Long-term outcome of acute respiratory distress syndrome caused by severe acute respiratory syndrome (SARS): an observational study

Thomas S T Li, Charles D Gomersall, Gavin M Joynt, Doris P S Chan, Patricia Leung and David S C Hui

ABSTRACT

Objective: We examined long-term outcome of pulmonary function, exercise capacity and health-related quality of life (HRQoL) in patients with acute respiratory distress syndrome (ARDS) caused by severe acute respiratory syndrome (SARS).

Methods: 59 critically ill patients with ARDS caused by SARS between March and July 2003 were studied prospectively and followed up for 1 year. Thirty-six underwent pulmonary function testing and a 6-minute walk test, and 35 underwent HRQoL evaluation by Short Form-36 questionnaire at 3, 6, and 12 months after illness onset.

Results: Mean age was 47 (SD, 15.7) years. Median APACHE II score was 10 (interquartile range [IQR], 7–12). Only 47% required invasive mechanical ventilation. Median admission and worst PaO_2/FIO_2 ratio were 142 (IQR, 94–177) mmHg and 86 (IQR, 66–122) mmHg, respectively. Median stay in ICU and hospital were 9 (IQR, 5–20) and 31 (IQR, 20–54) days, respectively. Mortality was 24% at hospital discharge and at 1 year. Mean lung volumes and spirometric measurements were nearly normal by 6 months. Except for diffusion capacity adjusted for haemoglobin concentration (DLCO) measured at 12 months, there was no significant difference in pulmonary function measurement between those who had mechanical ventilation and those who did not. The 6-minute walk distance (6MWD) improved from 3 to 6 months, with no further significant change. Younger patients had near normal HRQoL by 6 months. Those aged over 40 years had impaired HRQoL at multiple domains even at 12 months. At 12 months, forced expiratory volume in 1 second, forced vital capacity and 6MWD correlated significantly with multiple SF-36 domain scores. DLCO correlated significantly only with domain scores reflecting physical function.

Conclusions: The mortality of SARS-related ARDS is similar to the mortality of ARDS from other causes. A substantial number of patients with SARS-related ARDS survived without receiving mechanical ventilation. Patients had good recovery of pulmonary function and HRQoL.

Crit Care Resusc 2006; 8: 302–308

For editorial comment, see page 279

The global outbreak of severe acute respiratory syndrome (SARS) in 2003 resulted in over 8000 people being infected worldwide, with a mortality of 9.6%.[1] About 20% to 30% of patients required admission to the intensive care unit, mostly because of respiratory failure.[2-4] More than 80% of these patients developed acute respiratory distress syndrome (ARDS),[5] of whom 50% to 80% needed mechanical ventilation. The 28-day mortality of patients requiring ICU admission was about 30% to 40%.[5-7]

Survival to hospital discharge and long-term outcome of these patients has not been described. This study aimed to document the clinical course, pulmonary function and health-related quality of life (HRQoL) of patients who had ARDS caused by SARS. The short- and long-term outcomes of about half the patients in this cohort have been described previously,[5,8,9] but the characteristics and outcome of those who met the definition of ARDS were not apparent from those data. Our study describes in detail the outcome of all survivors of SARS who developed ARDS, with a focus on patients who did not require endotracheal intubation and mechanical ventilation.

Methods

This retrospective study of prospectively collected data was approved by the ethics committee of The Chinese University of Hong Kong.

Patient population

The study was a longitudinal follow-up of all patients admitted to the ICU at the Prince of Wales Hospital in Hong Kong during the SARS epidemic between March and July 2003. During this period, the ICU was used exclusively for the management of SARS patients. Diagnosis of ARDS was based on the criteria of the American–European Consensus Conference on ARDS in 1994.[10] The diagnosis of SARS was initially based on the criteria of the US Centers for Disease Control and Prevention,[11] with subsequent confirmation by seroconversion or fourfold rise in SARS coronavirus IgG antibody titre measured by an immunofluorescence assay. The data collected and definitions have been described elsewhere.[5]

Criteria for endotracheal intubation and mechanical ventilation were either persistent failure to maintain arterial oxygen saturation of 90% while receiving 15 L/min of oxygen via non-breathing mask, or onset of respiratory muscle fatigue as evidenced by increase in $PaCO_2$, profuse sweating, severe tachycardia, tachypnoea and feeling of exhaustion. A deliberate attempt was made to avoid intubation and mechanical ventilation because of the perceived high incidence of barotrauma and the fact that most patients had single-organ failure. Non-invasive positive pressure ventilation was not used. A low tidal volume, low pressure strategy, adapted from the Acute Respiratory Distress Syndrome Network study protocol, was used for mechanical ventilation of patients who were intubated.[5]

Table 1. Characteristics of 59 patients with SARS-related acute respiratory distress syndrome

