

Severe Acute Respiratory Syndrome (SARS): A Brief Review With Exploration of the Outcomes, Prognostic Factors and Sequelae

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Abstract: Severe Acute Respiratory Syndromes (SARS) is a novel infectious disease with significant morbidity and mortality. While heated debates and vigorous scientific investigations are still ongoing over the treatment, prevention and infection control of this deadly disease, substantial data has been accumulated concerning the outcomes and prognostic factors. Postmortem findings of the deceased have revealed diffuse alveolar damage, together with evidence of fibrosis and organization. A number of predicting indicators such as advanced age, presence of co-morbidities, extensive radiological involvement, high coronaviral load and elevated serum lactate dehydrogenase have been identified to be independent predictors for adverse clinical outcomes such as admission to intensive care unit, mechanical ventilation, and death. A number of recovered SARS patients experienced exertional breathlessness, malaise, asthenia during the early recovery phase, while restriction and isolated reduction in diffusion capacity were the commonest lung function abnormalities identified during the subsequent follow-up visits. Radiological abnormalities including residual ground-glass appearance and fibrosis were still detectable in these patients from their high-resolution computed tomography after recovery. Some recovered SARS patients were found to be suffering from psychological problems and avascular necrosis of the large joints.

(A) CLINICAL OVERVIEW

Introduction

Severe acute respiratory syndrome (SARS) has caused a major outbreak in 2003, with more than 8000 reported cases and 774 deaths worldwide, [1] affecting 29 countries including mainland China [2], Hong Kong [3-4], Taiwan [5], Singapore [6], Vietnam and Canada [7]. In Hong Kong, there were altogether 1755 SARS cases with 299 deaths [8]. Apart from the direct effects to the infected patients in terms of morbidity and mortality, the impact to travel, business and world economy has been enormous [9].

Etiology, Case definition and Diagnosis

The disease was found to be caused by a novel coronavirus, now called SARS coronavirus (SARS-CoV) [10-12]. The diagnosis of SARS has been based on clinical, epidemiological and laboratory criteria, with case definitions laid down by both World Health Organization (WHO) [13] and Centers for Disease Control and Prevention (CDC), the latter now being superseded by an updated version 2 [14]. The clinical case definition of Hospital Authority of Hong Kong was adopted from the WHO definition: a person with a history of fever $\geq 38^{\circ}\text{C}$ AND one or more symptoms of lower respiratory tract illness (cough, difficulty in breathing and shortness of breath) AND radiographic evidence of lung infiltrates consistent with pneumonia or adult respiratory distress syndrome AND no alternative diagnosis that can fully explain the illness [15]. The epidemiological criteria

include travel within 10 days of symptom onset to an area with documented or suspected SARS or close contact within 10 days of symptoms with a person known or suspected to have SARS infection. The updated CDC guidelines [14] has also included exposure to a domestic location (like a laboratory with live SARS-CoV) with documented or suspected SAR-CoV, or close contact with an ill person with such an exposure history, which would be relevant in recent reports of laboratory outbreaks [16-17]. CDC has also stressed on the importance of early symptoms like fever, chills, rigors, myalgia, in the absence of radiographic pneumonic changes, in persons who have epidemiological link to SARS.

The laboratory diagnostic criteria include: (1) Polymerase chain reaction (PCR) positive for SARS-CoV using a validated method from at least two different clinical specimens (e.g. nasopharyngeal and stool), OR the same clinical specimen collected on two or more occasions during the course of the illness, OR two different assays or repeat PCR using a new RNA extract from the original clinical sample on each occasion of testing; (2) Seroconversion by ELISA or IFA: negative antibody test on acute serum followed by positive antibody test on convalescent phase serum tested in parallel, OR four-fold or greater rise in antibody titer between acute and convalescent phase sera tested in parallel; (3) Virus isolation: isolation in cell culture of SARS-CoV from any specimen and PCR confirmation using a validated method [14-15]. Since the infectivity and hence the detection rate by RT-PCR has been demonstrated to be the highest in the second week of illness [18], the epidemiological and clinical criteria remain to be important in the early management of any suspected cases. However, a more recent report described a second generation assay of real-time PCR for SARS CoV with a sensitivity of 80% on nasopharyngeal aspirates in the first 3 days of illness [19].

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Mode of Transmission

During the SARS outbreak, the primary mode of transmission appears to be mediated through direct mucous membrane (eyes, nose and mouth) contact with droplets [3, 20-21] and/or fomites [20, 22]. Droplet spread in hospitals during SARS was also supported by the effectiveness of protection by precautions against droplets [23]. Aerosol-generating procedures such as use of aerosolized medication might also amplify the transmission [3]. In a large community (Amoy) outbreak in Hong Kong, suggestions of airborne spread [24] and animal vectors such as roof rats [25] have been raised, while faecal-oral route was another possibility since profuse watery diarrhoea was a common feature in these SARS patients and SARS-CoV was found in large quantities in stool [18].

Clinical, Laboratory and Radiological Features

The most common clinical features include fever, chills, rigors, myalgia, cough and dyspnea, while productive cough and coryza are relatively uncommon [3-4,8,26-28]. Diarrhoea, as mentioned above, was found in over 50% in the Amoy outbreak [18]. However, atypical presentations have been reported [29-31], particularly in the older patients, where fever might be absent and decrease in appetite and general condition be the presenting clinical problems [32]. The disease is relatively less common and milder in children [33]. A triphasic pattern of clinical course has been described: [18] Phase 1 (viral replication) is characterized by fever, myalgia, and other systemic symptoms in the first week. Phase 2 (immunopathologic damage) is characterized by recurrence of fever, oxygen desaturation, and radiological progression of pneumonia from week 2. Twenty percent of patients might progress to phase 3, characterized by adult respiratory distress syndrome (ARDS) and the necessitation of ventilatory support.

