RAPID COMMUNICATION

Outcome of coronavirus-associated severe acute respiratory syndrome using a standard treatment protocol

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Objective: There is so far no consensus on the optimal treatment strategy for the coronavirus-associated severe acute respiratory syndrome (SARS). We aimed to analyse the outcomes of a standard treatment strategy comprising antibiotics, a combination of ribavirin, a 3-week step-down course of corticosteroids, and the possibility of pulsed methylprednisolone rescue in the event of deterioration.
Methodology: This was a prospective cohort study performed at a major public-funded hospital in Hong Kong. Eighty-eight World Health Organisation/Centers for Disease Control and Prevention probable cases of SARS (97% laboratory-confirmed) were treated with a standard protocol previously reported. Seventy-one patients treated *de novo* were analysed in detail with regard to time to clinical stabilization after combination treatment, requirement of additional therapy (pulsed methylprednisolone; assisted ventilation); and final outcomes (recovery, mortality).
Results: The mean age was 42. Twenty-one patients (24%) had comorbidities. Three of 71 treated *de novo* recovered with antibiotics alone. The remaining 68 received combination treatment at a mean of 5.8 days after symptom onset, of whom 30 subsequently required pulsed methylprednisolone rescue (independent predictors: older age and higher LDH) and 18 required assisted ventilation (independent predictors: older age, higher oxygen requirement and creatinine level). Their median time to clinical stabilization was 8.0 days after combination treatment (independent predictor for longer time to stabilization: median age of 41 or above). Common complications were hyperglycaemia (58%), pneumo-mediastinum/thoraces (13%), psychiatric manifestations (7%) and ventilator-associated pneumonia (2%). One patient (1%) died of SARS-related respiratory failure. All-cause mortality was 3.4%, occurring in patients aged > 65 years only. None of the discharged survivors required continuation of oxygen therapy.
Conclusions: This standard treatment protocol resulted in overall satisfactory outcomes. Randomized controlled trial is suggested to confirm its efficacy.

Key words: corticosteroid, outcome, ribavirin, severe acute respiratory syndrome, standard treatment protocol.

INTRODUCTION

The coronavirus-associated[1–4] severe acute respiratory syndrome (SARS) caused a worldwide outbreak in 2003. There is so far no consensus on the treatment strategy for this potentially deadly disease.[5–8] We reported the development of a standard treatment protocol for our first 31 SARS patients comprising antibiotics and ribavirin, and explained the rationale of how our corticosteroid regimen was derived by titration of dosages to achieve satisfactory clinical responses in our initial patients.[9] In the following prospective observational cohort study, we aimed to analyse in detail the outcomes of all patients treated with this protocol.

METHODS

Study population

All consecutive patients admitted to Pamela Youde Nethersole Eastern Hospital, Hong Kong between 9 March and 28 April 2003 were included in the analysis if they were diagnosed to be suffering from SARS and had ever been treated with the standard treatment protocol.[9] All patients fulfilled the latest definitions for probable cases of SARS of both the World Health Organization (WHO) and the Centers for Disease Control and Prevention (CDC).[10,11]

Study design

We prospectively collected the demographic data, exposure history, comorbidities, presenting features, vital signs and oxygen requirements of all patients studied. Daily blood tests included haematology (complete blood counts with differentials) and biochemistry (electrolytes, glucose, liver and renal functions, creatine kinase and lactate dehydrogenase). Blood, sputum and urine samples were collected for routine bacteriological studies. Nasopharyngeal samples were collected for virological studies, including immunofluorescent tests and cultures for influenza, parainfluenza, respiratory syncytial and adenoviruses. Clotted blood sera (both acute and convalescent) were collected for serological studies against Legionella species, *Chlamydia pneumoniae* and *Mycoplasma pneumoniae*. Human metapneumovirus was not specifically looked for. Hepatitis B surface antigen (HBsAg) was checked. Laboratory diagnosis of the SARS-associated coronavirus (SARS-CoV) was performed by reference laboratories at the University of Hong Kong and the Central Public Health Laboratory, Hong Kong, including nasopharyngeal and stool samples for reverse transcriptase polymerase chain reaction (RT-PCR) studies of coronaviral ribonucleic acids (RNA),[12] and acute and convalescent sera tested in parallel for IgG antibody.

CXR of each patient on admission, on starting combination treatment, on starting pulsed methylprednisolone, and on discharge were semiquantified using a scoring system previously described, in which each lung was separated into six sections (upper, middle, and lower zones; medial and lateral divisions) and scored on a four-point scale: 0, clear; 1, subtle haziness or mild infiltrates; 2, ground-glass appearance or prominent infiltrates; and 3, confluent or dense opacities.[9] Scoring was independently performed by two pulmonologists blinded to the patients' clinical information.

