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Sequential Symptomatic Analysis in Probable Severe Acute Respiratory Syndrome Cases

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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 (B100.3°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.[1] 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,[2,3] the accuracy of the currently available rapid assays is not well established.[4]

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,[5,6] 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 (B100.3°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 (B100.3°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

Table 1.
Demographic data of febrile patients.

	SARS Patients*				Non-SARS Patients†	
Characteristic	No.	Percentage	RT-PCR,‡ No. (%)	Serology,§ No. (%)	No.	Percentage
Sex						
Men	35	44.3			124	56.4
Women	44	55.7			96	43.6
Risk exposure						
Travel‖	8	10.1	1/5 (20)	3/3 (100)	69	31.4
Hospital						
A	33	41.8	6/20 (30)	15/16 (94)	47	21.4
B	4	5.1	1/2 (50)	0/0	1	0.04
C	4	5.1	1/3 (33)	2/2 (100)	1	0.04
D	13	16.5	4/12 (33)	11/11 (100)	13	5.9
Contact history¶	8	10.1	6/7 (86)	3/3 (100)	2	0.1
None of risks listed	9	11.4	4/8 (50)	3/3 (100)	87	39.5

RT-PCR, Reverse transcriptase-polymerase chain reaction.
*Mean age: 44.6 y (IQR 30–53 y).
†Mean age: 37.8 y (IQR 26–47 y).
‡RT-PCR: the results mean positive numbers in total check.
§Seroconversion of SARS coronavirus by immunofluorescence assay.
‖Travel means returning from infected areas.
¶Contact history with probable SARS cases.

(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±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 arrival at the ED in 59 (26.8%) of 220 non-SARS patients and in 47 (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 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 frequently 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.

		SARS			Non-SARS			
Items and Numbers With Results	**Normal Range**	**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±18.6	43–160	219	.623
Oxygen saturation, %		97±3	83–100	77	98±7	80–100	219	.778
WBC count, $\times 10^9$/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, $\times 10^9$/L	4,000±1,000	4,062±2,413	1,225–17,231	79	6,481±3,738	729–27,019	216	<.01
Lymphocyte count, $\times 10^9$/L	2,000±500	878±351	190–1,480	79	1,470±793	269–5,915	215	<.01
Thrombocyte count, $\times 10^9$/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	4.1–36.6	186	.255
Creatinine, mg/dL	0.6–1.2	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	27.6±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	135–148	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.

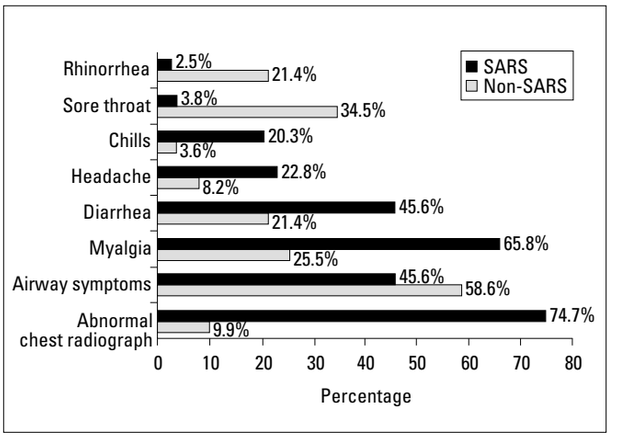
or 1 day before fever, whereas lower respiratory symptoms, including cough and dyspnea, occurred later in the clinical course, appearing on an average of 3.17 (SD 2.03) days after fever. The non-SARS group did not exhibit such characteristics, as shown in Figure 3.

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.
Percentage of initial symptoms and abnormal chest radiograph infiltration.



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.

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 3.2 days) in the clinical course would favor the diagnosis of SARS. Furthermore, in 32 (40.5%; 95% CI 0.30 to 0.51) SARS patients, abnormal chest radiographic infiltrate was identified before the onset of lower respiratory tract symptoms. The finding suggests that the absence of lower respiratory tract symptoms is not useful in ruling out SARS and indicates the importance of chest radiographic examination in screening procedures.[9]

Although the SARS and the non-SARS groups were significantly different in many laboratory indices, these results should be interpreted carefully. In our study, the SARS patients had longer duration of fever before presenting to the ED than the non-SARS patients. The laboratory samples were obtained at different points of the

disease course for the 2 groups, with regard to the onset of fever. These laboratory indices may be useful in diagnosis of SARS at later course of the disease but not necessarily applicable to the early stage of the disease.

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.

