Early clinical predictors of severe acute respiratory syndrome in the emergency department

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ABSTRACT

Objectives: To assess the association of diagnostic predictors available in the emergency department (ED) with the outcome diagnosis of severe acute respiratory syndrome (SARS).

Methods: This retrospective cohort study describes all patients from the Amoy Garden complex who presented to an ED SARS screening clinic during a 2-month outbreak. Clinical and diagnostic predictors were recorded, along with ED diagnoses. Final diagnoses were established independently based on diagnostic tests performed after the ED visit. Associations of key predictors with the final diagnosis of SARS were described.

Results: Of 821 patients, 205 had confirmed SARS, 35 undetermined SARS and 581 non-SARS. Multivariable logistic regression showed that the strongest predictors of SARS were abnormal chest x-ray (odds ratio [OR] = 17.4), subjective fever (OR = 9.7), temperature >38°C (OR = 6.4), myalgias (OR = 5.5), chills and rigors (OR = 4.0) and contact exposure (OR = 2.6). In a subset of 176 patients who had a complete blood cell count performed, the strongest predictors were temperature ≥38°C (OR = 15.5), lymphocyte count <1000 (OR = 9.3) and abnormal chest x-ray (OR = 5.7). Diarrhea was a powerful negative predictor (OR = 0.03) of SARS.

Conclusions: Two components of the World Health Organization case definition — fever and contact exposure — are helpful for ED decision-making, but respiratory symptoms do not discriminate well between SARS and non-SARS. Emergency physicians should consider the presence of diarrhea, chest x-ray findings, the absolute lymphocyte count and the platelet count as significant modifiers of disease likelihood. Prospective validation of these findings in other clinical settings is desirable.

Key words: SARS; diagnosis; emergency department; sensitivity; severe acute respiratory syndrome

RÉSUMÉ

Objectifs : Évaluer l'association entre les facteurs de prédiction diagnostiques disponibles au département d'urgence (DU) et le diagnostic final du syndrome respiratoire aigu sévère (SRAS).

Méthodes : L'étude de cohorte rétrospective décrit tous les patients du complexe Amoy Garden reçus à une clinique de dépistage du SRAS d'un DU au cours d'une épidémie d'une durée de deux mois. Les facteurs de prédiction cliniques et diagnostiques furent notés, ainsi que les diagnostics

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posés au DU. Les diagnostics finaux furent établis indépendamment à partir des épreuves diagnostiques effectuées après la visite au DU. Les associations de facteurs de prédiction clés avec le diagnostic final du SRAS furent décrites.

Résultats : Parmi 821 patients, 205 étaient des cas confirmés de SRAS, 35 étaient des cas indéterminés et 581 n'étaient pas atteints du SRAS. La régression logistique à variables multiples révéla que les facteurs de prédiction les plus solides étaient les clichés pulmonaires anormaux (rapport de probabilité [RP] = 17,4), la fièvre subjective (RP = 9,7), une température >38°C (RP = 6,4), les myalgies (RP = 5,5), les frissons (RP = 4,0) et l'exposition par contact (RP = 2,6). Chez un sous-groupe de 176 patients ayant subi une numération globulaire complète, les facteurs de prédiction les plus solides étaient une température >38°C (RP = 15,5), une numération lymphocytaire <1 000 (RP = 9,3) et des radiographies pulmonaires anormales (RP = 5,7). La diarrhée était un facteur de prédiction négatif important (RP = 0,03) dans le diagnostic du SRAS.

Conclusions : Deux composantes de la définition des cas de l'Organisation Mondiale de la santé, soit la fièvre et l'exposition par contact, sont utiles à la prise de décision au DU, mais les symptômes respiratoires ne permettent pas d'identifier de façon définitive les cas de SRAS. Les médecins d'urgence doivent tenir compte de la présence de diarrhée, des résultats des clichés pulmonaires, de la numération lymphocytaire absolue et de la numération plaquettaire comme facteurs importants modifiant les probabilités de la maladie. Une validation prospective de ces constatations dans d'autres environnements cliniques serait souhaitable.

Introduction

Accurate early diagnosis of severe acute respiratory syndrome (SARS) is a difficult challenge, particularly given the limited diagnostic resources and the large number of patients presenting to emergency departments (EDs). Previous studies have described substantial variability in SARS presentation, and SARS may present like a non-specific viral illness.[1–3]

The World Health Organization (WHO) case definition criteria — fever >38°C, cough or breathing difficulty, and contact history or travel to an area with recent local transmission — are widely used to screen for SARS; however, early in the course of disease when SARS patients present to the ED, they may not yet have evolved the classic symptoms and signs that later become apparent in full-blown cases.[4] In addition, some of the typical SARS characteristics, including fever and respiratory symptoms, are features of many other conditions, therefore may not help distinguish SARS from more common illnesses. Recognition of sporadic cases will be especially difficult in non-endemic areas and at times when disease prevalence and diagnostic suspicion are low.

