Evaluation of WHO criteria for identifying patients with severe acute respiratory syndrome out of hospital: prospective observational study

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Abstract

Objectives To determine the clinical and radiological features of severe acute respiratory syndrome (SARS) and to evaluate the accuracy of the World Health Organization's guidelines on defining cases of SARS.
Design Prospective observational study.
Setting A newly set up SARS screening clinic in the emergency department of a university hospital in Hong Kong's New Territories.
Participants 556 hospital staff, patients, and relatives who attended the screening clinic and who had had contact with someone with SARS.
Main outcome measure Number of confirmed cases of SARS.
Results Of the 556 people, 141 were admitted to hospital, and 97 had confirmed SARS. Fever, chills, malaise, myalgia, rigor, loss of appetite, vomiting, diarrhoea, and neck pain but not respiratory tract symptoms were significantly more common among the 97 patients than among the other patients. The overall accuracy of the WHO guidelines for identifying suspected SARS was 83% and their negative predictive value was 86% (95% confidence interval 83% to 89%). They had a sensitivity of 26% (17% to 36%) and a specificity of 96% (93% to 97%).
Conclusions Current WHO guidelines for diagnosing suspected SARS may not be sufficiently sensitive in assessing patients before admission to hospital. Daily follow up, evaluation of non-respiratory, systemic symptoms, and chest radiography would be better screening tools.

Introduction

Initial reports on severe acute respiratory syndrome (SARS) described the clinical features of confirmed cases.[1–4] Later reports have described the epidemiology and progression of the illness in greater detail.[5 6] On the basis of early findings in hospitals, the World Health Organization and the Hospital Authority of Hong Kong produced case definitions for suspected and probable cases of SARS that may be used for screening patients before admission to hospital and in non-clinical contexts such as airports.[7 8] The discovery of the virus and the development of rapid serological tests may improve case definition, but the tests are not yet widely available.[9–11]

In the first two weeks of March 2003, 15 doctors, 15 nurses, 17 medical students, and five other staff (auxiliary staff, a clerk, and cleaning staff) associated with ward 8A of the Prince of Wales Hospital were infected with SARS. In response to this outbreak the hospital set up an emergency screening clinic on 12 March to evaluate all staff and their immediate contacts. The clinic gave us the opportunity to study the clinical response to the virus in a high contact environment. We investigated the clinical features of SARS in the early stages of infection to evaluate the WHO criteria for identifying suspected and probable cases of SARS and to report the safety of our current strategies to prevent the spread of SARS among our staff.

Methods

The study was conducted from 12 March to 31 March 2003 in the newly opened SARS clinic in the emergency department of the Prince of Wales Hospital, a 1400 bed university teaching hospital in the New Territories of Hong Kong. Health advice was given to all hospital staff, patients, and relatives who attended the clinic (see bmj.com for details).

Defining cases of SARS

As no diagnostic investigations for SARS were available at the time the clinic opened, we based diagnosis on exclusion of other diseases and on the WHO guidelines (box).[7 12] For suspected cases, we took a broad interpretation of the respiratory symptoms in the WHO criteria to include upper and lower tract clinical features. We confirmed a diagnosis of SARS when a patient was known to have contact with someone with SARS, had documented persistent fever (>38°C), a consistent clinical course of the illness, and evidence of pneumonia.

We used plain radiography or computed tomography to diagnose pneumonia. We diagnosed non-SARS pneumonia if the patient responded well to antibiotics within 48 hours. Final diagnoses were made by a team of general medical, respiratory, and infectious diseases clinicians. The recent discovery of the virus and the development of an immunofluorescence assay based

P+ *Details of health advice given to attenders at the screening clinic are on bmj.com*

WHO case definitions for suspected and probable SARS

SARS is suspected in patients with:

- High fever (>38°C)
- One or more respiratory symptoms (such as cough, shortness of breath, or breathing difficulty), and
- Close contact with a person previously diagnosed with SARS (having cared for, lived with, or had direct contact with bodily secretions of a person with SARS).

SARS is probable when a patient meets the criteria of a suspected case and there is radiological evidence of infiltrates consistent with pneumonia or respiratory distress syndrome.

on vero cells infected with coronavirus have since allowed us to confirm diagnoses by measuring levels of anti-coronavirus IgG antibody in saved serum samples.