Characteristic	Value
Age (years) (mean ± SD)	47 ± 16
Male (%)	58%
Current smoker or history of smoking (%)	5%
History of chronic disease (%)	17%
Median APACHE II score (IQR)	10 (7–12)
Median PaO_2/FIO_2 ratio at ICU admission (mmHg) (IQR)	142 (94–177)
Required mechanical ventilation (%)	46%
Barotrauma (%)	19%
Median MOD score at ICU admission (IQR)	3 (2–4)
Median maximum MOD score (IQR)	5 (3–9)
Median worst PaO_2/FIO_2 ratio (mmHg) (IQR)	86 (66–122)
Median ICU stay (days) (IQR)	9 (5–20)
Median total hospital stay (days) (IQR)	31 (20–54)
ICU mortality (%)	24%
Hospital mortality (%)	24%
12-month mortality (%)	24%

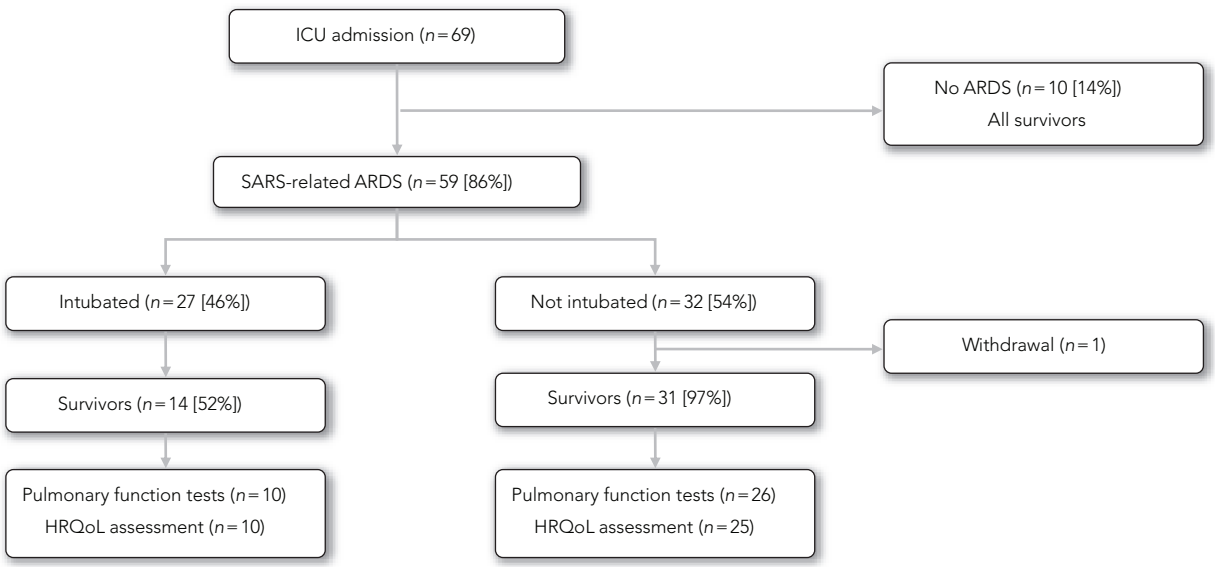
APACHE = Acute Physiology and Chronic Health Evaluation.
IQR = interquartile range. MOD = multiple organ dysfunction. ◆

Patient follow-up

After discharge from hospital, the patients were followed up at 3, 6 and 12 months after the onset of illness. At each visit, they were interviewed and underwent a physical examination. They were invited to undergo pulmonary function tests[12] and standardised 6-minute walk tests,[13,14] and to complete the Hong Kong version of the Medical Outcomes Study 36-item Short-Form General Health Survey (SF-36).[15,16] Written informed consent was obtained from participants for follow-up, pulmonary function tests and assessment of HRQoL.

The pulmonary function tests included forced expiratory volume in 1 second (FEV_1), forced vital capacity, total lung capacity, and diffusion capacity adjusted for haemoglobin concentration (DLCO). Lung function parameters were measured using the SensorMedic V_{max} system (Yorba Linda, Calif, USA). DLCO was measured by the single-breath carbon monoxide technique with infrared analyser. Spiro-

Figure 1. Recruitment and follow-up of patients with SARS-related acute respiratory distress syndrome



SARS = severe acute respiratory syndrome. ARDS = acute respiratory distress syndrome. HRQoL = health-related quality of life. ◆

metric tests were performed according to the standards of the American Thoracic Society.[12]

The SF-36 questionnaire has eight multiple-item scales which assess physical functioning, role limitation due to physical problems, bodily pain, general health, vitality, social functioning, role limitation due to emotional problems, and mental health. The score for each scale ranges from 0 to 100.[15] Higher scores reflect better health status. The results were compared with the reference values found by an SF-36 Health Survey of the adult Chinese population in Hong Kong.[16]

Patients who refused to undergo pulmonary function tests and quality of life assessment were contacted by telephone 12 months after the illness to confirm survival.

