Clinical Features and Short-term Outcomes of 144 Patients With SARS in the Greater Toronto Area

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Context Severe acute respiratory syndrome (SARS) is an emerging infectious disease that first manifested in humans in China in November 2002 and has subsequently spread worldwide.

Objectives To describe the clinical characteristics and short-term outcomes of SARS in the first large group of patients in North America; to describe how these patients were treated and the variables associated with poor outcome.

Design, Setting, and Patients Retrospective case series involving 144 adult patients admitted to 10 academic and community hospitals in the greater Toronto, Ontario, area between March 7 and April 10, 2003, with a diagnosis of suspected or probable SARS. Patients were included if they had fever, a known exposure to SARS, and respiratory symptoms or infiltrates observed on chest radiograph. Patients were excluded if an alternative diagnosis was determined.

Main Outcome Measures Location of exposure to SARS; features of the history, physical examination, and laboratory tests at admission to the hospital; and 21-day outcomes such as death or intensive care unit (ICU) admission with or without mechanical ventilation.

Results Of the 144 patients, 111 (77%) were exposed to SARS in the hospital setting. Features of the clinical examination most commonly found in these patients at admission were self-reported fever (99%), documented elevated temperature (85%), nonproductive cough (69%), myalgia (49%), and dyspnea (42%). Common laboratory features included elevated lactate dehydrogenase (87%), hypocalcemia (60%), and lymphopenia (54%). Only 2% of patients had rhinorrhea. A total of 126 patients (88%) were treated with ribavirin, although its use was associated with significant toxicity, including hemolysis (in 76%) and decrease in hemoglobin of 2 g/dL (in 49%). Twenty-nine patients (20%) were admitted to the ICU with or without mechanical ventilation, and 8 patients died (21-day mortality, 6.5%; 95% confidence interval [CI], 1.9%-11.8%). Multivariable analysis showed that the presence of diabetes (relative risk [RR], 3.1; 95% CI, 1.4-7.2; $P=.01$) or other comorbid conditions (RR, 2.5; 95% CI, 1.1-5.8; $P=.03$) were independently associated with poor outcome (death, ICU admission, or mechanical ventilation).

Conclusions The majority of cases in the SARS outbreak in the greater Toronto area were related to hospital exposure. In the event that contact history becomes unreliable, several features of the clinical presentation will be useful in raising the suspicion of SARS. Although SARS is associated with significant morbidity and mortality, especially in patients with diabetes or other comorbid conditions, the vast majority (93.5%) of patients in our cohort survived.

JAMA. 2003;289:2801-2809 www.jama.com

In March 2003, the World Health Organization (WHO) issued a global alert describing cases of atypical pneumonia of unknown cause appearing in Hong Kong, China, and Vietnam.[1] As of April 28, 2003, severe acute respiratory syndrome (SARS) has been described in 28 countries involving 5050 individuals

For editorial comment see p 2861.

Early Release: This article as posted online at http://www.jama.com on May 6, 2003.
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and causing 217 deaths.[2] Subsequent information has emerged that suggests that SARS has been present in the Guangdong province of China since November 2002.[3]

As defined by WHO, a suspected case of SARS is an individual with fever (temperature >38°C [100.4°F]), cough or dyspnea, and contact with an individual believed to have SARS or to have traveled to a region where there has been documented transmission of the disease. A probable case is an individual meeting criteria for a suspected case along with radiographic features of pneumonia, respiratory distress syndrome, or an unexplained respiratory illness resulting in death with autopsy results demonstrating pathology of respiratory distress syndrome without an identifiable cause.[3]

Investigators involved in international collaboration have attempted to determine a specific viral etiology in order to convert what is currently best described as a syndrome into a specific disease. At present, a novel coronavirus is the prime suspect.[4,5] Genomic sequencing of this virus has recently been completed.[6,7] Laboratory assays designed to identify this virus or serologic evidence of exposure to this virus are being developed.

Initial reports described the clinical features of small numbers of patients.[8,9] Clinical and laboratory features of a larger Hong Kong cohort have recently been published.[10] Anecdotal experience with empirical treatment using ribavirin and steroids has been described, but none of these regimens has been studied systematically to determine whether they are effective therapy.[10] Further information is urgently needed to better characterize the clinical features and outcome of this disease. These data may allow physicians worldwide to anticipate the course of the disease and risk-stratify patients based on prognostic variables.

This retrospective case series sought to describe the clinical features and short-term outcomes of patients with SARS in the greater Toronto, Ontario, area. The current case definition of SARS relies heavily on a history of contact exposure. At present, contact history is still intact in the greater Toronto area. However, it is possible that both there and elsewhere, this valuable component of the clinical assessment may be unavailable for some patients in the future. Thus, one goal of this study is to describe SARS in the event that the ability to reliably determine contact is lost before an objective diagnostic test is found. We also examine which treatments are being used and their potential toxicities, and we assess clinical and laboratory features that may predict a combined outcome of death, intubation, or the need for intensive care unit (ICU) admission.

