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Value of Initial Chest Radiographs for Predicting Clinical Outcomes in Patients with Severe Acute Respiratory Syndrome

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PURPOSE: To determine whether the initial chest radiograph is helpful in predicting the clinical outcome of patients with severe acute respiratory syndrome (SARS).

METHODS: Of 343 patients who met the World Health Organization's case definition of probable SARS and who had been admitted to a regional hospital in Hong Kong, 201 patients had laboratory evidence of SARS coronavirus infection. The initial frontal chest radiographs of these 201 patients were assessed in a blinded fashion by 3 radiologists; individual findings were accepted if at least 2 of the radiologists concurred. Independent predictors of an adverse outcome, defined as the need for assisted ventilation, death, or both, were identified by multivariate analysis.

RESULTS: Bilateral disease and involvement of more than two zones on the initial chest radiograph were associated with a higher risk of liver impairment and poor clinical outcome. Forty-two patients (21%) developed an adverse outcome. Multivariate analysis showed that lung involvement of more than two zones (odds ratio [OR] = 7.0; 95% confidence interval [CI]: 2.7 to 17.9), older age (OR for each decade of life = 1.5; 95% CI: 1.1 to 2.0), and shortness of breath on admission (OR = 2.8; 95% CI: 1.1 to 7.4) were independent predictors of an adverse outcome.

CONCLUSION: Frontal chest radiographs on presentation may have prognostic value in patients with SARS. **Am J Med. 2004;117:249–254.** ©2004 by Elsevier Inc.

Severe acute respiratory syndrome (SARS) has become a global health hazard, and a novel virus, the SARS-associated coronavirus, has been identified as the causal agent (1–3). More than 8221 persons worldwide have been affected by this disease, and 735 patients have died since June 2003. The case fatality rate is estimated to be 13% for patients younger than 60 years and 43% for those older than 60 years (4). The 2003 outbreak in Asia demonstrated how SARS can exert tremendous stress on local health care systems and intensive care services, emphasizing the need to identify patient characteristics on presentation that can lead to stratification into different management groups.

Together with the clinical characteristics of SARS, such as fever and chest symptoms, and a recent history of contact with a suspected or confirmed SARS patient, radiographic evidence of infiltrates consistent with pneumonia or acute respiratory distress syndrome is important in establishing the diagnosis (5). However, chest radiographs, which may be normal during the febrile prodrome, may be abnormal in 71% to 100% of SARS patients at the onset of fever (6–9). Studies involving patients with community-acquired pneumonia (10), acute interstitial pneumonia (11), or idiopathic pulmonary fibrosis (12) have shown that quantitative and qualitative changes on chest radiographs might predict clinical outcome. We conducted a retrospective study to determine whether the initial chest radiograph has prognostic value in patients with SARS.

METHODS

Between February 26, 2003, and April 10, 2003, 343 patients who met the World Health Organization's case definition of suspected or probable SARS were admitted to isolation wards at Princess Margaret Hospital in Hong Kong (13). Two hundred and one patients had laboratory evidence of SARS coronavirus infection and were included in this study. Ten of these patients had an underlying illness prior to admission: 4 were chronic hepatitis B virus carriers, 1 had hepatitis B compensated cirrhosis, 2 had mental retardation, 1 had chronic rheumatic heart disease, and 2 had ischemic heart disease requiring percutaneous coronary angioplasty. The study was approved by the hospital's ethics committee. Standard entry forms were used to collect data on clinical history, physical examination, laboratory findings, and subsequent clinical course. Adverse clinical outcome was assessed using the

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Manuscript submitted June 9, 2003, and accepted in revised form March 15, 2004.

endpoint of the need for assisted ventilation, death, or both.

