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Sequential Symptomatic Analysis in Probable Severe Acute Respiratory Syndrome Cases

Study objective: Previous reports on severe acute respiratory syndrome (SARS) described mainly its symptoms. However, the time sequence of symptom development was rarely discussed. The objective of this study is to chronologically document the time sequence of symptom development in probable SARS cases and compare that of the febrile non-SARS cases, thus providing valuable information for early recognition of the disease.

Methods: This prospective, descriptive, cohort study was conducted in an academic university hospital in Taipei, Taiwan, from March 14 through May 12, 2003. Patients presenting to the emergency department (ED) with a temperature of at least 38.0°C (100.3°F) and exposure history were evaluated with a structured protocol. Detailed time sequences of individual symptoms were recorded, and chest radiography and laboratory test results were obtained. Probable SARS cases were determined by the Center of Disease Control Taiwan. Children younger than 15 years and suspected SARS patients with negative polymerase chain reaction results were excluded from final analysis.

Results: Seventy-nine SARS and 220 non-SARS cases were analyzed. The major clinical symptoms of SARS patients on ED presentation were myalgia, loose stool or diarrhea, nonproductive cough or dyspnea, headache, and chills. Upper airway symptoms, including rhinorrhea and sore throat, were rarely seen in the SARS patients but were common in the non-SARS group. Characteristic symptom sequence, consisting of initial fever accompanied by diarrhea and myalgia and then progressive respiratory symptoms, was identified in 55 SARS patients (69.6%; 95% confidence interval [CI] 0.60 to 0.80) but only 7 (3.2%; 95% CI 0.008 to 0.05) non-SARS patients. Chest radiographic abnormality may precede lower respiratory tract symptoms in some SARS patients.

Conclusion: During an outbreak period, recognition of possible SARS cases depends on the heightened awareness of its clinical presentation. Aside from travel and contact history, the time sequence of the accompanying symptoms of SARS should help first-line physicians screen SARS patients at an early stage.

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Capsule Summary

What is already known on this topic
Previous severe acute respiratory syndrome (SARS) reports have focused on selected, non–laboratory-confirmed populations with certain clinical characteristics at presentation, and only evaluated the frequency of findings at the time of diagnosis.

What question this study addressed
This study systematically collected information on the onset and duration of 8 symptoms among 299 febrile emergency department patients, 79 of whom were subsequently diagnosed with probable SARS, and most of whom had laboratory confirmation based on serology or polymerase chain reaction results.

What this study adds to our knowledge
This article provides data on the time-course clinical findings and suggests that SARS may often begin as a diarrheal illness, with or without fever, or a nonspecific “viral” presentation with myalgias.

How this might change clinical practice
If or when there are future SARS outbreaks, more inclusive clinical screening criteria that include the evolution of symptoms may be necessary.

INTRODUCTION

Background
Severe acute respiratory syndrome (SARS) is a major public health challenge to human beings in the beginning of the 21st century. As of July 11, 2003, SARS has been described in 32 countries, involving 8,437 individuals and causing 813 deaths. Although the immediate crisis surrounding SARS now is subsiding, the threat of recurrence remains possible. Even though the cause of SARS has been identified as coronavirus, the accuracy of the currently available rapid assays is not well established.

Importance
Because SARS is highly contagious, early suspicion of the disease according to clinical presentation still plays a significant role in timely diagnosis. Previous studies have described the major clinical symptoms of SARS, but these reports were inadequate in 2 areas: first, retrospective data collected by medical record review or patient interviews long after presentation introduced recall bias. Second, summary of symptoms without description of the detailed time sequence of each symptom provides little help for clinical decision-making when physicians are confronted with patients presenting with a constellation of symptoms.

Goals of This Investigation
This prospective study was designed to chronicle the time sequence of symptom development in probable SARS cases in comparison to febrile non-SARS cases. It depicts a more clearly clinical course of SARS and identifies a few symptom-based diagnostic clues that may guide clinicians in the early diagnosis of SARS in endemic areas.

MATERIALS AND METHODS
On March 14, 2003, a febrile Taiwanese merchant working in Guangdong Province in southern China was diagnosed as having the first case of SARS after coming back from mainland China. Until July 5, 2003, when Taiwan was removed from the World Health Organization (WHO) SARS-affected areas, there were 674 probable SARS cases in Taiwan, including 84 deaths. Taiwan experienced the third-largest outbreak of SARS in the world. This study was conducted in an academic university hospital in Taipei, the city with the largest number of SARS cases in Taiwan during the outbreak. Soon after SARS was reported, the emergency department (ED) of the hospital was inundated by febrile patients returning from affected areas or local people wary of the disease. The situation worsened after consecutive outbreaks within 3 local hospitals and the presence of SARS cases without traceable exposure history, leading to a cessation of emergency service on May 12, 2003.

