Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Journal of Critical Care (2008) **23**, 557–564

ELSEVIER

Journal of Critical Care

Characteristic features and outcomes of severe acute respiratory syndrome found in severe acute respiratory syndrome intensive care unit patients

Te-Cheng Lien MD, FCCP[a,g], Chun-Sung Sung MD, PhD[b,g], Chen-Hsen Lee MD[c,g], Hsin-Kuo Kao MD[a,d,g], Ying-Che Huang MD[b,g], Cheng-Yi Liu MD[e,g], Reury-Perng Perng MD, FCCP[f,g], Jia-Horng Wang MD, FCCP[a,g,*]

[a]*Department of Respiratory Therapy, Taipei Veterans General Hospital, Taipei 112, Taiwan, ROC*
[b]*Department of Anesthesiology, Taipei Veterans General Hospital, Taipei 112, Taiwan, ROC*
[c]*Taipei Veterans General Hospital, Taipei 112, Taiwan, ROC*
[d]*Institute of Clinical Medicine, National Yang-Ming University School of Medicine*
[e]*Division of Infection, Department of Internal Medicine, Taipei Veterans General Hospital, Taipei 112, Taiwan, ROC*
[f]*Chest Department, Taipei Veterans General Hospital, Taipei 112, Taiwan, ROC*
[g]*National Yang-Ming University School of Medicine*

Keywords:
Coronavirus;
Intensive care;
Reverse transcriptase–polymerase chain reaction;
Severe acute respiratory syndrome

Abstract

Purpose: The aim of the study was to identify characteristic clinical features and outcomes of critically ill patients with confirmed severe acute respiratory syndrome (SARS).

Materials and Methods: This retrospective study enrolled all patients admitted to a 12-bed SARS intensive care unit (ICU) in a tertiary care medical center in Taipei between May 15 and July 17, 2003. Patients with positive results of either reverse transcriptase–polymerase chain reaction or antibody to SARS coronavirus were defined as SARS cases and others with negative results as control cases.

Results: Of the 50 patients, 14 had confirmed SARS. Demographics were similar between the 2 groups. The highest leukocyte and neutrophil counts, lactate dehydrogenase, and creatine kinase; positive end-expiratory pressure; and use of corticosteroids, ribavirin, and intravenous immunoglobulin were higher in the SARS group. In contrast, the lowest lymphocyte count and the ratio of Pao_2 to the fraction of inspired oxygen were lower in the SARS group. Of the 15 deaths in the control group, 12 (80%) occurred during the first 2 weeks after ICU admission. However, in the confirmed SARS group, 5 (55.6%) of the 9 deaths occurred within the third or fourth week. This difference in timing between these 2 groups was significant ($P = .004$).

Conclusions: In a SARS ICU, patients with a confirmed diagnosis of SARS had significantly different clinical features and timing of mortality from those of the control group.

* Corresponding author. Department of Respiratory Therapy, Taipei Veterans General Hospital, Taipei 112, Taiwan, ROC. Tel.: +886 02 28757455; fax: +886 02 28757610.
E-mail address: kuohsink@ms67.hinet.net (J.-H. Wang).

0883-9441/$ – see front matter © 2008 Elsevier Inc. All rights reserved.
doi:10.1016/j.jcrc.2007.05.004

1. Introduction

Severe acute respiratory syndrome (SARS) is a infectious disease caused by a novel coronavirus (CoV) [1,2]. It emerged from southern China in late 2002 and spread rapidly throughout the world. After the first warning of SARS from the World Health Organization (WHO) in March 2003, 774 of 8098 patients with reported SARS died within 4 months [3]. Besides China and Hong Kong, Taiwan had the third largest population of patients with SARS in the world.

After the major SARS outbreak at the Municipal Hoping Hospital in Taipei, Taiwan, on April 24, 2003, there were several outbreaks involving at least 5 other hospitals within 40 days. Most of the patients with SARS were treated in major tertiary teaching hospitals with isolation rooms in Taipei. During this period, contact history was difficult to determine. Because of fear of further disease spread and concerns over possible legal liability, the clinicians tended to raise the suspicion of SARS. By the WHO definition and after reconfirmation by government expert teams, there were 664 SARS probable cases from late February to June, 2003, in Taiwan [4]. Of these cases, only 346 (52.1%) patients had tested positive by reverse transcriptase–polymerase chain reaction (RT-PCR) or antibody to SARS CoV. This detection rate was remarkably lower than that reported by others (85%-97%) [5,6]. This overreporting of SARS cases was even more striking in critically ill patients with multiple comorbidities whose radiographic pulmonary infiltrations were commonly attributed to underlying diseases.