The admission frontal chest radiographs of the 201 patients were retrospectively and separately reviewed by 3 radiologists (POL, CML, and KFM) who were blinded to the clinical outcomes. The laterality, zones and site of involvement, type of opacification, and dominant pattern of disease were recorded. Each lung field was divided into three zones by drawing imaginary lines at the level of the inferior anterior angle of the second and fourth ribs (14). A peripheral location was defined as involvement confined to the outer one third of the lung; a central location was defined as involvement confined to the inner two thirds. Consolidation was defined as air space opacity obscuring the underlying vasculature, whereas ground-glass opacity was defined as clouding or hazes over the lungs without obscuration of lung vasculature. The dominant patterns were classified as lobar, lobular, interstitial, or diffuse (15). A diffuse pattern has been associated with acute respiratory distress syndrome. Individual findings were accepted if at least 2 of the radiologists concurred.

Treatment

All patients received antimicrobial treatment for community-acquired pneumonia after admission. Combination therapy using intravenous ribavirin (24 mg/kg/d) and hydrocortisone (8 mg/kg/d) was started if patients did not respond to treatment within 48 hours. Methylprednisolone, administered intravenously for two to three pulses each time at a dose of 500 mg to 1000 mg daily, was offered to patients who had persistent fever, radiological progression of lung infiltration, or signs of respiratory distress despite the initial antiviral treatment.

Statistical Analysis

The κ statistic and complete concordance were used to assess the level of agreement among the three radiologists in chest radiograph interpretation. Complete concordance was defined as the percentage of identical findings among the 3 radiologists for the various radiographic parameters. Clinical features and laboratory findings of patients were analyzed using various radiographic features as independent variables. Bivariate analysis was performed with the chi-squared test for categorical variables and an unpaired Student *t* test for continuous variables. Data with positive skewed distribution were log-transformed for comparison. A receiver operating characteristic (ROC) curve was plotted to determine the appropriate cutoff value with maximum sensitivity and specificity, if necessary. Multivariate analysis using backward stepwise regression was employed to identify variables that were associated with an adverse outcome (need for mechanical ventilation or death). A *P* value of less than 0.05 (two-tailed) was considered statistically significant. All analyses were performed using SPSS, version 10.0 (SPSS Inc, Chicago, Illinois).

Table 1. Characteristics of Initial Chest Radiographic Findings for the 201 Patients

Characteristic	Number (%)
Abnormal chest radiograph	185 (92)
Laterality	
Right	73 (36)
Left	61 (30)
Bilateral	51 (25)
Site of involvement	
Right upper	30 (15)
Right middle	78 (39)
Right lower	79 (39)
Left upper	28 (14)
Left middle	79 (39)
Left lower	68 (34)
Number of zones involved	
0	16 (8)
1	94 (47)
2	55 (28)
3	12 (6)
4	7 (4)
5	9 (5)
6	8 (4)
Presence of consolidation	169 (84)
Presence of ground-glass opacity	23 (11)
Location of abnormality	
Central	46 (23)
Peripheral	49 (24)
Both	90 (45)
Disease pattern	
Lobar	15 (8)
Lobular	158 (79)
Diffuse	12 (6)

RESULTS

Initial frontal chest radiographs were obtained for the 201 patients (84 male and 117 female). Fifteen patients were health care workers and 116 were residents of Amoy Gardens, a residential area where a community SARS outbreak had occurred. Fifty-two patients had a history of recent travel to SARS-infected areas in Mainland China. Nasopharyngeal aspirate or stool specimens from 135 patients (67%) yielded positive results by reverse-transcriptase polymerase chain reaction (RT-PCR). Of 182 patients who underwent serology testing for the SARS coronavirus, 169 (93%) had a fourfold or greater increase in antibody titers between acute-phase and convalescent-phase sera tested in parallel. Overall, 50 patients (25%) required intensive care. Forty-two patients (21%) needed assisted ventilation, of whom 24 (12%) died.

Normal chest radiographs were seen in 16 patients (8%) on admission. The middle and lower zones were more often affected than were the upper zones (Table 1). Almost half of the patients (47%) had single zone involvement. The majority (79%) had a predominant lobular pattern of disease.

