Impact of severe acute respiratory syndrome (SARS) on pulmonary function, functional capacity and quality of life in a cohort of survivors

D S Hui, G M Joynt, K T Wong, C D Gomersall, T S Li, G Antonio, F W Ko, M C Chan, D P Chan, M W Tong, T H Rainer, A T Ahuja, C S Cockram, J Y Sung

Objective: To examine the impact of severe acute respiratory syndrome (SARS) on pulmonary function, exercise capacity, and health-related quality of life (HRQoL) among survivors.

Methods: 110 survivors with confirmed SARS were evaluated at the Prince of Wales Hospital, HK at the end of 3 and 6 months after symptom onset. The assessment included lung volumes (TLC, VC, RV, FRC), spirometry (FVC, FEV1), carbon monoxide transfer factor (TLco adjusted for haemoglobin), inspiratory and expiratory respiratory muscle strength (Pimax and Pemax), 6 minute walk distance (6MWD), chest radiographs, and HRQoL by SF-36 questionnaire.

Results: There were 44 men and 66 women with a mean (SD) age of 35.6 (9.8) years and body mass index of 23.1 (4.8) kg/m². Seventy (64%) were healthcare workers. At 6 months 33 subjects (30%) had abnormal chest radiographs; four (3.6%), eight (7.4%), and 17 (15.5%) patients had FVC, TLC, and TLco below 80% of predicted values; and 15 (13.9%) and 24 (22.2%) had Pimax and Pemax values below 80 cm H2O, respectively. The 6MWD increased from a mean (SD) of 464 (83) m at 3 months to 502 (95) m (95% CI 22 to 54 m, p<0.001), but the results were lower than normal controls in the same age groups. There was impairment of HRQoL at 6 months. Patients who required ICU admission (n = 31) had significantly lower FVC, TLC, and TLco than those who did not.

Conclusion: The exercise capacity and health status of SARS survivors was considerably lower than that of a normal population at 6 months. Significant impairment in surface area for gas exchange was noted in 15.5% of survivors. The functional disability appears out of proportion to the degree of lung function impairment and may be related to additional factors such as muscle deconditioning and steroid myopathy.
surviving the major outbreak in 2003. The patients came from our previously reported cohort1 recruited over a period of 2 weeks from 11 March to 25 March 2003. The diagnosis of SARS was based on the CDC criteria at the time,22 and all patients had subsequent laboratory confirmation of SARS.23 The treatment and outcome of these patients during hospitalisation has been reported in detail elsewhere.22 This prospective outcome study of SARS survivors was approved by the ethics committee of the Chinese University of Hong Kong.

Assessment

Following discharge from hospital, patients were evaluated in the lung function laboratory at the end of 3 and 6 months after disease onset. During the visit, subjects were interviewed and underwent a physical examination, pulmonary function testing, respiratory muscle strength measurement, postero-anterior chest radiography, resting oximetry, and a standardised 6 minute walk test (6MWT).24,25 In addition, they completed the Medical Outcomes Study 36-item Short Form General Health Survey (SF-36) to measure HRQoL.26

6 minute walk test (6MWT)

This provides a standardised, objective, integrated assessment of cardiopulmonary and musculoskeletal function that is relevant to daily activities.24,25 The self-paced 6MWT assesses the sub-maximal level of functional capacity and has been applied in a long term follow up study of survivors of ARDS.26 The 6 minute walk distances (6MWD) were compared with the normative reference data collected from a population survey of 538 normal healthy subjects in 2004 by the Coordinating Committee in Physiotherapy, HK Hospital Authority, on two separate days. The mean (SD) 6MWD of the controls (n = 538) on days 1 and 2 of assessment were 598.4 (98.7) m and 609.2 (100.4) m, respectively, with an intra-class correlation coefficient of 0.87 (95% CI 0.84 to 0.89), standard error of measurement 35.3 m, minimum detectable change 97.8 m, and limits of agreement 10.8 (95% CI −87.1 to 108.6) m. The 6MWD data stratified into different age groups are available for comparison with the SARS patients, although we have no access to individual data of this population survey.

SF-36

This includes eight multiple item domains that assess physical functioning (PF), social functioning (SF), role limitation due to physical problems (RP), role limitation due to emotional problems (RE), mental health (MH), bodily pain (BP), vitality (VT), and general health (GH).26 Scores for each aspect can range from 0 (worst) to 100 (best) with higher scores indicating better HRQoL. The validated Chinese (HK) version of the SF-3627 was used for this study and the results were compared with the HK normative data collected from a random telephone survey of 2410 Chinese adults aged 18 years or above.22 Based on this survey, SF-36 domain scores stratified into two age groups (18–40 years and 41–64 years) are available29 for comparison with those of our SARS survivors.

Lung function testing

Lung volumes (total lung capacity (TLC), vital capacity (VC), residual volume (RV), functional residual capacity (FRC) using the nitrogen washout method), spirometric parameters (pre and post bronchodilator forced vital capacity (FVC), forced expiratory volume in 1 second (FEV1), FEV1/FVC ratio), and surface area for gas exchange (carbon monoxide transfer factor adjusted for haemoglobin (TLCO) and carbon monoxide transfer coefficient (KCO)) were measured using the SensorMedic Vmax System, USA. TLCO was determined by the single breath carbon monoxide technique using an infrared analyser. Spirometric tests (FEV1 and FVC pre and post bronchodilator) were performed according to the standards of the American Thoracic Society.29 After the pre-bronchodilator measurement, salbutamol 400 μg was given via a metered dose inhaler with a spacer. Spirometric testing was repeated 10 minutes later. An increase in FEV1 of more than 12% and more than 0.2 l was regarded as a positive bronchodilator response.30 The results were compared with the normative data31 which have been widely adopted as the reference data in HK.

