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# Establishing a Clinical Decision Rule of Severe Acute Respiratory Syndrome at the Emergency Department

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**Study objective:** In the absence of reliable rapid confirmatory tests during severe acute respiratory syndrome (SARS) endemics, we designed a 2-phase cohort study to establish a scoring system for SARS and to evaluate whether it could improve the sensitivity and specificity of the World Health Organization (WHO) criteria.

**Methods:** According to the clinical characteristics and initial laboratory findings of 175 suspected cases defined by the WHO criteria (20 confirmed as cases of SARS) in 3 university teaching hospitals in Taipei between March 1 and April 20, 2003, the scoring system for SARS was designed by multivariate analysis and stepwise logistic regression as the simple arithmetic sum of point values assigned to 7 parameters. We thereafter applied the scoring system for SARS to the consecutive 232 patients (the validation group) who met the WHO criteria of suspected cases from April 21 to May 22, 2003. Final diagnosis of SARS was determined by the results of real-time polymerase chain reaction and paired serum.

**Results:** The scoring system for SARS was defined as radiographic findings of multilobar or bilateral infiltrates (3 points), sputum monocyte predominance (3 points), lymphocytopenia (2 points), history of exposure (1 point), lactate dehydrogenase more than 450 U/L (1 point), C-reactive protein more than 5.0 mg/dL (1 point), and activated partial prothrombin time more than 40 seconds (1 point). Of the validation group, 60 patients (group A) were confirmed as having cases of SARS, and the other 172 (group B) patients tested negative for SARS. The total points of the scoring system for SARS at initial presentation were significantly higher in the SARS group (median 9; range 6 to 11) than in the non-SARS group (median 4; range 3 to 7; $P<.001$). At the cutoff value of 6 points, the sensitivity and specificity of the scoring system for SARS in diagnosing SARS were 100% and 93%, respectively. The positive and negative predictive values of the scoring system for SARS were 83% and 100%, respectively.

**Conclusion:** The scoring system for SARS can provide a rapid and reliable clinical decision to help emergency physicians detect cases of SARS more accurately in the endemic area.

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**Capsule Summary**

***What is already known on this topic***

No tests or predictive models exist to establish a diagnosis of severe acute respiratory syndrome (SARS) in the emergency department (ED) setting.

***What question this study addressed***

A SARS diagnostic scoring system using information available in the ED was developed from 175 suspected SARS cases and validated in 232 subsequent cases.

***What this study adds to our knowledge***

A scoring system based on radiographic infiltrates, history of exposure, and 5 laboratory tests was helpful in discriminating true SARS cases.

***How this might change clinical practice***

Although this scoring system may not perform as well in areas with different SARS epidemiology, it is an important first step in developing diagnostic strategies for this new illness.

## INTRODUCTION

Severe acute respiratory syndrome (SARS) is a disease manifested by atypical pneumonia and rapid progression to respiratory distress.[1-4] It has been proven to be caused by the coronavirus.[5-7] According to the definition of the World Health Organization (WHO),[8] characteristics of a suspected case are a documented fever (body temperature >38°C [>100.3°F]), lower respiratory symptoms, and contact with index patients. A patient with chest radiographic findings of pneumonia, acute respiratory distress syndrome, or unexplained respiratory disease resulting in death with autopsy results demonstrating the pathology comparable with SARS is considered a probable case. Although the WHO has provided the guidelines for SARS control and some diagnostic tools such as polymerase chain reaction,[6,7,9] indirect fluorescent antibody, or enzyme-linked immunosorbent assay antibody are being developed,[9] there are still many clinical difficulties in diagnosing the disease quickly. For example, the sensitivity of polymerase chain reaction is still uncertain, and the antibody titer may be detectable at the 10th to 21st day after the onset of SARS.[9] It is a difficult issue for emergency physicians to detect patients with SARS specifically if there is neither a reliable history of exposure nor a rapid diagnostic tool.