The identification of clinical and diagnostic test parameters that are present early in the course of disease, and that are strongly associated with a final diagnosis of SARS, will increase clinician diagnostic accuracy and help identify a subset of patients who require specific SARS coronavirus (SARS-CoV) testing. Our objective was to identify clinical predictors that are present during the ED phase of care, and that are most useful in differentiating SARS from other more common conditions. This information will prove invaluable in developing a clinical guideline to help physicians in the ED and in other primary care settings make more rapid and accurate diagnoses.

Methods

Setting and patients

Amoy Garden in Hong Kong was the site of the world's largest community SARS outbreak, in which 323 patients were infected and 11% died. Most of the Amoy Garden residents who developed SARS-like symptoms were managed at the United Christian Hospital (UCH). Early during the outbreak, the UCH established an ED-based screening clinic for patients with SARS-like symptoms. This retrospective cohort study includes all patients from the Amoy Garden complex who presented to the ED SARS screening clinic between Mar. 10 and May 10, 2003. Patients who presented to the ED but did not live in Amoy Garden were excluded. For study purposes, we defined *cases* as "Amoy Garden patients with a final diagnosis of confirmed SARS", and *non-cases* as "Amoy Garden patients with a final diagnosis of non-SARS."

Data collection

On arrival, all patients were screened for WHO case definition criteria. In addition, presenting symptoms, vital signs, investigation results, ED diagnoses and subsequent disposition were documented on standard charts, which were scanned and stored in the hospital's electronic database. After the outbreak, trained research assistants, blinded to

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the final diagnosis, reviewed the clinical data and collated the following information: patient age, gender, presence of chronic illness (any medical problem requiring regular follow up), primary symptoms, presence or absence of subjective fever, type of contact (none, social, close, clustering, or health care worker), results of laboratory tests and chest x-rays, and ED diagnosis. Data were entered into a statistical database system (Statistical Package for Social Science 11.5) for subsequent analysis.

Patient follow-up

Patients considered very unlikely to have SARS were discharged with information pamphlets, general guidelines for household hygiene measures and public health contact numbers. Patients with some SARS features who were not ill enough to require hospitalization received teaching about home quarantine, personal isolation and strict hygiene measures. Daily ED follow-up was arranged with senior doctors who monitored symptom progression and changes in the blood picture or chest x-ray. All Hong Kong patients who ultimately received a diagnosis of SARS were recorded in the Hong Kong Authority eSARS system and the Department of Health's Master List. This included patients who were discharged from the ED with a non-SARS diagnosis and later were confirmed to have SARS.

Outcome diagnosis

Final outcome diagnoses for the study cohort were retrieved from the eSARS system and the Department of Health's Master List, which contained all Hong Kong patients with suspected or confirmed SARS. Patients were defined as *confirmed SARS* if they had clinical SARS **and** virology confirmation (antibody to SARS-CoV or SARS-CoV ribonucleic acid [RNA] reverse transcription polymerase chain reaction [RT-PCR] positivity). Patients were defined as *undetermined SARS* if they had clinical SARS without virology confirmation (i.e., laboratory testing was not performed or incomplete). Patients were defined as *non-SARS* if their final diagnosis was unrelated to SARS. Final diagnoses were made independently by Hong Kong Public Health experts according to WHO recommendations for interpreting SARS-related laboratory tests (www.who.int/csr/sars/labmethods/en).

Data analysis

Patients with undetermined SARS were excluded from the analyses so that we could compare patients with confirmed SARS to those with non-SARS. Descriptive statistics including means, standard deviations and ranges were used to characterize the study population. In presenting the results of analysis, wherever appropriate, missing data were reported within tables and text. We considered p values less than 0.05 as statistically significant, and all reported p values are two-tailed. Receiver operator characteristic (ROC) curves were drawn to compare the relative sensitivity and specificity of white blood cell (WBC), lymphocyte, platelet, and neutrophil counts at different cut-off points. The modified Wilcoxon rank-sum test was used to compare the difference in areas under the ROC curves.

Univariable analyses based on likelihood ratios (LRs) were conducted to assess the association of individual clinical, laboratory and x-ray data with the final diagnosis of SARS. Categorical data were assessed using chi-squared analysis, while interval data, including blood cell counts, were analyzed using a t-test. Assumptions underlying the t-test (homogeneity of variances and normality of distribution) were met in the study population. Type of contact exposure and complete blood count (CBC) data were analyzed based on the linear trend of the LR over successive categories. A p value of less than 0.05 denotes a significant linear trend.