Common laboratory features include lymphopenia, thrombocytopenia, elevated lactic dehydrogenase (LDH), creatine phosphokinase and alanine aminotransferase (ALT) [3, 18, 26, 29, 35]. The degree of hepatic dysfunction [34] and lymphopenia [35] have been shown to correlate with clinical disease activity. Recently, we have also reported the potential use of serum amyloid A protein, an acute phase reactant, for the same purpose [36].

Airspace consolidation and ground glass opacities are the most common abnormality found at presentation [37, 38], with a peripheral distribution and lower zone predominance, and the absence of pleural effusions [3, 38]. However, 13% of our patients had normal chest radiographs upon admission [27], a feature of which was also described in other published series. High resolution computed tomography (HRCT) has been shown to be useful to detect early lung lesions for these patients [1, 38-40]. The characteristic HRCT features upon presentation were ground-glass opacities, sometimes with consolidation, and were associated with interlobular and intralobular septal thickenings. It has also been shown that radiographic and HRCT appearances were correlated to clinical and laboratory parameters [41, 42].

Pharmacological Treatment

It is perhaps one of the most controversial issues in SARS. Like many others [18, 29, 43], our patients [26] received ribavirin (as anti-SARS CoV therapy) and corticosteroids (as anti-inflammatory therapy). With this treatment regimen, four patterns of response have been reported: good responder, good responder with early relapse, fair and poor responders [44]. A study of Queen Mary and our hospital showed that patients being given "initial pulse" methylprednisolone therapy (500mg/day) for three days, followed by maintenance oral steroids, had less oxygen requirement, better radiographic outcome, and less likelihood of requiring rescue pulse corticosteroid therapy [45]. However, doubt has been thrown on the efficacy [46] and potential side effects of using high dose steroids in the management of an infectious disease [47, 48]. Lopinavir/ritonavir [49, 50] and integrative Chinese/Western medicine [51] were subsequently shown retrospectively to be associated to improve the clinical outcomes. To substantiate their effects, further randomized placebo-controlled trials are necessary. Despite these controversies, we have reported a subset of individuals that might require no specific treatment and recovered spontaneously [52]. That might imply a subset of patients, with characteristics yet to be identified, might not need any treatment at all.

(B) EARLY OUTCOMES OF SARS

There have been notable variations in the figures of adverse outcomes in the published series of SARS patients, even within Hong Kong itself (Table 1) [3, 7, 18, 26, 27, 53-57]. Most of these studies included intensive care admission, mechanical ventilation and mortality as the adverse outcomes indicators. The mean or median age of patients in these series are all relatively young at around 40, and in those with the data provided, most have virological documentation in about 80-90% of their cases. However, they differed quite considerably in the methodology, patient number and duration of follow-up. An example would be the crude mortality rate obtained in the study by Tsui *et al.*, [53] where the authors had admitted the possible underestimation because of the sampling bias. As pointed out by Donnelly *et al.*, [58] determination of the true mortality of the disease while the epidemic is still continuing is difficult. As a result, the bigger and more recent studies, like those of Choi *et al.*, [27] Sung *et al.*, [56] might provide a clearer picture of the adverse outcomes of the disease. The low reported mortality figure by Lau *et al.*, [55], with case fatality and crude mortality rates of 1.1% and 3.4% respectively, has been suggested to reveal the efficacy of their standard treatment regimen [43] and the use of non-invasive ventilation in their patients [59]. However, like most, if not all, studies describing efficacies of treatment or intervention strategies in SARS, their retrospective nature and the unavoidable lack of controls would require such hypotheses to be further substantiated in future randomized controlled studies. Figures from WHO (revised at 26 September 2003) [1] indicated the overall case fatality rate for SARS is 9.6%, and ranged from 7 to 17% in

Table 1. Outcome Studies in SARS

Study	Country	Age	Patient	Admission	Mechanical	Mortality
		(Mean)	No.	To ICU (%)	Ventilation (%)	(%)
Booth <i>et al.</i> [7]	Canada	45*	144	20	13.9	6.5 (21-day)
Chan <i>et al.</i> [26]	HK	41	115	34	26	10 (21-day) 15.7 (crude mortality rate))
Tsui <i>et al.</i> [53]	HK	41	323	21	13	7.9 (crude mortality rate)
Choi <i>et al.</i> [27]	HK	39	267	26	21	12 (3-month)
Wang <i>et al.</i> [54]	Taiwan	46.5*	76	NR	30.2	19.7 (case fatality rate)
Lau <i>et al.</i> [55]	HK	42.1	88	24	10	1.1 (case fatality rate) 3.4 (crude mortality rate)
Sung <i>et al.</i> [56]	HK	39.3	138	26.8	15.2	10.9 (crude mortality rate)
Peiris <i>et al.</i> [18]	HK	39.8	75	32	25	6.7 (21-day)
Zhao <i>et al.</i> [57]	China	37	108	NR	NR	12.9 (overall mortality)

ICU, intensive care unit; HK, Hong Kong; NR, not reported
*median

the 6 most severely affected regions. The high mortality might be related to the underlying severity of the pathological findings. Studies have described SARS post-mortem findings, which revealed mainly various stages of diffuse alveolar damage (DAD), with evidence of organization and fibrosis being identified for those patients who had longer disease durations before death [60, 61]. No specific pathological patterns have been identified that is characteristic of SARS and appearances might be complicated with superimposed infections and immunomodulatory treatment modalities [62].