Recent epidemiologic studies in Hong Kong[1,2] and Canada[3,10] demonstrated the clinical characteristics and important laboratory findings of SARS. To improve the possibly low sensitivity of the WHO criteria, we reported a 2-phase study that included developing a scoring system for SARS in a cohort population and validating it in a second cohort.

## METHODS

The febrile patients who consulted our institutes (3 university teaching hospitals, accounting for a population of 700,000 in Taipei, Taiwan) and met with the WHO criteria of suspected SARS were prospectively enrolled in this study beginning March 2003. The history of exposure and associated symptoms such as cough, dyspnea, myalgia, diarrhea, and rigor were recorded. All patients were completely evaluated in isolated facilities at an emergency department (ED) within 3 hours and underwent CBC count (with a differential count), clotting profiles (prothrombin time, activated partial-thromboplastin time, international normalized ratio), and biochemical measurements. In addition, chest radiographs were obtained. Throat swab, sputum, or both were collected for Gram's stain and screening tests for common viruses, notably influenza A and B and respiratory syncytial virus. Legionella and pneumococcal urinary antigen testing were also examined. Final diagnosis of SARS was documented by the Center for Disease Control in Taiwan after polymerase chain reaction and paired serum for coronavirus antibody were measured. With positive polymerase chain reaction, positive paired serum, or both, the patients were confirmed as having SARS. Patients considered probable cases according to the WHO criteria were admitted, and the others were disposed to be isolated at home for 10 days. Convalescent serum was obtained during admission for the former patients and at 14 days at our clinics for the latter patients. Anyone who had clinical deterioration during home isolation was immediately transported back to the hospital by ambulance. The protocol was approved by our institutional review board, and informed consent was obtained.

### Developing a Screening Scoring System for SARS

Performance of the multivariate analysis and derivation of the risk score were based on the derivation patients with complete data at presentation. Univariate relationships between baseline characteristics (including clinical symptoms and signs and radiologic and laboratory examinations mentioned previously) and the diagnosis of SARS were assessed by logistic regression analysis. Independent predictors of SARS were identi-

fied by stepwise logistic regression. All variables at presentation entered the initial model and were maintained if the *P* value was less than .05.

Selection of independent predictors for inclusion in the scoring system for SARS was based on their relative predictive contribution in the full logistic regression model. Variables were ranked by *z* score, and those with the least contribution were sequentially removed from the model until 7 variables that captured 98% of the overall prognostic information from the full multivariate model (evaluated as a ratio of the global $\partial^2$ statistic from the reduced compared with full model) were reached. For each patient, the scoring system for SARS was calculated as the simple arithmetic sum of point values assigned to each risk factor according to the multivariate-adjusted risk relationship: 1 point for an odds ratio (OR) of 1.0 to less than 2.0, 2 points for an OR of 2.0 to 3.0, and 3 points for an OR of more than 3.0. For evaluation of the risk score in the suspected cases, missing variables contributed a point value of 0 to the total score.

The discriminatory capacity of the risk score was assessed by using the area under the receiver operating characteristic (ROC) curve as an index of model performance in both derivation and validation phases. The ROC curve reflects the concordance of predictions with actual outcomes in rank order, with an ROC curve of 1.0 indicating perfect discrimination. Analyses were performed by use of SPSS software (version 10.0X, Chinese version; SPSS, Inc., Chicago, IL).

The sensitivity (true positive/[true positive + false negative]), specificity (true negative/[true negative + false positive]), positive predictive value (true positive/[true positive + false positive]) and negative predictive value (true negative/[true negative + false negative]) of the scoring system for SARS and the WHO criteria were calculated as comparisons.

## RESULTS

In the derivation phase, we studied 175 patients enrolled between March 1, 2003, and April 20, 2003, to develop the scoring system for SARS. These patients consulted the ED because they met the WHO criteria of suspected SARS. Twenty of the patients were confirmed as having cases of SARS, whereas the other 155 patients tested negative for SARS. Each of the initial clinical characteristics was evaluated by univariate analysis (Table 1). When all of the candidate variables were assessed simultaneously by multivariate analysis, 7 remained significant predictors of SARS (Table 2). In addition, the 7-variable regression model demonstrated a good discriminatory capacity with a c statistic of 0.750. These 7 characteristics accounted for 98% of the predictive capacity of the multivariate model and were selected for inclusion in the scoring system for SARS.

