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Original Contributions

VIRAL LOAD AND OUTCOME IN SARS INFECTION: THE ROLE OF PERSONAL PROTECTIVE EQUIPMENT IN THE EMERGENCY DEPARTMENT

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□ **Abstract—This study was conducted to evaluate the effectiveness of personal protective equipment (PPE) against severe acute respiratory syndrome (SARS). Sixteen patients in a SARS cluster, including 4 health care workers (HCWs) and 12 non-HCWs were studied. We compared the initial viral load by nasopharyngeal swabs, clinical progression, and outcome of this cluster. The HCWs had a lower viral load. The non-HCWs had a higher mean C-reactive protein, lower oxygen saturation, and a higher incidence of intubation and death. Secondary household transmission developed in three of the non-HCWs' families. One month after discharge, non-HCWs had more signs of fibrosis on high resolution computed tomography (HRCT) scan and an impaired pulmonary function test. Although most of the PPE do not confer absolute protection against SARS, it seems that they may lower exposure to the virus, leading to a lower risk of secondary transmission, and be associated with relatively mild disease and a better early outcome. © 2006 Elsevier Inc.**

□ **Keywords—personal protective equipment; health care worker; pulmonary function test; severe acute respiratory syndrome, SARS**

INTRODUCTION

On March 12, 2003, the World Health Organization (WHO) issued a worldwide alert for cases of atypical pneumonia with severe respiratory illness that was rapidly spreading among hospital staffs (1). The transmission route of the emerging disease was believed to be by inhalation of contaminated aerosols or by oral route through contact with a contaminated environment (2,3). Both specific droplet and rigorous universal precautions were thus recommended for healthcare workers (HCWs) taking care of patients with severe acute respiratory syndrome (SARS) (4). Early in the SARS epidemic, investigators reported that surgical masks were equivalent to N-95 masks in protecting against SARS, but it was later shown that even N-95 masks were not completely protective (3,5,6). This confusion, plus the fact that many HCWs became infected despite wearing masks, contributed to the tremendous fear and chaos in some areas affected by SARS (7,8).

From 1 November 2002 to 31 July 2003, a total of 8098 patients were probably infected with SARS, of whom 21% were HCWs (9). Nosocomial spread was one of the major striking features of SARS outbreaks (10–12). Most infected HCWs were young, previously healthy, and immunocompetent. Many had a relatively mild SARS infection, and seemed to be at a lower risk for death (13,14). In addition, in Hong-Kong and Singapore, secondary household transmission was less likely to occur in HCWs' families compared with non-HCWs (15,16).

The outcome of SARS has been adversely associated with factors such as old age, increased levels of C-

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reactive protein (CRP) and even hepatitis B carrier (2,17). It has also been reported that higher viral loads in nasopharyngeal aspirates (NPS) is a useful prognostic indicator of respiratory failure and mortality (18). Given that the NPS procedure has not been well standardized, it is quite possible that inconsistency in performing sampling may render inaccurate the comparison between different individuals' results of real-time polymerase chain reaction (PCR) or comparison between a series of the same individual's data.

We designed this study to explore the relationship between personal protective equipment (PPE) used by HCWs and the clinical course, outcome, and viral load in both HCWs and non-HCWs involved in a SARS cluster stemming from exposure to a single index case in our Emergency Department. The cluster was carefully selected because the spread of transmission occurred in a very short time, making the cause-relationship unambiguous. We also used the human 18s-rRNA as an internal control to avoid sampling variation. Although we could not control for a number of other factors that might have affected transmission, we believe it is worth attempting to assess the effect of PPE, including an N-95 mask, on viral load and subsequent outcome of SARS.

MATERIALS AND METHODS

Patients in the Case Series

The Mackay Memorial Hospital in Taiwan is a 2000-bed teaching hospital that employs approximately 4500 doctors, nurses, allied health professionals, and clerical staff members. Between April 27 and June 16, 2003, a total of 167 patients diagnosed as probable (n = 71) and suspected (n = 96) SARS were treated in the hospital wards and Emergency Department (ED). Since May 12, a total of 41 negative pressure isolation rooms (including four in the ED) were established for these patients. Clearly, it is very difficult to track and clarify every transmission route in facing such variable sources of patients. Therefore, we carefully selected a cluster of victims whose source of infection can be tracked back to a common index patient. On May 4, 2003, a 50-year-old male was sent to the ED of Mackay Memorial Hospital in Taipei. He had had fever for the previous 6 days, and a severe cough with dyspnea for 1 day. He was a cook, and had no travel history or specific contact history for SARS. On arrival in the ED, he was given bronchodilatator therapy by nebulization for his respiratory distress. Two hours later, his chest X-ray study showed multi-focal air space consolidations, and the patient was then immediately isolated. Five hours later, he developed intractable hypoxia and respiratory failure, so he was intubated and mechanically ventilated. Twenty-four hours later, he died of SARS in the ED isolation unit.