Statistical analysis

Statistical analysis was performed with SPSS version 11.0 (SPSS Inc, Chicago, Ill, USA). Continuous normally distributed data were compared using Student's unpaired *t* test, and categorical data using the χ^2 test. Non-normally distributed data were compared using the Mann–Whitney U test. Paired *t* test was used to assess the serial changes in the 6-minute walk distance (6MWD). Associations between pulmonary function parameters and quality of life domain scores were determined with Pearson correlation coefficients. All statistical tests were two-tailed. Statistical significance was taken as $P < 0.05$.

Results

During the SARS outbreak, 69 patients were admitted, eight of whom were admitted twice. Only the data collected in the first ICU admission were analysed. There were 59 patients with ARDS. All subsequent data relates to these patients only.

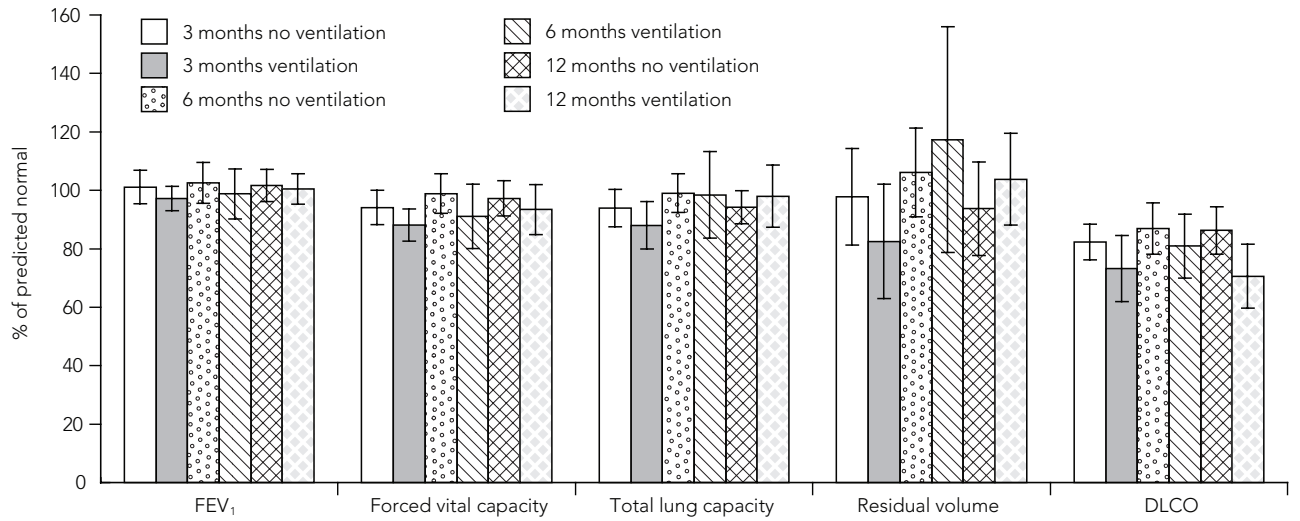
Of the 59 patients with SARS-related ARDS, 45 survived, and 36 agreed to follow up pulmonary function testing

Table 2. Factors associated with 1-year mortality and with mechanical ventilation (figures are median and interquartile range unless otherwise stated)