Treatment intervention

We developed a treatment protocol for SARS comprising antibiotics, ribavirin and corticosteroids, and finalized the dosage regimen of corticosteroids on 18 March 2003.[9] Briefly, antibiotics (levofloxacin, or amoxicillin-clavulanic acid plus clarithromycin) were given to all suspected SARS patients. Combination treatment with ribavirin and corticosteroids was only started if any of the following occurred: (i) extensive or bilateral CXR involvement; or (ii) persistent CXR involvement and persistent high fever for 2 days; or (iii) clinical, CXR, or laboratory findings suggestive of worsening; or (iv) oxygen saturation (S_PO_2) < 95% in room air. Ribavirin was given for 10–14 days as per protocol at 400 mg every 8 h (1200 mg daily) intravenously for at least 3 days (or until stabilization), then 1200 mg twice daily (2400 mg daily) orally. The corticosteroid regimen was standardized as follows: methylprednisolone 3 mg/kg daily intravenously for 5 days, then 2 mg/kg daily intravenously for 5 days, then prednisolone 1 mg/kg daily orally for 5 days, 0.5 mg/kg daily orally for 3 days and 0.25 mg/kg daily orally in the last 3 days. Additional pulsed methylprednisolone 500 mg twice daily intravenously for 2 days (total 2 g) were given as rescue medication in cases with no response to at least 2 days of a second course of antibiotics to treat possible sepsis; persistent lymphopenia; and deterioration in at least two out of the following three parameters: clinical condition, CXR, and oxygen saturation. After such pulsed therapy, the standard corticosteroid regimen was restarted and tailed down as per protocol. All patients gave verbal consent to the above treatment.

Outcome measures

The following primary outcomes were studied: compliance to protocol, treatment outcomes, predictors for additional therapy (pulsed methylprednisolone, assisted ventilation) and time to clinical stabilization. Clinical stabilization was defined as the first day (i) when the body temperature was persistently ≤ 37.2°C, (ii) SaO_2 in room air was persistently ≥ 94%, and (iii) with no requirement for additional therapy which is defined as pulsed corticosteroids or assisted ventilation. All complications were recorded. Hyperglycaemia denoted blood glucose level > 10 mmol/L. Secondary outcomes were death or recovery.

Statistical analysis

Interobserver agreement of CXR scores was assessed by Bland-Altman plot.[13] Mean scores were used for subsequent analysis. Characteristics between patient groups were compared using Mann–Whitney U-test for continuous variables and χ^2 test for categorical variables. Statistical significance was taken as $P < 0.05$ (two-tailed). Independent predictors were studied with multiple logistic regression with forward stepwise entry of parameters having $P < 0.05$. Within-subject comparisons were done using Wilcoxon signed-rank test. Kaplan-Meier analysis with log-rank tests was done to identify predictors for the time to clinical stabilization; continuous variables were categorized using medians as cut-off values. Independent predictors were studied with Cox proportional hazards regression analysis with forward stepwise entry of parameters having $P < 0.05$. Fulfilment of the assumption of proportional hazards was confirmed

with log-minus-log survival plots. SPSS® (SPSS Inc., Chicago, IL, USA) version 9 was used for all analyses.

RESULTS

Demographics

Over a period of 51 days from 9 March to 28 April 2003, 90 probable cases of SARS were admitted. Two were excluded because they had never been treated according to our standard protocol; one had been transferred from another hospital for continuation of treatment, and the other for coronary care of acute myocardial infarction post-SARS treatment with recovery. Characteristics of the 88 patients recruited are shown in Table 1. Of these, six had prior treatment in other hospitals before they were transferred for intensive care, 11 were treated with the developmental-phase protocol (between 12 and 17 March), and 71

Table 1   Patient characteristics of 88 cases treated using a standard protocol[9]

