Clinical Features and Outcomes of Severe Acute Respiratory Syndrome and Predictive Factors for Acute Respiratory Distress Syndrome

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Background: Severe acute respiratory syndrome (SARS) is an emerging infectious disease, and indeed, the SARS epidemic in Taiwan from March to July 2003 had a great impact. This study depicts the clinical characteristics and short-term outcomes of patients with SARS treated at Taipei Veterans General Hospital; potential predictive factors for acute respiratory distress syndrome (ARDS) are also analyzed.

Methods: This study retrospectively analyzed data for 67 SARS patients, who were grouped according to whether or not ARDS developed during the clinical course of SARS.

Results: There were 32 males (mean age, 50.3 years; range, 20–75 years) and 35 females (mean age, 51.1 years; range, 23–86 years). Twenty-five patients (37.3%) were health care workers. At admission, 50 patients (74.6%) had abnormal chest radiographs, and all patients developed pulmonary infiltrates during the following week. During hospitalization, lymphopenia was found in 57 patients (85.1%); and elevated levels of lactate dehydrogenase (LDH; *n* = 55; 83.3%), C-reactive protein (*n* = 55; 83.3%), aminotransferases (*n* = 44; 65.7%), and creatine kinase (*n* = 14; 20.9%) were also noted. ARDS developed in 33 patients (49.3%), who were generally older than the patients in whom ARDS did not develop, male, non-health care workers, and who generally had dyspnea at the time of diagnosis, and a history of diabetes mellitus, hypertension or cerebrovascular accident. Patients with, versus those without, ARDS also tended to present with more severe lymphopenia and leukocytosis, and with higher levels of LDH and aspartate aminotransferase. The overall mortality rate was 31.3% (21/67), whereas the rate for patients who developed ARDS was 63.6% (21/33). Multivariate analyses showed that age greater than 65 years (odds ratio, OR, 10.6; 95% confidence interval, CI, 2.1–54.1), pre-existing diabetes mellitus (OR, 13.7; 95% CI, 1.3–146.9), and elevated levels of LDH (OR, 8.4; 95% CI, 1.9–36.9) at admission, were independent predictors of ARDS.

Conclusion: The clinical manifestations of SARS showed high variability, and were related to the underlying health status of individual patients. Importantly, the development of ARDS was associated with significant mortality, despite aggressive therapy. [*J Chin Med Assoc* 2005;68(1):4–10]

Key Words: acute respiratory distress syndrome, pneumonia, severe acute respiratory syndrome

Introduction

Severe acute respiratory syndrome (SARS) is an infectious pulmonary disease that appears to have originated in southern China in the fall of 2002. The disease then spread to other parts of Asia, Europe and North America, with more than 8,000 cases now reported worldwide.[1–5]

The first two SARS cases in Taiwan were diagnosed in a couple on March 14, 2003;[6] the man had traveled to Guangdong Province and Hong Kong in February 2003. The couple was treated successfully in an intensive

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care unit (ICU) at medical center A. Subsequently, most SARS patients were treated at that medical center, until two clusters of cases were noted in late April, 2003, in Taipei. The origin of the outbreak was a laundry worker, aged 42 years, with diabetes mellitus, who was employed at hospital B.[7] As the index patient had been symptomatic for 6 days before SARS was diagnosed, the number of potentially exposed persons was estimated to be 10,000 patients and visitors, and 930 staff. Within less than 2 weeks, another outbreak of SARS clusters occurred in hospital C, which is near hospital B. Taipei Veterans General Hospital undertook the care of critically ill SARS patients, who were mainly transferred from hospital B and hospital C.

The cause of SARS is a novel coronavirus.[8–11] Natural clinical histories have ranged from febrile respiratory symptoms, without hypoxemia, to respiratory distress requiring intubation and, occasionally, resulting in death.[3–4] Worldwide, the substantial mortality associated with SARS has varied markedly from 15–27%.[5] This paper provides a retrospective review of predictive factors for acute respiratory distress syndrome (ARDS) in patients with SARS treated at Taipei Veterans General Hospital.