One-fifth to one-third of the reported patient series required intensive care admissions, and a large proportion of these were eventually intubated and required mechanical ventilation (Table 1). This has obviously provided witness for the fulminant cause of the disease, as well as the heavy demand on intensive care resources encountered in the affected regions during the epidemic. Respiratory failure was the predominant feature, with relatively few other organ failures, in those that required mechanical ventilation, [63] and which can be protracted [64]. The outcomes of those under critical care, whether intubated or not, have been reported to be dismal, with overall 28-day mortality of 26% [63] to 34% [64] and 13-week mortality of 52.2%. [65] As a result, with the encouraging results [28, 59] and reported safety of utilizing non-invasive ventilation (NIV) in SARS patients, NIV might be considered before intubation and subsequent mechanical ventilation.

On the other hand, the outcomes of the paediatric population have been found to be more favourable. In a case series of 44 children, [66] 11.4% and 6.8% required intensive care and mechanical ventilation respectively, with no mortality found. It was observed that teenagers may present with features resembling adults with respect to disease progression and propensity to develop severe illness.

A variety of complications has been reported in the various series (Table 2). Most of these could be related to the pharmacological treatment with ribavirin (hemolysis and

anaemia) and high-dose potent corticosteroids (hyperglycaemia, nosocomial infections and hypokalaemia). The relatively frequent occurrence of barotraumas could be related to assisted ventilation, but spontaneous occurrence has not been uncommon, which was related to the peak LDH levels [67]. The exact pathogenesis of such increased occurrence is still uncertain.

Table 2. Reported Complications Developed During Management of SARS

Study	Complications (incidence)
Booth <i>et al.</i> [7]	hemolysis (76%), anaemia (49%), bradycardia (14%)
Chan <i>et al.</i> [26]	hyperglycaemia (15%), hypokalaemia (39%), gastrointestinal bleeding (3%), hypertension (7%)
Wang <i>et al.</i> [54]	bacterial superinfection (13%), rhabdomyolysis (5.3%), peripheral neuropathy (6.6%), acute renal failure (3.9%), gastrointestinal bleeding (2.6%), acute MI (1.3%)
Choi <i>et al.</i> [27]	barotraumas (2%), acute renal failure (6%), acute hepatic failure (1%)
*Tsui <i>et al.</i> [53]	hyperglycaemia, hypokalaemia, flare-up of hepatitis B infection, hospital-acquired infection and steroid psychosis
Peiris <i>et al.</i> [18]	spontaneous pneumomediastinum (12%), hospital-acquired infection (9.3%)
Sung <i>et al.</i> [56]	hemolysis (36%), anaemia (59%), hyperglycaemia (16%), nosocomial infections (12%), hypokalaemia (11%), barotrauma (6%), psychiatric manifestations (1%)
Lau <i>et al.</i> [55]	barotrauma (13%), nosocomial infections (5%), acute MI (1%), ischaemic stroke (1%), psychiatric manifestations (7%)

MI, myocardial infarction

* no figures on incidences of the complications were provided

Table 3. Prognostic Factors Associated with Adverse Outcomes

Studies	Risk factors	*Adverse Outcomes
Booth <i>et al.</i> [7]	DM Other comorbid conditions	a, b, c
Lee <i>et al.</i> [3]	Advanced age High peak LDH level Neutrophil count above normal	a, b
Chan <i>et al.</i> [26]	Age>60 DM and/or heart disease Other comorbid conditions (DM and/or heart disease for a, b and c)	a
Peiris <i>et al.</i> [18]	Advanced Age Chronic hepatitis B infection	d
Tsui <i>et al.</i> [53]	Advanced age High admission neutrophil count High initial LDH level	a, b, e
Wang <i>et al.</i> [54]	Underlying disease High initial CRP levels	a
Choi <i>et al.</i> [27]	Age> 60 High initial LDH levels	a
Chan <i>et al.</i> [68]	positive virological tests for SARS-CoV	a, b, c
Tsang <i>et al.</i> [69]	positive RT-PCR on NPA	a
Hung <i>et al.</i> [70]	serum viral load	a, c
Chau <i>et al.</i> [71]	Advanced age Shortness of breath on admission More extensive involvement on initial CXR	a, c
Chan <i>et al.</i> [75]	Advanced age Serum LD1 activity	a

DM, diabetes mellitus; LDH, lactate dehydrogenase; CRP, C-reactive protein;
NPA, nasopharyngeal aspirate; LD1, lactate dehydrogenase isoenzyme 1

*a, mortality; b, intensive care admission; c, mechanical ventilation; d, oxygen dependency of more than 3L/min

(C) PROGNOSTIC INDICATORS OF ADVERSE OUTCOMES

A no. of prognostic indicators has been put forward in the various analyses in outcome studies. (Table 3).

Advanced Age

This has been consistently identified as an independent poor prognostic indicator after multivariate analyses in many series [3, 18, 26, 27, 53, 71, 73]. The adverse effects of age on mortality on community acquired pneumonia (CAP) [78] and adult respiratory distress syndrome (ARDS) [79, 80] have been noted in the past and that both should have at least a small contribution in the clinical course of SARS. In an epidemiological analysis from SARS patients in Hong Kong, [58] it was found that the estimated case fatality rate was 13.2% for patients younger than 60 and more than 40% for patients aged over 60.

