Clinical Characteristics, Management and Prognostic Factors in Patients with Probable Severe Acute Respiratory Syndrome (SARS) in a SARS Center in Taiwan

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Background: Severe acute respiratory syndrome (SARS) is an emerging viral infectious disease. We report our experience in treating SARS patients.

Methods: From April 27 to May 24, 2003, a total of 36 patients with probable SARS were admitted and treated in a hospital rearranged as a special center for the management of SARS patients. Medical records for the patients were retrospectively reviewed. Univariate and multivariate analyses were performed to determine factors associated with respiratory failure and intubation.

Results: Of the 36 patients with probable SARS (median age, 37 years; range, 22–66 years), 9 were male and 27 were female. Thirty-two patients (88.9%) were infected in the hospital setting. All patients presented with fever, and 33 eventually developed lymphopenia during hospitalization. Chest radiography showed no unique pattern, but pleural effusion was not seen. All patients initially received empiric antibacterial therapy against common causative pathogens of atypical pneumonia. Ribavirin was given to all except 1 patient. Twenty-two patients received immunoglobulin therapy, and 32 were given corticosteroids. A total of 20 patients (55.6%) required supplemental oxygen, and 8 (22.2%) were intubated with mechanical ventilatory support. Two of these patients died. A higher body temperature at presentation (median 39.5 vs 38.6°C), and higher peak values of lactate dehydrogenase (410 vs 282 U/L) and C-reactive protein (10.2 vs 2.5 mg/dL), were associated with subsequent respiratory failure. Multivariate analysis showed that peak level of C-reactive protein was the only independent predictor of respiratory failure and intubation (odds ratio for every increment of 1 mg/dL = 1.45; 95% confidence interval = 1.003, 2.097; $p = 0.048$).

Conclusion: All patients with probable SARS who were admitted to hospital presented with fever and lymphopenia. While the efficacy of different treatments could not be evaluated from this retrospective study, a higher value of C-reactive protein was associated with the development of respiratory failure and subsequent intubation. [*J Chin Med Assoc* 2005;68(3):110–117]

Key Words: clinical characteristics, C-reactive protein, prognostic factors, severe acute respiratory syndrome (SARS)

Introduction

In November 2002, 305 cases of highly contagious, rapidly progressive and sometimes fatal atypical pneumonia of unknown cause were reported from Guangdong Province in southern China.[1] In March 2003, as the condition began to spread from China, the World Health Organization (WHO) issued a

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global alert about outbreak of the illness, which was named severe acute respiratory syndrome (SARS). At this time, there were known SARS cases in China (both the mainland and the special administrative region of Hong Kong), Vietnam, Singapore, and Canada. By May 31, 2003, a cumulative total of 8,360 cases of SARS, with 764 deaths, had been reported by 30 countries.[2]

The first probable case of SARS reported in Taiwan was that of a 54-year-old businessman who traveled to Guangdong Province and returned to Taipei, via Hong Kong, on February 21, 2003.[3] From the beginning of March, Taiwan experienced a gradual increase in the number of probable cases of SARS. Initially, most reported cases were either imported or secondary.[3] However, the number increased markedly at the end of April, when local transmission in hospitals became the source of most new infections. Up to June 27, 2003, there was a cumulative total of 681 probable SARS cases in Taiwan, with 84 deaths. However, few articles were written describing the clinical characteristics and management of SARS patients in Taiwan.[4–8] This study delineates clinical features, laboratory data, chest radiography, management and outcomes for patients with probable SARS at a SARS center in Taipei, and determines factors associated with respiratory failure and subsequent intubation in such patients.

Methods

Study population

The Armed Forces Sung-Shan Hospital is a local community hospital, with about 500 beds, and is located in Taipei City. During the outbreak of SARS in Taiwan, the hospital was rearranged as a special center for the management of SARS patients from April 27, 2003. The hospital was equipped with roughly 70 isolation rooms with negative pressure. Strict infection-control measures were established when caring for patients with probable SARS.