Approximately 25% of patients with SARS are likely to progress to severe respiratory failure. Although ICU admission rates were as high as 20% to 38% [6-10], only 2 cohort studies focusing on this group of patients have been conducted [11,12]. Furthermore, the diagnosis of SARS in both studies was based on the clinical case definition only.

In the critical care setting, health care workers (HCWs) are at a higher risk of SARS because of exposure during patient care and more invasive procedures (such as the endotracheal intubation and airway suctioning) used in more severe cases [13,14]. Actually, up to 28% to 54% of patients with SARS were HCWs [7-9]. Under these circumstances, case isolation and contact precautions must be strictly carried out during outbreaks. According to our observation and those of others [15], health care was inevitably delayed while awaiting the HCWs to put on their protective clothing. And when patient management is emergent and crucial, as is the case when critically ill patients with SARS are involved, this delay may, at least to some extent, influence patient outcomes. However, none of the previous studies surveying outcomes of SARS could avoid this problem.

The overreporting of SARS during the outbreak in Taiwan permits direct comparison of the clinical presentations and outcomes of critically ill patients with confirmed SARS to those of a control group without confirmed SARS treated in the same SARS ICU. Exploiting the difference between these 2 groups, we hope to identify more clearly the clinical features and outcomes of critically ill patients with confirmed SARS.

2. Patients and methods

2.1. Study population

The study enrolled all patients admitted into a 12-bed SARS ICU in Taipei Veterans General Hospital between May 14 and July 17, 2003. Most of the patients met the WHO definition of suspected or probable SARS. Suspected SARS was defined by the presence of fever (temperature, >38°C), respiratory symptoms, and a positive travel or contact history. Probable SARS required the presence of pulmonary infiltrates on chest radiograph.

Physical restraints and intravenous sedation were used liberally in patients with agitation. Treatment including broad-spectrum antibiotics, ribavirin, intravenous immunoglobulin (IVIG), and corticosteroids was prescribed as needed. Briefly, patients who had stable hemodynamics, stable cough reflex, and tolerated at least 2 hours of pressure support ventilation at a level of ≤10 cm H_2O with arterial oxygen saturation >90% and Pa_{O_2} >60 mm Hg on a fraction of inspired oxygen (F_{IO_2}) of <0.4 were weaned.

Routine laboratory studies were performed on admission and during the ICU stay. In addition, the sputum, blood, and urine of patients with fever were cultured. For diagnostic purposes, swabs from patients' nasopharynx and stool were taken on admission (emergency department or hospital) and every 2 days during the ICU period, whereas blood samples were collected on admission (emergency department or hospitalization) and every 3 days during the ICU period.

2.2. Data collection

The demographic information was obtained for each patient. The Acute Physiology and Chronic Health Evaluation (APACHE) II score was calculated only on the day of admission to the ICU. The data before the date of fever onset and after ICU discharge were not taken into account in this study. For those patients without obvious fever, data collection began on the day of hospital admission. The mechanical ventilation data extracted from the respiratory therapy records included mode of ventilation, highest positive end-expiratory pressure (PEEP), and lowest Pa_{O_2}/F_{IO_2} and Pa_{O_2}/F_{IO_2} on ICU admission. Among the specific treatments recorded were corticosteroids, ribavirin, IVIG, and antibiotics.

2.3. Definition of confirmed SARS diagnosis

For all the patients admitted to our SARS ICU, RT-PCR test and antibody to SARS CoV were used to detect the virus

in nasopharyngeal aspirates, blood, and fecal samples. Patients with either a positive RT-PCR test or a positive SARS CoV antibody test were defined as confirmed SARS cases.

2.4. Outcome measures

The primary outcome was mortality 120 days after ICU admission. The secondary outcomes included ventilator dependence at 30 days after ICU admission, duration of ICU stay, duration of hospitalization, and mortality rate in the ICU.

2.5. Statistical analysis

All data are presented as mean ± SD. The statistical analysis was performed with SPSS statistical software (SPSS, Chicago, Ill). Categorical data were compared with the Fisher exact test, whereas continuous variables were compared with the Mann-Whitney *U* test. The Kaplan-Meier product-limit estimator was used to estimate survival. The survival time was counted from the day of ICU admission, and patients were censored if they were still alive 120 days after ICU admission. A 2-tailed *P* value of less than .05 was considered statistically significant.

