行政院國家科學委員會專題研究計畫　成果報告

（總計畫與子計畫一）臺灣地區嚴重急性呼吸道症候群病患病患之臨床表現與治療成效

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計畫主持人：張上淳
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行政院國家科學委員會補助專題研究計畫 ☑ 成 果 報 告 □期中進度報告

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成果報告類型(依經費核定清單規定繳交)：□精簡報告　☑完整報告

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執行單位：國立臺灣大學醫學院內科

中　華　民　國　93 年　　9 月　　6 日

目錄

中文摘要：

關於急性嚴重呼吸道症候群（SARS）在臨床和實驗室上的發現，目前所能得到的資料仍十分有限。從 92 年 3 月 10 日至 92 年 6 月 15 日，總共有 76 位合併有肺炎的 SARS 病患，在台大醫院接受完整的治療。針對此 76 位病人進行分析，發燒是他們最常見的臨床症狀，其次包括有咳嗽、肌肉酸痛、呼吸困難和腹瀉。其中 24 位病人有嚴重的潛在性系統疾病。在剛到醫院就醫時，大部分的病人有 C 反應性蛋白升高及淋巴球低下的現象，而其它常見的實驗室意常包含白血球低下、寫小板偏低、肝功能異常、lactate dehydrogenase（LDH）升高、和 creatine kinase（CK）升高等。大多數的病人，在並程的第二個星期會經歷臨床上及實驗室檢查異常最嚴重的時間點。整體而言，病患的死亡率為 19.7%。利用多因子迴歸分析的統計結果，最初的 CRP 值和潛在性系統疾病是唯一的兩個和死亡有關的預測因子。

關鍵詞：嚴重急性呼吸道症候群、C 反應性蛋白、靜脈注射用免疫球蛋白

英文摘要：

The data of detailed whole clinical pictures and temporal progression of abnormal laboratory findings of severe acute respiratory syndrome (SARS) remains limited. From 10 March to 15 June 2003, 76 adult patients diagnosed as probable SARS with pneumonia and treated at a university hospital in Taiwan were enrolled for analysis. Fever was the most frequent presentation symptom followed by cough, myalgia, dyspnea, and diarrhea. Twenty-four patients had various underlying diseases. At presentation, most patients had elevated C-reactive protein (CRP) level and lymphopenia. Other common abnormal laboratory findings included leukopenia, thrombocytopenia, elevated aminotransferase, lactate dehydrogenase, and creatine kinase level. Most patients experienced exacerbations of above clinical and laboratory parameters during the second week of the disease courses. The overall case fatality rate was 19.7%. Using multivariate analysis, underlying disease and initial CRP level were the two factors predictive for the mortality of SARS patients. In conclusion, SARS is a new emerging infectious disease associated with a high mortality rate and the initial CRP level and patients' underlying conditions are two independent factors for mortality.

Key words: severe acute respiratory syndrome, C-reactive protein, intravenous immunoglobulin

前言：

Severe acute respiratory syndrome (SARS) is a new communicable disease. The pathogen, which is a new virus belonging to the family of coronavirus, of SARS has just been documented. So far, there have been 26 countries all over the world affected by SARS, resulting in infections in over 3,500 people and 86 deaths. Because SARS can be spread via close person-to-person contact involving exposure to infectious droplet, result in respiratory failure as well as even death, and no existed human immunity can neutralize the viral particles causing SARS, departments of health in many countries have considered SARS as a most important public-health issue.

The first SARS patient in Taiwan, diagnosed by doctors at National Taiwan University Hospital (NTUH), has been documented on March 14, 2003. Till now, there have been 28 probable SARS patients in Taiwan. By using intensive supportive care, no SARS patients in Taiwan dies. However, because SARS is a new emerging disease, its clinical manifestations and effective as well as necessary therapeutic strategies are still obscure. The purposes of current project include clarifying the clinical manifestation of SARS in Taiwanese, trying to discover the laboratory surrogate of clinical course, and trying to infer effective therapeutic strategies. We hope our effort can contribute to the better clinical care of SARS patients in Taiwan in the future.