Comorbidities

This is another independent poor prognostic factor that has been frequently reported, [7, 26, 54] and has also been

associated with poor outcomes in CAP [78] and ARDS [79, 80]. Diabetes mellitus is one of the risk factors identified in an well-known meta-analysis of CAP outcomes by Fine *et al.*, [77] and can itself lead to superinfection by other microorganisms like *Staphylococcus aureus* [81], which is associated with a high mortality [82]. The presence of cardiac diseases in critically ill patients with hypoxaemia would definitely pose a severe challenge to the underlying compromised cardiac reserves, and we had observed diastolic impairment of myocardial function in SARS patients during the active phase [83]. The coexisting illnesses that have been described by PORT prediction rule model [84] to predict mortality includes chronic obstructive lung disease, bronchiectasis, malignancy, diabetes mellitus, chronic renal failure, congestive heart disease, chronic liver disease and cerebrovascular disease. However, different definitions of “comorbidities” or “coexisting conditions” have been observed in different studies. Tsui *et al.*, [53] had included pregnancy as one of the co-existing conditions in their analysis, while Wang *et al.*, [54] had stratified the severity of the underlying conditions into rapidly fatal, ultimately fatal or non-fatal, according to the system proposed by McCabe [85]. While differential impact or weighing should be given to different comorbid conditions such as the systems proposed by McCabe *et al.*, or Charlson *et al.*, [86]

these rules developed in the eighties should be interpreted carefully as the standard of care has progressed rapidly in these 20 years. An example would be that AIDS, a deadly disease in the eighties, was categorized with the same weight as metastatic solid tumour in the Charlson's rule [86].

Virological Test Results

It was found that positive RT-PCR tests for SARS-CoV are associated with adverse outcomes [68, 69]. However, the limited sensitivity of the early tests, differential sensitivities of tests from different sample origins [26, 68] and the expertise of carrying out nasopharyngeal aspirates were all potential confounding factors to such observations. Recently, the possibility of the correlation of disease activity with viral load from these findings has been supported by the evidence that serum viral load was associated with oxygen desaturation, mechanical ventilation, diarrhea, hepatic dysfunction and death [70]. This would help to eliminate the latter two uncertainties raised above.

Radiological Appearance

It was noted in a study of more than 200 patients [71] that the initial chest radiograph appearance would have prognostic significance in that involvement in more than two zones was an independent predictor of adverse outcomes. However, the initial chest radiograph appearance might be confounded by the timing of admission, in that those admitted early with a contact history of confirmed SARS patients might have little or no plain chest radiographs. Similar findings were obtained from another study in Taiwan [73]. Paul *et al.*, [72] focused on the radiographic pattern and found that multifocal opacities that progressed to diffuse air-space opacification and patients with diffuse airspace opacification had a high fatality rate. Hui *et al.*, [74] also found that more extensive radiographic involvement at presentation and on day 7 after fever onset were both associated with adverse outcomes of ICU admission and/or death. Ooi *et al.*, [75] identified that larger maximal radiographic scores, lower oxygen saturation at maximal radiographic change, longer time from treatment to maximal radiographic score and diffuse consolidations at maximal radiographic score were associated with oxygen supplementation, yet no association was observed with treatment response.

Gender

It was found that males had a significantly higher case fatality rate than females (21.9% versus 13.2%, $p < 0.0001$) in a study based on the cumulated 1755 SARS cases in Hong Kong. However, the exact explanation remains unknown.

Laboratory Parameters

A high serum LDH level has been found to be a prognostic factor in several studies [3, 27, 53], which might reflect the extent of tissue damage. The level of LD1 isoenzyme, which originates from erythrocytes and body

tissues rather than myocardium, was found to be a better prognostic indicator in predicting death than the total LDH levels in SARS patients [76]. While lymphopenia is commonly observed, [35] Blood CD3+, CD4+, CD8+ and natural killer cell counts were found to be good prognostic factors for predicting ICU admission [77]. On the other hand, high neutrophil counts have been identified by 2 groups in Hong Kong to be related to poor outcomes [3, 53]. The initial level of C-reactive protein, an acute phase reactant, was identified to be of prognostic value in only one study [54].

(D) SEQUELAE AND LONGER TERM OUTCOMES OF SARS

Persistent Symptoms

It was noted [87] that some symptoms were still reported from recovered SARS patients in the first follow-up, scheduled at about 6 to 7 weeks from disease onset. These include palpitation, exertional dyspnea, malaise, easy forgetfulness, chest discomfort, etc.

Quality of Life Measures

A Chinese study of recovered patients at around 4 weeks post-discharge from hospital [88] revealed moderately increased St. George's respiratory questionnaire (SGRQ) scores, with significant correlation between all 4 parts of SGRQ and diffusion capacity of the lung for carbon monoxide (DLCO). Our unpublished data of SARS patients at 6 weeks post-discharge, as summarized by Chan *et al.*, [89] in a review article, showed a decrease in health-related quality of life scores using MOS 36-items Short Form Health Survey (SF-36), particularly in the domains of physical functioning, role physical, social functioning and bodily pain.

Radiological Appearance

Thin section CT thorax of recovered SARS patients obtained at on average 36.5 days after initial hospital admissions revealed parenchymal abnormalities in 96% of patients that include residual ground-glass opacification, interstitial thickening and fibrosis [90]. Older patients and those with more severe disease during treatment were associated with fibrotic findings. Our study [91] at 6-month post disease onset revealed abnormalities in 75% of patients and the extent of involvement was observed to be mild in most cases. The use of pulse corticosteroids, which might reflect the severity of the disease during treatment, was the only independent factor identified to be associated with persistent CT abnormalities.