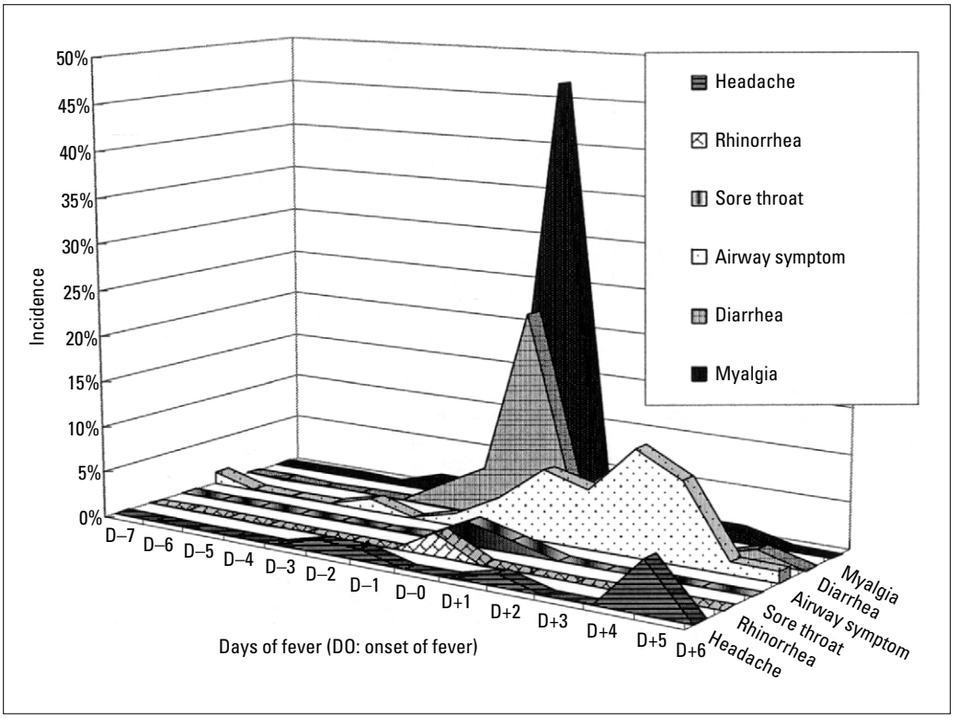
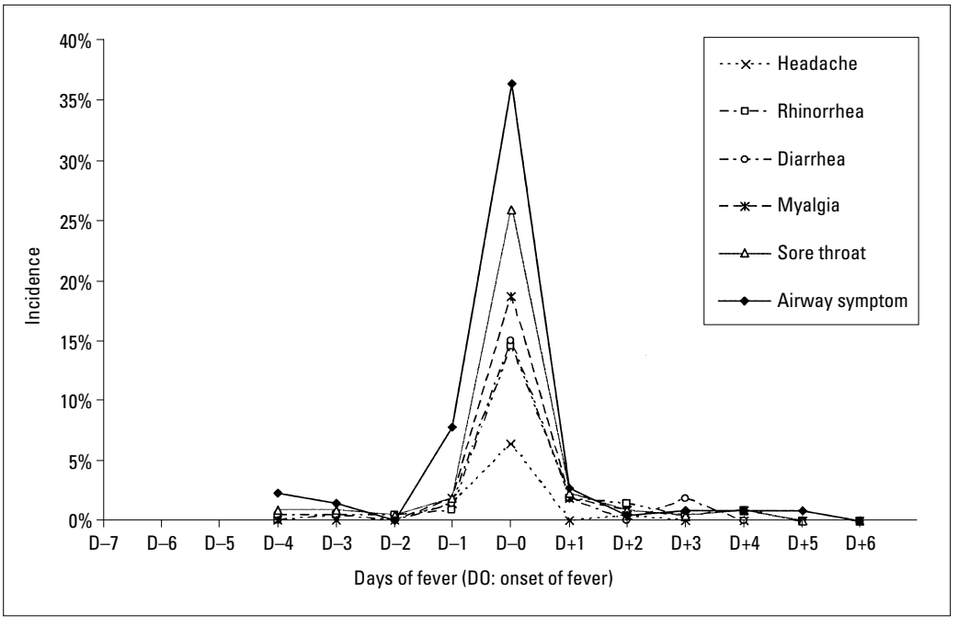


Figure 3.
Sequential symptoms in non-SARS patients.



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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Author contributions: SYC and WCC conceived and designed the studies. CPS, CYH, SJL, and JLW contributed to acquisition of the data. The manuscript was prepared by SYC, WCC, and PCIK and then revised by MHMM. FYS and KCT critically reviewed the manuscript for important intellectual content. ZSY and MHMM were responsible for statistical consultation. The trial was supervised and conducted by SCC, SCC, and WJC. SYC, WCC, and WJC take responsibility for the paper as a whole.

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