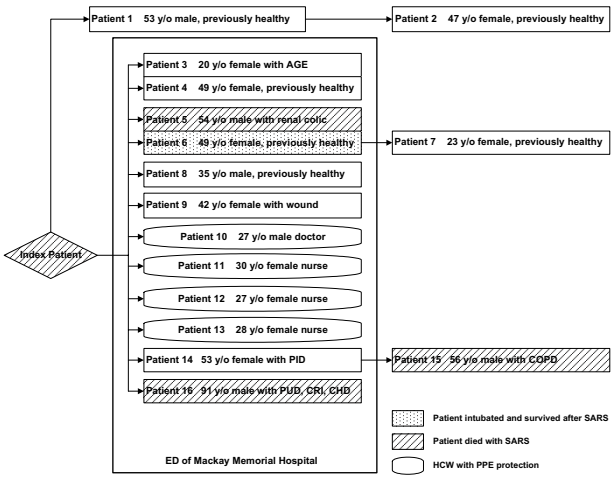

Figure 1. Transmission of 16 cases of definite SARS in a case cluster. A nosocomial outbreak occurred on May 4–5, 2003, in the Emergency Department (ED) of Mackay Memorial Hospital, Taipei, Taiwan. Patient 1, who was not part of the ED cluster, had had dinner with the index patient on May 1, 2003, and developed a fever on May 10. His wife, patient 2, became febrile on May 20. Patient 3 was seen in the ED on May 4 with acute gastroenteritis and was accompanied by her mother, patient 4. Both subsequently developed fevers on May 10 and May 9, respectively, and were found to have SARS. Patient 5 was seen in the ED on May 4 for a renal stone, accompanied by his wife, patient 6. He developed a fever on May 9, his wife on May 12, and their daughter, patient 7, on May 15. Patient 8 was in the ED on May 4 accompanying an ill family member and developed fever on May 10. Patient 9 was in the ED with a leg wound on May 4 and developed a fever May 8. Patients 10, 11, 12, and 13 were ED staff (one doctor and three nurses) who took care of or were working near the index patient May 4 and early May 5. Patient 10 (an ED doctor) did not know he'd been exposed to SARS and developed a fever on May 9 while traveling in Japan. Patients 12 and 13 assisted during the intubation of the index patient early on May 5. Their fevers began May 9 and May 10. Patient 14 was seen in the ED on May 4 for pelvic inflammatory disease and developed a fever on May 12. Her husband, patient 15, became febrile May 23. Patient 16 was seen in the ED with upper gastrointestinal symptoms May 4 and became febrile May 9. Health care workers (HCWs) wore personal protective equipment, including N-95 masks, while working. Non-HCWs infected in the ED had been wearing only surgical or cloth masks. Three of the non-HCWs transmitted the infection to secondary household contacts. Four of the non-HCWs had respiratory failure, 3 of whom died. AGE = acute gastroenteritis; CHD = coronary heart disease; COPD = chronic obstructive pulmonary disease; CRI = chronic renal insufficiency; PID = pelvic inflammatory disease.

Sixteen individuals who were directly or secondarily linked to this index patient, including 4 HCWs and 12 non-HCWs (Figure 1), subsequently fulfilled the modified WHO SARS case definition (revised 1 May 2003) (19). All 16 had a positive reverse transcriptase polymerase chain reaction (RT-PCR) nasopharyngeal swab for SARS-CoV or positive serologic

antibody tests (except for 3 who died before an antibody test was available).

Clinical and Laboratory Studies

The clinical course of each patient, including vital signs, the use of O_2, oxygenation status, and chest X-ray were collected for comparison. Laboratory tests consisted of consecutive hematological examinations, including absolute lymphocyte and platelet counts, and serum biochemistry, including lactate dehydrogenase (LDH), creatine kinase (CK), aspartate aminotransferase (AST), alanine aminotransferase (ALT), and C-reactive protein (CRP). To define the chronological progression, the first day of documented fever $>$ 38°C was designated as FD 1. O_2 saturation was recorded after admission to the hospital. A nasopharyngeal swab was taken to detect SARS-CoV as soon as patients were admitted to an isolation room.

Quantitative RT-PCR Specific for SARS-CoV

The nasopharyngeal swab specimens were collected in Trizol reagent and total RNA was extracted according to the manufacturer's instructions (GIBCO/BRL, Grand Island, NY). Primers and probes for SARS Co-V and human 18s rRNA were purchased from Assays-on-Demand™ Gene Expression Products (Applied Biosystems, Foster City, CA). Quantitative RT-PCR was done by using SARS-specific primers and a 5'-nuclease probe as prepared in the Assays-on-Demand™ Gene Expression Products (Applied Biosystems). The 381-bp target fragment of SARS-CoV RNA was transcribed and amplified in an ABI PRISM 7700 sequence detection system (Applied Biosystems). Plasmids supplied by the Center for Disease Control of Taiwan were used with the target sequence to generate a standard curve.

