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Original Article

Long-term outcomes in patients with severe acute respiratory syndrome treated with oseltamivir: a 12-year longitudinal study

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Abstract: *Background*: Clinical follow-ups of patients that have recovered from severe acute respiratory syndrome (SARS) have demonstrated radiological, physical, and psychological abnormalities to varying degrees. It is important that follow-ups be carried out to assess the clinical significance and persistence of such abnormalities. Oseltamivir has been widely used to treat viral diseases in clinical settings. *Objectives:* The aim of this study was to describe the long-term outcomes of patients with SARS and to describe the effects of oseltamivir on SARS, along with variables associated with outcomes. *Study design:* This study evaluated 67 survivors of severe acute respiratory syndrome treated with or without oseltamivir for 12 years after discharge from the hospital. At each visit, patients underwent physical examinations, pulmonary-function testing, echocardiographic examinations, and quality-of-life evaluations. *Results:* All survivors were asymptomatic and had normal clinical examinations. Mild pulmonary abnormalities were detected by lung function tests in 7 (10.45%) subjects, including residual ground-glass opacification or fibrosis (n=6) and air trapping (n=1). The need for mechanical ventilation (P=0.02) during the illness was a significant risk factor in predicting pneumonic fibrosis. There were no significant cardio-pulmonary function differences between those survivors treated with or without oseltamivir. Median scores for the physical role domain of the 36-item Short-Form General Health Survey decreased more than scores in the normal population, along with no significant differences between the two groups. *Conclusions:* After a complete clinical resolution, a considerable proportion of patients affected with SARS recovered. There were no significant differences in cardio-pulmonary function and quality-of-life measures between those treated with or without oseltamivir.

Keywords: Long-term outcomes, severe acute respiratory syndrome, oseltamivir

Background

Severe acute respiratory syndrome (SARS) is an emerging infectious disease caused by identified coronavirus (CoV) known as *SARS-associated CoV* (SARS-CoV) [1]. It first manifested in humans in China in November 2002 and has subsequently spread worldwide [2]. Although many studies have addressed short-term outcomes, no studies have provided detailed information beyond 10 years of follow-up.

It has been reported that fatality rates in patients affected with SARS-CoV have exceeded 10% [3]. Moreover, long-term pulmonary sequelae in the form of bronchiectasis and pulmonary fibrosis may be as high as 20% [4]. Other physical and psychological abnormalities may also be observed in severe cases, namely decreased quality of life and neurocognitive function impairment. Therefore, it is important to study long-term outcomes of patients with SARS to determine whether patients affected with SARS can return to normal and to determine variables associated with bad outcomes.

Published clinical trials have found that neuraminidase inhibitors, namely oseltamivir, selectively inhibit influenza A and B viral neuraminidase (a highly conserved active site that plays an essential role in viral replication), thereby inhibiting influenza virus release from infected

cells and reducing viral spread within the respiratory system [5]. During the SARS epidemic, many patients have received oseltamivir therapy to counter symptoms of acute respiratory distress, according to clinical practical guidelines [6]. The efficacy of oseltamivir in treatment of SARS and long-term follow-ups has not yet been established. Also, based on findings for other human coronaviruses, such as Middle East respiratory syndrome coronavirus, it is important to know the efficacy and safety of oseltamivir in the treatment of diseases caused by coronaviruses.

Objectives

The aim of this follow-up study was to delineate the characteristics and outcomes of patients affected with SARS, at 12 years after an acute episode of SARS, and to correlate the development of complications with clinical indices and laboratory abnormalities during the illness. Furthermore, this study investigated the efficacy of oseltamivir in prophylaxis against coronavirus.

