation Outcome***

	Mechanical ventilation		
Variable†	No (n=9)	Yes (n=5)	P value‡
Age (y)	33±10	41±19	.27
Neutrophil count (4.5-11.0 × 10^9/L)	9.2±5.1	11.6±3.0	.37
Lymphocyte count (1.0-8.0 × 10^9/L)	0.8±0.3	0.6±0.4	.17
Platelet count (150-350 × 10^9/L)	162±56	178±38	.59
Activated partial thromboplastin time (21-33 seconds)	29.7±5.0	34.36±5.0	.15
Sodium (137-147 mEq/L)	139.8±2.6	139.4±5.0	.79
Urea nitrogen (7-20 mg/dL)	12.9±3.9	10.2±1.9	.17
Creatinine (0.5-1.5 mg/dL)	0.89±0.22	0.72±0.08	.13
ALT (0-40 U/L)	38.6±32.4	68.6±78.2	.32
AST (5-45 U/L)	47.8±42.0	62.0±53.8	.59
CK (24-168 U/L)			
Initial	42.2±27.0	69.7±69.2	.42
Peak	95.4±10.1	57.6±24.7	.44
LDH (95-213 U/L)			
Initial	273.1±83.4	371.8±146.0	.13
Peak	377.5±70.8	510.6±136.0	.03
Peak CRP (0-0.5 mg/dL)	2.08±2.30	16.8±6.8	<.001

*Values are presented as mean ± SD unless indicated otherwise. ALT = alanine aminotransferase; AST = aspartate aminotransferase; CK = creatine kinase; CRP = C-reactive protein; LDH = lactate dehydrogenase.
†All laboratory values are initial values unless indicated otherwise. Reference ranges are shown parenthetically.
‡Wilcoxon rank sum test.

rate has ranged from 3.6%[8] to 16.8%.[16,20] Variable mortality rates were associated with variations in age, comorbid disease states, access to medical support care, and the approach to medical management. Age appears to affect the mortality rate associated with SARS, which has been estimated to be a mean of 13.2% (range, 9.8%-16.8%) for patients younger than 60 years and 43.3% (range, 35.2%-52.4%) for patients older than 60 years.[20] Five of our patients (36%) developed ARDS and required mechanical ventilation compared with 20% and 23% reported in 2 previous studies.[8,16] Preliminary results from our treatment regimen, which resulted in a relatively low mortality rate, appear promising but need further evaluation in clinical trials.

In this 8-month follow-up evaluation of patients with SARS, 9 of 13 survivors had residual focal, multifocal, or bilateral lung infiltrates on chest HRCT. Only 1 patient had mildly restrictive pulmonary impairment, and 5 other patients had a decreased diffusing capacity. All our patients who survived ARDS had abnormal diffusing capacity that was reduced compared with that in our SARS patients who did not have ARDS. Orme et al[21] found that approximately 80% of their ARDS survivors who did not have SARS had reduced diffusing capacity. Our study found no evidence of pronounced airway obstruction in SARS survivors, an outcome similar to that reported by Aggarwal et al[22] and Schelling et al.[23] In the latter study, surviving SARS patients not experiencing ARDS had no long-term airflow limitations. In contrast, Orme et al[21] reported that 20% of their ARDS survivors who did not have SARS had long-term airflow obstruction. Although the discrepancy of airway obstruction is unclear, it might be due to patient selection bias because some ARDS survivors had a history of chronic airway disease. In our study, 1 SARS-ARDS survivor (25%) had long-term mildly restrictive pulmonary impairment with reduced TLC. The main reason for impaired pulmonary function might be the same as for all ARDS survivors, regardless of whether they experienced SARS. The reduced TLC and reduced FVC were due to lung fibrosis and neuromuscular weakness, respectively.[22] Our findings in SARS-ARDS survivors showed only mild reductions in pulmonary function 6 to 8 months after the acute severe illness, consistent with the natural history of ARDS survivors in other studies.[21,22]

TABLE 4. **Results of Pulmonary Function Tests in 9 Patients With SARS 6 Months After Discharge From the Hospital***

Patient	TLC (L)	FVC (L)	FEV_1 (L)	FEV_1/FVC ratio	Diffusing capacity (mL/min/mm Hg)
1	5.12 (100)	3.20 (96)	2.80 (97)	88 (98)	24.30 (98)
2	4.21 (94)	2.06 (69)	1.52 (62)	74 (92)	15.40 (63)
3	2.93 (71)	1.92 (67)	1.87 (77)	98 (115)	12.79 (52)
4	4.90 (98)	2.90 (95)	2.60 (97)	86 (97)	20.30 (98)
5	3.71 (82)	1.74 (53)	1.67 (59)	96 (111)	10.20 (39)
6	3.99 (94)	2.33 (80)	2.19 (90)	94 (113)	16.17 (66)
7	4.52 (103)	2.87 (91)	2.52 (92)	88 (102)	18.34 (71)
8	3.85 (87)	1.85 (57)	1.64 (58)	88 (101)	12.20 (49)
9	4.18 (100)	2.56 (84)	2.41 (90)	94 (106)	22.90 (89)

*Values in parentheses are percentage predicted. FEV_1 = forced expiratory volume in 1 second; FVC = forced vital capacity; SARS = severe acute respiratory syndrome; TLC = total lung capacity.

SARS is highly infectious among close contacts. Although the predominant pathology of SARS involves the lungs, other organs can be involved with the SARS coronavirus.[24] An accurate and rapid diagnostic test will be of great importance for managing this disease in the future. Until such a diagnostic test is available, a clear picture of the clinical presentation of SARS should help physicians recognize this condition. Early recognition, prompt isolation, and appropriate supportive therapy are the keys to reducing the mortality and morbidity associated with this potentially deadly infection.

