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ORIGINAL ARTICLE

Hematological and Biochemical Factors Predicting SARS Fatality in Taiwan

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Background/Purpose: Severe acute respiratory syndrome (SARS) has a high fatality rate worldwide. We examined the epidemiologic and clinical factors associated with death for all laboratory-confirmed SARS patients in Taiwan.

Methods: Using initial data in medical records reported by hospitals to the Center for Disease Control in Taiwan, we analyzed whether hematological, biochemical and arterial blood gas measures could predict fatality in 346 SARS patients.

Results: Both fatalities (n = 73; 21.1%) and survivors had elevated plasma concentration of initial C-reactive protein (CRP), but the mean CRP concentration was higher in fatalities (47.7 ± 43.3 mg/L) than in survivors (24.6 ± 28.2 mg/L). Initial lymphocyte counts were low in both fatalities (814 ± 378/μL) and survivors (1019 ± 480/μL). After controlling for age and sex, multiple logistic regression analysis showed that hematological factors significantly associated with fatality included initial neutrophil count > 7000/μL (odds ratio [OR] = 6.4), initial CRP concentration > 47.5 mg/L (OR = 5.8) and lactic acid dehydrogenase (LDH) > 593.5 IU/L (OR = 4.2). Factors significantly associated with initial CRP concentration > 47.5 mg/L included dyspnea (OR = 4.3), red blood cell count < 4.1×10^6/μL (OR = 4.3) and serum aspartate aminotransferase > 57 IU/L (OR = 3.1).

Conclusion: Initial neutrophil count, CRP and LDH levels are important predictors of mortality from SARS.
[*J Formos Med Assoc* 2006;105(6):439–450]

Key Words: C-reactive protein, dyspnea, fatality, lactic acid dehydrogenase, lymphopenia, severe acute respiratory syndrome

Severe acute respiratory syndrome (SARS) is an emerging respiratory infectious disease which first appeared in Guangdong, China in November 2002. The disease spread concurrently to Vietnam, Hong Kong, Canada, Singapore and Taiwan in February 2003 and later throughout the world,[1–3] and was controlled rapidly in a few months with a peak in April 2003 in Taiwan. During the epidemic, a total of 8422 probable SARS patients were reported to the World Health Organization (WHO) from 32 countries, with an estimated case fatality rate of 10.9% (n = 916) from November 1, 2002 to August 7, 2003.[4]

Patients in the early stages of SARS generally suffered from fever, malaise, myalgia, dyspnea, headache, nonproductive cough, chills and shortness of breath.[5–18] A few patients had upper respiratory tract symptoms such as sore throat and rhinorrhea. Diarrhea, nausea and vomiting were also reported. Studies also reported the presence

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Received: April 12, 2005
Revised: September 21, 2005
Accepted: December 6, 2005

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of high rates of comorbidities in SARS patients, particularly diabetes mellitus (DM), cardiac disease or hypertension.[5–7,12,19,20] Laboratory findings for SARS patients included lymphopenia, and elevated lactic acid dehydrogenase (LDH), hepatic transaminase, creatine phosphokinase (CPK), and hepatic transaminases.[5,7–13,16,21,22] White blood cell (WBC) counts and renal function remained normal.[15] However, only age (advanced or > 60 years), shortness of breath, comorbidity (DM, cardiac or other diseases), elevated neutrophil count and LDH were independent predictors of death from SARS.[5,7,13,16,20–22] Singh et al found elevated levels of initial C-reactive protein (CRP) in SARS patients.[12] Wang et al also reported a high prevalence of lymphopenia ($< 1 \times 10^9$/L, 64.5%) and elevated CRP levels (> 8.0 mg/L, 77.9%) in SARS patients treated at a medical center in Northern Taiwan.[22]

Using a comparison design, we examined the epidemiologic and clinical patterns of death for all reported SARS patients in Taiwan. The main focus of this study was to compare the laboratory features between fatalities and survivors and to estimate the risk of death based on initial hematological and biochemical measures and arterial blood gas characteristics. We also attempted to determine if the elevated initial CRP concentration in SARS patients was associated with other clinical and laboratory parameters.