	Standard protocol *de novo* (*n* = 71)	Standard protocol with prior treatment (developmental-phase protocol) (*n* = 11)	Standard protocol with prior treatment (regimen of other hospital)[†] (*n* = 6)	All patients (*n* = 88)
Demographics				
Age (years) (mean ± SD)	42.5 ± 14.8	39.6 ± 10.5	41.5 ± 10.9	42.1 ± 14.0
Age (years) (median ± range)	41 (13–74)	38 (27–65)	41 (29–55)	40.5 (13–74)
Male gender	27 (38%)	4 (36%)	2 (33%)	33 (38%)
Smokers (active/ex-)	8 (11%)	2 (18%)	0	10 (11%)
Alcohol drinkers	4 (6%)	0	1 (17%)	5 (6%)
Exposure history				
Health care workers	9 (13%)	7 (64%)	1 (17%)	17 (19%)
Definite close contact	22 (31%)	3 (27%)	1 (17%)	26 (30%)
Housing estate outbreak	17 (24%)	1 (9%)	4 (67%)	21 (24%)
Travel to affected countries	13 (18%)	0	0	14 (16%)
Others	10 (14%)	0	0	10 (11%)
Comorbidities				
Any comorbidities	17 (24%)	2 (18%)	2 (33%)	21 (24%)
Diabetes mellitus	8 (11%)	0	1 (17%)	9 (10%)
Coronary artery disease	3 (4%)	0	0	3 (3%)
Hypertensive heart disease	1 (1%)	0	0	1 (1%)
Underlying neoplasm	0	1 (9%)	0	1 (1%)[‡]
Chronic renal impairment	1 (1%)	0	0	1 (1%)
Asthma	1 (1%)	0	0	1 (1%)
Chronic obstructive pulmonary disease	0	0	0	0
Epilepsy	1 (1%)	0	0	1 (1%)
Psychiatric disease	3 (4%)	0	1 (17%)	4 (5%)
Chronic Hepatitis B virus carrier	4 (6%)	2 (18%)	0	6 (7%)
Presenting clinical features				
Symptom duration (days)	4.1 ± 2.8	2.5 ± 3.0	3.0 ± 7.1	3.8 ± 3.3
Temperature (°C)	38.7 ± 0.8	39.2 ± 0.5	38.9 ± 0.8	38.8 ± 0.8
Respiratory rate (breaths/min)	19.5 ± 1.8	20.0 ± 1.9	20.5 ± 0.7	20.4 ± 7.9
O_2 requirement (L/min) (mean ± SD)	0.6 ± 1.5	0.5 ± 1.5	2.0 ± 1.6	0.6 ± 1.5
O_2 requirement (L/min) (range)	0–8	0–5	0–4	0–8
Presenting blood test results				
Neutrophil count ($\times 10^9$/L)	4.6 ± 2.5	3.4 ± 1.3	3.1 ± 1.2	4.3 ± 2.4
Lymphocyte count ($\times 10^9$/L)	0.87 ± 0.36	0.87 ± 0.16	0.93 ± 0.48	0.88 ± 0.34
Platelet count ($\times 10^9$/L)	166.9 ± 53.3	139.2 ± 26.9	194.0 ± 30.5	165.3 ± 50.7
Creatinine (µmol/L)	84.8 ± 31.0	91.2 ± 21.2	64.5 ± 17.1	84.3 ± 29.6
Alanine transaminase (IU/L)	44.2 ± 63.1	22.8 ± 12.6	62.0 ± 63.0	42.7 ± 59.4
Creatine kinase (IU/L)	303.3 ± 548.4	178.3 ± 125.8	137.3 ± 143.9	286.2 ± 520.2
Lactate dehydrogenase (IU/L)	258.2 ± 133.5	199.3 ± 50.0	296.7 ± 198.6	258.9 ± 136.4
Positive laboratory diagnosis of SARS-CoV	68 (96%)	11 (100%)	6 (100%)	85 (97%)
Admission chest radiograph score	7.9 ± 5.7	7.9 ± 4.9	10.2 ± 8.2	8.1 ± 5.8

Values are number (%) or mean ± SD unless stated otherwise.
[†] Conditions on presentation to other admitting hospitals.
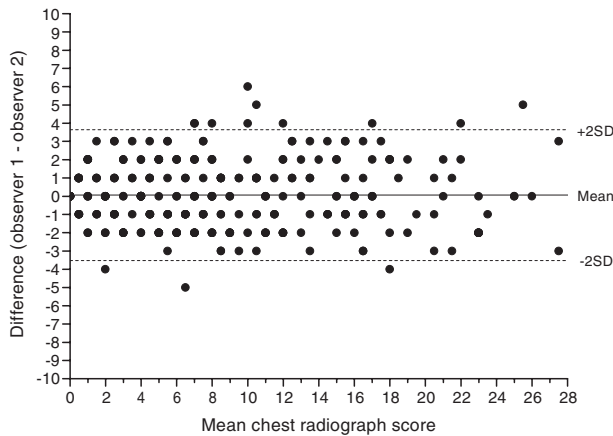[‡] Poorly differentiated non-small cell carcinoma of chest wall.

Figure 1 Bland-Altman plot of CXR scores. CXR scores from two independent observers blinded to clinical information were compared. The mean ± 2 SD score difference was 0.06 ± 3.58.

were treated *de novo* with the final protocol (after 18 March 2003). Data from these 71 were analysed in detail and presented below.

Chest radiography

We scored 305 CXR of these 71 patients, with Bland-Altman plot confirming good interobserver agreement (Fig. 1). Mean ± SD scores at the time of admission ($n = 71$), commencement of combination treatment (ribavirin and methylprednisolone) ($n = 68$), pulsed methylprednisolone ($n = 30$), clinical stabilization ($n = 68$) and hospital discharge ($n = 68$) were 7.9 ± 5.7, 10.2 ± 5.7, 16.2 ± 6.5, 8.2 ± 6.1 and 4.4 ± 5.2, respectively.

Microbiology

Positive laboratory diagnosis for SARS-CoV infection was confirmed in 68/71 patients in Group C; 67/68 had a four-fold or greater rise of IgG titre in convalescent sera at a mean of 19.9 ± 6.5 days after symptom onset. Since the coronaviral RNA test by PCR and viral culture were only available in April 2003, 21/49 were PCR-positive in the nasopharyngeal samples, and 25/39 had positive stool culture for the virus. On admission, five patients were coinfected with other organisms: *Mycoplasma pneumoniae* ($n = 2$), *Haemophilus influenzae* ($n = 1$), *Klebsiella species* ($n = 1$), and *influenza A virus* ($n = 1$). Compared with those with negative samples, patients with positive nasopharyngeal PCR for the SARS-CoV were not associated with a longer time to stabilization ($P = 0.1351$).

Compliance to treatment protocol

All 71 patients received first-line antibiotics as per protocol:[9] in addition to amoxicillin-clavulanic acid, 65 received levofloxacin and six clarithromycin.