Study design

Study participants

This prospective study was conducted at the Guangdong Provincial Hospital of Chinese Medicine, a major hospital in South China designated to treat cases of SARS during the SARS epidemic of 2003. Patients with SARS had probable cases of the disease, according to a modified definition of SARS provided by the Chinese Medical Association [7]. Patients had high fever (body temperature of 38°C or higher), evidence of lung infiltrate according to chest radiography or computed tomography of the thorax with or without respiratory symptoms (cough, dyspnea, or hypoxemia), relevant history of close contact with a suspected or defined case of SARS, and visitation history to a SARS-affected area within 10 days. Diagnosis of SARS was confirmed by either SARS-CoV RNA detected by reverse-transcription polymerase chain reaction. Patients were excluded if an alternative medical or microbiological diagnosis explained their clinical presentation. Of the 103 patients that were diagnosed during the outbreak, 7 patients died. The remaining patients with SARS were invited to participate in the study. Written consent for follow-ups was obtained directly from patients at the time of discharge from the hospital.

Treatment

All patients received antibiotics (penicillin, fluoroquinolone, or macrolides) treatment of community-acquired pneumonia after admission. A total of 34 patients received oral oseltamivir 75 mg, twice a day for 5 days. Afterward, 75 mg once a day for another 7 days. A total of 69 patients in the cohort did not receive this antiviral therapy because there were no guidelines recommending the use of oseltamivir at the first stage. In accordance with recommendations, therapy with intravenous corticosteroids was initiated if patients did not respond to antibiotic therapy within 48 hours and other symptoms were compatible with SARS, including severe toxic symptoms and illness progressing into acute lung injury (ALI) or acute respiratory distress syndrome (ARDS) [8]. The recommended dose of methylprednisolone for adults was 50-500 mg/day, intravenously, but modifications were made according to the needs of individual patients.

Collection of specimens and information

After informed consent was obtained from each patient, epidemiological data and past clinical information were retrieved from medical records and through patient interviews. Serum samples were collected from each patient at regular intervals and were frozen at -20°C until analysis could be performed. Other characteristics of patients during their stay in the hospital are outlined in **Table 1**.

Follow-up protocol

Following discharge from the hospital, patients were evaluated. At each visit, patients were interviewed and underwent physical examinations, pulmonary-function testing, posteroanterior chest radiographies, and echocardiographic examinations. They also completed the SF-36 to measure health-related quality of life (HRQoL) [9].

Statistical analysis

An intention-to-treat (ITT) analysis was carried out and presented retaining all enrolled participants regardless of whether they received oseltamivir or not. Baseline clinical and demographic characteristics are distributed as mean ± SD, median, or inter quartile range (IQR) for continuous variables and as frequencies or percent-

Table 1. Baseline characteristics

	Patients treated with oseltamivir (n=34)	Patients treated without oseltamivir (n=69)	*P* Value
Age, yr	29.91±10.11	36.97±13.24	0.007
Men, no. (%)	11 (32)	33 (48)	0.146
APACHE-II score, at admission	16.52±7.78	16.24±7.53	0.898
Any underlying medical conditions, no. (%)			
Ischaemic heart disease	2 (6)	2 (3)	
Pulmonary	1 (3)	1 (1)	0.553
Diabetes	0 (0)	1 (1)	1.000
Malignancy	0 (0)	1 (1)	
Immunocompromising condition	1 (3)	0 (0)	
Clinical illness, no. (%)			
Fever	34 (100)	69 (100)	1.000
Cough	26 (76)	51 (74)	1.000
Sore throat	7 (21)	8 (12)	0.245
Chills	20 (59)	45 (65)	0.664
Myalgias or arthralgias	10 (29)	9 (13)	0.059
Difficulty breathing	4 (12)	5 (7)	0.480
Severity of illness, no. (%)			
Treatment with mechanical ventilation	25 (74)	19 (28)	0.000
ARDS	7 (21)	11 (16)	0.588
Respiratory failure	18 (53)	27 (39)	0.209
Severe pneumonia	30 (88)	47 (68)	0.122
Shock	4 (12)	5 (7)	0.473
Dosage of steroid, mg	1941.46±245.20	712.71±178.41	0.000
Received steroid replacement therapy at follow-up, no. (%)	4 (12)	3 (4)	0.215
Hospital Courses and Outcomes			
Heating time, h	11.21±3.355	10.25±5.725	0.288
The total mortality rate, no. (%)	3 (9)	4 (6)	0.682
Mechanical ventilation time, h	224.23±148.21	225.67±214.79	0.981
From admission to death	18.0±7.0	27.25±1.25831	0.044
ICU admission, day	24.03±8.40	16.26±7.24	0.000
ICU stay cost, yuan	58146.77±33457.06	26256.27±37704.07	0.000
The total duration of hospitalization cost, day	24.03±8.40	16.26±7.24	0.000