Multivariable analyses were then conducted to evaluate the association of each clinical, laboratory and x-ray variable (adjusted for other variables in the model) with the final diagnosis of SARS. Two separate multivariable logistic regression models were developed. The first was developed using a forward selection procedure (p-to-enter = 0.05), including clinical, contact exposure and chest x-ray data from the entire cohort (n = 786). The second was developed in a similar fashion but based on 176 patients (71 SARS, 101 non-SARS) who had a CBC performed in the ED. Because it included fewer patients, only 7 of the previously described independent variables were selected for potential inclusion, based on having the strongest univariable association with the final diagnosis of SARS. In addition, 4 CBC variables were dichotomized (*a posteriori*) at the following cut-points: WBC count <4000, lymphocyte count <1000, neutrophil count <3000 and platelet count <200 000. Variable selection was again performed using a forward selection procedure (p-to-enter = 0.05). The fit of each model to the data was assessed using the Hosmer–Lemeshow goodness-of-fit chi-squared statistic. Expected versus observed beta co-efficients were inspected visually for outlying data points. Since the primary purpose of these analyses was prediction, no interaction terms were included in either model. All analyses were done using SPSS (Version 11.5).

Results

During the study period, 821 eligible patients were evalu-

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ated in the ED SARS screening clinic. Table 1 shows that cases and controls were similar with respect to age, gender and comorbid illness prevalence. The final diagnosis was confirmed SARS in 205 cases, undetermined SARS in 35 cases, and non-SARS in 581 cases, for a disease prevalence of 26%. Overall, 281 patients were admitted after their index visit, 430 were discharged with unspecified follow-up and 110 were discharged and asked to return for ED follow up. Figure 1 illustrates patient disposition and final diagnoses in the study cohort.

Table 2 shows that chills and rigors, myalgias, malaise, abnormal chest x-ray, history of fever, and temperature >38ºC at ED presentation were the variables most strongly associated with a final diagnosis of confirmed SARS. Respiratory symptoms such as dyspnea, cough and sputum production were weakly associated (LR = 1.0–1.4) and appear to be of limited diagnostic value. Gastrointestinal symptoms, including abdominal pain, vomiting and diarrhea were negatively associated with SARS (LR = 0.2–0.8).

Table 3 shows that patients presenting to the ED were more likely to have a final diagnosis of SARS if they had been exposed to more than 2 family members with SARS

Table 1. Demographic characteristics of the study population

Variable	SARS		Non-SARS‡	*p* value
	Confirmed*	Undetermined†		
No. of patients	205	35	581	
Age, mean (and SD)	35.9 (16.2)	34.1 (14.5)	33.7 (17.1)	0.46
Male gender, no. (and %)	90 (44)	14 (39)	302 (52)	0.15
Chronic illness, no. (and %)	29 (14)	6 (17)	99 (17)	0.57

*Patients were defined as Confirmed SARS if they had clinical SARS and virology confirmation (antibody to SARS-CoV or SARS-CoV RNA RT-PCR positivity).
†Patients were defined as Undetermined SARS if they had clinical SARS without virology confirmation (i.e., laboratory testing was not performed or incomplete).
‡Patients were defined as Non-SARS if their final diagnosis was unrelated to SARS.
SD = standard deviation; SARS-CoV = SARS-associated coronavirus; RNA = ribonucleic acid; RT-PCR = reverse transcription polymerase chain reaction
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Table 2. Univariable association of key predictors for patients with a final diagnosis of severe acute respiratory syndrome (SARS)

Presenting features	Confirmed SARS (*n* = 205), no. (and %)		Non-SARS (*n* = 581), no. (and %)		LR	*p* value
	Yes	No	Yes	No		
Chills and rigors	91 (44)	114	40 (7)	535	6.4	<0.000
Myalgia	85 (41)	120	38 (7)	537	6.3	<0.000
Temperature >38°C	129 (63)	75	61 (11)	485	5.7	<0.000
Malaise	67 (33)	138	44 (8)	530	4.3	<0.000
Abnormal chest x-ray	177 (86)	24	66 (20)	258	4.3	<0.000
History of fever	196 (96)	9	195 (34)	380	2.8	<0.000
Sore throat	24 (12)	181	102 (18)	472	0.7	0.04
Abdominal pain	2 (1)	203	24 (4)	550	0.2	0.01
Headache	31 (15)	174	60 (10)	514	1.5	0.08
Dyspnea	10 (5)	195	20 (4)	554	1.4	0.39
Cough	95 (46)	110	223 (39)	352	1.2	0.06
Sputum	19 (9)	185	53 (9)	522	1.0	0.97
Nausea	6 (3)	199	19 (4)	556	0.9	0.79
Vomiting	4 (2)	201	15 (3)	559	0.8	0.59
Rhinitis	26 (13)	179	102 (18)	473	0.7	0.09
Diarrhea	6 (3)	199	29 (5)	546	0.6	0.19

*Findings documented at the time of the ED visit.
LR = likelihood ratio.
Note: Column totals may not equal diagnostic group totals because of missing data.

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(LR = 6.0) or if they had cared for, lived with or had direct contact with respiratory secretions and body fluids of a person with SARS (LR = 1.4).