Pulmonary Function and Exercise Capacity

A study from Singapore described presence of residual pulmonary function defects in half of the recovered SARS patients at 3 months post discharge [92]. Abnormalities in forced vital capacity (FVC), forced expiratory volume in 1

second (FEV₁), FEV₁/FVC and diffusion capacity measured by single-breath carbon monoxide (TLCO) technique were present in 15%, 26%, 2% and 39% respectively. Most of these abnormalities were described to be mild. Our data [91] revealed presence of pulmonary function abnormalities in 75% of cases at 6-months from symptom onset, with restrictive defects of mild and moderate degrees being the most common (28%). However, isolated reductions in TLCO were observed in 46.5%, which might represent a phase in the course of recovery or pulmonary fibrosis, as was also identified in the recovery phase of ARDS [93]. Ong *et al.*, [92] revealed that 41% of their patients had maximum exercise capacity below the lower limit of normal range, but many of such could not be accounted by impairment of pulmonary function. Respiratory muscle weakness or, as Ong *et al.*, pointed out, other extrapulmonary causes might possibly account for such functional outcomes. It was found that HRCT findings correlated well with clinical symptoms and pulmonary function parameters, especially TLCO, in the recovery phase of SARS [42].

Psychological Sequelae

Psychological impact of SARS has been observed during the outbreak in Hong Kong, involving SARS patients, their family members and the society [94]. A questionnaire survey carried out at the peak of the outbreak revealed the presence of general stress and negative psychological effects in SARS patients, particularly among infected health care workers [95]. Our study involving discharged SARS patients in the outpatient clinic at 2 months post-discharge showed the persistence of such symptoms, with 12.1% classified as moderate to severely anxious while 12.1% classified as moderately to severely depressed [96]. The number of disruption areas measured by the Disruption Scale and the lack of satisfaction with social support were found to be significant correlates of psychological distress in our study.

Avascular Necrosis of Bone

Avascular necrosis (AVN) of hips and knees were reported in 30 to 42% of 2 reports of post-discharge Chinese SARS patients [97, 98]. Similar high percentage (45%) of AVN were also reported in recovered paediatric SARS patients [99]. Although the use of corticosteroids in the SARS treatment regime appears to be an attractive explanation, additional factors specific to SARS itself may be present and remained to be discovered.

(E) CONCLUSION

SARS is a novel disease that has resulted in significant mortality and morbidity worldwide during the 2003 epidemic. In the absence of prospective randomized data, the most efficacious treatment is still largely uncertain. From the numerous case series and studies published since the outbreak, a clearer picture has been obtained over the outcomes of the disease, as well as the prognostic factors that are related. These are useful since patients with higher risk of adverse outcomes would be monitored more closely in a more intensive manner. On the other hand, as time

moves on, more sequelae of this previously unknown disease might be unveiled.

REFERENCES

- [1] World Health Organization. Cumulative number of reported probable cases of severe acute respiratory syndrome (SARS). Available at: http://www.who.int/csr/sars/country/table2003_09_23/en/ (accessed 11 October, 2004)
- [2] Zhong NS, Zheng BJ, Li YM, *et al.* Epidemiological and aetiological studies of patients with severe acute respiratory syndrome (SARS) from Guangdong in February 2003. *Lancet* 2003; 362: 1353-8.
- [3] 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: 1986-94.
- [4] 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.
- [5] Twu SJ, Chen TJ, Chen CJ, *et al.* Control measures for severe acute respiratory syndrome (SARS) in Taiwan. *Emerg Infect Dis* 2003; 9: 718-720.
- [6] Hsu LY, Lee CC, Green JA, *et al.* Severe acute respiratory syndrome in Singapore: clinical features of index patient and initial contacts. *Emerg Infect Dis* 2003; 9: 713-717.
- [7] Booth CM, Matukas LM, Tomlinson GA, *et al.* Clinical features and short-term outcomes of 144 patients with SARS in the greater Toronto area. *JAMA* 2003; 289: 2801-2809.
- [8] Department of Health, Hong Kong. Latest figures on 2003 Severe Acute Respiratory Syndrome outbreak (as at 19 January 2004). Available at: <http://www.info.gov.hk/dh/diseases/ap/eng/infected.htm> (accessed at 12 October 2004)
- [9] Lam WK, Zhong NS, and Tan WC. Overview of SARS in Asia and the world. *Respirology* 2003; 8: S2-S5.
- [10] Peiris JS, Lai ST, Poon LL, *et al.* Coronavirus as a possible cause of severe acute respiratory syndrome. *Lancet* 2003; 361: 1319-25.
- [11] Drosten C, Gunther S, Preiser W, *et al.* Identification of a novel coronavirus in patients with severe acute respiratory syndrome. *N Engl J Med* 2003; 348: 1967-76.
- [12] Ksiazek TG, Erdman D, Goldsmith CS, *et al.* A novel coronavirus associated with severe acute respiratory syndrome. *N Engl J Med* 2003; 348: 1953-66.
- [13] World Health Organization. Case definitions for surveillance of Severe Acute Respiratory Syndrome (SARS) (revised 1 May 2003). Available at: <http://www.who.int/csr/sars/casedefinition/en/> (accessed 12 Oct 2004)
- [14] Centers for Disease Control and Prevention. Clinical guidance on the identification and evaluation of possible SARS-CoV disease among persons presenting with community-acquired illness (version 2) (updated January 8 2004). Available at: <http://www.cdc.gov/ncidod/sars/clinicalguidance.htm> (accessed 12 Oct 2004)
- [15] Hospital Authority of Hong Kong. Case definition of SARS (English version-9/2/2004) Available at: http://ha.home/ho/ps/SARS_case_definition.htm (accessed 12 Oct 2004)
- [16] Lim PL, Kurup A, Gopalakrishna G, *et al.* Brief report: laboratory-acquired severe acute respiratory syndrome. *N Engl J Med* 2004; 350(17): 1740-45.
- [17] World Health Organization. China's latest SARS outbreak has been contained, but biosafety concerns remain (update 7). Available at: http://www.who.int/csr/don/2004_05_18a/en/ (accessed 12 Oct 2004)
- [18] Peiris JSM, Chu CM, Cheng VC, *et al.* Clinical progression and viral load in a community outbreak of coronavirus-associated SARS pneumonia: a prospective study. *Lancet* 2003; 361: 1761-66.
- [19] Poon LLM, Chan KH, Wong OK, *et al.* Early diagnosis of SARS coronavirus infection by real time RT-PCR. *J Clin Virol* 2003; 28: 233-8.
- [20] World Health Organization. Consensus document on the epidemiology of severe acute respiratory syndrome (SARS). Available at: <http://www.who.int/csr/sars/en/WHOconsensus.pdf> (accessed 12 Oct 2004)
- [21] Varia M, Wilson S, Sarwal S, *et al.* Investigation of a nosocomial outbreak of severe acute respiratory syndrome (SARS) in Toronto, Canada. *CMAJ* 2003; 169(4): 285-92.