Values are expressed as median (interquartile range) or n (%); Scores for the Acute Physiology, Age, and Chronic Health Evaluation (APACHE II) can range from 0 to 71; higher scores indicate more severe illness. ICU, Intensive Care Unit; ARDS, Acute Respiratory Distress Syndrome; APTT, activated partial thromboplastin time; ALT, Alanine aminotransferase.

ages for categorical variables. For all analyses, a value of $P<0.05$ is considered statistically significant. No adjustments were performed for multiple comparisons. All analyses were conducted using SPSS software version 12.0 (IBM, USA), unless otherwise noted.

Results

Study population

During the study period, this study enrolled 103 of 108 eligible patients. Reasons for exclusion are outlined in **Figure 1**. Two patients declined to participate in the study and one patient with a history of psychiatric disease was excluded after the audit. Consent was obtained from 103 survivors, these patients were included in the study (**Figure 1**).

The rate of in-person follow-up at the one-month visit was 93.2 percent, as 9 patients died in hospital. Three patients died with multi-system organ failure, two died of severe pneumonia, one died suddenly at home, and three died of respiratory arrest.

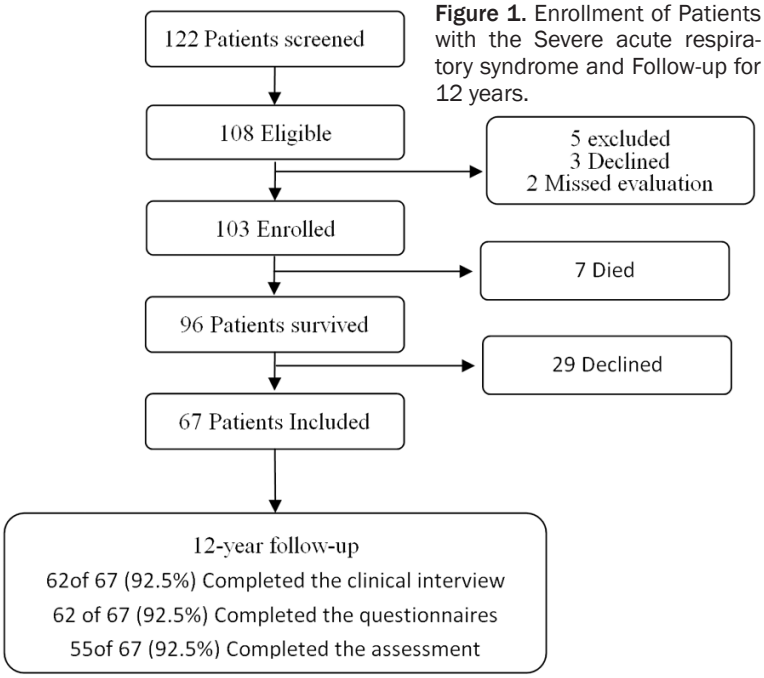

Figure 1. Enrollment of Patients with the Severe acute respiratory syndrome and Follow-up for 12 years.

A total of 29 patients were not evaluated because they were inaccessible or declined a visit. Finally, there were 67 of the 96 survivors that finished follow-up, with a rate of 69.79%.

Clinical features and short outcomes

This study retrospectively reviewed and analyzed data from records of SARS patients, from onset throughout the hospital stay. These included underlying medical conditions, clinical symptoms, laboratory variables, duration of mechanical ventilation, and short-time mortality rates.

Demographic details and comorbidities are shown in **Table 1**. The median age of the study population was 33 years (24-57 years), with 57% females. Seventy-three patients (81%) were health care workers (nurses, physicians, ward assistants, radiology and electrocardiogram technicians, medical students, security personnel, paramedics, and research assistants). Sixty-six (60%) patients were women.