Patients were referred from other hospitals when a diagnosis, according to the WHO definition, was made of suspected SARS (fever, cough, or breathing difficulty; and a known history of exposure to SARS patients, or travel to an area with local transmission of SARS) or probable SARS (radiographic evidence of pneumonia or respiratory distress syndrome [RDS]; an autopsy result of RDS without identifiable cause; or a positive result of ≥ 1 assays for SARS-associated coronavirus).[9] Patients admitted from April 27 to May 24, 2003, and who met WHO criteria for probable SARS, were included in the analysis. Patients who initially met the criteria for suspected SARS, but who were later reclassified as probable cases, were also included. Patients who had another diagnosis for their pneumonia were excluded.

Study protocol

The medical records of patients were reviewed retrospectively: data about demographics, clinical characteristics, laboratory data, chest radiography, treatment and outcomes were analyzed. Whole blood-cell counts and serum biochemistry for all patients were examined using automatic machines and standard methods. An independent radiologist read and reported on all chest radiographs. Sputum and blood samples from all patients were sent for bacterial culture. Samples for SARS-virus assays (including nasopharyngeal swabs, serum and urine samples), and for serologic testing for the common pathogens of atypical pneumonia (*Mycoplasma* spp., *Chlamydia* spp., and *Legionella* spp.), were taken and sent to laboratories of the Taiwan Center for Disease Control, after which cases were reported to the sanitary authorities in Taiwan. Leukopenia was defined as a white blood-cell count < 3,500/μL, lymphopenia as a lymphocyte count < 1,000/μL, and thrombocytopenia as a platelet count < 150,000/μL.

Statistical analyses

Continuous data were presented as median values and ranges, unless stated otherwise. Factors associated with respiratory failure requiring intubation were determined. Fisher's exact test was used for analysis of categorical variables, and the Mann-Whitney test for that of continuous variables. All analyses were carried out using Statistical Package for the Social Sciences version 10.0 for Windows (SPSS Inc, Chicago, IL, USA). Factors with a p value of less than 0.1 were included in a multivariate analysis, by using stepwise logistic regression, to identify independent risk factors for the development of respiratory failure and subsequent intubation. A p value of less than 0.05 was considered significant; all probabilities were 2-tailed.

Results

Study population

During the study period, a total of 206 patients were referred to the Armed Forces Sung-Shan Hospital. Thirty-six patients met WHO criteria and were included in the analysis. Nine patients were male and 27 female, with ages ranging from 20–66 years (median, 37 years). Thirty-two patients (88.9%) were health care

workers, patients or hospital visitors who were exposed to SARS patients in the hospital setting; 18 (50%) were medical staff. Seven patients had underlying disease: diabetes mellitus (n = 2); cardiovascular disease (1); ovarian teratoma (1); hydronephrosis (1); thyroid disease (1); and diabetes plus gallstones (1). Four patients had a history of smoking, and 3 of these consumed alcohol frequently.

Clinical characteristics

The patients had had symptoms for a median of 2 days (range, 0–8 days) before admission. The most common symptoms at presentation were fever (100%), chills (75%), non-productive cough (44.4%), diarrhea (41.7%), myalgia (38.9%), and productive cough (19.4%). Less common presenting symptoms included headache (8.3%), sore throat (5.6%), and shortness of breath (2.8%). The mean body temperature of patients recorded at admission was 38.8°C (38.0–40.1°C).