Of these, three recovered on antibiotics alone: nasophayngeal aspirate positive for SARS-CoV ($n = 1$), nasopharyngeal aspirate PCR and SARS serology positive ($n = 1$), and stool culture and serology ($n = 1$). The remaining 68 were given the standard combination treatment 5.8 ± 3.0 days after symptom onset (1.8 ± 1.2 days after admission). Of these, 30 required additional pulsed methylprednisolone at 3.0 ± 2.4 days and two required a second pulse at 15.5 ± 13.4 days after commencement of combination treatment.

Compliance to protocol was confirmed by comparing the administered doses of each drug against the standard regimens. Ribavirin: mean ± SD daily dose was 1052.7 ± 106.3 mg (18.5 ± 3.3 mg/kg bodyweight) intravenously and 2673.7 ± 675.3 mg (46.1 ± 13.9 mg/kg) orally for a total of 13.2 ± 2.1 days. Corticosteroids: methylprednisolone was administered intravenously at daily doses of 2.9 ± 0.7 mg/kg followed by 2.0 ± 0.3 mg/kg for 10.2 ± 1.1 days, then prednisolone orally at 1.0 ± 0.1 mg/kg followed by 0.5 ± 0.1 mg/kg and 0.28 ± 0.04 mg/kg daily for a total of 11.5 ± 0.6 days. Pulsed methylprednisolone rescue: 2266.7 ± 626.1 mg intravenously per patient who required corticosteroid rescue. Corticosteroid doses resumed after pulsed methylprednisolone therapy did not show any significant deviation from the standard regimens.

Appropriateness of pulsed methylprednisolone rescue was confirmed by the following comparisons: oxygen requirement (1.8 ± 2.4 L/min at steroid commencement *vs* 4.4 ± 3.8 L/min at pulsed steroid initiation; $P < 0.001$), CXR score (12.3 ± 5.9 *vs* 16.2 ± 6.5; p = 0.002) and lymphocyte count (0.71 ± 0.28 *vs* 0.50 ± 0.27 × 10⁹/L; $P = 0.002$) were all significantly worse at the start of pulsed steroid rescue.

Predictors for additional therapy

Pulsed methylprednisolone rescue was required in 30/68 patients given combination therapy (44%) and non-invasive or invasive ventilation in 18/68 (26%). Comparison of characteristics at commencement of combination treatment between those requiring and those not requiring such therapies is shown in Table 2. Multiple logistic regression showed the independent predictors for pulsed methylprednisolone rescue to be age (adjusted Odds ratio (OR) for every 10 years' increase 1.54; 95% confidence interval (CI), 1.05–2.27; $P = 0.0271$) and LDH (adjusted OR for elevation by every 50 IU/L 1.35; 95% CI, 1.09–1.67; $P = 0.0068$). Independent predictors for assisted non-invasive or invasive ventilation were age (adjusted OR for every 10 years' increase 2.08; 95% CI, 1.23–3.50; $P = 0.0059$), need for oxygen supplementation (adjusted OR 5.78; 95% CI, 1.44–23.16; $P = 0.0225$), and creatinine level (adjusted OR for elevation by every 10 μmol/L 1.86; 95% CI, 1.09–3.16; $P = 0.0134$).

Time to clinical stabilization

The time (median ± SE) to clinical stabilization of the 68 patients given combination therapy as estimated

Table 2 Comparisons between patients who required and did not require additional therapy (pulsed methylprednisolone, assisted ventilation)

Characteristics at commencement of combination treatment	Required additional pulsed methylprednisolone rescue			Required assisted ventilation[†]		
	Yes ($n = 30$)	No ($n = 38$)	*P*-value[‡]	Yes ($n = 18$)	No ($n = 50$)	*P*-value[‡]
Age (years)	48.0 ± 13.5	38.5 ± 15.0	0.005	53.1 ± 13.8	38.9 ± 13.7	0.001
Male gender	15 (50%)	12 (32%)	0.123	11 (61%)	16 (32%)	0.030
Smoker (active/ex-)	4 (13%)	4 (11%)	0.721	3 (17%)	5 (10%)	0.452
Diabetes mellitus	5 (17%)	3 (8%)	0.265	5 (28%)	3 (6%)	0.014
Requirement of O_2 supplementation	13 (43%)	8 (21%)	0.048	11 (61%)	10 (20%)	0.001
Respiratory rate (breaths/min)	20.8 ± 4.6	18.8 ± 2.3	0.030	21.6 ± 5.7	19.0 ± 2.3	0.041
Neutrophil count ($\times 10^9$/L)	5.0 ± 2.7	3.9 ± 2.4	0.028	5.2 ± 2.4	4.1 ± 2.6	0.038
Lymphocyte count ($\times 10^9$/L)	0.71 ± 0.28	0.88 ± 0.39	0.086	0.72 ± 0.30	0.84 ± 0.37	0.263
Platelet count ($\times 10^9$/L)	171.1 ± 56.0	155.7 ± 47.0	0.440	160.7 ± 42.3	163.1 ± 54.6	0.922
Creatinine (μmol/L)	85.1 ± 24.2	78.1 ± 12.8	0.263	91.7 ± 27.3	77.4 ± 13.1	0.009
Alanine transaminase (IU/L)	73.3 ± 106.5	51.4 ± 97.4	0.027	55.3 ± 45.5	63.2 ± 115.3	0.131
Creatine kinase (IU/L)	428.4 ± 747.4	142.9 ± 160.3	0.026	589.7 ± 918.3	153.4 ± 184.3	0.012
Lactate dehydrogenase (IU/L)	364.6 ± 160.6	254.2 ± 107.5	0.002	388.4 ± 170.0	272.2 ± 120.4	0.007
Chest radiograph score	12.3 ± 5.9	8.5 ± 4.9	0.005	12.7 ± 6.5	9.3 ± 5.1	0.031