Methods

Clinical diagnostic criteria

The following criteria were used to evaluate the probability of SARS:

1. A history of close contact with a SARS patient, or evidence of traveling to SARS-endemic areas within 10 days before symptom onset.
2. Acute onset of fever > 38°C.
3. Respiratory symptoms, including cough or dyspnea.
4. Chest radiograph showing patchy or spotty pulmonary infiltrates.
5. ARDS without an identifiable cause.
6. Evidence of the transmission of pneumonia.

Patients fulfilling criteria 1+2+3 were defined as suspected cases, while those meeting criteria 1+2+3+4, 2+3+5, or 2+3+4+6 were defined as probable cases. A diagnosis of SARS was not made if an alternative diagnosis could fully explain the illness. Reverse transcriptase-polymerase chain reaction (RT-PCR), or antibodies for SARS-coronavirus (SARS-CoV), were used to confirm the diagnosis, but were not part of the diagnostic criteria.

Study patients

This study included all patients with SARS admitted to Taipei Veterans General Hospital between March 20 and July 5, 2003, even though 14 cases in our cohort were reported previously by Chiang et al.[12] Thirty-three patients were referred due to evidence of SARS noted at another hospital. These patients were categorized according to the most severe clinical condition, i.e. non-ARDS or ARDS, with ARDS defined according to the American-European consensus conference:[13]

1. Non-ARDS: patients with a ratio of partial arterial oxygen pressure (PaO_2)/fractional inspired oxygen (FIO_2) > 200 mmHg, and who did not develop ARDS during their stay in the ward.
2. ARDS: patients with $PaO_2/FIO_2 \leq 200$ mmHg, and with bilateral lung infiltrates at admission or during their stay in the ward.

Treatment

All patients were isolated for treatment, which included antibiotics to prevent secondary bacterial infection. The choice of antibiotics was based on empirical knowledge of the common atypical pathogens encountered in the community. Other antibiotics were administered to patients with established bacterial infection according to the results of drug-sensitivity testing after bacterial culture. The administration of ribavirin, intravenous immunoglobulin or corticosteroids was determined by physicians. Patients were intubated when respiratory failure developed, i.e. PaO_2 < 90% during the administration of 100% supplemental oxygen with or without a respiratory rate of more than 35 breaths per minute.

Study design

A clinical database was constructed to document patient demographics, including the following: date of onset of initial symptoms; initial abnormal radiographic findings; date of admission to the hospital; tracheal intubation with mechanical ventilation; other comorbid conditions; and treatments for, and short-term outcomes of, the acute illness. The main parameters monitored at, and every 2–3 days after, hospital admission comprised complete blood count (CBC), aspartate aminotransferase (AST), alanine aminotransferase (ALT), blood urea nitrogen, creatinine, creatine kinase (CK), lactate dehydrogenase (LDH), C-reactive protein (CRP), and blood gases. Chest films were taken daily during the early hospital stay, and every 2–5 days during convalescence. RT-PCR for SARS-CoV was performed routinely on nasopharyngeal swabs on days 1 and 7 of hospitalization. Assays for anti-SARS-CoV antibodies were performed on day 21 of hospitalization, and 2 weeks after hospital discharge.

Statistical analysis

We compared differences in epidemiologic, clinical, and laboratory measures between patients who developed ARDS and those who did not. Square-root transformation was performed, for CBCs and biochemical parameters, for the normality of data. The Kolmogorov-Smirnov test was used to check normality. The Student's *t* test was adapted to normal-distribution data. For continuous variables not fitted to a normal distribution, median and interquartile ranges (IQRs) were calculated as summaries of distribution, and a Wilcoxon rank-sum test was adapted for comparison. A Chi-squared test was used to compare the category variables. For calculating the odds ratio of ARDS in the logistic regression analysis, each variable was dichotomized using a "normal-limits" value as cut-off (except for CRP [cut-off, 5 mg/L] and age [65 years]). To dichotomize the variable "comorbidities", the study group was divided into patients with (value of 1) or without underlying disease (value of 0). A p value of less than 0.05 was considered statistically significant. All analyses were carried out using Statistical Package for the Social Sciences version 11.0 (SPSS Inc, Chicago, IL, USA).