METHODS

Description of the Outbreak

As described in a recent publication, the first cases of SARS in Canada involved a family of Hong Kong descent who live in Toronto.[8] A 78-year-old woman and her husband traveled to Hong Kong from February 13 through February 23, 2003, to visit relatives. They stayed at a hotel where a cluster of 13 persons with suspected or probable SARS are known to have stayed.[11] Two days after returning home, the woman developed fever, myalgia, sore throat, cough, and progressive dyspnea. She died at home on March 5. Several family members who had close contact with the index case subsequently developed respiratory symptoms. One family member was subsequently admitted to a local community hospital that became the epicenter for the Toronto outbreak.

SARS spread to other patients and health care workers within this hospital prior to significant awareness of SARS by the Canadian medical community and before intensive respiratory precautions for patients and contacts were known to be necessary and were implemented. Other Toronto hospitals were affected when patients were transferred between institutions. This led to additional infection of patients, health care workers, and hospital visitors.

As of April 27, 139 probable and 128 suspected cases had been reported (based on WHO case criteria) in the province of Ontario, accounting for 247 hospital admissions and 21 deaths. These cases were almost exclusively in the greater Toronto area.[12] There is strong evidence that the outbreak is winding down. There were only 18 new cases of suspected or probable SARS in Ontario between April 19 and April 27, 2003. There have been no cases of community spread since April 9, and the only cases that have occurred outside the health care setting have been among 2 home contacts of an affected health care worker.[12,13]

Study Population

This study included patients with SARS who were admitted to hospitals in the greater Toronto area between March 7 and April 10, 2003. Nine of the patients in our cohort have been described previously by Poutanen et al[8] and 11 of these patients have been reported recently by Dwosh et al.[14] We included hospitals that were providing care to the vast majority of SARS patients in the greater Toronto area.

Adult patients were included if they met the Centers for Disease Control and Prevention (CDC) criteria for a suspected case as of April 10: fever, a known exposure to SARS, and either respiratory symptoms or infiltrates observed on chest radiograph.[15] (Note that the CDC criteria for a suspected case were revised on April 20, 2003.) Known exposure to SARS was defined as 1 of the following: close contact with (ie, having cared for, lived with, or had face-to-face contact with) a suspected or probable case of SARS; travel to Hong Kong, China, Vietnam, Singapore, or Taiwan; or visit to a SARS-affected hospital in the greater Toronto area. Respiratory symptoms included cough, dyspnea, or hypoxemia (oxygen saturation <95% with room air as defined by our study protocol). Patients were excluded if an alternative medical or microbiological diagnosis explained their clinical presentation.

Study Design

This retrospective case series was conducted during the SARS outbreak in the

greater Toronto area. Clinicians from participating hospitals identified patients who met the study inclusion criteria through surveillance of all patients in their hospitals. The authors of this article include the physicians who supervised or directly provided care for all of the patients with SARS in these hospitals during the study period, ensuring complete identification of all cases. Because of the ongoing outbreak and the restrictions on research personnel traveling from site to site, patient charts were copied and sent to 2 data collection centers.

A trained team of physicians and medical students reviewed the patient charts and recorded demographic, clinical, and laboratory information on a standardized data collection form (available from the authors on request). The individual components of all of the definitions of SARS (CDC, WHO, and Health Canada) were recorded separately and checked by a supervising author. The proportion of patients who met each of the various definitions was then determined by computer following an algorithm for each definition. The data were entered in duplicate into a computerized database. Patient confidentiality was maintained by recording only date of birth and sex on the data collection form. The research ethics board at each participating hospital and the University of Toronto approved the study.

Statistical Analysis

Medians and interquartile ranges (IQRs) were calculated as summaries of continuous variables. For categorical variables, percentages of patients in each category were computed. The Wilcoxon rank sum test[16] was used to compare distributions of continuous variables at admission between patients who subsequently had a poor outcome and patients who did not. Poor outcome was defined as the earliest of death, need for mechanical ventilation, or ICU admission. Time to discharge, time to death, and time to a poor outcome were investigated using survival analysis, with follow-up for all patients starting at hospital admission and ending on April 17, 2003. Patients were censored if at the end of follow-up they were still in the hospital (for time to discharge), still alive (for time to death), and did not have a poor outcome (for time to poor outcome). The Kaplan-Meier product-limit estimator was used to estimate survival and for the time-to-event plot.[17] Comparisons between groups of time-to-event data were made using the Cox proportional hazards model, with graphical and statistical checks for proportionality of hazards.[18,19] With only 30 poor outcomes, we followed accepted statistical practice and considered only 3 variables in our multiple regression model.[20] In particular, because of a priori hypotheses, we examined 3 binary variables: diabetes, other comorbidities (chronic obstructive pulmonary disease, cancer, cardiac disease), and age of 60 years or older. All analyses were carried out using S-Plus 2000 Professional Release 3 statistical software (Mathsoft, Seattle, Wash).