Table 1 Characteristics of patients on admission to the SARS ICU

Characteristics	Patients (n = 50)
Age, y (range)	73.7 ± 13.6 (27-91)
Male/female	37/13
HCW (%)	2 (4)
Comorbidities	
Diabetes mellitus	20 (40)
Hypertension	19 (38)
Cerebrovascular disease	17 (34)
Ischemic heart disease	11 (22)
Chronic renal insufficiency	6 (12)
COPD	5 (10)
Symptoms	
Fever	47 (94)
Diarrhea	29 (58)
Cough	24 (48)
Chills	4 (8)
Myalgia	3 (6)
Headache	2 (4)
Pa_{O_2}/F_{IO_2}	265.8 ± 136.7
APACHE II score	20.6 ± 8.1
Days between fever onset and ICU admission	10.9 ± 1.8
No. requiring mechanical ventilation	44 (88)

Data are presented as mean ± SD or n (%) unless otherwise indicated.
COPD indicates chronic obstructive pulmonary disease.

Table 2 Comparison of confirmed SARS and control patients in the SARS ICU with respect to demographics, comorbidities, and clinical features

Variable	Patients with confirmed SARS (n = 14)	Patients without confirmed SARS (n = 36)	*P*
Age, y (range)	67.0 ± 18.1 (24-84)	76.3 ± 10.6 (41-91)	.122
Male	8 (57.1)	29 (80.6)	.149
HCW (%)	2 (14.3)	0	.074
APACHE II score on admission	19.3 ± 8.8	21.1 ± 7.8	.514
Comorbidities			
Diabetes mellitus	8 (57.1)	12 (33.3)	.198
Hypertension	4 (28.6)	15 (41.7)	.522
Cerebral vascular disease	3 (21.4)	14 (38.9)	.327
Ischemic heart disease	3 (21.4)	8 (22.2)	1.000
Chronic renal failure	1 (7.1)	5 (13.9)	.663
COPD	1 (7.1)	4 (11.1)	1.000
Selected symptoms and signs on admission to ICU			
Fever	13 (92.9)	32 (88.9)	1.000
Diarrhea	5 (35.7)	25 (69.4)	.052
Cough	6 (42.9)	18 (50.0)	.767
Chills	2 (14.3)	2 (5.6)	.260
Myalgia	0	3 (8.4)	.538
Headache	0	2 (5.6)	.511

Data are presented as mean ± SD or n (%) unless otherwise indicated.

3. Results

3.1. Demographics and clinical features of the study population

As shown in Table 1, 50 critically ill patients were admitted to the SARS ICU, and 74% of them were male. Most patients were relatively old (mean age, 73.7 ± 13.6 years) and had multiple comorbidities such as diabetes mellitus, hypertension, and cerebrovascular disease. Only 4% of the patients were HCWs (nurses). The most common presenting symptoms on ICU admission were fever (94%), diarrhea (58%), and cough (48%). However, there were 3 patients without fever before ICU admission. Only one of them, an 84-year-old man with a positive RT-PCR for SARS CoV, developed fever 3 days later and died 25 days after ICU admission. The other 2 patients never developed fever, and the laboratory diagnostic results were all negative. Although the mean APACHE II score of the study population was relatively high on ICU admission (20.6), the severity of lung injury was only mild (with a mean value of Pa_{O_2}/F_{IO_2}, 265.8). All patients received aggressive respiratory therapy (non–re-breathing mask, endotracheal or tracheostomy intubation), and 88% of them underwent mechanical ventilation.

3.2. Demographic differences between the SARS and the control groups

Of these 50 patients, 14 were confirmed SARS by RT-PCR or antibody testing. The other 36, with negative RT-PCR and antibody tests, were categorized as the control group. Demographics including age, sex, and APACHE II score on ICU admission were similar between these 2 groups (Table 2). The 2 HCWs admitted to the ICU were confirmed SARS cases. In contrast, none of the patients in the control group were HCWs. However, the difference was statistically insignificant (P = .074). There was also no remarkable difference in comorbidities and initial presenting symptoms between the 2 groups. However, the incidence of diarrhea was higher, but not significantly, in the control group than in the SARS group (69.4% vs 35.7%, P = .052; Table 2).