	1-year mortality			Mechanical ventilation		
Factors	Survived ($n = 45$)	Died ($n = 14$)	*P*	Not used ($n = 31$)	Used ($n = 27$)	*P*
Age (years) (mean±SD)	42.0±12.1	65.5±14.3	<0.001	39.2±10.9	55.1±15.0	<0.001
Male (%)	53%	71%	0.23	52%	67%	0.25
APACHE II score	9.0 (7.0–11.5)	12.5 (10.8–19.0)	0.002	9.0 (6.0–11.0)	11.0 (9.0–16.0)	0.002
Chronic disease or immunosuppression (%)	11%	36%	0.047	10%	26%	0.16
Hospital–ICU delay (days)	6 (3–8)	7 (2–8)	0.70	7 (2–9)	5 (2–7)	0.12
ICU stay (days)	7 (5–16)	19 (12–30)	0.008	6 (4–7)	17 (10–38)	<0.001
Total hospital stay (days)	31 (21–60)	28 (19–41)	0.31	23 (19–42)	38 (22–77)	0.04
Admission PaO_2/FIO_2 ratio (mmHg)	142 (106–198)	133 (76–171)	0.18	142 (107–199)	140 (79–175)	0.24
Worst PaO_2/FIO_2 ratio (mmHg)	93 (75–129)	67 (58–73)	<0.001	105 (83–140)	69 (59–87)	<0.001
Required mechanical ventilation (%)	31%	93%	<0.001	0	100%	NA
Duration of mechanical ventilation (days)	0 (0–7)	14 (7–33)	<0.001	NA	11 (7–27)	NA
Tidal volume (mL/kg)	7.0 (6.3–8.7)	7.0 (5.7–9.0)	0.84	NA	7.0 (6.2–8.6)	NA
PEEP (cmH_2O)	6.9 (5–9.3)	6.8 (6.8–9.4)	0.77	NA	7.1 (5.1–9.8)	NA
Barotrauma or air leak (%)	16%	29%	0.43	0	41%	<0.001
Average daily fluid balance (mL)	89 (–139 to 285)	331 (177 to 611)	0.001	–14 (–364 to 161)	301 (169 to 429)	<0.001
Average daily steroid dose (mg)	178 (123–309)	158 (94–245)	0.37	247 (154–450)	158 (95–188)	0.02
Admission LDH (U/L)	378 (320–520)	484 (417–791)	0.06	348 (297–436)	484 (418–804)	<0.001
Admission lymphocyte count ($\times 10^6$/mL)	0.41 (0.36–0.57)	0.34 (0.24–0.69)	0.42	0.40 (0.29–0.48)	0.58 (0.32–0.67)	0.38
Peak ALT (U/L)	112 (58–239)	176 (96–442)	0.05	98 (52–243)	147 (95–302)	0.05
Peak INR	1.25 (1.14–1.45)	1.46 (1.28–2.42)	0.02	1.19 (1.12–1.34)	1.42 (1.25–2.50)	0.001
MOD score at ICU admission	3 (2–3)	3 (2–5)	0.13	3.0 (2.0–3.0)	3.0 (3.0–5.0)	0.01
Maximum MOD score	4 (3–6)	10 (6–12)	<0.001	4.0 (3.0–5.0)	9.0 (6.0–12.0)	<0.001
No. of episodes of nosocomial sepsis	0 (0–0)	1 (0–2)	0.008	0 (0–0)	1 (0–1)	<0.001

APACHE = Acute Physiology and Chronic Health Evaluation. PEEP = positive end-expiratory pressure. NA = not applicable.
LDH = serum lactate dehydrogenase level. ALT = serum alanine aminotransferase level. INR = international normalised ratio. MOD = multiple organ dysfunction. ◆

Figure 2. Pulmonary function tests (95% CI) for survivors of SARS-related acute respiratory distress syndrome ($n = 36$)



FEV_1 = forced expiratory volume in 1 s. DLCO = diffusion capacity adjusted for haemoglobin concentration. ◆

(Figure 1). One patient who agreed to pulmonary function testing declined to complete the quality of life assessment questionnaire. Characteristics of the 59 patients are shown in Table 1. Mortality in the ICU, in hospital and at 12 months was 24% (14/59). Twenty-seven patients (46%) received invasive mechanical ventilation. Intubation and mechanical ventilation was withheld in one patient with the consensus agreement of the ICU and medical teams, the patient and her relatives. Eleven patients (19%) had evidence of barotrauma, with radiological evidence of pneumothorax, pneumomediastinum or subcutaneous emphysema.

The factors associated with long-term mortality and mechanical ventilation are shown in Table 2. Results of pulmonary function tests are shown in Figure 2. Mean DLCO at 12 months was significantly higher for patients who had not required mechanical ventilation than for those who required mechanical ventilation (% predicted DLCO ±SD, 86% ±21% versus 70% ±18%; $P = 0.04$). Otherwise, there was no significant difference in various lung function parameters between those who were mechanically ventilated and those who were not. The changes in 6MWD are shown in Table 3. The 6MWD increased between 3-month and 6-month follow-up irrespective of whether patients had received mechanical ventilation while in the ICU. There was no significant improvement after 6 months.

SF-36 domain scores depend on age. Previously reported normal values in the Hong Kong population have been stratified into the age groups 18–40 years, 41–64 years, and 65 years and older.[17] We stratified and analysed the SF-36 domain scores of our patients accordingly, to allow comparison with the normal population.

The SF-36 domain scores for patients aged 18–40 years improved to the near-normal range from 6-month follow-up onwards, irrespective of whether they had received invasive mechanical ventilation (Figure 3). Patients aged 41–64 years had low scores at multiple domains at 3-, 6- and 12-month follow-up (Figure 3). There was no clear trend of improvement. Those who had been ventilated had impairment in more domains than those who had not.