To avoid variation in the sampling procedures, quantitative RT-PCR for 18s-rRNA was also done in each sample as an internal control. Individual quantitative RT-PCR for SARS-CoV was normalized to the same level of 18s-rRNA, in this study 10^6 copies/mL. The initial and the normalized data will be compared and presented.

Quantification of mRNA was performed by using a TaqMan one-step RT-PCR Master Mix Reagent kit (Applied Biosystems). Real-time fluorescence measurements were taken and a cycle threshold (CT) value for each sample was calculated by determining the point at which the fluorescence exceeded a threshold limit. A standard curve of the CT values obtained from serial dilutions of the standard was compiled. The coefficient of linear regression and the slope for each standard curve were calculated. The CT values from samples were plotted on the standard curve for calculating the number of genomes.

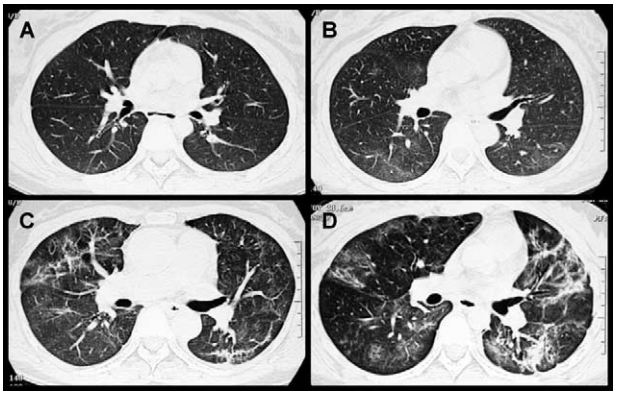

Figure 2. Typical HRCT scans through the middle lungs zones of SARS patients at 1 month after discharge. (A) No evidence of residual interstitial disease in Patient 11 (score = 0). (B) Mild disease (score = 1) in Patient 9. Note subtle ground-glass opacification at both superior segments of lower lobes. (C) Moderate disease (score = 2) in Patient 6. Note diffuse ground-glass opacification, thickening of interlobular septa, and mild traction bronchiectasis. (D) Severe disease (score = 3) in Patient 3. Note diffuse ground-glass opacification with coarse reticulation and consolidation, peribronchovascular thickening, and traction bronchiectasis with slight architectural distortion.

Patient Follow-up Protocol

The follow-up protocol for all surviving patients included an outpatient interview, physical examination, high-resolution computed tomography (HRCT) scan, pulmonary function test (PFT), and a 6-min walk test (6MWT). HRCT, PFT and 6MWT were performed at 1 month after discharge. HRCT and PFT were done again 6 months after discharge.

The HRCT images were all reviewed by one chest physician (C.L.L.) and one radiologist (C.Y.S.). The thorax was divided into upper, middle, and lower lung zones, and the HRCT findings in each zone were recorded. HRCT scores were based on the following scheme: 0 = normal CT; 1 = mild disease (patches of ground-glass opacification); 2 = moderate disease (moderate reticulation, traction bronchiectasis, peribronchovascular thickening); 3 = severe disease (areas of parenchymal consolidations, diffuse areas of peribronchovascular thickening, and traction bronchiectasis) (20). Examples of HRCT scans with corresponding scores are shown in Figure 2. The final HRCT score was the mean value of the scores from all three zones.

Statistical Analysis

For quantitative RT-PCR, the viral RNA loads were expressed as mean ± SEM, whereas all other data were expressed as mean ± SD. Categorical variables were analyzed by Fisher's exact test and continuous variables by Student's *t* test. Differences between the quantitative RT-PCR values for SARS-CoV in nasopharyngeal swab and HRCT scores in HCWs and non-HCWs were tested for significance using the Mann-Whitney *U* test. We considered a p of < 0.05 to be significant. We used SPSS 10.0 software (SPSS Inc., Chicago, IL) for all analyses.

RESULTS

Patient Demographics

The 16 patients in this cluster had a mean age 42.9 ± 17.9 years (range 20 to 91). The HCWs were younger than non-HCWs (28.0 ± 1.4 vs. 47.8 ± 18.2 years, respectively, $p = 0.051$). The majority of patients (10 of 16) were female. Only 1 patient (patient 15) had a history of smoking and chronic obstructive pulmonary disease (COPD). All patients presented with fever as the initial specific manifestation of SARS. All but one (patient 15 with COPD) had several days of high fever before developing respiratory symptoms. The mean incubation period between exposure to the index patient and onset of fever (> 38°C) was 5.5 ± 0.6 days in HCWs and 6.2 ± 1.8 days in non-HCWs. Patients sought medical treatment at a mean of FD 2.3 ± 2.5 days in HCWs and FD 4.0 ± 3.0 days in non-HCWs.

