Original Article

SARS in Singapore – Predictors of Disease Severity

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Abstract

Introduction: Severe acute respiratory syndrome (SARS) affected 8096 individuals in 29 countries, with 774 deaths. In Singapore, there were 238 cases of SARS with 33 deaths. A retrospective analysis was performed to identify predictors of poor outcome in patients with SARS locally. Materials and Methods: Clinical, laboratory and outcome data of 234 patients admitted to Tan Tock Seng Hospital and Singapore General Hospital were collected and analysed. Only data collected at the time of admission were used in the analysis for predictors of poor outcome. Adverse events were defined as admission to the intensive care unit or death. Results: Clinical (temperature, FiO_2) and laboratory [leukocyte, lymphocyte, neutrophil, platelet, lactate dehydrogenase (LDH), albumin] trends in groups with and without an adversarial event were presented. Fifty patients experienced an adverse event. On univariate analysis, male gender, advanced age, presence of comorbidities, neutrophilia, lymphopaenia, hyponatraemia, hypoalbuminaemia, transaminitis and elevated LDH or C-reactive protein were found to be significant predictors. On multivariate analysis, predictors of poor outcome were increased age [odds ratio (OR) 1.73 for every 10-year increase; 95% CI, 1.35 to 2.21], neutrophilia (OR 1.06 for every $1x10^9$/L increase; 95% CI, 1.02 to 1.11) and high LDH (OR 1.17 for every 100 U/L increase; 95% CI, 1.02 to 1.34). None of the 12 paediatric patients had an adverse event. Conclusion: Advanced age, neutrophilia and high LDH predict poor outcomes in patients with SARS.

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Key words: Prognosis, SARS virus, Singapore

Introduction

Severe acute respiratory syndrome (SARS) is a recently defined illness caused by a novel coronavirus.[1-3] The outbreak in Singapore originated from Hong Kong via mainland China.[4] The first noted victim was a businessman from the city of Foshan in Guangdong Province, China.[5] As of December 2003, there were 8422 cases reported, with 916 deaths (10.9%) worldwide.

A high mortality has been associated with this illness. Various authors have attempted to prognosticate the disease by examining several clinical and laboratorial parameters. Risk factors identified included the presence of comorbidities, age, and high lactate dehydrogenase (LDH) levels.[6-13]

In this paper, we attempt to identify predictive factors leading to a poor outcome in patients with probable SARS in Singapore.

Materials and Methods

A total of 238 patients were diagnosed with SARS in Singapore. Two hundred and six patients were diagnosed to have probable SARS during their hospital admission, or at autopsy. Another 32 patients were reclassified as probable SARS when the serology results were available after

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discharge. In this study, only patients (234) admitted to Tan Tock Seng Hospital (TTSH) or Singapore General Hospital (SGH) were included. Demographic, clinical and laboratory data, and outcome measures were collected retrospectively through the review of clinical notes and computerised laboratory results by a dedicated team of doctors.

An "adverse event" was said to occur when there was a poor outcome, i.e., admission to the intensive care unit (ICU) or death. The criterion for admission to the ICU was either (1) failure to maintain oxygen saturation ≥95% despite oxygen supplementation of FiO_2 0.5 or (2) hypotension (blood pressure <90/60 in the absence of inotropes), or both. "Comorbidities" were existent chronic illnesses that were diagnosed prior to admission. These were asthma, chronic obstructive lung disease, diabetes mellitus, ischaemic heart disease, hypertension, cardiac failure, chronic or end-stage renal failure, liver impairment, and/or cerebral vascular disease. "Day one of illness" was defined as the day of onset of fever.