Values are number (%) or mean ± SD unless stated otherwise.
[†] Either non-invasive ventilation or mechanical ventilation.
[‡] Mann–Whitney *U*-test or χ^2 tests.

by Kaplan-Meier analysis was 14.0 ± 0.9 (95% CI, 12.2–15.8) days after symptom onset and 8.0 ± 1.2 (95% CI, 5.6–10.4) days after commencement of combination treatment. Multivariate Cox regression analysis (Table 3) showed that the only independent predictor for a longer time to stabilization was a median age of 41 or above (adjusted hazards ratio 2.58; 95% CI, 1.50–4.45; $P = 0.0006$). To further delineate its effect on outcome, age was stratified into three groups (< 30; ≥ 30 to < 60 and ≥ 60 years) for analysis. It could be shown that the older age groups took longer time to reach clinical stabilization (Fig. 2).

Complications

Of all 85 recruited patients ever treated with combined ribavirin and corticosteroid, no significant side-effects were recorded from ribavirin. Uncomplicated hyperglycaemia after corticosteroid occurred in 51 (58%) patients. Eleven (13%) developed pneumomediastinum/thoraces: spontaneously ($n = 6$), or during assisted ventilation ($n = 5$). Thirty-six patients were prescribed a second course of antibiotics (piperacillin/tazobactam in 34) to treat possible sepsis, as manifested by fever recrudescence and radiographic and/or respiratory deterioration during treatment. Two patients (2%) had major sepsis due to ventilator-associated pneumonia with acute respiratory distress syndrome (one due to methicillin-resistant *Staphylococcus aureus* (MRSA) who subsequently died, the other had *Xanthomonas maltophilia* and *Escherichia coli* and recovered). The patient with MRSA was elderly, and was also the only one tried on IgM-enriched immunoglobulin 5 mg/kg/day for 3 days (Pentaglobin; Biotest Pharma GmbH, Dreieich, Germany)
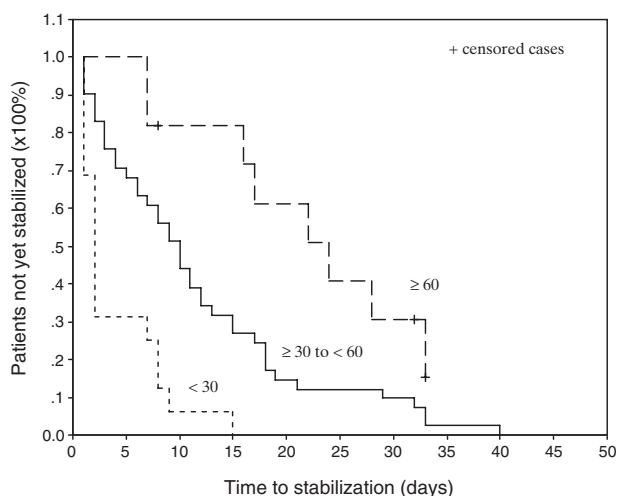

Figure 2 Kaplan-Meier plot of time to clinical stabilization. The median (± SE) time to clinical stabilization from the commencement of combination treatment in patients treated *de novo* with standard protocol ($n = 68$) was 2.0 ± 0.3 days for patients aged < 30 ($n = 16$), 10.0 ± 1.3 days for aged ≥ 30 to < 60 ($n = 41$), and 24.0 ± 5.3 days for aged ≥ 60 ($n = 11$); $P < 0.0001$ by log-rank test.

late in the course of the illness but without clinical efficacy. None of the other 67 patients required other antivirals or immunomodulating agents. Three (3%) had urinary tract infection: *E. coli* ($n = 2$) or Group B streptococcus ($n = 1$). None of the six HBsAg-positive patients had hepatitis flare-up. Two patients (2%) had transient pancytopaenia associated with positive parvovirus B19 serology, one of whom also had mild

Table 3 Kaplan-Meier analysis of time to clinical stabilisation from commencement of combination treatment for 68 patients given the standard combination therapy