A total of 176 patients, 71 with confirmed SARS and 105 with non-SARS, had a CBC performed in the ED. Figures 2 to 5 demonstrate that patients with SARS had lower (mean ± standard deviation [SD]) WBC counts (5.8±2.0 v. 7.7±2.9; $p = 0.00$) (Fig. 2), lower neutrophil counts (4.2±1.8 v. 5.3±2.5; $p = 0.002$) (Fig. 3), lower lymphocyte counts (1.1±0.6 v. 1.9±0.7; $p < 0.001$) (Fig. 4) and lower platelet counts (164.2±45.7 v. 242.5±74.3; $p = 0.002$) (Fig. 5) than patients with non-SARS.* Table 4 shows that WBC counts over 8000 were negatively associated with SARS, that neutrophil counts were relatively weak predictors, and that low lymphocyte and platelet counts were the strongest diagnostic predictors. Figure 6, an ROC analysis, illustrates the diagnostic strength of the lymphocyte count and platelet count relative to the neutrophil and WBC counts. Optimal cut-off value for the lymphocyte count was 1400 (sensitivity, 80%; specificity, 80%) and optimal cut-off for the platelet count was 190 000 (sensitivity, 80%; specificity, 75%).

Table 5 shows crude odds ratios (ORs) based on univariable analysis and adjusted ORs based on multiple logistic regression modeling, for the key clinical predictors studied. After adjustment for other variables in the model, abnormal chest x-ray, history of fever, temperature >38ºC in the ED, myalgias, chills, and significant contact history were, respectively, the strongest positive predictors while a history of diarrhea was the most powerful negative predictor. The Hosmer–Lemeshow goodness-of-fit chi-squared value for this model was 7.8 ($p = 0.45$), indicating adequate fit of this model to the data.

Table 6 shows adjusted and crude ORs for key clinical predictors, based on multiple logistic regression modeling in 176 patients who had a CBC drawn in the ED. After adjustment for other variables in the model, temperature >38ºC in the ED, lymphocyte count <1000, abnormal chest x-ray, chills, and platelet count <200 000 were the strongest positive predictors, while a history of diarrhea was the most powerful negative predictor. The Hosmer–Lemeshow goodness-of-fit chi-squared value for this model was 5.9 ($p = 0.75$), indicating a good fit of this model to these data.

*Note: All cell counts are "value" × 10^3.

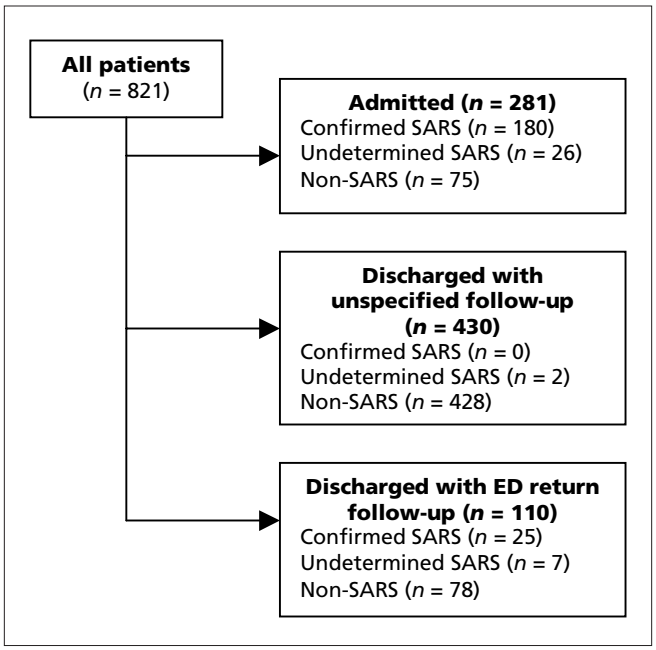

Fig. 1. Emergency department disposition and diagnostic outcome. See Table 1 for definitions of "confirmed," "Undetermined" and "Non-SARS". Reprinted from Wong et al[4] with the permission of the Canadian Association of Emergency Physicians.

Discussion

Patients who present to EDs are often early in their disease course and have not yet evolved classic symptoms and signs. In this early phase of illness, the WHO case definition criteria are not sufficiently sensitive or specific to guide screening and disposition decisions.[4] To increase diagnostic accuracy, physicians need to know which clinical features are most likely to appear early and which are most

Table 3. Association of exposure type with final diagnosis*

Type of contact	Confirmed SARS (*n* = 205), no. (and %)	Non-SARS (*n* = 578), no. (and %)	LR
None	18 (9)	112 (19)	0.5
Social†	130 (63)	390 (67)	0.9
Close‡	28 (14)	56 (10)	1.4
Clustering§	25 (12)	12 (2)	6.0
Health care worker¶	4 (2.0)	8 (1.4)	1.4

LR = likelihood ratio
*The *p* value for linear trend for all types of contact is <0.000.
†Social contact refers to persons who did not meet criteria for close contact but had contact with a SARS case.
‡Close contact refers to persons who cared for, lived with or had direct contact with respiratory secretions and body fluids of a person with SARS.
§Clustering refers to an exposure where more than 2 family members were infected with SARS.
¶Health care workers were patients working in private clinics or public hospitals who had contact with SARS cases.
Note: column totals may not equal diagnostic group totals because of missing data.