RESULTS

Demographics

The initial study cohort comprised 147 adult patients. Three patients who contracted SARS while in the hospital during the course of a prolonged stay that began well before the SARS outbreak (eg, for hip fracture) were excluded from this cohort because of difficulty in determining the inception of their disease, leaving 144 patients for subsequent analysis. Demographic details and comorbidities are shown in TABLE 1. The median (IQR) age of the study population was 45 years (34-57 years) and 61% were female. Seventy-three patients (51%) were health care workers (nurses, respiratory therapists, physicians, radiology and electrocardiogram technicians, housekeepers, clerical staff, security personnel, paramedics, and research assistants).

A total of 111 patients (77%) were exposed to SARS in the hospital setting (as health care workers, patients, or visitors). Most exposure occurred in hospital A, which treated 1 of the sons of the index case early in the outbreak. Home exposure occurred when family members or friends of hospital-associated cases had close contact with affected individuals.

Table 1. Demographic Information and Exposure to SARS

Study Population	No. (%) of Individuals
Patients (N = 144)*	
Median (IQR) age, y	45 (34-57)
Women	88 (61)
Comorbid illness	
Diabetes	16 (11)
Cardiac disease	12 (8)
Cancer	9 (6)
COPD	2 (1)
Chronic renal failure†	2 (1)
Exposure history‡	
Travel	3 (2)
Hospital	111 (77)
A§	82 (74)
B	8 (7)
C	7 (6)
Other	14 (13)
Home	35 (24)
Health Care Workers	
Total	73 (51)
Nurse	29 (40)
Physician	14 (19)
Other	30 (41)

Abbreviations: COPD, chronic obstructive pulmonary disease; IQR, interquartile range; SARS, severe acute respiratory syndrome.
*Three additional patients contracted SARS while hospitalized for other conditions; they have been excluded from all analyses.
†Defined as having a baseline serum creatinine greater than 1.7 mg/dL (150 µmol/L).
‡These numbers add up to greater than 144 because several individuals had multiple sources of possible exposure.
§The epicenter of the Toronto outbreak.

Course of Illness

The median (IQR) time from self-reported earliest known exposure to onset of symptoms was 6 days (3-10 days) for prodrome (headache, malaise, or myalgia), 7 days (4-10 days) for self-reported fever, 8 days (4-11 days) for diarrhea, and 9 days (5-12 days) for cough or dyspnea. Because this information relies on patient recall and includes the earliest possible exposure among cases in which more than 1 possible exposure existed, any inferences about incubation period must be made with caution.

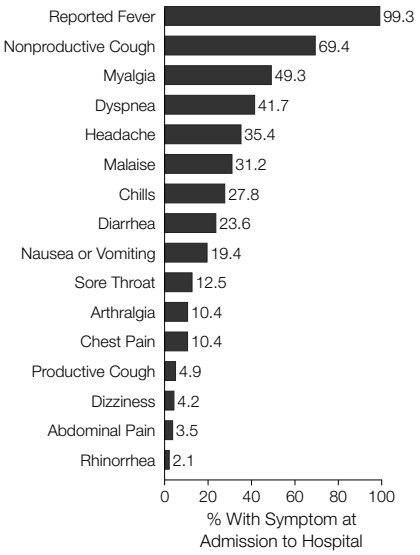
The earliest symptoms of SARS are shown in TABLE 2. The majority of individuals reported fever (74%) or prodromal symptoms (51%) as part of the

Table 2. Earliest Symptoms of SARS*

Symptom	No. (%) of Patients (N = 144)
Fever (n = 106)	
Alone	33 (23)
With prodrome	33 (23)
With prodrome and cough or dyspnea	16 (11)
With cough or dyspnea	15 (11)
With other combinations	9 (6)
Prodrome alone	19 (13)
Cough or dyspnea alone	13 (9)
Symptom reported first	
Prodrome	74 (52)
Fever	106 (74)
Cough or dyspnea	51 (35)
Diarrhea	9 (6)

*Prodrome includes headache, malaise, or myalgia.

Figure 1. Symptoms of SARS Reported at Admission to Hospital (N=144)



SARS indicates severe acute respiratory syndrome.

first constellation of symptoms. Respiratory symptoms were less frequently reported as the initial symptoms of SARS. Forty-nine individuals (34%) had been assessed by a physician and sent home prior to being admitted to the hospital, usually because their initial symptoms did not suggest SARS at all or because they did meet the case definition requiring admission. For the latter group, home quarantine and follow-up procedures were instituted. The median (IQR) time until these individuals were admitted to the hospital was 3 days (2-5 days).

The relative frequencies of all reported symptoms at the time of admission are shown in FIGURE 1. Common clinical features include fever (99%), nonproductive cough (69%), myalgia (49%), and dyspnea (42%). Only 2% of patients reported rhinorrhea, all in conjunction with 1 or more other symptoms.

