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SARS

Clinical trials on treatment using a combination of Traditional Chinese medicine and Western medicine

Report of the WHO International Expert Meeting to review and analyse clinical reports on combination treatment for SARS
8–10 October 2003
Beijing, People's Republic of China

World Health Organization
Geneva
2004

WHO Library Cataloguing-in-Publication Data

SARS: Clinical trials on treatment using a combination of Traditional Chinese medicine and Western medicine

1.Severe acute respiratory syndrome - therapy 2.Medicine, Chinese traditional 3.Clinical trials 4.Cross-cultural comparison I. Title.

ISBN 92 4 154643 3 (NLM Classification: WC 505)

Cover photograph: WHO/P. Virot

Please click on the different underlined parts for access to the PDF files.

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Acknowledgements

The World Health Organization (WHO) would like to acknowledge its indebtedness to all the authors of the reports on clinical trials contained within this document. Their hard work and dedication is reflected within each report.

Special thanks is given to the Nippon Foundation for providing their generous support throughout the entirety of this project, including funding the WHO International Expert meeting to review and analyse clinical reports on combination treatment for SARS, 8-10 October 2003, Beijing, People's Republic of China, as well as publishing the document.

WHO would like to express its appreciation to the State Administration of Traditional Chinese Medicine of the People's Republic of China for their involvement in the development of this document by collecting the reports, as well as kindly hosting the above-mentioned meeting to review them.

WHO would also like to thank the participants of the above-mentioned meeting, who contributed their comments and expertise in order to ensure that the reports on clinical trials contained within this document are acceptable and provide adequate and reliable information.

In addition, thanks are due to Mr Ruiping An for his assistance in referencing the original Chinese documents to clarify questions regarding the translation.

Finally, due to the complexity of this document, the Traditional Medicine Team (TRM) at WHO Headquarters relied on the advice and support of many colleagues during the development of this document. Therefore, TRM would like to extend a thank you, in particular, to the Department of Communicable Disease Surveillance and Response and relevant staff at the Regional Office for the Western Pacific.

Introduction

Background

In the winter of 2002, severe acute respiratory syndrome (SARS) began to spread throughout the world. More than 5000 cases were reported in the People's Republic of China, including over 1700 cases in China, Hong Kong Special Administrative Region (Hong Kong SAR). The total number of cases reported from Canada and Singapore was more than 200. The total number of SARS worldwide reached 8437 with incidences in 29 counties. Mortality from SARS is estimated at 10–12%.

The World Health Organization (WHO) took effective control measures including international collaboration supported at the highest political level. The global outbreak of SARS was successfully contained in early July 2003.

However, two isolated cases — in Singapore in September 2003 and Taipei in November 2003 — were caused by contamination in a laboratory. Furthermore, in December 2003, two more new SARS cases were confirmed in Guangdong, China where the first ever SARS case had been reported in 2002. Thus far, the source of infection and the mode of transmission for these two cases have not been clarified.

Research on the use of traditional medicine for treatment of SARS patients in China

China has a long history of the use of traditional medicine that has long been integrated into the national health system. When the SARS outbreak occurred in China, the State Administration of Traditional Chinese Medicine of the People's Republic of China immediately initiated clinical research projects on the use of integrated Traditional Chinese medicine (TCM) and Western medicine for treating SARS. A total of 21 research projects were initiated to cover three aspects of SARS, namely, prevention, treatment and rehabilitation. Local governments in Beijing, Guangdong, Shanghai and Tianjin also established similar research projects.

Practitioners of TCM are estimated to have participated in the treatment of SARS in 102 of the 195 SARS-specific hospitals. Ninety-six TCM hospitals sent 2163 professionals to 93 SARS-specific hospitals. Of the 5327 patients with confirmed SARS, 3104 received treatment with TCM, which was 58.3% of the total SARS patients in China. In Hong Kong SAR, research on the use of TCM for the prevention and treatment of SARS, and during convalescence was reported. From the above-mentioned reports, it is clear that TCM and traditional medical physicians made a major contribution to combating SARS in China.

WHO International Expert Meeting

In order to better understand the potential of complementary treatment for patients with SARS and to encourage robust clinical research on SARS and its treatment with traditional medicine, the Chinese Government requested the guidance of WHO and support for 13 clinical trials of integrated treatment with TCM and Western medicine for SARS patients. The Nippon Foundation provided the financial support for WHO to organize an International Expert Meeting on Review of Treatment of SARS by Traditional Chinese Medicine, and the Integration of Traditional Chinese Medicine with Western Medicine, in Beijing, China from 8 to 10 October 2003. Sixty-eight experts from seven countries including Hong Kong SAR, Japan, the Netherlands, the People's Republic of China, Thailand, Viet Nam and the United States of America, attended the meeting (Annex 1: list of participants).

The participants reviewed and evaluated the 13 research reports one by one (10 were from the People's Republic of China, Reports 1-10, and three from Hong Kong SAR, Reports A-C), covering the areas of clinical treatment, convalescence and prevention. After 3 days of discussion, the participants recognized the contribution made by the TCM professionals in providing treatment to SARS patients under very trying conditions. In addition, they had carried out the prospective clinical research in such a way as to produce fruitful results and accumulated a substantial amount of data and valuable experience. Subsequently, the reports were modified to reflect the discussions and comments made during the meeting.

Results of research based on the level of evidence

The research data and findings were reviewed and debated at the meeting and the recommendations of the experts were divided into three levels as described below.

First level
There were sufficient data in the clinical reports to show that integrated treatment with TCM and Western medicine for patients with SARS is safe.

Second level
Of the reported trials, only two clinical trials included patients who were randomly selected for the studies, the others were prospective cohort studies or retrospective studies. The experts considered that the data were insufficient although it was concluded that there could be potential clinical benefits from integrated treatment with TCM and Western medicine for patients with SARS. Such potential benefits include the alleviation of fatigue, shortness of breath and other clinical symptoms; facilitation of lung inflammation absorption; reduction of the risk of oxygen desaturation and the stabilization of abnormal fluctuation of oxygen saturation in the blood; reduction in the dosage of glucocorticoid and antiviral agents (and therefore in their associated side-effects) and reduction of cost (treatment with TCM alone costs less than treatment with Western medicine alone).

Third level
The experts noted that the data in the reports were inconclusive. An example of this is the clinical observation that the mortality rate is lower for the patients treated with integrated TCM and Western medicine than for those treated with Western medicine alone. As the diagnosis of SARS is very difficult to confirm, and some cases may be misdiagnosed, this could lead to a lower recorded mortality rate. In the prevention studies, the response rate to the questionnaires was only 40% among those subjects who had taken the prevention formula; this was too low to enable an accurate assessment of its effects. In the study on convalescence, the comparison was made between only two groups, one treated with TCM and one with exercise. There was no comparison group that received neither treatment nor exercise programmes.

Utilization of the document

SARS is a newly identified human infection caused by a corona virus unlike any other known human or animal virus in its family. The analysis of epidemiological information obtained from the sites of the outbreak of SARS is still underway, but the overall case fatality ratio is known to approach 11%, although the rate among the elderly is much higher.

Currently, the major challenges for the treatment of SARS are:
- the source of the SARS virus and mode of transmission are still not well understood;
- there are problems with diagnostic tools;
- there is no effective treatment; and
- there is no vaccine for SARS.

The above-mentioned difficulties and challenges have motivated national authorities, health workers and scientists to explore the potential of complementary treatment.

The results of research on integrated treatment with TCM and Western medicine showed that it is safe and that it also has some potential clinical benefits. Therefore, the experts suggested that records of such experience could serve as reference material for treatment of SARS in the future.

This publication is intended to:
- share experience in the complementary treatment of SARS patients;
- share the experience of clinical studies in the field of traditional medicine for treatment of SARS between the physicians and researchers; and
- to further encourage and promote the quality of research in the field of traditional medicine

It must be emphasized that the purpose of this document is to report on some clinical studies on treatment and prevention selected by the Chinese government, and to record the review of these studies by an international meeting of experts. Only national health authorities have the right to determine what treatment for SARS can be recommended.

Please note that the reports contained in this document were originally written in Chinese, therefore much of the specific terminology and medical descriptions are

direct translations of the original text. It is particularly the case for terms regarding Traditional Chinese medicine though this applies to Western medical terms as well. At the moment there is no standardized international English terminology for Traditional Chinese medicine. WHO is currently working on developing standard terms in English for Traditional Chinese medicine. It is not the scope of this document to propose terminologies or descriptions in the field of Traditional Chinese medicines or SARS. If clarification of anything contained within the reports is necessary, it is recommended that the original reports be referenced.

Report of the International Expert Meeting to review and analyse clinical reports on combination treatment for SARS

Background

Beginning in November 2002, severe acute respiratory syndrome (SARS) spread to 32 countries and areas, reaching a peak between April and May 2003. Up to 7 August 2003 the total number of cases was 8422, of which 5327 occurred in the People's Republic of China, 1755 in China, Hong Kong Special Administrative Region (Hong Kong SAR), 655 in China, Province of Taiwan, 251 in Canada and 238 in Singapore. The average mortality rate was 11%. In China the mortality rate was 7%, in Hong Kong SAR, 17% and in China, Province of Taiwan, 27%. The mortality rates in the other countries were 17% in Canada and 14% in Singapore.

SARS not only had great impact on the global public health system and revealed a general lack of preparedness for handling an outbreak of severe infectious disease, but it also prompted the readjustment and improvement of the existing public heath system infrastructure for fighting against epidemics in all countries and areas, including China.

SARS had a direct impact on the economic situation of the world, especially on the tourism industry, its influence surpassing that of any outbreak of typical influenza. Business in the epidemic-affected areas was almost paralysed and tourism in the surrounding areas was also affected. In Asia alone, a total of US$ 18 billion of tourism revenue was lost. The impact of SARS also spread to other areas of society and the economy.

The Chinese government took the epidemic extremely seriously and adopted decisive measures, making centralized arrangements to fight SARS using appropriate precautions and sound scientific methods. The State Administration of Traditional Chinese Medicine (SATCM) of China established the Working Group on the Treatment of SARS by Traditional Chinese medicine (TCM) to make overall arrangements to coordinate and provide leadership for developing clinical treatment and conducting scientific research on the application of TCM in the treatment of SARS. On 11 April 2003, SATCM, on the basis of its summing up of the experiences gained in Guangdong Province, formulated and issued the *Technical scheme on the prevention and treatment of SARS with TCM* (provisional), which was subsequently revised twice (on 19 April and 11 May 2003). At the beginning of June 2003, the *Recommendation on the treatment of SARS at the convalescence period* was published. The issuance of technical guidance has played an important role in the prevention and treatment of SARS by TCM. In early May 2003, at the invitation of the Hospital Authority of Hong Kong SAR, TCM experts were sent from Guangdong to Hong Kong SAR to participate in clinical research on SARS treatment using integrated TCM and Western medicine.

It is estimated that TCM practitioners participated in the treatment of SARS in 102 of the 195 SARS-specific hospitals in the People's Republic of China. Ninety-

six TCM hospitals sent 2163 professionals to 93 SARS-specific hospitals. Among the 5327 confirmed SARS cases, 3104 (58.3% of the total SARS patients in China) received TCM intervention.

SATCM immediately initiated basic and clinical research projects on integrated TCM and Western medicine for the treatment of SARS. A total of 21 research projects were established. Local governments in Beijing, Guangdong, Shanghai and Tianjin also established similar research projects.

The prevention and treatment of SARS poses great challenges. Firstly, SARS is a completely new infectious disease, so there is a lack of scientific knowledge. The research results acquired thus far have not produced methods for making an early diagnosis of SARS in order to reduce its spread. Secondly, there is still no specific treatment for SARS. The use of high dosages of antiviral drugs and glucocorticoids is controversial because serious side-effects have been noted during the treatment process. Summarizing the experiences and potential benefits of TCM in treating SARS may be a productive way to find effective approaches for the prevention and treatment of SARS.

The WHO International Expert Meeting to Review and Analyse Clinical Reports on Integrated Treatment for SARS hosted by WHO and SATCM was held from 8 to 10 October 2003 in Beijing, People's Republic of China. Officers from WHO Headquarters, the Western Pacific Region and the China office, as well as 51 official representatives and 17 observers from Hong Kong SAR, Japan, the Netherlands, the People's Republic of China, Thailand, Viet Nam and the United States of America attended the meeting. Officials from the Chinese Ministry of Health, National Commission of Development and Reform, Ministry of Science and Technology, Ministry of Education and SATCM attended the opening ceremony.

Dr Xiaorui Zhang, Coordinator of Traditional Medicine, Department of Essential Drugs and Medicines Policy, WHO, hosted the opening ceremony of the meeting; She Jing, Vice-Minister of Health and Head of SATCM, made a speech; and Dr Henk Bekedam, WHO Representative in China, gave the inaugural speech. Dr Bekedam acknowledged the importance of the efforts and contributions made by TCM in the treatment of SARS. The meeting elected Professor Weng Weiliang of the China Academy of TCM and Dr Vason Pinyowiwat of the Thailand Ministry of Public Health Department of Disease Control to serve as co-chairpersons; Hong Kong SAR representative Dr Andrew Yip and Professor Hong Jing of the China SATCM served as rapporteurs.

Objectives

The objectives of the meeting were to:

- Review and analyse clinical reports on the integrated treatment of SARS with TCM and Western medicine;
- Objectively evaluate the efficacy and safety of integrated treatment of SARS with TCM and Western medicine;
- Discuss the efficacy or underlying efficacy of treatment of SARS with integrated TCM and Western medicine; and
- Share experiences and knowledge of the treatment of SARS.

Review and analysis

The experts participating in the meeting reviewed and evaluated each of 13 reports (3 of which, Reports A-C, were from Hong Kong SAR), which were relevant to clinical treatment of SARS, convalescence and prevention research.

After 3 days of discussion, the participants recognized the contribution made by the TCM professionals working in the clinical and research fields in providing treatment to many SARS patients in an extremely dangerous and urgent situation, while at the same time carrying out prospective clinical research that produced fruitful results and accumulating a considerable amount of data and experience.

The experts recognized the difficulties and challenges in conducting research on the treatments of SARS while the epidemic of this new disease was spreading. Due to the relative scarcity of medical resources and the heavy clinical workload, clinical research on SARS faced difficulties never previously encountered. The researchers nevertheless made every effort to improve the research design to assure quality and reduce bias.

The experts recognized that integrated treatment by TCM and Western medicine for SARS is generally safe. The following potential benefits were also recognized:

- alleviation of clinical symptoms such as fatigue, shortness of breath and tachypnoea among others;
- facilitation of absorption of lung inflammation;
- reduction of the risk of oxygen desaturation and the stabilization of abnormal fluctuation of oxygen saturation in the blood;
- promotion of normalization of levels of peripheral blood lymphocyte and increase in levels of T cell subgroups;
- decrease in the dosage of glucocorticoid and antiviral agents and consequently in their associated side-effects;
- decrease in the incidence of abnormal levels of alanine aminotransferase (ALT), lactate dehydrogenase (LDH) and blood urea nitrogen (BUN), suggesting that integrated treatment with TCM and Western medicine is safe;
- the cost of treatment by TCM only is lower than that of treatment with Western medicine.

The following clinical observations were also noted:

- A group of patients at the early stage of SARS treated only with TCM all recovered without the need for glucocorticoid, antiviral agents, antibiotics or immunomodulators and were discharged from hospital.
- For those cases with comparable age, disease severity and underlying disease, analysis showed that the mortality rate was lower for the patients treated with integrated TCM and Western medicine than for those treated with Western medicine only.
- No SARS cases occurred among health care workers exposed to SARS patients and who had taken TCM for prophylaxis.
- During the convalescence period, treatment with TCM improved physical strength, alleviated clinical symptoms and decreased lung inflammation.

These last two situations are unique in that no specific treatments with Western medicine were evaluated for these cases so no comparison can be made.

Recommendations

The following recommendations were made by the experts who attended the meeting:

- According to the 13 clinical reports, treating SARS with integrated TCM and Western medicine is safe, provided that treatment is applied according to TCM principles; the potential benefits may be greater if treatment is started at an early stage.
- Continued follow-up of SARS patients is needed and the long-term effects of various treatments should be observed and compared.
- Design of clinical research projects would be further improved by paying attention to the clinical features of SARS and the individualized diagnosis and treatment principles of TCM, while strengthening the quality control of clinical research in order to minimize bias.
- Improve epidemiological research on SARS and its treatment schemes and increase the efficacy of treatment with integrated TCM and Western medicine. Research and develop effective TCM treatments and perfect quality control standards.
- Strengthen research on health economics, especially the evaluation of the effectiveness of prevention.
- Fully utilize TCM resources by bringing TCM into the clinical treatment system for public health emergencies, establish research networks, prepare plans for responding promptly to SARS outbreaks and for conducting research, and strengthen staff training.
- The experiences of treating SARS with integrated TCM and Western medicine described in the 13 clinical reports can serve as a reference for other countries in developing strategies for preventing and treating acute epidemics.