Theoretical Model of the Problem
According to the global alert from the WHO, patients with SARS present with fever, airway symptoms, and risks of exposure, such as recent travel to an affected area or close contact with SARS patients, including their families or health care providers. Although the possible associated symptoms had been described in the WHO Web site at that time, the detailed time sequence of various symptom developments was not clarified. From clinical observations of the SARS patients, we theorized that the SARS-related symptoms present in a distinctive time sequence compared with those of non-SARS febrile patients, and this information could help clinicians in the early recognition of the disease.

Study Design and Setting
This prospective observational study was approved by the hospital’s institutional review board. The study was conducted in an academic tertiary hospital in Taipei, Taiwan, from March 14 through May 12, 2003.
Selection of Participants
Patients presenting to the ED with risks of exposure and temperature of 38.0°C or greater (G100.3°F) were enrolled. Initially, the risks of exposure included traveling to an affected area within the previous 2 weeks, contact history with known SARS patients, or both. However, after Taiwan became an endemic area after the outbreak in a municipal hospital and community spread of the virus, all febrile patients presenting to the ED were considered coming from a SARS-affected area and meeting our enrollment criteria. Fever was defined as body temperature greater than 38.0°C (G100.3°F), either at home or at the ED. Patients with only subjective chills or sweating without documented fever were not enrolled.

Methods of Measurement
All patients were evaluated by emergency physicians using a structured recording form designed by the principal investigators. Items in the questionnaire included baseline demographic data, travel and contact history, the occurrence and time sequence of various symptoms before presentation to the ED, ancillary laboratory tests, and chest radiography. Details of the occurrence of each of the 8 symptom items were obtained and recorded. Lower respiratory symptoms included cough and shortness of breath. Diarrhea included loose stool. Because symptoms after hospitalization could be modified by various treatments, they were not recorded.

Outcome Measures
The outcome measures of the study were clinical symptoms over time among probable SARS and non-SARS patients. Probable SARS or non-SARS was determined by the Center of Disease Control Taiwan according to patients' clinical courses and the WHO criteria defined on May 1, 2003.\(^7\)

Primary Data Analysis
The baseline demographic data, initial laboratory tests, and time sequence of symptoms were analyzed. Children younger than 15 years, because of their different clinical presentation from that of the adults,\(^8\) were excluded from final analysis. The suspected SARS cases by the WHO criteria with negative polymerase chain reaction results were also excluded from final analysis. The results of reverse transcriptase–polymerase chain reaction were obtained from Center of Disease Control Taiwan. Seroconversion for SARS coronavirus was confirmed by immunofluorescence assay. Means and SDs were calculated as summaries of continuous variables. For categorical variables, percentages and 95% confidence intervals (CIs) of patients in each category were computed. For the analysis of symptom development, we defined the first day with fever as day 0 and calculated the incidences of various symptoms with reference to day 0 for SARS and non-SARS patients. Data were entered into a Microsoft Excel database (Microsoft Excel 2001; Microsoft Corporation, Seattle, WA) and analyzed with SPSS software for Windows (Release 10.0; SPSS, Inc., Chicago, IL).

RESULTS
A total of 349 febrile patients were enrolled during the study. Twenty-nine patients younger than 15 years and 21 patients categorized as suspected SARS cases whose reverse transcriptase–polymerase chain reaction results were negative were excluded from final analyses.