Initial laboratory indices showed leukopenia in 19.4% of patients. Twenty-seven patients (75%) had a normal neutrophil count (2,000–7,500/μL) and 24 (66.7%) had a normal monocyte count (200–700/μL). However, 23 patients (63.9%) had lymphopenia, and 17 (47.2%) had thrombocytopenia at presentation. Thirty-three patients (91.7%) developed lymphopenia after a median of 8 days (range, 1–29 days) from the onset of symptoms. During admission, lactate dehydrogenase (LDH) was measured in 30 patients, and 20 (66.7%) had elevated values (> 200 U/L). Other laboratory indices at presentation are shown in Tables 1 and 2. During the course of illness, several laboratory parameters, including LDH, creatine kinase (CK), alanine aminotransferase (ALT), and C-reactive protein (CRP), were elevated (Table 1). The highest peak values for LDH (14,770 U/L) and CK (24,949 U/L) were noted in a 49-year-old female after intubation. These markedly abnormal values were attributed to multi-organ failure, which resulted in death. The results of sputum culture revealed either no growth or growth of normal mixed flora in all cases, and no blood cultures or serologic tests were positive. Among the 28 patients whose nasopharyngeal swabs were tested for SARS-associated coronavirus by real-time polymerase chain reaction (RT-PCR), 15 (53.6%) had positive results, and 5 of these had viruses isolated from viral culture.

Radiographic findings

The initial chest radiographs showed normal findings in 11 patients (30.6%), unifocal infiltration in 17 (47.2%), and multifocal or bilateral involvement in 8 (22.2%) (Figures 1–4). Peripheral-zone involvement

Table 1. Initial and highest values [median (range)] of laboratory data in 36 patients with probable SARS

Laboratory data	On admission	Peak value during hospitalization
Leukocyte count, /μL	4,940 (2,140–18,380)	12,990 (5,220–44,500)
Lymphocyte count, /μL	844 (202–1,921)	ND
Platelet count, $\times 10^3$/μL	152 (91–271)	ND
LDH, U/L*	249 (127–909)	324 (167–14,770)
CK, U/L	81 (20–461)	114 (20–24,949)
ALT, U/L	28 (5–141)	46 (6–184)
CRP, mg/dL	2.0 (0.3–10.4)	4.9 (0.5–26.2)

**Only 30 patients had LDH measured at admission.*
ALT = alanine aminotransferase; CK = creatine kinase; CRP = C-reactive protein; LDH = lactate dehydrogenase; ND = no data.

Table 2. Laboratory abnormalities on admission and during hospitalization in 36 patients with probable SARS

Laboratory data (abnormal value)	On admission, *n* (%)	During hospitalization, *n* (%)
Leukopenia (< 3,500/μL)	7 (19.4)	17 (47.2)
Lymphopenia (< 1,000/μL)	23 (63.9)	33 (91.7)
Thrombocytopenia (< 150 × 10^3/μL)	17 (47.2)	21 (58.3)
LDH (> 200 U/L)*	20 (66.7)	31 (86.1)
CK (men > 170 U/L; women > 120 U/L)	11 (30.6)	19 (52.8)
ALT (> 40 U/L)	8 (22.2)	22 (61.1)
CRP (> 0.5 mg/dL)	22 (61.1)	35 (97.2)

**Only 30 patients had LDH measured at admission.*
ALT = alanine aminotransferase; CK = creatine kinase; CRP = C-reactive protein; LDH = lactate dehydrogenase.

with focal consolidation or ground-glass appearance were the most common infiltration patterns. Chest radiographs remained normal throughout the hospital course in a 49-year-old male who presented with dry cough and a positive RT-PCR result. However, radiographs progressed from normal or unifocal infiltration to unilateral, multifocal or bilateral involvement in 14 of the 28 patients (50%) during hospitalization (Table 3). Radiographic progression occurred in 25 patients (69.4%) and reached a peak 8