Results

Demographics and clinical information

A total of 67 patients with SARS were admitted to our hospital between March 20 and July 5, 2003, which represented 10% (67 of 668) of all documented, probable SARS cases in Taiwan. The patients comprised 32 men and 35 women; mean age ± standard deviation (SD) was 51.0 ± 21.9 years (range, 23–86 years) (Table 1). Twenty-five patients (37.3%) were medical professionals and the others had various occupations. Thirty-three (49.3%) patients required mechanical ventilatory support.

Patients without ARDS were significantly younger than patients with ARDS (39.1 ± 16.5 years vs 63.4 ± 20.0 years). All patients received nasopharyngeal-swab RT-PCR tests routinely on days 1 and 7 of hospitalization, and only 22 patients (32.8%) had positive findings. Thirty-three patients had assays for anti-SARS-CoV antibodies on day 21 of hospitalization; 28 of them (84.8%) had positive findings. The most common initial clinical symptoms were fever (95.5% of patients), cough (65.7%) and dyspnea (49.3%); watery diarrhea was noted in less than 20% of patients. Forty-two patients (62.7%) had other comorbid conditions, which principally included diabetes mellitus (n = 16), viral hepatitis (n = 12), hypertension (n = 13), and cerebrovascular accident (CVA; n = 8). Levofloxacin was used in a total of 49 patients (73.1%), whereas other antibiotics were used significantly more frequently in patients with ARDS rather than in those without (26 vs 17; p = 0.021). The administration of ribavirin, intravenous immunoglobulin or corticosteroids did not differ significantly between patients with ARDS and those without, although pulse corticosteroid therapy (methylprednisolone 500 mg intravenously every 12 hours for 2–3 days) was given to four patients with ARDS versus none of the non-ARDS patients (p = 0.053). The mean length of hospital stay was significantly shorter for patients without ARDS than for survivors of ARDS (19.8 days vs 39.3 days; p < 0.001) (Table 1).

The overall mortality rate was 31.3% (21 of 67 patients), whereas the mortality rate for patients who underwent mechanical ventilation was 63.6% (21 of 33).

Laboratory data

Laboratory indices during hospitalization are summarized in Table 2. Sixteen patients (23.9%) had a leukocyte count < 3,500/mm^3, 57 (85.1%) had a lymphocyte count < 1,000/mm^3, and 15 (22.4%) had a platelet count < 100,000/mm^3. CK levels increased to > 200 U/L in 14 of 67 patients (20.9%) and, among a group of 66 evaluable patients, elevated levels of the following parameters were noted: AST > 45 U/L in 42 patients (63.6%); LDH > 213 U/L in 55 (83.3%); and a CRP increase of up to 1 mg/dL in 55 patients (83.3%), and of up to 5 mg/L in 41 (62.1%).

Radiographic findings

Chest radiographs revealed changes relating to pneumonia, although 17 patients (25.4%) did not have pulmonary infiltrates at initial radiograph. Combined central and peripheral lesions were evident in most patients, and most had rapid progression from a single localized lesion. The most common locations were the bilateral lower lung regions (Table 3). In the 17 patients with an initial normal radiograph, and who subsequently developed consolidation, the average time from fever onset to an abnormal radiograph was 4.6 ± 6.8 days (range, 1–13 days).

Predictive factors for ARDS

We used a logistic multiple regression model to uncover risk factors for the development of ARDS. This model included LDH, CRP, age more than 65 years, diabetes mellitus, hypertension, previous CVA, and male gender, from univariate logistic regression analyses. Odds ratios for ARDS development in the 67 patients with SARS