Table 3 Comparison of SARS and control groups with respect to laboratory variables

Variable	Patients with confirmed SARS (n = 14)	Patients without confirmed SARS (n = 36)	P
Highest respiratory rate (breaths/min)	26.5 ± 9.2	26.1 ± 9.1	.927
Highest temperature (°C)	38.1 ± 2.9	38.4 ± 0.7	.451
Highest WBC count (μL^{-1})	27 090 ± 8930	16 736 ± 8592	<.001
Highest neutrophils (μL^{-1})	25 014 ± 9285	14 169 ± 7012	<.001
Lowest lymphocytes (μL^{-1})	354 ± 277	661 ± 533	.029
Lowest platelets ($\times 10^3/\mu L$)	135 ± 64	147 ± 92	.863
Highest CRP (mg/dL)	20.0 ± 10.6	14.9 ± 11.1	.075
Highest lactate (mEq/L)	3.9 ± 1.4	3.2 ± 2.8	.015
Highest glucose (mg/dL)	336 ± 114	248 ± 160	.023
Highest LDH (U/L)	688 ± 513	458 ± 237	.029
Highest CK (U/L)	728 ± 1094	171 ± 197	.043
Highest sodium (mEq/L)	148 ± 6	144 ± 8	.112
Lowest sodium (mEq/L)	125 ± 28	131 ± 8	.778
Highest potassium (mEq/L)	5.3 ± 1.0	5.2 ± 1.4	.787
Lowest potassium (mEq/L)	3.0 ± 0.8	3.0 ± 0.4	.820
Highest creatinine (mg/dL)	2.1 ± 1.7	2.4 ± 1.9	.619
Highest urea (mg/dL)	74.8 ± 60.0	65.5 ± 42.1	.880
Lowest phosphorus (mg/dL)	2.8 ± 1.0	2.5 ± 0.8	.317
Lowest albumin (g/dL)	2.5 ± 0.4	2.6 ± 0.4	.744

Data are presented as mean ± SD or n (%). CRP indicates C-reactive protein.

Table 4 Comparisons of SARS and control groups in SARS ICU with respect to ventilatory parameters, medications, and complications

Variable	Patients with confirmed SARS (n = 14)	Patients without confirmed SARS (n = 36)	P
Mechanical ventilation			
Duration of ventilator (d)	28.8 ± 39.8	22.5 ± 29.2	.624
Highest PEEP (cm H_2O)	9.3 ± 3.0	7.7 ± 3.9	.042
Pao_2/Fio_2 on admission	216 ± 140	287 ± 132	.063
Lowest Pao_2/Fio_2	119 ± 116	220 ± 137	.007
Highest $PaCO_2$	64.7 ± 21.3	51.4 ± 18.1	.069
Medications			
Corticosteroids	12 (85.7)	14 (38.9)	.004
Ribavirin	7 (50)	5 (13.9)	.023
IVIG	6 (42.9)	5 (13.9)	.052
Antibiotics	12 (85.7)	29 (80.6)	1.000
Complications			
Pneumothorax	2 (14.3)	3 (8.3)	.611
Self-extubation	2 (14.3)	1 (2.8)	.186
Acute renal failure requiring hemodialysis	1 (7.1)	1 (2.8)	.486

Data are presented as mean ± SD or n (%).

3.3. Clinical features

With respect to blood counts, the lowest blood lymphocyte count was significantly lower in the SARS than in the control group (354 ± 277 vs 661 ± 553 μL^{-1}; P = .029); however, both the highest white blood cell (WBC) and neutrophil counts were significantly higher in the SARS than in the control group (27 090 ± 8930 vs 16 736 ± 8592 μL^{-1} and 25 014 ± 9285 vs 14 169 ± 7012 μL^{-1}, respectively; both P < .001) (Table 3). Similarly, among the biochemical variables, the highest levels of LDH and creatine kinase (CK) were significantly higher in the SARS than in the control

Table 5 Outcomes of SARS and control groups

Variable	Patients with confirmed SARS (n = 14)	Patients without confirmed SARS (n = 36)	P
Ventilator dependence at 30 d	2 (14.3)	7 (19.4)	.788
Duration of ICU stay (d)	18.8 ± 15.5	11.1 ± 7.6	.056
Duration of hospital stay (d)	39.5 ± 58.5	40.1 ± 34.8	.415
ICU mortality	6 (42.9)	12 (33.3)	.533
Mortality at 120 (d)	9 (64.3)	15 (41.7)	.211

Data are presented as mean ± SD or n (%).

group (688 ± 513 vs 458 ± 237 U/L [P = .029] and 728 ± 1094 vs 171 ± 197 U/L [P = .043], respectively). Moreover, patients with SARS also had a higher blood lactate level (3.9 ± 1.4 vs 458 ± 237 U/L, P = .015) and worse blood glucose control (336 ± 114 vs 248 ± 160 U/L, P = .023) than the control patients (Table 3). No other laboratory parameters differed significantly between these 2 groups.