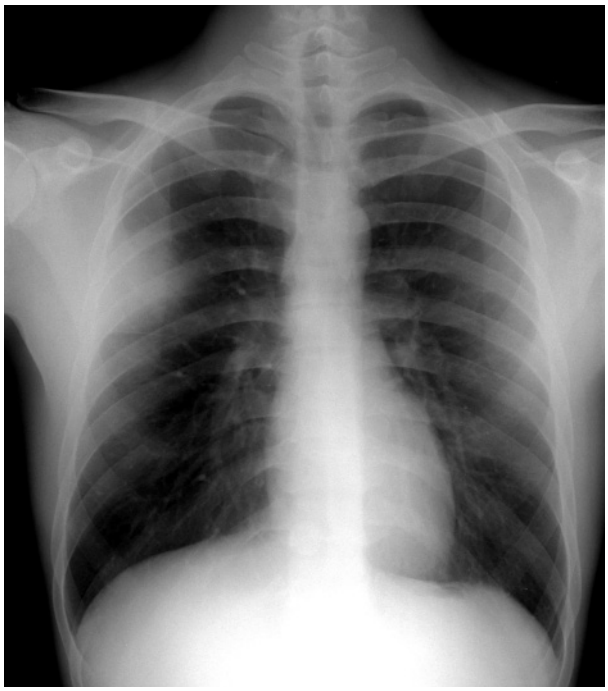

Figure 1. Frontal chest radiograph of a 20-year-old male, taken 4 days after symptom onset, showing a pleural-based consolidation over the right upper lung field.

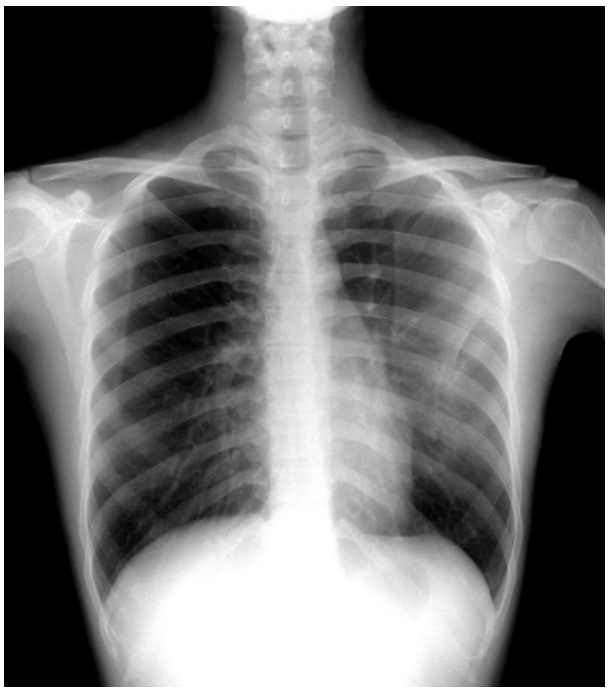

Figure 2. Frontal chest radiograph of a 27-year-old female, taken 8 days after symptom onset, showing ground-glass infiltration in the left-middle lung zone.

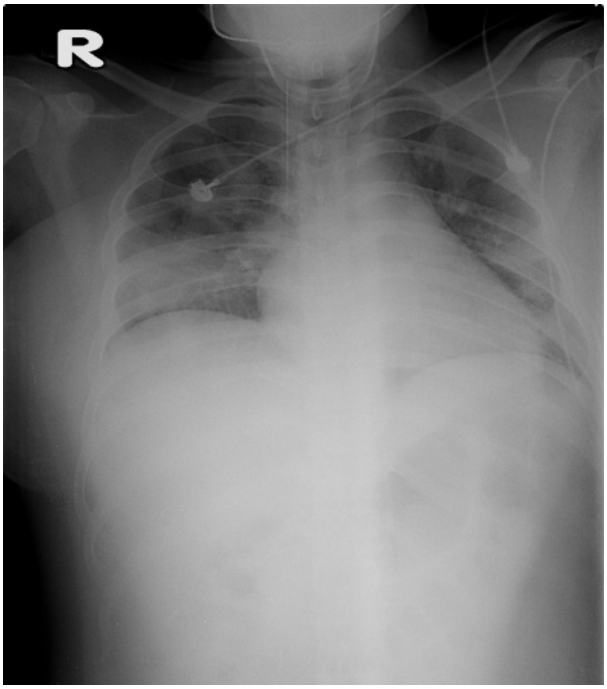

Figure 3. Frontal chest radiograph of a 29-year-old female, taken 7 days after symptom onset, showing patchy infiltration in both lung fields.