Methods

Patients

In accordance with the WHO criteria published in May 2003,[23] and modified for Taiwan, 664 people were initially diagnosed as probable SARS cases, presenting with a history of fever of 38° C or above, symptom(s) of lower respiratory tract illness, radiographic evidence of infiltrates consistent with pneumonia, respiratory distress syndrome or autopsy findings consistent with pneumonia without identifiable cause, and with exposure such as close contact with a suspected or probable case of SARS and/or residing in an affected area (including hospitals that had cared for SARS patients during the outbreak in Taiwan) 10 days prior to the onset of symptoms. On August 14, 2003, the WHO proposed a new case definition as clinical cases with positive laboratory findings for SARS-CoV based on one or more of the diagnostic criteria, including reverse transcriptase polymerase chain reaction (RT-PCR), seroconversion or virus isolation.[24] This study included all 346 cases from Taiwan who met the revised WHO criteria.

Data collection

All hospitals that had cared for SARS patients reported patient medical records to the Center for Disease Control of the Taiwan Department of Health. Data available included initial clinical symptoms, and hematological, biochemical and arterial blood gas measures at admission. In addition, we obtained information on sociodemographic characteristics, contacts prior to the onset of illness, date of diagnosis of the disease, survival status, and cause of death.

Statistical analysis

The contact history of patients and epidemic curve of fatalities and survivals of SARS patients were depicted graphically. This study emphasized the identifying factors considered most likely to predict death from SARS and the comparison between fatalities and survivors of the disease. Prior to performing this analysis, however, the clinical symptoms and laboratory manifestations of positive and negative cases were compared and briefly summarized in the results.

The case fatality rate was determined based on all SARS cases according to the WHO definition and irrespective of immediate causes of death. The chi-square test was used to explore differences in demographic characteristics, clinical symptoms and comorbidity, while the *t* test was used to identify proportional differences in clinical laboratory manifestations. Mean values ± standard deviations (SD) of initial hematological and biochemical variables and arterial blood gas were also compared between fatalities and survivors and against normal ranges of these measures.[25] Each potential risk

factor for death was first estimated with odds ratio (OR) and corresponding 95% confidence interval (CI) using univariate logistic regression. All variables were categorized. The normal ranges of hematological and biochemical determinations were not consistent among hospitals. However, in order to facilitate comparison of factors associated with risk of fatality, quartile values were adapted to determine the associated OR of death based on univariate analyses.

Because SARS was characterized by inflammation in most patients, this study also emphasized identification of factors associated with CRP level among patients. The percentile distributions of initial CRP concentrations were compared with major comorbidities, such as DM, cardiac disease, chronic obstructive pulmonary disease (COPD), cerebrovascular accident (CVA) and malignancy. Mean concentrations and SD were calculated as well. The risk of elevated initial CRP for each potentially associated factor was estimated with OR and corresponding 95% CI with all variables categorized. Consideration of various CRP cut-off values revealed that more variables were significantly associated with CRP at the cut-off value of 47.5 mg/L (75th percentile) than 5 mg/L (normal value) or 29.1 mg/L (mean value).

When a variable had upper and/or low quartile values beyond the normal range, the 75th percentile value was used for the estimation of positive correlation, and the 25th percentile value for negative correlation. Otherwise, the normal value was used to determine the cut-off value.

Hematological, biochemical and arterial blood gas data were based on the initial measures available from the reported records provided by hospitals. Variables with a p value of less than 0.05 in the univariate analyses were included in the downward stepwise multiple logistic regression analyses. Sex, age, DM and neutrophil count were forced in the multiple logistic regression analysis because of potential confounding effects, although sex became an insignificant factor in doing so. Data analyses were performed using SAS version 8.0 (SAS Institute Inc, Cary, NC, USA). Sex and age were forced in the adjusted model.

Results

Study population

A total of 664 probable SARS cases had been reported by the time the WHO officially removed Taiwan from the list of SARS-affected areas in July 2003.[3] Among them, 346 cases were later confirmed by serological tests (either PCR or Ab positive) based on WHO criteria announced in August 2003[24] (Figure). The epidemic curve shows that almost all fatal cases occurred between April 16 and June 7, 2003, while the incidence showed a bimodal pattern in the week of April 21 and the week of May 11.