The experts who attended the meeting reached consensus that while the government and health workers of different countries are implementing clinical

treatment of SARS, they should first reinforce preventive and protective measures to reduce all nosocomial transmission.

Recommendations to WHO

Experts made the following recommendations to WHO:

- Continue to support research to improve trial design and implementation for traditional medicine in treating SARS and other diseases.
- Provide and support training courses, facilitate the sharing of experience and information on treatment of SARS with integrated TCM and Western medicine.
- Publish research relating to treatment of SARS with integrated TCM and Western medicine.

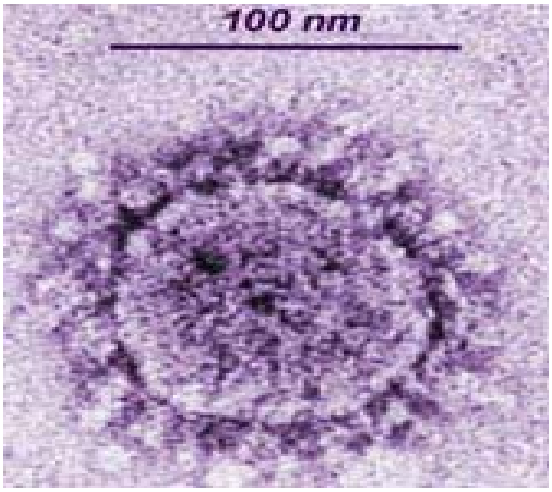
Report 1
Clinical research on treatment of SARS with integrated Traditional Chinese medicine and Western Medicine

Clinical Research Task Force for Treatment of SARS with Integrated TCM and Western Medicine [1]

Background

In November 2002, cases of an atypical pneumonia with serious life-threatening respiratory symptoms and having an unknown cause appeared in the Guangdong province of China. The illness soon spread to over 30 countries and areas. In February 2003, the World Health Organization (WHO) named this illness "severe acute respiratory syndrome" (SARS). It was later discovered that the causative agent is a new variation of corona virus (*1–6*) (Fig. 1). The spread of SARS represented a tremendous threat to social life, the economy and public health. Various countries around the world took diverse measures in response to the threat of SARS and developed comprehensive prevention strategies based on Western medicine. The spread of the disease had been brought under control by July 2003.

Fig. 1. The SARS virus



[1] State Administration Of Traditional Chinese Medicine (SATCM), Beijing, People's Republic of China

Epidemiology

Global picture

The first case of SARS outside China was reported in Viet Nam in November 2002; the epidemic had spread beyond mainland China to Canada, China, Hong Kong Special Administrative Region (SAR) and Singapore by March 2003. WHO issued a global warning for SARS on 12 March 2003. The global SARS epidemic peaked in April and May 2003. According to the statistics (7), during the outbreak of SARS from 1 November 2002 to 7 August 2003, there were 32 countries and areas in the world that had reported cases of SARS (a total of 8422 cases) (Fig. 2). The global case fatality rate was 11%, and Fig. 3 shows the case fatality rate for each country or area. The statistics produced by WHO indicated that SARS patients were predominantly middle-aged and young people, whereas there were fewer cases in the elderly and in children. The percentage of cases in health care workers was also high, but the percentages varied during the different epidemic periods.

Fig. 2. Number of patients with SARS worldwide on 7 August 2003

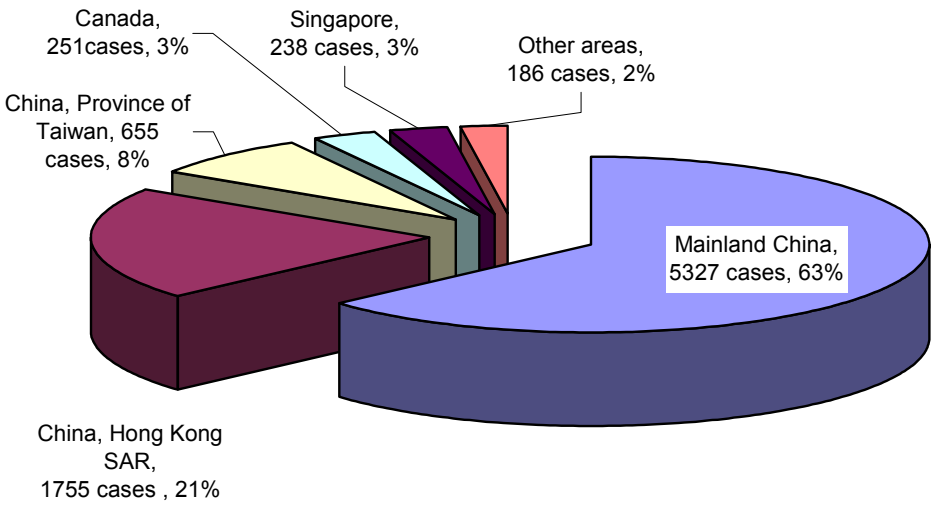
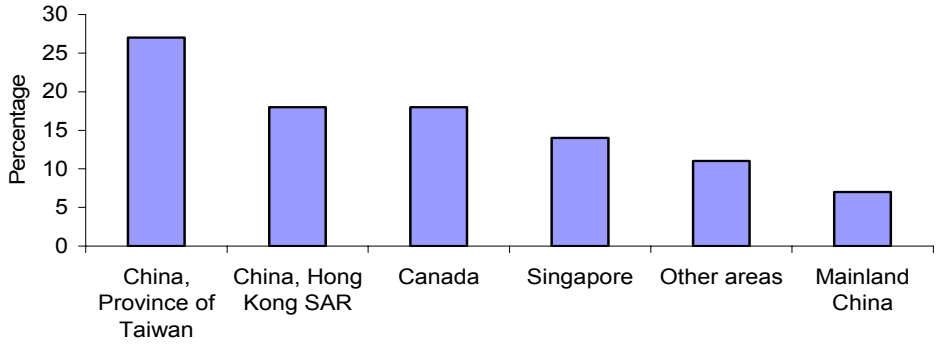


Fig. 3. Case fatality rate of SARS in specific countries and areas on 7 August 2003

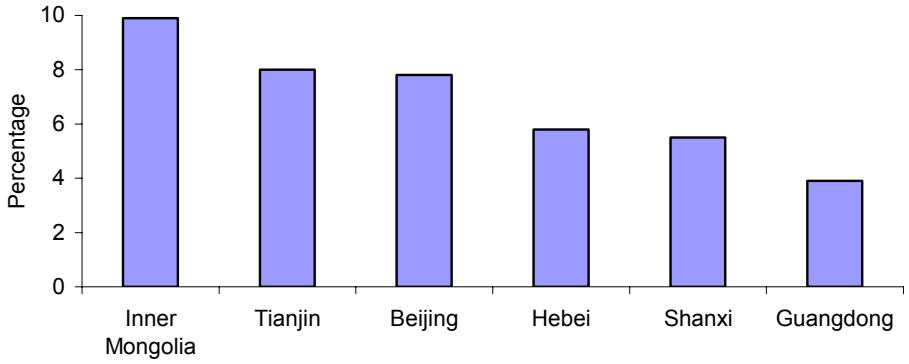


China

Based on the statistics from the Ministry of Health of the People's Republic of China (*8*) and WHO, during the period between 1 November 2002 and 7 August 2003, in particular between the second half of April and the first half of May, SARS had shown a tendency to break out and flare up in mainland China. The cases were distributed as follows: 2521 in Beijing; 1512 in Guangzhou; 448 in Shanxi; 282 in Inner Mongolia; 215 in Hebei; and 175 in Tianjin.

By 14 July 2003, the SARS case fatality rate in mainland China was 7%, lower than that of the rest of the world (Fig. 3). Fig. 4 shows the case fatality rate in different areas of mainland China (*8*).

Fig. 4. Case fatality rate from SARS in different areas of mainland China on 14 July 2003



Most of the SARS patients in mainland China were middle-aged and young people. The numbers of elderly patients and children were relatively low. Patients had many different occupations. During part of the peak of the outbreak from 26 April to 30 April 2003, 19.6% of the SARS patients were health care workers whereas in Hong Kong SAR, the percentage was 22%.

Clinical symptoms

Symptoms and signs

The onset of the illness is sudden with fever as the primary symptom. The body temperature is usually higher than 38 °C, and the patients have headache, aching joints, muscle pains and fatigue. There are also symptoms of feeling chilly and diarrhoea, but there are no upper respiratory catarrhal symptoms. Often there is just dry cough, with a little phlegm, occasionally streaked with blood. There might be a feeling of tightness in the chest, with serious conditions such as rapid breathing or obvious respiratory distress. Some of the patients have some wet rale in breathing or signs of consolidation in the lungs. A few patients do not have fever as the primary symptom, especially those who have had operations or recent underlying disease.

Laboratory examinations

The white blood cell count in the peripheral circulation is normal or even decreased. The numbers of lymphocytes often decrease.

Chest X-ray examinations

The presence of different patch shapes, spots soakage shadow or net-shaped shadows is observed. The illness develops rapidly in some patients, and large areas of shadow are seen. There are usually changes in multiple lobes or bilateral changes, and the shadow shrinks and disperses slowly. The shadow in the lung may not be consistent with other symptoms.

Pathological characteristics

Pathological changes in the lungs
Both lungs show substantial pathological changes, engorgement and congestion; they show spots and massive acute diffuse lobe interstitial inflammation. Alveoli are filled with proliferative epithelial cells and exudative protein, mononuclear cells, lymphocytes and plasmocytes. There are hyaline membranes. Some alveolar exudation shows glomerulus-like organized pneumonic changes. A virus can be found in alveolar epithelial cells and mononuclear macrophages which look like SARS virus in size and shape.

Effects on the spleen and lymph nodes
Massive necrosis is seen in spleen lymph tissue and spot necrosis in lymph nodes.

Myelogenic haematopoietic tissue inhibition
Myelogenic haematopoietic tissue proliferation is slowed down, karyocytes are obviously decreased, especially the numbers of granulocytes and lymphocytes. However, numbers of erythrocytes are increased, and plasmocytes, mononuclear and polynuclear giant cells proliferate.

General effects
Degeneration and necrosis of cells are observed in lungs, liver, kidney, heart and adrenal gland (*9*).

Main challenges in the treatment of SARS

Difficulties in stopping the transmission and in early detection

The results of research on SARS did not help to stop the transmission of the infection. The main reason for this is the difficulty of preventing and detecting SARS at an early stage. Clinically, the diagnosis of SARS depends mainly on virus antibody detection, rather than virus isolation. However, the appearance of virus antibodies usually occurs during the later stage of the illness. Furthermore, the transmission mechanism in nature is still unknown. All these factors lead to tremendous difficulty in the diagnosis of SARS at an early stage.

Lack of safe and effective treatment

The value of the treatment of SARS with high doses of antivirals and glucocorticoid is still uncertain. Furthermore, serious side-effects of using large doses of hormone have already been noted. Therefore, research into a safe and effective SARS treatment is a priority. As part of this research, summarizing and using the potential advantages and experience of treatment with Traditional Chinese medicine (TCM) might offer a shortcut to curing SARS.

Influence of SARS on global health, tourism and the economy

SARS has had a significant impact on the global public health system, and has revealed the fragility of the current public health system in dealing with the occurrence of a severe epidemic disease. As a result, all countries and regions, including China, will need to make adjustments and improvements to their current public health systems.

SARS had a significant influence on the global economic situation, especially on tourism. The tourist industry in the epidemic areas was almost paralysed, and that in nearby areas was also affected.

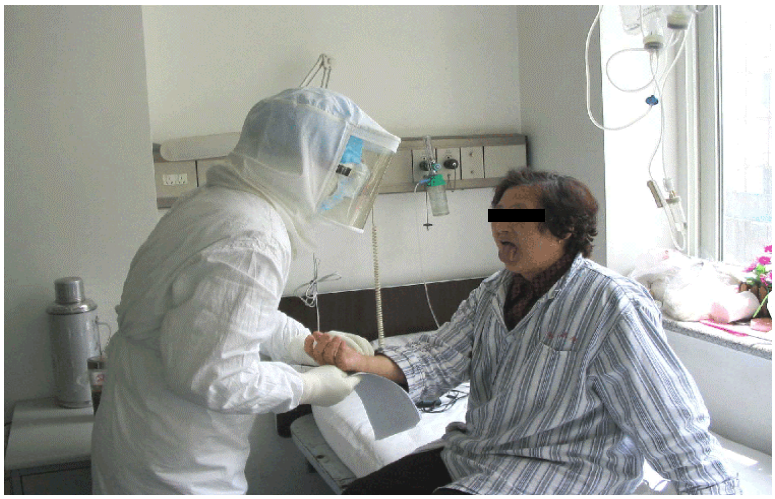
Recognition of SARS from the point of view of Traditional Chinese medicine

TCM is a complete systematic science based on the experience of disease prevention and treatment in China during the past several thousand years. It takes the holistic approach of "integration of nature and people", recognition of "testing and seeking for reasons", and diagnosis and treatment on the basis of an overall analysis of the illness and the patient's condition. Its core principles include the five-element theory and *yin* and *yang*, viscera-state doctrine, meridian doctrine, theory of the six exogenous factors causing illness, three-factor doctrine,

and four diagnoses and eight outlines. The theories of prevention are the essence of TCM, which advocates: "Sage doesn't treat but prevents disease, and doesn't solve disorder but prevents disorder" (*Plain questions/theories on four natures of adjustment*). As early as the sixteenth century, the method of human vaccination against smallpox was developed, which made a valuable contribution to vaccination worldwide. Chinese medicine considers that "health-*qi* inside the body can prevent the illness" (*Plain questions/theories on acupuncture*), and "if a person is sick, his *qi* must be weak" (*Plain questions/theories on fever*). Even when facing unknown causes, pathological changes and state of illness evolution principles, TCM is able to carry out a reasonable analysis on new epidemic diseases with difficult symptoms using its unique recognition theory systems. By taking the patient's pulse and knowing the characteristics of the illness, TCM could analyse the cause of disease and decide on an appropriate diagnosis and treatment.

SARS, despite being a new infectious disease, complies with the description that "epidemics of communicable diseases affect people irrespective of whether they are young or old, and the symptoms are similar", and is coincident with the symptoms of five infectious diseases illustrated in *Plain questions/theories on acupuncture*, as judged from the clinical symptoms of the disease and its evolution rules. It is characterized as a pestilence in TCM. There are many records about clinical diagnosis, treatment methods and experiences related to diseases such as pestilence, epidemic febrile diseases and enteric fever in the documentation on TCM. For instance, the *Treatise on pestilence* written by Wu Youke during the Ming Dynasty, *Treatise on epidemic febrile diseases* by Ye Tianshi during the Qing Dynasty, the *Treatise on differentiation and treatment of epidemic febrile diseases* written by Wu Jutong written during the Qing Dynasty and other such works are all monographs on the treatment of infectious diseases. Abundant details of medical cases and diagnosis and treatment experiences provide reference material and favourable conditions to facilitate studies on the diagnosis and treatment of SARS with TCM.

TCM states that pathogenic factors first invade lungs and then go upwards to the heart (See *Treatise on epidemic febrile diseases*). SARS is an epidemic disease. The cause is a virus, invading from the mouth or nose, with fever as the main symptom, accompanied by weakness, dry cough and difficulty in breathing. The pathogenicity comes from the virus gathering in the lung, phlegm blocking the *qi* of the lung and weakened *qi* and *yin*. The onset of the disease is rapid with serious symptoms; it spreads quickly, locates in lung, and affects the heart, kidney, stomach and other key organs. The illness is treated according to different stages and different symptoms, stressing that the illness is driven out and the body's resistance is strengthened, and on the basis that preventing transmission and deterioration can have worthwhile results.



Treatment with integrated Traditional Chinese medicine and Western medicine

General situation

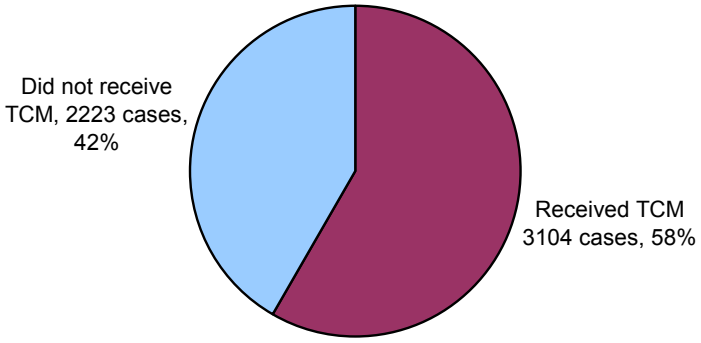
Since the outbreak of SARS began, the Chinese government has given unified orders and deployment of resources. The SATCM and various provincial and city TCM management departments have used the advantages of TCM in prevention, treatment, and aiding recovery from illness with unknown cause, and have participated in the clinical care and scientific research.