研究目的：

1. To clarify the clinical manifestations of patients of severe acute respiratory syndrome (SARS) in Taiwan.
2. To evaluate the mortality, morbidity, and complication of SARS patients in Taiwan.
3. To find out the surrogate of clinical course of SARS patients in Taiwan by tracing the serial change of results of laboratory examination, including hemogram, transaminase (ALT & AST), creatine kinase (CPK), lacate dehydrogenase (LDH), and C-reactive protein (CRP).
4. To evaluate the clinical effects and significances of variable proposed therapeutic strategies for SARS patients in Taiwan.
5. To try to infer the effective and necessary treatment for SARS.
6. Using immunoflrorescence assay to measure the specific antibody response of SARS in patients of probable SARS and as assistance to confirm the diagnosis.

文獻探討：

SARS is a new communicable disease, which is first found in Guangdong Province, China in November 2002 [1]. The pathogen, which is a new virus belonging to the family of coronavirus, of SARS has just been documented [2, 3]. So far, there have been 26 countries all over the world affected by SARS, resulting in infections in over 3,500 people and 86 deaths [4]. It has caused a major impact on the health of human beings.

The preliminary data indicates the incubation period of SARS is usually 2-7 days but may be as long as 10 days. The illness generally begins with a prodrome of fever (>38°C), which is often high, sometimes associated with chills and rigors and sometimes accompanied by other symptoms including headache, malaise, and myalgias. At the onset of illness, some cases have mild respiratory symptoms. After 3-7 days, a lower respiratory phase begins with the onset of a dry, non-productive cough or dyspnea that may be accompanied by or progress to hypoxemia. In 10%-20% of cases, the respiratory illness is severe enough to require intubation and mechanical ventilation. The case fatality is around 3%. Chest radiographs may be normal during the febrile prodrome and throughout the course of illness. However, in a substantial proportion of patients, the respiratory phase is characterized by early focal infiltrates progressing to more generalized, patchy, interstitial infiltrates. Some chest radiographs from patients in the late stages of SARS have also shown areas of consolidation. Early in the course of disease, the absolute lymphocyte count is often decreased. Overall white cell counts have generally been normal or decreased. At the peak of the respiratory illness, up to half of patients have leukopenia and thrombocytopenia or low-normal platelet counts (50,000 – 150,000 / μl). Early in the respiratory phase, elevated CPK levels (up to 3000 IU / L) and AST / ALT (2- to 6-times the upper limits of normal) have been noted. Renal function has remained normal in the majority of patients. Treatment regimens have included a variety of antibiotics to presumptively treat known bacterial agents of atypical pneumonia. In several locations, therapy has also included antiviral agents such as ribavirin. Steroids have also been given orally or intravenously to patients in combination with ribavirin and other antimicrobials. At present, the most efficacious treatment regime, if any is unknown [5]. Previous study has also pointed out that peak serum CPK and LDH levels are possible indicators of worse prognosis in patients of SARS [6-8].

Although the case definition of SARS patients has been proposed by WHO (9), however, the detailed clinical manifestations of SARS patients in Taiwan have not been illuminated. In addition, no patient has died of SARS in Taiwan so far. Whether some specific intervention, such as the use of IVIG, conducted in clinical practice in Taiwan plays a role in the better treatment outcome is also obscure. Current project is designed to illuminate the whole clinical pictures of SARS patients in Taiwan and try to infer the effective and important treatment strategies for SARS.

On the other hand, it is necessary to find a laboratory surrogate to predict the clinical course of

a specific disease. There is still no report addressing the possible surrogate of SARS till now. Current study is also designed to try to figure out a possible laboratory surrogate of SARS by means of undergo some laboratory examinations regularly, including hemogram, transaminase, ALP, γ-GT, LDH, CPK, and CRP.

References:

1. World Health Organization. SARS epidemiology to date. April 11. Available at http://www.who.int/csr/sars/epi2003_04_11/en/.
2. Drosten C, Gunther S, Preiser W, van der Werf S, Brodt HR, Becker S, et al. Identification of a novel coronavirus in patients with severe acute respiratory syndrome. N Engl J Med, 2003. (Accessed April 10, 2003, at http://www.nejm.org/).
3. Ksiazek TG, Erdman D, Goldsmith C, Zaki S, Peret T, Emery S, et al. A novel coronavirus associated with severe acute respiratory syndrome. N Engl J Med, 2003. (Accessed April 10, 2003, at http://www.nejm.org/).
4. World Health Organization. Cumulative number of reported cases of severe acute respiratory syndrome (SARS). Available at http://www.who.int/csr/sarscountry/2003_04_19/en/.
5. World Health Organization. Preliminary clinical description of severe acute respiratory syndrome. Available at http://www.who.int/csr/sars/clinical/en/.
6. Tsang KW, Ho PL, Ooi GC, Yee WK, Wang T, et al. A cluster of cases of severe acute respiratory syndrome in Hong Kong. N Engl J Med, 2003. (Accessed March 31, 2003, at http://www.nejm.org/.)
7. Poutanen SM, Low DE, Henry B, Finkelstein S, Rose D, Green K, et al. Identification of severe acute respiratory syndrome in Canada. N Engl J Med, 2003. (Accessed March 31, 2003, at http://ww.nejm.org/.)
8. Lee N, Hui D, Wu A, Chan P, Cameron P, Joynt GM, et al. A major outbreak of severe acute respiratory syndrome in Hong Kong. N Engl J Med, 2003. (Accessed April 7, 2003, at http://www.nejm.org/.)
9. World Health Organization. Case definitions for surveillance of severe acute respiratory syndrome (SARS). Available at http://www.who.int/csr/sars/casedefinition/en.

研究方法：

All patients fulfilled the revised WHO definition of probable SARS, developed pneumonia during the disease course, and received their treatment at NTUH during March 8 to June 15, 2003, were enrolled in this study.

Except for the first patient, who did not receive any of the following treatment, and the second, third, as well as fourth patients, who received steroid in the first week of their disease courses, the other patients all received treatments following the treatment guideline as described below. Oral ribavirin was used soon after establishing the diagnosis of SARS with a loading dose of 2000 mg followed by 1200 mg per day if the body weight was over 75 kilogram or 1000 mg per day if the body weight was less than 75 kilograms. The duration was 10 days unless the patient developed adverse effects. Antimicrobial agents for community-acquired pneumonia, either moxifloxacin alone or ceftriaxone plus azithromycin, were also administered at the same time. Methylprednisolone was usually administered in the second week of the disease course if the patient developed a flare of fever, progressed clinical symptoms (such as dyspnea or diarrhea), a surge or re-surge of CRP level, or rapid deterioration of chest radiographic findings (development of new infiltration). It was indicated in the first week of disease course only if there were very rapidly progressed clinical symptoms or laboratory abnormalities, such as elevated CK, LDH, CRP, and the progression of chest radiographic findings. The dosage of methylprednisolone was 2 mg/kg/day for five days and then it was tapered off. Pulse therapy with methylprednisolone 500 mg/day for three days was used if there was a significant disease progress under the standard regimen. Intravenous immunoglobulin (IVIG) was administrated while existence of severe leukopenia ($< 2 \times 10^9$/L) and/or thrombocytopenia ($< 100 \times 10^9$/L), or if there was a marked local progression of lesions on chest radiography in the first week of disease course. The dosage of IVIG was 1 gm/kg/day for two days. Once patients were intubated and supported by a mechanical ventilator, respiratory care according to the principles suggested for managing acute respiratory distress syndrome was applied.

In addition to the work for SARS, the other etiologic workup included the sputum Gram stain and acid-fast stain, sputum culture for bacteria, sputum chlamydial antigen, throat swab for virus isolation, urine pneumococcal antigen, and urine legionellar antigen. We tested serum antibody reaction of both acute and convalescent phase, 4 weeks apart, for mycoplasma, chlamydia, influenza virus, parainfluenza virus, adenovirus, coxsackievirus, respiratory syncytial virus, and SARS related coronavirus (SARS-CoV), and we also did throat swabs for rt-PCR for SARS-CoV. The other routine laboratory tests, such as the hemogram, serum AST, ALT, CK, LDH, and CRP level, were examined every other day during hospitalization. A chest radiography was also undertaken every other day during hospitalization.

A standard case report form modified from that designed by the Centers of Disease Control and Prevention (CDC) for SARS was used to collect the demographic and clinical data (8). The severity of underlying disease was classified using the modified risk stratification proposed by McCabe as rapidly fatal, ultimately fatal, or non-fatal.