On admission, 85% of patients had a recorded temperature of 38°C (100.4°F) or greater. The remaining 15% either developed fever while in the hospital or reported fever prior to presentation. By day 4 of hospitalization, only 28% of patients remained febrile. Tachycardia (heart rate >100/min) was found in 46% of patients on admission, while tachypnea (respiratory rate >20/min) and rales were noted in 37% and 26% of patients, respectively. No patient had purpura or rash. One third of patients (34%) were given supplemental oxygen during their hospital course.

Chest radiography on admission was normal in 25% of individuals, while unilateral and bilateral infiltrates were observed in 46% and 29% of patients, respectively. Thirty-one percent of individuals (45/144) had progression of their pulmonary infiltrates while in the hospital (TABLE 3). However, 15 patients (10%) never developed an infiltrate. Some characteristic radiographic features of SARS are shown in FIGURE 2. Although there was quite a bit of variability in the pattern of the infiltrates (focal, lobar, diffuse), most patients had multifocal opacities. Three percent of patients developed a pneumothorax while in the hospital.

Laboratory Indices

Laboratory indices on admission are shown in TABLE 4. More than half (54%) of the cohort presented with moderate lymphopenia (<1000/µL). The median (IQR) lymphocyte count was 900/µL (700-1300/µL) on admission and decreased to a low of 500/µL (400-900/µL) while in the hospital. Electrolyte and biochemical abnormalities present on admission worsened the hospital course. These changes are shown in TABLE 5. During hospitalization, many patients had hypocalcemia (70%), hypokalemia (43%), hypomagnesemia (57%), and hypophosphatemia (53%).

Treatment and Associated Toxicities

The vast majority of patients (95%) received empirical antibiotic therapy during the course of their hospitalization. Ribavirin was used in 126/144 (88%) of patients. Ninety-one percent of these individuals received ribavirin within the first 48 hours of hospitalization. While there was variability between hospitals, most patients received a loading dose of 2 g intravenously, followed by 1 g intravenously every 6 hours for 4 days, followed by 500 mg every 8 hours for 3 days.[21] The median (IQR) treatment course of ribavirin was 6 days (5-7 days). Forty percent of individuals received steroids; however, less than half of these patients received them in the first 48 hours. Although there was variability among hospitals, most patients received approximately 20 to 50 mg/d of hydrocortisone for 10 days. Only 1 patient received pulse dosages.

The use of ribavirin was temporally associated with significant toxicity. Seventy-one patients (49%) experienced a decrease in hemoglobin level of at least 2 g/dL after ribavirin was initiated. Seventy-six percent of these patients had evidence of hemolysis (defined as a 1.5-fold increase in bilirubin or decreased haptoglobin level). Many patients with hemolysis were unable to mount an adequate reticulocyte response. The median (IQR) reticulocyte count in individuals with hemolysis was 25000 cells/µL (16000-35000 cells/µL). Elevation of transaminases (defined as a 1.5-fold rise in aspartate aminotransferase or alanine aminotransferase) was observed in 40% of patients receiving ribavirin, while bradycardia and sore throat were reported in 14% and 4% of patients, respectively. These toxicities led to the premature discontinuation of ribavirin in 18% of patients.

Outcomes

There were 8 deaths in our cohort of 144 hospitalized SARS patients (21-day mortality, 6.5%; 95% confidence

interval [CI], 1.9%-11.8% by Kaplan-Meier analysis). Six of these patients had diabetes. Of the other 2 patients, one had cancer and the other had no comorbid disease other than being a former smoker. As of April 17, most individuals (103/144 [72%]) had recovered and were discharged from the hospital. Among patients who survived, median (IQR) hospital stay was 10 days (6-15 days), and 74% of patients were discharged by day 14 (95% CI, 65%-81%). Most of these patients had an uneventful progressive recovery over the 2 weeks of their hospital stay.

A small proportion (<10%) had a return of fever, other symptoms, or worsening infiltrates observed by chest radiograph during the second week of their illness. Some of these patients had not received ribavirin or steroids at first but were subsequently treated with these regimens. Others had a flare-up of their symptoms after treatment was stopped. For this latter group, practice varied, with only some having therapy reinstituted. In any case, all of these patients recovered thereafter.

As of April 17, 2003, 23% of patients (33/144) were still hospitalized; 8 of these were still receiving mechanical ventilation. Of the entire cohort, 20% of patients (29/144) were admitted to the ICU and 69% (20/29) of these received mechanical ventilation. Among the 20 patients who received mechanical ventilation, 7 (35%) died, 2 (1%) were discharged, and 11 (55%) remained hospitalized as of April 17, 2003. The eighth patient who died declined mechanical ventilation.

At 21 days, 30 patients in our cohort (21%; 95% CI, 14%-28% by Kaplan-Meier analysis) met the criteria for a poor outcome (death or ICU admission with or without mechanical ventilation). The majority of these poor outcomes occurred in the first 6 days of hospitalization, with only 3 occurring after the first week in the hospital. TABLE 6 shows summaries of age, sex, and initial laboratory results classified by poor outcome. Univariate analysis of these data showed that increased age, male sex, and increased neutrophil count, creatine kinase, and urea were significantly associated with poor outcome.