Medical treatment

To strengthen the use of TCM to prevent SARS in various locations, the Administration organized a team of experts to develop the "*Tecnnical Scheme on the prevention and treatment of SARS with TCM*" on 11 April 2003. They further revised the prevention component of the programme on 19 April and the treatment component on 11 May 2003. At the beginning of June 2003, they also published the *Recommendation on the treatment of SARS at the convalescence period with TCM* based on the symptoms of the patients. They also included acupuncture as part of the treatment plan. The publication of these regimens played an important role in encouraging and helping the TCM community to participate in the prevention and treatment of SARS.

On the basis of incomplete statistics, it is estimated that 195 hospitals in mainland China are designated for the treatment of SARS patients. Of these, 102 hospitals have professional staff in the field of TCM participating in the treatment of SARS patients, accounting for 52% of all the designated hospitals. Ninety-six Chinese medicine hospitals have sent out 2163 medical personnel to 93 designated hospitals. Of the 5327 patients diagnosed with SARS across the country, 3104 cases received TCM treatment (Fig. 5).

Fig. 5. Percentage of 5327 patients with confirmed SARS in mainland China who received or did not receive treatment with traditional Chinese medicine



The clinical results of integrated treatment with TCM and Western medicine have received the close attention of medical practitioners both in the People's Republic of China and elsewhere.

Scientific research

After the outbreak of SARS, the SATCM initiated a research project that included basic research and clinical scientific investigation of SARS. At the same time, local government agencies at all levels also cooperated by setting up a number of research and development projects for the prevention and treatment of SARS with TCM. For instance, the Beijing area undertook 25 SARS-specific projects. Such projects have looked at clinical efficacy and safety evaluation, regimen optimization, basic features of the syndrome and so on, for both TCM and integrated Chinese and Western medicine in treating SARS.

Method of clinical research on treatment of SARS with integrated Traditional Chinese medicine and Western medicine

We reviewed nine representative studies, involving 777 cases, that evaluated the clinical effectiveness and safety of integrated treatment for SARS; the approaches taken are outlined below.

Study subjects

All the study subjects were inpatients with clinically diagnosed SARS. The diagnosis was based on the diagnostic criteria for SARS issued by the Ministry of Public Health of the People's Republic of China (namely, *Clinical diagnosis criteria for infectious SARS* (trial)) issued on 18 April 2003, and *Explanation of the revised edition of clinical diagnosis criteria for infectious SARS* (trial) issued on 3 May 2003). The clinical diagnosis was based mainly on the epidemiological history, clinical symptoms and physical signs, laboratory tests, chest X-ray examination and ineffectiveness of antibiotic treatment. In addition, the "atypical pneumonias" that might be caused by other pathogens were excluded and some of the cases were tested for serum antibodies.

Observation period

The observations were made from November 2002 to July 2003 when SARS was prevalent. The studies started at the time the patients were included in the groups for observation and continued until the course of treatment ended. Some of the cases were followed up for a certain period of time after they had been

discharged from hospital, so as to monitor their convalescence. The criteria for discharge from hospital after 3 May 2003 followed the relevant reference criteria issued on 3 May 2003 by the Ministry of Public Health of the People's Republic of China.

Research design
Two out of the nine studies were case–control studies using randomly allocated controls, and the remaining seven were prospective cohort studies or retrospective studies.

Therapeutic regimens
Before 11 April 2003, therapeutic regimens of TCM and integrated treatment developed in individual hospitals were adopted. After this time, the "integrated treatment" used was the TCM regimen for SARS recommended by the SATCM on 11 April 2003. After 3 May 2003, the therapy with Western medicine for SARS refers to the therapeutic regimens recommended by the Ministry of Public Health of the People's Republic of China.

Organization of implementation and quality control
Government agencies attached great importance to, and paid close attention to, the clinical studies of SARS by organizing researchers, integrating research resources and coordinating these studies. Importance was also attached to the study design and the establishment of the coordinated multicentre implementation network. Studies were coordinated through workshops and conferences. Multicentre facilities for quality control of clinical research data and real-time integrated analytical data were also set up. Appropriate standard operating procedures were developed for the studies; they covered the collection of clinical data, the collection of case report forms and data verification. By these means, the data management and quality control were strengthened.

Research results

Clinical symptoms

The analysis of the 524 SARS patients suffering from symptoms such as respiratory difficulty, is described in Report 2. The investigators made dynamic and longitudinal comparisons and analyses. They adopted the accumulative logistic model and the "mixed statistical process" using the SAS software package to study the difference in improvement of the symptoms between two therapeutic regimens. The regimens compared were integrated treatment with TCM and Western medicine, and treatment with Western medicine alone. The integrated treatment was found to be superior to the treatment with Western medicine alone in improving symptoms such as hypodynamia, shortness of breath and tachypnoea (p-values were 0.0343, 0.0457 and 0.0573, respectively). The observation on 63 SARS patients described in Report 7 showed that the severity of symptoms (headache, joint or muscular stiffness, cough, blood-tinged sputum, pectoralgia, poor appetite, nausea, vomiting, sweating, palpitations and some other symptoms) in the integrated treatment group in weeks 2 and 3, was obviously lower than that of the control group treated with Western medicine

alone. These findings show that treatment with integrated TCM and Western medicine was more effective than treatment with Western medicine alone.

Inflammation in the lungs

The study described in Report 2 suggested that when integrated treatment was administered to patients in the early stage of the disease (within 7 days of onset), the total scores of lung inflammation shown on the chest radiographs (4.40 ± 4.97, median 3.0) were significantly lower than those of the group treated with Western medicine alone (6.39 ± 6.48, median 4.5), and the difference was statistically significant ($Z = 3.32$; $p = 0.0004$) (Fig. 6). In the comparison of patients with severe SARS between the two treatment groups, the score in the integrated treatment group (5.30 ± 5.48, median 4.0) was also significantly lower than that (9.14 ± 7.24, median 6.0, $Z = 3.45$; $p = 0.034$) of the group treated with Western medicine alone (Fig. 7). However, among the patients with normal SARS, the difference between the integrated treatment group (3.99 ± 4.67, median 3.0) and the group treated with Western medicine alone (4.59 ± 5.22, median 4.0) was not significant ($Z = 1.17$; $p = 0.12$), which suggested that intervention with integrated treatment in the early stage of disease can help reduce lung inflammation and that this tendency was more pronounced in the patients with severe SARS.

Fig. 6. Total score (median) of lung inflammation on chest radiographs of patients within 7 days after onset of SARS

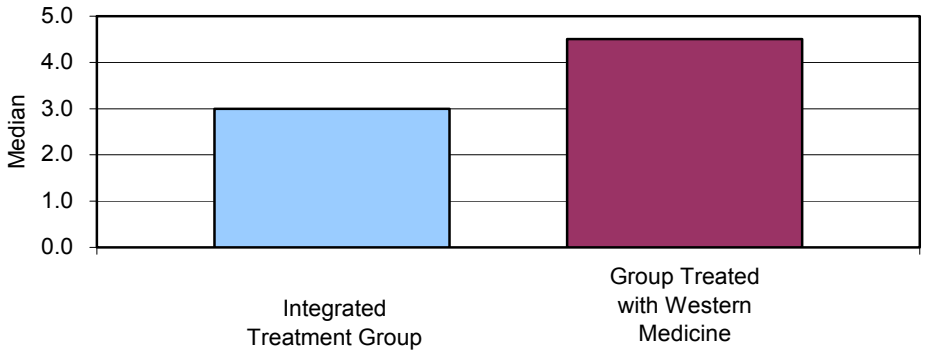
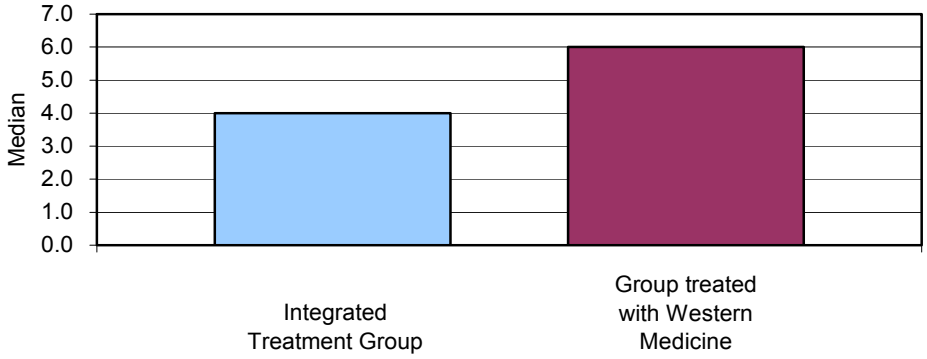
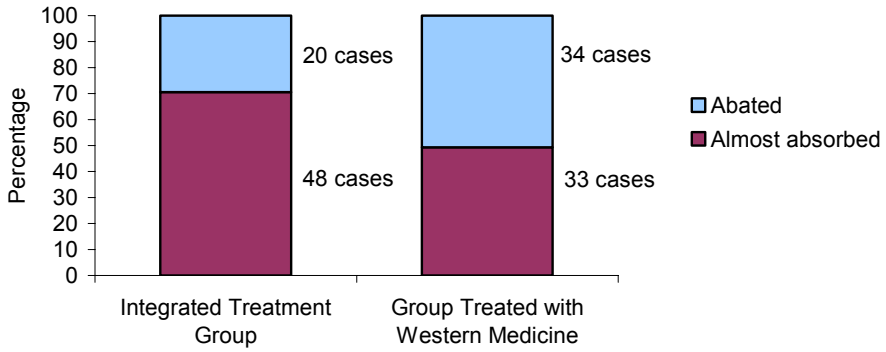


Fig. 7. Total score (median) of lung inflammation on chest radiographs of patients with severe disease treated within 7 days after onset of SARS



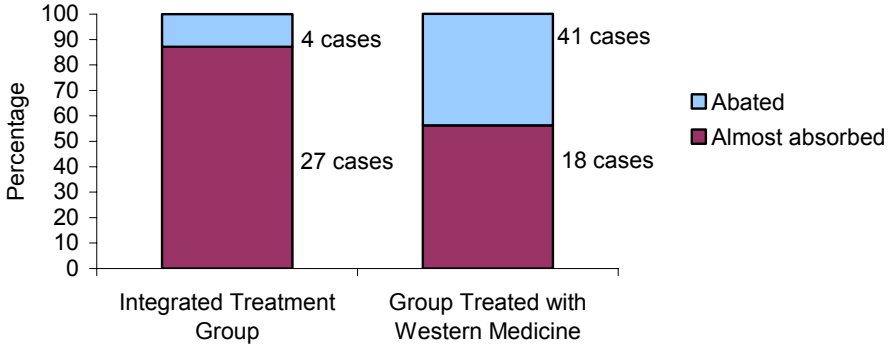
Report 9 described the observations on 135 SARS patients after a treatment period of 3 weeks. It was found that among the 68 patients included in the integrated treatment group, the inflammation in the lungs of 48 of the patients was almost absorbed and that of the remaining 20 patients was abated, whereas in the group treated with Western medicine alone, the inflammation in the lungs of 33 patients was almost absorbed and the remaining 34 patients showed no obvious improvement. The difference between the two groups was statistically significant ($p = 0.014$) (Fig. 8).

Fig. 8. Absorption of lung inflammation in 135 patients with SARS after 3 weeks of treatment (data from Report 9)



Report 7 describes the observations on 63 SARS patients. After a treatment period of 3 weeks the lung inflammation of 27 (out of 31) cases in the integrated treatment group was almost absorbed, whereas the corresponding number in the group treated with Western medicine was 18 (out of 32 cases); the difference between the two treatment groups was statistically significant ($p < 0.05$) (Fig. 9).

Fig. 9. Absorption of lung inflammation in 63 patients with SARS after 3 weeks of treatment (data from Report 7)



Report 5 described a study in which 11 patients with normal SARS were treated with TCM alone. The average absorption time for the lung shadows in nine of the patients was 14.56 ± 6.71 days, indicating that the treatment with TCM facilitated the absorption of lung inflammation.

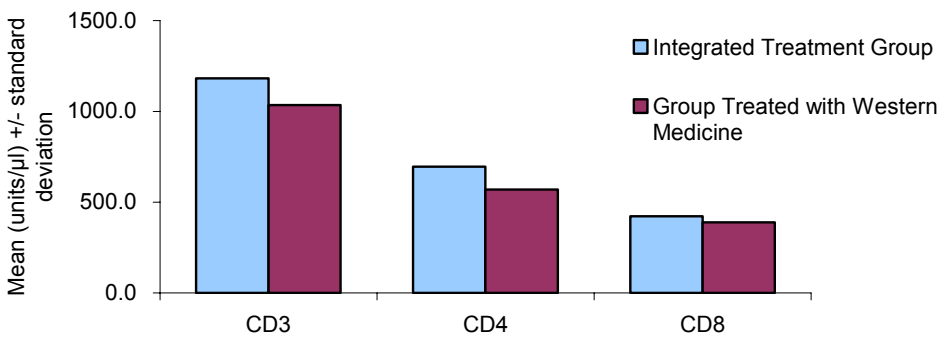
Degree of blood oxygen saturation

The study described in Report 2 used the logistic regression model with SAS statistical software in a study of 447 SARS patients. An analysis of the difference in blood oxygen saturation between the two treatment groups found that there was no significant difference between the groups after 0–2 days of treatment ($p = 0.4464$) when compared with that of the group treated with Western medicine alone. However, after a treatment period of 3–14 days, and after 15 days, the difference between the two groups was significant ($p = 0.0038$ and $p = 0.0007$, respectively), which indicates that the integrated treatment can reduce the likelihood of reduced blood oxygen saturation. More specifically, from day 3 to day 14, the odds ratio (OR) of both groups was exp (–0.6582) = 0.5178, and after day 15, OR = exp(–1.4164) = 0.2426. After adjustment for age, for the patients with normal SARS, the results of the integrated treatment and the treatment with Western medicine alone were not significantly different ($p = 0.4745$) in reducing the risk of low blood oxygen saturation. However, for the severely ill patients, the integrated treatment was superior to the treatment with Western medicine alone in reducing the risk of low blood oxygen saturation: OR = exp(–1.7173) = 0.18 ($p = 0.0001$). The observations recorded in Report 3 and other reports on the blood oxygen saturation of 45 patients with severe SARS on day 7, day 13 and day 23 suggested that the integrated treatment can help stabilize the abnormal fluctuations in blood oxygen saturation.

Immunological functions

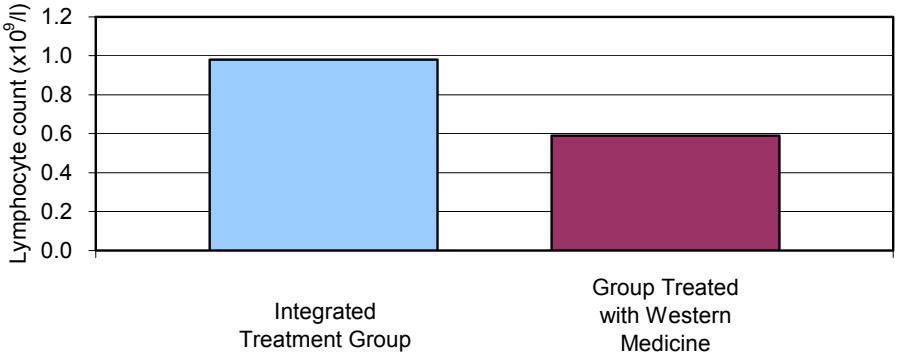
Report 9 was a study on the peripheral blood lymphocytes and T-lymphocyte subpopulations of 135 patients with SARS. The counts of peripheral blood lymphocytes and T-lymphocyte subpopulations in the integrated treatment group after 20 days of treatment (mean ± standard error of blood lymphocytes, CD3, CD4 and CD8 were 1.84 ± 0.12 × 10^9/l, 1182.48 ± 67.24 units/μl, 695.21 ± 46.33 units/μl and 421.65 ± 27.30 units/μl) exceeded those of the group treated with Western medicine alone (mean ± standard error of blood lymphocytes, CD3, CD4 and CD8 were 1.54 ± 0.14 × 10^9/l, 1034.38 ± 70.94 units/μl, 570.29 ± 40.36 units/μl and 389.81 ± 36.40 units/μl), and the p values were 0.458, 0.027, 0.034 and 0.006 respectively (Fig. 10).