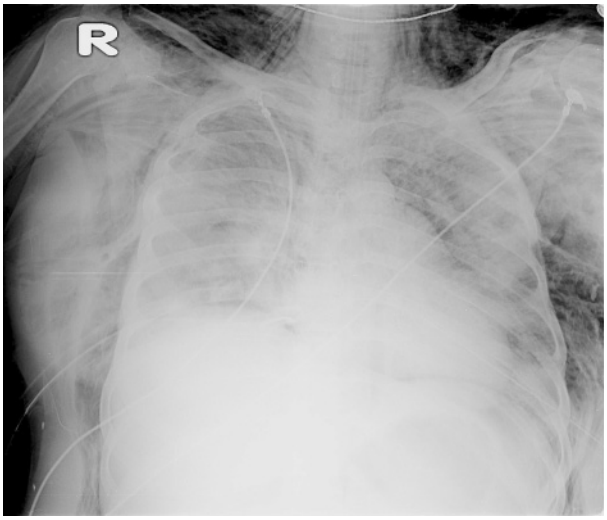

Figure 4. Chest radiograph of a 29-year-old female (see also Figure 3) that progressed after 6 days to extensive, bilateral air-space opacities resembling the radiographic pattern of adult respiratory distress syndrome. The patient died 15 days after symptom onset.

Table 3. Changes in chest radiographs in 36 patients with probable SARS

Initial chest radiograph	*n* (%)	Progression of radiograph	*n* (%)
Normal	11 (30.6)	No change	1 (9.1)
		Unifocal infiltration	3 (27.3)
		Multifocal infiltration	7 (63.6)*
Unifocal infiltration	17 (47.2)	No change	10 (58.8)
		Multifocal infiltration	7 (41.2)†
Multifocal infiltration	8 (22.2)†	No change	0 (0)
		Multifocal infiltration (increased area of involvement > 25%)	8 (100)*

**All patients had bilateral lung involvement; †2 patients had unilateral, multifocal lung involvement; ‡1 patient had unilateral, multifocal infiltration and 7 others had bilateral, multifocal lung involvement.*

days (median; range, 5–20 days) after the onset of symptoms. In the 8 patients with respiratory failure and who were intubated, chest radiographs showed multifocal lesions in all cases, but in the 28 patients who were not intubated, only 13 (46.4%) had such lesions ($p = 0.012$).

Treatment

All patients received empiric antibacterial therapy, such as a macrolide or fluoroquinolone, to provide coverage against the common pathogens of atypical pneumonia. All except 1 patient received ribavirin (loading dose 2 g, followed by 1–1.2 g/day for 10 days [median; range, 3–18 days]) within 0–7 days (median, 1 day) of hospitalization. Patients with persistent fever, clinical deterioration, or progressive chest-radiograph changes were treated with intravenous immunoglobulin (IVIG) 500 mg/kg/day for 2 days and/or methylprednisolone 2–4 mg/kg/day, with stepwise dosage tapering for a median total duration of 6 days (range, 3–45 days). Seven intubated patients and 15 non-intubated patients received IVIG ($p = 0.115$), while methylprednisolone was used in all intubated patients and 24 non-intubated patients. Corticosteroid therapy was started a median of 4 days (range, 1–10 days) after, and IVIG a median of 6 days (range, 2–19 days) after, symptom onset. There were no significant differences between the intubated and non-intubated groups regarding the times of starting IVIG (7 vs 6 days) and corticosteroids (3 vs 6 days). However, methylprednisolone was given to the intubated versus non-intubated group for a longer period (20 vs 5 days; $p = 0.004$). Patients who developed hypoxemia (oxygen saturation < 90% under room air) were oxygenated through a nasal cannula, or intubated, as necessary. A total of 20 patients (55.6%) required oxygen therapy and, of the entire cohort, 8 patients (22.2%) were intubated and received mechanical ventilation a median of 8 days (range, 5–15 days) after symptom onset.