CONCLUSION

The clinical course of our 14 patients with hospital-acquired SARS consisted of atypical pneumonia associated with lymphopenia, elevated serum levels of LDH, rapid clinical progression, and lack of response to empirical antibiotic therapy. Substantially increased levels of LDH and CRP correlated with severe disease that required mechanical ventilation. In those who needed mechanical ventilatory support, pulmonary function was only mildly decreased 6 to 8 months after onset of SARS.

We are indebted to the frontline medical and nursing staff who demonstrated selfless and heroic devotion to duty in the face of this SARS outbreak despite the potential threat to their own lives and those of their family members.

REFERENCES

1. World Health Organization. Acute respiratory syndrome in China—update 3: disease outbreak reported. February 20, 2003. Available at: www.who.int/csr/don/2003_2_20/en. Accessibility verified September 30, 2004.
2. World Health Organization. Cumulative number of reported cases (SARS): from 1 Feb 2003 to 27 Mar 2003. Available at: www.who.int/csr/sarscountry/2003_03_27/en. Accessibility verified September 30, 2004.
3. Centers for Disease Control and Prevention. Updated interim U.S. case definition for Severe Acute Respiratory Syndrome (SARS). January 8, 2004. Available at: www.cdc.gov/ncidod/sars/casedefinition.htm. Accessibility verified September 30, 2004.
4. Drosten C, Günther S, Preiser W, et al. Identification of a novel coronavirus in patients with severe acute respiratory syndrome. *N Engl J Med*. 2003; 348:1967-1976.
5. Centers for Disease Control and Prevention. Update: outbreak of severe acute respiratory syndrome—worldwide, 2003 [published correction appears in *MMWR Morb Mortal Wkly Rep*. 2003;52:284]. *MMWR Morb Mortal Wkly Rep*. 2003;52:241-246, 248.
6. Centers for Disease Control and Prevention. Severe acute respiratory syndrome—Taiwan, 2003. *MMWR Morb Mortal Wkly Rep*. 2003;52:461-466.
7. Tsang KW, Ho PL, Ooi GC, et al. A cluster of cases of severe acute respiratory syndrome in Hong Kong. *N Engl J Med*. 2003;348:1977-1985.
8. Lee N, Hui D, Wu A, et al. A major outbreak of severe acute respiratory syndrome in Hong Kong. *N Engl J Med*. 2003;348:1986-1994.
9. Poutanen SM, Low DE, Henry B, et al, Canadian Severe Acute Respiratory Syndrome Study Team. Identification of severe acute respiratory syndrome in Canada. *N Engl J Med*. 2003;348:1995-2005.
10. Bellini WJ. SARS-CoV specific RT-PCR primers. Available at: www.who.int/csr/sars/CDCprimers.pdf. Accessibility verified September 30, 2004.
11. Acute Respiratory Distress Syndrome Network. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. *N Engl J Med*. 2000;342:1301-1308.
12. American Thoracic Society. Lung function testing: selection of reference values and interpretative strategies. *Am Rev Respir Dis*. 1991;144:1202-1218.
13. Peiris JS, Chu CM, Cheng VC, et al, HKU/UCH SARS Study Group. Clinical progression and viral load in a community outbreak of coronavirus-associated SARS pneumonia: a prospective study. *Lancet*. 2003;361:1767-1772.
14. Hong Kong Department of Health. Outbreak of severe acute respiratory syndrome (SARS) at Amoy Gardens, Kowloon Bay, Hong Kong: main findings of the investigation. Available at: www.info.gov.hk/info/ap/pdf/amoy_e.pdf. Accessibility verified October 1, 2004.
15. Zhang JZ. Severe acute respiratory syndrome and its lesions in digestive system. *World J Gastroenterol*. 2003;9:1135-1138.
16. Booth CM, Matukas LM, Tomlinson GA, et al. Clinical features and short-term outcomes of 144 patients with SARS in the greater Toronto area [published correction appears in *JAMA*. 2003;290:334]. *JAMA*. 2003;289:2801-2809.
17. Wong RS, Wu A, To KF, et al. Haematological manifestations in patients with severe acute respiratory syndrome: retrospective analysis. *BMJ*. 2003; 326:1358-1362.
18. Panesar NS. Lymphopenia in SARS [letter]. *Lancet*. 2003;361:1985.
19. Wong KT, Antonio GE, Hui DSC, et al. Severe acute respiratory syndrome: radiographic appearances and pattern of progression in 138 patients. Available at: http://radiology.rsnajnls.org/cgi/content/full/2282030593v1. Accessibility verified October 1, 2004.
20. Donnelly CA, Ghani AC, Leung GM, et al. Epidemiological determinants of spread of causal agent of severe acute respiratory syndrome in Hong Kong. *Lancet*. Published online May 7, 2003. Available at: http://image.thelancet.com/extras/03art4453web.pdf. Accessibility verified October 1, 2004.
21. Orme J Jr, Romney JS, Hopkins RO, et al. Pulmonary function and health-related quality of life in survivors of acute respiratory distress syndrome. *Am J Respir Crit Care Med*. 2003;167:690-694.
22. Aggarwal AN, Gupta D, Behera D, Jindal SK. Analysis of static pulmonary mechanics helps to identify functional defects in survivors of acute respiratory distress syndrome. *Crit Care Med*. 2000;28:3480-3483.
23. Schelling G, Stoll C, Vogelmeier C, et al. Pulmonary function and health-related quality of life in a sample of long-term survivors of the acute respiratory distress syndrome. *Intensive Care Med*. 2000;26:1304-1311.
24. Ding Y, Wang H, Shen H, et al. The clinical pathology of severe acute respiratory syndrome (SARS): a report from China. *J Pathol*. 2003;200:282-289.