The demographic data of the 299 patients in the final analyses are shown in Table 1. Seventy-nine patients were judged as probable SARS cases, including 2 suspected cases with positive reverse transcriptase–polymerase chain reaction test results for SARS coronavirus. The mean age of the SARS group was 44.6 years.
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(INTERQUARTILE RANGE [IQR] 30 TO 53 YEARS). THERE WERE 35 (44.3%) MALE PATIENTS AND 44 (55.7%) FEMALE PATIENTS. FIFTY-FOUR (68.5%) PATIENTS WERE INFECTED BECAUSE OF EXPOSURE TO SARS IN A HOSPITAL SETTING. IN 9 (11.4%) SARS CASES DISCOVERED AFTER TAIWAN BECAME A SARS-AFFECTED AREA, NO RISK OF EXPOSURE COULD BE IDENTIFIED. REVERSE TRANSCRIPTASE–POLYMERASE CHAIN REACTION TESTS FOR SARS CORONAVIRUS WERE USED FOR 57 PATIENTS, WITH 23 POSITIVE RESULTS (40.4%; 95% CI 0.28 TO 0.53). SEROCONVERSION FOR SARS CORONAVIRUS WAS DEMONSTRATED IN 37 OF 38 PATIENTS HOSPITALIZED IN OUR HOSPITAL (97.4%; 95% CI 0.92 TO 1.00). IN THE 220 NON-SARS FEBRILE PATIENTS, THE AVERAGE AGE WAS YOUNGER (37.8 YEARS) THAN THAT OF THE SARS GROUP. THE LEADING DIAGNOSIS WAS UPPER RESPIRATORY TRACT VIRAL INFECTION. MEAN DURATION OF FEVER IN THE SARS GROUP WAS 4.3 DAYS (4.3 TO 2.2 DAYS; RANGE 1 TO 12 DAYS) BEFORE HOSPITAL PRESENTATION COMPARED WITH 1.9 DAYS (1.9±1.5 DAYS; RANGE 1 TO 9 DAYS) IN THE NON-SARS GROUP.

INITIAL VITAL SIGNS AND LABORATORY DATA IN BOTH GROUPS ARE SUMMARIZED IN TABLE 2. FEVER WAS DOCUMENTED ON AVERAGE 4.8 DAYS (4.8 TO 20.3 DAYS) BEFORE HOSPITAL PRESENTATION IN 59 (26.8%) OF 220 NON-SARS PATIENTS, AND IN 45 (59.5%) OF 79 PROBABLE SARS PATIENTS. BODY TEMPERATURE, SYSTOLIC AND DIASTOLIC BLOOD PRESSURE, WBC COUNT, NEUTROPHIL AND LYMPHOCYTE COUNT, THROMBOCYTE COUNT, SERUM LEVEL OF ASPARTATE AMINOTRANSFERASE, SODIUM, C-REACTIVE PROTEIN, AND CREATINE KINASE WERE SIGNIFICANTLY DIFFERENT BETWEEN SARS AND NON-SARS GROUPS. THE CLINICAL SYMPTOMS MORE COMMONLY FOUND IN THE SARS GROUP WERE MYALGIA (N=52; 65.8%; 95% CI 0.55 TO 0.76), LOOSE STOOL OR DIARRHEA (N=36; 45.6%; 95% CI 0.35 TO 0.57), LOWER RESPIRATORY TRACT SYMPTOMS (COUGH OR DYSPNEA; N=36; 45.6%; 95% CI 0.35 TO 0.57), HEADACHE (N=18; 22.8%; 95% CI 0.14 TO 0.32), AND CHILLS (N=16; 20.3%; 95% CI 0.11 TO 0.29).

UPPER RESPIRATORY SYMPTOMS, INCLUDING SORE THROAT (N=3; 3.8%; 95% CI 0.0 TO 0.08) AND RHINORRHEA (N=2; 2.5%; 95% CI 0 TO 0.06), WERE RARELY FOUND IN THE SARS COHORT BUT WERE COMMON IN THE NON-SARS COHORT (Figure 1). INITIALLY, INFILTRATIONS ON CHEST RADIOGRAPHY WERE FOUND IN 59 SARS (74.7%; 95% CI 0.65 TO 0.85) AND 22 NON-SARS (9.9%; 95% CI 0.06 TO 0.14) CASES. THE FINAL DIAGNOSES OF FEBRILE NON-SARS CASES WITH INFILTRATION ON CHEST RADIOGRAPHY WERE BRONCHOPNEUMONIA, PULMONARY TUBERCULOSIS, EMPYEMA, AND 1 NEWLY DIAGNOSED AIDS PATIENT WITH PNEUMOCYSTIS CARINII INFECTION. AMONG THE SARS PATIENTS, INFILTRATION ON CHEST RADIOGRAPHY APPEARED MORE OFTEN THAN THE PRESENCE OF LOWER RESPIRATORY TRACT SYMPTOMS (74.7% versus 45.6%).

A DETAILED WITHIN-PATIENT ANALYSIS OF THE TIME SEQUENCE OF VARIOUS SYMPTOMS IN THE SARS COHORT REVEALED THAT MYALGIA, LOOSE STOOL OR DIARRHEA, AND FEVER WERE THE 3 EARLIEST SYMPTOMS (Figure 2). THE APPEARANCE OF MYALGIA AND LOOSE STOOL OR DIARRHEA PEAKED ON THE SAME DAY.