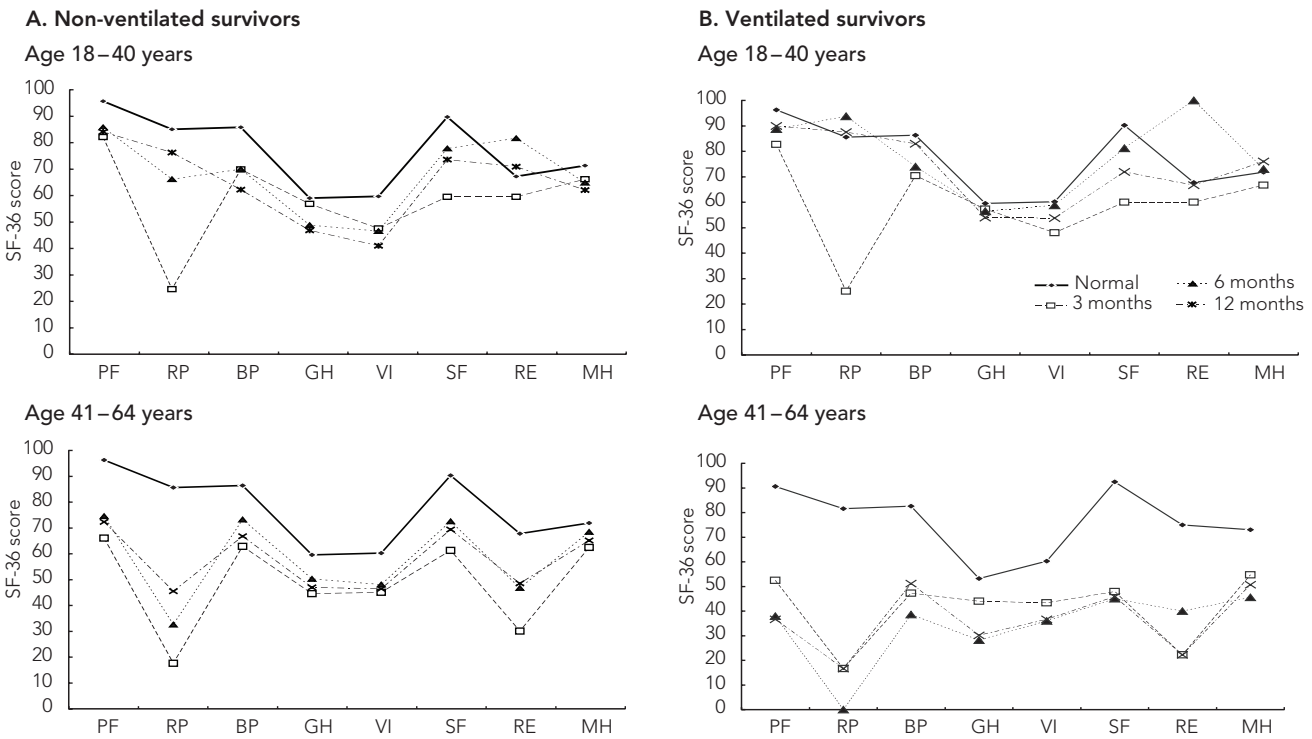
At 12-month follow-up, FEV_1, forced vital capacity and 6MWD correlated significantly with multiple SF-36 domain scores reflecting both physical function and emotion (Table 4). DLCO correlated significantly only with domain scores reflecting physical function.

Table 3. Six-minute walk distances at 3, 6 and 12 months for SARS-related acute respiratory distress syndrome

	Mean 6-minute walk distance (m) ±SD (mean % of predicted normal)				
Ventilation status	3 months	P*	6 months	$P^{\dagger}$	12 months
Non-ventilated	475 ±94 (72%)	0.002	524 ±107 (79%)	0.89	523 ±95 (79%)
Ventilated	400 ±90 (67%)	0.02	451 ±91 (72%)	0.21	461 ±140 (74%)

* P for comparison between 6 months and 3 months. † P for comparison between 6 months and 12 months. ◆

Figure 3. Health-related quality life by SF-36 questionnaire in survivors of SARS-related acute respiratory distress syndrome



PF = physical functioning. RP = role limitation due to physical problems. BP = bodily pain. GH = general health. VI = vitality. SF = social functioning. RE = Role limitation due to emotional problems. MH = mental health. ◆

Discussion

This study demonstrates that mortality among patients with SARS-related ARDS who underwent mechanical ventilation was similar to mortality reported for ARDS from other causes. A substantial proportion of patients with ARDS caused by SARS did not require mechanical ventilation.