Measurement of the maximum static inspiratory pressure that a subject can generate at the mouth (Pimax) or the maximum static expiratory pressure (Pemax) is a simple way to gauge inspiratory and expiratory muscle strength.32,33 Since respiratory muscle weakness may lead to a restrictive pattern on lung function testing, Pimax and Pemax were assessed with a mouth pressure meter via a flanged mouthpiece34 after full lung function testing. In a study of 24 normal subjects (23 Chinese and one Indian of mean age 29.2 years) in Singapore, the mean (SD) maximal static inspiratory effort from residual volume (Pdi Pimax) for the group was 83.5 (35.5) cm H2O.35 A Pimax of −80 cm H2O or a Pemax of +80 cm H2O generally excludes clinically significant weakness of the inspiratory or expiratory muscles.35

To protect lung function laboratory staff, extra exhaust fans were installed in the lung function room and staff wore personal protective equipment including N95 respirators, protective goggles, gloves, and gowns. In addition, a disposable viral and bacterial filter (Spiroguard 2800/01, USA) was used for each patient during each visit.

Radiographic assessment

Frontal chest radiographs were performed at 3 and 6 months using standardised techniques with computed radiography equipment as reported during the major hospital outbreak.3 The images were assessed using a PACs system (Siemens Magicview Version VA22E, Germany) viewer (Siemens 2K monitor). Each lung was divided into three zones (upper, middle and lower) on the frontal radiograph. The observers assessed the presence, appearances (airspace opacities or reticular opacities), distribution, and size of lung parenchymal abnormalities on each chest radiograph of all patients. The size of the lesion was assessed by visually estimating the percentage area occupied in each zone on each side. The overall percentage of involvement was obtained by averaging the percentage involvement of the six lung zones. The frontal chest radiograph closest to the date of the lung function test was assessed by two radiologists, both blinded to the clinical information. Agreement was reached by consensus. The assessment method was as described in our previous study.27

Analysis of data

Statistical analysis was performed using Statistical Package for Social Science (SPSS) Version 11.0. Cumulative steroid dosage during inpatient treatment and outpatient follow up was converted into hydrocortisone (mg) to facilitate analysis of the study. Continuous variables were compared using an independent sample t test and the Mann-Whitney U test was used for non-parametric data. Categorical variables were compared using the χ2 test. All statistical tests were two tailed. Statistical significance was taken as p<0.05. Univariate analyses were performed to evaluate the potential determinants of exercise capacity expressed as the 6MWD. Variables significant in the univariate analyses (p<0.01) were included in the multivariate analysis. Age and sex were included in the final multivariable models because they are independent determinants of the 6MWD.38
RESULTS

Of the first 138 patients infected with SARS in March 2003, 15 (10.9%) died. Among the 123 survivors, 13 (10.6%) did not attend for follow up (three returned overseas and 10 refused to participate in the study). A total of 110 were included in the analysis. Among the 110 patients, 31 (28.2%; 17 men and 14 women) had required admission to the ICU with a mean (SD) age was 35.6 (9.8) years and the body mass index (BMI) was 23.1 (4.8) kg/m² during the visit at 3 months from illness onset. The mean (SD) length of stay (LOS) in hospital for the group was 22.0 (13.9) days. There were only three smokers (2.7%) among the whole group.

Seventeen patients had medical co-morbidities which included chronic obstructive pulmonary disease (COPD; n = 1 (0.9%)), ischaemic heart disease (IHD; n = 1 (0.9%)), ischaemic stroke (n = 1 (0.9%)), breast cancer stable on tamoxifen (n = 1 (0.9%)), diabetes mellitus (n = 3 (2.7%)), cirrhosis (n = 1 (0.9%)), hypertension (n = 4 (3.6%), and five asymptomatic hepatitis B carriers (4.5%).

Among the 110 patients, 31 (28.2%; 17 men and 14 women) had required admission to the ICU with a mean (SD) LOS of 13.5 (15.6) days (median 7, range 2–64); six (5.5%) required invasive mechanical ventilation. Based on our ICU admission criteria, all the 31 patients would have a PaO₂/FiO₂ ratio <300 mm Hg while the six patients who were intubated had a PaO₂/FiO₂ ratio <200 mm Hg. Among these 31 patients, six had medical co-morbidities (one IHD, one diabetes mellitus, two hypertension, and two asymptomatic hepatitis B carriers), but none had any history of smoking or pulmonary disease.

Lung function tests and respiratory muscle strength

An overview of the serial lung function test and respiratory muscle strength results for the group is shown in table 1. At 3 months 89 patients (80.9%) had an FEV₁/FVC ratio of >80% while one patient with COPD (0.9%) had an FEV₁/FVC ratio of <70%. Overall, the lung volume parameters and surface area for exchange were well preserved at 3 and 6 months. A significant proportion of patients appeared to have increased RV at 3 and 6 months (median (interquartile range, IQR) 108 (71–141)% and 115 (84–140)%), respectively. Although none complained of symptoms of asthma, seven (6.4%) had a significant bronchodilator response with increments of FEV₁ >200 ml after inhalation of salbutamol at 3 months. 22 (20.6%) and eight (7.5%) patients, respectively, had Pimax and Pemax values below 80 cm H₂O.