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helpful for differentiating patients with and without SARS. In this ED cohort study, we determined that fever, lymphopenia, abnormal chest x-ray, thrombocytopenia, myalgia and chills are most strongly associated with a final diagnosis of SARS, and diarrhea is a powerful negative predictor. Our data suggest that cough and dyspnea, elements of the WHO case definition, are unlikely to be useful predictors at the time of ED presentation.

Clinical findings

We used LRs to assess the (univariate) diagnostic association of key clinical predictors with the final diagnosis of SARS. This approach equates history-taking and physical examination with the application of diagnostic tests, where each clinical finding (e.g., fever/no fever) is likened to a test result. LRs are the best single indicator of a test's diagnostic strength, therefore the degree to which it can modify pretest probability and facilitate decision-making. As the positive LR (LR+) increases, the test becomes a stronger positive predictor, and as the negative LR (LR–) decreases, the test becomes a stronger negative predictor. Positive LRs between 1.0 and 3.0 are very weak, while those greater than 10 generate large and often conclusive changes in post-test probability. Negative LRs between 0.3 and 1.0 are relatively weak, and those less than 0.1 generate large and often conclusive changes in post-test probability.[5]

In this study, the symptoms most closely associated with a final diagnosis of SARS were chills and rigors (LR+ = 6.4), myalgias (LR+ = 6.3), malaise (LR+ = 4.3) and a history of fever (LR+ = 2.8). Of these, fever was reported by 96% of SARS patients, but the other symptoms were usually absent, as were cough and dyspnea, key components of the WHO case definition (see Table 2). Further, because cough and dyspnea occurred in many non-SARS patients, these symptoms appear to be poor predictors (LR+ =1.2 and 1.4 respectively) in the ED setting. Measured temperature >38ºC, the only clinical sign evaluated, was positively

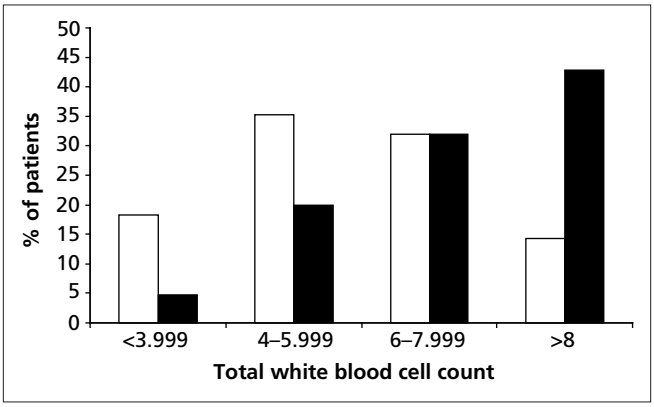

Fig. 2. Association between total white blood cell count and outcome diagnosis. White bars = Confirmed SARS; black bars = Non-SARS

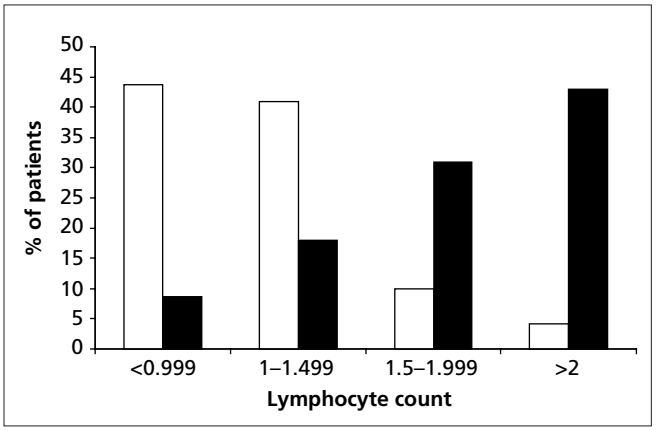

Fig. 4. Association between lymphocyte count and outcome diagnosis. White bars = Confirmed SARS; black bars = Non-SARS

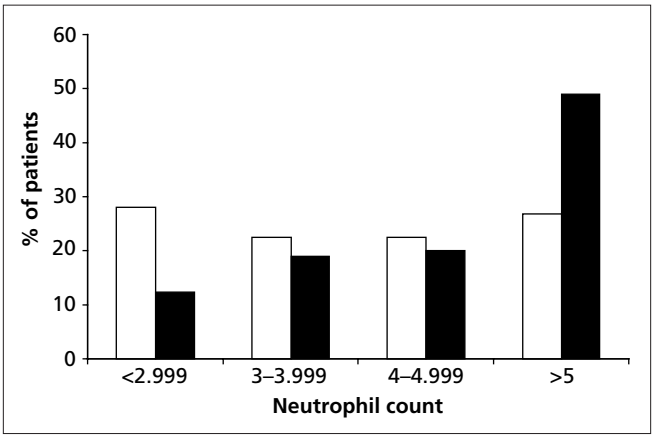

Fig. 3. Association between neutrophil count and outcome diagnosis. White bars = Confirmed SARS; black bars = Non-SARS