Fig. 10. Peripheral blood T lymphocyte subpopulations (mean ± standard error × count/μl) in 135 patients with SARS after 20 days of treatment (data from Report 9)



Report 8 compares the counts of lymphocytes before and after the treatment of 35 (out of 47) SARS patients who had abnormal counts of lymphocytes in peripheral blood before treatment. The results showed that the increase in the count of peripheral blood lymphocytes ($0.98 \pm 0.65 \times 10^9$/l) in patients in the integrated treatment group before and after treatment was greater than that ($0.59 \pm 0.34 \times 10^9$/l, $p = 0.0332$) of the group treated with Western medicine alone. For the nine cases in the integrated treatment group and 10 in the group treated with Western medicine alone who had abnormally low CD3 levels before the treatment, after being treated for 3 weeks, the numbers of cases that had normalized were seven and two respectively ($p = 0.023$). Fifteen patients in the integrated treatment group and 13 in the group treated with Western medicine alone had abnormally low CD4/CD8 counts before the treatment, the numbers that had returned to normal after the treatment were 10 and three, respectively ($p = 0.03$) (Fig. 11). The number of patients in the integrated treatment group with T-lymphocyte subpopulations that had been normalized tended to be greater than that in the group treated with Western medicine alone.

Fig. 11. Differential values ($X \pm SD \times 10^9$ /μl) of peripheral blood lymphocytes in 47 patients with SARS before and after treatment



Administration of glucocorticoid

The analysis described in Report 2 on the dosage of glucocorticoid administered to 461 hospitalized SARS patients in the integrated treatment group showed that the average daily dosage of hormone (calculated on the basis of methylprednisolone) administered during the hospitalization period was 115.78 ± 87.51 mg/day with a median of 84.40 mg/day. The average daily dose administered to patients in the group treated with Western medicine was 130.78 ± 85.63 mg/day with a median of 115.33 mg/day. The dosage of hormone used in the integrated treatment group was obviously less than that in the Western medicine treatment group ($p < 0001$) (Fig. 12). Report 2 also showed that, of the 318 patients in the integrated treatment group and 206 patients in the group treated with Western medicine, the numbers of patients who had received antiviral drugs were 244 (76.7%) and 177 (85.9%), the numbers who had received antibiotics were 286 (89.9%) and 190 (92.2%), the numbers treated with glucocorticoid were 272 (82.9%) and 189 (96.4%), and the numbers who had received an immunopotentiator were 222 (69.8%) and 174 (84.5%) (Fig. 13). Except for antibiotics ($\chi^2 = 0.712$, $p = 0.374$), the difference between the use of antiviral drugs ($\chi^2 = 6.690$, $p = 0.01$), hormone ($\chi^2 = 4.529$, $p = 0.033$) and

immunopotentiator (χ^2 =15.544, p = 0.001) for the two treatment groups was significantly different, suggesting that the use of antiviral drugs, glucocorticoid and immunopotentiator in the integrated treatment group was lower than that in the group treated with Western medicine.

Fig. 12. The dosage of glucocorticoid administered to 461 patients with SARS during hospitalization (median mg/day)

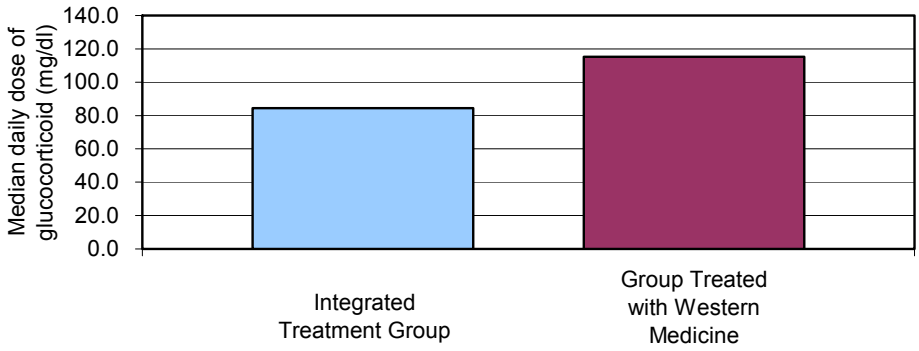
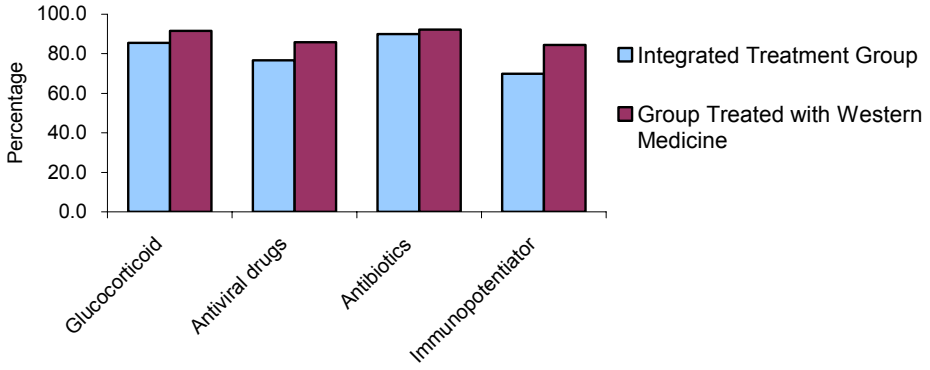


Fig. 13. Percentage of patients treated with glucocorticoid, antiviral drugs, antibiotics and immunopotentiator (data from Report 2)



Report 5 stated that 11 patients with normal SARS who were admitted to hospital and treated with TCM alone, without using hormone, recovered and were discharged from hospital. Report 4, describes how 34 SARS patients (including 20 severe cases and 14 normal cases) who received integrated treatment without hormone all recovered and were discharged from hospital.

Case fatality rate

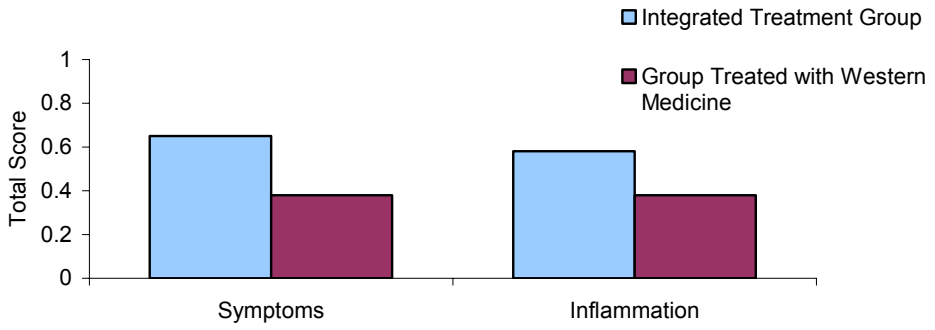
Report 2 gives details on the clinical outcome of 524 SARS patients. The investigators observed that there were no deaths in the group of 318 patients treated with integrated medicine, but seven out of the 206 patients in the group treated with Western medicine alone died (3.4%). The seven patients who died were 40 years old or more, and three of them had underlying diseases, three had none and the condition of the other was unclear. Report 9 described the final outcome of the treatment of 135 patients with SARS. It was reported that one of

the 68 patients in the integrated group died, and seven in the group treated with Western medicine alone died. Report 3 presented observations on 45 patients with severe SARS and showed that the case fatality rate was 20% (5/25) in the integrated treatment group and 30% (6/20) in the group treated with Western medicine alone. Report 7 followed 31 patients who received the integrated treatment, and the case fatality rate was 9.67% (3/31) after 3 weeks of treatment. The case fatality rate was 12.5% in the group treated with Western medicine alone: there were four deaths among the 32 cases).

Treatment during the convalescent stage

Report 10 presents observations on 85 patients convalescing from SARS over a period of 2–3 weeks. The investigators reported that the scores for improvement in the patients' symptoms after treatment with TCM recipes were superior to those obtained in the control group. (The total scores (mean ± standard error) for improvement of the symptoms in the TCM group and the control group before and after treatment were 0.65 ± 0.06 and 0.38 ± 0.14 respectively, $p < 0.05$) and TCM treatment was also more effective in improving lung inflammation. (The scores for relieving inflammation as judged from chest X-rays of the group that received TCM and the control group before and after the treatment were 0.58 ± 0.05 and 0.38 ± 0.08 respectively.) (Fig. 14).

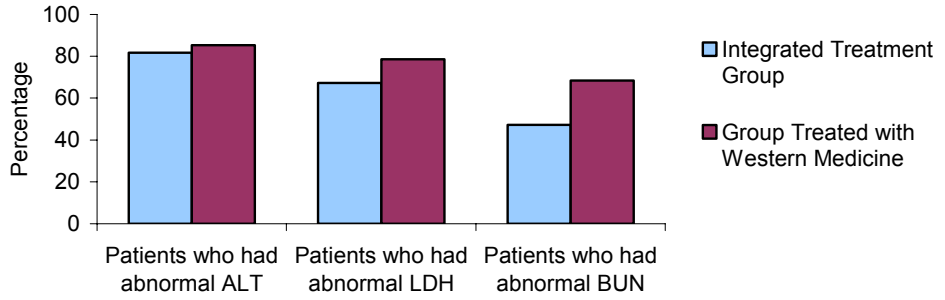
Fig. 14. Comparison of scores for symptoms and inflammation in 85 patients convalescing from SARS (mean ± standard deviation)



Alanine aminotransferase, lactate dehydrogenase and urea nitrogen

From observations conducted during the treatment of 524 SARS patients, the authors of Report 2 noted that the number and the incidence rate of patients whose alanine aminotransferase (ALT), lactate dehydrogenase (LDH) and blood urea nitrogen (BUN) levels were outside the normal range at least once in the group that received integrated treatment (318 cases) were 260 (81.8%), 214 (67.3%) and 150 (47.2%) respectively, whereas the number of cases and the incidence rate in the group treated with Western medicine alone were 176 (85.4%), 162 (78.6%) and 141 (68.4%), respectively (Fig. 15). These data show that the occurrence of abnormal increases in ALT, LDH and BUN in the group treated with Western medicine alone tended to be greater than that in patients in the integrated treatment group.

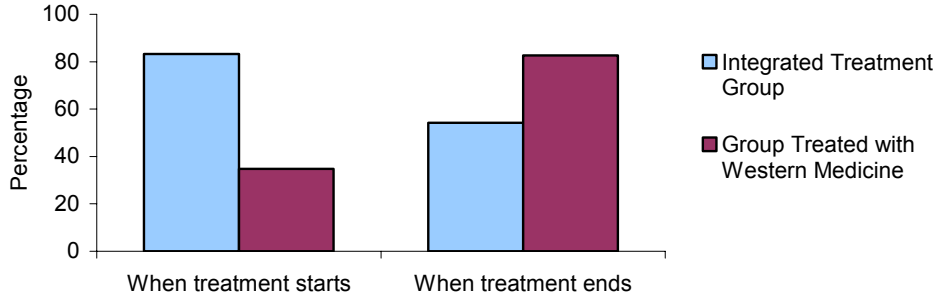
Fig. 15. Incidence rate of abnormal alanine aminotransferase, lactate dehydrogenase and blood urea nitrogen in 524 patients with SARS (data from Report 2)



ALT, alanine aminotransferase; LDH, lactate dehydnitrogen; BUN, blood urea nitrogen

The follow-up observation on 47 SARS patients described in Report 6 showed that, during the observation period, all the 47 patients showed an abnormal rise of ALT. The numbers of patients with abnormally elevated ALT in the integrated group and the group treated with Western medicine alone at the time when the treatment was started were 20 and eight respectively, and the numbers at the end of the course were 13 and 19 respectively (Fig. 16). The numbers of patients who had an abnormal rise in total bilirubin in the integrated treatment group and the group treated with Western medicine alone at the start of treatment were 11 and six respectively, and at the end of the course, only one patient in each group had an abnormally high concentration, which suggests that the integrated treatment for SARS is safe.

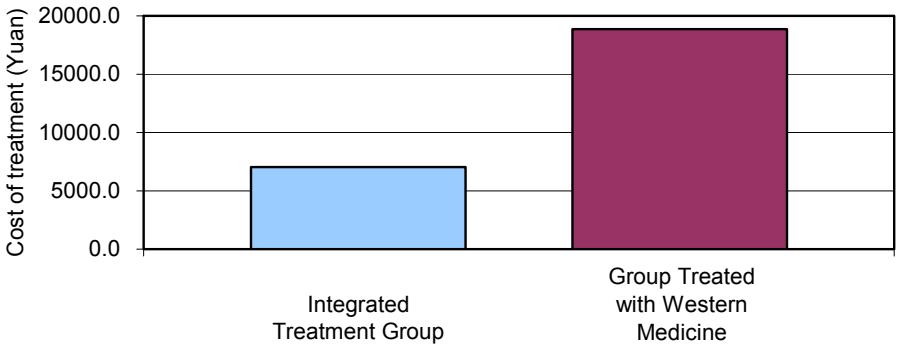
Fig. 16. Incidence rate of abnormal alanine aminotransferase in 47 patients with SARS before and after treatment (data from Report 6)



Cost of treatment

Report 5 stated that the average cost for the treatment of 11 SARS patients with TCM was 7 024.41 Yuan, whereas that for the treatment with Western medicine of concurrent cases with an identical state of illness was 18 867.36 Yuan (Fig. 17).

Fig. 17. Comparison of average cost (Yuan) for treating patients with SARS (data from Report 5)



Discussion

Relative advantages of treatment with Traditional Chinese medicine

There are certain advantages in treatment with TCM.

- Firstly, TCM is not targeted only at a specific etiology or a certain pathological link, but also at the pathological status of the patients at that particular time. Therefore, comprehensive readjustment was made through various angles, targets and channels to restore the balance of the body.
- Secondly, there are advantages in the differentiation of disease and the treatment. Based on the different symptoms of the patient, TCM enables the physician to adopt the most suitable principle, provide individual treatment and to administer medicine in accordance with the actual process and nature of the illness.
- Thirdly, there are advantages in the results of the treatment; TCM can relieve symptoms, promote absorption of lung inflammation, improve the degree of blood oxygen saturation, regulate immunological functions, reduce the required dosage of glucocorticoid and other Western medicines, and reduce case fatality rate, in addition to lowering the cost of treatment.

Problems with the research

Although the researchers tried their best to take measures to perfect the design and to reduce possible bias, the SARS studies were generally initiated urgently under the most severe conditions of the outbreak. A lack of medical resources meant the clinical workload was very heavy. The clinical research on SARS has encountered many difficulties that have not been met before in normal clinical research. These can be summarized as follows.

Choice of control group and random allocation of study subjects

In the clinical research on TCM, the choice of the control group and the testing group as well as the random allocation of cases to the different observation groups is always problematic. Some studies used random allocation of cases, but

most of the clinical studies were cohort studies or case–control studies. In the cohort and case–control studies, attention was paid to the choice of cases, to ensure the balance of factors other than the experimental factors in the different groups. Nevertheless, it is difficult to avoid potential bias when assigning patients to the different treatment groups and to ensure impartiality.

Loss to follow-up

To guarantee the timely quarantine and treatment of SARS patients, the Government Departments coordinated the arrangements for the admission and transfer of the patients in a unified way. This caused difficulties in following up the patients, leading to loss of some cases in the observation period. Clinical research on therapy with integrated TCM and Western medicine for SARS patients requires improved study designs.

Suggestions for further work

Improve understanding of, and scientifically evaluate the advantages of, TCM in treating acute and infectious diseases.

TCM and integrated therapeutics are safe and they have shown advantages over Western medicine alone in treating SARS. Clinical research has shown that TCM should be applied early in the course of disease and used rationally taking patients' individual differences into consideration. The research has also suggested that in the case of an outbreak of an acute and infectious disease such as SARS, attention should be paid to the advantages of TCM, so that integrated therapy with TCM and Western medicine can be applied.

Perfect emergency clinical treatment and the research network of TCM

It is recommended that the relevant authorities should improve, as soon as possible, the rapid feedback network of clinical TCM practice and research for use in emergency situations. Preparations should be made for large sample studies in the future in case of another outbreak of SARS. Further evaluation of the effectiveness and safety of TCM in treating SARS is desirable.

Share the experience of treating SARS with TCM

TCM is the accumulation of thousands of years of experience of the Chinese nation in fighting disease. In the face of unknown reasons for, or complicated pathological causes of, disease, traditional Chinese medical theory and treatment principles have obvious advantages. It will also enable the whole world to share the fruits of Chinese medicine culture, resources and the related industry.

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Report 2
Clinical efficacy of the treatment of SARS with integrated Traditional Chinese medicine and Western medicine: an analysis of 524 cases

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Background

Severe acute respiratory syndrome (SARS) is an acute respiratory infectious disease caused by a corona virus. The drugs used for the treatment of SARS include antivirals, glucocorticoid, antibiotics and immunomodulator. On the basis of the therapeutic experience accumulated in the treatment of similar diseases, most clinical experts consider that these drugs should be helpful in treating SARS, but lack sufficient evidence. The administration of herbal decoctions and injections is the characteristic system of therapeutics adopted in China. An issue of public concern is whether a therapeutic regimen integrating Western medicine with Traditional Chinese medicine (TCM) leads to improved clinical efficacy when compared with treatment of SARS with Western medicine alone. This report presents the results of research on the clinical curative effects by comparing 318 SARS patients who received integrated treatment with 206 patients treated with Western medicine alone.