Table 2.
Initial vital signs and laboratory results of febrile patients.

| Items and Numbers With Results | SARS                  | Non-SARS               |
|-------------------------------|-----------------------|------------------------|
|                               | Mean±SD Range No.     | Mean±SD Range No. P Value |
| Body temperature, °C          | 38.1±1.0 35.8–40.3 79 | 37.4±0.9 35.3–39.5 218 <.01 |
| Systolic blood pressure, mm Hg| 131±21 86–184 79     | 141±24 99–240 218 <.01 |
| Diastolic blood pressure, mm Hg| 76±15 51–132 79     | 81±36 46–143 219 <.01 |
| Pulse rate, beats/min         | 100±14 78–134 78     | 101±16 43–160 219 .823 |
| Oxygen saturation, %          | 97±3 83–100 77       | 98±7 80–100 219 .778 |
| WBC count, ×109/L             | 7.500±3.500 5.356–2.562 2.540–17.930 79 | 8.704±3.963 1.870–31.750 216 <.01 |
| Hemoglobin, g/dL              | 13.3±2 13.5±2.4 8.7–16.2 79 | 13.3±1.7 4.3–17 216 .017 |
| Neutrophil count, ×109/L      | 4.000±1.000 4.062±2.413 1.225–17.221 79 | 6.401±3.788 729–27.019 216 <.01 |
| Lymphocyte count, ×109/L      | 2.000±500 0.878±351 190–1,480 79 | 1.470±793 269–5,915 215 <.01 |
| Thrombocyte count, ×109/L     | 220±100 157±56 78–162 79 | 227±72 50–606 215 <.01 |
| Urine nitrogen, mg/dL         | 4.5–24 10.5±4.3 4.8–20.3 76 | 11.2±4.5 4.1–26.6 188 .255 |
| Creatinine, mg/dL             | 0.8–1.2 0.9±0.2 0.6–1.7 75 | 0.8±0.2 0.2–4.1 188 .541 |
| Aspartate aminotransferase, U/L| <35 56.6±73.6 18–530 77 | 27.8±20.3 11–252 194 <.01 |
| Alanine aminotransferase, U/L  | <35 40.5±48.5 4–280 36 | 29.8±32.2 5–160 63 .196 |
| Sodium, mmol/L                | 135–146 137.5±4.2 126.9–144.1 78 | 140.2±3.3 128.9–147 192 <.01 |
| Potassium, mmol/L             | 3.5–5.3 4.1±0.5 3.0–5.3 72 | 4.1±0.2 3.2–5.8 181 .921 |
| C-reactive protein, mg/dL     | <0.8 3.9±2.8 0–12 65 | 2.1±2.8 0–12 182 <.01 |
| Creatine kinase, U/L          | 38–160 467.8±1,729.9 31–13,862 73 | 121.3±134.7 1.4–994 172 <.01 |

*Numbers with result.
The initial case definition of SARS by the WHO focused on fever, cough or dyspnea, and exposure history. It provided a diagnostic basis for physicians at the beginning of the outbreak, but this definition has its limitations. First, when the disease became endemic rather than imported, the contact history of some patients could not be traced, creating a diagnostic difficulty. Second, because cough is a nonspecific symptom, describing the presence of cough only fails to be the benchmark used to discriminate SARS from a variety of other respiratory tract infections. Third, in the early stage, febrile patients may have acquired the SARS coronavirus without developing respiratory symptoms. Excluding the diagnosis of SARS in this patient group according to the absence of cough exposes the community to the risk of further disease spread.

The results of the study supplement the description of clinical symptoms of SARS issued by the WHO. Our study revealed that fever, myalgia, and loose stool or diarrhea were the earliest symptoms of SARS. Upper respiratory tract symptoms such as coryza and sore throat, previously reported to range from 22.3% to 35%,5,9 were rare in our SARS cohort. Similar findings were observed in the greater Toronto area.6 On the contrary, coryza and sore throat were frequently mentioned symptoms in our control group. The occurrence of upper respiratory tract symptoms might be useful in discriminating SARS from common upper respiratory tract viral infection in the early stage.