In a univariate Cox proportional hazards model, risk of a poor outcome was almost doubled for those aged 60 years or older (relative risk [RR], 1.9; 95% CI, 1.3-2.7; $P<.001$). The presence of any comorbid disease (diabetes, chronic obstructive pulmonary disease, cancer, or cardiac disease) was found to increase the risk of a poor outcome (RR, 4.4; 95% CI, 2.1-8.9; $P<.001$), as was the presence of diabetes alone (RR, 5.4; 95% CI, 2.5-11.5; $P<.001$). Although poor outcomes were more common for those treated with ribavirin, this was not statistically significant (RR, 1.9; 95% CI, 0.45-8.0; $P=.36$).

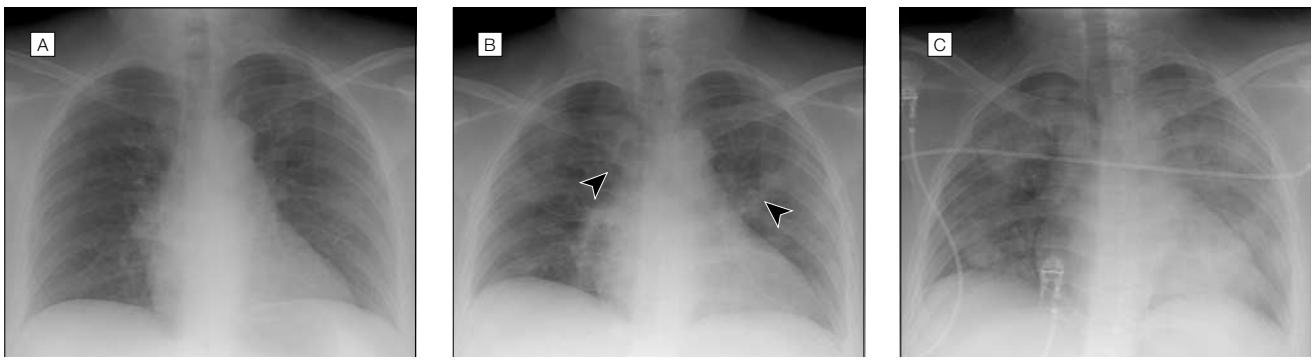
Multivariable Cox proportional hazards analysis was carried out assuming the a priori hypothesis that age and comorbid diseases would be independently associated with poor outcome (Table 6). In a model with diabetes, other comorbid diseases, and age of 60 years or older, a moderate association was found between advanced age and poor outcome (RR, 1.4; 95% CI, 0.95-2.10; $P=.09$). Both diabetes (RR, 3.1; 95% CI, 1.4-7.2; $P=.01$) and other comorbid diseases (chronic obstructive pulmonary disease, cancer, and car-

Table 3. Initial Chest Radiographic Features and Progression During Hospitalization

At Admission		During Hospitalization	
Radiographic Findings	No. (%)	Progression	No. (%)
Normal	36 (25)	No change	15 (42)
		Unilateral infiltrate	12 (33)
		Bilateral infiltrate	9 (25)
Unilateral infiltrate	66 (46)	No change	42 (64)
		Bilateral infiltrate	24 (36)
Bilateral infiltrate	42 (29)	NA	NA

Abbreviation: NA, not applicable.

Figure 2. Chest Radiograph of a 33-Year-Old Woman



A, On day 4 of admission, the chest radiograph was normal. B, On day 8, there were early signs of disease as indicated by arrows. C, On day 11, extensive, bilateral, patchy air-space opacities were noted.

diac disease) (RR, 2.5; 95% CI, 1.1-5.8; $P=.03$) were independently associated with poor outcome.

Although age of 60 years or older, diabetes, and presence of other comorbidities are all positively associated, a comparison of parameter estimates and SEs from the single and multivariable models indicated that collinearity was not a problem. The SE for the age parameter was only marginally larger in the multiple regression model than in the age-only model, while the parameter estimate itself was almost 50% smaller. FIGURE 3 shows Kaplan-Meier survival curves for the 4 groups defined by the presence and absence of diabetes and other comorbidities. There was no evidence for nonproportional hazards in any of the Cox model analyses.