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Method

Design

The study designs were randomized or non-randomized case–control studies.

Grouping of study subjects

Randomized distribution
Patients were grouped randomly by some clinical subcentres. The clinical subcentre represented the unit for the randomized grouping. Random numbers were generated by the application of an SAS software package in an independent data centre, and the clinical subcentres allocated patients randomly to the different treatment groups according to serial number.

Non-randomized grouping
Patients were distributed selectively by some clinical subcentres. When patients were assigned to the different groups, cases and controls were matched on sex, age, time of onset of disease, state of illness and therapeutic conditions.

Study subjects

The observation cases were inpatients admitted to the 11 designated SARS hospitals in the Beijing area from April 2003 to June 2003 who had been clinically diagnosed as having SARS.

Clinical diagnostic criteria for SARS

The diagnosis of SARS was based on the clinical diagnosis criteria of severe acute respiratory syndrome (proposed) promulgated by the Ministry of Health of the People's Republic of China. The diagnostic criteria for SARS promulgated on 3 May 2003 are listed below.

1. Epidemiological history
1.1 Having had close contact with SARS patients or belonging to one of the affected groups, or having obvious evidence of infecting others;
1.2 Having visited or resided in areas that have been reported to have SARS patients and secondary infection two weeks before being attacked by the disease.

2. Symptoms and signs
The onset of the disease is acute with high fever as the primary symptom, with a body temperature usually higher than 38 °C; sometimes the patients may have chills accompanied by headache, arthralgia, muscular aching, hypodynamia and diarrhoea; usually without catarrh of the upper respiratory tract; may cough, mostly dry cough with little sputum; may have blood-streaked sputum; may experience chest discomfort and patients with severe illness may suffer from accelerated respiration, shortness of breath or obvious respiratory distress. Physical signs in the lung are not obvious, and some patients may have some wet rale or signs of pulmonary consolidation.

Note: A few patients may not have high fever as the primary symptom. This is particularly true for those patients who have recently had an operation or who suffer from underlying diseases.

3. Laboratory tests

The white blood cell count in the peripheral blood is usually unchanged; lymphocyte count (LC) usually goes down.

4. Chest X-ray examination

Patchy and spot-shaped infiltration shadows or reticular change are present in the lung, and develop rapidly in some patients; changes are usually seen in several lung lobes or in both lungs, with shadows being absorbed and dissipated slowly; the lung shadow may not be consistent with the physical symptoms. If the examination result is negative, a re-examination should be done after 1 or 2 days.

5. Effects of treatment with antibacterial drugs

No obvious effects of treatment with antibiotics are seen and clinical diagnostic criteria comply with item 1.1, item 2 and item 4 or more, or items 1.2, 2, 4 and 5, or items 1.2, 2, 3 and 4.

Clinical diagnostic grouping of SARS

A diagnosis of severe disease was made if the following criteria were met:

- general symptoms of toxicity are obvious (persistent high fever for more than 48 hours, or hyperventilation, $PaCO_2$ < 35 mmHg, white blood cell count < 3.0×10^3;
- lesions on several lung lobes or lesions visible on chest radiograph that have increased in size by more than 50% within 48 hours;
- respiratory frequency greater than 28 breaths/minute and hypoxemia;
- patients aged over 50 years; and
- patients who already have underlying disease.

Patients were classified as critical if they met the following criteria:

- acute lung injury (ALI) or acute respiratory distress syndrome (ARDS);
- respiratory frequency > 28/min; arterial partial pressure of oxygen (PaO_2)/ (fractional concentration of oxygen in inspired air (FiO_2) < 300 (for instance, PaO_2 < 60 mmHg when indoor air was inhaled; PaO_2 < 150 mmHg when air with an oxygen level of 50% was inhaled);
- PaO_2 < 70 mmHg or blood oxygen saturation (SpO_2) < 93% when oxygen is inhaled at 3–5 l/min;
- diffuse patchy image on chest radiograph of both lungs;
- shock; and
- multiple organ dysfunction syndrome (MODS).

Patients were classified as having normal SARS if they did not meet the criteria listed above for severe or critical disease.

Inclusion criterion

All the cases that met the diagnostic criteria for SARS, with the approval of the patients concerned, were eligible for inclusion.

Exclusion criteria

Patients were not eligible for inclusion in the study if:

- they failed to meet the diagnostic criteria for SARS;
- they were pregnant or lactating; or
- they did not consent to participate in the study.

Therapeutic regimens

For treatment with Western medicine, the therapeutic regimen for SARS recommended by the Ministry of Health was adopted. This consisted of supportive treatment with glucocorticoid, antiviral drugs, antibiotics, immunomodulator and so on. For treatment with TCM, the therapeutic regimen for SARS recommended by the Beijing Municipal Administration for TCM was adopted, and the treatment was based on overall analysis of the disease at different stages (e.g. high-fever stage or coughing and gasping stage). The treatment was based mainly on herbal decoctions with the support of injections or Chinese patent drugs whenever appropriate.

Treatment with Western medicine as recommended by the Ministry of Health, People's Republic of China

Monitoring

Most of the patients were in the progressive stage within 14 days after the onset of disease. The change of the state of the illness therefore had to be observed closely and the factors to be monitored included the symptoms, body temperature, respiratory frequency, SpO_2 or arterial blood gas analysis, haemogram, chest radiograph (time interval for early-stage re-examination not exceeding 2–3 days), function of heart, liver and kidneys.

Regular and specific treatment

Treatment included the following:

- bed rest and avoidance of fatigue and physical exertion;
- avoidance of violent coughing; patients with severe cough were treated to relieve the cough, and patients who coughed up sputum were treated with an expectorant;
- patients with a fever and a body temperature exceeding 38.5 °C were offered antipyretics and analgesics, and patients with high fever were cooled down physically. Aspirin was not administered to children as it can cause Reye Syndrome;
- appropriate treatment was provided whenever there was any impairment of the functions of the heart, liver, kidneys or other organs; and
- nutritional support was provided and attention paid to the water–electrolyte balance.

Shortness of breath

Patients who were short of breath or who had a $PaO_2 < 70$ mmHg or $SpO_2 < 93\%$ received continuous oxygen inhalation through a nasal tube or face mask.

Treatment with glucocorticoid
Indications for glucocorticoid treatment included:

- patients with severe symptoms of toxicity and with high fever that could not be allayed after 3 days of treatment;
- an increase in the size of the lung shadow of more than 50% in 48 hours;
- acute lung lesion or appearance of acute respiratory distress syndrome (ARDS). The usual dose for an adult was equal to 80–320 mg/day of methylprednisolone: the dose was increased if necessary, bearing in mind that it is advisable not to take a high dose for too long a period. The exact dose and the course of treatment were adjusted according to the state of the illness, and the dose was gradually reduced and stopped when the condition of the patient improved or once the shadow on the chest radiograph had been absorbed to certain extent. Hormones with a short half-life were recommended.

Prevention and treatment of secondary bacterial infection
Appropriate antibiotics such as quinolones were used as appropriate, depending on the clinical situation.

Treatment with antivirals
The use of antiviral drugs could be considered in the earlier stage of the illness.

Drugs to enhance immunological function
Drugs enhancing immunological functions could be considered for the treatment of severe cases.

Treatment for SARS with Traditional Chinese medicine

This treatment was developed by experts authorized by the Beijing Municipal Administration for TCM, and is recommended by this body.

For patients whose major symptom is high fever
Main symptoms: fever, dry cough, headache, muscular stiffness, inertia, thirst, thin white or white greasy fur on the margin and tip of the tongue, slippery pulse (a pulse coming and going smoothly, feeling slick to the finger like beads rolling on a plate, indicating excess heat syndrome, phlegm and dyspepsia as well as pregnancy).

Principles of treatment: to clear away heat and toxic materials; dispel the "wind" and ventilate the lung

Prescription:
Parched ephedra 5 g, almond 12 g, fossilia chitonis 45 g, Rhizoma Anemarrhenae 10 g, honeysuckle flower 15 g, Fructus Forsythiae 12 g, parched Fructus Gardeniae 12 g, Fructus Scutellariae 12 g, perilla leaf 10 g, Herba Artemisiae 15 g, Radices Puerarire 15 g, pseudostellaria root 15 g.

To be decocted for oral administration; each prescription is decocted into two bags (150 ml/bag); to be taken three times a day, one bag each time.

With the exception of the first, the preparations listed below are prepared with the above herbs to treat patients with the following specific symptoms:

- For patients with persistent high fever: *angongniuhuangwan* with water.
- For patients with nausea and vomiting: plus 10 g of bamboo shavings, 10 g of Rhizoma Pinelliae and 10 g of ginger.
- For patients with diarrhoea: remove fossilia chitonis and add 12 g of Herba Pogostemi, 12 g of Herba Eupatorii and 10 g of Rhizoma Atractylodis.
- For patients with poor appetite: plus 30 g of three scorched herbs (scorched germinating barley, hawthorn fruit and medicated leaven).
- For patients with severe cough: plus 12 g of Folia Eriobotryae and 12 g of Radix Asteris

Houttuynia injection, *qingkailing* or *xingnaojing* injection and *shenmai* injection can be administered by intravenous drip.

For patients whose major symptoms are cough and shortness of breath

Main symptoms: cough, shortness of breath, chest distress, asthma, thirst, sweating, feeling listless and inert, may or may not be accompanied by fever, cyanosis, flaccid tongue with decreased saliva, feeble pulse.

Principles of treatment: to supplement *qi* and nourish the *yin*, remove pathogenic heat and promote blood circulation, relieve cough and asthma.

Prescription:

Radix Panacis Quinquefolii 15 g (to be decocted separately and mixed with other decoction before use), lilyturf root 10 g, Fructus Schizandrae 10 g, and Fructus Corni 12 g, Semen Lepidii 15 g, Radix Asteris 15 g, Folia Eriobotryae 12 g, and Guangdong earthworm 12 g, Radix Salviae Miltiorrhizae 12 g, Radix Paeoniae Rubra 12 g, Chinese globeflower 8 g, Fructus Scutellariae 10 g, Trichosanthes kirilowii Maxim 15 g.

To be decocted for oral administration; each prescription is decocted into two bags (150 ml/bag); to be taken three times a day, one bag each time. The following may be taken in addition to the decoction described above.

- For patients with symptoms accompanied by high fever: plus 30–60 g of unprepared gypsum, 15 g of abrotanum, 0.6–1.2 g of cornu saigae tatariace talcum; or the above decoction may be taken with *angongniuhuangwan*.
- For patients with poor appetite: plus 30 g of three scorched herbs (scorched germinating barley, hawthorn fruit and medicated leaven) and 10 g of ventriculi galli mucosa.
- For patients with bradycardia: plus shenfu injection for intravenous injection; or plus 10 g of processed Radix Aconiti Carmichaeli, 6 g of Rhizoma Zingiberis and 3 g of asarum herb.
- For patients with copious sputum: plus 30 g of herba nouttuyniae, 30 g of golden buckwheat rhizome and 10 g of Radix Platycodi.
- *Shenmai* injection or *shengmai* injection can be used selectively in an intravenous drip.

For patients at the convalescent stage

Main symptoms: chest distress, shortness of breath, sweating, palpitations, fatigue, occasional cough, loss of appetite, abdominal distension or loose stool, flaccid tongue with white or greasy fur, slippery and thready pulse.

Principles of treatment: to supplement *qi*, nourish the *yin* and strengthen the spleen and stomach.

Prescription:
Pseudostellaria root 15 g, lilyturf root 15 g, Radix Adenophorae 15 g, parched Atractyloides macrocephala 15 g, honey-fried loquat leaf 15 g, Semen Amomi 6 g, three scorched herbs (scorched germinating barley, hawthorn fruit and medicated leaven) 30 g, Radix Astragli 15 g, Radix Puerarire 15 g, Radix Salviae Miltiorrhizae 15 g, Pericarpium Citri Reticulatae 6 g, Rhizoma Polygonati 15 g.

To be decocted for oral administration; each prescription is decocted into two bags (150 ml/bag); to be taken twice a day, one bag each time.

For patients with abdominal distension: replace Radix Adenophorae with 6–10 g of Radix Saussureae and 5g of round cardamon seed.

Chinese caterpillar fungus mycelium preparation or rhodiola root preparation can be administered.

Physicians should tailor the treatment with TCM to fit the specific needs of the individual patient and the different stages of the disease.

Patients characteristics and duration of observations

Records included demographic characteristics (age and sex distribution), basic clinical features of the onset of disease (symptoms, physical signs and results of laboratory examinations), treatment (e.g. administration of hormone, antibiotics, immunomodulator and TCM, and use of a respirator), recent clinical outcome (discharged from hospital, transferred to another hospital or died) and so on. The observation started from the time when the patients were included in the group and continued until they were discharged from the hospital or had died.

Quality control

The following measures were taken to strengthen the quality control of the research process:

- selection of suitable clinical centres and appropriately qualified researchers and clinicians to participate in the studies;
- centralized training of personnel in charge of the clinical centres prior to the start of the studies;
- coordination and settlement of relevant data collection issues through numerous teleconferences;
- appointment of a central coordinator, designated by each clinical centre, and under the leadership of the centre manager, with responsibility for coordinating and handling issues relating to data collection at that centre; and
- strengthening of data management and the verification of original data.

Data management and statistical analysis

The head physicians in the designated hospital filled in a case report form (CRF) for each patient and the details were sent to an independent data centre. After the data in the CRF had been verified, they were entered into the central database. The data were then "locked" (i.e. made read-only) for statistical analysis. ACCESS and SQL Server 2000 were used to set up the database and the SAS6.12 statistical software package was used for the analysis. The data on rates were analysed by $\chi 2$ testing; the mean value between different groups was tested by *t*-testing or analysis of variance, and the frequency of classified data was calculated with the rank-sum test. Symptom persistence time was analysed by the LIFETEST procedure, and the mixed effects model used for data from replicate measurements.

Ethical approval

The research project was approved by the State Ministry of Science and Technology, and the research programme was approved by the Independent Ethics Committee of Guang'anmen Hospital affiliated to the China Academy of Traditional Chinese Medicine.

Basic information on the cases

Altogether 549 inpatients clinically diagnosed with SARS, were included in the observation. During the observation period, 14 patients diagnosed with SARS and 11 patients for whom the observation time was shorter than 6 days, due to factors such as hospital transfer, were excluded. The number of SARS patients finally included in the statistical analysis was 524. Patients in both the treatment groups were comparable in terms of age, sex and the state of the illness (Table 1).

Results

Influence on lung inflammation shown in chest radiographs

Digitized scanning of the chest radiographs was conducted for all the patients included in the study. The data were used to set up a SARS chest radiograph library. A team of experts for reviewing and commenting on chest radiographs from SARS patients was organized to discuss and establish the quantitative criteria for assessing chest radiographs, and to conduct quantitative evaluations of the lung inflammation seen on the chest radiographs.
The scores were assigned as follows:

- A high-density consolidation image (similar to mediastinum) scored 3.
- A low-density image (similar to hilar density image) indicating pathological changes due to exudation scored 2.
- A fibrosis image indicating the change in the ultra-early stage of disease or after incomplete absorption scored 1.

The left and right lungs were divided into 12 areas in the upper, middle and lower lobes and the inner and outer zones. Any enlargement or pleural lesions were given a score of 1 for each.

The total possible number of accumulated points was 38. Each chest radiograph was studied by a team consisting of three experienced radiological and respiratory experts who were not informed of the identity of the patient, to determine the pathological areas and the classification of the shadow density on the chest radiographs.

Table 1. Basic information on the cases

Parameter	Case load (percentage)
No of days after disease onset (*n* = 524)	
1-7	142 (27.1)
8-14	182 (34.7)
≥ 15	200 (38.3)
Onset time (*n* = 522)[a]	
14-31 March	28 (5.4)
01-15 April	183 (35.1)
16-30 April	250 (47.9)
01-15 May	58 (11.1)
16-27 May	3 (0.6)
Sex (*n* = 524)	
Male	247 (47.1)
Female	277 (52.9)
Age (years) (*n* = 524)	
≥ 20	47 (9.0)
21-30	162 (30.9)
31-40	138 (26.3)
41-50	106 (20.2)
> 50	71 (13.5)
Occupation (*n* = 503)[b]	
Manual labourers (except farmers)	84 (16.7)
Farmers	12 (2.4)
Students and teachers	58 (11.5)
Hospital staff	113 (22.5)
Employees and cadres	93 (18.5)
Army personnel and armed police officers	18 (3.6)
Restaurant workers	29 (5.8)
Retired people	21 (4.2)
Others	15 (3.0)
Unemployed people	60 (11.9)
Classification of illness (*n* = 524)	
Normal	360 (68.7)
Severe	153 (29.2)
Critical	11 (2.1)
Underlying diseases (*n* = 493)[c]	
Yes	64 (13.0)
No	429 (87.0)
Treatment group (*n* = 524)	
Integrated (Traditional Chinese medicine + Western medicine)	318 (60.7)
Western medicine	206 (39.3)

[a]Time of onset of disease in two patients was not known. [b]Twenty-one patients did not state their profession. [c]No records were available for 31 patients.