Although the consensus definition of ARDS does not require that the patient undergo mechanical ventilation, almost all recent studies report only the outcome of mechanically ventilated patients. The mortality rate for mechanically ventilated patients with SARS-related ARDS in our series is within the range previously reported for heterogeneous groups of patients with ARDS (47%–69%).[18-25] However, mortality from ARDS is usually associated with severity of multi-organ failure[23] and, given the low multiple organ dysfunction (MOD) score in our patients, the mortality is unexpectedly high, although not dissimilar from mortality in a previous report of ARDS caused by SARS.[7]

It is noteworthy that 31 patients did not require mechanical ventilation despite developing ARDS. Not only did these non-ventilated patients meet the consensus criteria for ARDS, admission PaO_2/FIO_2 ratios were similar to those reported in previous studies of patients ventilated for ARDS.[18,25-27] Furthermore, the condition of many of these patients deteriorated, with median worst PaO_2/FIO_2 ratio of 105 mmHg, and they would normally have been ventilated were it not for our policy of avoiding mechanical ventilation if possible. In addition, changes on computed tomography seen in a sample of these patients were those of chronic ARDS.[28] Despite this, all patients in this group survived, suggesting that it may not be necessary to ventilate all patients with ARDS. However, a number of caveats must be borne in mind. When patients eventually require endotracheal intubation, the procedure needs to be done skilfully and rapidly, as patient respiratory reserve is likely to be exhausted. This can only be achieved in the ICU, with regular on-site staff experienced in airway management. Furthermore, many of these patients were young and healthy before the onset of SARS and had isolated respiratory failure; they may thus represent a particular subgroup of patients with ARDS.

Interestingly, patients who did not receive mechanical ventilation had a lower average daily fluid balance. In our ICU during the SARS outbreak, there was a general policy of using vasopressors to maintain adequate blood pressure with minimisation of the use of fluid infusion. The aim was to

Table 4. Correlation between pulmonary function and health-related quality of life

SF-36 domain	Pearson's correlation coefficient (*r*)						
	FEV_1	FVC	TLC	RV	DLCO	KCO	6MWD
Physical functioning	0.46*	0.59*	0.36†	–0.08	0.53*	0.12	0.75*
Role limitation (physical)‡	0.43†	0.53*	0.25	–0.21	0.37†	–0.19	0.56*
Bodily pain	0.19	0.38†	0.27	0.04	0.26	0.01	0.28
General health	0.40†	0.58*	0.30	–0.15	0.42†	–0.12	0.71*
Vitality	0.27	0.38	0.14	–0.18	0.25	–0.23	0.52*
Social functioning	0.41†	0.46*	0.21	–0.18	0.33	–0.04	0.52*
Role limitation (emotional)§	0.45*	0.51*	0.25	–0.16	0.33	–0.17	0.52*
Mental health	0.23	0.32	0.17	–0.17	0.18	–0.02	0.26

SF-36 = Medical Outcomes Study 36-item Short-Form General Health Survey. FEV_1 = forced expiratory volume in 1 second. FVC = forced vital capacity. TLC = total lung capacity. RV = residual lung volume. DLCO = diffusion capacity adjusted for haemoglobin concentration. KCO = carbon monoxide transfer coefficient. 6MWD = 6-minute walk distance.

* Significant at $P < 0.01$. † Significant at $P < 0.05$.
‡ Role limitation due to physical problems.
§ Role limitation due to emotional problems. ◆

maintain zero daily fluid balance. This was done because patients presented with isolated respiratory failure leading to profound hypoxaemia. Although it is possible that the relationship between fluid balance and need for mechanical ventilation is due to confounding factors, a recent observational study found that mean fluid balance was independently associated with mortality in patients with acute lung injury and ARDS.[29] An earlier study also showed that patients with pulmonary oedema with less positive fluid balance had better survival, and shorter duration of mechanical ventilation and ICU stay.[30]

The stratification of patients according to age to allow comparison with normal values of HRQoL revealed a major difference in recovery between the younger and older age groups. Patients in the younger group had good outcomes, with substantial recovery of HRQoL by 6 months. However, as well as being younger, these patients had lower APACHE II scores, lower maximum MOD scores and were less likely to undergo mechanical ventilation. They also had shorter ICU and hospital length of stay. The less severe disease in the younger group is consistent with several reports describing the association between older age and greater severity of SARS.[2,31,32] Patients in the older group had poorer outcomes, with slow, inconsistent recovery and poor health status even at 1-year follow-up. Poor medium- to long-term HRQoL following ARDS has been reported by a number of investigators.[27,33-36]

Granja et al demonstrated a trend in a small patient cohort for survivors with normal lung function after ARDS to be younger.[36] However, Heyland et al found that age was not an independent predictor of HRQoL,[27] and Herridge et al showed that age was not independently associated with 6-minute walk distance,[35] suggesting that the age-related outcome seen in our patients might be due to the confounding effect of less severe disease. Unfortunately, the cohort size was too small to carry out a valid multiple regression analysis, and therefore we are unable to confirm or refute this possibility.