Clinical outcomes

By June 11, 2003, only 1 patient was hospitalized and receiving mechanical ventilation. Two patients died of severe acute RDS, 14 (38.9%) recovered with complete resolution of chest radiographs, and 19 (52.8%) recovered but still had abnormal chest radiographs at discharge. Excluding the patient who was hospitalized, the median duration of hospital stay was 19 days (range, 7–41 days). Intubated versus non-intubated patients were hospitalized for longer (median 22 vs 15 days; $p = 0.048$).

Factors associated with respiratory failure

Univariate analysis of categorical (Table 4) and continuous variables (Table 5) showed that higher body temperature at presentation (median 39.5 vs 38.6°C), and higher peak levels of LDH (410 vs 282 U/L) and CRP (10.2 vs 2.5 mg/dL), were associated with respiratory failure in SARS patients. In the multivariate analysis, however, only peak level of CRP remained an independent predictor of respiratory failure (odds ratio for every increment of 1 mg/dL, 1.45; 95% confidence interval, 1.003–2.097; $p = 0.048$).

Discussion

Patients with suspected SARS were not included in the present study because of the low specificity of clinical criteria for suspected SARS. In addition, a recent study showed that the positive predictive value of WHO criteria for suspected SARS was only 54% (39–69%).[10]

We found that the clinical features of our patients were similar to those reported in other studies: fever, chills and dry cough were the most common initial

Table 4. Categorical variables for SARS patients with or without respiratory failure

Variable	ETT + MV (*N* = 8) *n* (%)	No ETT + MV (*N* = 28) *n* (%)	*p*
Gender (male/female)	2/6	7/21	1.000
In-hospital exposure*	7 (87.5)	26 (92.9)	0.553
Medical staff	5 (62.5)	13 (46.4)	0.691
Comorbid disease	3 (37.5)	5 (17.9)	0.346
Smoking	1 (12.5)	3 (10.7)	1.000
Alcohol	1 (12.5)	2 (7.1)	0.553
Multifocal radiographic involvement on presentation	3 (37.5)	5 (17.9)	0.346

**Exposed to SARS in the hospital setting (health care workers, patients, or visitors).*
ETT = endotracheal tube intubation; MV = mechanical ventilation.

Table 5. Continuous variables associated with respiratory failure and subsequent intubation in 36 patients with probable SARS

Variable	ETT + MV (*N* = 8) Median (range)	No ETT + MV (*N* = 28) Median (range)	*p*
Age, yr	34 (22–66)	37 (20–66)	0.53
Initial body temperature, °C	39.5 (38.0–40.1)	38.6 (38.0–40.0)	0.013
Interval between symptom onset and admission, d	2 (1–5)	2 (0–8)	0.752
On admission			
Leukocyte count, /μL	4,155 (2,200–13,830)	5,040 (2,140–18,380)	0.384
Lymphocyte count, /μL	843 (202–1,921)	844 (300–2,642)	0.832
Platelet count, $\times 10^3/\mu L$	145 (97–196)	152 (91–271)	0.446
LDH, U/L	375 (130–641)	240 (127–909)	0.845
CK, U/L	108 (62–461)	71 (20–436)	0.178
ALT, U/L	30 (14–52)	27 (5–141)	0.817
CRP, mg/dL	3.4 (0.3–10.4)	2.0 (0.5–10.4)	0.916
Peak values*			
Leukocyte count, /μL	12,015 (3,900–20,290)	12,740 (5,220–25,270)	0.451
LDH, U/L	410 (303–2,103)	282 (167–1,315)	0.021
CK, U/L	119 (20–461)	83 (20–1,966)	0.530
ALT, U/L	38 (20–78)	42 (6–183)	0.765
CRP, mg/dL	10.2 (5.4–20.4)	2.5 (0.5–18.0)	0.001
Duration of ribavirin therapy, d	11 (3–18)	10 (3–17)	0.450