3.4. Treatment and outcomes

Table 4 compares mechanical ventilation parameters, medications, and complications between the SARS and control groups. Although we did not intend to monitor routine medication in each of our SARS ICU patients either before or after the confirmation of SARS diagnosis, interestingly, higher PEEP (9.3 ± 3 vs 7.7 ± 3.9; P = .042) was found, and more corticosteroids (85% vs 38.9%; P = .004) and ribavirin (50% vs 13.9%; P = .023) were used in the SARS group. Among the respiratory parameters, the lowest Pao_2/Fio_2 ratio was markedly lower in patients with SARS than in control patients (119 ± 116 vs 220 ± 137; P = .007). However, the duration of mechanical ventilation and the incidence of complications were not significantly different between the 2 groups (Table 4).

Eighteen patients (36%) died in the ICU (6 [42.9%] in the SARS group and 12 [33.3%] in the control group), and no statistical between-group difference in mortality rate was found (P = .533) (Table 5). There was still no significant difference by day 120 after the ICU admission (P = .211) (Table 5) when another 6 patients (3 in each group; cumulative mortality rate, 48%) died. Similarly, there were no statistical between-group differences in either ventilator dependence 30 days after ICU admission or duration of hospital stay (Table 5). However, patients with SARS tended to have longer ICU stays (18.8 ± 15.5 vs 11.1 ± 7.6 days; P = .056, Table 5).

After survival analysis, the cumulative survival rate by day 120 after ICU admission was insignificantly lower in the SARS than in the control group (35.7% vs 58.3%, P = .211; Fig. 1). Furthermore, patients in the control group most commonly died within the first 2 weeks after ICU admission (12/15), whereas patients with confirmed SARS mostly died in the third to fourth week after ICU admission (5/9). The between-group difference in mortality occurrence at 2 weeks and 3 to 4 weeks was remarkably significant (P = .004, Fig. 2).

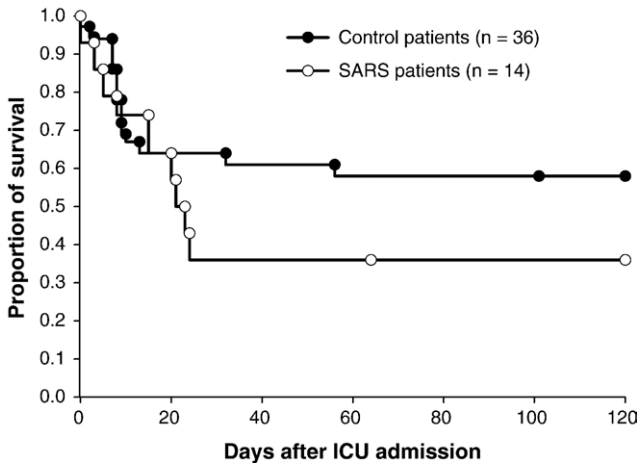

Fig. 1 Survival meta-analysis in the confirmed SARS and control patients 120 days after ICU admission.

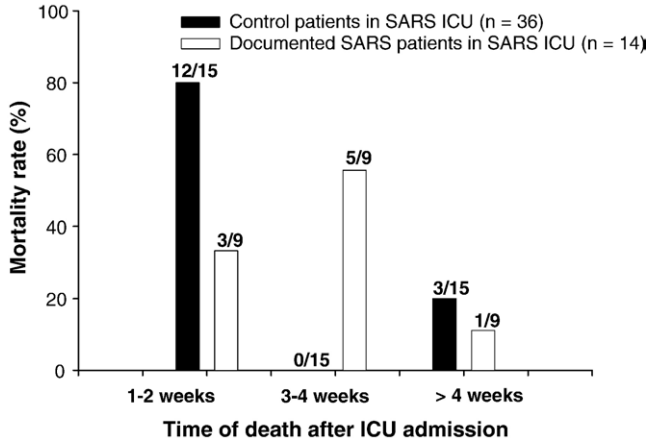

Fig. 2 Numbers of deaths in the confirmed SARS and control patients 1 to 2, 3 to 4, and more than 4 weeks after ICU admission. Most of the deaths of patients with SARS occurred 3 to 4 weeks after admission, whereas most of the deaths of control patients occurred within 2 weeks after ICU admission.