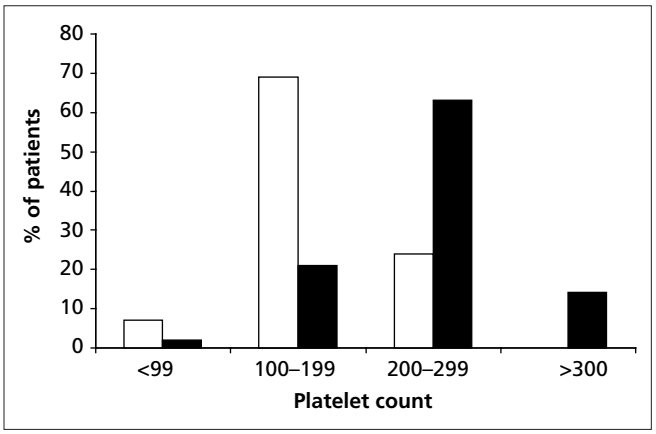

Fig. 5. Association between platelet count and outcome diagnosis. White bars = Confirmed SARS; black bars = Non-SARS

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associated with SARS (LR+ = 5.7), but more than one-third of confirmed SARS patients had a normal temperature (≤38ºC) at the time of ED presentation.

The type of contact exposure was strongly related to final diagnosis, and a dose-response effect was apparent: the likelihood of SARS increased with the level of contact intimacy. Of note, health care workers had only slightly increased risk (LR+ =1.4), but we believe this finding is spurious, based on the fact that most infected health care workers did not live in Amoy Garden and were excluded from the study.

X-ray and laboratory findings

Chest x-ray abnormalities, including unilateral or bilateral infiltrates, haziness or consolidation, were present in 86% of confirmed SARS patients and in only 20% of non-SARS patients (LR+ = 4.3), making the chest x-ray a powerful discriminator. Chest x-ray abnormalities were apparent before respiratory symptoms developed in 53% of confirmed SARS patients.

Like patients with other serious viral illnesses, our patients with SARS had significantly lower WBC, neutrophil, lymphocyte and platelet counts. The strongest predictors of SARS were a lymphocyte count <1000 (LR = 5.0) and a platelet count <100 000 (LR = 3.5), and the strongest negative predictors were a lymphocyte count >2000 (LR = 0.1) and a total WBC >8000 (LR = 0.3). Readers should be cautious in generalizing these findings to all patients because those who had a chest x-ray and blood testing were probably sicker at presentation, introducing a potentially important selection bias. This is illustrated by the fact that SARS prevalence was 40.3% (71/176) in patients who had a CBC drawn and only 26% in the overall study group.

Importance of the multivariable analyses

The LRs discussed above describe the association of individual predictors with the outcome diagnosis of SARS; however, because predictors interact in different ways, their relative importance may change when they are considered in the context of other predictors. For example, an abnormal chest x-ray may have different diagnostic meaning in a patient with leukopenia than in a patient with leukocytosis. To assess this possibility, we developed 2 multiple logistic regression models, one including data from all patients and the other including data from the subset who underwent CBC testing. In the former, after adjusting for other variables in the model, the symptoms most strongly associated with SARS were a history of fever (OR = 9.7), a temperature >38ºC in the ED (OR = 6.4), myalgias (OR = 5.5) and chills and rigors (OR = 4). In this model, significant contact exposure, defined as clustering, close contact or health care worker, was associated (OR = 2.6) and abnormal chest x-ray was very strongly associated (OR = 17.4) with a final diagnosis of SARS.

In the second multivariable model, temperature >38ºC in the ED (OR = 15.5), lymphocyte count <1000 (OR = 9.3), abnormal chest x-ray (OR = 5.3), chills and rigors (OR = 3.7) and platelet count <200 000 (OR = 3.2) were most strongly associated with SARS. A reported history of fever, myalgias and contact exposure were weak predictors, but because of the smaller sample size, the measures of association estimated in this model are less precise.

In all analyses performed, diarrhea had a strong negative association with SARS; this knowledge should be useful in leading physicians toward other non-SARS diagnoses. It is

Table 4. Complete blood count results by final diagnosis (*N* = 176)

Variable	Confirmed SARS (*n* = 71), no. (and %)	Non-SARS (*n* = 105), no. (and %)	LR	*p* value*
White blood cell count				
<4000	13 (18)	13 (12)	1.5	<0.000
4000–5999	25 (35)	20 (19)	1.8	
6000–7999	23 (32)	21 (20)	1.6	
>8000	10 (14)	51 (49)	0.3	
Neutrophil				
<3000	20 (28)	13 (11)	2.5	0.002
3000–3999	16 (23)	21 (18)	1.3	
4000–4999	16 (23)	24 (21)	1.1	
>5000	19 (26)	56 (49)	0.5	
Lymphocyte				
<1000	32 (45)	9 (9)	5.0	<0.000
1000–1499	29 (41)	19 (18)	2.3	
1500–1999	7 (10)	32 (30)	0.3	
>2000	3 (4)	45 (43)	0.1	
Platelets ($\times 10^3$)				
<100	5 (7)	2 (2)	3.5	<0.000
100–199	49 (69)	22 (21)	3.3	
200–299	17 (24)	66 (63)	0.4	
>300	0 (0)	15 (14)	0.0	

LR = likelihood ratio
**p* values based on linear trend analysis.