The chest radiographs of 231 patients in the integrated treatment group and 130 patients in the group treated with Western medicine, comprising a total of 1561 sheets of chest radiographs, were included in the evaluation. There was no significant difference between the treatment groups in terms of age, sex, hormone administration and time at which chest radiographs were taken. Comparison of the degree of illness between the two groups showed that the illness of patients in the integrated treatment group was more severe than that of those in the group treated with Western medicine.

Overall comparison of lung inflammation scores between the two treatment groups

The Wilcox rank-sum test was not statistically significant, which indicates that there was no significant difference between the overall curative effects in terms of inflammation absorption in the two treatment groups. Comparison of the scores from the chest radiographs of the two treatment groups (Figs. 1 and 2) showed that in terms of the overall efficacy of treatment, the scores on the chest radiographs from the integrated treatment group were lower than those from the group treated with Western medicine. In the patients with severe disease, the total scores from the chest radiographs of the integrated treatment group were clearly lower than that of the group treated with Western medicine (Fig. 3), but showed better curative effects.

Table 2. Comparison of lung inflammation scores between SARS patients treated with traditional Chinese medicine plus Western medicine and with Western medicine alone

Treatment group	No of subjects	Number of chest radiographs	Mean ± SD	Median	Z value	*p*
All patients						
Western medicine	130	523	5.85 ± 6.59	4	-0.81	0.21
Integrated treatment (TCM + Western medicine)	231	1017	6.67 ± 7.61	4		
Patients with normal type SARS						
Western medicine	105	396	4.79 ± 5.60	3	0.18	0.43
Integrated treatment (TCM + Western medicine	153	635	5.40 ± 6.86			
Patients with severe type SARS						
Western medicine	23	115	7.67 ± 6.34	6	- 0.03	0.488
Integrated treatment (TCM + Western medicine)	72	350	8.16 ± 7.60	6		

SD, Standard deviation; TCM, Traditional Chinese medicine.

Fig. 1. Dynamic comparison between total scores from chest radiographs of all SARS patients in the two treatment groups (traditional Chinese medicine plus Western medicine and Western medicine alone)

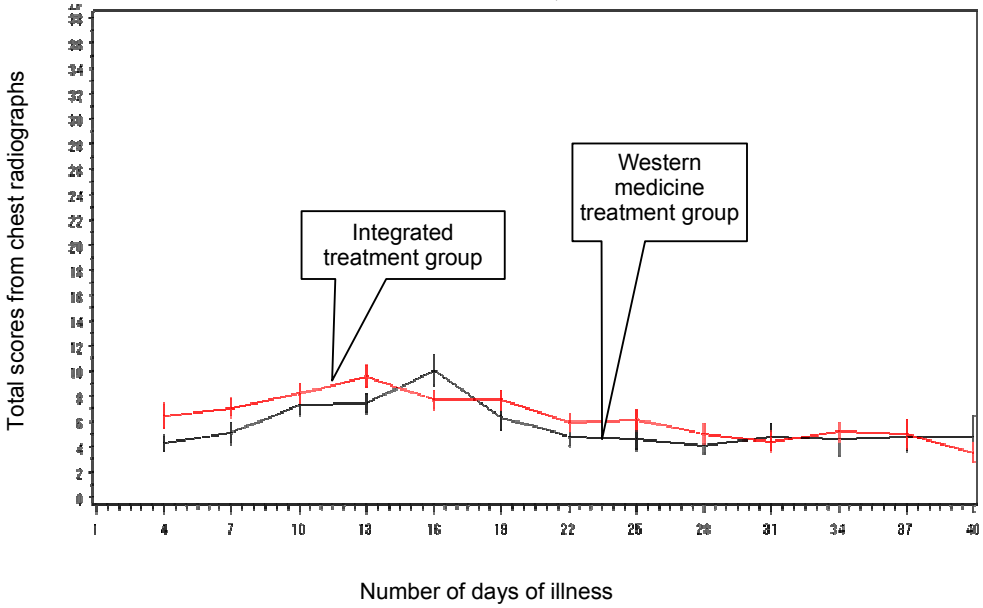


Fig. 2. Dynamic comparison between total scores of patients with normal SARS in the two treatment groups (traditional Chinese medicine plus Western medicine and Western medicine alone)

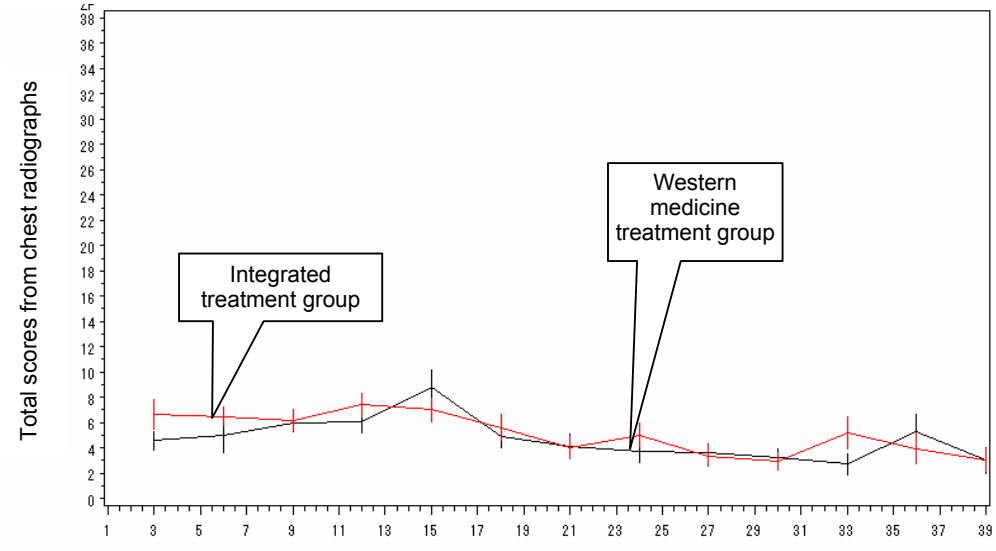
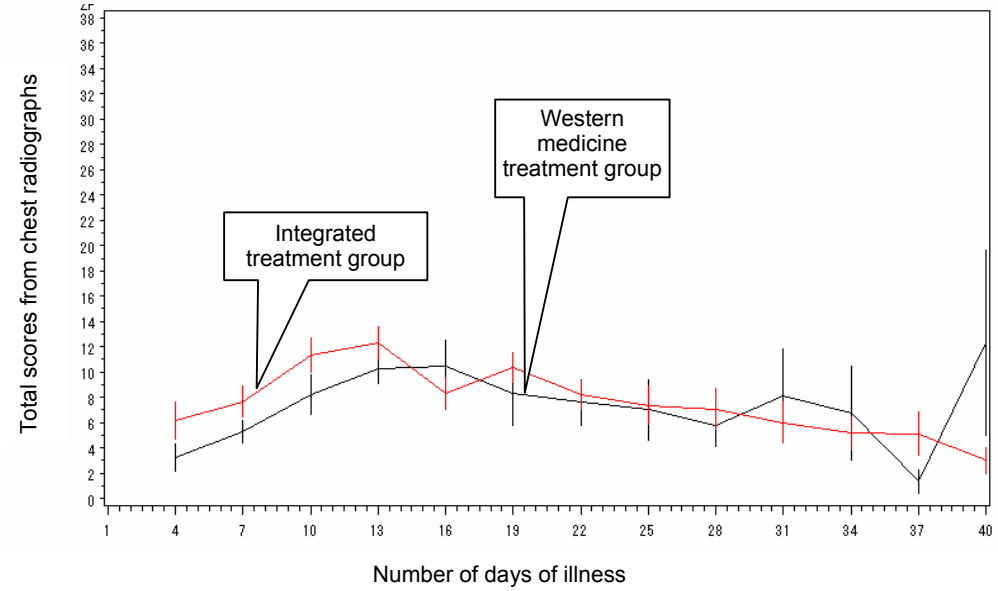


Fig. 3. Dynamic comparison between total scores of patients with severe SARS in the two treatment groups (traditional Chinese medicine plus Western medicine and Western medicine alone)



Figures 1, 2 and 3 show that, in the early stage of the disease, the scores of chest radiographs from patients in the integrated treatment group were higher than those of the group treated with Western medicine alone, which indicates that the degree of illness of the SARS patients in the integrated treatment group, at the earlier stage, was more severe than that of the patients in the Western medicine-treated group. This may be the reason why no significant difference was found when the curative effects were compared between the two groups. The results of further analyses at different intervention time-points are described below.

Comparison between scores for lung inflammation in the two treatment groups following early intervention (within 7 days of the onset of disease)

Generally, the total scores from the chest radiographs were obviously lower in the integrated treatment group than in the group treated with Western medicine, and the difference was statistically significant ($Z = 3.32$, $p = 0.0004$) (Table 3). This indicates that when intervention begins within 7 days after the onset of disease, the curative effects of the integrated therapy in promoting the absorption of lung inflammation will be better than those of treatment with Western medicine alone (Figs 3 and 4).

For patients with normal-type SARS, the effects of intervention with integrated treatment within 7 days after disease onset on the absorption of lung inflammation were not significantly different from those in the group treated with Western medicine alone ($Z = 1.17$, $p = 0.12$).

A comparison of the total scores, before and after the treatment, from the chest radiographs of patients with severe SARS in whom intervention took place within 7 days after the onset of disease, showed that the scores of the integrated treatment group were obviously lower than those of the group treated with Western medicine alone, and the statistical test showed that the difference was significant ($p = 0.034$; Table 4, Fig. 6), which indicates that if intervention with

integrated treatment begins within 7 days after the onset of disease, the absorption of lung inflammation is better than that in the group treated with Western medicine alone.

Table 3. Comparison between scores for lung inflammation in the two treatment groups following intervention within 7 days of the onset of disease

Treatment group	No of patients	Number of chest radiographs	Mean ± SD	Median	Z value	*p*
All patients						
Western medicine	36	144	6.39 ± 6.48	4.5	3.32	0.000
Integrated treatment (TCM + Western medicine)	51	228	4.40 ± 4.97	3		
Patients with normal-type SARS						
Western medicine	27	87	4.59 ± 5.22	4	1.17	0.12
Integrated treatment (TCM + Western medicine)	37	156	3.99 ± 4.67	3		
Patients with severe-type SARS						
Western medicine	9	57	9.14 ± 7.24	6	3.45	0.034
Integrated treatment (TCM + Western medicine)	14	72	5.30 ± 5.48	4		

SD, Standard deviation; TCM, Traditional Chinese medicine.

Fig. 4. Dynamic comparison of overall curative effects between patients in the integrated treatment group and the group treated with Western medicine within 7 days after onset of SARS

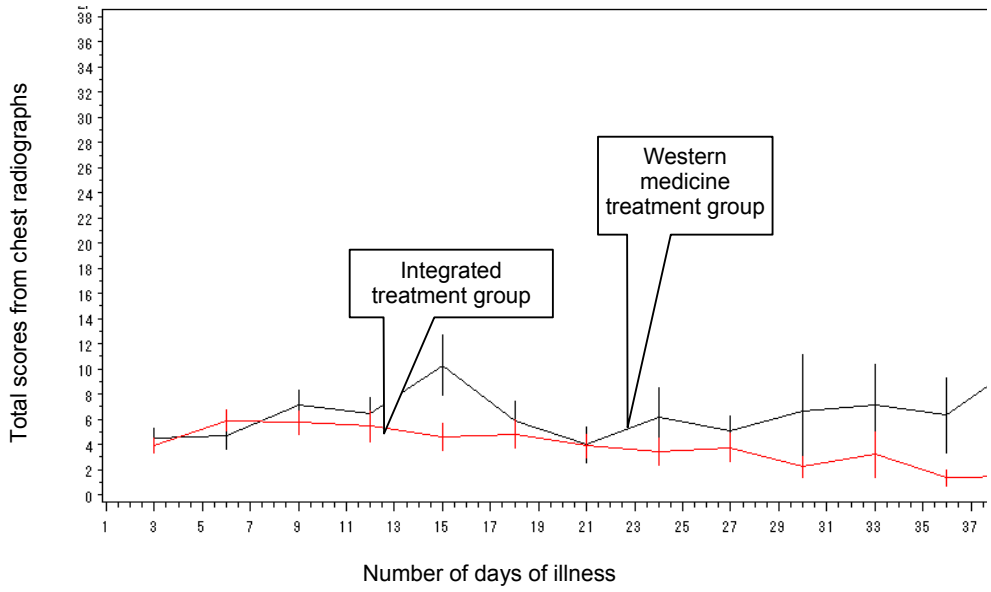


Fig. 5. Comparison of curative effects on patients with normal SARS of intervention (within 7 days after onset of SARS) with integrated treatment and treatment with Western medicine alone

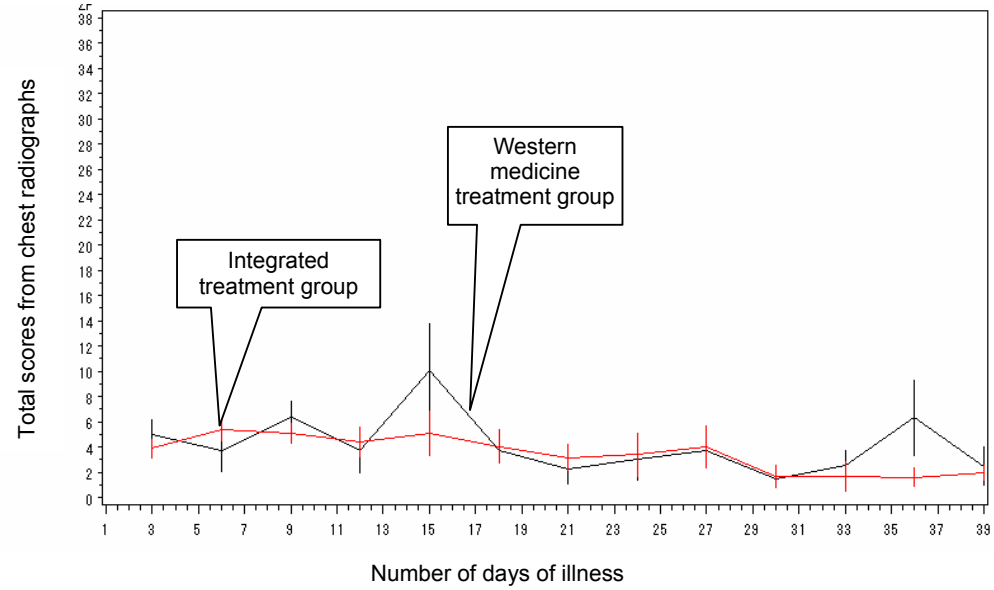
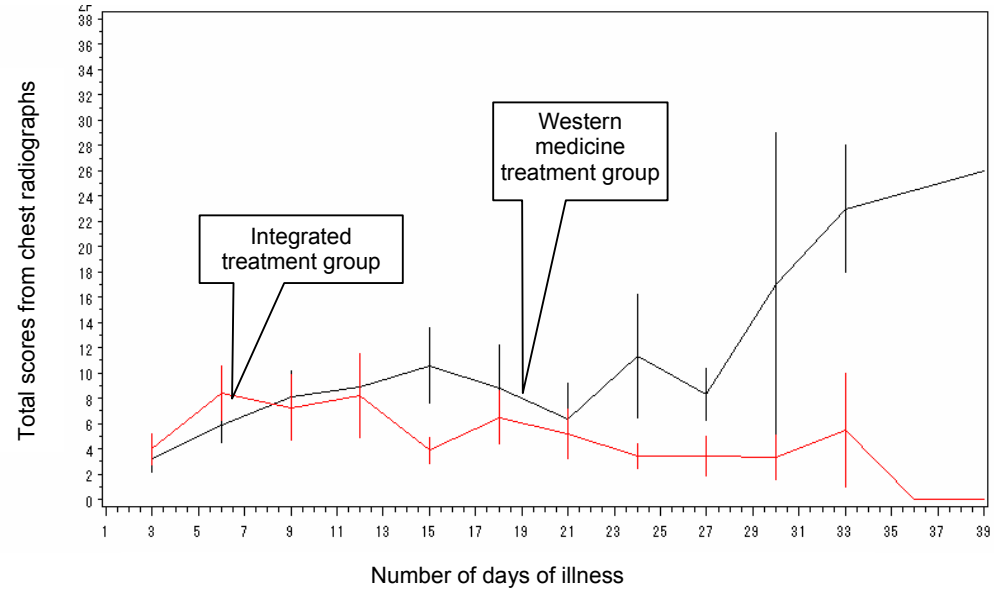


Fig. 6. Dynamic comparison of curative effects on patients with severe SARS of intervention (within 7 days after onset of disease) with integrated treatment and treatment with Western medicine alone



The above results indicate that intervention with integrated treatment during the early stage of the disease can alleviate inflammation in the lung, and the effect is more marked in the patients with severe SARS.