Accordingly, the scoring system for SARS was defined as radiographic findings of multilobar or bilateral infiltrates (3 points), monocyte predominance on sputum Gram's stain (which was defined as the monocyte: polymorphs more than 1:1, 3 points), peripheral lymphocytes less than $1.0\times10^9$/L (2 points), history of exposure to index patients (1 point), lactate dehydrogenase more than 450 U/L (upper normal limit 225 U/L; 1 point), C-reactive protein more than 5.0 mg/dL (upper normal limit 0.5 mg/dL; IMMAGE Immunochemistry System, Beckman Coulter, Fullerton, CA ; 1 point), and activated partial prothrombin time more than 40 seconds (1 point).

We have prospectively tested the diagnostic accuracy of the scoring system in SARS since April 21, 2003. A total of 232 patients with suspected SARS were enrolled to test the predictive capacity of the scoring system in

**Table 1.**
*Risk stratification of SARS by presenting characteristics (univariate analysis).*

| Characteristic | SARS, No. (%) (n=20) | Non-SARS, No. (%) (n=155) |
|---|---|---|
| **History of exposure or traveling** | 20 (100) | 65 (42) |
| **Clinical symptoms** | | |
| Fever | 20 (100) | 155 (100) |
| Cough | 12 (60) | 99 (64) |
| Dyspnea | 6 (30) | 31 (20) |
| Myalgia | 11 (55) | 64 (41) |
| Chill or rigor | 8 (40) | 62 (40) |
| Diarrhea | 10 (50) | 70 (45) |
| **Chest radiographs** | | |
| Multilobar or bilateral infiltrates | 15 (95) | 20 (13) |
| Pleural effusion | 0 (0) | 2 (1) |
| Cavitation | 0 (0) | 0 (0) |
| **Laboratory findings** | | |
| Leukopenia | 2 (10) | 12 (8) |
| Lymphocytopenia | 14 (70) | 38 (24) |
| Thrombocytopenia | 9 (45) | 36 (23) |
| C-reactive protein >5.0 mg/dL | 12 (60) | 47 (30) |
| Monocyte predominance on sputum Gram's stain | 16 (80) | 11 (7) |
| aPTT B40 s | 9 (45) | 40 (26) |
| INR B1.5 | 3 (15) | 28 (18) |
| Creatine kinase B400 IU/L | 5 (25) | 46 (30) |
| Lactate dehydrogenase B450 IU/L | 15 (65) | 51 (33) |
| Alanine aminotransferase B80 IU/L | 5 (25) | 37 (24) |

**aPTT,** Activated partial prothrombin time; **INR,** international normalized ratio.

diagnosing SARS. Sixty patients (group A) were confirmed as having cases of SARS. The remaining 172 patients (group B) tested negative for SARS by polymerase chain reaction and paired serum. In the non-SARS group, there were 20 cases of atypical pneumonia caused by *Mycoplasma pneumoniae*, 10 cases caused by *Hemophilus influenzae*, 5 cases caused by *Streptococcus pneumoniae*, 1 case caused by *Klebsiella pneumoniae*, 12 cases caused by mixed flora, and 37 cases caused by common viruses. In addition, there were 32 cases of tonsilitis, and 55 cases of pharyngitis.