Inclusion and exclusion criteria

All hospital staff, patients, and relatives of staff or patients had access to the clinic. People attending the clinic were included in the study if they had had contact with anyone with SARS. We excluded children aged less than 11 years because their laboratory results and the clinical course of the disease are likely to differ from those of adults. Patients admitted to hospital with pneumonia but who had a diagnosis of non-SARS pneumonia were not excluded from the analysis.

Discharge and follow up criteria

Patients were discharged after their first attendance at the clinic if they had vague or no symptoms, no fever, and normal radiological and laboratory test results. These patients were given hygiene advice and told to return if they became feverish. Patients were followed up daily after their first attendance at the clinic if they had had contact with someone with SARS, had one or more symptoms (upper and lower respiratory tract symptoms, gastrointestinal symptoms, or systemic symptoms), were feverish (>38°C) on at least one occasion, and had a normal or indeterminate chest radiograph and if the results of investigations were abnormal (such as leucopenia, lymphopenia, monocytosis, or thrombocytosis). These patients were clinically assessed and had anteroposterior chest radiography daily. Patients were given hygiene advice and a follow up appointment for the next day. Patients who were followed up daily and who were clear of symptoms for 48 hours, with no documented fever and normal chest radiographs and laboratory tests, were discharged.

Data collection and measurement

All patients completed a health questionnaire and saw a doctor. Basic observations were recorded, including pulse, systolic and diastolic blood pressure, respiratory rate, tympanic temperature, and oxygen saturation in room air. All patients had daily frontal, plain chest radiography until either their symptoms subsided or a pneumonic change was seen. Patients whose fever and symptoms persisted for more than two days underwent standard and high resolution computed tomography, even if their chest radiographs were normal, to confirm or exclude occult pneumonia. Chest radiographs were evaluated firstly by a specialist emergency physician with reference to clinical details and then by a radiologist without reference to details. The primary clinical outcome was confirmed cases of SARS.

Statistical analysis

We used the unpaired Student's *t* test to analyse continuous data and the χ^2 test or Fisher's exact test for categorical data. We used Statview for Windows version 5.0 (Abacus Concepts, SAS Institute, Cary, NC). All analyses were two tailed. P values of <0.05 were considered statistically significant.

Results

Between 11 March and 31 March 2003 a total of 556 people with a history of contact with someone with

Table 1 Characteristics of patients presenting to the SARS screening clinic who had previous contact with someone with SARS. Values are numbers (percentage) unless otherwise stated

Characteristic	All patients (n=556)	Patients without SARS (n=459)	Patients with SARS (n=97)	P value*
Mean (SD) age (years)	35.8 (14.0)	35.6 (13.7)	37.0 (15.4)	0.73
No (%) of men	168 (30)	131 (29)	37 (38)	0.06
Median No of days (interquartile; range) between onset of symptoms and first presentation	3.0 (1.0 to 5.0; 1 to 30)	3.0 (1.0 to 5.0; 1 to 30)	3.0 (1.75 to 4.25; 1 to 15)	0.22
Status:				
Healthcare worker	325 (59)	262 (57)	63 (65)	0.01
Other hospital staff	82 (15)	77 (17)	5 (5)	
Patients and relatives of staff or patients	149 (27)	120 (26)	29 (30)	
Presentation:				
Without symptoms	41 (7)	41 (9)	–	0.0022
With symptoms	515 (93)	418 (91)	97 (100)	
Patients who met WHO definitions for suspected SARS	46 (8)	21 (5)	25 (26)	<0.0001
Disposal:				
Follow up without admission	374 (67)	372 (81)	2 (2)	<0.0001
Admission to hospital	141 (25)	46 (10)	95 (98)	
Admission at first presentation	79 (14)	33 (7)	46 (47)	
Admission during follow up	62 (11)	13 (3)	49 (51)	
Final diagnosis:				
Pneumonia†	114 (21)	17 (4)	97 (100)	<0.0001
Upper respiratory tract infection	81 (15)	81 (18)	–	

*Student's *t* test or χ^2 test.
†Typical pneumonia was diagnosed in 17 patients who recovered quickly after treatment with antibiotics alone.