The infected HCWs had all been wearing PPE, including an N-95 mask, gloves, gown, and head covering when working in the ED (Figure 3). Patients 12 and 13, who cared for the index patient in isolation and assisted with the intubation, wore an additional gown and eye protection when in the isolation unit. The procedures were double-checked (including N-95 mask with fit-testing) by their colleagues according to WHO recommendations. The non-HCWs, apparently exposed to the index patient in the ED, had no specific protective equipment, except that some wore surgical, cloth, or paper masks.

Viral Load Studies

Nasopharyngeal swabs were taken at a mean of FD 6.0 ± 1.8 days, when the patients were in a negative isolation room or had been started on our SARS treatment protocol. A total of 18 samples were obtained from 11 patients

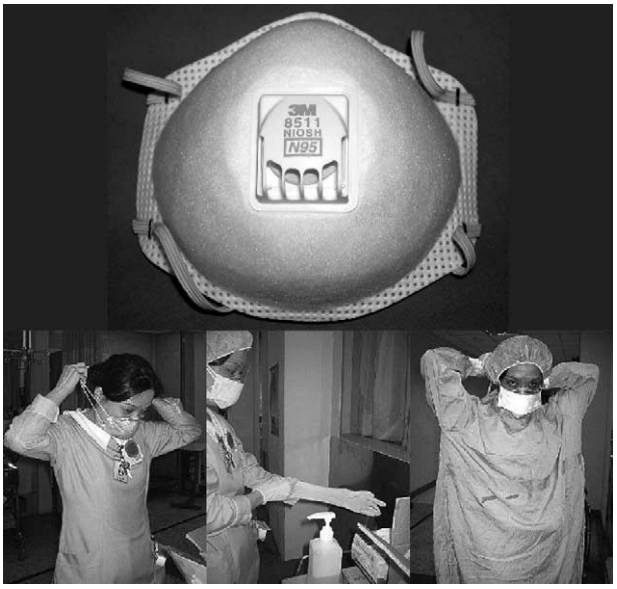

Figure 3. N-95 mask and personal protective equipment. During the SARS epidemic, the HCWs had been required to, and were wearing PPE, including an N-95 mask, gloves, gown, and head covering when working in the ED.

for quantitative RT-PCR. Initial RT-PCR data showed that HCWs had a significantly lower viral load than the non-HCWs (24.36 ± 15.84 vs. 4346 ± 3246 copies/mL, respectively, $p < 0.0001$) (Figure 4). HCWs also had a significantly lower level human 18s-rRNA than the non-HCWs (80.97 ± 35.2 vs. 5945 ± 1674 copies/μL, respectively, $p < 0.001$), indicating that mucosal shedding was more extensive in non-HCW (Figure 5). Figure 6 shows that non-HCWs had a significantly higher viral load in their NPS after normalization than the HCWs (463.8 ± 450.2 vs. 9349 ± 7687 copies of RNA/mL, respectively). Although non-HCWs still had a higher viral load after normalization, the difference between

Figure 4. The un-normalized viral load of HCW and non-HCW by quantitative PCR showing HCW with an average of 24.36 ± 15.84 copies of RNA/mL and non-HCW with 4346 ± 3284 copies of RNA/mL ($p < 0.0001$).

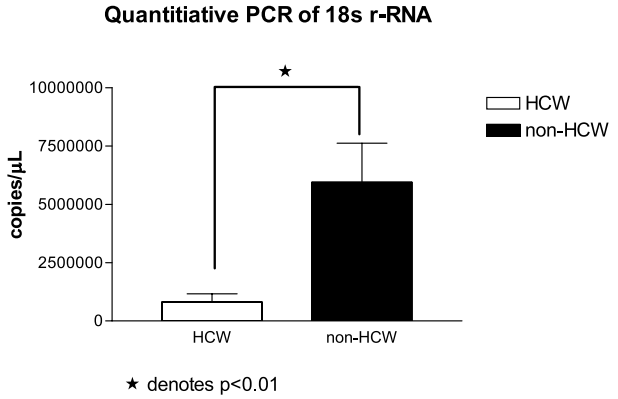

Figure 5. The extent of mucosal shedding was significantly greater in non-HCWs ($p < 0.001$) as indicated by the greater amount of 18s-rRNA in the nasopharyngeal swabs.

non-HCWs and HCWs was reduced from about 200 times to 20 times (Table 1).