At 6 months 79 (71.8%) had an FEV₁/FVC ratio of >80% while the same patient with COPD had an FEV₁/FVC ratio of <70%. None had a significant bronchodilator response after inhalation of salbutamol. 15 (13.9%) and 24 (22.2%) subjects, respectively, had Pimax and Pemax values below 80 cm H₂O. There was a slight increase in KCO but no change in other lung function parameters at 6 months compared with 3 months (table 1).

The frequency of lung function parameters below 80% of predicted values in SARS survivors is shown in table 2. Seventeen patients (15.5%) had impaired TLC while up to 7.3% of patients had reduced lung volume measurements at 6 months.

6MWD

The 6MWD of the SARS survivors at 3 and 6 months, compared with normative data, is shown in table 3. The mean 6MWD increased significantly from 464 m at 3 months to 502 m at 6 months (95% CI of difference 22 to 54, p<0.01). When the subjects were stratified into different age groups and compared with the corresponding normative values, their exercise capacity was significantly lower than the normal subjects (table 3). There was no difference in oxygen saturation after exercise at 3 and 6 months (97.8 (2.6)% v 97.4 (8.8)%), p=0.61. Two patients and one patient, respectively, had SaO₂ <88% after 6MWT at 3 and 6 months.

Univariate analysis was performed to look for factors associated with 6MWD. At 3 months, age (ß coefficient −2.48 (SE 0.79), p=0.002), female sex (ß coefficient −43.33 (15.82), p=0.007), and hospital LOS (ß coefficient −1.72 (0.55), p=0.002) were significant negative predictors of 6MWD whereas total dose of steroid (ß coefficient 0.00 (0.00), p=0.86), ICU admission (ß coefficient −8.27 (17.81), p=0.64), baseline lactate dehydrogenase (LDH) (ß coefficient −0.02 (0.05), p=0.69), peak LDH (ß coefficient −0.01 (−0.02), p=0.848), BMI (ß coefficient −2.16 (1.66), p=0.20), and peak CRP (ß coefficient 0.25 (0.17), p=0.143) were not. Following multivariate analysis (adjusted R² = 0.17), the independent negative predictors

Table 1 Results of serial pulmonary function tests and respiratory muscle strength among SARS survivors (n = 110)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>3 months</th>
<th>6 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>FVC (% of predicted)</td>
<td>104.5 (95.0–114.0)</td>
<td>104.5 (95.0–113.0)</td>
</tr>
<tr>
<td>FEV₁ (% of predicted)</td>
<td>108.0 (99.0–118.8)</td>
<td>106.0 (97.8–116.0)</td>
</tr>
<tr>
<td>TLC (% of predicted)</td>
<td>104.0 (93.3–115.8)</td>
<td>108.0 (98.0–117.0)</td>
</tr>
<tr>
<td>VC (% of predicted)</td>
<td>105.0 (95.0–115.5)</td>
<td>105.5 (95.0–112.5)</td>
</tr>
<tr>
<td>RV (% of predicted)</td>
<td>108.0 (70.5–140.8)</td>
<td>115.0 (84.0–139.8)</td>
</tr>
<tr>
<td>TCO₂ (% of predicted)</td>
<td>98.0 (88.5–107.0)</td>
<td>95.5 (85.0–106.0)</td>
</tr>
<tr>
<td>KCO (% of predicted)</td>
<td>106.0 (98.0–115.5)</td>
<td>110.5 (100.0–119.0)*</td>
</tr>
<tr>
<td>Pimax (% of predicted)</td>
<td>104.0 (88.0–127.0)</td>
<td>101.0 (87.5–125.0)</td>
</tr>
<tr>
<td>Pemax (% of predicted)</td>
<td>7.40 (62.0–86.0)</td>
<td>7.70 (59.0–86.0)</td>
</tr>
</tbody>
</table>

TLC, total lung capacity; VC, vital capacity; FVC, forced vital capacity; FEV₁, forced expiratory volume in 1 second; RV, residual volume; TCO₂, carbon monoxide transfer factor adjusted for haemoglobin; KCO, transfer coefficient (transfer factor per alveolar volume); Pimax, Pemax, maximum static inspiratory and expiratory pressures.

Values are expressed as median (interquartile range). *p<0.05.

*Values not significantly different were noted between other lung function parameters at 3 and 6 months.

Table 2 Frequency of lung function parameters below normal range in SARS patients

<table>
<thead>
<tr>
<th>Parameter</th>
<th>3 months</th>
<th>6 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>FEV₁ &lt;60% predicted value</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>N &lt;70% predicted value</td>
<td>2 (1.8%)</td>
<td>1 (0.9%)</td>
</tr>
<tr>
<td>N &lt;80% predicted value</td>
<td>3 (2.7%)</td>
<td>1 (0.9%)</td>
</tr>
<tr>
<td>FVC &lt;60% predicted value</td>
<td>1 (0.9%)</td>
<td>1 (0.9%)</td>
</tr>
<tr>
<td>N &lt;70% predicted value</td>
<td>1 (0.9%)</td>
<td>1 (0.9%)</td>
</tr>
<tr>
<td>N &lt;80% predicted value</td>
<td>6 (5.5%)</td>
<td>6 (5.5%)</td>
</tr>
<tr>
<td>VC &lt;60% predicted value</td>
<td>2 (1.8%)</td>
<td>2 (1.8%)</td>
</tr>
<tr>
<td>N &lt;70% predicted value</td>
<td>3 (2.7%)</td>
<td>3 (2.7%)</td>
</tr>
<tr>
<td>N &lt;80% predicted value</td>
<td>6 (5.5%)</td>
<td>6 (5.5%)</td>
</tr>
<tr>
<td>TLC &lt;60% predicted value</td>
<td>2 (1.8%)</td>
<td>2 (1.8%)</td>
</tr>
<tr>
<td>N &lt;70% predicted value</td>
<td>7 (6.4%)</td>
<td>7 (6.4%)</td>
</tr>
<tr>
<td>N &lt;80% predicted value</td>
<td>14 (12.7%)</td>
<td>17 (15.5%)</td>
</tr>
<tr>
<td>TCO₂ &lt;60% predicted value</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>N &lt;70% predicted value</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>N &lt;80% predicted value</td>
<td>2 (1.8%)</td>
<td>2 (1.8%)</td>
</tr>
</tbody>
</table>