Table 2 Clinical characteristics of people presenting to screening clinic with symptoms. Values are numbers (percentage) of patients

Characteristic	Total (n=515)	Patients without SARS (n=418)	Patients with SARS (n=97)	P value*
Clinical features (No (%) of patients)				
Fever	233 (45)	154 (37)	79 (81)	<0.0001
Chills	139 (27)	87 (21)	52 (54)	<0.0001
Malaise	118 (23)	85 (20)	33 (34)	0.004
Myalgia	76 (15)	50 (12)	26 (27)	0.0002
Rigor	27 (5)	15 (4)	12 (12)	0.0005
Neck pain	4 (<1)	1 (0.2)	3 (3)	0.004
Cough	363 (70)	301 (72)	62 (64)	0.12
Sputum	146 (28)	121 (29)	25 (26)	0.52
Sore throat	195 (38)	161 (39)	34 (35)	0.53
Runny nose	161 (31)	136 (33)	25 (26)	0.20
Chest pain	5 (1)	4 (1)	1 (1)	0.95
Shortness of breath	40 (8)	28 (7)	12 (12)	0.04
Loss of appetite	9 (2)	4 (1)	5 (5)	0.005
Vomiting	15 (3)	9 (2)	6 (6)	0.03
Abdominal pain	11 (2)	7 (2)	4 (4)	0.14
Diarrhoea	19 (4)	12 (3)	7 (7)	0.04
Night sweats	3 (<1)	2 (0.5)	1 (1)	0.52
Anorexia	5 (1)	5 (1)	0 (0)	0.28
Headache	110 (21)	85 (20)	25 (26)	0.24
Dizziness	28 (5)	22 (5)	6 (6)	0.72
Rash	0	0	0	
Basic observations (mean (SD))				
Heart rate per minute	95.2 (17.4)	94.0 (17.0)	104.5 (16.8)	<0.0001
Systolic blood pressure (mm Hg)	136.6 (19.5)	137.3 (19.0)	132.8 (20.8)	0.04
Diastolic blood pressure (mm Hg)	75.8 (12.7)	76.1 (12.8)	73.7 (12.4)	0.1
Respiratory rate per minute	18.6 (3.3)	18.7 (3.6)	18.8 (2.0)	0.74
Highest temperature while at clinic	37.0 (0.9)	36.8 (0.8)	37.9 (0.8)	<0.0001

*χ^2 test, Fisher's exact test, or Student's *t* test.

SARS attended the screening clinic (table 1). We excluded 41 patients who had no symptoms. Table 2 shows the clinical features and observations in the other 515 patients. Symptoms that were more common (though not significantly) among patients who did not develop SARS than in patients with confirmed SARS were cough (72% of patients), sputum production (29%), sore throat (39%), and runny nose (33%). Clinical symptoms that were significantly more common among patients with confirmed SARS were fever, chills, malaise, myalgia, rigor, neck pain, loss of appetite, shortness of breath, vomiting, and diarrhoea. Of the common upper and lower respiratory tract symptoms only shortness of breath was significantly more common among patients with SARS.

Only two patients with obvious radiological evidence of consolidation had chest signs that were detectable on physical examination. Compared with patients who did not develop SARS, patients with confirmed SARS had a significantly higher heart rate, lower mean systolic blood pressure, and higher mean temperature. Respiratory rate did not differ between the groups.

Table 3 Accuracy of WHO criteria for identifying suspected severe acute respiratory syndrome (SARS)

	SARS confirmed (No of patients)		
	No	Yes	Total
Suspected SARS according to WHO criteria			
No	438	72	510
Yes	21	25	46
Total	459	97	556

Sensitivity 25.8% (95% confidence interval 17.4% to 35.7%), specificity 95.4% (93.1% to 97.1%), positive predictive value 54.3% (39.0% to 69.1%), negative predictive value 85.9% (82.6% to 88.8%).

Predictive ability of the WHO criteria for diagnosing suspected SARS

Of the 97 patients with confirmed SARS, 25 met the criteria for suspected SARS in the WHO guidelines (table 3). The criteria had an overall accuracy of 83% (463 of 556 cases correctly identified). They had a negative predictive value of 86% (95% confidence interval 83% to 89%), a positive predictive value of 54% (39% to 69%), a sensitivity of 26% (17% to 36%), and a specificity of 95% (93% to 97%). Applying the WHO criteria for suspected SARS in our group of patients would have missed 72 cases (74%). The odds ratios of predicting SARS for particular symptoms were 12.0 (6.8 to 21.0) for fever, 1.0 (0.6 to 1.7) for cough, and 1.5 (0.7 to 3.5) for shortness of breath.

Radiological changes

All patients had chest radiography. Pneumonic change was evident in 129 patients (23%): 72 (56%) on the first presentation and 57 (44%) on follow up. Chest x ray changes were unifocal (figure 1), bifocal, or diffuse. The odds ratio for radiological findings predicting SARS was 32.1 (18.0 to 57.3).