- [22] Dowell SF, Simmerman JM, Erdman DD, *et al.* Severe acute respiratory syndrome coronavirus on hospital surfaces. *Clin Infect Dis* 2004; 39(5): 652-7.
- [23] Seto WH, Tsang D, Yung RW, *et al.* Effectiveness of precautions against droplets and contact in prevention of nosocomial transmission of severe acute respiratory syndrome (SARS). *Lancet* 2003; 361 (9368): 1519-20.
- [24] Yu ITS, Li Y, Wong TW, *et al.* Evidence of airborne transmission of the severe acute respiratory syndrome virus. *N Engl J Med* 2004; 350(17): 1731-39.
- [25] Ng SKC. Possible role of an animal vector in the SARS outbreak at Amoy Gardens. *Lancet* 2003; 362 (9383): 570-2.
- [26] Chan JW, Ng CK, Chan YH, *et al.* Short term outcome and risk factors for adverse clinical outcomes in adults with severe acute respiratory syndrome (SARS). *Thorax* 2003; 58: 686-689.
- [27] Choi KW, Chau TN, Tsang O, *et al.* Outcomes and prognostic factors in 267 patients with severe acute respiratory syndrome in Hong Kong. *Ann Intern Med* 2003; 139: 715-723.
- [28] Zhao Z, Zhang F, Xu M, *et al.* Description and clinical treatment of an early outbreak of severe acute respiratory syndrome (SARS) in Guangzhou, PR China. *J Med Microbiol* 2003; 52: 715-20.
- [29] Fisher DA, Lim TK, Lim YT, *et al.* Atypical presentations of SARS. *Lancet* 2003; 361: 1740.
- [30] Wu EB, Sung JJ. Haemorrhagic-fever-like changes and normal chest radiograph in a doctor with SARS. *Lancet* 2003; 361: 1520-1.
- [31] Li G, Zhao ZX, Chen LB, *et al.* Mild severe acute respiratory syndrome. *Emerg Infect Dis* 2003; 9: 1182-3.
- [32] Chan TY, Miu KY, Tsui CK, *et al.* A comparative study of clinical features and outcomes in young and older adults with severe acute respiratory syndrome. *J Am Geriatr Soc* 2004; 52(8) 1321-5.
- [33] Hon K, Leung C, Cheng W, *et al.* Clinical presentations and outcome of severe acute respiratory syndrome in children. *Lancet* 2003; 361: 1701-3.
- [34] Wong WM, Ho JC, Hung IF, *et al.* Temporal patterns of hepatic dysfunction and disease activity in patients with SARS. *JAMA* 2003; 290 (20): 2663-4.
- [35] Wong RSM, Wu A, To KF, *et al.* Haematological manifestations in patients with severe acute respiratory syndrome: retrospective analysis. *BMJ* 2003; 326: 1358-62.
- [36] Yip TT, Chan JW, Cho WC, *et al.* Protein chip array profiling analysis in patients with severe acute respiratory syndrome identified serum amyloid A protein as a biomarker potentially useful in monitoring the extent of pneumonia. *Clin Chem* 2004 Sep 13 [Epub ahead of print] (in press)
- [37] Wong KT, Antonio GE, Hui DS, *et al.* Severe acute respiratory syndrome: radiological appearances and pattern of progression in 138 patients. *Radiology* 2003; 228: 401-6.
- [38] Muller NL, Ooi GC, Khong PL, *et al.* Severe acute respiratory syndrome. Radiographic and CT findings. *Am J Roentgenol* 2003; 181(1): 3-8.
- [39] Muller NL, Ooi GC, Khong PL, *et al.* High-resolution CT findings of severe acute respiratory syndrome at presentation and after admission. *Am J Roentgenol* 2004; 182(1): 39-44.
- [40] Hui JY, Hon TY, Yang MK, *et al.* High-resolution computed tomography is useful for early diagnosis of severe acute respiratory syndrome-associated coronavirus pneumonia in patients with normal chest radiographs. *J Comput Assist Tomogr* 2004; 28(1): 1-9.
- [41] Ooi GC, Khong PL, Bing L, *et al.* Severe acute respiratory syndrome: relationship between radiologic and clinical parameters. *Radiology* 2003; 229(2): 492-9.
- [42] Hsu HH, Tzao C, Wu CP, *et al.* Correlation of high resolution CT, symptoms, and pulmonary function in patients during recovery from severe acute respiratory syndrome. *Chest* 2004; 126: 149-158.
- [43] So LKY, Lau ACW, Yam LYC, *et al.* Development of a standard treatment protocol for severe acute respiratory syndrome (SARS). *Lancet* 2003; 361: 1615-7.
- [44] Tsang KW, Lam WK. Management of severe acute respiratory syndrome. The Hong Kong University experience. *Am J Respir Crit Care Med* 2003; 168: 417-424.
- [45] Ho JC, Ooi GC, Mok TY, *et al.* High-dose pulse versus nonpulse corticosteroid regimens in severe acute respiratory syndrome. *Am J Respir Crit Care Med* 2003; 168: 1449-1456.