Clinical and Laboratory Studies

Non-HCWs had significantly higher CRP values (11.0 ± 6.1 vs. 3.5 ± 4.0 mg/dL, respectively, $p = 0.038$) and lower O_2 saturation (peak pO_2/FiO_2 ratio, 167.6 ± 91.9 vs, 274.5 ± 58.6, respectively, $p = 0.049$), than HCWs (Table 2). Four of the 12 non-HCWs required intubation and 3 died, compared with none of the 4 HCWs ($p = 0.516$, $p = 0.529$, respectively). There were no differences in lymphocyte or platelet counts, LDH, CK, AST, or ALT between the HCWs and non-HCWs. The FD on which abnormal laboratory findings occurred also did not differ significantly between the two groups.

Secondary Household Transmission

Secondary household transmission occurred in 3 of 7 non-HCWs' families compared with none of the HCW families (3/7 vs. 0/4, $p = 0.505$).

Follow-up

Three patients, all non-HCWs, died with SARS. All surviving patients were able to return to normal daily activities after discharge. All of these patients had a normal body mass index (Table 3). However, 4 of the 9 surviving non-HCWs (4/9, 44%) noted dyspnea on exertion at the 1-month follow-up visit. Some survivors had an uncomplicated skin rash or mild hair loss. Symptoms of post-traumatic stress disorder and minor depression were also seen in 2 of the non-HCW survivors at the initial outpatient follow up. However, these symptoms gradually improved, and all survivors had normal psychosocial daily activity at the 6-month telephone follow-up.

Twelve surviving patients completed the follow-up protocol. On the 1-month HCRT, parenchymal abnormalities were found in 8 of 8 non-HCWs and 3 of 4 HCWs. The abnormalities included areas of ground-glass opacification or reticulation of varying size, interlobular septal or intralobular interstitial thickening, traction bronchiectasis with distortion of the architecture, or crazy-paving with consolidations. The middle lung zone was predominantly involved (Figure 2). There were signs interpreted as consistent with pulmonary fibrosis (parenchymal bands, irregular interfaces, and traction bronchiectasis) and peribronchovascular interstitial thickening in 6 of 8 non-HCWs and 2 of 4 HCW patients. Patient 10 had had a pneumomediastinum during his hospitalization, but this had spontaneously resolved by the 1-month follow-up. There were no masses, nodules, emphysema, cavitation, or calcification seen. The mean HRCT score

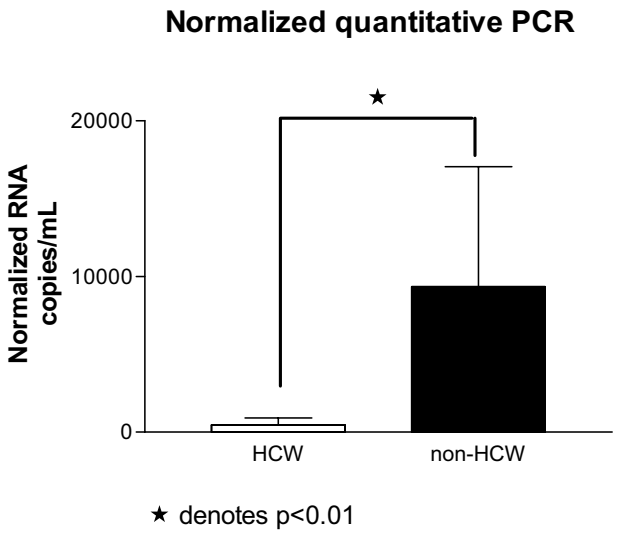

Figure 6. Column statistics of HCW and non-HCW with normalized quantitative PCR showing HCW with an average of 463.8 ± 450.2 copies of RNA/mL and non-HCW with 9349 ± 7687 copies of RNA/mL.

Table 1. The Amount of Viral RNA in Patients' Nasopharyngeal Swab Measured by Quantitative RT-PCR

	Un-normalized data (copies of RNA/mL)	Normalized (copies of RNA/mL)
HCW	24.36 ± 15.84	463.8 ± 450.2
Non-HCW	4346 ± 3284	9349 ± 7687

Results are presented as un-normalized row data and normalized data (copies of RNA/mL).