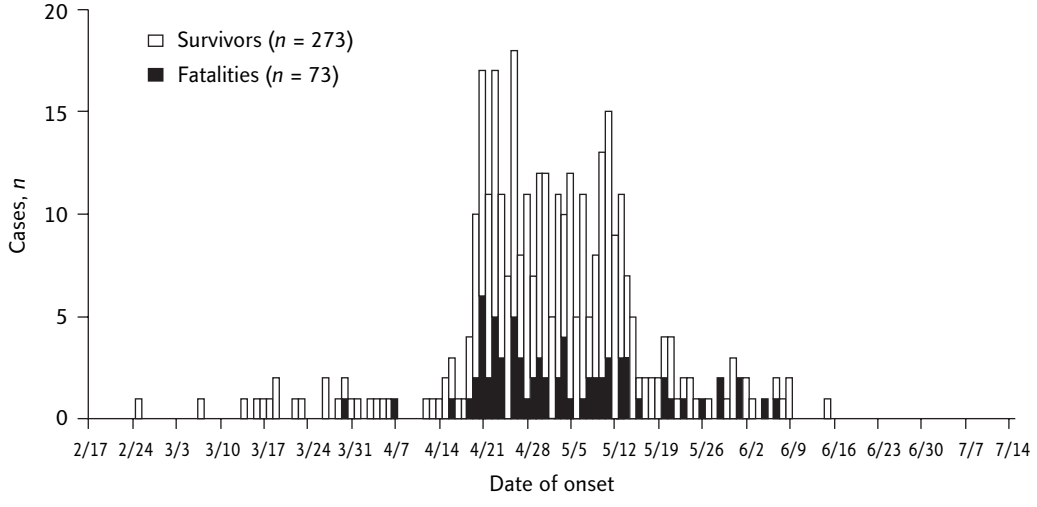

Figure. Epidemiologic curve of SARS fatalities and survivors by date of onset in Taiwan, February 24 to July 15, 2003.

The confirmed positive SARS cases (n = 346) were younger (42.3 *vs.* 53.0 years old) and included more females (63.0% *vs.* 40.9%) than the SARS-negative cases (n = 318) (data not shown). Symptomatic signs at presentation showed that positive cases were more likely than negative cases to have chills, diarrhea and myalgia but less likely to have increased sputum production, cough, dyspnea and shortness of breath. Comorbidity was more prevalent in negative than in positive cases (29.2% *vs.* 17.1%), particularly in patients with COPD and malignancy. Negative cases had higher mean counts than positive cases for white blood cells (WBC), neutrophils, lymphocytes, monocytes and platelets and blood urea nitrogen (BUN). However, CRP was higher in positive cases.

Characteristics of fatalities and survivors

The overall case fatality rate was 21.1% (n = 73), and increased from 7.2% for patients younger than 40 years to 58.9% for those aged 60 years or older ($p < 0.0001$) (Table 1). This outbreak involved 105 healthcare employees, who were less likely than non-healthcare persons to die from the disease (11.4% *vs.* 25.3%). An increased risk was also found for men (30.5%) and patients with hospital contact (26.3%). All imported cases survived.

Clinical characteristics

SARS fatalities had a higher rate of intubation (Table 2). Analysis of symptomatic signs showed that fatalities were more likely than survivors to have dyspnea (41.1% *vs.* 17.2%), but less likely to have headache and rhinorrhea. Comorbidity was also more prevalent in fatalities than in survivors (48.0% *vs.* 8.8%, $p < 0.0001$), particularly DM, COPD and CVA.

Table 3 compares the mean values of initial hematological and biochemical measures and arterial blood gas between fatalities and survivors

Table 1. Comparison of demographic characteristics and contact history between fatalities and survivors in SARS patients in Taiwan

Variable	Fatalities (n = 73) n (%)	Survivors (n = 273) n (%)	Total (n = 346) n (%)	p*
Age, mean (SD)†	57.5 (17.6)	38.2 (14.9)	42.3 (17.4)	< 0.0001
Age, yr				< 0.0001
< 40	12 (7.2)	155 (92.8)	167 (100)	
40–59	28 (22.8)	95 (77.2)	123 (100)	
≥ 60	33 (58.9)	23 (41.1)	56 (100)	
Sex				0.001
Female	34 (15.6)	184 (84.4)	218 (100)	
Male	39 (30.5)	89 (69.5)	128 (100)	
Occupation				0.004
Healthcare worker	12 (11.4)	93 (88.4)	105 (100)	
Physician	1	11	12	
Nurse	2	54	56	
Allied	9	28	37	
Non-healthcare worker	61 (25.3)	180 (74.7)	241 (100)	
Contact history				0.002
Imported	0 (0.0)	21 (100)	21 (100)	
Household	3 (7.7)	36 (92.3)	39 (100)	
Hospital	65 (26.3)	182 (73.7)	247 (100)	
Unidentified	5 (12.8)	34 (87.2)	39 (100)	