Table 2. Level of Agreement and Complete Concordance among the Three Radiologists Regarding Interpretation of Chest Radiographic Findings

	κ Statistic (Interobserver Agreement)*			Complete Concordance
	#1 vs. #2	#1 vs. #3	#2 vs. #3	
Normality	0.62	0.62	0.69	91%
Laterality	0.85	0.87	0.88	85%
Zonal involvement >2	0.61	0.63	0.72	90%
Location of lesion	0.44	0.49	0.66	48%
Consolidation	0.59	0.48	0.48	87%
Ground-glass opacity	0.29	0.14	0.37	75%

* Level of agreement: 0.93 to 1 = excellent; 0.81 to 0.92 = very good; 0.61 to 0.8 = good; 0.41 to 0.6 = fair; 0.21 to 0.4 = slight; 0.01 to 0.2 = poor.

Most patients (84%) showed air space consolidation. One patient had right pleural effusion on the initial chest radiograph. An interstitial pattern and other associated findings such as cavitation or lymphadenopathy were not seen in any of the patients. The level of agreement and the percentage of complete concordance among the radiologists regarding assessment of the various radiographic features varied (Table 2). Interobserver agreement was generally good for normality, laterality, and number of zones involved, but fair to poor for location and type of opacification.

Patients with more than two zones of lung involvement presented significantly later than patients with fewer zones of involvement (6 ± 3 days vs. 4 ± 2 days after onset of symptoms, $P = 0.001$) (Table 3). Although patients with more zones of involvement had significantly higher levels of total white blood cell and neutrophil counts, the absolute value of these variables for the two groups of patients were within normal range. Patients with greater lung involvement more often had elevated alanine aminotransferase levels (56% vs. 24%, $P = 0.001$). They also had significantly worse outcomes in terms of admission to the intensive care unit and mortality.

Patients with bilateral disease had a significantly higher rate of admission to the intensive care unit (47% [24/51] vs. 19% [25/134], $P = 0.001$), assisted ventilation (45% [n = 23] vs. 13% [n = 18], $P = 0.001$), and greater mortality (25% [n = 13] vs. 7.5% [n = 10], $P = 0.001$) as compared with patients with unilateral disease.

Forty-two patients (21%) reached the endpoint of the need for assisted ventilation, death, or both. One patient

Table 3. Clinical Features of and Laboratory Findings in the 201 Patients. According to Zonal Involvement on the Initial Chest Radiograph

Characteristic	Involvement		*P* Value
	0 to 2 Zones (n = 165)	3 to 6 Zones (n = 36)	
	Mean ± SD or Number (%)		
Age (years)	38 ± 13	46 ± 15	0.008
Male sex	65 (39)	19 (53)	0.14
Onset of symptoms before admission (days)	4 ± 2	6 ± 3	0.001
Comorbidity	6 (4)	4 (11)	0.02*
Shortness of breath	28 (17)	11 (31)	0.03
White blood cell count ($\times 10^3/\mu L$)	4.9 ± 1.8	7.8 ± 4.1	0.001
Neutrophil count ($/\mu L$)	3700 ± 1600	6800 ± 3900	<0.001
Lymphocyte count ($/\mu L$)	800 ± 300	600 ± 300	0.001
Albumin (g/dL)	3.7 ± 0.4	3.3 ± 0.4	<0.001
Alanine aminotransferase (U/L)	34 ± 30	78 ± 55	0.001
Lactate dehydrogenase (U/L)	247 ± 101	401 ± 134	0.001
Duration of hospital stay (days)	16 ± 5	16 ± 5	0.87
Admission to intensive care unit	28 (17)	22 (61)	<0.001
Mechanical ventilation	21 (13)	21 (58)	<0.001
Death	12 (7)	12 (33)	0.001
Death/need for mechanical ventilation	21 (13)	21 (58)	<0.001

* Fisher exact test.

