

## SARS: prognosis, outcome and sequelae

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### SARS: prognosis, outcome and sequelae

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Severe acute respiratory syndrome (SARS) is associated with considerable morbidity and mortality in the acute phase. Worldwide case fatality rate is 11% (range 7 to 27%) for the most severely affected regions. Several adverse prognostic factors have been identified, including advanced age, presence of comorbidity, higher lactose dehydrogenase levels and initial neutrophil count, but the impact of viral and other host factors on outcome is unknown. Published data on sequelae of SARS are limited. Clinical follow-up of patients who recovered from SARS has demonstrated radiological, functional and psychological abnormalities of varying degrees. In the early rehabilitation phase, many complained of limitations in physical function from general weakness and/or shortness of breath. In a small series of subjects who underwent CT scan of the chest, over half showed some patchy changes consistent with pulmonary fibrosis. Lung function testing at 6–8 weeks after hospital discharge showed mild or moderate restrictive pattern consistent with muscle weakness in 6–20% of subjects. Mild decrease in carbon monoxide diffusing capacity was detected in a minority of subjects. Preliminary evidence suggests that these lung function abnormalities will improve over time. Psychobehavioural problems of anxiety and/or depression were not uncommon in the early recovery phase, and improved over time in the majority of patients. Avascular necrosis of the hip has been reported as another complication. The long-term sequelae of SARS are still largely unknown. It is important to follow up these patients to detect and appropriately manage any persistent or emerging long-term sequelae in the physical, psychological and social domains.

**Key words:** prognosis, sequelae, severe acute respiratory syndrome.

Severe acute respiratory syndrome (SARS) has caused multinational outbreaks affecting 8422 individuals with 916 deaths within a period of 6 months.<sup>1</sup>

### OUTCOMES

Severe acute respiratory syndrome patients may present with a spectrum of disease severity ranging from relatively asymptomatic infection to fulminant pneumonitis and death. Several studies have reported on short-term outcomes in adult patients up to about one month of the onset of illness. Various outcome measures have been examined, including admission to intensive care unit (ICU), development of acute lung injury (ALI), adult respiratory distress syndrome (ARDS) and mortality.

About one-third of patients have prompt resolution of fever and pneumonitis with treatment<sup>2</sup> and even without specific treatment in a minority. However, the remaining run a much more stormy course – 19 to 34% of SARS patients required admission to ICU, 13 to 26% required assisted ventilation, 20 to 22.6% developed ALI or ARDS and 3.6 to 10.1% died at day 21 to day 28. (Table 1).<sup>2–9</sup> Protracted ventilation is not uncommon for SARS-induced respiratory failure.<sup>9</sup> This has posed considerable strain on critical care resources in the affected regions. Even with vigorous support and treatment, half of those who required mechanical ventilation eventually died.<sup>9</sup> The reported mortality in ICU was 34% at 28 days<sup>8</sup> and 52.2% at 13 weeks.<sup>9</sup>

As the SARS epidemic abates, a clearer picture of the mortality of the disease is emerging. The most recent WHO update<sup>1</sup> indicated that the worldwide case fatality rate (CFR) is 11% and ranged from 7 to 27% for the most severely affected regions (Table 2). Most deaths were attributed to complications related to sepsis, ARDS and multiorgan failure,<sup>8</sup> which

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**Table 1** Outcome studies in SARS

Study	No. of patients	Virological documentation	Follow up duration	ICU admission	End-points		Mortality	Prognostic factors implicated
					Ventilation support	ICU admission		
Lee <i>et al.</i> <sup>3</sup>	138	NR	NR	32(23.2%)	19 (13.8%)	3.6% (21-day)	Age, peak LDH, neutrophil count above normal	
Booth <i>et al.</i> <sup>4</sup>	144	NR	21 days	29 (20%)	20 (14%)	6.5% (21-day)	Comorbidity (Diabetes)	
Wong <i>et al.</i> <sup>5</sup>	157	87.9%	Median 26 days	NR	NR	NR	Age, initial LDH level, low initial CD4, CD8 count	
Chan <i>et al.</i> <sup>6</sup>	115	89%	Median 62 days	39 (34%)	30 (26%)	10% (21-day)	Age, comorbidity (Diabetes, heart disease)	
Peiris <i>et al.</i> <sup>7</sup>	75	93%	24 days	24 (32%)	19 (25%) (ARDS: 20%)	6.7% (21-day)	Age, comorbidity (hepatitis B)	
Tsui <i>et al.</i> <sup>2</sup>	323	89%	<5 weeks	67 (21%)	42 (13%)	NR	Age, initial LDH, neutrophil count	
Lew <i>et al.</i> <sup>8</sup>	199	NR	28 days	46 (23%)	39 (19.5%) (ALI/ARDS: 22.6%)	10.1% (28-day)	APACHE II score, baseline PaO <sub>2</sub> /FIO <sub>2</sub> ratio	
Fowler <i>et al.</i> <sup>9</sup>	196	NR	28 days	38 (19%)	29 (14.8%)	6.6% (28-day)	Age, Diabetes, bilateral lung infiltrates	

ICU, intensive care unit; ALI, acute lung injury; ARDS, acute respiratory distress syndrome; NR, not reported.