Table 1. Characteristics of SARS patients at Taipei Veterans General Hospital

	Non-ARDS (*n* = 34)	ARDS (*n* = 33)	Total (*n* = 67)	*p**
Age (yr), mean (range)	39.1 (23–76)	63.4 (27–86)	51.0 (23–86)	< 0.001
Male gender, *n* (%)	12 (35.3)	20 (60.6)	32 (47.8)	0.038
Health care workers, *n* (%)	17 (50.0)	8 (24.2)	25 (37.3)	0.029
Positive RT-PCR for SARS, *n* (%)	6 (17.6)	16 (48.5)	22 (32.8)	0.010
Positive for anti-SARS-CoV antibodies†, *n* (%)	17/17 (100)	11/16 (68.8)	28/33 (84.8)	0.018
Symptoms, *n* (%)				
Fever	34 (100)	30 (90.9)	64 (95.5)	0.114
Cough	21 (61.8)	23 (69.7)	44 (65.7)	0.494
Dry	17 (50.0)	18 (54.5)	35 (52.2)	0.710
Productive	4 (11.8)	5 (15.2)	9 (13.4)	0.734
Dyspnea	9 (26.5)	24 (72.7)	33 (49.3)	< 0.001
Diarrhea	7 (20.6)	5 (15.2)	12 (17.9)	0.562
Malaise	6 (17.6)	3 (9.1)	9 (13.4)	0.476
Myalgia/arthralgia	7 (20.6)	2 (6.1)	9 (13.4)	0.150
Headache	2 (5.9)	4 (12.1)	6 (9.0)	0.427
Comorbidities, *n* (%)				
Diabetes mellitus	1 (2.9)	15 (45.5)	16 (23.9)	< 0.001
HBV carrier	9 (26.5)	3 (9.1)	12 (17.9)	0.109
Hypertension	3 (8.8)	10 (30.3)	13 (19.4)	0.035
CVA	1 (2.9)	7 (21.2)	8 (11.9)	0.027
HCV infection	2 (5.9)	3 (9.1)	5 (7.5)	0.673
Old pulmonary TB	3 (8.8)	2 (6.1)	5 (7.5)	0.667
COPD or asthma	1 (2.9)	3 (9.1)	4 (6.0)	0.356
Cardiac disease	3 (8.8)	4 (12.1)	7 (10.4)	0.709
Thyroid disease	1 (2.9)	1 (3.0)	2 (3.0)	0.983
Treatment, *n* (%)				
Levofloxacin	29 (85.3)	20 (60.6)	49 (73.1)	0.029
Other antibiotics‡	17 (50.0)	26 (78.8)	43 (64.2)	0.021
Ribavirin	16 (47.1)	19 (57.6)	35 (52.2)	0.466
IVIG	18 (52.9)	19 (57.6)	37 (55.2)	0.807
Non-pulse corticosteroid	19 (55.9)	21 (63.6)	40 (59.7)	0.621
Pulse corticosteroid	0 (0)	4 (12.1)	4 (6.0)	0.053
Mean length of hospital stay, d (IQR)	19.8 (11.0–24.3)	39.3 (29.0–50.0)§	24.9 (14.8–33.3)‖	< 0.001

**ARDS vs non-ARDS; †33 patients received assays for anti-SARS-CoV antibodies on day 21 of hospitalization and 27 patients received enzyme-linked immunosorbent assay for IgM and IgG SARS-CoV antibodies 2 weeks after discharge; ‡azithromycin, ampicillin/sulbactam, clindamycin, cefuroxime, ceftriaxone, ceftazidime, cefepime, cefpirome, imipenem, meropenem, or teicoplanin; §length of hospital stay for survivors of ARDS; ‖length of hospital stay for all survivors.*

SARS = severe acute respiratory syndrome; ARDS = acute respiratory distress syndrome; RT-PCR = reverse transcriptase-polymerase chain reaction; SARS-CoV = SARS-coronavirus; HBV = hepatitis B virus; CVA = cerebrovascular accident; HCV = hepatitis C virus; TB = tuberculosis; COPD = chronic obstructive pulmonary disease; IVIG = intravenous immunoglobulin; IQR = interquartile range.