- [46] Cyranoski D. Critics slam treatment for SARS as ineffective and perhaps dangerous. *Nature* 2003; 423: 4.
- [47] Oba Y. The use of corticosteroids in SARS. *N Engl J Med* 2003; 349: 2034-5.
- [48] Wang H, Ding Y, Li X, *et al.* Fatal aspergillosis in a patient with SARS who was treated with corticosteroids. *N Engl J Med* 2003; 349: 507-8.
- [49] Chan KS, Lai ST, Chu CM, *et al.* Treatment of severe acute respiratory syndrome with lopinavir/ritonavir: a multicentre retrospective matched cohort study. *Hong Kong Med J* 2003; 9: 399-406.
- [50] Chu CM, Cheng VCC, Hung IFN, *et al.* Role of lopinavir/ritonavir in the treatment of SARS: initial virological and clinical findings. *Thorax* 2004; 59(3): 252-256.
- [51] Li J, Li SD, Du N. Clinical study on treatment of severe acute respiratory syndrome with integrative Chinese and Western medicine approach. *Zhongguo Zhong Xi Yi Jie He Za Zhi* 2004; 24: 28-31.
- [52] Chan JW, Lee S. SARS patients and need for treatment. *Emerg Infect Dis* 2004; 10(10): 1877-8.
- [53] Tsui PT, Kwok ML, Yuen H, *et al.* Severe acute respiratory syndrome: clinical outcomes and prognostic correlates. *Emerg Infect Dis* 2003; 9(9): 1064-69.
- [54] Wang JT, Sheng WH, Fang CT, *et al.* Clinical manifestations, laboratory findings and treatment outcomes of SARS patients. *Emerg Infect Dis* 2004; 10(5): 818-24.
- [55] Lau AC, So LK, Miu FP, *et al.* Outcome of coronavirus-associated severe acute respiratory syndrome using a standard treatment protocol. *Respirology* 2004; 9: 173-183.
- [56] Sung JJ, Wu A, Joynt GM, *et al.* Severe acute respiratory syndrome: report of treatment and outcome after a major outbreak. *Thorax* 2004; 59(5): 414-420.
- [57] Zhao CH, Guo YB, Wu H, *et al.* Clinical manifestation, treatment, and outcome of severe acute respiratory syndrome: analysis of 108 cases in Beijing. *Zhonghua Yi Xue Za Zhi* 2003; 83(11): 897-901. [article in Chinese]
- [58] Donnelly CA, Ghani AC, Leung GM, *et al.* Epidemiological determinants of spread of casual agent of severe acute respiratory syndrome in Hong Kong. *Lancet* 2003; 361: 1761-6.
- [59] Cheng TM, Yam LY, So LK, *et al.* Effectiveness of noninvasive positive pressure ventilation in the treatment of acute respiratory failure in severe acute respiratory syndrome. *Chest* 2004; 126: 845-850.
- [60] Nicholls JM, Poon LL, Lee KC, *et al.* Lung pathology of fatal severe acute respiratory syndrome. *Lancet* 2003; 361: 1773-78.
- [61] Cheung OY, Chan JW, Ng CK, *et al.* The spectrum of pathological changes in severe acute respiratory syndrome (SARS). *Histopathology* 2004; 45: 119-124.
- [62] Nicholls J, Dong XP, Jiang G, *et al.* SARS: clinical virology and pathogenesis. *Respirology* 2003; 8: S6-S8.
- [63] Gomersall CD, Joynt GM, Lam P, *et al.* Short-term outcome of critically ill patients with severe acute respiratory syndrome. *Intensive Care Med* 2004; 30(3): 381-7.
- [64] Fowler RA, Lapinsky SE, Hallett D, *et al.* Critically ill patients with severe acute respiratory syndrome. *JAMA* 2003; 290(3): 367-73.
- [65] Lew TW, Kwek TK, Tai D, *et al.* Acute respiratory distress syndrome in critically ill patients with severe acute respiratory syndrome. *JAMA* 2003; 290: 374-80.
- [66] Leung CW, Kwan YW, Ko PW, *et al.* Severe acute respiratory syndrome among children. *Paediatrics* 2004; 113(6): 535-543.
- [67] Chu CM, Leung YY, Hui JY, *et al.* Spontaneous pneumomediastinum in patients with severe acute respiratory syndrome. *Eur Respir J* 2004; 23(6): 802-4.
- [68] Chan KS, To WK, Ng KC, *et al.* Laboratory diagnosis of SARS. *Emerg Infect Dis* 2004; 10(5): 825-31.
- [69] Tsang OT, Chau TN, Choi KW, *et al.* Coronavirus-positive nasopharyngeal aspirate as predictor for severe acute respiratory syndrome mortality. *Emerg Infect Dis* 2003; 9(11): 1381-87.
- [70] Hung IF, Cheng VC, Wu A, *et al.* Viral loads in clinical specimens and SARS manifestations. *Emerg Infect Dis* 2004 Sep. Available from: <http://www.cdc.gov/ncidod/EID/vol10no9/04-0058.htm>
- [71] Chau TN, Lee PO, Choi KW, *et al.* Value of initial chest radiographs for predicting clinical outcomes in patients with severe acute respiratory syndrome. *Am J Med* 2004; 117: 249-254.