**Table 2** Summary table of SARS cases by country, 1 November 2002–7 August 2003<sup>1</sup>

Areas	Cumulative number of cases			Status				
	Female	Male	Total	No. cases currently hospitalized	No. cases recovered	No. deaths	No. health care workers(%)	CFR† (%)
Canada	151	100	251	10	200	41	108 (43)	17
China			5327	29	4949	349	1002 (19)	7
China, Hong Kong	977	778	1755	7	1448	300	386 (22)	17
Special Administrative Region								
China, Taiwan	349 <sup>3</sup>	319 <sup>3</sup>	665	10	475	180	86 (13)	27
Singapore	161	77	238	0	205	33	97 (41)	14
Vietnam	39	24	63	0	58	5	36 (57)	8
United States	16	17	33	7	26	0	1 (3)	0

<sup>1</sup> Case fatality based on cases with known outcome and irrespective of immediate cause of death.

occurred commonly in the elderly with comorbidities. There were notable differences in case-mix among different regions (i.e. differences in distribution of age, sex, disease severity as reflected by surrogate markers such as LDH level, proportion of infected healthcare workers (HCW) and the proportion of SARS confirmed by virological tests). The CFR of HCW in Hong Kong was 2% (8 out of 386). It is noteworthy that in the United States, only 8 out of 47 probable cases and none of the 162 suspected cases have had virological confirmation of SARS-CoV infection.<sup>10</sup> The variation in CFR across different regions has to be interpreted in the light of these differences.<sup>11</sup>

## PROGNOSTIC FACTORS

Prognostic factors examined were essentially patient characteristics and laboratory findings. Few studies reported prognosis in relation to drug treatment, and little is known about the differences in host response caused by SARS-coronavirus.

Age and comorbidity (e.g. diabetes mellitus, heart disease) were consistently found to be significant independent predictors of various adverse outcomes in SARS. Initial experience suggests that children with SARS have better prognosis than adults.<sup>12,13</sup> Three studies reported that LDH level (two on the initial LDH level<sup>2,5</sup> and one on the peak LDH level<sup>3</sup>) was a predictive factor. Two studies reported the initial neutrophil count<sup>2,3</sup> and one study reported the initial CD4, CD8 count<sup>5</sup> as predictive of outcome. The analysis by the SARS Collaborative Group of the Hong Kong Hospital Authority on 889 patients has identified the following as risk factors for death: advanced age, male sex, presence of comorbidity, higher peak LDH level and higher initial neutrophil count.<sup>14,15</sup> The mortality rate was 6% for patients aged between 25 and 44, in contrast to 60% for age over 65. The use of ribavirin did not appear to have an independent favourable or deleterious effect on patient outcome.<sup>11,14,15</sup> Unpublished data in Hong Kong suggested that initial viral load obtained from the nasopharyngeal aspirate might be an additional predictor of ARDS and ultimate mortality, in addition to the known risk factors (KY Yuen, pers. comm.).

Old age and comorbidity are well established adverse risk factors in pneumonia, but they are non-modifiable. Parameters such as LDH level and neutrophil count might serve as surrogate markers of disease severity to guide treatment plans in individuals. It is important to have more understanding of other potentially modifiable prognostic factors, such as the relationship of the viral load or transmission route and the host response, so that treatment can be promptly tailored to the needs of the individuals and hopefully improve their eventual outcome.

## SEQUELAE AND FOLLOW UP

Although published data on the sequelae of SARS are limited, patients who have recovered from SARS have

been noted to manifest radiological, functional and psychological abnormalities to varying degrees.

In the early rehabilitation phase, many patients complained of limitation in physical function from general weakness and/or shortness of breath. In a series from United Christian Hospital (UCH) in Hong Kong, comprising 42 patients with a mean age of 40 years seen at about one month after hospital discharge, about one-third of patients had moderate to severe degree of dyspnoea on exertion or general malaise, and felt that their performance of household tasks or at work was moderately or severely impaired (E Wong, pers. comm.).

Computerized tomography of the thorax in 24 patients at about 5 weeks after discharge from hospital showed that changes consistent with pulmonary fibrosis occurred in 62% (15 of 24 patients), who tended to be older and had more severe disease during the acute phase.<sup>16</sup> However, the fibrosis was patchy and not extensive in the majority, and hopefully would not have a significant impact on lung function.