Table 2. Characteristics and Laboratory Findings in a Cluster of SARS Patients

	HCWs (n = 4)	Non-HCWs (n = 12)	*p* Value
General data*			
Age (years)	28.0 ± 1.4	47.8 ± 18.2	0.051
Female/male	3/1	7/5	NS
Lymphopenia			
Peak ($\times 10^6$/L)	299.8 ± 197.1	355.0 ± 249.8	NS
On fever day†	10.5 ± 3.3	10.3 ± 3.8	NS
Thrombocytopenia			
Peak ($\times 10^9$/L)	157.8 ± 96.5	147.8 ± 54.8	NS
On fever day	7.3 ± 1.9	7.8 ± 3.5	NS
Lactate dehydrogenase elevation			
Peak (U/L)	426.0 ± 335.2	434.9 ± 190.0	NS
On fever day	10.3 ± 2.4	12.3 ± 3.7	NS
Creatine kinase elevation			
Peak (U/L)	140.3 ± 64.1	210.7 ± 130.2	NS
On fever day	8.5 ± 1.3	9.2 ± 4.7	NS
Aspartate aminotransferase elevation			
Peak (U/L)	92.8 ± 79.9	79.5 ± 44.3	NS
On fever day	13.3 ± 3.0	10.8 ± 4.4	NS
Alanine aminotransferase elevation			
Peak (U/L)	129.0 ± 94.9	107.8 ± 49.3	NS
On fever day	14.8 ± 1.7	14.9 ± 4.6	NS
C-reactive protein elevation			
Peak (mg/Dl)	3.5 ± 4.0	11.0 ± 6.1	0.038
On fever day	11.8 ± 1.3	11.9 ± 4.0	NS
Desaturation			
Peak (pO_2/FiO_2 ratio)	274.5 ± 58.6	167.6 ± 91.9	0.049
On fever day	12.5 ± 3.1	11.9 ± 2.2	NS
Intubation and mortality			
Intubation	0/4	4/12	0.516
Mortality	0/4	3/12	0.529

* Data are presented as mean ± SD. NS = not significant.
† On fever day indicates when the laboratory abnormalities peaked in relation to the number of days after the onset of documented fever > 38°C.

in non-HCWs was higher than that of HCWs (1.46 ± 1.02 vs. 0.67 ± 0.72, respectively, $p = 0.198$) (Table 3). At the 6-month follow-up, most patients had significant resolution of their HRCT abnormalities. The previously seen signs of pulmonary fibrosis had substantially resolved, leaving only mild residual linear or reticular opacifications in 4 of 8 non-HCWs and 1 of 4 HCWs. The HRCT score decreased in both groups, but it was still higher in the non-HCWs (0.75 ± 0.53 vs. 0.25 ± 0.17, respectively, $p = 0.058$).

At the 1-month follow-up, 1 of 4 HCWs and 4 of 8 non-HCWs had a restrictive ventilatory defect (vital capacity < 80% predicted). None of the HCWs had evidence of impaired diffusion (D_{LCO} < 80% of predicted), but 5 of 8 non-HCWs did. The non-HCWs had a lower mean D_{LCO} than HCWs (13.4 ± 5.7 vs. 19.3 ± 2.3 mL/min/mmHg, respectively, $p = 0.031$) (Table 3). The functional vital capacity and total lung capacity were mildly decreased in both HCWs (84.5 ± 10.3% and 82.3 ± 14.6%, respectively, of predicted) and non-HCWs (75.6 ± 18.8% and 76.3 ± 15.7%, respectively, of predicted), whereas residual volume was markedly reduced (69.3 ± 33.4% of predicted in HCWs and 76.0 ± 19.7% in non-HCWs). D_{LCO} corrected for lung volume (D_{LCO}/V_A) was normal (105.3 ± 12.7% of predicted in HCWs and 99.0 ± 25.3% in non-HCWs). These findings suggest that parenchymal lung damage led to a restrictive lung defect and impaired diffusion capacity. At the 6-month follow-up, lung function was normal in all HCWs and most of the non-HCWs. Among the latter, however, one person had a restrictive defect and two had diffusion impairment.

At the 1-month follow-up, all survivors were able to perform the 6MWT. However, the non-HCWs walked a shorter distance (648.3 ± 64.2 m) and had a lower SpO_2 (93.8 ± 3.1%) at the end of the test than did HCWs (677.5 ± 51.7 m and 96.5 ± 3.0%), although the differences were not statistically significant (Table 3).

DISCUSSION

We have described a better clinical outcome after SARS in 4 HCWs compared with 12 non-HCWs; despite all having been involved in a cluster related to one index