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interesting to note, however, that many Amoy Garden patients developed gastrointestinal symptoms later in the course of their illness, but these were not prominent at the time of ED presentation.

Clinical application

Use of the WHO case definition as a SARS screening tool is likely to lead to an unacceptable rate of misdiagnosis.[4] Our data suggest that 2 components of the case definition — fever and contact exposure — are useful in the ED setting, but that physicians should, in particular, consider the presence of diarrhea, chest x-ray findings, the absolute lymphocyte count, and the platelet count as important modifiers of disease likelihood.

Despite a better awareness of early clinical and diagnostic predictors, physicians will not be able to make an accurate diagnosis without confirmatory SARS-CoV virology testing. Unfortunately, such testing is rarely available in the ED and test results are not currently available in time to influence disposition decisions. Because SARS is infectious and often lethal, it is a high priority to make confirmatory testing available in the ED setting to reduce public health risk.[6] The clinical predictors identified in this study will help define a future risk stratification model to guide SARS-CoV testing.

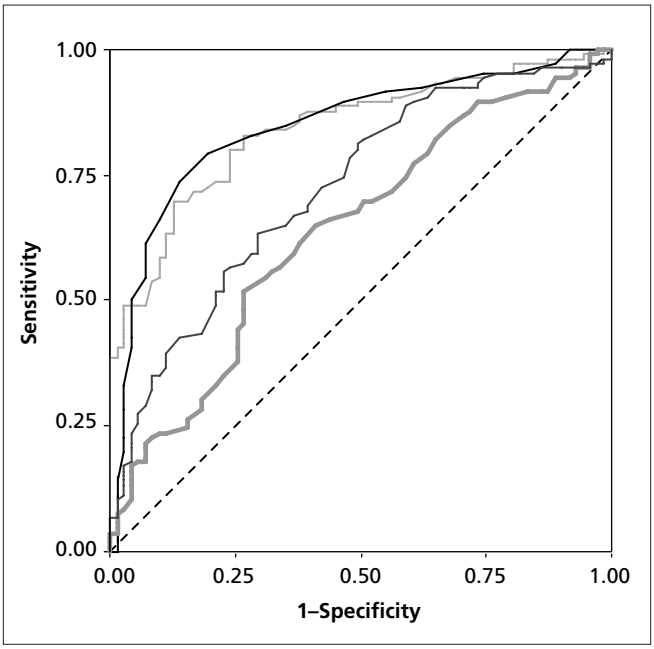

Fig. 6. Receiver operator characteristic (ROC) curves for components of the complete blood count. Area under the curve (AUC) represents the overall accuracy of the test. AUC for the white blood cell (WBC), neutrophil, lymphocyte and platelet counts were 0.72, 0.64, 0.85 and 0.84 respectively ($p < 0.005$). Diagonal segments are produced by ties. Source of the curve: Top line (black) = Lymphocyte; next line (light grey) = Platelet; 3rd line (dark grey) = WBC; 4th line (thick grey) = Neutrophil; dotted line = Reference line.

Limitations

This study has a number of limitations. First, data collection was retrospective and we could not assess the reliability of some of the predictors discussed. This is less of a concern for relatively objective tests like measured temperature, CBC and chest x-ray, but it may be a significant concern for historical variables like diarrhea, which may not have been recorded in a reliable fashion. A second concern is that the reference standard (SARS-CoV virology testing) was not performed on all non-SARs patients; therefore it is possible that milder and sub-clinical cases of SARS were missed. The resulting misclassification could have skewed the reported measures of association (LR, OR) toward or away from the null value of 1. Of note, recent studies have determined the prevalence of "asymptomatic or subclinical SARS" among exposed health care workers to be in the range of 0%–1%.[7,8] Although similar data in the exposed general population in the community remain to be eluciated, current belief suggests that if a misclassification bias exists in our study, it is probably of limited effect only. A third potential limitation is that fever, contact exposure and respiratory symptoms were evaluated as predictors, but they are also components of the case definition used to assign final diagnosis; therefore the relevant ORs and LRs derived from the data may be spuriously increased, making these items appear to be stronger predictors than they actually are. This form of circular logic is described as incorporation bias.