Table 4. Initial Laboratory Indices

	Median Value (IQR) (N = 144)	Reference Values
Hematologic		
White blood cells, µL	5200 (3600-7300)	4000-11 000
Neutrophils, /µL	3600 (2400-5700)	2000-7500
Lymphocytes, /µL	900 (700-1300)	1500-4000
Platelets, × 10^3/µL	183 (147-223)	150-400
Partial thromboplastin time, s	34.0 (29.7-36.1)	28-40
International normalized ratio, s	1.0 (1.0-1.1)	0.8-1.2
Biochemical		
Sodium, mEq/L	138 (135-140)	135-145
Potassium, mEq/L	3.7 (3.4-4.0)	3.5-5.0
Calcium, mg/dL*	8.52 (8.2-9.16)	8.8-10.5
Phosphorus, mg/dL	3.10 (2.79-3.72)	2.79-4.34
Magnesium, mg/dL	1.94 (1.70-2.19)	1.70-2.43
Urea, mg/dL	11.2 (9.52-14.0)	8.4-19.6
Creatinine, mg/dL	0.86 (0.75-1.1)	<1.1
Lactate dehydrogenase, U/L	396 (219-629)	<190
Creatine kinase, U/L		
Men	222 (165-514)	<240
Women	95 (62-173)	<150
Alkaline phosphatase, IU/L	65 (55-82)	<110
γ-Glutamyltransferase, IU/L	35 (25-53)	<45
Amylase, units/dL	37.8 (29.2-55.7)	<62.2
Aspartate aminotransferase, U/L	37 (29-56)	<35
Alanine aminotransferase, U/L	29 (20-51)	<40
Bilirubin, mg/dL	0.41 (0.29-0.65)	<1.29

Abbreviation: IQR, interquartile range.
SI conversions: To convert calcium to mmol/L, multiply by 0.25. To convert phosphorus to mmol/L, multiply by 0.323. To convert magnesium to mmol/L, multiply by 0.411. To convert urea to mmol/L, multiply by 0.357. To convert creatinine to µmol/L, multiply by 88.4. To convert bilirubin to µmol/L, multiply by 17.1.
*Calcium values have been corrected for serum albumin.

Table 5. Laboratory Features of SARS at Admission and During Hospitalization

	At Admission		During Hospitalization*	
	Median (IQR)	No./Total (%) Abnormal†	Median (IQR)	No./Total (%) Abnormal†
Lymphocytes, /µL	900 (700-1300)	104/122 (85)	500 (400-800)	106/120 (88)
Lactate dehydrogenase, U/L	396 (219-629)	86/99 (87)	630 (363-1156)	115/123 (94)
Creatine kinase, U/L	157 (70-310)	43/109 (39)	370 (208-959)	64/118 (54)
Potassium, mEq/L	3.7 (3.4-4.0)	36/137 (26)	3.2 (2.9-3.4)	60/140 (43)
Calcium, mg/dL‡	8.52 (8.2-9.16)	53/89 (60)	8.1 (7.76)	71/101 (70)
Magnesium, mg/dL	1.94 (1.7-2.19)	12/68 (18)	1.43 (0.97-1.51)	55/96 (57)
Phosphorus, mg/dL	3.10 (2.76-3.69)	17/64 (27)	2.17 (1.83-2.48)	41/78 (53)

Abbreviations: IQR, interquartile range; SARS, severe acute respiratory syndrome.
SI conversions: To convert calcium to mmol/L. multiply by 0.25. To convert magnesium to mmol/L, multiply by 0.411. To convert phosphorus to mmol/L, multiply by 0.323.
*The most abnormal value recorded is used.
†Defined as lymphocytes <1500/µL; lactate dehydrogenase >190 U/L; creatine kinase >240 U/L for men and >190 U/L for women; potassium <3.5 mEq/L; calcium <8.8mg/dL; magnesium <1.70 mg/dL; phosphate <2.79 mg/dL.
‡Calcium values have been corrected for serum albumin.

Case Definitions of SARS

Because SARS is an emerging infectious disease, the case definition is evolving and not consistent among countries. We examined the effect of varying the definition on our cohort. Prior to April 20, 2003, the CDC case definition of SARS included 1 category labeled suspected SARS and had no definition for probable SARS. This differed from the WHO and Health Canada definitions, which included 2 categories, suspected SARS and probable SARS. As of April 20, 2003, the CDC revised their definition to include both suspected and probable SARS, and the definition of suspected cases used by all 3 institutions was identical and consisted of fever, significant contact or travel history, and respiratory signs or symptoms.[3,16,22] Probable cases defined by WHO and the CDC (after April 20, 2003) include all suspected cases with a radiographic chest infiltrate, whereas probable cases by Health Canada criteria include all suspected cases with "severe progressive respiratory disease." We chose to define severe progressive respiratory disease as having 2 of the following: progressive pulmonary infiltrates, hypoxemia (oxygen saturation <95% with room air), and need for ICU admission.

TABLE 7 shows the proportion of patients in our cohort who met each of these case definition criteria on hospital admission and subsequently as new clinical features developed in the hospital. All patients in our cohort did meet the original CDC definition before it was changed on April 20. However, using the most recent definitions, 16 (11%) of the 144 individuals in our cohort would not meet criteria for suspected SARS because they had no reported respiratory symptoms despite

having fever, contact history, and chest infiltrates.

COMMENT

We describe a cohort of 144 adult patients who were hospitalized with SARS in the greater Toronto area. The majority of cases were acquired in hospitals by health care workers, patients, and visitors. Most cases occurred in 1 hospital early in the outbreak prior to significant awareness of SARS by the Canadian medical community and before intensive respiratory precautions were instituted for patients and their contacts. One third of patients had been seen by a physician and sent home in the days prior to their admission with early symptoms of SARS.