Table 4. Bivariate Analysis of Initial Clinical, Radiographic, and Laboratory Variables Associated with Assisted Ventilation or Death

Variable	Survivor (n = 159)	Patients Requiring Ventilation or Who Died (n = 42)	*P* Value
	Mean ± SD or Number (%)		
Age (years)	37 ± 13	47 ± 14	<0.001
Male sex	61 (38)	22 (52)	0.01
Shortness of breath	25 (16)	14 (33)	0.002
Days between onset of symptoms and admission	4 ± 2	5 ± 3	0.06
Normal chest film	14 (9)	2 (5)	0.20*
More than two zones involved	15 (9)	21 (50)	<0.001
Bilateral disease	29 (18)	23 (55)	<0.001
Location of infiltrate			0.002
Central	42 (26)	4 (10)	
Peripheral	42 (26)	7 (17)	
Both	61 (38)	29 (69)	
Disease pattern			<0.001
Lobar	15 (9)	0	
Lobular	126 (79)	32 (76)	
Diffuse	4 (3)	8 (19)	
RT-PCR positivity on nasopharyngeal aspirate	110/140 (79)	25/27 (93)	0.16
SARS coronavirus serology positivity	150/159 (94)	19/22 (86)	0.23
Alanine aminotransferase >40 U/L	40 (25)	21 (50)	<0.001
Lactate dehydrogenase >230 U/L	79 (50)	27 (64)	0.08

* Fisher exact test.

RT-PCR = reverse-transcriptase polymerase chain reaction; SARS = severe acute respiratory syndrome.

with hepatitis B compensated cirrhosis died of liver failure. Three patients with underlying heart disease (1 with chronic rheumatic heart disease, 2 with ischemic heart disease requiring percutaneous coronary angioplasty) died of respiratory failure. The risk of an adverse outcome increased significantly from 13% (21/165) to 58% (21/36) for patients with more than two zones involved. In the ROC curve analysis, involvement of more than two zones was selected as a cutoff with a sensitivity of 0.51 and a specificity of 0.91. The area under the ROC curve was 0.7 (95% confidence interval: 0.6 to 0.8).

In the bivariate analysis, variables associated with an adverse outcome were bilateral disease, involvement of more than two zones, diffuse infiltrate and infiltrates in both peripheral and central locations, older age, male sex, shortness of breath, and elevated alanine aminotransferase level (Table 4). Days between the onset of symptoms and admission were not significantly associated with clinical outcome. As there was a strong collinearity among involvement of more than two zones, bilateral disease, and diffuse pattern and distribution (both peripheral and central) of disease, zonal involvement was chosen for analysis as it represented the extent of disease involvement and was easily assessed objectively. Other factors associated significantly with an adverse outcome by bivariate analysis were included in the multivariate analysis. Multivariate analysis showed that older age (odds ratio [OR] per 10 years = 1.5; 95% CI: 1.1 to 2.0; $P = 0.01$), shortness of breath (OR = 2.8; 95% CI: 1.1 to 7.4; $P = 0.04$), and involvement of more than two zones (OR = 7.0; 95% CI: 2.7 to 17.9; $P = 0.01$) were independently associated with an adverse outcome.

DISCUSSION

Chest radiography has been shown to be important in the diagnosis and management of patients with pneumonia. Bilateral disease, multilobar shadows, and the presence of pleural effusion on initial chest radiographs are predictive of adverse outcomes in patients with community-acquired pneumonia (16–18). The initial radiographic features of patients with SARS have been described (6,19,20). Our present study of the predictive value of initial chest radiography adds to these earlier studies. We observed that patients with more extensive lung involvement in terms of bilateral disease and more than two zones of involvement had more systemic disease and worse outcomes. Patients with involvement of more than two zones had a higher risk of liver impairment and more severe lymphopenia, which may reflect systemic viral infection. A recent study reported that patients requiring

intensive care had higher serum SARS coronavirus concentrations as detected by RT-PCR (21). This new assay, however, is not widely available, and its correlation with radiographic abnormalities is not known. We also found higher lactate dehydrogenase levels and neutrophil counts in patients with greater lung involvement, which suggests that greater lung damage may occur in patients with extensive lung infiltrate on chest radiographs (7).