Characteristics at commencement of combination treatment	Group	No. patients ($n = 68$)	Time (days) to clinical stabilization (median ± SE)	*P*-value*
Age	< 41	32	5.0 ± 3.5	0.0002
	≥ 41	36	12.0 ± 2.9	
Gender	Male	27	12.0 ± 2.5	0.0636
	Female	41	7.0 ± 1.8	
Smoker (active/ex-)	Yes	8	12.0 ± 7.8	0.8846
	No	60	8.0 ± 1.1	
Diabetes mellitus	Yes	8	24.0 ± 9.0	0.0050
	No	60	8.0 ± 1.1	
Requirement for O_2 supplementation	Yes	21	12.0 ± 2.9	0.0965
	No	47	7.0 ± 2.3	
Neutrophil count ($\times 10^9$/L)	< 3.65	34	7.0 ± 2.5	0.0690
	≥ 3.65	34	10.0 ± 3.4	
Lymphocyte count ($\times 10^9$/L)	< 0.78	34	8.0 ± 2.1	0.9794
	≥ 0.78	34	8.0 ± 1.3	
Platelet count ($\times 10^9$/L)	< 158	33	10.0 ± 2.9	0.7846
	≥ 158	35	8.0 ± 1.4	
Creatinine (μmol/L)	< 77	34	6.0 ± 1.8	0.0363
	≥ 77	34	11.0 ± 1.9	
Alanine aminotransferase (IU/L)	< 31	34	7.0 ± 2.2	0.1013
	≥ 31	34	9.0 ± 2.3	
Creatine kinase (IU/L)	< 93	34	7.0 ± 1.5	0.3040
	≥ 93	34	10.0 ± 1.6	
Lactate dehydrogenase (IU/L)	< 262	34	7.0 ± 2.3	0.1096
	≥ 262	34	12.0 ± 2.8	
CXR score	< 8.5	32	7.0 ± 2.4	0.0383
	≥ 8.5	36	12.0 ± 2.9	

[†] Log-rank test.

haemolytic anaemia. Two elderly patients with diabetes mellitus (2%) had fatal vascular events: acute myocardial infarction ($n = 1$) and ischaemic brainstem stroke ($n = 1$). Six (7%) had psychiatric manifestations: acute confusion ($n = 2$) and anxiety depression ($n = 4$), which could have been related to corticosteroids or the illness *per se*.

Final outcome

Outcomes of all 88 patients are summarized in Table 4. As of 15 July 2003, all patients have been observed for 104 ± 13 days (range, 78–128) from admission. There was one death (1.1%) attributable to SARS and MRSA pneumonia, and two due to comorbidities. All-cause mortality rate in this series was 0/76 in patients aged < 60, and 3/12 (25%) in those aged ≥ 60. CXR of all 85 survivors were significantly clearer on discharge (score 4.8 ± 5.4 *vs* 7.8 ± 5.6 on admission; $P < 0.001$), with most having little residual changes (60% scored ≤ 4; 79% scored ≤ 8). No discharged patient required oxygen therapy or had SARS relapse.

DISCUSSION

We reported the outcomes of 88 patients who were WHO/CDC-defined probable cases of SARS, of whom

97% had laboratory-confirmed SARS-CoV infection. The cohort that was studied represented an unselected group of SARS patients who had been treated with a standard protocol since mid-March 2003, at a time when knowledge about this disease was still scarce.[9] Given the uniformity of intervention, we could evaluate in detail the actual dosages and efficacy of drugs administered, and draw inferences on outcome predictors for this disease. In comparison, the type, route and dosages of drugs administered have not been uniform in other reported series.[5–8] Similar to these series, however, inclusion of appropriate internal controls was impossible and unethical during a rapidly evolving outbreak of a new and life-threatening disease.

Our 88-patient cohort had a lower mortality rate compared with most reported series, as well as the estimated overall case fatality rates of SARS in Hong Kong, which were 13.2% for patients younger than 60, and 43.3% for patients aged 60 or older.[14] Our cohort had zero mortality below the age of 60 and 25% all-cause mortality in those aged 60 or above, among whom there was only one death attributable to SARS. The presenting demographic and clinical characteristics of our patients (Table 1) were similar to or worse than those reported by the larger series in the literature,[5–8] but only one patient received Pentaglobin as additional immunomodulatory agent. Other modalities of experimental treatment (e.g. lopinavir-

Table 4 Outcomes of 88 severe acute respiratory syndrome (SARS) patients ever treated with the standard protocol*

Outcomes	Standard protocol *de novo* (n = 71)	Standard protocol with prior treatment (developmental phase protocol) (n = 11)	Standard protocol with prior treatment (regimen of other hospital) (n = 6)	All patients (n = 88)
Non-invasive ventilation only	11 (15%)	1 (9%)	0	12 (14%)
Mechanical ventilation	7 (10%)	1 (9%)	1 (17%)	9 (10%)
Intensive care unit admission	15 (21%)	2 (18%)	4 (67%)	21 (24%)
Length of intensive care unit stay (days)	5.8 ± 6.0	8.5 ± 3.5	16.3 ± 26.0	8.0 ± 12.0
Total hospital length of stay (days)	25.1 ± 6.8	34.5 ± 14.0	41.8 ± 18.7	27.4 ± 10.3
Time to clinical stabilization (median ± SE)				
From admission (days)	10.0 ± 1.4	12.0 ± 4.4	26.0 ± 4.5	12.0 ± 1.0
From symptom onset (days)	14.0 ± 1.0	15.0 ± 2.1	33.0 ± 3.7	15.0 ± 0.9
Deaths[†]				
SARS	1 (1.4%)	0	0	1 (1.1%)
Other causes	2 (2.8%)	0	0	2 (2.3%)
Discharged home	68 (96%)	11 (100%)	6 (100%)	85 (97%)

  Values are number (%) or mean ± SD unless stated otherwise.