In the SARS group, the most common presentations at the early stage were the presence of abnormal chest radiograph results (97%; 58/60), followed by monocyte-predominant sputum smear (80% of the patients with SARS, or 100% of the sputum smears for 48 patients whose sputum samples could be obtained), lymphocytopenia (67%, 40/60), elevated lactate dehydrogenase level (53%; 32/60) and abnormal C-reactive protein level (50%; 30/60; Table 3). The criteria of prolonged partial prothrombin time, thrombocytopenia, abnormal creatine kinase level, and alanine transaminase depicted in Table 1 were met in 41% (25/60), 33% (20/60), 23% (14/60), and 23% (14/60) of patients. In contrast, the patients in the non-SARS group had a significantly lower incidence of these manifestations (Table 3).

The total points of the scoring system for SARS at initial presentation were significantly higher in the SARS group (median 9; range 6 to 11) than in the non-SARS group (median 4; range 3 to 7; $P<.001$). All of the victims in group A had a scoring system for SARS of at least 6 points. Twelve patients of group B had 6 points, and the remaining 160 had a scoring system for SARS less than or equal to 5 points. At this cutoff value of 6 points, the sensitivity and specificity of the scoring system for SARS were 100% and 93%, respectively. The positive and negative predictive values were 83% and 100%, respectively. In contrast, the sensitivity of the WHO criteria for suspected cases was only 26%. The sensitivity and specificity of the WHO criteria for probable cases were 96% and 57%, respectively, and its positive and negative predictive values were 44% and 98%, respectively.

**Table 2.**
*Independent predictors in diagnosing SARS (multivariate analysis).*

| Predictor | Multivariate OR (95% CI) | Z Score |
|---|---|---|
| **History of exposure or traveling*** | 1.5 (1.3–1.6) | 3.4 |
| **Clinical symptoms** | | |
| Dyspnea | 1.1 (1.0–1.3) | 2.1 |
| Myalgia | 1.2 (1.0–1.3) | 2.2 |
| **Chest radiographs** | | |
| Multilobar or bilateral infiltrates* | 4.9 (4.4–5.4) | 11.4 |
| **Laboratory findings** | | |
| Lymphocytopenia* | 2.1 (1.8–2.5) | 6.1 |
| Thrombocytopenia | 1.2 (1.1–1.4) | 2.2 |
| C-reactive protein >5.0 mg/dL* | 1.4 (1.3–1.5) | 3.3 |
| Monocyte predominance on sputum Gram's stain* | 5.8 (5.3–6.4) | 14.6 |
| aPTT B40 s* | 1.4 (1.2–1.5) | 3.1 |
| Lactate dehydrogenase B450 IU/L* | 1.5 (1.3–1.6) | 3.2 |

*These 7 variables account for 98% of all clinical information.

## LIMITATIONS

There are still some limitations in our study. First, the coronavirus that is the pathogen of SARS has been reported to have many genetic variations. Whether the genetic variations can produce different clinical manifestations remains to be elucidated. Therefore, the scoring system for SARS may be continuously modified to maintain its diagnostic reliability. Second, there were 2 patients who had coronavirus and bacterial infections (*Acinetobacter* sp and *S pneumoniae*). Mixed infection may produce confusing clinical pictures that reduce the accuracy of the scoring system for SARS in diagnosing SARS. Third, the scoring system for SARS is a clinical decision rule for suspected cases of SARS instead of a

**Table 3.**
*Comparisons of clinical data between SARS and non-SARS groups.*

| Characteristics | SARS, No. (%) (n=60) | Non-SARS, No. (%) (n=172) |
|---|---|---|
| **History of exposure or traveling** | 43 (73) | 69 (40) |
| **Clinical symptoms** | | |
| Dyspnea | 14 (23) | 38 (23) |
| Myalgia | 38 (63) | 34 (19) |
| **Chest radiographs** | | |
| Multilobar or bilateral infiltrates | 58 (97) | 74 (43) |
| **Laboratory findings** | | |
| Lymphocytopenia | 40 (67) | 19 (11) |
| Thrombocytopenia | 20 (33) | 17 (10) |
| C-reactive protein >5.0 mg/dL | 30 (50) | 21 (12) |
| Monocyte predominance on sputum Gram's stain | 48 (80)* | 19 (11) |
| aPTT B40 s | 25 (41) | 22 (13) |
| INR B1.5 | 8 (13) | 21 (12) |
| Creatine kinase B400 IU/L | 14 (23) | 31 (18) |
| Lactate dehydrogenase B450 IU/L | 32 (53) | 31 (18) |
| Alanine aminotransferase B80 IU/L | 14 (23) | 38 (22) |