High resolution computed tomography was requested for 27 patients (5%) who had normal chest radiographs but persistent fever and symptoms. Eighteen of the 27 scans (67%) were positive and one was indeterminate. Figure 2 shows two patients' scans that were taken on the same day: one with a retrocardiac lesion and one with a retrodiaphragmatic lesion. The median time from onset of symptoms to identification

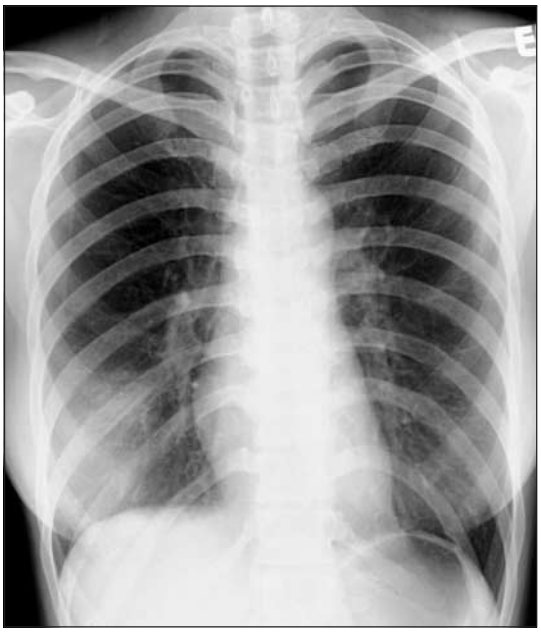

Fig 1 Frontal chest radiograph showing an area of opacification in the right lower zone

of positive radiological changes was four days and to identification of changes in scans was seven days.

Secondary infections and serology

No healthcare workers in the clinic were infected once it was fully operational, and no secondary infections occurred among the patients with suspected SARS. A preliminary serological analysis of samples from 179 patients who have attended the clinic have shown that 98 samples from 99 people with confirmed SARS were positive for coronavirus and that all the samples from 80 people who did not develop SARS were negative.

Discussion

The WHO guidelines on diagnosing SARS emphasise respiratory tract symptoms such as cough, shortness of breath, and breathing difficulty. However, these clinical symptoms in the WHO case definitions do not feature strongly in the early stages of the illness, when patients are highly infectious but before they are hospitalised. In screening patients for SARS systemic symptoms such as fever, chills, malaise, myalgia, and rigors may be better discriminators than the symptoms listed in the WHO guidelines, which were based on study of patients who were already in hospital. The absence of clinical signs in all but a few of our patients when they were screened—even in patients with obvious pneumonic changes in radiographs—means that chest radiography ought to be mandatory for all patients being screened for SARS. Of all the predictors we tested, chest radiological changes had the highest odds ratio. Almost 75% of patients in our study with history of contact with SARS and evidence of pneumonia on radiography did not have a high fever.

One limitation of our study is that it took place in a single centre with a high proportion of healthcare workers and primary contacts, and thus the results may not be generalisable to the wider community. Establishing whether patients have had contact with someone with SARS is difficult and sometimes impractical. However, one advantage of our group was that contact was highly likely and was documented. Screening may be more difficult in situations where a contact history is difficult to establish.

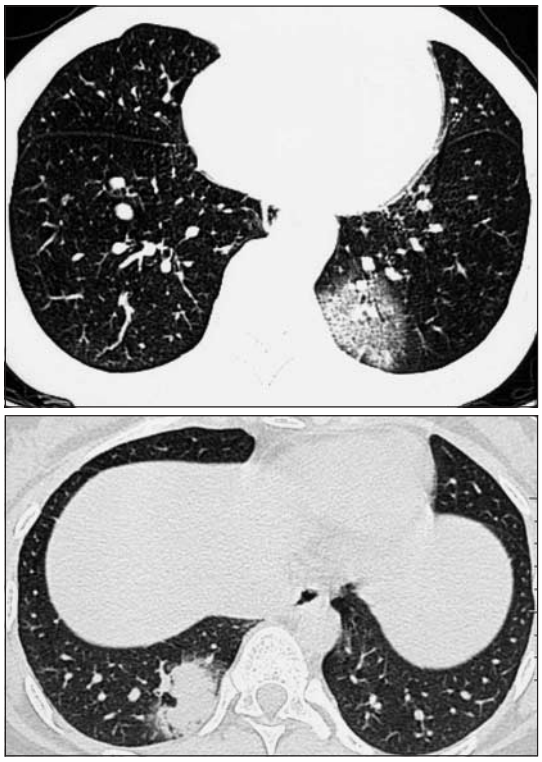

Fig 2 High resolution computed tomograms of two patients whose chest radiographs were normal: (above) ground glass opacification in the posterior segments of the left lower lobe (difficult to identify on a frontal chest radiograph because of location behind the heart); (below) ground glass opacification in the posterior segments of the right lower lobe (difficult to identify on a frontal chest radiograph because of location behind the diaphragm)