4. Discussion

Severe acute respiratory syndrome is a highly contagious respiratory disease that is most likely spread via respiratory droplets and transmitted primarily via close contact with infected persons. Most patients with SARS develop respiratory distress, and 10% to 20% will progress to respiratory failure and need mechanical ventilatory support [16]. The present study revealed that critically ill patients with confirmed SARS had characteristic clinical presentations in contrast to patients whose disease fulfilled the WHO case definition of, but not the laboratory criteria for, SARS. In addition to the laboratory diagnostic tests for confirmed SARS infection, these results may help HCWs improve the treatment protocol and care quality of these critically ill patients with SARS.

First, in addition to laboratory diagnostic features, characteristic clinical features are of great importance in the diagnosis of SARS. Although both RT-PCR and serologic tests for SARS CoV are more specific and valuable to the SARS diagnosis, there are limitations in their clinical use. Peiris et al [6] found that SARS CoV RNA detection by RT-PCR testing in the nasopharyngeal aspirate has a sensitivity of only 32% in week 1 of infection. Although the sensitivity of a single specimen examination can increase to 68% by day 14 [6], it is still too low to reliably document SARS infection. Therefore, testing of at least 2 different clinical specimens or

the same clinical specimen collected on 2 or more days is recommended to increase the sensitivity of RT-PCR test. In addition, although the sensitivity of serologic testing was reported as high as 93% by day 28 [2,6,17], this delay in SARS diagnosis inevitably decreases the diagnostic rate in the early phase of SARS infection and the turnover rate in an isolation ICU. In our study population, 12 (80%) of 15 of the deceased control patients died within 2 weeks after ICU admission. Possibly, SARS might have been ruled out in some of the deceased control patients by false-negative findings. Fortunately, clinical specimens (nasopharyngeal swabs, blood, and stool) were routinely collected in the SARS ICU, which would, at least in part, increase the accuracy of SARS testing. The need to interpret all laboratory diagnostic test results in the context of clinical and epidemiological findings has been suggested. Therefore, early recognition of the characteristic clinical features of critically ill patients with SARS isolated in the ICU should be stressed.

However, rate of false-positive diagnosis (overreporting) of SARS was high when we simply followed the WHO case definition. Only 14 (28%) of the 50 patients in our study were confirmed SARS cases, and laboratory testing failed to identify SARS in 72% of SARS ICU patients, which supported the suggestion by the Taiwan Centers for Disease Control that overreporting was very common. Taiwan Centers for Disease Control case cluster data indicated that RT-PCR and serologic testing failed to document SARS in 318 (48%) of 664 of reported SARS cases [4]. This overreporting might have been due to several factors. Severe acute respiratory syndrome was a newly emerging infectious disease that was unfamiliar to us. Moreover, the contact and travel histories of patients were not easily established in the chaos that followed the SARS outbreak. In addition, other diseases shared features of the SARS case definition (such as radiologic finding of lung infiltration, fever [temperature, >38°C], lymphopenia, and elevated LDH level). The ambiguity of symptoms made the diagnosis even more difficult among the critically ill patients in our SARS ICU (Table 2). For example, Peiris et al reported that watery diarrhea occurred in 73% of patients with SARS, which was different from our result and those of others [7,9]. In our present study, watery diarrhea occurred in only 35.7% of patients with SARS but more frequently (69.4%) in control patients in our SARS ICU. Furthermore, physicians who delayed or failed to report probable or suspected SARS cases would be accused of criminal incompetence in Taiwan. Actually, one hospital president in Taipei who delayed the report of an in-hospital SARS outbreak was sentenced to 3 years in prison in September, 2004. Overreporting consequently increased and in turn overloaded not only the health care system but also the whole society.

Second, the lowest lymphocyte count was significantly lower in patients with confirmed SARS than in the control patients. *Lymphopenia*, defined as a blood lymphocyte count of less than 1000 μL^{-1}, is a common finding in patients with SARS [5,6,9]. In the present study, we found that lymphopenia was common in the whole study population but more severe in patients with confirmed SARS. Nonetheless, the lowest lymphocyte count in our control group was still as low as 661 μL^{-1} (Table 3). Therefore, we suggest

Table 6 Characteristics and outcomes of 14 patients with a confirmed diagnosis of SARS