Reverse Transcription Polymerase Chain Reaction (RT-PCR)

RT-PCRs were performed at 5 different laboratories located throughout Singapore. They were SGH, TTSH, National University Hospital, the Defence Medical Research Institute and the Defence Science Organisation. The last 2 are research laboratories. Specimens collected at TTSH were randomly dispatched to the various laboratories. Weekly meetings ensured standardised testing procedures. RT-PCR was performed on various clinical samples. Initial RT-PCR assays, available at the end of March 2003, used the primers SARS1S/As as described in the paper by Drosten et al,[3] as well as primers Cor1/2 from the Government Virus unit, Hong Kong.[14] A positive result must be confirmed by re-extraction from the original sample and has to be positive on both sets of primers. After 2 May 2003, RT-PCR tests were done using the RealArt HPA SARS-coronavirus RT PCR kit (Artus GmbH, Germany) on the Lightcycler®, a real-time PCR instrument (Roche Molecular Systems, Pleasanton, USA). A positive result was defined as the detection of ≥2500 copies/mL of specimen. A negative result was defined as the detection of <2500 copies/mL. Specimens with positive results were further confirmed by re-extraction from the original sample with a second RT-PCR using primers designed by the Genome Institute of Singapore[15] or by the Institute of Molecular and Cell Biology.[16] The latter primers targeted the proteinase gene region, while the rest targeted the polymerase gene of the SARS-CoV. Various specimens were accepted for clinical testing, including respiratory samples (sputum, nasopharyngeal aspirate, endotracheal aspirate, throat swab), urine, conjunctival swab, stool and blood (plain and EDTA-anticoagulated blood).

Serology

Patients were tested for virus-specific IgM, IgG and IgA using an indirect enzyme immunoassay[17] with SARS coronavirus (SARS-CoV) lysate as the antigen.[2] Positive and negative controls were performed concurrently. Detection of fluorescence at a titre ≥400 constituted a positive test. Positive sera were re-tested for IgG and IgM by an immunofluorescence assay using SARS-CoV infected Vero cells spotted onto microscope.

Statistical Analysis

In terms of data analysis, the logistic regression model was used to identify factors that were significantly associated with poor outcome. For the multivariate model, the likelihood ratio test was used to determine if the inclusion of additional covariates helped improve the fit of the model. Odds ratios and their associated 95% confidence intervals (CIs) were used as measures of effect size. For some of the parameters such as creatinine, alanine transaminase and LDH, odds ratios that were associated with clinically relevant increases (i.e., every 10 or 100 unit increase) were used. Data were analysed using Stata version 6.0 software (Stata Corp., College Station, Texas, USA), and all tests were conducted at the 5% level of significance.

Results

Two hundred and thirty-four patient records were studied; 231 in TTSH and 3 in SGH. Laboratory confirmation of probable SARS was available for 214 patients. A rising titre was demonstrated in their serology test results for 213 patients while 1 patient had >1 positive PCR test in the samples processed. One other patient had autopsy-proven SARS. The other 19 patients were diagnosed purely on clinical grounds in the presence of a strong epidemiological link; 7 had SARS and were established to have transmitted SARS to other individuals; 5 were members of the same household with a patient who had SARS; 5 had come in contact with patients who had SARS either as healthcare workers (HCWs), visitors, or as fellow patients in the same ward; 1 had had exposure to a patient with SARS at work (not in hospital); 1 had contracted it while overseas. All patients satisfied the probable SARS criteria. The criteria for diagnosis of probable SARS did not differ from the World Health Organization's recommendations.[18]

The demographics and overall clinical manifestation and laboratory results of the patients have been described elsewhere.[19] The mean age of the patients was 21 years (range, 1.3 to 83.4). Seventy-four (31.6%) were male, and 98 (41.8%) were HCWs. The most common symptoms were fever, myalgia, cough and headache. Rhinorrhoea was uncommon. RT-PCR testing of respiratory and stool

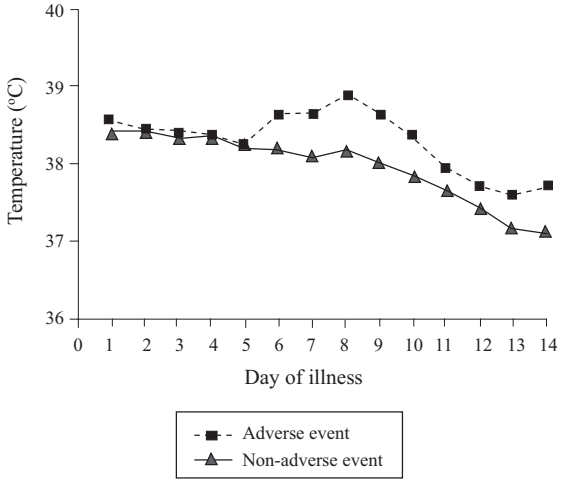

Fig. 1a. Temperature by day of illness.