**Chi-square test or Fisher's exact test; †mean and standard deviation (SD) by t test.*

Table 2. Comparison of clinical features and comorbidity between fatalities and survivors in SARS patients in Taiwan

Characteristic	Fatalities (n = 73) n (%)	Survivors (n = 273) n (%)	p*
Intubation	19 (26.0)	22 (8.1)	< 0.0001
Initial clinical symptom			
Fever	73 (100.0)	273 (100.0)	
Cough	45 (61.6)	163 (59.7)	0.764
Dyspnea	30 (41.1)	47 (17.2)	< 0.0001
Diarrhea	23 (31.5)	63 (23.1)	0.139
Shortness of breath	4 (5.5)	12 (4.4)	0.695
Sputum production	14 (19.2)	34 (12.5)	0.140
Chills	9 (12.3)	47 (17.2)	0.314
Myalgia	12 (16.4)	55 (20.2)	0.476
Sore throat	7 (9.6)	40 (14.7)	0.262
Vomiting	6 (8.2)	12 (4.4)	0.191
Headache	6 (8.2)	50 (18.3)	0.038
Chest pain	3 (4.1)	10 (3.7)	0.741
Abdominal pain	3 (4.1)	13 (4.8)	1.000
Nausea	3 (4.1)	11 (4.0)	1.000
Rhinorrhea	0 (0.0)	15 (5.5)	0.048
Comorbidity			
Diabetes mellitus	18 (25.7)	12 (4.5)	< 0.0001
Cardiac disease	13 (18.6)	6 (2.2)	< 0.0001
Chronic obstructive pulmonary disease	9 (12.9)	5 (1.9)	< 0.0001
Hypertension	12 (17.1)	11 (4.1)	0.0001
Malignancy	1 (1.4)	2 (0.7)	0.502
Cerebrovascular accident	8 (11.4)	4 (1.5)	< 0.0001
End-stage renal disease	1 (1.4)	2 (0.7)	0.502
Immunologic disease	2 (2.9)	0 (0.0)	0.042
Liver disorder	0 (0.0)	2 (0.7)	1.000
Coexisting medical disease†	35 (48.0)	24 (8.8)	< 0.0001

**Chi-square test or Fisher's exact test; †includes any one of following diseases: diabetes mellitus, cardiac disease, chronic obstructive pulmonary disease, hypertension, malignancy, cerebrovascular accident, end-stage renal disease, immunologic disease and liver disorder.*

and against normal ranges.[25] Parameters with means exceeding the normal range were blood sugar, BUN, LDH, CRP, and serum aspartate aminotransferase (AST). These values were all significantly higher for fatalities than for survivors. The initial lymphocyte count was significantly lower in fatalities than in survivors (814/μL *vs.* 1019/μL, p = 0.004). Initial mean counts of WBC, neutrophils and monocytes were significantly higher in fatalities than in survivors. The mean counts of WBC, neutrophils and monocytes, however, were in the normal range.

Factors associated with death

Variables with $p < 0.05$ in the univariate analyses were entered into the multiple logistic regression model with sex and age forced in the model. Men were at higher risk of death than women in the univariate analysis, but not in the final multiple logistic regression analysis (Table 4). Age was a significant factor associated with death together with dyspnea, DM, hematological and biochemical measures in the model. Patients ≥ 60 years old had the highest risk of death (OR = 12.4; 95% CI = 1.8, 83.3). Neutrophil count > 7000/μL was also

Table 3. Comparison of initial laboratory tests between fatalities and survivors in SARS patients in Taiwan