Influence on clinical symptoms

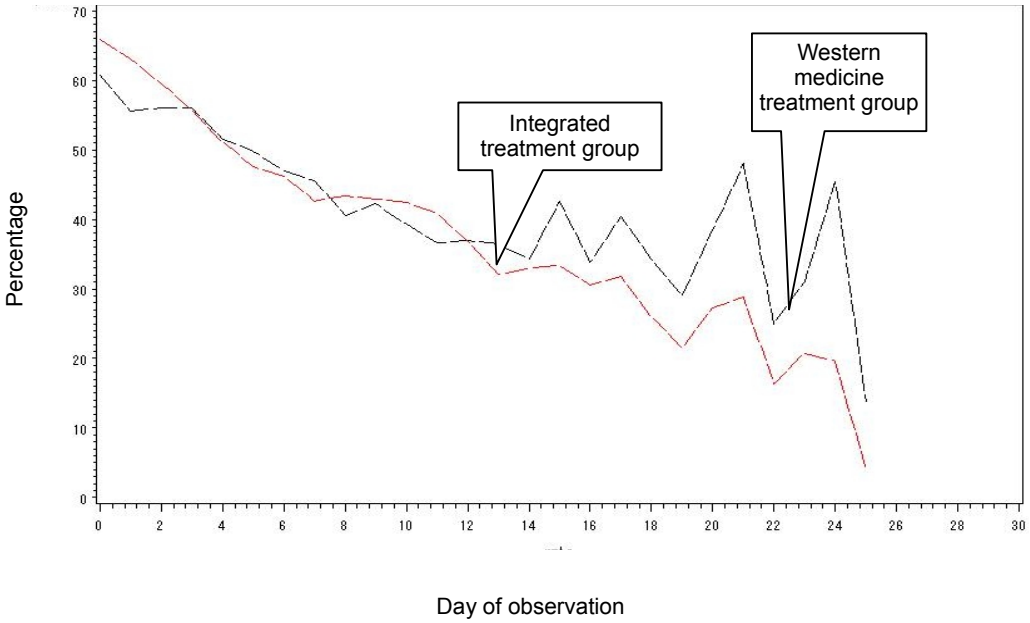
An analysis of the changes in the symptoms of the 524 SARS patients indicated that the integrated treatment (i.e. TCM plus Western medicine) was better than the treatment with Western medicine alone at alleviating symptoms such as inertia, tachypnoea and shortness of breath.

Dynamic changes in the main symptoms of both treatment groups during the course of the treatment

Hypodynamia

Two hundred and nine patients (65.9%) in the integrated treatment group and 124 patients (60.8%) in the group treated with Western medicine had hypodynamia at the time when they were assigned to a treatment group. After 14 days of treatment, the number of patients suffering from hypodynamia in the integrated treatment group had dropped by 33.0% to 58 (33.0%), while that in the group treated with Western medicine had dropped by 26.5% to 36 (34.3%), a difference in percentage decrease between the two groups of 6.5%. After 14 days, the curative effects in the integrated treatment group were therefore better than those of the treatment with Western medicine alone (Fig. 7).

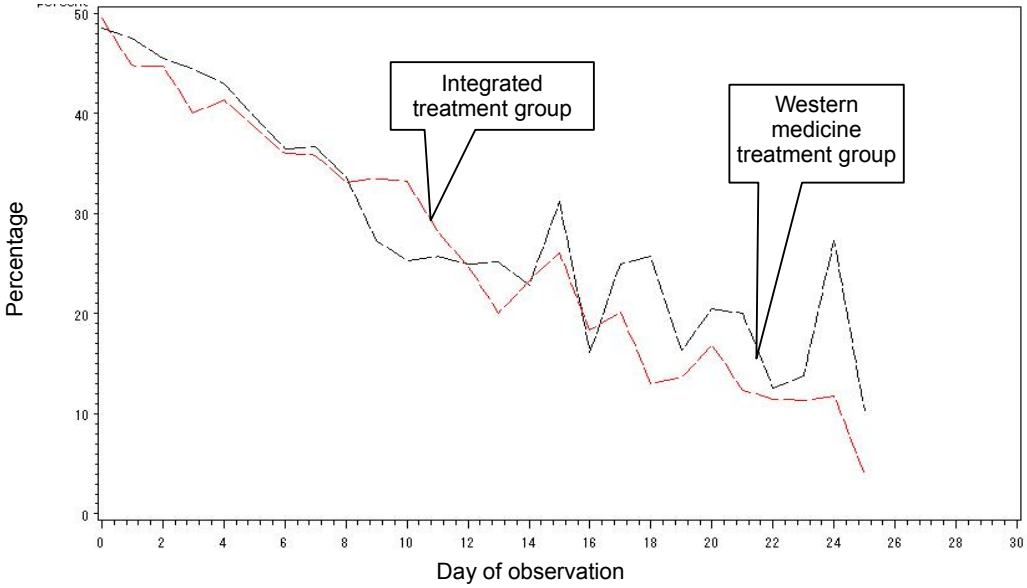
Fig. 7. Comparison of symptoms of hypodynamia between the two treatment groups



Shortness of breath

One hundred and fifty-seven patients (49.5%) in the integrated treatment group and 99 patients (48.5%) in the group treated with Western medicine had shortness of breath at the time they were assigned to the treatment groups. After 14 days of treatment, the number of patients with shortness of breath in the integrated treatment group had dropped by 26.2% to 41 (23.3%), whereas that in the group treated with Western medicine had dropped by 25.67% to 24 (22.86%). After 14 days, the curative effects of the integrated treatment were therefore greater than those of the treatment with Western medicine (Fig. 8).

Fig. 8. Comparison of changes in symptoms of shortness of breath between the two treatment groups



Tachypnoea

One hundred and thirty patients (41.0%) in the integrated treatment group and 78 patients (60.8%) in the group treated with Western medicine showed tachypnoea at the time when they were assigned to the treatment groups. After 14 days of treatment, the number of patients with tachypnoea in the integrated treatment group had dropped by 22.3% to 33 (18.8%), whereas that in the group treated with Western medicine decreased by 23.0% to 16 (15.2%). After 14 days, the curative effects of the integrated treatment were therefore greater than those of the treatment with Western medicine alone (Fig. 9).

When decreases in the severity of symptoms such as dry cough, muscular pain and headache were compared between the two treatment groups, no significant difference was found ($p < 0.05$).

Statistical model analysis

In order to analyse the improvement of hypodynamia resulting from integrated treatment and treatment with Western medicine alone, over time, and to exclude the influence of age, severity of illness, duration of disease, course of treatment and dosage of hormone on the analytical results of curative effects, the accumulative logistic model, known as the MIXED statistical process in SAS software was adopted. Variables for the two therapeutic methods, age, severity of illness, duration of disease, course of treatment, dosage of hormone as well as the interactive influence between therapies and the severity of illness were used to set up the model, which was adjusted for different parameters. The results are shown in Table 4.

Fig. 9. Change in the occurrence of tachypnoea after treatment with traditional Chinese medicine plus Western medicine or with Western medicine alone

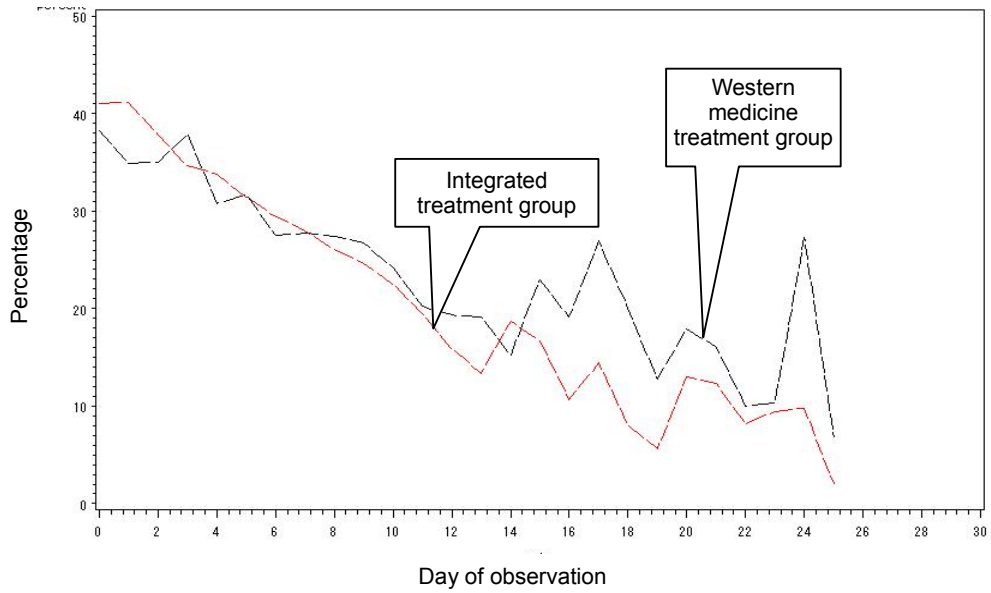


Table 4. Improvement of hypodynamia after integrated treatment in a multi-factor accumulative logistic model analysis

Effect (parameters of model)	Estimate	Standard error	DF	*t*-value	$p > \|t\|$
Intercept	2.5709	0.2057	3518	12.50	< 0.0001
Group	–0.2640	0.1247	3246	–2.12	0.0343
Typing of Western medicine	–0.7977	0.09548	3223	8.35	< 0.0001
Age	–0.4659	0.1006	3242	4.63	< 0.0001
Duration of disease	–0.007139	0.003971	3273	1.80	0.0723
Group*typing of Western medicine	0.3406	0.1545	3259	2.21	0.0275
Course of treatment	0.1022	0.006232	4817	16.39	< 0.0001
Hormone accumulation	0.000011	0.000034	3560	0.31	0.7534

DF, degrees of freedom.

The results show that the influence of factors such as age, type of Western medicine, duration of disease and course of treatment on the improvement of hypodynamia was significant ($p < 0.05$): the older the patient, the less satisfactory the effects; the more severe the disease, the less satisfactory the effects. The dosage of hormone had no significant influence on the improvement of hypodynamia. After adjustment for the influence of age, course of treatment, severity of illness, duration of disease and the dosage of hormone, the influence of both therapeutic regimens on the improvement of hypodynamia was significant ($p < 0.05$). In combination with the above analysis on the occurrence of hypodynamia, we conclude that the integrated treatment was more effective than treatment with Western medicine alone in improving hypodynamia.

The same procedure was used to analyse the improvement of shortness of breath by integrated treatment and treatment with Western medicine alone as that described above for the analysis of the effects on hypodynamia, and the results are given in Table 5.

Table 5. Improvement of shortness of breath after integrated treatment in a multi-factor accumulative logistic model analysis

Effect (parameters of model)	Estimate	Standard error	DF	*t*-value	$p > \|t\|$
Intercept	4.1079	0.2164	4357	18.98	< 0.0001
Group	–0.2418	0.1210	3593	–2.00	0.0457
Typing of Western medicine	0.6796	0.09527	3608	7.13	< 0.0001
Age	–0.6617	0.09681	3600	6.84	< 0.0001
Group*typing of Western medicine	0.2385	0.1537	3621	1.55	0.1207
Course of treatment (first 3 days)	1.0692	0.09441	1533	–11.32	< 0.0001
Course of treatment (first 14 days)	0.6818	0.08084	1433	–8.43	< 0.0001
Hormone accumulation	0.000115	0.000033	4808	3.51	0.0005

DF, degrees of freedom.

Table 6. Improvement of tachypnoea after integrated treatment in multi-factor accumulative logistic model analysis

Effect (parameters of model)	Estimate	Standard error	DF	*t*-value	$p > \|t\|$
Intercept	2.5709	0.2057	3518	12.50	< 0.0001
Group	–0.2413	0.1269	3892	–1.90	0.0573
Typing of Western medicine	–0.9766	0.1050	3919	9.30	< 0.0001
Age	–0.8314	0.1020	3911	8.15	< 0.0001
Course of disease	–0.004211	0.004373	3961	0.96	0.3356
Group*typing of Western medicine	0.1365	0.1651	3938	0.83	0.4086
Course of treatment	0.1167	0.007812	5411	14.94	< 0.0001
Hormone accumulation	–0.00013	0.000038	4168	–3.37	0.000

DF, degrees of freedom.

The results of the analysis were essentially similar to those obtained for hypodynamia. The influence of both therapeutic regimens on the improvement of shortness of breath was significant ($p < 0.05$). However, in combination with the above analysis on shortness of breath, the researchers concluded that the integrated treatment was more effective than treatment with Western medicine alone in improving the symptom of shortness of breath.

The improvements of tachypnoea using integrated treatment and treatment with Western medicine alone were compared using the same procedure as that described above for hypodynamia, and the results are given in Table 6.

The results of the analysis were essentially similar to those obtained for hypodynamia and shortness of breath. The influence of both therapeutic regimens on the improvement of tachypnoea was significant ($p < 0.05$). However, in combination with the above analysis on tachypnoea, the researchers concluded that the integrated treatment was more effective than Western medicine alone in improving the symptom of tachypnoea.

Table 7. Comparison of the average dosages of hormone used and duration of usage in the two treatment groups

Treatment group	Total dosage of hormones (mg)			Daily dosage (mg)			No of days of hormone use		
	Mean	(SD)	Median	Mean	(SD)	Median	Mean	(SD)	Median
Integrated (traditional Chinese + Western) (n = 272)	1884.51	(1834.19)	1277.00	115.78	(87.51)	84.40	15.16	(5.77)	15.00
Western medicine alone (n = 189)	1992.55	(1586.65)	1680.00	130.78	(85.63)	115.33	14.56	(4.50)	15.00
Z		3.000			5.026			0.696	
p		0.0833			0.0250			0.4041	

The analysis showed that the integrated treatment had certain advantages over that with Western medicine alone in improving the symptoms of dry cough, muscular pain and headache. However, after adjustment for the influence of age, severity of illness, duration of disease, course of treatment and dosage of hormone on the analytical results of curative effects, the two therapeutic regimens were not significantly different in their ability to improve the symptoms of dry cough, muscular pain and headache.

Influence on the dosage of glucocorticoid

Analysis of the dosage of glucocorticoid used to treat 461 (out of 524) patients with SARS showed that, if there was no significant difference in the time required for the absorption of lung inflammation between the integrated treatment group (272 patients, 18.8 ± 9.7 days) and the group treated with Western medicine (189 cases, 20.8 ± 10.5 days), the daily average dosage of hormone (calculated on the basis of methylprednisolone) for the integrated treatment group was 115.78 ± 87.51 mg/day with a median of 84.40 mg/day, and that for the group treated with Western medicine was 130.78 ± 85.63mg/day with a median of 115.33 mg/day.

Of the 524 patients, 244 (76.7%) in the integrated treatment group and 117 (85.9%) in the group treated with Western medicine had received antiviral drugs, whereas 286 (89.9%) and 190 (92.2%), respectively, had been treated with antibiotics. Two hundred and seventy-two patients (82.9%) and 189 (96.4%), respectively, had been treated with glucocorticoid, and 222 (69.8%) and 174 (84.5%), respectively, had received immunomodulator. After all treatments, except for that with antibiotics ($\chi 2 = 0.712$, $p = 0.374$), statistically significant differences were seen between the two treatment groups: antiviral drugs; $\chi 2 = 6.690$, $p = 0.01$: hormone; $\chi 2 = 4.529$, $p = 0.033$: immunomodulator; $\chi 2 = 15.544$, $p = 0.00$).

Influence on the degree of blood oxygen saturation

The dynamic change of blood oxygen saturation of 447 (out of 524) SARS patients was analysed. Of these patients, 276 were in the integrated treatment group and the remainder (171) were in the group treated with Western medicine. The results

of the analysis found no significant difference in terms of age, sex or severity of the disease.

After adjustment for the difference in age, severity of disease and the duration of treatment, the general effects on oxygen saturation in the two groups during the entire course of treatment were not significantly different ($p = 0.088$).

To take into account the influence of different durations of treatment and the severity of illness on blood oxygen saturation, we conducted further stratified analyses and the results, after adjustment for age, are shown in Tables 8 and 9.

The results shown in Table 8 indicate that there was no significant difference at the baseline (0–2 days after being included in the groups), but that the difference between the two groups after a treatment period of 3–14 days, and after more than 15 days was significant, and that the integrated treatment could reduce the risk of an abnormal level of blood oxygen saturation. After a treatment period of 3–14 days, the odds ratio (OR) of the two groups was exp (–0.6582) = 0.5178, and after 15 days, OR = exp(–1.4164) = 0.2426. After adjustment for age, for the patients with normal SARS, there was no significant difference ($p = 0.4745$) in reduction in the risk of abnormal blood oxygen concentration between the integrated treatment group and the group treated with Western medicine; for patients with severe SARS, the integrated treatment was more effective than the treatment with Western medicine in lowering the risk of abnormal blood oxygen concentration, OR = exp(–1.7173) = 0.18; $p = 0.0001$.