A total of 34 patients (23.3%) were treated with oseltamivir. APACHE-II scores at admission were 16.52±7.78. Four patients had medical comorbidities including ischemic heart disease (n=2, 6%), chronic obstructive pulmonary disease (n=1, 3%), and immunocompromising condition (n=1, 3%). At presentation, patients had the following symptoms: fever >38°C (100%), chills (59%), coughs (76%), myalgia or arthralgias (29%), dyspnea (12%) and sore throats (21%).

Twenty-five patients (74%) were admitted to the ICU with mechanical ventilation and 3 patients died (21-day mortality, 9%; 95% confidence interval [CI], 5.9%-15.8%).

Multivariable analysis showed that presence of diabetes (relative risk, 3.1; 95% CI, 1.4-7.2; P=0.01) and other comorbid conditions (RR, 2.5; 95% CI, 1.1-5.8; P=0.03) were independently associated with poor outcomes (death, ICU admission, or mechanical ventilation).

Of the 69 patients treated without oseltamivir, 19 (28%) required mechanical ventilation with APACHE-II scores of 16.24±7.53. Features of the clinical examination most commonly found in these patients, at admission, were fever (100%), coughs (74%), myalgia (13%), and dyspnea (7%). Common laboratory features included elevated lactate dehydrogenase (87%), hypocalcemia (60%), and lymphopenia (54%). Epidemiologic and clinical characteristics did not significantly differ between the two groups.

In addition, there were no statistically significant differences between the two group in terms of incidence of ARDS (p=0.588), respiratory failure (p=0.588), severe pneumonia (p=0.122), and shock (p=0.473), as well as heating time (p=0.288), mechanical ventilation time (p=0.981), and total mortality rate (p=0.682).

Multiple logistic regression was used to assess whether oseltamivir treatment was independently associated with improved outcomes. Results show that oseltamivir treatment was not found to be associated with significantly better outcomes (p>0.05, data not shown).

Pulmonary function testing and chest radiological outcomes

Even though symptoms were not systematically recorded, most (if not all) patients were free of

Table 2. Findings in Heart Function Tests

Item	Patients treated with oseltamivir (n=26)	Patients treated without oseltamivir (n=38)	*P* Value
EF%	69.78±4.994	70.28±4.008	0.790
FS%	39.56±4.53	39.31±3.920	0.886
CO, L/min	5.100±1.0014	7.736±12.837	0.292
SV, mL	65.250±8.7953	61.046±13.5767	0.311
Right ventricular outflow tract, mm	23.33±2.06	22.90±2.968	0.626
AR, mm	26.67±5.050	23.17±3.48	0.024
LA, mm	29.00±2.179	28.24±4.006	0.472
RV, mm	17.44±2.128	17.07±2.137	0.651
Ventricular septal	9.67±1.803	9.03±1.295	0.350
LV(D), mm	45.89±2.369	44.34±2.468	0.113
LV(S), mm	27.67±2.236	26.76±2.516	0.318
LVPW, mm	9.56±1.424	8.97±1.052	0.275
PA, mm	21.00±1.323	19.31±1.795	0.007

EF indicates ejection fraction; FS, fractional shortening; CO, cardiac output; SV, stroke output; AR, aortic root wide; LA, left atrium wide; RV, Right ventricle; LV(D), Left ventricular (diastolic) wide; LV(S), Left ventricular (systolic) wide; LVPW, Left ventricular posterior wall; PA, Pulmonary artery wide.

respiratory symptoms at follow-up. Lung function abnormalities were detected in 7 patients (20.58%) treated with oseltamivir, with mild obstructive defect in one (6.25%), mild restrictive defect in three (18.75%), and moderate restrictive defect in three (18.75%). Isolated reductions in carbon monoxide transfer factor (TLCO) were found in 6 patients.

No significant differences were identified between patients with or without oseltamivir (P>0.05). The need for mechanical ventilation (P=0.02) during the illness was a significant risk factor in predicting pneumonic fibrosis.