[†] Deaths: SARS (aged 74); acute myocardial infarction (aged 67); acute brainstem and cerebellar stroke (aged 72).

ritonavir combination,[15] convalescent serum therapy,[16] thymosin-α 1 (SciClone Pharmaceuticals Inc, San Mateo, CA, USA),[17] pentoxyfylline, tumour necrosis factor blocking agents (etanercept (Amgen Inc, Thousand Oaks, CA, USA and Wyeth Pharmaceuticals, Madison, NJ, USA) and infliximab), had not been required in other patients because of satisfactory response to the standard protocol. We did not find HbsAg carrier state to be an adverse factor, and lamivudine had not been used for prophylaxis of hepatitis B relapse.[6,8] We venture to postulate therefore that the differences in outcome between ours and other reported series could possibly be related to differences in the details of treatment interventions given.

Although ribavirin had been commonly used in the 2003 SARS outbreak,[5–7,9] it is now widely believed that it has no benefits on outcome.[18,19] We continued to use ribavirin because of the continuing recovery of our patients and because of theoretical benefits from its immunomodulatory activities.[20,21] Where the drug was given at higher dosages,[7] major adverse effects had occurred without improvement in outcome. We therefore think that ribavirin *per se* is unlikely to be the reason for the satisfactory outcome in our patients. However, the effect of ribavirin in the present study could not be independently assessed because most patients had received both corticosteroid and ribavirin. The utility of corticosteroids in SARS has also been much debated. Activation of the immune system by acute bacterial or viral infection is known to stimulate the production of pro-inflammatory cytokines. Corticosteroids can decrease the release of macrophage-derived inflammatory cytokines,[22] and there are anecdotal reports suggesting benefits from high-dose corticosteroids in the management of other viral pneumonitis.[23–26] Since the dose regimens employed were dissimilar between

series,[1,4–9] we believe that differences in timing, dosage and duration of corticosteroid use may account for differences in outcome.[19]

Our group commenced methylprednisolone at a mean of 5.8 ± 3.0 days after symptom onset, when clinical criteria we had defined *a priori* as representing an excessive host response were fulfilled. The pathogenesis of SARS is proposed to comprise three stages, namely viral replication, lung inflammation and fibrosis.[6] Based on this assumption, we speculate that our treatment criteria had enabled our patients to be covered with an anti-inflammatory agent very soon after the onset of immune lung damage. In another series in which a similar combination was started based solely on lack of clinical response to antibiotics after 48 h without explicit radiological criteria, or even earlier if patients had epidemiological history of contact,[8] mortality was 7.9% which the authors stated was an underestimation because of sampling bias. The comparatively higher mortality could have reflected an earlier use of corticosteroid without considering clinical indicators of onset of pulmonary immunopathological damage. If this hypothesis is correct, such timing would possibly be still in the pure viral replicative phase in some of the patients, with the possible risk of further increasing the viral load without corresponding beneficial effect on immunopathological lung damage. While nasopharyngeal aspirate PCR status for SARS-CoV aspirate was a predictor of mortality in another series,[27] there was no relationship between this status and the time to stabilization in our patients. We therefore believe that appropriate timing of steroid commencement could be a more important factor predicting outcome.

Experience derived from our protocol development suggests that starting corticosteroids at lower dosages
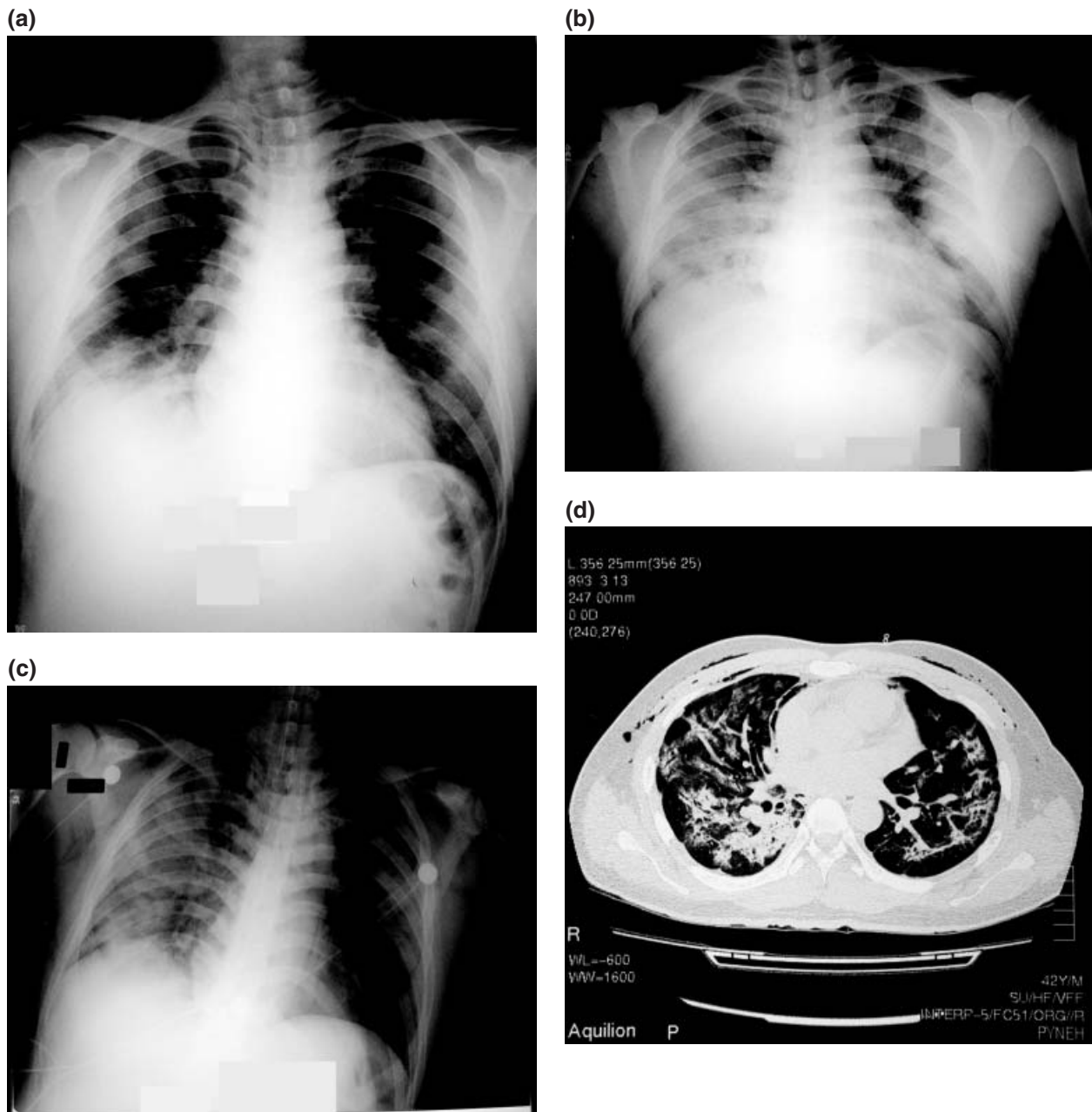
(a)