SARS prevalence in the study population was very high, and in this cohort, most patients had identifiable contact exposures. Similar studies performed in settings with few exposed patients would likely find that the absence of contact exposure is a powerful negative predictor. Our data may therefore underestimate the importance of contact exposure as a risk factor.

A final important limitation is that this study recorded clinical and diagnostic findings at the time of ED presentation; consequently its conclusions may not be generalizable to patients who are late in the course of their illness and to those in other settings like inpatient wards or intensive care units.

Conclusion

Two components of the WHO case definition — fever and contact exposure — are helpful for ED decision-making, but respiratory symptoms do not discriminate well between SARS and non-SARS. Emergency physi-

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cians should consider the presence of diarrhea, chest x-ray findings, the absolute lymphocyte count, and the platelet count as important modifiers of disease likelihood. Diagnostic certainty will only be possible when emergency physicians have access to rapid SARS-CoV testing, but until then, awareness of early clinical predictors will improve ED diagnostic accuracy for this lethal public health menace.

Table 5. Logistic regression analysis of key predictor variables for all patients (*n* = 786)

Clinical predictor	Adjusted OR*	95% CI	*p* value	Crude OR†	95% CI	*p* value
Abnormal chest x-ray	17.4	8.8–34.0	<0.000	28.8	17.4–47.8	<0.000
History of fever	9.7	3.6–26.4	<0.000	42.4	21.3–84.6	<0.000
Temperature >38°C	6.4	3.2–12.8	<0.000	13.5	9.2–20.0	<0.000
Myalgias	5.5	2.6–11.3	<0.000	10.0	6.5–15.4	<0.000
Chills	4.0	2.0–8.1	<0.000	10.7	7.0–16.3	<0.000
Significant contact‡	2.6	1.2–5.5	0.01	2.5	1.7–3.8	<0.000
Diarrhea	0.1	0.08–0.7	0.01	0.6	0.2–1.4	0.21
Malaise	3.8	0.9–10.2	0.06	5.8	3.8–8.9	<0.000
Headache	1.4	0.6–3.2	0.50	1.5	1.0–2.4	0.07
Nausea	1.4	0.7–3.4	0.82	0.9	0.3–2.2	0.79
Abdominal pain	1.2	0.6–18.2	0.10	0.2	0.01–1.0	0.03
Sore throat	1.0	0.4–2.7	0.93	0.6	0.4–1.0	0.04
Cough	1.0	0.5–1.8	0.93	1.4	1.0–1.9	0.06
Dyspnea	0.9	0.2–3.9	0.89	1.4	0.7–3.1	0.38
Rhinitis	0.7	0.3–1.6	0.37	0.7	0.4–1.1	0.10
Sputum	0.5	0.2–1.5	0.23	1.0	0.6–1.7	0.98
Vomiting	0.5	0.1–1.9	0.62	0.7	0.2–1.4	0.60

OR = odds ratio; CI = confidence interval
*Adjusted ORs were determined by controlling for other predictors in the multiple logistic regression model.
†Crude ORs were derived from univariate analysis without adjustment.
‡Significant contact was defined by either "close contact," "clustering" or "health care worker." See Table 3 for a detailed description of these terms.
Note: Shaded cells highlight the most powerful statistically significant clinical predictors of a final diagnosis of SARS.

Table 6. Logistic regression analysis of predictor variables in patients with complete blood count (CBC) data (*n* = 176)

Clinical predictor	Adjusted OR*	95% CI	*p* value	Crude OR†	95% CI	*p* value
Temperature >38°C	15.5	4.5–53.3	<0.000	15.3	7.5–32.5	<0.000
Lymphocyte <1000	9.3	2.0–42.0	0.004	8.4	3.9–20.2	<0.000
Abnormal chest x-ray	5.7	1.7–18.5	0.004	9.4	7.2–32.5	<0.000
Chills	3.7	1.1–11.7	0.03	3.4	1.7–6.6	<0.000
Platelet count <200 000	3.2	1.6–10.7	0.04	9.8	4.8–19.7	<0.000
Diarrhea	0.03	0.01–0.12	0.003	1.7	1.5–2.0	0.002
History of fever	3.2	0.7–14.7	0.14	14.9	4.4–50.4	<0.000
Myalgia	2.5	0.8–8.1	0.12	4.1	2.0–8.2	<0.000
Significant contact	2.4	0.6–9.2	0.19	0.6	0.3–1.2	0.16
WBC count <4000	0.5	0.1–6.7	0.63	5.4	1.9–15.7	0.001
Neutrophil count <3000	1.4	0.3–7.9	0.70	2.8	1.3–6.1	0.008

OR = odds ratio; CI = confidence interval; WBC = white blood cell
*Adjusted ORs were determined by controlling for other predictors in the multiple logistic regression model.
†Crude ORs were derived from univariate analysis without adjustment.
‡Significant contact was defined by either "close contact," "clustering" or "health care worker." See Table 3 for a detailed description of these terms.
Note: Analyses in this table are based on the subset of patients (*n* = 176) who had a CBC drawn in the emergency department.

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