No.	Sex	Age (y)	Days of fever to mortality	Lowest lymphocyte count	Highest WBC count	Days of highest WBC count to mortality	Confirmation of SARS		Cause of death
							RT-PCR	Antibody	
1	F	46	NA	455	13 015	NA	+	+	Survived
2	F	27	NA	266	12 500	NA	−	+	Survived
3	M	79	NA	879	20 700	NA	+	−	Survived
4	F	41	NA	302	28 800	NA	+	+	Survived
5	F	73	NA	516	30 100	NA	−	+	Survived
6	M	79	21	232	30 900	0	−	+	Bacterial fungus RTI, arrhythmia
7	F	76	16	924	20 200	1	−	+	Bacterial RTI
8	M	80	16	286	49 700	1	+	−	Bacterial RTI
9	M	83	4	406	21 000	1	+	−	Bacterial RTI
10	M	64	46	176	23 300	1	+	−	Peritonitis
11	M	75	45	97	37 700	1	+	+	Fungus UTI
12	F	52	82	470	33 400	2	+	+	Bacterial, fungus RTI, UTI, MOF
13	M	84	25	206	20 000	9	+	−	Arrhythmia
14	M	79	25	876	27 300	14	−	+	AMI

NA indicates not applicable; RTI, respiratory tract infection; UTI, urinary tract infection; MOF, multiple organ failure; AMI, acute myocardial infection.

that lymphopenia used to establish a diagnosis of SARS in the critically ill might be lowered to a lymphocyte count less than 500 μL^{-1}.

Third, high serum levels of LDH and CK could be used as clinical diagnostic criteria and predictors of poor outcome in SARS. High LDH level (>3.8 μkat/L) has been suggested to be a predictor of poor outcome among patients with SARS [5,7]. Previous studies of critically ill patients with SARS found that nonsurvivors had significantly higher serum levels of LDH and CK than survivors, which suggested that both LDH and CK data could help predict SARS outcomes [11,12]. Our present study agrees with these previous studies and found in addition that LDH and CK levels were significantly higher in patients with SARS than in critically ill, control patients. Besides their negative prognostic effect on survival, high serum levels of LDH and CK can be effective clinical diagnostic criteria for SARS in critically ill patients. In addition, blood lactate and glucose levels were significantly higher in our SARS group than in our control group.

Fourth, our present study (unlike other studies) [5,6,9] found critically ill patients with SARS had markedly higher WBC and neutrophil counts. We think that the use of corticosteroids and concomitant bacterial or fungal infections might contribute to this result. Several reports have advocated aggressive and earlier use of corticosteroids in patients with SARS, especially those who were deteriorating rapidly [11,12,18]. So et al [18] proposed a standard treatment protocol for SARS consisting of ribavirin, empiric broad-spectrum antibiotics, and high-dose methylprednisolone (3 mg/kg/d for 5 days, followed by 11-day tapering, and with pulsed therapy of 500 mg twice daily for 2 days, if the lung condition worsened), and none of their 31 patients with SARS was intubated. We at first followed that treatment protocol but later excluded ribavirin owing to its ineffectiveness and potential for hemolysis [19]. As a result, only 50% of our study population received ribavirin. In our study population, a significantly higher proportion of the SARS group (12/14; 85.7%) compared to the control group received corticosteroid therapy (85.7% vs 38.9%; P = .004). Corticosteroids carry the risk of lowering or compromising patients' immunity, which will in turn increase their susceptibility to nosocomial infections. The effect of this factor may be even more critical because our patients were older, critically ill, mechanically ventilated, and had comorbidities. Moreover, all of our patients with SARS had leukocytosis and increased neutrophil count, and 9 (64.3%) died during the ICU stay. Among the deceased patients with SARS, 7 (78%) had concomitant bacterial and/or fungal infections, and their peak WBC count occurred within 2 days before death (Table 6). The above findings implied that corticosteroid use and concomitant bacterial/fungal infections might contribute to leukocytosis and high mortality in critically ill patients with SARS. Also, Lee et al [7] had suggested that advanced age and high neutrophil count were independent predictors of poor outcomes among patients with SARS. Accordingly, it might be better to use corticosteroids more cautiously in the old, comorbid, and critically ill patients with SARS.

Fifth, the later occurrence of high cumulative mortality rate was apparent in our critically ill patients with SARS. Most (56%) of the deaths in our SARS group occurred in the third to fourth week after ICU admission. This was remarkably different from the deaths in our non-SARS group, which occurred mostly (80%) within 2 weeks after ICU admission (P = .004, Fig. 2). Old age, comorbidities, and concomitant infections might have been contributing factors. However, other factors might also have been responsible for the time-related discrepancies in mortality between these 2 groups. Peiris et al [6] had shown that there were 2 peaks of acute respiratory distress syndrome development in patients with SARS. The first peak occurred between 10 and 12 days and the second between 19 and 21 days after fever onset. Maybe this second peak of acute respiratory distress syndrome development in patients with SARS impaired their lung functions and partly contributed to the relatively late occurrence of high mortality in our patients with SARS. In addition, the cumulative mortality rate at 120 days after ICU admission was relatively higher in our patients with SARS than in our control patients (64% vs 42%). However, the difference is not statistically significant (P = .21).