TLC, total lung capacity; VC, vital capacity; FVC, forced vital capacity; FEV₁, forced expiratory volume in 1 second; TCO₂, carbon monoxide transfer factor adjusted for haemoglobin; KCO, transfer coefficient (transfer factor per alveolar volume).
for 6MWD were female sex (β coefficient = −38.02 (15.18), p = 0.014) and hospital LOS (β coefficient = −1.28 (0.57), p = 0.028), with a trend for age being a negative predictor (β coefficient = −1.54 (0.82), p = 0.063). Based on this model, the mean (SE) difference in 6MWD between women and men after adjusting for hospital LOS was −34.0 (14.8) m (95% CI: −63.5 to −4.6), p = 0.024.

At 6 months, age (β coefficient = −3.31 (SE 0.88), p<0.001), female sex (β coefficient = −67.62 (17.41), p<0.001), and hospital LOS (β coefficient = −1.39 (0.65), p = 0.036) were significant negative predictors of 6MWD whereas total dose of steroid (β coefficient 0.00 (0.00), p = 0.66), ICU admission (β coefficient 28.17 (20.37), p = 0.17), baseline LDH (β coefficient 0.06 (0.06), p = 0.31), peak LDH (β coefficient 0.07 (0.13), p = 0.19), BMI1 (β coefficient = −2.59 (2.04), p = 0.21), and peak CRP (β coefficient 0.26 (0.21), p = 0.20) were not. Following multivariate analysis (adjusted R² = 0.20), the independent negative predictors for 6MWD were age (β coefficient = −2.53 (0.91), p = 0.006) and female sex (β coefficient = −60.11 (16.74), p<0.001) whereas hospital LOS was no longer a factor (β coefficient = −0.71 (0.63), p = 0.264). Based on this model, the adjusted mean (SE) difference in 6MWD between women and men was −55.3 (16.3) m, (95% CI: −87.6 to −30.8), p = 0.001.

### Chest radiographs and correlations with lung function and 6MWD

Thirty-eight patients (35.8%) had abnormal total chest radiographic scores at 3 months involving a mean (SD) of 3.9 (3.5%) (range 0.5–15) of the total lung fields. These included eight patients with abnormal scores in both airspace opacity and reticular shadows, 16 with an abnormal airspace score, and 14 with an abnormal reticular score. At 6 months 33 subjects (30%) still had abnormal chest radiographic scores involving 3.1 (3.3%) (range 0.8–15) of the lung fields. These included three patients with abnormalities in both

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### Table 3 Six minute walking distance (6MWD) among SARS survivors (n=110) at 3 and 6 months after the onset of illness compared with Hong Kong normative data

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Normal (Mean [SD])</th>
<th>3 months (Mean [SD])</th>
<th>6 months (Mean [SD])</th>
<th>p value†</th>
</tr>
</thead>
<tbody>
<tr>
<td>All survivors</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(n=110)*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age group (years)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>21–30 (n=37)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>Mean (SD)</td>
<td>651 (105.1)</td>
<td>487 (58.1)</td>
<td>0.01</td>
</tr>
<tr>
<td></td>
<td>Mean difference (95% CI)</td>
<td>−164 (−201 to −127)**</td>
<td>−102 (−155 to −49)**</td>
<td></td>
</tr>
<tr>
<td>Women</td>
<td>Mean (SD)</td>
<td>600 (84.1)</td>
<td>461 (75.9)</td>
<td>0.13</td>
</tr>
<tr>
<td></td>
<td>Mean difference (95% CI)</td>
<td>−139 (−180 to −98)**</td>
<td>−107 (−149 to −65)**</td>
<td></td>
</tr>
<tr>
<td>31–40 (n=40)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>Mean (SD)</td>
<td>645 (93.1)</td>
<td>513 (80.1)</td>
<td>0.06</td>
</tr>
<tr>
<td></td>
<td>Mean difference (95% CI)</td>
<td>−132 (−178 to −86)**</td>
<td>−94 (−141 to 46)**</td>
<td></td>
</tr>
<tr>
<td>Women</td>
<td>Mean (SD)</td>
<td>606 (86.1)</td>
<td>476 (71.1)</td>
<td>0.11</td>
</tr>
<tr>
<td></td>
<td>Mean difference (95% CI)</td>
<td>−130 (−169 to 91)**</td>
<td>−101 (−139 to −63)**</td>
<td></td>
</tr>
<tr>
<td>41–50 (n=21)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>Mean (SD)</td>
<td>623 (80.1)</td>
<td>477 (82.1)</td>
<td>0.09</td>
</tr>
<tr>
<td></td>
<td>Mean difference (95% CI)</td>
<td>−146 (−212 to −79)**</td>
<td>−80 (−151 to −9)**</td>
<td></td>
</tr>
<tr>
<td>Women</td>
<td>Mean (SD)</td>
<td>541 (67.1)</td>
<td>404 (83.1)</td>
<td>**</td>
</tr>
<tr>
<td></td>
<td>Mean difference (95% CI)</td>
<td>−137 (−177 to −97)**</td>
<td>−68 (−107 to −29)**</td>
<td></td>
</tr>
<tr>
<td>51–60 (n=11)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>Mean (SD)</td>
<td>588 (68.1)</td>
<td>331 (83.1)</td>
<td>0.18</td>
</tr>
<tr>
<td></td>
<td>Mean difference (95% CI)</td>
<td>−257 (−361 to −152)**</td>
<td>−183 (−288 to −78)**</td>
<td></td>
</tr>
<tr>
<td>Women</td>
<td>Mean (SD)</td>
<td>534 (89.1)</td>
<td>399 (92.1)</td>
<td>0.67</td>
</tr>
<tr>
<td></td>
<td>Mean difference (95% CI)</td>
<td>−135 (−203 to −67)**</td>
<td>−163 (−232 to −94)**</td>
<td></td>
</tr>
</tbody>
</table>