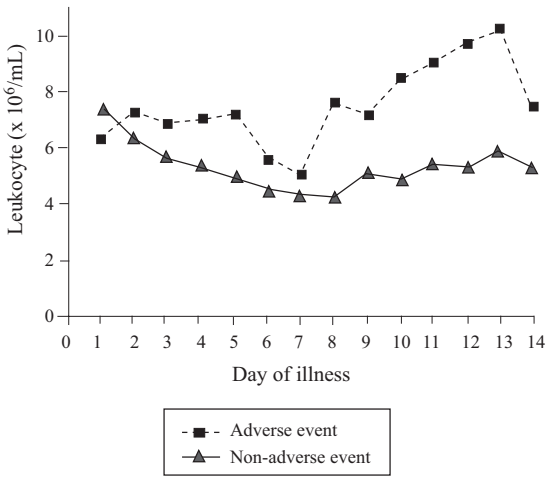

Fig. 1b. Leukocytes by day of illness.

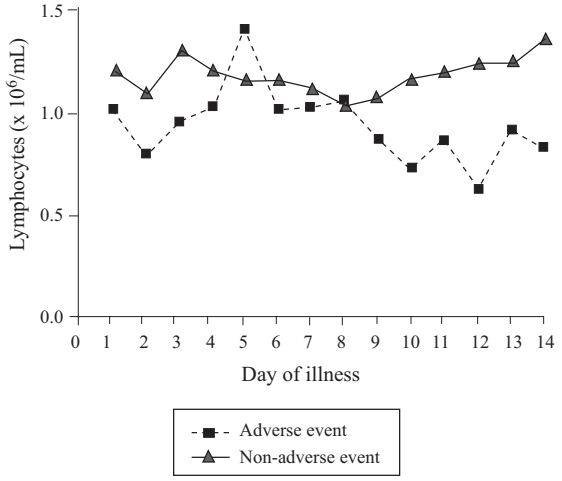

Fig. 1c. Lymphocytes by day of illness.

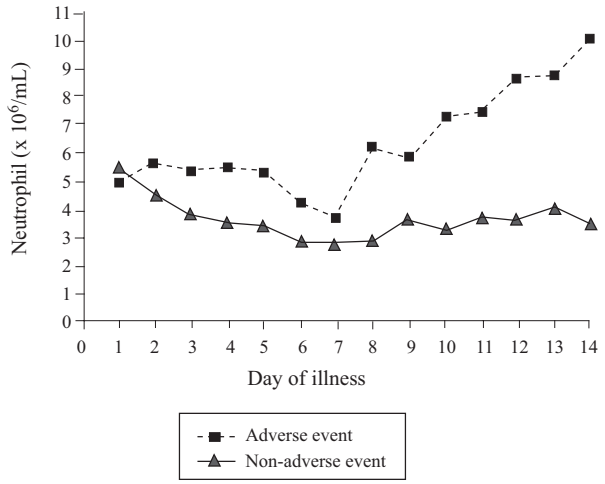

Fig. 1d. Neutrophils by day of illness.

samples provided the best diagnostic yield at the end of the first week of illness.

The patients were divided into 2 groups, those with and without an adverse event. Fifty patients (21.4%) were identified to have had an adverse event, to have been admitted to the ICU or to have died. Figures 1a to 1h show the plots of the clinical and laboratorial data against the first 14 days of illness stratified by the presence or absence of an adverse event. Only clinical parameters that were documented on hospital records were accepted in the analysis. For example, the plots for the temperature were made only using data collected in hospital.