Table 3. Follow-up of SARS Survivors

	1 month after discharge			6 months after discharge		
	HCW (n = 4)	Non-HCW (n = 8)	*p* Value	HCW (n = 4)	Non-HCW (n = 8)	*p* Value
General data*						
Age, years	28.0 ± 1.4	42.3 ± 13.3	0.019	28.0 ± 1.4	42.3 ± 13.3	0.019
Male/female gender, n	1/3	1/7	NS	1/3	1/7	NS
BMI, kg/m^2	21.6 ± 1.3	21.9 ± 2.0	NS	21.0 ± 1.0	22.2 ± 2.0	NS
High-resolution CT findings						
HRCT score†	0.67 ± 0.72	1.46 ± 1.02	0.198	0.25 ± 0.17	0.75 ± 0.53	0.058
Spirometry, lung volume and gas exchanges tests						
FEV_1, % predicted	87.0 ± 13.3	79.1 ± 19.4	NS	93.0 ± 12.4	89.6 ± 13.1	NS
FVC, % predicted	84.5 ± 10.3	75.6 ± 18.8	NS	86.5 ± 7.9	85.6 ± 12.3	NS
FEV_1/FVC ratio, %	88.5 ± 3.1	89.1 ± 3.4	NS	87.5 ± 2.1	89.0 ± 6.1	NS
VC, % predicted	88.3 ± 12.3	76.9 ± 17.9	NS	93.3 ± 12.1	87.6 ± 11.8	NS
TLC, % predicted	82.3 ± 14.6	76.3 ± 15.7	NS	89.8 ± 10.5	82.7 ± 10.2	NS
FRC, % predicted	72.3 ± 27.2	69.1 ± 14.9	NS	85.8 ± 22.1	72.8 ± 13.1	NS
RV, % predicted	69.3 ± 33.4	76.0 ± 19.7	NS	83.5 ± 28.4	73.8 ± 17.6	NS
RV/TLC ratio, %	24.8 ± 9.2	33.1 ± 6.6	NS	27.8 ± 8.2	28.8 ± 5.8	NS
D_{LCO}, mL/min/mmHg	19.3 ± 2.3	13.4 ± 5.7	0.031	23.6 ± 8.8	17.7 ± 3.3	0.135
D_{LCO}, % predicted	87.3 ± 6.9	68.0 ± 24.8	0.072	105.8 ± 26.5	88.3 ± 10.0	0.142
D_{LCO}/V_A, mL/min/mmHg	4.86 ± 0.58	4.18 ± 1.08	NS	5.24 ± 0.93	4.87 ± 0.65	NS
D_{LCO}/V_A, % predicted	105.3 ± 12.7	99.0 ± 25.3	NS	111.5 ± 12.7	112.9 ± 25.3	NS
6-min walk test						
6-min walk, m	677.5 ± 51.7	648.3 ± 64.2	NS	–	–	–
SpO_2 after 6-min walk, %	96.5 ± 3.0	93.8 ± 3.1	NS	–	–	–

* Data are presented as mean ± SD.
† Differences between HRCT scores were tested using the Mann-Whitney *U* test.
BMI = body mass index; D_{LCO} = diffusing capacity of the lung for carbon monoxide; FVC = functional viral capacity; FRC = functional residual capacity; NS = not significant; TLC = total lung capacity; V_A = alveolar volume; VC = vital capacity; RV = residual volume.

patient, with 13 apparently directly infected by that patient and 3 others by secondary transmission. In several previous reports on SARS, HCWs were less likely to die than non-HCWs (9,13,21). Possible reasons for this may be that they were often younger than non-HCWs, sought treatment earlier, and were less likely to have coexisting illnesses (especially diabetes mellitus and heart disease) (11,13,14,17). It has also been postulated that HCWs may have had lower exposure to the virus and thus a lower viral load, possibly due to the use of PPE (13,14,22). The initial exposure to the virus and viral load seem to correlate with disease severity. We speculate that the PPE worn by our HCWs, in particular the N-95 masks, may have minimized their exposure to the virus, resulting in lower viral loads, a relatively mild disease course, and a better outcome.

It is likely that a lower exposure to the virus may also reduce the risk of secondary household transmission. Patient 10, who went to Japan after unknowingly having been exposed to the index patient, traveled in the company of other doctors for several days after he developed a fever. However, no one in contact with him, either among his traveling companions or Japanese, became infected, despite the understandable fear in Japan when the patient was diagnosed with SARS on his return to Taiwan (23). None of the other three HCWs transmitted the disease to coworkers or family members despite contact with others during the incubation period. It should be noted that all 3 were isolated immediately after they developed fever, which presumably also decreased the risk of spread, because the patients with SARS were apparently contagious only with the onset of fever. This contrasts with the non-HCWs, who had not worn N-95 masks, had a higher vial load by quantitative RT-PCR, and 3 of whom transmitted SARS to family members. Although immediate reporting of symptoms with early diagnosis and immediate isolation is key to controlling the spread of SARS, use of a high quality mask may minimize initial exposure and thus reduce secondary household transmission.