Preliminary blood testing for coronavirus indicates that our screening and diagnostic criteria are over 99% accurate. Our patients showed no secondary infection or severe secondary deterioration, prevention of which was the main reason for setting up the screening clinic,

What is already known on this topic

The main criteria in WHO's case definitions for suspected SARS among people who have had close contact are fever (>38°C) and respiratory symptoms such as cough or breathing difficulty

WHO's case definitions, which are based on study of patients in hospital, have not been evaluated in the context of screening patients before admission to hospital

What this study adds

In the early stages of SARS the main discriminating symptoms are not cough and breathing difficulty but fever, chills, malaise, myalgia, rigors, and, possibly, abdominal pain and headache

Documented fever (>38°C) is uncommon in the early stages, and radiological evidence of pneumonic changes often precedes fever

WHO case definitions for suspected SARS have a negative predictive value of 85% and a sensitivity of 26% for detecting SARS in patients who have not been admitted to hospital

and thus our protocols seem to be safe. No healthcare workers in the clinic or close contacts of the patients became infected.

As SARS continues to spread worldwide, other healthcare settings will need to screen staff and patients who have symptoms and who have had close contact with SARS patients after an outbreak.[13] With a sensitivity of 26% and a negative predictive value of 85%, the WHO criteria should be refined to include routine daily follow up, documentation of non-respiratory systemic symptoms, and daily chest radiography until patients have passed at least 48 hours without symptoms.

Contributors: THR had the idea for the study, oversaw its planning and execution and the statistical analysis, and prepared the manuscript. PAC, DS, and KLO participated in the planning, execution, and analysis. ANWH, DCPN, and ATA were responsible for assessment of radiographs and scans. LCYS planned the epidemiological follow up. JJYS supervised the clinical assessment of patients after admission. All authors contributed to the final version of the paper. THR will act as guarantor.

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Haematological manifestations in patients with severe acute respiratory syndrome: retrospective analysis

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Abstract

Objectives To evaluate the haematological findings of patients with severe acute respiratory syndrome (SARS).

Design Analysis of the demographic, clinical, and laboratory characteristics of patients with SARS.

Setting Prince of Wales Hospital, Hong Kong.

Subjects All patients with a diagnosis of SARS between 11 March and 29 March 2003 who had no pre-existing haematological disorders.

Main outcome measures Clinical end points included the need for intensive care and death. Univariate and multivariate analyses were performed to examine factors associated with adverse outcome.

Results 64 male and 93 female patients were included in this study. The most common findings included lymphopenia in 153 (98%) of the 157 patients, neutrophilia in 129 (82%), thrombocytopenia in 87 patients (55%), followed by thrombocytosis in 77 (49%), and isolated prolonged activated partial thromboplastin time in 96 patients (63%). The haemoglobin count dropped by more than 20 g/l from baseline in 95 (61%) patients. Four patients (2.5%) developed disseminated intravascular coagulation. Lymphopenia was shown in haemato-lymphoid organs at postmortem examination. Multivariate analysis showed that advanced age and a high concentration of lactate dehydrogenase at presentation were independent predictors of an adverse outcome. Subsets of peripheral blood lymphocytes were analysed in 31 patients. The counts of CD4 positive and CD8 positive T cells fell early in the course of illness. Low counts of CD4 and CD8 cells at presentation were associated with adverse outcomes.

Conclusions Abnormal haematological variables were common among patients with SARS. Lymphopenia and the depletion of T lymphocyte subsets may be associated with disease activity.

Introduction

An outbreak of severe acute respiratory syndrome (SARS) has recently been reported from Hong Kong.[1] A novel coronavirus has been identified as the aetiological agent of the syndrome.[2 3] Viral infection may produce various haematological changes. Early studies have shown that lymphopenia and thrombocytopenia are common among patients with SARS.[1 4] This study summarises the haematological findings in patients with SARS who were treated at the Prince of Wales Hospital, Hong Kong.