	Fatalities Mean (SD)	Survivors Mean (SD)	*p* (*t* test)	Normal range
Hematological variables				
WBC (/μL)	8312 (4509)	6084 (3092)	< 0.0001	4500–11,000
Neutrophils (/μL)	6554 (3750)	4608 (2874)	< 0.0001	3000–7000
Lymphocytes (/μL)	814 (378)	1019 (480)	0.004	1500–4000
Monocytes (/μL)	473 (306)	354 (210)	0.001	100–500
Platelets (10^3/μL)	190.6 (95.7)	171.6 (68.6)	0.070	140–380
RBC (10^6/μL)	4.4 (0.4)	4.4 (0.6)	0.625	4.5–6.2
Hemoglobin (g/dL)	12.9 (1.9)	13.0 (1.8)	0.674	13.5–18.0
Mean cell volume (fL)	87.1 (8.6)	86.5 (9.2)	0.675	80–100
Biochemical variables				
Sugar (mg/dL)	181.9 (101.5)	119.4 (45.9)	0.0003	70–105
BUN (mg/dL)	23.5 (22.7)	11.4 (9.0)	< 0.0001	6–20
CPK (IU/L)	297.5 (758.3)	159.7 (385.8)	0.117	15–130
LDH (IU/L)	583.9 (514.1)	435.9 (317.4)	0.020	180–460
CRP (mg/L)	47.7 (43.3)	24.6 (28.2)	0.0001	< 5
AST (IU/L)	77.3 (102.8)	43.7 (43.3)	0.002	10–30
ALT (IU/L)	45.4 (54.2)	36.9 (39.5)	0.211	6–35
Na (mmol/L)	136.7 (5.1)	137.5 (3.6)	0.183	137–145
K (mmol/L)	4.0 (0.9)	4.0 (0.5)	0.554	3.5–5.0
Arterial blood gas				
pH	7.42 (0.11)	7.44 (0.07)	0.417	7.31–7.45
pCO_2 (mmHg)	33.5 (6.2)	33.8 (5.2)	0.809	35–46
pO_2 (mmHg)	79.2 (36.7)	89.6 (21.2)	0.087	90–104
O_2SAT (%)	91.6 (13.5)	96.1 (3.0)	0.131	95–98

WBC = white blood cells; RBC = red blood cells; BUN = blood urea nitrogen; CPK = creatine phosphokinase; LDH = lactic acid dehydrogenase; CRP = C-reactive protein; AST = aspartate aminotransferase; ALT = alanine aminotransferase; Na = sodium; K = potassium; pCO_2 = partial carbon dioxide pressure; pO_2 = partial oxygen pressure; O_2SAT = blood oxygen saturation rate.

Table 4. Factors predicting death from SARS using a multiple logistic regression model for patients in Taiwan

Variable	OR	95% CI	*p*	Normal range
Age, yr				
< 40	1.0			
40–59	5.0	1.0–25.4	0.054	
≥ 60	12.4	1.8–83.3	0.010	
Sex (male)	1.0	0.1–2.5	0.488	
Dyspnea	1.9	0.5–8.2	0.376	
Diabetes mellitus (yes/no)	5.2	0.9–28.3	0.058	
Neutrophils (> 7000/μL)	6.4	1.1–36.0	0.034	3000–7000
Lymphocytes (< 700/μL)	3.9	1.0–15.8	0.053	1500–4000
LDH (> 593.5 IU/L)	4.2	1.0–17.3	0.048	180–460
CRP (> 47.5 mg/L)	5.8	1.5–23.0	0.013	< 5

OR = odds ratio; CI = confidence interval; LDH = lactic acid dehydrogenase; CRP = C-reactive protein.

independently associated with death (OR = 6.4; 95% CI = 1.1, 36.0). Initial biochemical measures of the highest quartiles significant for death were CRP > 47.5 mg/L (OR = 5.8; 95% CI = 1.5, 23.0) and LDH > 593.5 IU/L (OR = 4.2; 95% CI = 1.0, 17.3).

Concentration of plasma CRP in SARS patients

Patients with (n = 211) and without (n = 135) CRP tests had similar distributions of age, sex, occupation, contact history, intubation status and fatality (data not shown). There were also no significant differences between these two groups for most variables of symptoms and comorbidities, except that patients who had CRP tests had a higher prevalence of myalgia (24.6% *vs.* 11.1%, p = 0.002), hypertension (9.0% *vs.* 3.0%, p = 0.043), but a lower prevalence of cough (55% *vs.* 68.1%, p = 0.015).