(b)

(d)

(c)

Figure 3 Radiological findings illustrating the clinical course of a 42-year-old-male patient (chronic smoker and drinker) responding to the treatment strategies in the protocol. (a) CXR at hospital admission. Combination treatment was given 1 day after admission (7 days after symptom onset) because of bilateral extensive peripheral patchy CXR involvement and desaturation. (b) Due to rapid clinical and radiological progression, pulsed methylprednisolone was given 2 days after admission. Non-invasive ventilation with bi-level positive airway pressure (BIPAP) was given for 7 days. If non-invasive ventilation had not been chosen as the initial mode of ventilatory assistance, the severity of his respiratory failure would have warranted intubation. (c) Due to failure to respond to non-invasive ventilation, intubation and mechanical ventilation was eventually required and had been instituted for 6 days. No ventilator-associated pneumonia was documented. Subcutaneous emphysema can be seen in bilateral axillary tissues on the CXR. Despite the persistence of lung infiltrates, no further pulsed steroid was given because CXR began to improve after his initial course of pulsed steroid therapy. (d) CT thorax after extubation. Pneumomediastinum and subcutaneous emphysema are seen. The lung infiltrates consisted mainly of thickened interstitium bilaterally suggestive of early scarring. The patient was prescribed tailing dosages of corticosteroid according to the protocol and continued to improve. (e) The patient began to be weaned off oxygen supplementation at 4 weeks after admission. The infiltrates appear to be different from those in the initial films, being consistent with resolution of lung scars after inflammation or infection. (f) CXR about 8 weeks after symptom onset. Scarring is minimal despite the initial extensive involvement and stormy course. Further resolution of the scarring was seen and his CXR returned to near normal on subsequent follow up.

(e)

(f)

may not be able to control immunopathological lung damage.[9] Since persistent elevation of proinflammatory cytokines may promote bacterial proliferation *in vitro,*[28] a state of immune balance achieved with an appropriate/optimal corticosteroid dosage could have contributed to our relatively low rate of nosocomial infection. Another SARS treatment protocol from China using similar high-dose corticosteroids commenced only on worsening of clinical criteria also produced lower mortality than regimens at lower dosages.[17] A series in Hong Kong which started treatment with pulse methylprednisolone of ≥500 mg per day also showed better outcomes than initial non-pulse (< 500 mg per day) methylprednisolone.[29,30] These two series appear to support our hypothesis that high-dose corticosteroids are required at the start of treatment to achieve disease control.

In the management of unresolving acute respiratory distress syndrome due to fibroproliferation[31] and *Pneumocystis carinii* pneumonia with desaturation,[32] a step-down course of corticosteroids for at least 21 days is recommended. In experimental acute lung injury, shorter corticosteroid courses may compromise recovery due to enhanced accumulation of collagen after discontinuing therapy.[33] Rapid corticosteroid withdrawal can be dangerous if proinflammatory cytokines resurge in the presence of persistently upregulated receptors.[34,35] We also observed that an adequate duration of corticosteroid usage was necessary to prevent rebound of SARS symptoms[9,19] While our patients received step-down corticosteroids strictly according to a standard protocol, details of steroid tapering in other studies was usually not described or were varied according to individual clinical conditions.[5–8] Such variations may also account for some of the differences in patient outcomes.

The present study is not a controlled study but the satisfactory results compared to other series are very encouraging. The reason for its success however, remains speculative. Further randomized controlled trials are suggested to confirm its efficacy.

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