- [72] Paul NS, Chung T, Konen E, *et al.* Prognostic significance of the radiographic pattern of disease in patients with severe acute respiratory syndrome. *Am J Roentgenol* 2004; 182(2): 493-8.
- [73] Ko SF, Lee TY, Huang CC, *et al.* Severe acute respiratory syndrome: prognostic implications of chest radiographic findings in 52 patients. *Radiology* 2004; 233: 173-181.
- [74] Hui DS, Wong KT, Antonio GE, *et al.* Severe acute respiratory syndrome: correlation between clinical outcome and radiological features. *Radiology* 2004; Sep 16 [Epub ahead of print] (in press).
- [75] Ooi CG, Khong PL, Ho JC, *et al.* Severe acute respiratory syndrome: radiographic evaluation and clinical outcome measures. *Radiology* 2003; 229(2): 500-6.
- [76] Chan MH, Wong VW, Wong CK, *et al.* Serum LD1 isoenzyme and blood lymphocyte subsets as prognostic indicators for severe acute respiratory syndrome. *J Intern Med* 2004; 255(4): 512-8.
- [77] Fine MJ, Smith MA, Carson CA, *et al.* Prognosis and outcomes of patients with community-acquired pneumonia: a meta-analysis. *JAMA* 1996; 275(2): 134-141.
- [78] Niederman MS, Mandell LA, Anzueto A, *et al.* American Thoracic Society guidelines for the management of adults with community-acquired pneumonia. *Am J Respir Crit Care Med* 2001; 163: 1730-54.
- [79] Montgomery AB, Stager MA, Carrico CJ, *et al.* Causes of mortality in patients with the adult respiratory distress syndrome. *Am Rev Respir Dis* 1985; 132: 485-9.
- [80] Suchyta MR, Clemmer TP, Elliot CG, *et al.* The adult respiratory distress syndrome : a report of survival and modifying factors. *Chest* 1992; 101: 1074-9.
- [81] Rello J, Quintana E, Austina V, *et al.* Risk factors for *Staphylococcus aureus* nosocomial pneumonia in critically ill patients. *Am Rev Respir Dis* 1990; 142: 1320-4.
- [82] Fine MJ, Orloff JJ, Arisumi D, *et al.* Prognosis of patients hospitalized with community-acquired pneumonia. *Am J Med* 1990; 88: 1N-8N.
- [83] Li SS, Cheng CW, Fu CL *et al.* Left ventricular performance in patients with severe acute respiratory syndrome: a 30-day echocardiographic follow-up study. *Circulation* 2003; 108: 1798-1803.
- [84] Fine MJ, Auble TE, Yealy DM, *et al.* A prediction rule to identify low-risk patients with community-acquired pneumonia. *N Engl J Med* 1997; 336: 243-250.
- [85] Kreger BE, Craven DE, McCabe WR. Gram-negative bacteremia. *Am J Med* 1980; 68: 344-355.
- [86] Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis* 1987; 40(5): 373-383.
- [87] Tso EY, Tsang OT, Choi KW, *et al.* Persistence of physical symptoms in and abnormal laboratory findings for survivors of severe acute respiratory syndrome. *Clin Infect Dis* 2004; 38: 1338.
- [88] Liu T, Peng M, Cai BQ, *et al.* Assessment of health-related quality of life in cured SARS patients. *Zhongguo Yi Xue Ke Xue Yuan Xue Bao* 2003; 25(5): 516-9. [article in Chinese]
- [89] Chan KS, Zheng JP, Mok YW, *et al.* SARS: prognosis, outcome and sequelae. *Respirology* 2003; 8: S36-S40.
- [90] Antonio GE, Wong KT, Hui DS, *et al.* Thin-section CT in patients with severe acute respiratory syndrome following hospital discharge: preliminary experience. *Radiology* 2003; 228(3): 810-15.
- [91] Ng CK, Chan JW, Kwan TL, *et al.* Six month radiological and physiological outcomes in severe acute respiratory syndrome (SARS) survivors. *Thorax* 2004; 59: 889-91.
- [92] Ong KC, Ng AW, Lee LS, *et al.* Pulmonary function and exercise capacity in survivors of severe acute respiratory syndrome. *Eur Respir J* 2004; 24: 436-442.
- [93] Herridge MS, Cheung AM, Tansey CM, *et al.* One-outcomes in survivors of the acute respiratory distress syndrome. *N Engl J Med* 2003; 348: 683-93.
- [94] Tsang HW, Scudds RJ and Chan EY. Psychological impact of SARS. *Emerg Infect Dis* 2004; 10(7): 1326-7.
- [95] Chua SE, Cheung V, McAlonan GM, *et al.* Stress and psychological impact on SARS patients during the outbreak. *Can J Psychiatry* 2004; 49(5): 201-206.
- [96] Au A, Chan I, Li P, *et al.* Correlates of psychological distress in discharged patients recovering from severe acute respiratory syndrome in Hong Kong. *Int J Psychosoc Rehabil* 2004; 8: 41-51.
- [97] Li YM, Wang SX, Gao HS, *et al.* Factors of avascular necrosis of femoral head and osteoporosis in SARS patients' convalescence. *Zhonghua Yi Xue Za Zhi* 2004; 84(16): 1318-53.
- [98] Hong N and Du XK. Avascular necrosis of bone in severe acute respiratory syndrome. *Clin Radiol* 2004; 59(7): 602-8.
- [99] Chan CW, Chiu WK, Chan CC, *et al.* Osteonecrosis in children with severe acute respiratory syndrome. *Pediatr Infect Dis J* 2004; 23(9): 888-890.