In patients with a better outcome, fever tended to resolve by day 12 of illness. Leukocyte count was normal throughout, with a nadir on day 7 of illness. Lymphopaenia was observed throughout the period. The platelet count appeared to rise with a rebound towards the end of the 14-day period. LDH had an upward trend as the disease progressed, and this was associated with falling albumin levels. Supplemental oxygen was not usually required in those with a better outcome.

In those with a poorer outcome, parameters demonstrated similar trends with differences in neutrophil counts, LDH levels, and albumin levels. These patients maintained a higher trend of absolute neutrophils and LDH, and these diverged as the disease progressed. These patients also maintained a lower mean albumin level, and required supplemental oxygen. Hypoxaemia was the commonest reason for admission to ICU, which was an adverse event.

In the entire cohort of 234 patients, 50 patients (21.4%) had an adverse event. A total of 46 patients were admitted to the ICU, of whom 26 (56.5%) died and 20 survived. An additional 4 patients died without having been admitted to the ICU. There were a total of 30 (11.8%) deaths. The cause

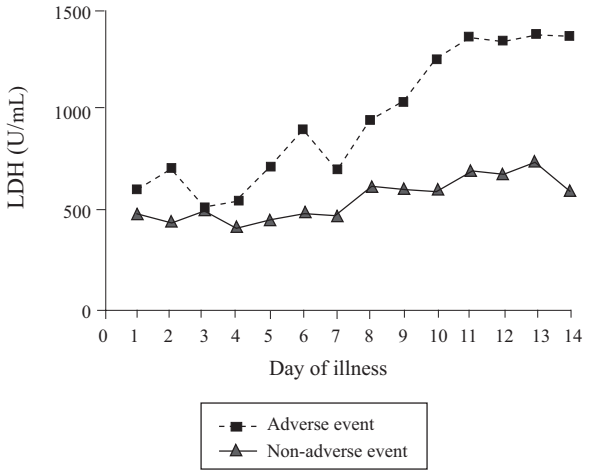

Fig. 1e. Lactate dehydrogenase by day of illness.

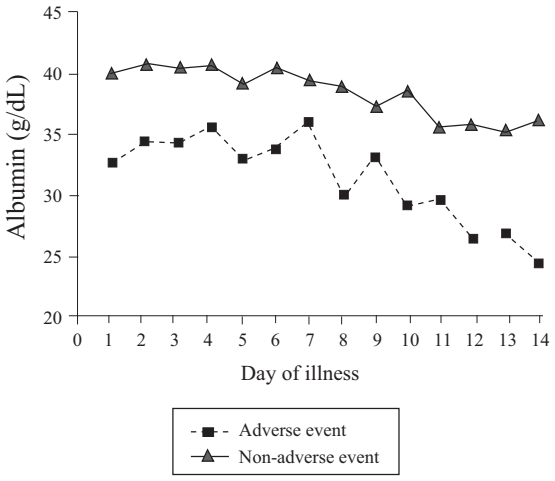

Fig. 1f. Albumin by day of illness.

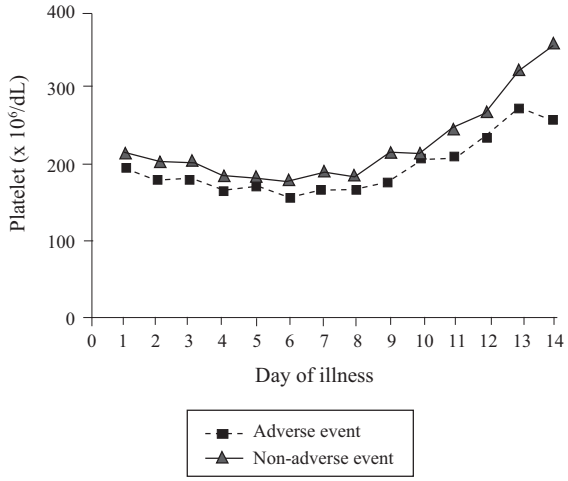

Fig. 1g. Platelets by day of illness.