Radiological abnormalities of any degree were detected in 7 patients (15.4%), either air trapping or residual ground-glass opacification. There were no significant differences in radiological abnormalities between subjects treated with or without oseltamivir (P>0.05).

Ventricular performance

In this study, several echocardiographic parameters were used to assess cardiac systolic and diastolic function. At present, the pulmonary artery wide was significantly higher (21.00± 1.323 vs. 19.31±1.795, P<0.001) in the group of patients that required oseltamivir compared to those that did not (**Table 2**). However, other parameters, including ejection fraction, fractional shortening, cardiac output, stroke output, left atrium wide, right ventricle, left ventricular (diastolic/systolic) wide, and left ventricular posterior wall, were not found to be significantly different between the two groups.

Quality of life

Twelve years after discharge from the hospital, 92.54 percent were working. Most patients had returned to their original position (**Table 3**). Reported reasons for not returning to work included immobility of large joints (femoral head necrosis), persistent fatigue, and weakness. There were no significant differences noted in the proportion of patients returning to their original work position between the two groups (P>0.05).

Medical Outcome Study 36-Item Short Form Health Survey (SF-36) was administered, at 12 years after hospital discharge, to assess health-related quality of life. Eight domains of the SF-36 (physical functioning, role-physical, bodily pain, general health, vitality, social functioning, role-emotional, and mental health) were clustered to form two higher order domains, physical and mental health scores. Each domain was scored from 0 to 100, with higher scores indicating better quality of life.

SF-36 domain scores of patients that did and did not require oseltamivir, compared with normative data, are shown in **Table 3**. There was

Table 3. Return to Work and Health-Related Quality of Life among Patients with the Acute Respiratory Distress Syndrome treated with or without oseltamivir

Outcome	Patients treated with oseltamivir (n=28)	Patients treated without oseltamivir (n=39)	*P* Value
Working status no./total no. (%)[¶]			
Not working	2/28 (7)	3/39 (8)	0.656
Returned to work	26/28 (93)	36/39 (92)	
SF-36 score[*]			
Physical functioning			0.082
Median (normal value)	80.63 (89)	88.52 (89)	
Interquartile range	67.5-95	85-95	
Physical role			0.084
Median (normal value)	60.94 (84)	84.26 (84)	
Interquartile range	25-100	25-100	
Body Pain			0.072
Median (normal value)	78 (77)	85.83 (77)	
Interquartile range	69.5-94	69.5-100	
General health			0.571
Median (normal value)	58 (77)	56.70 (77)	
Interquartile range	43-77	40-72	
Vitality			0.723
Median (normal value)	64.06 (68)	66.11 (68)	
Interquartile range	61.25-75	55-75	
Social functioning			0.865
Median (normal value)	87.50 (88)	86.57 (88)	
Interquartile range	87.5-100	62.5-100	
Emotional role			0.316
Median (normal value)	64.58 (84)	74.07 (84)	
Interquartile range	33.33-100	66.67-100	
Mental health			0.820
Median (normal value)	67.75 (78)	68.59 (78)	
Interquartile range	65-76	60-80	

[¶]This category includes return to school, home duties, volunteer work, or paid employment. [*]The domains of the Medical Outcomes Study 36-item Short-Form General Health Survey (SF-36) are defined as follows: physical functioning, the extent to which health limits physical activity; physical role, the extent to which physical health interferes with work or limits activity; pain, the intensity of pain and the effect of pain on patient's ability to work; general health, patient's own evaluation of his or her health or health outlook; vitality, the degree of energy the patient has; social functioning, the extent to which health or emotional problems interfere with social activities; emotional role, the extent to which emotional problems interfere with work or activities; and mental health, general mental health. Scores for each domain can range from 0 to 100; higher scores denote a better health-related quality of life. The normal Chinese values are from Li et al. A total of 1 patients with oseltamivir and 2 without oseltamivir at 12 year did not complete the questionnaires. The numbers evaluated were therefore 31 with oseltamivir and 54 without oseltamivir.

impairment of HRQoL among SARS survivors treated with oseltamivir at 12 years. Physical functioning and role physical domains were lower than in survivors treated without oseltamivir. However, there were no significant differences in SF-36 domains between the two groups ($p > 0.05$).