*Including one woman aged 61 years with 6MWD 492 m and 465 m at 3 and 6 months, respectively.
**p<0.01
†6 months v 3 months.

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### Table 4 Comparison of demographic characteristics, biochemical markers, and steroid dosage in SARS survivors who required ICU care versus those treated on medical wards

<table>
<thead>
<tr>
<th></th>
<th>ICU (n=31)</th>
<th>Non-ICU (n=79)</th>
<th>95% CI</th>
<th>p value†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>38.4 (9.8)</td>
<td>33.9 (9.4)</td>
<td>−8.6 to −0.5</td>
<td>0.03*</td>
</tr>
<tr>
<td>Male sex</td>
<td>17/31</td>
<td>26/79</td>
<td>1</td>
<td>0.05</td>
</tr>
<tr>
<td>BMI (kg/m²), 3 months</td>
<td>24.0 (3.8)</td>
<td>22.6 (5.1)</td>
<td>−3.4 to 0.6</td>
<td>0.17</td>
</tr>
<tr>
<td>BMI (kg/m²), 6 months</td>
<td>24.3 (3.8)</td>
<td>23.0 (4.7)</td>
<td>−3.1 to 0.7</td>
<td>0.20</td>
</tr>
<tr>
<td>Hospital LOS (days)</td>
<td>32.4 (19.8)</td>
<td>17.9 (7.7)</td>
<td>−29.8 to −7.3</td>
<td>&lt;0.01*</td>
</tr>
<tr>
<td>CRP baseline (mg/dl)</td>
<td>26.4 (28.1)</td>
<td>23.2 (32.1)</td>
<td>−17.1 to 10.8</td>
<td>0.65</td>
</tr>
<tr>
<td>CRP peak (mg/dl)</td>
<td>77.1 (61.6)</td>
<td>36.4 (39.2)</td>
<td>−65.6 to −15.8</td>
<td>&lt;0.01*</td>
</tr>
<tr>
<td>LDH baseline (U/l)</td>
<td>357.8 (201.3)</td>
<td>274.6 (155.9)</td>
<td>−167.6 to 1.4</td>
<td>0.05</td>
</tr>
<tr>
<td>LDH peak (U/l)</td>
<td>522.3 (157.0)</td>
<td>349.4 (165.5)</td>
<td>−244.7 to −101.1</td>
<td>&lt;0.01*</td>
</tr>
<tr>
<td>Cumulative steroid dosage (hydrocortisone, mg)</td>
<td>18881 (11425)</td>
<td>8217 (5874)</td>
<td>−15044 to −6284</td>
<td>&lt;0.01*</td>
</tr>
<tr>
<td>Radiographic total score (%), 6 months</td>
<td>1.9 (3.7)</td>
<td>0.6 (1.3)</td>
<td>−2.7 to 0.1</td>
<td>0.06</td>
</tr>
</tbody>
</table>

*Values are expressed as mean (SD).
BMI, body mass index; CRP, C-reactive protein; LOS, length of stay; LDH, lactate dehydrogenase; 95% CI, 95% confidence interval of the difference between groups.
*Statistically significant.
hydrocortisone dosage, graphic abnormalities (% of lung fields) and the cumulative significant positive correlation between the extent of radiometers, and 6MWD at 6 months were examined. There was a reality and cumulative steroid dosage, lung function para-
airspace and reticular shadows, 16 with abnormal airspace shadows, and 14 with abnormal reticular shadows.
Correlations between the extent of radiographic abnormality and cumulative steroid dosage, lung function parameters, and 6MWD at 6 months were examined. There was a significant positive correlation between the extent of radiographic abnormalities (% of lung fields) and the cumulative hydrocortisone dosage (r = 0.38, p < 0.01), and a significant negative correlation between the extent (%) of radiographic abnormalities and FVC (r = -0.23, p = 0.02), TLC (r = -0.22, p = 0.02), TLCO (r = -0.29, p < 0.01), and KCO (r = -0.22, p = 0.02) with a trend towards a negative correlation with VC (r = -0.17, p = 0.07). However, no significant correlations were noted between the extent of radiographic abnormalities and 6MWD (r = -0.14, p = 0.15), FEV1 (r = -0.12, p = 0.20), RV (r = -0.11, p = 0.25), Pimax (r = 0.10, p = 0.29), and