Our finding of a correlation between pulmonary function test results at 12 months and the physical domain of HRQoL confirms the findings of previous investigators.[27,33,34]

Our study had a number of limitations. It was a single-centre, observational study. We were unable to achieve 100% follow-up. The sample size did not allow us to perform a valid multivariate analysis to look for independent predictors of requirement for mechanical ventilation or outcome. In common with most other studies, we were unable to measure premorbid HRQoL as it was difficult to obtain this information for emergency ICU admissions, and we therefore cannot exclude the possibility that HRQoL was impaired before admission. We are aware that cardiopulmonary exercise testing is a more sensitive method of assessing the exercise capacity in patients recovering from ARDS, but this was not performed because of funding constraints and the requirement for considerable cooperation from enthusiastic participants. Because of the absence of a reference equation for the 6-minute walk test in a Chinese population, we used the reference equation of Enright and Sherrill.[37]

Conclusion

The mortality in patients with SARS-related ARDS who undergo mechanical ventilation is similar to the mortality in patients with ARDS from other causes, but is surprisingly high given the relative absence of other significant organ failure. A substantial number of patients with SARS-related ARDS survived without receiving mechanical ventilation, suggesting that mechanical ventilation may not be necessary in all patients with ARDS. Patients had good recovery of pulmonary function and HRQoL.

Acknowledgements

We acknowledge funding support from the Research Fund for the Control of Infectious Diseases (Health, Welfare and Food Bureau, HKSAR). The study was performed in the intensive care unit of the Department of Anaesthesia and Intensive Care and the pulmonary function laboratory of the Department of Medicine, Prince of Wales Hospital, Hong Kong.

Author details

Thomas S T Li, Associate Consultant[1]
Charles D Gomersall, Associate Professor[1]
Gavin M Joynt, Professor[1]
Doris P S Chan, Research Assistant[1]
Patricia Leung, Research Assistant[1]
David S C Hui, Associate Professor[2]

1 Department of Anaesthesia and Intensive Care, Prince of Wales Hospital, Chinese University of Hong Kong, Shatin, Hong Kong.
2 Department of Medicine and Therapeutics, Prince of Wales Hospital, Chinese University of Hong Kong, Shatin, Hong Kong.