結果：

During the study period, there were 76 patients, in total, enrolled for analysis. The male to female ratio was 34/42. Their age ranged from 24 to 87 years with a median of 46.5 years. Twenty-four patients had various underlying diseases, including cardiovascular disorders in 13 patients, diabetes mellitus in 10, hepatobiliary disorders in six, cerebrovascular accidents in three, chronic renal diseases in two, pulmonary fibrosis in one, abuse of intravenous drugs in one, and adrenal insufficiency in one. Fourteen of these 24 patients had underlying diseases classified as rapidly fatal (diabetes mellitus plus ischemic heart disease plus congestive heart failure in four patients, diabetes mellitus plus ischemic heart disease plus cerebrovascular accident with bed ridden in three, diabetes mellitus plus ischemic heart disease plus end-staged renal disease in two, diabetes mellitus plus decompensated liver cirrhosis in one, and ischemic heart disease plus massive ischemic bowel in one) or ultimately fatal (severe pulmonary fibrosis in one, ischemic heart disease in two). The ranking of most frequently presentation symptoms included fever, cough, myalgia, dyspnea, diarrhea, and rigor sensation. Three of the 24 patients who presented with diarrhea had received various antimicrobial agents before their presentation. The duration from symptom onset to presentation ranged from one to 12 days with a median of three days. Leukopenia ($< 4 \times 10^9$/L) was found in 19.7% of patients, and lymphopenia ($< 1 \times 10^9$/L) in 64.5%. Thrombocytopenia ($< 150 \times 10^9$/L) was found in 46.1% of patients. At presentation, serum AST level, ALT level, LDH level, CK level, and CRP level were only available in 68, 46, 16, 65, and 68 patients, respectively. Twenty-four patients (35.3%) had elevated AST level (> 35 U/L) and 11 patients (23.9%) had elevated ALT level (> 35 U/L). Elevation of serum LDH level (> 460 U/L), CK level (> 190 U/L) and CRP level (> 0.8 mg/dL) were noted in 9 (56.3%), 17 (26.1%), and 53 patients (77.9%), respectively. Lesions of increased infiltration on chest radiography were found in 56 of the 76 patients with lesions restricted in one lobe in 33 patients, in two lobes in 15 patients, in three lobes in four patients, in four lobes in two patients, and in five lobes in two patients. The other 20 patients developed abnormalities on chest radiography after admission. The duration from disease onset to the time when abnormalities on the chest radiography were first noted ranged from one to 12 days with a median of four days.

During hospitalization, 69 patients (90.8%) experienced respiratory distress and needed oxygen supplements. The duration from disease onset to when respiratory distress became most severe was 9.8 ± 3.0 days. Among these 69 patients, endotracheal intubation with ventilator support was indicated in 26 patients but was actually given to 23 patients (three patients refused to undergo intubation). Among the 23 patients who were intubated, the duration from disease onset to intubation was 8.4 ± 3.3 days. Eight of these 23 patients were successfully extubated 12.1 ± 6.1 days later. Twelve of the 23 patients died and three patients remained intubated at the end of the current study because of marked lung fibrosis with severely impaired lung function.

Thirty-one patients (40.8%) experienced exacerbation of diarrhea after admission. All of them had received various antimicrobial agents since hospitalization. The duration from disease onset to

when diarrhea became most severe was 8.9 ± 4.7 days.

During the whole disease courses, leukopenia, lymphopenia, and thrombocytopenia were found in 40, 72, and 61 patients. Elevation of AST and ALT was noted in 66 and 59 patients, respectively. Elevation of serum LDH, CK, and CRP level were found in 73, 34, and 71 patients, respectively. The most severe data of above abnormal laboratory parameters usually developed in the second week of disease courses.

Sixty-four patients developed new lesions on chest radiography during hospitalization, including new lesions limited in one lung lobe in 21 patients, in two lobes in 13, in three lobes in 16, in four lobes in seven, and in five lobes in seven. The duration from disease onset to the most severe chest radiography findings was 9.6 ± 2.9 days.

The sputum Gram stain and acid fast stain, sputum culture for bacteria, sputum chlamydial antigen, throat swab for virus isolation, and urine legionellar as well as pneumococcal antigen tests were available for all 76 patients, all had negative results. Paired serum was available for 41 patients till the close of this study. Tests for antibody reaction of mycoplasma, chlamydial, influenza virus, parainfluenza virus, adenovirus, coxsackievirus, and respiratory syncytial virus were all negative.