The timing of cough could be another useful feature to discriminate SARS from non-SARS cases. Although cough before or during fever is more likely to be associated with non-SARS cases, lower respiratory tract symptoms developing later (on an average of 3.17 (SD 2.03) days after fever) than fever, whereas lower respiratory symptoms, including cough and dyspnea, occurred later in the clinical course, appearing on an average of 3.17 (SD 2.03) days after fever. The non-SARS group did not exhibit such characteristics, as shown in Figure 3.

Fifty-five (69.6%; 95% CI 0.60 to 0.80) SARS patients, compared with only 7 (3.2%; 95% CI 0.008 to 0.05) non-SARS patients, followed the abovementioned characteristic clinical course. On the other hand, only 6 (7.6%; 95% CI 0.02 to 0.13) SARS patients developed cough before or with onset of fever compared with 112 (50.9%; 95% CI 0.44 to 0.58) non-SARS patients.

**Limitations**

There were a few limitations in the study. First, the duration of fever before hospitalization was self-reported and was subject to individual sensitivity to the change of body temperature. However, this limitation should not affect the chronologic sequence of various symptoms. Second, symptoms after hospitalization were not included in our analysis. Although these later symptoms may be helpful in making the diagnosis of SARS, they may not be useful in making early diagnosis. Third, the study was conducted in a single medical center in northern Taiwan, so the findings may not be extrapolated to other patients across the island. However, because the institution was the leading SARS hospital during the outbreak, reporting in total about 24% of the probable SARS cases in Taiwan, the samples should be considered representative.

![Figure 1](https://example.com/figure1.png)

**Figure 1.** Percentage of initial symptoms and abnormal chest radiograph infiltration.

| Symptom              | SARS   | Non-SARS |
|----------------------|--------|----------|
| Rhinorrhea           | 2.5%   | 21.4%    |
| Sore throat          | 3.8%   | 34.5%    |
| Chills               | 20.3%  | 32.8%    |
| Headache             | 18.2%  | 22.8%    |
| Diarrhea             | 21.4%  | 45.6%    |
| Myalgia              | 75.5%  | 58.6%    |
| Airway symptoms      | 65.8%  |          |
| Abnormal chest radiograph | 74.7% |          |

**DISCUSSION**

The initial case definition of SARS by the WHO focused on fever, cough or dyspnea, and exposure history. It provided a diagnostic basis for physicians at the beginning of the outbreak, but this definition has its limitations. First, when the disease became endemic rather than imported, the contact history of some patients could not be traced, creating a diagnostic difficulty. Second, because cough is a nonspecific symptom, describing the presence of cough only fails to be the benchmark used to discriminate SARS from a variety of other respiratory tract infections. Third, in the early stage, febrile patients may have acquired the SARS coronavirus without developing respiratory symptoms. Excluding the diagnosis of SARS in this patient group according to the absence of cough exposes the community to the risk of further disease spread.

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The high seroconversion rates against SARS coronavirus (97.4%) among our SARS cohort suggested that most patients classified as having probable SARS in this study actually had coronavirus infections. Meanwhile, only 40.4% of SARS patients in this study had positive

![Figure 2. Sequential symptoms in SARS patients.](image1)

![Figure 3. Sequential symptoms in non-SARS patients.](image2)
reverse transcriptase–polymerase chain reaction results. Although reverse transcriptase–polymerase chain reaction is an important laboratory test and should be obtained for all patients with suspected SARS, it may not be useful and practical for screening purposes.

Nearly 70% of the SARS patients exhibited the characteristic time sequence of symptoms: myalgia and loose stool or diarrhea around the onset of fever, without coryza or sore throat, followed by progressive lower respiratory tract symptoms. Similar clinical presentation was observed in only 3.2% of the control group. The consistency of clinical presentation in most probable SARS patients further substantiates the usefulness of careful history taking in the early differential diagnosis of SARS.

In retrospect, we did not check the reverse transcriptase–polymerase chain reaction and serologic data for SARS coronavirus in febrile patients classified as low risk and non-SARS, because the ED was severely constrained in space and staff during the outbreak. If such information could be available, a subset of patients with minor or atypical presentations could have been identified.

This study chronicles in detailed time sequence the early symptoms of the febrile probable SARS and non-SARS patients. During the outbreak, the characteristic presentation of fever accompanied by diarrhea and myalgia, along with the absence of upper respiratory tract symptoms, followed by progressive respiratory symptoms should prompt the awareness of possible SARS. Besides travel and contact history, the time sequence of accompanying symptoms may help first-line physicians screen SARS patients at an early stage.

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