Approximately 69.9% of patients with CRP tests had initial levels greater than the normal value of 5 mg/L, and women had lower values than men (median: 10.4 *vs.* 25.3 mg/L). In general, CRP concentrations in SARS patients were lower for young patients than for old patients. The overall mean CRP level was 29.1 mg/L (SD = 32.9 mg/L), the median was 12.6 mg/L, the 75th percentile value for those with comorbidity was 83.3 mg/L and for those without comorbidity was 34.3 mg/L (Table 5). Patients with COPD, CVA and cardiac disease had higher mean CRP (all approximately 61.5 mg/L).

Factors associated with elevated initial CRP

Factors significantly associated with CRP > 47.5 mg/L in the univariate analyses were old age, male gender, non-healthcare worker, fatal cases, and patients with dyspnea, DM, COPD, cardiac disease, hypertension, CVA, lymphocyte count < 700/μL, red blood cell (RBC) < 4.1×10^6/μL, creatine phosphokinase (CPK) > 158 IU/L, LDH > 593.5 IU/L, serum AST > 57 IU/L, serum alanine aminotransferase (ALT) > 42 IU/L, partial pressure of dioxide < 71.7 mmHg and oxygen saturation < 93.9%, etc. Since CRP likely changed during the different clinical stages and patients were admitted in different clinical stages, the day on which initial CRP was measured, which was counted from the first day of fever, should be very important. The univariate analysis, however, found no significant association between elevated CRP and the time of measurement after fever onset. But after controlling for age and sex in the stepwise multiple logistic regression model, an elevated initial CRP level > 47.5 mg/L had a significant positive association with dyspnea (OR = 4.3; 95% CI = 1.7–11.2), lower RBC (OR = 4.3; 95% CI = 1.6–11.4), and elevated AST (OR = 3.1; 95% CI = 1.3–7.6) (Table 6).

Since dyspnea is an important symptom for SARS patients, we also assessed the association

Table 5. Percentile distribution and average plasma C-reactive protein levels by comorbidity

Comorbidity	*n*	C-reactive protein (mg/L)					Mean ± SD
		100%	75%	50%	25%	0%	
Diabetes mellitus	20	120.0	81.9	31.5	5.8	1.5	42.5 ± 39.7
Cardiac disease	11	128.0	86.4	56.4	10.0	4.7	61.4 ± 42.5
COPD	6	128.0	80.4	73.4	8.3	5.7	61.5 ± 47.0
Hypertension	19	128.0	83.3	51.0	12.0	3.8	54.3 ± 42.1
Cerebrovascular accident	10	120.0	92.4	61.9	38.4	4.7	61.5 ± 36.6
Other comorbidity*	9	128.0	85.0	15.2	11.1	8.3	49.7 ± 49.6
Subtotal (A)	39	128.0	83.3	51.0	10.0	1.5	49.0 ± 40.8
No comorbidity (B)	172	159.0	34.3	11.4	4.0	0.0	24.6 ± 29.1
Total (A+B)	211	159.0	47.5	12.6	4.6	0.0	29.1 ± 32.9

**Includes any one of the following diseases: malignancy, end-stage renal disease, immunologic disease, liver disorder. SD = standard deviation; COPD = chronic obstructive pulmonary disease.*

Table 6. Factors predicting plasma C-reactive protein level > 47.5 mg/L in SARS patients using a multiple logistic regression model

Risk factor	OR	95% CI	*p*	Normal range
Age, yr				
< 40	1.0			
40–59	1.0	0.4–2.5	0.965	
≥ 60	1.3	0.4–4.5	0.671	
Sex (male)	2.3	1.0–5.7	0.063	
Dyspnea	4.3	1.7–11.2	0.003	
Comorbidity (yes/no)*	2.5	0.9–7.4	0.093	
RBC (< 4.1 × 10^6/μL)	4.3	1.6–11.4	0.003	4.5–6.2
AST (> 57 IU/L)	3.1	1.3–7.6	0.011	10–30

**Includes any one of the following diseases: diabetes mellitus, cardiac disease, chronic obstructive pulmonary disease, hypertension, malignancy, cerebrovascular accident, end-stage renal disease, immunologic disease, liver disorder. OR = odds ratio; CI = confidence interval; RBC = red blood cells; AST = aspartate aminotransferase.*

Table 7. C-reactive protein (CRP) levels for SARS fatalities and survivors by dyspnea status and age-sex-adjusted odds ratios of having CRP > 47.5 mg/L