### Table 5
Comparison of lung function indices, respiratory muscle strength, and 6MWD in SARS survivors who had required ICU care (n = 31) versus those treated on the wards (n = 79)

<table>
<thead>
<tr>
<th>3 months</th>
<th>6 months</th>
<th>Mean (SE) difference 6–3 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>FVC (% of predicted)</td>
<td>94.3 (14.0) v 107.6 (12.1)</td>
<td>98.6 (15.8) v 106.1 (13.5)</td>
</tr>
<tr>
<td>95% CI</td>
<td>7.9 to 18.7</td>
<td>1.5 to 13.5</td>
</tr>
<tr>
<td>p value</td>
<td>&lt; 0.01*</td>
<td>p = 0.02*</td>
</tr>
<tr>
<td>FEV1 (% of predicted)</td>
<td>102.0 (13.1) v 111.1 (14.7)</td>
<td>103.8 (12.7) v 108.2 (15.4)</td>
</tr>
<tr>
<td>95% CI</td>
<td>3.0 to 15.1</td>
<td>-1.8 to 10.6</td>
</tr>
<tr>
<td>p value</td>
<td>&lt; 0.01*</td>
<td>p = 0.17</td>
</tr>
<tr>
<td>VC (% of predicted)</td>
<td>94.7 (15.1) v 107.9 (12.5)</td>
<td>98.4 (16.4) v 105.0 (17.9)</td>
</tr>
<tr>
<td>95% CI</td>
<td>7.4 to 18.9</td>
<td>-0.9 to 14.1</td>
</tr>
<tr>
<td>p value</td>
<td>&lt; 0.01*</td>
<td>p = 0.08</td>
</tr>
<tr>
<td>TLC (% of predicted)</td>
<td>94.6 (16.1) v 110.3 (16.4)</td>
<td>98.2 (19.3) v 110.1 (14.1)</td>
</tr>
<tr>
<td>95% CI</td>
<td>8.7 to 22.7</td>
<td>4.0 to 19.7</td>
</tr>
<tr>
<td>p value</td>
<td>&lt; 0.01*</td>
<td>p = 0.01*</td>
</tr>
<tr>
<td>RV (% of predicted)</td>
<td>96.7 (39.4) v 115.7 (49.7)</td>
<td>99.9 (51.6) v 118.6 (38.5)</td>
</tr>
<tr>
<td>95% CI</td>
<td>-1.2 to 39.2</td>
<td>-2.4 to 39.7</td>
</tr>
<tr>
<td>p value</td>
<td>&lt; 0.06</td>
<td>p = 0.08</td>
</tr>
<tr>
<td>TLCO (% of predicted)</td>
<td>84.3 (17.9) v 101.4 (13.4)</td>
<td>87.7 (21.0) v 98.3 (16.6)</td>
</tr>
<tr>
<td>95% CI</td>
<td>10.9 to 23.4</td>
<td>3.0 to 18.2</td>
</tr>
<tr>
<td>p value</td>
<td>&lt; 0.01*</td>
<td>p = 0.01*</td>
</tr>
<tr>
<td>Pimax (% of predicted)</td>
<td>104.9 (13.5) v 107.4 (13.7)</td>
<td>109.4 (15.3) v 110.1 (13.6)</td>
</tr>
<tr>
<td>95% CI</td>
<td>-3.4 to 8.2</td>
<td>-5.3 to 6.7</td>
</tr>
<tr>
<td>p value</td>
<td>p = 0.41</td>
<td>p = 0.83</td>
</tr>
<tr>
<td>Pemax (% of predicted)</td>
<td>104.2 (29.1) v 108.5 (29.8)</td>
<td>105.6 (30.6) v 105.8 (25.8)</td>
</tr>
<tr>
<td>95% CI</td>
<td>-8.5 to 17.0</td>
<td>-11.4 to 11.8</td>
</tr>
<tr>
<td>p value</td>
<td>p = 0.51</td>
<td>p = 0.97</td>
</tr>
<tr>
<td>6MWD (m)</td>
<td>458.2 (86.8) v 466.4 (80.7)</td>
<td>519.7 (101.4) v 491.5 (92.9)</td>
</tr>
<tr>
<td>95% CI</td>
<td>-27.1 to 43.6</td>
<td>-11.4 to 11.8</td>
</tr>
<tr>
<td>p value</td>
<td>p = 0.64</td>
<td>p = 0.97</td>
</tr>
</tbody>
</table>

FVC, forced vital capacity; FEV1, forced expiratory volume in 1 second; VC, vital capacity; TLC, total lung capacity; RV, residual volume; TLCO, carbon monoxide transfer factor adjusted for haemoglobin; KCO, transfer coefficient (transfer factor per alveolar volume); Pimax, Pemax, maximum static inspiratory and expiratory pressures; 6MWD, 6 minute walk distance.

Values are shown as mean (SD) ICU v non-ICU with 95% CI of difference and p values.

*Statistically significant.