**In the intubated group, peak values were the highest values collected before intubation.*
ALT = alanine aminotransferase; CK = creatine kinase; CRP = C-reactive protein; ETT = endotracheal tube intubation; LDH = lactate dehydrogenase; MV = mechanical ventilation.

presentations.[10–13] Approximately 1-half to 2-thirds of the patients presented with moderate lymphopenia (63.9%), mild thrombocytopenia (47.2%), and an elevated LDH level (66.7%), on admission. Interestingly, all but 3 patients developed lymphopenia during hospitalization, and in most cases, this occurred during the second week of the disease. This finding is consistent with that found by Wong et al, who proposed that lymphocyte depletion might result from a direct effect of the virus, or various cytokines, on lymphocytes.[14] Panesar suggested that lymphocyte margination due to glucocorticosteroid therapy or stimulation of the hypothalamic-pituitary-adrenal axis might be another explanation for lymphopenia,[15] while O'Donnell et al pointed out that apoptosis might also play a role.[16]

The chest radiograph presentations in our study are also compatible with findings in previous studies.[11,12,17] In the early disease stages, a peripheral/pleural-based opacity may be the only abnormality. This may range from a ground-glass appearance to consolidation. Unilateral (50%) infiltration is more common than bilateral or multifocal infiltration in the initial presentation, whereas cavitation and pleural effusion are not features of this disease. The radiographic involve-

ment usually progresses to bilateral infiltration, including a pattern compatible with adult RDS.[4,5,18–20] Our univariate analysis showed that initial, multifocal, radiographic involvement was not associated with the development of respiratory failure ($p = 0.346$). Peiris et al also showed that neither apparently normal nor multilobar involvement on chest radiograph at admission was associated with the development of adult RDS.[13]

In the current, retrospective study of a small number of patients, the efficacy of different treatments could not be elucidated. IVIG has been used in combination therapy for respiratory syncytial virus (RSV) pneumonia and cytomegalovirus pneumonia in bone marrow transplant recipients, and for treating RSV pneumonia in selected infants and children.[21–24] IVIG has also demonstrated efficacy in the treatment of other viral pneumonias.[25–27] Nevertheless, our preliminary results showed that, in SARS patients, the development of respiratory failure was not associated with less frequent or delayed use of IVIG.

The mortality rate in our study was 5.6% (2 patients), which is lower than the average reported by the WHO (14–15%).[28] This lower rate may be due to the age distribution in our study, which comprised patients of a younger age than in other trials. In addition, few of our patients had comorbid diseases associated with a poor prognosis.

Our study showed that higher body temperature on presentation, and higher peak LDH and CRP levels during hospitalization, were associated with respiratory failure and mechanical ventilation. However, only peak CRP level was independently associated with poor outcome. CRP, which has various biologic properties and functions,[29] has a disputed role as a marker of infection and/or inflammation in daily clinical practice. A study of community-acquired pneumonia showed that high interleukin-6 or CRP levels were associated with a long duration of fever and hospital stay, and less frequent clinical or radiographic recovery during follow-up after discharge.[30] Moreover, elevated serum levels of CRP on admission to the intensive care unit correlate with an increased risk of organ failure and death, and persistently high CRP levels correlate with a poor outcome in critically ill patients.[31] We suggest that CRP might reflect the severity of inflammation caused by the SARS virus and be related to immunopathologic damage to the lung, thus predicting a poor outcome.

SARS is an emerging viral disease, many aspects of which are being studied. In this retrospective study, a high value of CRP was associated with the development of respiratory failure and subsequent intubation.

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