Discussion

SARS is a life-threatening illness resulting in significant long-term morbidity, including cardiopulmonary impairment and decreased quality of life. Ten years after the SARS outbreak, it is worth recounting these events in detail and summarizing subsequent understanding of SARS-CoV. This may be important as we continue to be confronted by novel emerging disease threats, including the novel Middle East respiratory syndrome (MERS) coronavirus. This threat can cause severe pneumonia and renal failure, with high fatality rates.

Histopathological changes from lung biopsy specimens suggested the possibility of immunopathological damage, a broad spectrum antiviral agent (oseltamivir), therefore, was recommended for empirical treatment. Oseltamivir has been demonstrated as an active neuraminidase inhibitor that significantly reduces the duration of symptomatic illness and hastens the return of activity to normal levels when initiated promptly in patients with naturally acquired influenza [10].

Few reports have described long-term outcomes of SARS survivors. The present study is the first to report more than ten years of effects on changes in both cardiopulmonary

function and health-related quality of life. At 12 years, residual abnormalities of cardiopulmonary function were still observed in some of the cohort, mostly consisting of a small number of restrictive defects, along with right heart dysfunction. Isolated abnormalities in pulmonary function could represent pulmonary fibrosis or a late phase in recovery, according to other longitudinal studies [11]. The rate of radiological abnormalities was lower than that reported in an earlier study, 12 years after admission, suggesting that radiological abnormalities caused by SARS might improve over time.

There were no significant differences between the two groups with respect to cardiopulmonary function, radiological abnormalities, and quality of life. Quality of life in the SARS survivors was lower than the normal population, as with previous reports with other SARS patients [12]. Interestingly, it was found that physical function, physical roles, pain, vitality, emotional roles, and mental health domains of patients treated with oseltamivir were lower than that those without oseltamivir 12 years after hospital discharge. These results raised the question as to why the mental health domain declined at 12 years. One possible reason for the decline in mental health at 12 years may be depression. Depression has been associated with decreased life satisfaction and lower quality of life [13].

This was not a randomized study, therefore, there are a few limitations. For example, the use of steroid treatment might have confounded the outcome because steroids can blunt host immune response and promote viral replication. However, both controls and oseltamivir-treated patients received the same protocol of corticosteroid therapy and cumulative methylprednisolone doses did differ between the two groups ($P<0.05$). Thus, the worse outcome in the treatment group was the result of higher steroid use. In subgroup analysis, patients that received oseltamivir as the initial treatment seemed to run a more severe disease course and had an increase in SARS-coronavirus load. Their need for higher doses of methylprednisolone for severe respiratory deterioration was therefore increased [14]. Therefore, oseltamivir-associated poor outcomes might be explained as immunopathological damage by steroid effects. In addition, the limitations of this study include the inability to measure premorbid cardiopulmonary function and quality of life. This study also did not follow a normal control group. However, it should be noted that demographics were used, namely age, gender, and underlying medical conditions. Corrected neuropsychologic test scores were used for statistical analyses, correcting for variables known to affect test performance [15].

In summary, this study revealed that a considerable proportion of patients with a history of SARS coronavirus-associated pneumonia could recover fully from their critical illness to a normal healthy status. Results suggest that complete recovery is possible. Long-term follow-up is important in assessing longitudinal changes of patients with SARS, allowing for better understanding of the disease and prognostic counseling of families.

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Disclosure of conflict of interest

None.

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References

[1] Peiris JS, Lai ST, Poon LL, Guan Y, Yam LY, Lim W, Nicholls J, Yee WK, Yan WW, Cheung MT, Cheng VC, Chan KH, Tsang DN, Yung RW, Ng TK and Yuen KY; SARS study group. Coronavirus as a possible cause of severe acute respiratory syndrome. Lancet 2003; 361: 1319-25.