### Table 6
Correlations between pulmonary function and HRQoL at 6 months (n = 110)

<table>
<thead>
<tr>
<th>SF-36</th>
<th>FVC</th>
<th>FEV1</th>
<th>VC</th>
<th>TLC</th>
<th>TLCO</th>
</tr>
</thead>
<tbody>
<tr>
<td>PF</td>
<td>0.31*</td>
<td>0.40*</td>
<td>0.42*</td>
<td>0.19</td>
<td>0.30*</td>
</tr>
<tr>
<td>RP</td>
<td>0.31*</td>
<td>0.39*</td>
<td>0.35*</td>
<td>0.18</td>
<td>0.34*</td>
</tr>
<tr>
<td>BP</td>
<td>0.16</td>
<td>0.29*</td>
<td>0.27*</td>
<td>0.03</td>
<td>0.17</td>
</tr>
<tr>
<td>GH</td>
<td>0.29*</td>
<td>0.32</td>
<td>0.29*</td>
<td>0.11</td>
<td>0.32*</td>
</tr>
<tr>
<td>VT</td>
<td>0.16</td>
<td>0.23†</td>
<td>0.12</td>
<td>0.01</td>
<td>0.13</td>
</tr>
<tr>
<td>SF</td>
<td>0.24‡</td>
<td>0.39*</td>
<td>0.24‡</td>
<td>0.13</td>
<td>0.27‡</td>
</tr>
<tr>
<td>RE</td>
<td>0.15</td>
<td>0.22†</td>
<td>0.22‡</td>
<td>-0.01</td>
<td>0.22‡</td>
</tr>
<tr>
<td>MH</td>
<td>0.13</td>
<td>0.22†</td>
<td>0.09</td>
<td>0.02</td>
<td>0.26‡</td>
</tr>
</tbody>
</table>

PF, physical functioning; SF, social functioning; RP, role limitation due to physical problems; RE, role limitation due to emotional problems; MH, mental health; BP, bodily pain; VT, vitality; GH, general health.

Values shown are Pearson’s correlation coefficients (r).

*p < 0.01; † p < 0.05; ‡ p = 0.05
Pemax ($r = 0.12, p = 0.21$). These data are shown in a supplementary file available on the Thorax website at http://www.thoraxjnl.com/supplemental.

Comparison of patients requiring ICU support with those treated on the wards

Patients who had required ICU admission ($n = 31$, 17 men and 14 women) were older with a higher peak LDH, a longer hospital LOS, and received a significantly higher total steroid dosage than those who did not require ICU care (table 4). The lung function tests at 6 months showed significantly lower FVC, TLC, and TLCO in survivors who had required ICU support than those who were treated on medical wards, although no significant differences were noted in 6MWD and respiratory muscle strength between the two groups (table 5).

HRQoL among SARS survivors and its correlation with lung function parameters

Correlations between lung function parameters and SF-36 domains at 6 months are shown in figure 1. There were significant positive correlations between lung function parameters (FVC, VC, FEV₁, and TLCO) and several SF-36 domains (PF, RP, GH, and SF).

SF-36 domain scores at 3 and 6 months after illness onset of patients who did and did not require ICU support during the acute illness compared with normative data are shown in figure 1 (more data are available in supplemental tables 2a and b on the Thorax website http://www.thoraxjnl.com/supplemental). There was significant impairment of HRQoL among the SARS survivors at 6 months.

DISCUSSION

During the global outbreak of SARS in 2003 there was an enormous demand on ICU support for patients who developed severe respiratory failure. Although the use of...
pulmonary function. Their results suggest that the inability to exercise in recovered SARS patients is primarily due to extrapulmonary disease and is probably caused by myopathy or physical deconditioning. In addition, at 6 months there was significant impairment in HRQoL as measured by the Chinese version of the SF-36 questionnaire in most domains. There were significant and positive correlations between lung function parameters (VC, FVC, FEV₁, and TLC) and SF-36 domains such as PF, RP, GH, and SF. The results are not surprising as, in addition to the physical impairment, the long period of isolation and extreme uncertainty during the SARS illness had created tremendous psychological and mood disturbances. Other contributing factors included intense media attention, bereavement, phobia, and rejection of SARS survivors by some members of the general public (particularly in the initial phase of the outbreak), and fear of transmission of SARS to others. Other studies on ALI or ARDS survivors unrelated to SARS have reported impaired HRQoL at 1–5 years after recovery, whereas pulmonary function abnormalities, especially TLC, were correlated with SF-36 domains.