Out of the 41 patients with paired serum test, the seroconversion for IgG antibody of SARS-CoV by immunofluorescent assay was positive in 38 patients (92.7%). However, only 26 patients (34.2%) out of total 76 patients had positive results of throat swab rt-PCR for SARS-CoV. Among the 50 patients whose throat swab rt-PCR for SARS-CoV results were negative, 28 patients had seroconversion for SARS-CoV. The other 22 patients, who had no direct microbiologic or serologic evidence for SARS-CoV infection till the close of this study, all had compatible clinical courses with those of probable SARS and clear relationships as well as exposures to the initial immigrant clusters and the later intrahospital outbreaks in Taiwan. And their diagnoses of SARS had also been confirmed by a committee of Center for Disease Control (Taiwan), which consisted of experts in chest medicine and infectious diseases.

Other than the first patient, five other patients did not receive ribavirin treatment because they had contraindications to use ribavirin, such as cardiac arrhythmia and cardiomyopathy, and seven patients did not receive steroids because they were rapidly fatal after diagnosis. These seven patients died mainly due to their underlying diseases, especially cardiac events, and their SARS was not so severe and did not progressed to the situations that steroid was indicated according to our treatment protocol even till their deaths.

Eight patients received pulse therapy of steroid for progressive clinical conditions under the usual dosage of steroid. Forty patients received IVIG infusion for severe cytopenia (22 patients) or marked local progression of pulmonary lesions on chest radiography in the first week of the disease course (18 patients). For those 22 patients who received IVIG due to severe cytopenia, they did not receive steroid at the same time when they were put on IVIG; and the WBC counts were 2.6 ± 1.2 X 10^9/L and 4.3±2.8 X 10^9/L, before and after the use of IVIG, respectively ($p = 0.014$, by paired *t*

test). The platelet counts were 104 ± 35 X 10^9/L and 141 ± 46 X 10^9/L, before and after IVIG, respectively (p = 0.002, by paired *t* test).

After a median follow-up of 47 days (range, 4 to 107 days), 18 patients developed various complications during their hospitalizations, including rhabdomyolysis, peripheral neuropathy, acute renal failure, and fungal or bacterial superinfection. Among the 18 episodes of nosocomial infection, six were blood stream infections of which three were caused by enterococci, two by methicillin-resistant *Staphylococcus epidermidis*, and one by methicillin-resistant *Staphylococcus aureus*. Eleven episodes were lower respiratory infections, which was diagnosed by the existence of new infiltration on chest radiography, purulent sputum, phagocytosis of bacteria by neutrophils in sputum revealed by sputum Gram stain, positive sputum culture for bacteria, and response to effective antibiotics. The last one episode was a catheter related infection caused by *Candida parapsilosis*.

The overall mortality rate was 19.7% (15/76). Among the 14 patients whose underlying diseases were classified as ultimately fatal or rapidly fatal, the mortality rate was 78.6% (11/14). For the other 62 patients with mild underlying diseases or without underlying disease, the mortality rate was only 6.5% (4/62). The time from disease onset to mortality in these fifteen patients ranged from four to 42 days with a median of 12 days. For the 26 patients whose clinical conditions indicated endotracheal intubation with ventilator support, the mortality rate was 57.7% (15/26). Using the logistic regression model for univariate analysis, age, underlying disease (non-fatal vs ultimately or rapidly fatal), initial CRP level, initial absolute neutrophil count (ANC), peak CK level, as well as peak CRP level were found to be predictive factors for mortality. Age, sex, underlying disease, initial chest radiographic findings, initial CRP level, initial ANC, peak CK level, lowest lymphocyte count, worst chest radiographic findings, peak LDH level, as well as peak CRP level were those for respiratory failure. However, using logistic regression for multivariate analysis, underlying disease and initial CRP level were the only two factors that were statistically significantly predictive for mortality (odds ratio, 83.333 and 1.447 every 1 mg/dL, respectively; p < 0.001 and = 0.006, respectively) and age, initial CRP level, and worst chest radiographic findings were predictive for respiratory failure (odds ratio, 1.076, 1.419 every 1 mg/dL, and 2.501 every one-lobe involvement, respectively; p = 0.01, 0.01, and 0.006 respectively). For the 65 patients who received steroid as the treatment protocol described above, three remained febrile and needed further pulse steroid therapy after the use of methylprednisolone with the dosage of 2 mg/kg/day. The other 62 patients all became afebrile initially. However, 12 of them had rebound of temperature two to three days after the temporal defervescence. Seven of the 12 patients became afebrile again and had no more fever one to two days after the transient rebound of fever without specific intervention. The other five patients received further pulse steroid therapy to control the fever and clinical exacerbation. For those 62 patients who remained alive at the end of this study, the time to defervescence after disease onset was 10.3 ± 5.1 days. Six of these 62 survived patients developed significant lung fibrosis directly due to SARS, which resulted in exertional dyspnea in two patients,

oxygen-supplement dependence in one, and respiratory failure in three. Till the end of the study, 58 of the 62 patients were successfully discharged from NTUH. The other four patients, including three patients had respiratory failure and one was dependent on oxygen supplement, remained hospitalized. The follow-up duration of these four patients was all over four weeks.