*One hundred percent for the 48 patients whose sputum samples were available.

screening tool for the general population. The sensitivity and specificity of the scoring may be expected to be different in other patient populations with a different mixture of comorbidities or in the setting of outbreaks of other respiratory diseases, such as influenza.

## DISCUSSION

There has been a major global outbreak of SARS.[1-4,10,11] Although confirmatory tests such as polymerase chain reaction and measurements of coronavirus antibody have been conducted in many laboratories,[9] they still cannot provide instant and correct information for clinicians initially. The WHO criteria may help screen suspected and probable cases,[8] but the low specificity may indicate the lack of cost-effectiveness in an endemic area. This study demonstrated the scoring system for SARS as a simple and reliable clinical decision rule to help emergency clinicians detect patients with SARS quickly and cost-efficiently.

During the endemic times, there was usually chaos when the isolated facilities were not sufficient and the WHO criteria could not discriminate definitely between victims of SARS and non-SARS febrile patients. Our report revealed that the WHO criteria for probable cases had only 44% specificity for patients who met the WHO criteria for suspected cases. This means there ought to be at least 2.3-fold reservation of isolated facilities and medical costs if all probable cases were admitted to hospitals. The average expenditure for each case to complete the workup for the scoring system for SARS was approximately US$200 in our series, whereas the medical cost during admission was US$1,100 per day. Although the total expenditure of completing the scoring system for SARS for our 232 validating patients was approximately US$46,400, the method saved at least 72 unnecessary admissions or US$1,108,800 (if the average duration of admission was 14 days). In addition, the rapid screening tests for common viruses and legionella and pneumococcal urinary antigen testing in our protocol were mainly for confirmation of the final diagnosis to establish the validity of the scoring system for SARS. Our primary objective was to develop a scoring system that used only common laboratory and radiographic examinations available at most EDs instead of other rapid tests. In other words, if no rapid screening tests were available, the scoring system still worked well.

The sensitivity of the WHO criteria for suspected cases was 26%, whereas that of the WHO criteria for probable cases was 97%. The sensitivity of the latter seemed relatively high but still not high enough. The 3% missing rate could become a pitfall in surveillance and possibly cause a devastating event in the endemic area. The only perfect clinical decision rule for such infectious diseases should have 100% sensitivity, as the scoring system for SARS provided. The use of the algorithm might also partially account for the absence of hospital staff infection in our institute during this event.

Our data demonstrated monocyte predominance on sputum smear presented as a critical finding in the early stage of SARS. Although the patients might have only dry cough and scanty sputum that resulted in relatively low availability of the data (80% in our series), we still strongly recommend examining sputum smear because of its strong positive predictive value for SARS and low cost.

To prompt early diagnosis, our study has focused on the early manifestations of SARS instead of its full-blown characteristics. In our series, patients with SARS had similar clinical manifestations during hospitalization, as investigators in Hong Kong reported.[2] Of 60 patients with SARS in this study, 100% had a temperature higher than 38°C (>100.3°F), 67% had cough, and 63% had myalgia along the whole course. The overall laboratory findings during hospitalization included lymphocytopenia (73%), thrombocytopenia (47%), elevated lactate dehydrogenase (>450 U/L; 77%), increased C-reactive protein (>5 mg/dL; 63%) and prolonged activated partial thromboplastin time (>40 seconds; 53%). The full-blown manifestations were different from the initial presentations that the emergency physicians always observed.

In summary, in the absence of available diagnostic tools that can provide confirmatory results at an early stage, the scoring system for SARS can help emergency physicians make rapid and accurate diagnosis of SARS quickly and cost-efficiently.

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