In a series of 46 patients from Queen Elizabeth Hospital (QEH) in Hong Kong who were examined at 6 weeks postdischarge, about 20% were found to have a mild restrictive defect (PMY Lau, pers. comm.). In another series of patients from Prince of Wales Hospital (PWH), the inspiratory and expiratory pressures were below normal range while carbon monoxide diffusing capacity measurements were not markedly decreased (D Hui, pers. comm.). Similarly, a study at 6–8 weeks after hospital discharge in 43 patients at the Guangzhou Institute of Respiratory Diseases showed that forced vital capacity and total lung capacity were mildly decreased at  $85 \pm 11\%$  and  $81 \pm 8\%$  of predicted, respectively, and residual volume was markedly reduced at  $63 \pm 10\%$  of predicted, while carbon monoxide diffusing capacity corrected for lung volume (DLCO/VA) was normal at  $109 \pm 18\%$  of predicted.<sup>17</sup> The findings suggested that respiratory muscle weakness rather than parenchymal lung damage was the major factor for the restrictive lung function defect. In addition, 50% of the patients from the QEH series have a decrease in hand grip strength. The observed weakness of respiratory and skeletal muscle could be due to several factors, including the previous use of high dose steroids, prolonged bed rest, physical deconditioning or residual systemic effect of the acute disease.

Lung function studies carried out on 258 patients from Xiaotangshan Hospital in Beijing 2 months after discharge showed that 21% patients (54 of 258 patients) had evidence of impaired diffusion ( $D_LCO < 80\%$ pred) while 6% (16 of 258 patients) had restrictive ventilatory defect ( $VC < 80\%$ pred).<sup>18</sup> Fifty-one of 54 patients had lung function tests repeated one month later.  $D_LCO$  was found to improve in 80.4% patients (41 of 51 patients), and FVC in 81.3% patients (13 of 16 patients) (Table 3). These findings suggest that lung function abnormality caused by SARS might improve spontaneously over time.

Severe acute respiratory syndrome patients may show a decrease in their aerobic capacity in the early rehabilitation period. In the QEH series, 41% (19 of

**Table 3** Changes in lung function test of SARS patients after discharge from Xiaotangshan Hospital ( $X \pm S$ )

	VC (L)	FEV <sub>1</sub> (L)	FEV <sub>1</sub> /FVC (%)	D <sub>L</sub> CO (ml/min/mmHg)	D <sub>L</sub> CO/V <sub>A</sub> (L/min/mmHg)
Second month	3.10 ± 0.68	2.47 ± 0.60	79.7 ± 0.09	15.8 ± 2.8	4.12 ± 0.60
Third month	3.33 ± 0.63	2.64 ± 0.57	79.8 ± 0.09	17.7 ± 2.9	4.35 ± 0.59
<i>t</i> -test	5.7132	5.0470	0.0521	6.8197	3.9212
<i>P</i> -value	0.000	0.000	0.958	0.000	0.000

46) of patients have diminished VO<sub>2</sub> max as measured by the Chester Strep test. Among 33 of the 42 patients in UCH, 97% had a 6 minute walking distance below 2 standard deviations of normal control (E Wong, pers. comm.). Possible contributing factors for their diminished cardiopulmonary fitness include muscle weakness, residual lung damage, anaemia and physical deconditioning.

Patients who have recovered from SARS show symptoms of psychological trauma. In the early recovery phase, about 5 weeks from onset of illness, one out of four (27 of 101) and one out of seven (16 of 101) inpatients in Wong Tai Sin Hospital in Hong Kong showed moderate to severe degrees of anxiety and depression, respectively (SP Lam, pers. comm.). It is assumed this psychological aftermath will probably improve over time, as suggested by data from another series of 75 patients in QEH who were evaluated at one to two months after hospital discharge. Only 5% of these patients were reported to have moderate to severe anxiety and depressive symptoms (A Au, pers. comm.). Other than anxiety or depression, post-SARS patients suffered from some impairment of health-related quality of life. Using the validated MOS 36-items Short Form Health Survey, the QEH series showed a decrease in health-related quality of life scores, particularly in the domains of physical functioning, role physical, social functioning and bodily pain. Isolated cases of steroid-induced psychosis have also been reported.

Clinical experience showed that SARS sequelae in other systems have also been encountered to varying extents, although systematic data is not yet available for reporting. Mild degree of anaemia was commonly seen in patients at the early follow-up period. Lymphocyte count appeared to have returned to the normal range for most patients but it is not known if body immune defence has been fully restored, and studies relating to lymphocyte subset or lymphocyte function may shed light on this aspect. Side-effects of high-dose steroids such as avascular necrosis of femoral head have been reported in a few patients and further follow-up for subclinical effects on bone or pituitary-adrenal axis is warranted. Neurological and psychobehavioural problems such as lack of concentration or poor memory have been reported by some patients and warrant further follow-up. It is also prudent to be alert to any potential problems that may arise in the long term from the use of unconventional treatment such as convalescent plasma.

In summary, SARS is associated with considerable morbidity and mortality in the acute phase. A signif-

icant proportion of patients who survive the acute illness have impairment in their overall functional capacity and health status in the first few months of recovery. However, the long-term sequelae are still largely unknown. It is necessary to follow up these patients and perform comprehensive assessments for detection and appropriate management of any persistent or emerging long-term sequelae in the physical, psychological and social domains.

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