討論：

SARS is a new emerging infectious disease and spread in several countries or areas during February to June 2003. Clinical experience is limited for most parts of the world. Our experience from 76 patients of probable SARS with pneumonia demonstrated a high case fatality rate (19.7%), especially in patients with major underlying diseases and high initial CRP levels. For those patients who needed endotracheal intubation with ventilator support during their hospitalization also had a high mortality rate (57.7%). Various complications developed in a high proportion of patients (23.7%) during their disease courses.

The yield rate of rt-PCR assay for SARS-CoV was lower (34.2%) in the current study than previous report. This might be because only throat swabs instead of nasopharyngeal aspirations or stools were obtained for rt-PCR in the present study.

Same as previous reports from other areas, fever was the most frequent symptom at presentation in our cases. Compared to those previous reports, more patients in our cases series presented with diarrhea (31.6% vs 1% ~ 19.6%). Therefore, according to our observations, diarrhea may be also considered as an early symptom and clue of SARS. In addition, 18 patients had initial symptoms of diarrhea when fever occurred. Gastrointestinal tract should be considered as another important primary infection site of SARS-CoV.

A previous study reported the temporal progression of clinical and radiological findings in SARS patients and indicated that several parameters would become more severe in the second and third week of the disease course. Our current study reveals similar findings. Although the exacerbation of diarrhea might be due to the use of antimicrobial agents, however, the diarrhea improved subsequently without change or discontinuation of the antimicrobial agents. Therefore, it is more likely that the exacerbation of diarrhea is due to SARS itself. In addition, our study also demonstrates that the abnormal laboratory findings of most patients, such as leukopenia, thrombocytopenia, lymphopenia, elevation of AST, ALT, CK, LDH, and CRP, may also become more severe in the second week of the disease courses.

The treatment protocol in the current study was somewhat different from that suggested by So et al. The timing of using steroids was modified according to our experiences in treating the second, third, and fourth patients, whose exacerbation of oxygen demand and chest radiography lesions were not prevented by the early use of steroid. Besides, steroid is an imunnosuppressive agent and thus facilitates the microorganisms' evasion of host immunity as well as their amplification in vivo. A previous study pointed out that the viral load of SARS Co-V in SARS patients arrived the peak levels at around the 10th day of the disease course. Using steroids as an adjunctive therapy for infectious diseases was to reduce the severity of inflammatory damage that can occur in the later stage of diseases. In addition, using steroids was a risk factor for subsequent nosocomial infection. For all these reasons, it seems reasonable to delay the timing of starting steroid usage, as we did in the treatment protocol of the current study. Among the 65 patients who received steroid as the treatment protocol, only 15 (23.1%) patients had rebound or persistence of fever after initial steroid

use. This is less frequent than those from prior reports (43.3% ~ 85.3%). However, the overall mortality rate in the current study was similar to that reported from Hong Kong (7% ~ 20.9%). It is difficult to compare the treatment results between our study and previous ones because of the different background of patients' disease severity, and also because of case definition as well as obscure description about complications of SARS patients, especially those due to nosocomial bacterial and fungal infection, in previous reports. All patients enrolled in our study met the revised criteria suggested by WHO for probable SARS and all had pneumonia during their disease courses, so the disease severity of our patients was more severe. Therefore, the best timing of starting steroid usage and the total duration of steroid usage in SARS patients to improve the treatment outcomes remain unclear and need further study.