Table 2. Laboratory findings during the hospital course of SARS*

	Non-ARDS, median (IQR)	ARDS, median (IQR)	*p*
Lowest leukocyte count (per mm^3)	4,050 (3,425–5,425)	6,300 (4,125–8,600)	0.012
Lowest lymphocyte count (per mm^3)	579 (448–983)	359 (372–766)	0.003
Lowest platelet count × 10^3 (per mm^3)	152 (120–185)	131 (85–170)	0.068
Highest ALT (IU/L)	54 (29–119)	66 (33–120)	0.818
Highest AST (IU/L)	41 (30–88)	92 (56–138)	0.004
Highest creatine kinase (IU/L)	54 (23–86)	138 (56–455)	< 0.001
Highest LDH (IU/L)	257 (200–392)	517 (363–758)	< 0.001
Highest CRP (mg/dL)	4.3 (0.7–8.9)	12.7 (10.0–23.6)	< 0.001

**Square-root transformation was performed for the normality of data.*

SARS = severe acute respiratory syndrome; ARDS = acute respiratory distress syndrome; IQR = interquartile range; ALT = alanine aminotransferase; AST = aspartate aminotransferase; LDH = lactate dehydrogenase; CRP = C-reactive protein.

were 13.71 (95% confidence interval, CI, 1.28–146.86) for patients with concurrent diabetes mellitus, 10.61 (95% CI, 2.08–54.14) for patients older than 65 years, and 8.43 (95% CI, 1.93–36.92) for patients with elevated LDH (Table 4).

Discussion

Taiwan has had the third largest number of SARS cases, after Hong Kong and China. To date, however, no large, formal analysis of the data from Taiwan can

Table 3. Radiographic patterns at admission in 67 SARS patients

	Non-ARDS (*n* = 34)	ARDS (*n* = 33)	Total, *n* (%)
Pattern of involvement			
Central	0	1	1 (1.5)
Peripheral	13	9	22 (32.8)
Central and peripheral	8	19	27 (40.3)
Number of lesions			
Unifocal	17	11	28 (41.8)
Multifocal, unilateral	3	7	10 (14.9)
Multifocal, bilateral	2	10	12 (17.9)
Number of involved zones			
1	17	13	30 (44.8)
2	3	7	10 (14.9)
> 2	2	8	10 (14.9)
Lung zone*			
Right upper	3	6	9 (13.4)
Right middle	4	12	16 (23.9)
Right lower	11	14	25 (37.3)
Left upper	0	3	3 (4.5)
Left middle	5	9	14 (20.9)
Left lower	7	16	23 (34.3)
Normal radiography	13	4	17 (25.4)

**Zone height was defined as one-third of the craniocaudal extent of the lungs.*
SARS = severe acute respiratory syndrome; ARDS = acute respiratory distress syndrome.

Table 4. Predictors of ARDS in patients with SARS

	Odds ratio (95% CI)	*p*
Univariate analysis		
Age > 65 yr	11.53 (3.28–40.48)	< 0.001
Male gender	2.82 (1.05–7.60)	0.04
Leukocyte count > 10,000/mm^3	3.77 (1.16–12.25)	0.027
Lymphocyte count < 1,000/mm^3	2.47 (0.87–7.02)	0.09
Platelet count < 10^5/mm^3	3.29 (0.33–33.35)	0.313
LDH > 213 IU/L	9.41 (3.01–29.41)	< 0.001
ALT > 40 IU/L	1.20 (0.13–3.37)	0.73
AST > 45 IU/L	5.24 (1.78–15.42)	0.003
Creatine kinase > 200 IU/L	5.89 (0.65–53.45)	0.115
Diabetes mellitus	31.04 (3.79–254.19)	0.001
HBV carrier	0.37 (0.07–2.08)	0.262
Hypertension	4.49 (1.11–18.19)	0.035
Cerebrovascular accident	8.88 (1.03–76.69)	0.047
Multivariate analysis		
Diabetes mellitus	13.71 (1.28–146.86)	0.030
Age > 65 yr	10.61 (2.08–54.14)	0.005
LDH > 213 IU/L	8.43 (1.93–36.92)	0.005