Correspondence: list@cuhk.edu.hk

References

1 World Health Organization. Summary of probable SARS cases with onset of illness from 1 November 2002 to 31 July 2003. Geneva: WHO, 2005. Available at: http://www.who.int/csr/sars/country/table2004_04_21/en/index.html (accessed Nov 2006).
2 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.
3 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: 715-23.
4 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: 686-9.
5 Gomersall CD, Joynt GM, Lam P, et al. Short term of outcome of critically ill patients with severe acute respiratory syndrome. *Intensive Care Med* 2004; 30: 381-7.
6 Fowler RA, Lapinsky SE, Hallett D, et al for the Toronto SARS Critical Care Group. Critically ill patients with severe acute respiratory syndrome. *JAMA* 2003; 290: 367-73.
7 Lew TWK, Kwek TK, Tai D, et al. Acute respiratory distress syndrome in critically ill patients with severe acute respiratory syndrome. *JAMA* 2003; 290: 374-80.
8 Hui DS, Joynt GM, Wong KT, et al. The impact of Severe Acute Respiratory Syndrome (SARS) on pulmonary function; functional capacity and quality of life in a cohort of survivors. *Thorax* 2005; 60: 401-9.
9 Hui DS, Wong KT, Ko FW, et al. The 1-year impact of severe acute respiratory syndrome on pulmonary function, exercise capacity, and quality of life in a cohort of survivors. *Chest* 2005; 128: 2247-61.
10 Bernard GR; Artigas A, Brigham KL, et al. The American-European Consensus Conference on ARDS. Definitions, mechanisms, relevant outcomes, and clinical trial coordination. *Am J Respir Crit Care Med* 1994; 149: 818-24.
11 Centers for Disease Control and Prevention. Updated interim US case definition for severe acute respiratory syndrome (SARS) — update, April 30 2003. Atlanta, Ga: CDC. Available at: http://www.cdc.gov/ncidod/sars/casedefinition.htm (accessed Nov 2006).
12 American Thoracic Society. Standardization of spirometry, 1994 update. *Am J Respir Crit Care Med* 1995; 152: 1107-36.
13 ATS Committee on Proficiency Standards for Clinical Pulmonary Function Laboratories, American Thoracic Society. Statement: guidelines for the six-minute walk test. *Am J Respir Crit Care Med* 2002; 166: 111-7.
14 Weisman IM, Zeballos RJ. Clinical exercise testing. *Clin Chest Med* 2001; 22: 679-701.
15 McHorney CA, Ware JE Jr, Lu JF, Sherbourne CD. The MOS 36-item Short-Form Health Survey (SF-36): III. Tests of data quality, scaling assumptions, and reliability across diverse patient groups. *Med Care* 1994; 32: 40-66.
16 Lam CL, Gandek B, Ren XS, Chan MS. Tests of scaling assumptions and construct validity of the Chinese (HK) version of the SF-36 Health Survey. *J Clin Epidemiol* 1998; 51: 1139-47.
17 Lam CL, Lauder IJ, Lam TP, Gandek B. Population based norming of the Chinese (HK) version of the SF-36 health survey. *Hong Kong Practitioner* 1999; 21: 460-70.
18 Brochard L, Roudot-Thoraval F, Roupie E, et al. Tidal volume reduction for prevention of ventilator-induced lung injury in acute respiratory distress syndrome. *Am J Respir Crit Care Med* 1998; 158: 1831-8.
19 Richard C, Warszawski J, Anguel N, et al. Early use of the pulmonary artery catheter and outcomes in patients with shock and acute respiratory distress syndrome. *JAMA* 2003; 290: 2713-20.
20 Hughes M, MacKirdy FN, Ross J, et al, on behalf of the Scottish Intensive Care Society. Acute respiratory distress syndrome: an audit of incidence and outcome in Scottish intensive care units. *Anaesthesia* 2003; 58: 838-5.
21 Lu Y, Song Z, Zhou X, et al, Shanghai ARDS Study Group. A 12-month clinical survey of incidence and outcome of acute respiratory distress syndrome in Shanghai intensive care units. *Intensive Care Med* 2004; 30: 2197-203.
22 Villar J, Pérez-Méndez L, Kacmarek RM. Current definitions of acute lung injury and the acute respiratory distress syndrome do not reflect their true severity and outcome. *Intensive Care Med* 1999; 25: 930-5.
23 Estenssoro E, Dubin A, Laffaire E, et al. Incidence, clinical course, and outcome in 217 patients with acute respiratory distress syndrome. *Crit Care Med* 2002; 30: 2450-6.
24 Gupta D, Ramanathan RP, Aggarwal AN, Jindal SK. Assessment of factors predicting outcome of acute respiratory distress syndrome in North India. *Respirology* 2001; 6: 125-30.
25 Roupie E, Lepage E, Wysocki M, et al. Prevalence, etiologies and outcome of the acute respiratory distress syndrome among hypoxaemic ventilated patients. *Intensive Care Med* 1999; 25: 920-9.
26 National Heart Lung Blood Institute ARDS Clinical Trials Network. Higher versus lower positive end-expiratory pressures in patients with the acute respiratory distress syndrome. *N Engl J Med* 2004; 351: 327-36.
27 Heyland DK, Groll D, Caeser M. Survivors of acute respiratory distress syndrome: relationship between pulmonary dysfunction and long-term health-related quality of life. *Crit Care Med* 2005; 33: 1549-56.
28 Joynt GM, Antonio GE, Lam P, et al. Late-stage adult respiratory distress syndrome caused by severe acute respiratory syndrome: abnormal findings at thin-section CT. *Radiology* 2004; 230: 339-46.
29 Sakr Y, Vincent JL, Reinhart K, et al. Sepsis Occurence in Acutely Ill Patients Investigators. High tidal volume and positive fluid balance are associated with worse outcome in acute lung injury. *Chest* 2005; 128: 3098-108.
30 Schuller D, Mitchell JP, Calandrino FS, Schuster DP: Fluid balance during pulmonary edema. Is fluid gain a marker or a cause of poor outcome? *Chest* 1991; 100: 1068-75.
31 Hon KLE, Leung CW, Cheng WT, et al. Clinical presentations and outcome of severe acute respiratory syndrome in children. *Lancet* 2003; 361: 1701-3.
32 Chiu WK, Cheung PC, Ng KL, et al. Severe acute respiratory syndrome in children: experience in a regional hospital in Hong Kong. *Pediatr Crit Care Med* 2003; 4: 279-83.
33 Schelling G, Stoll C, Vogelmeier C, et al. Pulmonary function and health-related quality of life in a sample of long-term survivors of the acute respiratory distress syndrome. *Intensive Care Med* 2000; 26: 1304-11.
34 Orme J, Romney JS, Hopkins RO, et al. Pulmonary function and health-related quality of life in survivors of acute respiratory distress syndrome. *Am J Respir Crit Care Med* 2003; 167: 690-4.
35 Herridge MS, Cheung AM, Tansey CM, et al. One-year outcomes in survivors of the acute respiratory distress syndrome. *N Engl J Med* 2003; 348: 683-93.
36 Granja C, Morujao E, Costa-Pereira A. Quality of life in acute respiratory distress syndrome survivors may be no worse than in other ICU survivors. *Intensive Care Med* 2003; 29: 1744-50.
37 Enright PL, Sherrill DL. Reference equations for the six-minute walk in healthy adults. *Am J Respir Crit Care Med* 1998; 158: 1384-7. ❑