We found that older age, shortness of breath, and lung involvement of more than two zones were independently associated with the need for assisted ventilation or death. Lee et al reported an odds ratio of 1.8 per decade of life (7), which is similar to our finding. Booth et al (20) found that comorbid conditions, particularly, diabetes mellitus, were independently associated with poor outcomes. In our study, patients with underlying heart disease had a greater risk of poor outcomes. Positive hepatitis B surface antigen status has been shown to be an independent risk factor for progression to acute respiratory distress syndrome in SARS (6). However, none of our patients with positive hepatitis B surface antigen status developed respiratory failure. One patient with hepatitis B compensated cirrhosis died of liver failure despite lamivudine therapy. A high absolute neutrophil count on presentation has been associated with an adverse outcome; this was thought to be related to severe lung injury (7). We could not establish this association in our study.

In the bivariate analysis, laterality and the number of zones involved were associated with clinical outcome. Peiris et al observed that 33% of patients with acute respiratory distress syndrome had multilobar involvement on presentation compared with only 18% of patients without the syndrome (6). However, multilobar change was not identified as an independent prognostic factor in their study, perhaps because their sample size was too small and their use of a single frontal chest radiograph was not adequate in defining the number of lobes involved. Other reports did not consider initial radiographic abnormalities as a confounding factor for clinical outcome (7,20). As there were correlations between chest radiographic findings and other confounding factors, we used multivariate analysis with logistic regression to determine the independent prognostic value of chest radiograph on presentation and found that involvement of more than two zones was independently associated with an adverse outcome.

Interobserver variability in the interpretation of chest radiographs has been a concern in the diagnosis of acute respiratory distress syndrome (22). In our study, the interobserver agreement on the normality, laterality, and number of zones was generally good. Complete concordance among the radiologists was greater than 80%, which is considered acceptable. It may be argued that quantitative assessment of the total area of infiltrate rather than the number of zones involved may be a more accurate indicator of disease severity. Area estimation, however, is highly subjective and may result in substantial interobserver variability. On the other hand, the level of agreement on assessment of type and distribution of opacification appeared unsatisfactory by the κ statistic.

SARS is a highly contagious infectious disease that is associated with substantial morbidity and mortality. Patients' conditions may deteriorate rapidly with acute respiratory failure. Indeed, 23% to 48% of patients require intensive care and mechanical ventilation (1,6,7), and short-term mortality rates range from 4% to 15% (7,23). Our study suggests that radiographic evidence, specifically, frontal chest radiograph on presentation, may have prognostic value in patients with SARS. Patients with more extensive lung involvement on the initial chest radiograph had a higher risk of mechanical ventilation or death. Involvement of more than two zones on initial chest film, older age, and shortness of breath on presentation were independent predictors of an adverse outcome.