Dyspnea	Death	*n*	Mean ± SD (mg/L)	OR (95% CI)	*p*
Yes			52.2 ± 44.8		
	Yes	15	64.6 ± 51.8	6.0 (1.8, 20.3)	0.004
	No	24	44.5 ± 38.9	3.5 (1.3, 9.0)	0.010
No			23.8 ± 27.1		
	Yes	26	38.0 ± 35.1	2.8 (1.0, 7.4)	0.046
	No	146	21.3 ± 24.7	1.0	

SD = standard deviation; OR = odds ratio; CI = confidence interval.

of dyspnea with initial CRP level. The mean ± SD CRP level was 52.2 ± 44.8 mg/L for patients with dyspnea and 23.8 ± 27.1 mg/L for patients without dyspnea (Table 7). The age-sex-adjusted OR in patients with CRP levels > 47.5 mg/L were 6.0 (95% CI = 1.8–20.3) for fatalities with dyspnea, 3.5 (95% CI = 1.3–9.0) for survivors with dyspnea, and 2.8 (95% CI = 1.0–7.4) for fatalities without dyspnea compared to survivors without dyspnea.

Discussion

This study found that sex, age, occupation and contact history were significantly associated with SARS fatality in univariate analyses. These associations disappeared, however, when dyspnea, neutrophil count, lymphocyte count, LDH or CRP were added to bivariate analyses, except for the association with age, which remained significant. Age ≥ 60 years, initial neutrophil count, CRP level and LDH level were significant predictors of death from SARS. Compared to survivors without dyspnea, the age-sex-adjusted OR in patients with initial CRP levels > 47.5 mg/L were 6.0 for fatalities with dyspnea, 3.5 for survivors with dyspnea, and 2.8 for fatalities without dyspnea. Therefore, initial CRP is not only a marker associated with SARS progression, but can also be used to predict the severity of this coronavirus infection.

The present study of 346 cases showed that the fatality rate was much greater for patients with comorbidity (59.3% or 35/59) than for those without comorbidity (13.2% or 38/287). For the 41 patients with endotracheal intubation, the case fatality rate was 46.3% (19/41). The overall case fatality rate from SARS in Taiwan was slightly

higher than that in a medical center reported by Wang et al,[22] but much higher than the WHO reported average fatality rates of 10.9% worldwide, 14% in Singapore and 16% in Canada.[4] The high proportion of hospital-associated infection during the outbreak period may explain the elevated fatality rate, particularly involving inpatients, as supported by the high comorbidity rate in the study patients.

Comparison of vital signs, clinical symptoms and comorbidity between fatalities and survivors revealed that initial hematological and biochemical characteristics may be attributable to the risk of fatality from SARS. This study had the advantage that hospitals were required to report these initial data for all potential SARS patients to the government health authority. In previous studies, comorbidity, particularly DM and cardiac disease, was significantly associated with higher risk of death from SARS.[5,7,13,22] Although we found similar patterns in the univariate analysis, only DM remained significant in the multivariate analysis. This is attributable to the predicative value of initial neutrophil count (> 7000/μL), LDH level (> 593.5 IU/L) and CRP level (> 47.5 mg/L) for fatality from SARS. Previous studies also found a significant association between death and high levels of initial LDH[5,7,13,16,20–22] and CRP.[12,22] Death is thus more likely to occur in patients with these conditions. Consistent with previous studies, we found that older patients were more likely to have higher LDH and neutrophil count.[5,7,16,20,21]

Both CRP and LDH are markers of inflammation. Initial LDH level was also an independent predictor of death in this study, but not in the study of Wang et al.[22] Our study included a nationwide sample of a much larger size than their single hospital study. Previous studies found strong evidence of an elevated risk for developing adverse outcomes or acute respiratory distress syndrome in SARS patients from Hong Kong with elevated LDH.[16,20,21] In agreement with these studies, we found that a high serum LDH level appeared to be associated with increased mortality in SARS cases in the multivariate analysis. This finding is also similar to results of studies in patients with *Pneumocystis carinii* pneumonia and AIDS.[26,27] Increased serum LDH has also previously been associated with several pulmonary infections, including tuberculosis and bacterial pneumonia.[28,29]

Several comorbidity variables were significant factors in the prediction of SARS fatality in the univariate analyses of this study. However, only DM remained significant when dyspnea was added to the model. The initial association of CRP with fatality was consistent with the findings of Singh et al[12] and Wang et al.[22] Singh et al's study in Singapore found that 7 of 11 SARS patients had elevated CRP with a higher proportion in fatalities than in survivors (75% *vs.* 25%).[12] Wang et al's study at a medical center also found that 77.9% (53/68) of SARS patients with elevated initial CRP were at higher risk of fatality (OR = 1.447 for every 1 mg/dL increase, $p = 0.006$).[22] We also found that elevated initial CRP was a factor associated with higher OR of deaths for all SARS patients in Taiwan. The present study had a greater sample size than previous studies from Taiwan, with initial CRP test results available for 211 of 346 SARS patients.