[2] Drosten C, Günther S, Preiser W, van der Werf S, Brodt HR, Becker S, Rabenau H, Panning M, Kolesnikova L, Fouchier RA, Berger A, Burguière AM, Cinatl J, Eickmann M, Escriou N, Grywna K, Kramme S, Manuguerra JC, Müller S, Rickerts V, Stürmer M, Vieth S, Klenk HD, Osterhaus AD, Schmitz H and Doerr HW. Identification of a novel coronavirus in patients with severe acute respiratory syndrome. N Engl J Med 2003; 348: 1967-76.

[3] Peiris JS, Chu CM, Cheng VC, Chan KS, Hung IF, Poon LL, Law KI, Tang BS, Hon TY, Chan CS, Chan KH, Ng JS, Zheng BJ, Ng WL, Lai RW, Guan Y and Yuen KY; 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.

[4] Hon KL, Leung CW, Cheng WT, Chan PK, Chu WC, Kwan YW, Li AM, Fong NC, Ng PC, Chiu MC, Li CK, Tam JS and Fok TF. Clinical presentation and outcome of severe acute respiratory syndrome in children. Lancet 2003; 361: 1701-1703.

[5] Gubareva LV, Kaiser L and Hayden FG. Influenza virus neuraminidase inhibitors. Lancet 2000; 355: 827-35.

[6] Ho W; Hong Kong Hospital Authority Working Group on SARS, Central Committee of Infection Control. Guideline on management of severe acute respiratory syndrome (SARS). Lancet 2003; 361: 1313-5.

[7] Chinese Medical Association, China Association of Chinese Medicine. [Consensus of the management of severe acute respiratory syndrome]. Zhonghua Yi Xue Za Zhi 2003; 83: 1731-52.

[8] Tsui PT, Kwok ML, Yuen H and Lai ST. Severe acute respiratory syndrome: clinical outcome and prognostic correlates. Emerg Infect Dis 2003; 9: 1064-9.

[9] Chua SE, Cheung V, McAlonan GM, Cheung C, Wong JW, Cheung EP, Chan MT, Wong TK, Choy KM, Chu CM, Lee PW and Tsang KW. Stress and psychological impact on SARS patients during the outbreak. Can J Psychiatry 2004; 49: 385-390.

[10] Chan KS, Zheng JP, Mok YW, Li YM, Liu YN, Chu CM and Ip MS. SARS: prognosis, outcome and sequelae. Respirology 2003; 8 Suppl: S36-40.

[11] Weinert CR, Gross CR, Kangas JR, Bury CL and Marinelli WA. Health-related quality of life after acute lung injury. Am J Respir Crit Care Med 1997; 156: 1120-8.

[12] Herridge MS, Cheung AM, Tansey CM, Matte-Martyn A, Diaz-Granados N, Al-Saidi F, Cooper AB, Guest CB, Mazer CD, Mehta S, Stewart TE, Barr A, Cook D and Slutsky AS; Canadian Critical Care Trials Group. One-year outcomes in survivors of the acute respiratory distress syndrome. N Engl J Med 2003; 348: 683-93.

[13] Hsu LY, Lee CC, Green JA, Ang B, Paton NI, Lee L, Villacian JS, Lim PL, Earnest A and Leo YS. Severe acute respiratory syndrome in Singapore: clinical features of index patient and initial contacts. Emerg Infect Dis 2003; 9: 713-7.

[14] Ho JC, Ooi GC, Mok TY, Chan JW, Hung I, Lam B, Wong PC, Li PC, Ho PL, Lam WK, Ng CK, Ip MS, Lai KN, Chan-Yeung M and Tsang KW. High-dose pulse versus nonpulse corticosteroid regimens in severe acute respiratory syndrome. Am J Respir Crit Care Med 2003; 168: 1449-56.

[15] World Health Organization. Summary table of SARS cases by country, 1 November 2002-7 August 2003 (available at www.who.int/csr/sars/country/en/country2003_08_15.pdf, accessed 8 September 2003).