Herridge et al reported that 20% of their ARDS survivors had minor abnormalities on the chest radiograph at 1 year. Our study has shown that 33 subjects (30%) still had abnormal radiographic scores at 6 months. The positive correlation between the extent of residual radiographic abnormalities and the cumulative steroid dosage used for SARS was not surprising as the former was an indication on the treatment protocol for more systemic steroid during the course of the disease. The long period of bed rest could lead to muscle wasting and deconditioning, while the use of systemic corticosteroids to suppress immune mediated lung injury could contribute to myopathy. In 13 patients given high dose steroids for acute lung transplant rejection over 5 days, about 45% developed acute generalised muscle weakness which was thought to be the result of diffuse alveolar damage and/or bronchiolitis obliterans organising pneumonia in the acute phase, followed by post-inflammatory changes such as atelectasis, ongoing alveolitis, and parenchymal fibrosis later in the course of the disease. Several studies on ARDS survivors have shown that their pulmonary function generally returns to normal or near normal by 6–12 months, but TLC may remain abnormal in up to 80% of patients at 1 year after recovery. The self-paced 6MWT was performed to evaluate the global and integrated responses to exercise, and these would include cardiorespiratory systems, systemic and peripheral circulation, blood, neuromuscular units, and muscle metabolism. However, the 6MWT does not provide specific information on the function of individual organs and systems. The 6MWD was substantially reduced for all age groups at 3 and 6 months compared with controls. Two previous studies have shown that 6MWD was substantially lower among ARDS survivors than controls 1–2 years after mechanical ventilation. While the absence of systemic steroid treatment, the absence of illness acquired and rapid resolution of lung injury, and rapid resolution of lung injury during ICU stay were important factors associated with a longer 6MWD at 3, 6, and 12 months, respectively. In contrast, our analysis has shown that a longer hospital stay and female sex were independent factors associated with lower 6MWD at 3 months whereas age and female sex were negative predictors for 6MWD at 6 months. During hospitalisation for an average of 3 weeks, most of our patients were on bed rest because of respiratory failure. Given the relatively well preserved lung function in the majority of our SARS survivors, the poor performance in 6MWT in all age groups could be due to additional factors such as muscle wasting, steroid myopathy, and possibly cardiac diastolic dysfunction. In a study of the physical profile of SARS survivors (n = 171 and including the current cohort) at 3 months after illness onset, Lau et al noted that muscle strength and endurance were more impaired in proximal than in distal muscles. This was reflected by “average” handgrip measured by a hand-held dynamometer and “below average” to “poor” performance for curl-up and push-up testing compared with the normative Hong Kong data. Ong et al recently reported that 18 of 44 SARS survivors in Singapore had reduced exercise capacity at 3 months after hospital discharge that could not be accounted for by impairment of pulmonary function. Their results suggest that the inability to
took about 2 months to recover. Similarly, myopathy has been observed in patients with status asthmaticus treated with high dose corticosteroid. Corticosteroids are thought been observed in patients with status asthmaticus treated

Interestingly, seven patients (6.4%) without any past history of airway disease had a significant bronchodiolar response to salbutamol with increments of FEV1 of at least 12% and over 200 ml from baseline at 3 months, but the positive response was not longer present at 6 months. Although these patients had neither wheeze nor persistent cough at follow up, the bronchodilator response suggested that transient bronchial hyperresponsiveness might develop after SARS. Although we did not perform bronchial challenge in our patients, bronchial reactivity has been observed in some survivors of ARDS. Viral respiratory infections may cause increased airway responsiveness which can be observed in response to inhalation of histamine, methacholine, citric acid, or allergen.

There are several limitations to this study. Firstly, we assessed inspiratory and expiratory muscle strength with mouth pressure, but low Pemax values do not always indicate expiratory muscle weakness and might result from technical difficulties such as mouth leakage. However, it is a well-established simple test and none of our patients suffered from facial muscle or bulbar weakness. Cough gastric pressure provides a useful complementary test for the assessment of expiratory muscle strength but it involves insertion of a gastric balloon catheter and cough. At the time of planning this study there was still some concern among our lung function staff about potential infectivity via respiratory secretion of SARS survivors even though published data suggested this to be unlikely. It was therefore decided not to involve any invasive procedure. Lastly, although full lung function tests and 6 MWT were conducted in our patients, we did not perform cardiopulmonary exercise testing as most of our patients were complaining of generalised muscle weakness on follow up. In addition, cardiopulmonary exercise testing would be too labour intensive for the pulmonary exercise testing would be too labour intensive for the

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Further data are given in a supplementary file available on the Thorax website at http://www.thoraxjnl.com/supplemental.

Authors’ affiliations

D S Hui, C S Cockram, J Y J Sung, Center for Emerging Infectious Diseases, Chinese University of Hong Kong, Prince of Wales Hospital, Shatin, NT, Hong Kong

D S Hui, F W Ko, M C Chan, D P Chan, M W Tong, C S Cockram, J Y J Sung, Department of Medicine and Therapeutics, Chinese University of Hong Kong, Prince of Wales Hospital, Shatin, NT, Hong Kong

G M Joynt, C D Gomersall, T S Li, Department of Anaesthesia and Intensive Care, Chinese University of Hong Kong, Prince of Wales Hospital, Shatin, NT, Hong Kong

K T Wong, G Antonin, A T Ajub, Department of Diagnostic Radiology and Organ Imaging, Chinese University of Hong Kong, Prince of Wales Hospital, Shatin, NT, Hong Kong

T H Rainer, Accident and Emergency, Chinese University of Hong Kong, Prince of Wales Hospital, Shatin, NT, Hong Kong

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REFERENCES


Molecular techniques improve organism identification from pleural fluid in empyema


This study compares a broad range molecular technique with bacterial culture for the detection of organisms from pleural fluid in 32 children with empyema. The concordance of organisms identified and influence of prior antibiotic treatment was also investigated. There was a median duration of 8 (1–42) days antibiotic therapy before pleural fluid aspiration.

The molecular assay is an established and validated broad range 16S rDNA PCR technique. This is based on bacterial ribosomal (r)DNA with sequencing of the PCR product to reveal the source organism. Significant organisms were detected in 19% of cases by culture, whilst 69% of cases were PCR positive. Of the six culture positive samples, five were PCR positive and the organism identified was identical using both techniques. The organism not detected by PCR was grown only after enrichment culture and was present at levels below the PCR detection limit. The presence of organisms detected by PCR but not culture was probably because of prior antibiotic treatment. The PCR negative cases had also all received antibiotic therapy, causing organism death and DNA degradation.

Molecular (non-culture) techniques improve organism identification from pleural fluid in children with empyema, even after commencement of antibiotics, but should be considered complementary to culture. This assay produces a result in 48 hours, allowing appropriate alterations in management soon within the inpatient stay.