ARDS = acute respiratory distress syndrome; SARS = severe acute respiratory syndrome ; CI = confidence interval; LDH = lactate dehydrogenase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; HBV = hepatitis B virus.

be found in the English literature. In April 2003, 7 health care workers, including 2 physicians and 3 nurses, died from SARS in Taiwan; most of these workers had worn surgical masks. Initial reports showed that SARS had a high degree of respiratory infectiousness and could possibly be transmitted through airborne infection. Faced with an unknown disease, we experienced much anxiety. Further, our ICU had no negative-pressure design, and to protect staff and patients, treatment was done in negative-pressure isolation rooms with an antechamber; these rooms were usually used for isolation of patients with tuberculosis or acquired immune deficiency syndrome. The transfer of patients from wards for examination required an absolute indication. Bronchoscopy was not recommended for patients with a typical clinical picture and clear epidemiologic link. Anesthesiologists stood by all day to perform intubations for SARS patients. The isolation rooms were guarded by security personnel, and infection control was guided by a team of specialists.

Since our hospital was responsible for the management of critical cases in northern Taiwan, the outcomes shown were more severe than in other medical settings. Initial clinical presentations and laboratory features were similar to those in other series. Symptoms of acute respiratory distress developed in about half of the patients (33/67; 49.3%); 21 of these patients (63.6%) died and the other 12 were discharged from hospital. The risk factors for ARDS were age more than 65 years, diabetes mellitus, and elevated LDH level. Other researchers have also documented independent predictors associated with poor outcomes, e.g. acute illness leading to death; the need for mechanical ventilation; and ICU admission.[2]

The diagnosis of SARS was based on a comprehensive contact history and precise laboratory tests. The World Health Organization diagnostic criteria for SARS have a reported sensitivity of 26% and specificity of 96%,[14] whereas the sensitivity of laboratory testing for SARS-CoV is less than 80%.[15] Since contact history has not been reliable after SARS cluster cases were noted in some community groups, one needed to be highly suspicious of any transmission of pneumonia. Our inclusion criteria added a component of transmission of pneumonia, and a high degree of clinical diagnostic accuracy was confirmed by laboratory tests.

Hematologic abnormalities, especially lymphopenia, were common in our cohort, probably because of ribavirin therapy. Intravenous immunoglobulin was given when more severe hematologic abnormalities occurred. Pancytopenia and hemophagocytosis were noted in 2 patients without ARDS. This phenomenon has been noted in other viral infections, and the outcome was fair after supportive treatment.[16,17] In our cohort, elevation of AST was more obvious than that of ALT in the ARDS group. Since carriers of hepatitis B virus did not show profound lung injury, whether SARS-CoV will interact with hepatitis B virus is not yet clear.

The location of pulmonary infiltration in SARS patients has been reported to be the peripheral lungs.[18,19] In our cohort, initial infiltrative lesions were mainly located in the central and peripheral lungs. The best explanation for this is that anterior and posterior peripheral lesions would be projected to a central location on posteroanterior chest radiograph. The efficacy of treatment was difficult to evaluate because patients usually received a combination of medications, including antiviral, broad-spectrum antibacterial and corticosteroid drugs, in addition to supportive therapy. Initially, because the cause of SARS was thought to be an atypical pathogen, 55 patients (82.1%) received empiric antibacterial therapy with a fluoroquinolone. Levofloxacin was the drug of choice in 49 patients (73.1%) because of its broad-spectrum activity against anaerobic and aerobic Gram-positive and Gram-negative bacteria. In patients who developed ARDS, stronger antibiotics such as fourth-generation cephalosporins, teicoplanin and carbapenems were more often used. There is no proven effective treatment for SARS; hence, there was no difference in the proportion of patients per group who received the antiviral ribavirin, intravenous immunoglobulin, or moderate amounts of corticosteroids. However, pulse corticosteroid therapy was more often used for ARDS than non-ARDS patients.

Our study has several limitations. It was retrospective and had no standard medical chart for following clinical courses. Some important information may, therefore, have been lost, which may have led to bias in the comparison. To date, however, this is the largest clinical analysis of SARS in Taiwan.

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