5. Conclusions

Overreporting of SARS is a common problem during SARS outbreaks especially in critically ill, older patients. In a SARS ICU, patients with confirmed SARS had significantly different clinical features from those of the control group. These different clinical features, along with RT-PCR and antibody tests, may strengthen the diagnosis of SARS and hasten the turnover rate in an isolation SARS ICU. Critically ill patients with SARS also die later than other critically ill patients in a SARS ICU, which might be a characteristic of the disease or be due to the use of corticosteroids and nosocomial infections.

Acknowledgment

The authors thank all the health care workers of the SARS ICU in Taipei Veterans General Hospital for their selfless devotion in the management of critically ill patients with SARS.

References

[1] Rota PA, Oberste MS, Monroe SS, et al. Characterization of a novel CoV associated with severe acute respiratory syndrome. Science 2003; 300:1394-9.

[2] Ksiazek TG, Erdman D, Goldsmith CS, et al. A novel CoV associated with severe acute respiratory syndrome. N Engl J Med 2003;348: 1953-66.

[3] World Health Organization. Cumulative number of reported cases of SARS. Available at: http://www.who.int/csr/sars/country/table2003_09_23/en/.
[4] Center for Disease Control, Taiwan. SARS data analysis for Taiwan from March to June 2003. Available at: http://www.cdc.gov.tw/sarsen/ (accessed November, 2003).
[5] Choi KW, Chau TN, Tsang O, et al. Outcomes and prognostic factors in 267 patients with severe acute respiratory syndrome in Hong Kong. Ann Intern Med 2003;139:715-23.
[6] Peiris JSM, Chu CM, Cheng VCC, et al. Clinical progression and viral load in a common outbreak of CoV-associated SARS pneumonia: a prospective study. Lancet 2003;361:1767-72.
[7] Lee N, Hui D, Wu A, et al. A major outbreak of severe acute respiratory syndrome in Hong Kong. N Engl J Med 2003;348: 1995-2005.
[8] Peiris JM, Lai ST, Poon LL, et al. Coronavirus as a possible cause of severe acute respiratory syndrome. Lancet 2003;361:1319-25.
[9] Booth CM, Matukas LM, Tomlinson GA, et al. Clinical features and short-term outcomes of 144 patients with SARS in the greater Toronto area. JAMA 2003;289:2801-9.
[10] Tsang KW, Ho PL, Ooi GC, et al. A cluster of cases of severe acute respiratory syndrome in Hong Kong. N Engl J Med 2003;348: 1977-85.
[11] Fowler RA, Lapinsky SE, Hallett D, et al. Critically ill patients with severe acute respiratory syndrome. JAMA 2003;290:367-73.
[12] Lew TWK, Kwek TK, Tai D, et al. Acute respiratory distress syndrome in critically ill patients with severe acute respiratory syndrome. JAMA 2003;290:374-80.
[13] Monacha S, Walley KR, Russell JA. Severe acute respiratory distress syndrome (SARS): A critical care perspective. Crit Care Med 2003;31: 2684-92.
[14] Fowler RA, Guest CB, Lapinski SE, et al. Transmission of severe acute respiratory syndrome during intubation and mechanical ventilation. Am J Respir Crit Care Med 2004;169:1198-202.
[15] Straus SE, Wilson K, Rambaldini G, et al. Severe acute respiratory syndrome and its impact on professionalism: qualitative study of physicians' behaviour during an emerging healthcare crisis. BMJ 2004;329:83.
[16] Lapinsky SE, Hawryluck L. ICU management of severe acute respiratory syndrome. Intensive Care Med 2003;29:870-5.
[17] World Health Organization Multicentre Collaborative Network for Severe Acute Respiratory Syndrome Diagnosis. A multicentre collaboration to investigate the cause of severe acute respiratory syndrome. Lancet 2003;361:1730-3.
[18] So LKY, Lau ACW, Yam LY, et al. Development of a standard treatment protocol for severe acute respiratory syndrome. Lancet 2003; 361:1615-7.
[19] Centers for Disease Control and Prevention. Severe acute respiratory syndrome (SARS) and coronavirus testing—United States, 2003. JAMA 2003;289:2203-6.