These observations have important infection control and public health implications. Hospitals and clinicians' offices must be prepared to institute appropriate respiratory precautions when assessing patients with undifferentiated respiratory conditions and their family members, in order to prevent the introduction of SARS in the hospital setting. Individuals such as health care workers or household contacts of cases who are exposed to SARS patients, especially those with early symptoms, need to be placed in isolation and have appropriate follow-up. These 2 recommendations may form the basis of containing the disease as it enters new communities.

We found the clinical features of SARS to be similar to those recently reported by Lee et al[10] in a cohort of 138 SARS patients in Hong Kong. The most common symptoms are fever, nonproductive cough, myalgia, and dyspnea. Dizziness was less frequently reported in our cohort than in Hong Kong. Fever is the first symptom as reported by many patients (74%). The presence of rhinorrhea alone suggests that the diagnosis is unlikely to be SARS. A significant portion of patients (25%) have normal chest radiograph results on admission to the hospital. The hallmark laboratory findings include lymphopenia (88%) and elevated lactate dehydrogenase (94%). These radiographic and laboratory findings are also consistent with those reported by Lee and colleagues.[10] Many patients also demonstrate low calcium, phosphorus, magnesium, and potassium levels and elevated creatine kinase on admission. These electrolyte abnormalities, present on admission, tend to worsen during hospitalization. It is unclear whether this represents the natural history of the disease or is second-

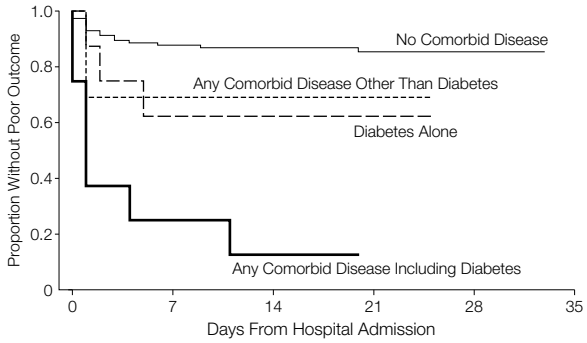
Table 6. Analysis of Poor Outcome and Clinical Features

Variable	Univariate Analysis, Mean (IQR)		
	No Poor Outcome	Poor Outcome*	*P* Value†
Age, y	42.5 (31.0-52.8)	57.0 (39.3-67.3)	.001
Men, %	33	60	.01
Platelets, × 10^3/μL	183 (149-222)	177 (130-232)	.61
Neutrophils, /μL	3100 (2200-4900)	5700 (4700-7500)	<.001
Lymphocytes, /μL	900 (700-1300)	1000 (700-1200)	.93
Partial thromboplastin time, s	32.7 (29.5-35.0)	35.9 (33.0-38.9)	.02
Sodium, mEq/L	139 (136-140)	136 (132-138)	.001
Urea, mg/dL	10.9 (9.24-13.2)	12.9 (11.2-20.7)	.003
Creatinine, mg/dL	0.84 (0.72-0.96)	0.94 (0.78-1.22)	.02
Creatine kinase, U/L	129 (66-211)	310 (135-558)	.005
Alanine aminotransferase, U/L	29 (19-49)	30 (21-67)	.41
Lactate dehydrogenase, U/L	431 (217-619)	359 (276-947)	.47

	Multivariable Analysis‡	
	Relative Risk (95% CI) of Poor Outcome§	*P* Value
Age ≥60 y	1.4 (0.95-2.1)	.09
Diabetes	3.1 (1.4-7.2)	.01
Other comorbid disease	2.5 (1.1-5.8)	.03

Abbreviations: CI, confidence interval; IQR, interquartile range.
SI conversions: To convert urea to mmol/L, multiply by 0.357. To convert creatinine to μmol/L, multiply by 88.4.
*Defined as death or intensive care unit admission with or without mechanical ventilation.
†Calculated using the Wilcoxon rank sum test for continuous variables and the χ^2 test for sex.
‡Results are from Cox proportional hazards model.
§Reference group is younger than 60 years, with no diabetes, and no other comorbid disease (chronic obstructive pulmonary disease, cancer, or cardiac disease).

Figure 3. Time From Admission to Poor Outcome by Comorbid Disease*



No. at Risk					
No Comorbid Disease	115	97	80	44	1
Any Comorbid Disease Other Than Diabetes	13	9	6	3	0
Diabetes Alone	8	5	5	2	0
Any Comorbid Disease Including Diabetes	8	2	1	0	0

Asterisk indicates that poor outcome was defined as death or intensive care unit admission with or without mechanical ventilation.