CRP is one of the most sensitive acute-phase reactants and is virtually absent from blood serum in the healthy person. CRP levels can increase dramatically after bacterial and viral infections, inflammation and severe trauma.[25] Higher blood CRP level plays an instructive role in the acquired immune response as innate recognition lectin,[30] a pentameric polypeptide initially reported in patients with *Streptococcus* pneumonia.[31] Furthermore, this nonspecific inflammation marker may predict the risk of cardiovascular events and hypertension development.[32–34] In the present study, we found that SARS patients with the comorbidities of cardiac disease, hypertension and CVA had high plasma CRP concentrations and were at high risk of fatality. This risk, however, was not as great as that of patients with the comorbidity of DM. High CRP has also been associated with acute dyspnea due to bacterial pneumonia and bronchitis.[35] Dyspnea was an important variable in predicting CRP level. Neutrophil and lymphocyte counts, BUN and CPK were significant predictors of CRP level in the

univariate analysis. These associations became insignificant, however, when dyspnea was added into the model in the bivariate analysis.

In this study, the initial serum samples for hematological and biochemical tests were collected an average of 3.1 days and 3.4 days after the onset of illness (median, 2 days). The mean initial CRP level was lower for the 191 cases with blood specimens collected in the first week than for the 18 cases with specimens collected in the second week after the onset of disease (mean ± SD: 27.6 ± 32.4 *vs.* 41.0 ± 36.7 mg/L). In other words, the CRP levels may increase to approximately 28 mg/L within 1 week after the disease is noted. The typical CRP concentration is < 5 mg/L in the normal population, and 74.5% of probable SARS patients had initial CRP values greater than the normal level. Overall CRP values in 75% of patients reached 83.3 mg/L for those with comorbidity and 34.3 mg/L for those without comorbidity. Therefore, elevated CRP level reflects its particular role in the pathogenesis of SARS in patients with cardiovascular events. This study further demonstrated that CRP levels were significantly associated with decreased RBC counts and elevated ALT levels, indicating the coexistence of abnormal liver function.

CRP is an excellent marker of inflammation but lacks specificity for differentiation between viral and bacterial infections.[36,37] The mean initial CRP value (23 mg/L) in patients with respiratory syncytial virus (RSV) pneumonia is lower than that in patients with pneumococcal pneumonia (145 mg/L). In mixed RSV with pneumococcal infection, mean CRP values increased to 85 mg/L.[38] Approximately 25% of SARS patients with comorbidity in this study had plasma CRP concentrations similar to those reported for RSV pneumonia patients. On the other hand, Kawasaki et al observed high CRP levels in patients with prolonged fever and strong inflammatory response due to adenovirus respiratory infection.[39] Patients with adenovirus respiratory infection have clinical features resembling those in patients with bacterial infection.[40,41] Although the inability to differentiate between viral and bacterial infection based on CRP level remains an inherent disadvantage of this marker, this study demonstrated a clear inflammatory response to coronavirus infection.

The initial CRP association with SARS fatality was apparently overlooked by most previous SARS studies. This factor may serve as an important predictor of SARS mortality. In conclusion, SARS is a serious respiratory illness with a high case fatality rate in Taiwan. Reasons for the conspicuously high case fatality of SARS patients in Taiwan remain speculative. High initial neutrophil counts, and plasma CRP and LDH are important early signs for predicting death from this disease. A clear presentation in hematological and biochemical measurements for SARS patients may help physicians to provide optimized care. Early recognition, prompt isolation, and appropriate therapy are key to effectively combat this deadly infection.

Acknowledgments

We thank physicians and administrators at all contributing hospitals for their efforts in providing the medical data for these probable SARS patients to the CDC in Taiwan. This study was completed as inhouse work at the CDC using no specific funds and involved no conflicts of financial or other interests related to this article.

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