It has been reported that genetic polymorphism in the human leukocyte antigen system (HLA-B* 4601) correlates with the risk and severity of SARS infection (24). HLA-B* 4601/B46 is seen in 13.2% to 15.4% of people of southern Chinese origin, 2.8% in those from northern China, and is seldom present in European populations (25). In our cluster, 4 of 9 non-HCWs and 1 of 4 HCWs had this particular allele. There is, however, no single laboratory study that has been definitively shown to define accurately the prognosis in SARS. In some studies, an increased LDH and an elevated neutrophil count at the time of admission, as

well as low CD4 and CD8 lymphocyte counts, were associated with a poor prognosis (2,11,13). In our series, CRP, an acute-phase protein synthesized by the liver after stimulus by various cytokines produced in response infection or inflammation, was markedly higher in non-HCWs than in HCWs. It has been correlated clinically with an increased risk of organ dysfunction and poor prognosis in a heterogeneous population of critically ill patients (26). In our series, the greatest hematologic and laboratory abnormalities and oxygen desaturation occurred during the second week after fever onset (FD 7 to FD 14). According to a report from Hong Kong, the second week was a critical period of SARS when patients either clinically improved or worsened and developed respiratory distress syndrome necessitating ventilatory support. In a subset of their series, these authors found that the second week marked the peak and subsequent fall in viral load, concurrent with the appearance of antibodies (17).

The quantitative RT-PCR analysis of nasopharyngeal swabs reveals interesting features of SARS-CoV infection. Other investigators have reported a relatively higher concentration of viral RNA in the sputum than in the serum, urine, and stool. Its presence in the latter suggests that viral replication occurs elsewhere in addition to the respiratory tract. However, the shedding of virus from the respiratory mucosa would seem to be the primary route of transmission (17,27). Such a conclusion is also supported by our observation that the amount of the virus was positively associated with the extent of mucosal shedding. Using human 18s-RNA as internal control in some samples, we found that sampling variation and mucosal shedding may significantly affect the virus numbers. Nevertheless, our findings support the contention that crude viral load on nasopharyngeal swab correlated with disease severity and outcome.

It has been reported that some patients discharged after SARS have some degree of respiratory impairment, possibly related to residual lung defects, muscle weakness, or systemic effects of the viral illness (28). Chest CT scan reportedly showed changes consistent with pulmonary fibrosis in 62% of 24 survivors of SARS at 5 weeks after discharge (28). For the majority of patients for whom data are available, the CT abnormalities interpreted as fibrosis had included a patchy ground-glass appearance that was not extensive and that might not have a significant impact on lung function (28–30). In our case series, abnormalities on HRCT scan were more common in non-HCWs than HCWs, even 6 months after discharge. The findings were predominantly ground-glass opacification rather than parenchymal bands and are therefore more suggestive of potentially reversible fibrosing alveolitis rather than pulmonary fibrosis. Pathophysiologically, the possibility of acute reversible lung damage suggests that SARS infection might cause some degree of chronic viral pneumonitis in addition to acute disease (personal communication).

Six percent to 20% of SARS survivors have had impaired diffusion or a restrictive ventilatory defect at 6 to 8 weeks post-discharge (28). Some of the restrictive defect might be attributable to skeletal muscle weakness rather than parenchymal lung damage alone. Such muscle weakness might be due to several factors, including the use of high-dose steroids, prolonged bed rest leading to physical deconditioning, or residual systemic effect of the acute disease (2,28). Whatever the cause, the outcome in our small series indicates that the lung function abnormality caused by SARS may improve spontaneously. We found improvement in radiologic, functional, and psychological abnormalities over time. At almost half a year after SARS, the survivors had normal lung function (including normal cardiopulmonary exercise test, data not shown), normal psychosocial behavior, and only minimal residual radiologic abnormalities.

A major limitation of this study is that we were not able to control for other factors besides PPE that might have affected transmission of the virus from the index case. These may have included ventilation in the ER, proximity of the subjects to the index case, duration of exposure, and perhaps other unknown elements involved in transmission. HCWs may have been more aware of and had better hygiene practices than the non-HCWs. However, the exact extent of the spread of infectious viral-laden droplets when the patient coughed is difficult to determine. RT-PCR for SARS-CoV was positive in samples taken from the floor, a desk, and a bed-rail in the ED (personal communication). Because both HCWs and non-HCWs moved around in the ED, we cannot be certain exactly when and where their exposures actually occurred. This is one reason we selected this one cluster of infection, because it is highly likely that all patients who were present in the ED when the index patient was there were infected at that time. Another limitation is that the numbers in this series are very small, making statistical analysis very uncertain. However, the HCWs did have a lower mean viral load, even though several had very close contact with the index patient, particularly during intubation, when one would expect an extremely high risk of exposure to a heavy viral load.

In conclusion, although PPE, including the N-95 mask, does not confer 100% protection against SARS infection, it seems that it may lessen the initial degree of exposure to the virus with a subsequently lower viral load in the upper respiratory tract. This may result in a milder disease clinically, less chance of secondary transmission, and a faster recovery.

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