Table 7. Proportion of Patients Meeting WHO, CDC, and Health Canada SARS Case Definitions

Variable	No. (%) of Patients (N = 144)	
	Admission	Subsequently
Suspected cases		
Health Canada/ WHO*†	117 (81)	128 (89)
CDC‡	133 (92)	144 (100)
Probable cases		
Health Canada	32 (22)	35 (24)
WHO	92 (64)	113 (78)

Abbreviations: CDC, Centers for Disease Control and Prevention; SARS, severe acute respiratory syndrome; WHO, World Health Organization.
*As of April 20, the CDC suspect definition is the same as Health Canada and the WHO.
†Met case definition criteria for both suspect and probable SARS.
‡These figures reflect the CDC definition prior to April 20.

ary to effects of ribavirin or other therapies on renal tubular function. In patients with SARS, it is important to closely monitor electrolytes and ensure adequate electrolyte replacement.

Given the retrospective nature of our study, it is difficult to determine whether there is any therapeutic benefit to the treatment regimens used in treating SARS, specifically ribavirin and steroids. Recent reports suggest that most patients recover from SARS despite not receiving either ribavirin or steroids.[23] Our study did find numerous adverse effects associated with ribavirin or other therapies, particularly, hemolysis and transaminase elevation. Nearly all patients received empirical antibiotics per the Canadian guidelines for management of community-acquired pneumonia.[24]

Fourteen percent of the patients in our cohort required mechanical ventilation, which is identical to the experience reported in Hong Kong. Although our overall crude mortality rate was slightly greater (5.6% vs 3.6%; $P = .60$ by χ^2 test), differences in completeness of follow-up between the 2 cohorts make comparisons difficult to interpret (eg, 45% of the Hong Kong cohort were still in the hospital at the time that the article was written compared with 23% of ours). When interpreting variation in outcome event rates, one must consider which definition was used to define the cohort. Our study shows that varying the case definition of SARS has an impact on which patients are included for description.

Univariate analysis showed age of 60 years or older, comorbid disease, male sex, and several biochemical abnormalities to be associated with poor outcome. In our multivariable Cox proportional hazards model, diabetes and other comorbid conditions were independently associated with poor outcome but age of 60 years older was not. Larger studies are needed to further elucidate which patients are at most risk of death or requiring mechanical ventilation.

The results of this study must be interpreted in light of several methodological limitations. This was a retrospective case series study that relied on abstracting data from clinical notes and patient charts. Accordingly, certain information was missing for various patients, and certain data that may have been based on patient memory, such as details concerning exposure history and timing of onset of symptoms, may be affected by recall bias. This study did not include patients who were evaluated for possible SARS but did not ultimately meet any of the case definitions. As such, it cannot provide a decision rule to distinguish SARS from non-SARS illness but, rather, provides a profile of patients with SARS (ie, the sensitivities of all of the findings but not the specificities). Finally, in an effort to quickly disseminate information to clinicians worldwide, we only assessed short-term outcomes. It will be important to perform follow-up evaluation of these patients to determine the long-term repercussions of this illness.

Currently there is no gold standard test for the diagnosis of SARS. At the current time, SARS is a syndrome, not a specific viral disease. The results of this study suggest that some features of the history, physical examination, and laboratory tests should alert clinicians to the possible diagnosis of SARS, even when the contact history is unreliable. These features are self-reported fever, prodromal symptoms (headache, malaise, or myalgia), documented elevated temperature, lymphopenia, elevated lactate dehydrogenase, and hypocalcemia. In regions where the syndrome enters the community at large and the contact history is lost (an event that has not happened in the greater Toronto area), these findings may prove to be important. Where the disease has never been seen, clinicians should also consider these findings in evaluating patients with respiratory illness. A chest radiograph should be obtained and oxygen saturation should also be measured when evaluating such patients, and a complete assessment to rule out alternative diagnoses or etiologies should be performed.

Current case definitions of SARS exclude a significant number of individuals who have fever, contact history, and pulmonary infiltrates but have no respiratory symptoms. This has important public health implications. Such individuals may actually have acquired the virus that causes SARS without developing the full syndrome. Accordingly, they and their contacts may require quarantine. At a minimum, these patients require close follow-up.

In conclusion, despite the widespread implications of SARS, overall 21-day survival in our study was 93.5%. The remarkable spirit of international collaboration among clinicians, researchers, and government agencies needs to continue in an effort to better understand and control this emerging infectious disease.

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Acknowledgment: We thank Michael D. Christian, MD, James Brunton, MD, Irving Salit, MD, Henry Solow, MD, Sigmund Krajden, MD, Lynn M. Nagle RN, PhD, Reena Lovinsky, MD, Marianna Ofner RN, MHSc, Martha Singleton, Cathy Sigalas, Robin Saunders, Sharon Tai-Young, Sandy Finkelstein, MD, Hans Schroeder, Heather Smith-St Kitts, Donald E. Low, MD, Angela Green, Darlene Malenkovich, Gina Cardona, Chandrika Thai, Richard E. Schabas, MD, Damon Scales, MD, Adrienne K. Chan, MD, Sharmistha Mishra, MD, Stephanie Wiesenthal, MD, Nicholas T. Lo, Harry H. L. Hong, MD, and especially Atilla Turgay, MD. We also acknowledge the health care workers in the greater Toronto area who risked their lives, and the lives of their families, to care for the patients and control the spread of this disease.

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