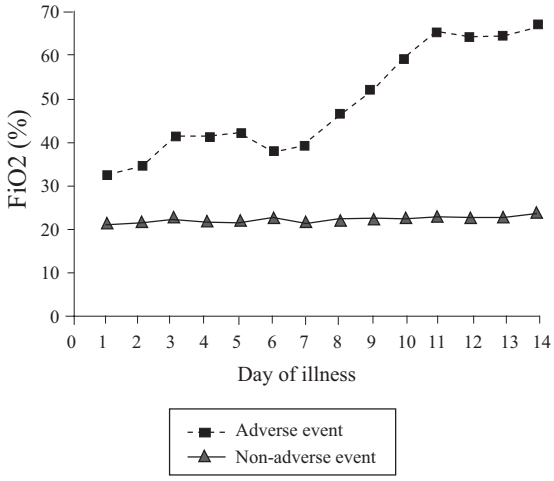

Fig. 1h. FiO_2 required by day of illness.
FiO_2 – fraction of inspired oxygen expressed in a percentage.

of death was attributable to SARS in all. All except 1 patient were admitted to the ICU for hypoxaemia (requiring more than 50% oxygen to maintain oxygen saturation ≥95%). The case in exception was for hypotension (blood pressure <90/60). None were admitted for hypotension and hypoxaemia. The number of days of illness on admission to the ICU was 9.2 (range, 2 to 21; SD, 3.65). Those who were admitted to the ICU (mean, 29.6 days; range, 3 to 101; SD, 22.8) stayed longer in hospital than those who were not (mean, 15.9 days; range, 1 to 101; SD, 14.8; P <0.001).

Data collected on the day of admission were analysed. On univariate analysis, gender, age, comorbidities, neutrophilia, lymphopaenia, hyponatraemia, renal impairment, hypoalbuminaemia, transaminitis, LDH and C-reactive protein (CRP) were found to be significant predictors (Table 1). Advanced age, male gender, the presence of comorbidities, elevated leukocyte count, lymphopaenia, hyponatraemia, transaminitis, raised LDH, and C-reactive protein were associated with poorer prognosis.

On multivariate analysis, we identified that increased age [odds ratio (OR) for every 10-year increase, 1.73; 95% CI, 1.35 to 2.21], neutrophilia (OR for every 1 x 10^9/L unit increase, 1.06; 95% CI, 1.02 to 1.11) and high LDH levels (OR for every 100 U/L increase, 1.17; 95% CI, 1.02 to 1.34) taken on the day of admission were predictive of a poorer outcome (Table 2).

Discussion

In this analysis, data collected on the day of admission were used to predict outcomes. This method of analysis was used by other authors[6-8,10,13,20] and provided more clinically useful data for the managing physician.

Other authors obtained similar results. Increased age,[6,13,21]

Table 1. Univariate Predictors of Poor Outcome

Covariates taken on admission	OR	95% CI		*P* value
Gender (male)	3.10	1.64	5.87	<0.001*
Age (10-year increase)	1.80	1.46	2.21	<0.001*
Day of illness on admission	1.07	0.98	1.17	0.133
Presence of diabetes mellitus	3.80	1.57	9.22	0.003*
Presence of comorbidities	3.87	1.96	7.62	<0.001*
Temperature on admission	1.09	0.77	1.55	0.616
Oxygen saturation	0.95	0.90	1.01	0.096
White cell count	1.24	1.09	1.40	0.001*
Haemoglobin	0.85	0.71	1.02	0.082
Haematocrit	0.95	0.89	1.01	0.073
Platelet	0.99	0.99	1.00	0.065
Absolute neutrophil	1.09	1.05	1.12	<0.001*
Absolute lymphocyte	0.92	0.88	0.96	<0.001*
Sodium	0.90	0.83	0.98	0.020*
Potassium	1.79	0.99	3.23	0.054
Urea	1.06	1.01	1.11	0.024*
Creatinine (100-unit increase)	1.51	1.07	2.12	0.020*
Albumin	0.86	0.81	0.91	<0.001*
Bilirubin	1.03	0.99	1.07	0.187
Alanine transaminase (ALT) (10-unit increase)	1.09	1.02	1.17	0.016*
Lactate dehydrogenase (LDH) (100-unit increase)	1.31	1.15	1.50	<0.001*
CRP (10 unit increase)	1.17	1.09	1.26	<0.001*

95% CI: 95% confidence interval; CRP: C-reactive protein; OR: odds ratio

P values with astericks indicate significance at the 5% level.