REFERENCES

1. Peiris JSM, Lai ST, Poon LLM, et al. Coronavirus as a possible cause of severe acute respiratory syndrome. *Lancet*. 2003;361:1319–1325.
2. Drosten C, Gunther S, Preiser W, et al. Identification of a novel coronavirus in patients with severe acute respiratory syndrome. *N Engl J Med*. 2003;348:1967–1976.
3. Rota PA, Oberste MS, Monroe SS, et al. Characterization of a novel coronavirus associated with severe acute respiratory syndrome. *Science*. 2003;300:1394–1399.
4. Donnelly CA, Ghani AC, Leung GM, et al. Epidemiological determinants of spread of causal agent of severe acute respiratory syndrome in Hong Kong. *Lancet*. 2003;361:1761–1766.
5. Centers for Disease Control and Prevention. Updated interim surveillance case definition for Severe Acute Respiratory Syndrome (SARS). Available at: http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5217a5.htm. Accessed April 29, 2003.
6. Peiris JSM, Chu CM, Cheng VCC, et al. Clinical progression and viral load in a community outbreak of coronavirus-associated SARS pneumonia: a prospective study. *Lancet*. 2003;301:1767–1772.
7. Lee N, Hui D, Wu A, et al. A major outbreak of severe acute respiratory syndrome in Hong Kong. *N Engl J Med*. 2003;348:1986–1994.
8. Tsang KW, Ho PL, Ooi GC, et al. A cluster of cases of severe acute respiratory syndrome in Hong Kong. *N Engl J Med*. 2003;348:1977–1985.
9. Poutanen SM, Low DE, Henry B, et al. Identification of severe acute respiratory syndrome in Canada. *N Engl J Med*. 2003;348:1995–2005.
10. Wilhelm K, Ewig S, Textor J, et al. Independent radiologic prognostic factors for fatal outcome of ambulatory-acquired pneumonia requiring inpatient treatment [in German]. *Rofo Fortschr Geb Rontgenstr Neuen Bildgeb Verfahr*. 1999;170:145–149.
11. Ichikado K, Suga M, Muller NL, et al. Acute interstitial pneumonia: comparison of high-resolution computed tomography findings between survivors and nonsurvivors. *Am J Respir Crit Care Med*. 2002;165:1551–1556.
12. King TE, Tooze JA, Schwarz MI, et al. Predicting survival in idiopathic pulmonary fibrosis: scoring system and survival model. *Am J Respir Crit Care Med*. 2001;164:1171–1181.

13. World Health Organization. Preliminary clinical description of Severe Acute Respiratory Syndrome. Available at: http://www.who.int/csr/sars/casedefinition/en/. Accessed April 1, 2003.
14. Simon G, Hamilton WJ. *X-Ray Anatomy*. London, United Kingdom: Butterworths Press; 1978:185.
15. Fraser RS, Pare JAP, Fraser RC, Pare PD. Synopsis of Disease of the Chest. Philadelphia; Saunders Press; 1994: p. 289–94.
16. Lim WS, Eerden MMVD, Laing R, et al. Defining community acquired pneumonia severity on presentation to hospital: an international derivation and validation study. *Thorax*. 2003;58:377–382.
17. Lim WS, Macfarlane JT. Defining prognostic factors in the elderly with community acquired pneumonia: a case controlled study of patients aged > or = 75 yrs. *Eur Respir J*. 2001;17:200–205.
18. Olivier L, Patrick D, Benoit G, et al. Simplified prediction rule for prognosis of patients with severe community-acquired pneumonia in ICUs. *Chest*. 1999;116:157–165.
19. Wong KT, Antonio GE, Hui DSC, et al. Severe Acute Respiratory Syndrome: radiographic appearances and pattern of progression in 138 patients. *Radiology*. 2003;228:401–406.
20. Booth CM, Matukas LM, Tomlinson GA, et al. Clinical features and short-term outcomes of 144 patients with SARS in the Greater Toronto area. *JAMA*. 2003;289:1–9.
21. Ng EKO, Hui DS, Chan KCA, et al. Quantitative analysis and prognostic implication of SARS-coronavirus RNA in the plasma and serum of patients with severe acute respiratory syndrome. *Clin Chem*. 2003;49:1976–1980.
22. Rubenfeld GD, Caldwell E, Granton J, et al. Interobserver variability in applying a radiographic definition for ARDS. *Chest*. 1999;116:1347–1353.
23. Hsu LY, Lee CC, Green JA, et al. Severe Acute Respiratory Syndrome (SARS) in Singapore: clinical features of index patient and initial contacts. *Emerg Infect Dis*. 2003;9:713–717.