Hemophagocytotic syndrome was documented in our second patient by bone marrow biopsy. Her clinical presentation included fever, severe leukopenia, and thrombocytopenia. Her hemophagocytotic syndrome was relieved after using IVIG. IVIG had been suggested as a treatment for infection-associated hemophagocytotic syndrome because of its effect of immune modulation. The other 21 patients who developed severe leukopenia and/or thrombocytopenia in the first week of their disease course also received IVIG therapy empirically. The effectiveness of IVIG for control leukopenia and thrombocytopenia seemed good, because after infusion of IVIG, their leukocyte and platelet counts were found to increase to a significantly higher level ($p = 0.002$). The increase of leukocyte and platelet counts might prevented some further complications directly resulting from severe leukopenia and thrombocytopenia, such as infection and tendency to bleed. Although there was no control group in the current study, IVIG might play a role in the treatment of selected SARS patients.

Advanced age, co-morbidity, high peak LDH level, and high ANC count at presentation had been reported as poor prognosis factors for SARS patients. By univariate analysis, many parameters, including those listed above, were found to be the predictive factors for mortality or respiratory failure in current cases series. However, using the logistic regression model to undergo multivariate analysis, severe underlying disease and high initial CRP level were the only two factors predicting mortality and age, initial CRP level, and worst chest radiographic findings were the three factor predicting respiratory failure. The role of CRP in predicting the outcome of SARS patients has never been discussed in previous studies. The discovery of CRP was reported in 1930 by Tillet and Francis. During the past decades, CRP had been found to be paralleling well with the severity of inflammation or tissue injury and to be a useful marker for the presence of disease, response to therapy, and ultimate recovery. Although initial CRP level was not available in eight patient in this cohort and this might affect the statistical result to some extent, our findings suggest that CRP also parallels well with the severity and outcome of SARS patients. In the current study, all patients with severe underlying disease were all aged patients (age > 65 years). So there was a strong correlation between age and underlying disease. During a statistical processing, these two factors might interfere each other and led to the result that age, not underlying disease, was an independent risk

for respiratory failure but underlying disease, not age, was an independent risk for mortality. The worst chest radiographic finding outlined the most severe extent of impaired lung function. This might explain why it was an independent factor for respiratory failure. However, mortality was affected by other conditions, such as underlying disease and/or complication during hospitalization, unrelated to pulmonary condition. This might explain why worst chest radiographic finding was not an independent factor for mortality.

Forty-two patients in this cohort were admitted to NTUH via the emergency department. In the emergence department of NTUH, there is no facility to check serum LDH level. In addition, during the period of intrahospital outbreaks of SARS, heavy clinical loading and frequent bed transfer made the primary care physician difficult to collect laboratory data as the schedule described above. Therefore, initial serum LDH level and CRP level were available in only 16 and 68 patients, respectively, in the current study. This made initial LDH level unable to be put into statistical analysis. Both CRP and LDH were markers of inflammation. Thus whether the initial LDH level is also an independent risk factor for mortality or respiratory failure needs further study.

Complications during the disease courses of SARS patients were also seldom or obscurely discussed in previous reports. Acute renal failure, which might be more likely caused directly by MRSA infection and rhabdomyolysis, was found in three patients. Acute myocardial infarction was found in a patient who had been diagnosed as having coronary artery disease for years. GI bleeding, which might be due to critical illness, was found in two patients. Rhabdomyolysis had been reported to be associated with viral infection. Our observation suggested that the SARS Co-V infection might also be associated with this complication. Although peripheral neuropathy had also been reported to be associated with viral infection, neuropathy due to steroid and/or acute illness should also be considered as the etiologies in the four patients who developed neuropathy, in the current study.

Eleven patients experienced bacterial or fungal superinfection during their hospitalization. All nosocomial infections occurred while patients were intubated and supported with a mechanical ventilator ($p < 0.001$ by Fisher's exact test). The nosocomial infection rate among these SARS patients was 237 per 1000 discharges, which was much higher than that of all patients at NTUH (49 per 1000 discharges). Steroid use and more severe clinical conditions, such as higher rate of respiratory failure, than usual patients might be the reasons. To prevent respiratory failure, and shortening the use of steroids in SARS patients should be considered to reduce the nosocomial infection rate.

In conclusion, the current study reveals that SARS is a new emerging and severe infectious disease with an overall complication rate of 23.7% and case fatality rate of 19.7%. Clinical symptoms and abnormal radiographic and laboratory findings might become most severe in the second week of disease course. In addition to ribavirin and steroids, IVIG might play a role in the treatment of selected patients. The underlying disease and initial CRP level were the two independent predicting mortality and age, initial CRP level, as well as worst chest radiographic

finding were the three independent factors predicting respiratory failure for adult SARS patients.