Comorbidities" is defined as the presence of existing chronic illnesses that were diagnosed prior to admission. These include asthma, chronic obstructive lung disease, diabetes mellitus, ischaemic heart disease, hypertension, cardiac failure, chronic or end-stage renal failure, liver impairment, and cerebral vascular disease.

Table 2. Multivariate Predictors of Poor Outcome

Covariates taken on admission	OR	95% CI		*P* value
Age (10-year increase)	1.73	1.35	2.21	<0.001*
Absolute neutrophil (for every 1 unit increase)	1.06	1.02	1.11	0.006*
Lactate dehydrogenase[6] (100 unit increase)	1.17	1.02	1.34	0.022*

95% CI: 95% confidence interval; OR: odds ratio

P values with astericks indicate significance at the 5% level

neutrophilia,[6-8,20] high initial LDH,[6,20] and the presence of comorbidities[8-10,13,20] were frequently reported as predictors of poor outcome. Lee et al[7] also reported poorer outcomes in patients with a high peak LDH.

Increased age and the presence of comorbidities (especially diabetes mellitus) are well recognised to increase the risk of death in patients with community-acquired pneumonia.[22,23] It is not surprising that this was observed for SARS as well.

In contrast, the young assumed a better risk profile with SARS.[24,25] In our cohort, none of the 12 paediatric patients (ages ≤17 years) had a poorer outcome compared to adults (Fisher's exact test, $P = 0.23$). Reports suggest that younger children do better than adolescents, and the latter's clinical progress resemble that of adults.[24,25] Appreciating that SARS may consist of a three-stage process,[26] the relative immaturity of the immune system in children may confer benefit in the immune response phase (second stage) of SARS.

Others have also reported neutrophilia to be a predictor of poor outcome.[6,7] Tsui et al[6] believed that this may be a representation of disease progression in hypersensitivity pneumonia or a high viral load exposure, or simply that the patient was late in seeking treatment. The former 2 reasons may explain the similar observation we made. In our patients, we did not see a correlation between late admission and neutrophilia. Alternatively, superimposed bacterial infections during SARS may cause neutrophilia, and this have been reported.[27] This is however uncommon. Steroids may cause neutrophilia and they have been used in the management of SARS.[28,29] This would not have skewed our data as admission data (i.e., prior to any treatment) were used for analysis.

LDH is a non-specific enzyme found ubiquitously in cells. The high level demonstrated probably reflects the degree of tissue necrosis and hence severity of the pneumonia. This observation has been reported by others.[7,8] It may be used as a marker to assess the efficacy of future treatment regimens.

Other predictors of severe pneumonia reported include an initial high viral load,[30] detection of a coronavirus-positive nasopharyngeal aspirate[31] and male gender.[32] The former probably represents the viral burden during the transmission. We need to better understand the pathogenesis of this viral infection before the observed increased risk in the male gender can be explained.

This study also showed that 184 patients (78.6%) did not have a poor outcome. In fact, 97 patients (41.5%) recovered spontaneously without the administration of specific therapy for SARS (ribavirin,[14] gammaglobulin or methyl-prednisolone[28]). This only argues strongly for targeted treatment strategies for at-risk groups should SARS recur. Predictors reported by this study and others will guide the

clinician in identifying patients requiring antiviral treatment. Potential candidates currently include use of interferons, small interfering RNAs and protease inhibitor. A review of potential therapeutic agents was done recently.[33]

Conclusion

In our cohort of 234 probable SARS patients, advanced age, neutrophilia and high LDH on admission predicted poorer outcomes. These findings might be used to identify at-risk individuals for future treatment strategies.

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