A stratified analysis of the blood oxygen concentration of patients included in the groups at different stages of illness (early, mid and later stages) was conducted. The results indicated that the difference between the two treatment groups in blood oxygen concentration measured in patients included in the early stage of illness (after 0–2 days) was not significantly different, whereas there was a significant difference between the two groups after 3–14 days of illness. After 15 days the difference was again nonsignificant. Blood oxygen concentration in patients included in the mid and later stages tended to be better in the integrated group than in the group treated with Western medicine, but the difference between the two groups was not statistically significant.

Table 8. Comparison of curative effects on the two groups after different durations of treatment

Duration of treatment (days)	**Estimate of difference**	**Estimated standard deviation**	***t*-value**	***p*-value**
0–2	–0.1982	0.2602	–0.76	0.4464
3–14	–0.6582	0.2271	–2.90	0.0038
> 15	–1.4164	0.4156	–3.41	0.0007

Table 9. Comparison of curative effects of both groups according to severity of illness

Disease severity	Estimate of difference	Estimated standard deviation	*t*-value	*p*-value
Normal	0.2021	0.2825	0.72	0.4745
Severe	-1.7173	0.3390	5.07	0.0001

A stratified analysis of the blood oxygen concentration of patients included in the groups at different stages of illness (early, mid and later stages) was conducted. The results indicated that the difference between the two treatment groups in blood oxygen concentration measured in patients included in the early stage of illness (after 0–2 days) was not significantly different, whereas there was a significant difference between the two groups after 3–14 days of illness. After 15 days the difference was again nonsignificant. Blood oxygen concentration in patients included in the mid and later stages tended to be better in the integrated group than in the group treated with Western medicine, but the difference between the two groups was not statistically significant.

Influence on case fatality rate and complications

During our observation of the clinical outcome of the 524 cases of SARS, no patients in the integrated treatment group (318 cases) died, but seven of the patients (3.4%) in the group treated with Western medicine alone (206 cases) died.

The number of patients who experienced complications such as fungal infection, ARDS, disseminated intravascular coagulation and multiple organ dysfunction syndrome and the incidence rates are shown in Table 10. The incidence of complications in the group treated with Western medicine tended to be higher than that in the integrated treatment group.

Table 10. Summary of complications experienced by the 524 patients with SARS

	Fungal infection	ARDS	MODS	DIC
No of cases (incidence rate)	20 (3.8)	11 (2.1)	6 (1.1)	2 (0.4)
Treatment group				
Integrated (Chinese traditional + Western)	11 (3.5)	7 (2.2)	1 (0.3)	0
Western medicine alone	9 (4.4)	4 (1.9)	5 (2.4)	2 (1.0
x^2	0.416	Precision Probability	Precision Probability	Precision Probability
p	0.519	1.000	0.037	0.522

ARDS, acute respiratory distress syndrome; DIC, disseminated intravascular coagulation; MODS, multiple organ dysfunction syndrome.

Table 11. Number of patients with abnormally high levels of alanine aminotransferase (ALT), lactate dehydrogenase (LDH) and blood urea nitrogen (BUN)

	ALT (> 40 µ/l)	**LDH (> 240 µ/l)**	**BUN (> 8.2 µmol/l)**
No of cases (incidence rate)	436 (83.2)	376 (71.8)	291 (55.5)
Treatment group			
Integrated (Chinese traditional + Western)	260 (81.8)	214 (67.3)	150 (47.2)
Western medicine alone	176 (85.4)	162 (78.6)	141 (68.4)
x^2	1.209	7.940	22.916
P	0.272	0.005	0.000

Change of alanine aminotransferase, lactate dehydrogenase and blood urea nitrogen

The numbers of patients in the two treatment groups whose alanine aminotransferase (ALT), lactate dehydrogenase (LDH) and blood urea nitrogen (BUN) were above the normal range and the incidence rate throughout the period of observation are given in Table 11. The results indicate that the incidence of abnormal rises in ALT, LDH and BUN in the group treated with Western medicine tended to be higher than in the integrated treatment group, which suggests that the integrated treatment does not increase the incidence of abnormal rises of ALT, LDH or BUN.

Conclusions

Our initial research results showed that the integrated treatment (TCM in combination with Western medicine) may have advantages over treatment with Western medicine alone, and the advantages are reflected in the following findings: the integrated treatment can help alleviate lung inflammation caused by SARS, improve the level of blood oxygen saturation, alleviate symptoms of hypodynamia, tachypnoea and shortness of breath, and reduce the required dose of Western medicines such as glucocorticoid. Our initial safety evaluation also suggested that the integrated treatment is safe.

Report 3
Manifestation of symptoms in patients with SARS and analysis of the curative effect of treatment with integrated Traditional Chinese medicine and Western medicine

Zhang Boli[19], Liang Shuren[20], Zhang Junping[19] and Wang Hongwu[19]

Abstract. The objective was to examine the manifestation of Traditional Chinese medicine (TCM) symptomatology in patients with severe acute respiratory syndrome (SARS) and observe the curative effects of a therapeutic regimen integrating TCM and Western medicine. A questionnaire on TCM symptomatology was adopted for research on patients with SARS to obtain data during the early, middle and late stages of the illness. Therapy integrating TCM and Western medicine was evaluated by comparison with a group of patients treated with Western medicine alone. Manifestation of TCM symptomatology in SARS patients could be divided into three stages and five syndromes. The three stages were: the pyretogenic stage (1–7 days), cough and gasp stage (5–14 days) and convalescence stage (14–21 days and later). The five syndromes were as follows: *invasion* of pathogenic factor into the lung which usually occurs in the pyretogenic stage; *retention* of virus in the lung and *impediment* of the activities of the lung which mainly occur in the cough and gasp stage; *deficiency* of both *qi* and *yin* and *stagnation* of phlegm in the lung which occur during the convalescence stage. Observation of the curative effects indicated that both integrated treatment and treatment with Western medicine alone could improve oxygen saturation and there was no obvious difference between the two groups. Once oxygen saturation had been normalized, fluctuations were reduced by integrated treatment. The case fatality rate in the integrated treatment group was 20% (5/20), whereas that in the group treated with Western medicine was 30% (6/20), indicating that the integrated treatment had a tendency to reduce the case fatality rate from SARS. This research indicates that therapy with integrated TCM and Western medicine was superior to therapy with Western medicine alone in treating SARS.

Introduction

Infectious atypical pneumonia, which is caused by a new kind of corona virus, has strong infectivity and can affect several internal organs. The World Heath Organization (WHO) has termed it severe acute respiratory syndrome (SARS) (*1*). Its clinical symptoms include constitutional symptoms (fever, hypodynamia, headache, muscle pain and aching joints) and respiratory symptoms (dry cough, chest distress and dyspnoea). Following the first imported case reported in Tianjin in April 2003, we conducted an investigation into the clinical

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symptomatology of SARS according to TCM, and studied the effects of intervention with integrated treatment in the designated SARS hospitals.

Objects and methods

Objects tested

Source of cases
The cases were some of the patients with confirmed SARS admitted to designated SARS hospitals in Tianjin from 19 April to 6 June 2003.

Diagnostic criteria
The diagnostic criteria used conformed to those set out in *Clinical diagnosis criteria for infectious SARS* and *Diagnostic criteria for severe SARS cases* promulgated by the Ministry of Health of the People's Republic of China. SARS was confirmed and diagnosed according to factors including the epidemiological history, fever, continuous increase of the peripheral leukocyte count, appearance of an infiltrative shadow in the lung and ineffectiveness of antibiotic treatment. In addition, diseases of the respiratory system having similar clinical manifestations, such as infection of the upper respiratory tract, influenza, and bacterial or fungal pneumonia were excluded.

Inclusion criteria
Patients who met the diagnostic criteria and agreed to participate in the studies were included. Those who received treatment with Western medicine alone were included in the Western-medicine-treated group, and those treated with integrated TCM and Western medicine were assigned to the integrated treatment group.

Exclusion criteria
Patients who did not meet the diagnostic criteria or who did not consent to participate in the study were excluded.

Study design

Symptomatology
The investigation tool used was a questionnaire on SARS TCM clinical symptomatology (see Annex).

Clinical therapy
The two treatment groups were studied concurrently to observe the curative effects of the two therapeutic regimens (integrated treatment and Western medicine alone) on SARS.

Therapeutic regimens

Therapeutic regimen with Western medicine
Therapy with Western medicine followed the recommended therapeutic regimen for severe SARS promulgated by the Ministry of Health, People's Republic of

China, on 3 May 2003. The principles of the therapeutic regimen are summarized as follows:

- Antiviral drug: ribavirin 0.4 g, every 12 hours for 7 days.
- Glucocorticoid: methylprednisolone 40–320 mg/day, increasing the dosage when necessary, and up to 1 g/day for a severe case. The dosage was gradually reduced and discontinued when the condition of the patient had improved or the shadow on the chest radiograph had been absorbed according to a predetermined extent. (All the SARS patients in the present study were treated with glucocorticoid.)
- Oxygen inhalation or assisted respiration: Oxygen inhalation through a nasal tube was provided to the patients immediately after they were admitted to hospital. Those patients whose oxygen saturation was lower than 93% were provided with oxygen inhalation through a face mask, with an oxygen flow of 5–10 l/min according to the severity of illness. Continuous positive airway pressure ventilation was given to 24 patients to promote oxygen supply.

Therapeutic regimens of traditional Chinese medicine

The TCM therapeutic regimen for SARS recommended by the State Administration of Traditional Chinese Medicine, People's Republic of China on 11 April 2003, concerning characteristics of SARS in Tianjin City, entitled *Traditional medicine therapeutic technical regimen of SARS in Tianjing area* (revision) was adopted (2). The course of disease was divided into three stages (pyretogenic stage, cough and gasp stage, and convalescent stage) and there were seven types of treatment. The herbal decoctions were prepared by the decoction department of the hospital, and administered twice per day. All herbs used in the decoctions conformed to the requirements specified in the *Chinese pharmacopoeia* (2000 Edition, Volume I) and the patent medicines used were prescription drugs available commercially and approved by the Chinese drug administration.

Duration of study period

The study period was from the date of admission to the end of therapy or death.

Observation indexes

Symptomatological study

The investigation comprised three parts: basic information (e.g. age and sex), symptoms and tongue pictures. The symptoms investigated were scored as follows according to how often they were observed: A, never; B, occasionally; C, sometimes; D, usually; E, always. The investigation was performed during the course of disease which was divided into three stages: the early stage, middle stage and the late stage.

Clinical examination

The clinical examination included:

1. General impression; and
2. Laboratory examination (including routine blood examinations, biochemical tests, oxygen saturation, blood gas monitoring for patients with severe illness) and chest radiographs.

Criteria for determining when SARS patients could be discharged from Hospital

The criteria used for determining whether patients were ready to be discharged from hospital followed the *Reference standard for the discharge of cases of infectious SARS* issued by the Ministry of Health, People's Republic of China.

Quality control standard

The proposed study protocol was tested in repeated demonstrations and pre-surveys. Training seminars were held for professionals and training in the standard recording of symptoms was provided to familiarize investigators with the contents of the questionnaire to enable them to fill them out correctly and completely. Training also included guidance on the procedure necessary to ensure that each questionnaire was completed in a single session and ensure legibility and consistency of faxed questionnaires. Original data were immediately checked and verified; questionnaires were coded; double data-entry was used; 10% of the data were randomly selected and checked.

Data management and statistical analysis

A database was established using Epi data 2.1 to handle data management. Data were entered twice and statistical analyses were made using SPSS 10.0 and SAS6.12 software which included the following:

- *Reliability test*: Cronbach's alpha coefficient was adopted. Effectiveness was assessed using a factor analysis method.
- *Inclusion of symptoms of SARS for analysis*: Factorial analysis and cluster analysis methods were used.

The statistical analysis of symptomatological and clinical effect data was done by means of frequency analysis, independent *t*-testing and chi-squared testing.

Results

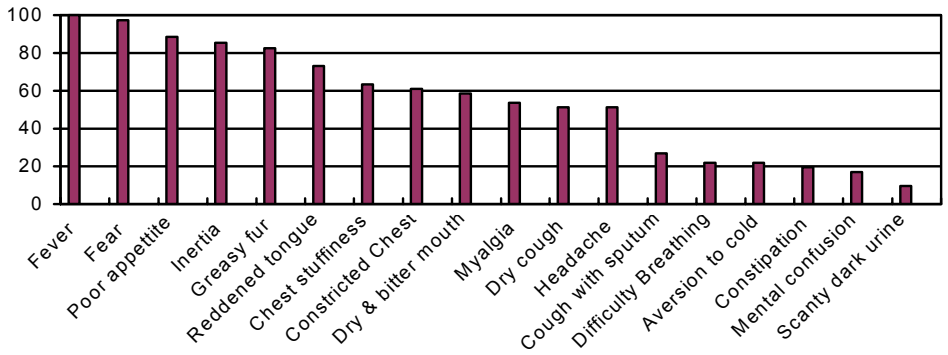
General situation

Among the 76 patients with SARS participating in this study, there were 31 patients with normal SARS, 19 of whom were in the integrated treatment group and 12 in the group treated with Western medicine. Forty-five of the patients had severe SARS (25 of these were in the integrated treatment group and 20 were in the group treated with Western medicine). Twenty-nine patients were male and 47 were female (a sex ratio of 1:1.6). The oldest was 83 years old and the youngest 19 years old. The average age was 42.2 ± 14.3 years (median age 44 years). The comorbidities included coronary heart disease (2 cases), hypertension (1 case), arrhythmia (1 case), nephritic syndrome (1 case), acute aplastic anaemia (1 case) and ascites due to cirrhosis (1 case). The average time from onset to admission was 1.6 ± 0.3 days for all patients.

Pattern of clinical symptoms during the early stage of illness

The first symptom of all 76 patients in this study was fever with a body temperature of more than 38 °C accompanied by anxiety, hypodynamia, headache, aching joints and myalgia (Fig. 1).

Fig. 1. Frequency of clinical symptoms of 76 patients with severe acute respiratory syndrome



Research on symptomatology

Reliability evaluation

Reliability evaluation was carried out using Cronbach's alpha coefficient: alpha = 0.8692.

Effectiveness evaluation (constructional effectiveness) (Table 1)

Table 1. Eigenvalues of the reduced correlation matrix: total = 35; average = 1

	Eigenvalue	Difference	Proportion	Cumulative
1	9.61764872	4.54607489	0.2748	0.2748
2	5.07157384	2.31671143	0.1449	0.4197
3	2.75486241	0.78248853	0.0787	0.4984
4	1.97237388	0.19231886	0.0564	0.5548
5	1.78005503	0.19464264	0.0509	0.6056
6	1.58541239	0.19882086	0.0453	0.6509
7	1.38659152	0.11318719	0.0396	0.6905
8	1.27340434	0.18520579	0.0364	0.7269
9	1.08819855	0.10683761	0.0311	0.7580
10	0.98136093	0.07239765	0.0280	0.7860

Six factors retained by the NFACTOR criterion.

Evolution of traditional Chinese medicine symptomatology

Through the evaluation of reliability and effectiveness of the investigations reported on SARS TCM symptoms, in combination with the results from cluster analysis and factor analysis, SARS TCM symptoms can be divided into three stages and five syndromes. The three stages are the pyretogenic stage (1–7 days), cough and gasp stage (5–14 days) and the convalescent stage (14–21 days and

later). The five syndromes are: invasion of pathogenic factor into lung, retention of virus in lung, impediment of the activities of the lung, deficiency of both *qi* and *yin* and stagnation of pathogenic phlegm.

The characteristics of the three stages are as follows:
- *during the pyretogenic stage*, toxin and heat;
- *during the cough and gasp stage*, stagnation and turbidity; and
- *during the convalescent stage*, weakened healthy-*qi* with stagnation of pathogenic phlegm.

The five syndromes usually occur as follows:
- invasion of pathogenic factor into lung usually occurs during the pyretogenic stage;
- retention of virus in the lung and impediment of the activities of the lung occur during the cough and gasp stage; and
- deficiency of both *qi* and *yin* and stagnation of pathogenic phlegm occur in the convalescent stage.

The patterns of symptoms are described below.
Invasion of pathogenic factor into lung syndrome: fever, fear, anxiety, hypodynamia, anorexia, headache, aching body, exhaustion in the limbs, insomnia, weakened tone, then dry cough with little sputum, shortness of breath, deep-red tongue with thick fur.

Retention of virus in lung syndrome: high fever, sweating without reducing heat (fever), chest distress, fatigue, shortness of breath, breathlessness; dizziness, feeling of heaviness, abdominal distension, tiredness, difficulty in falling asleep and possibly agitation, reddened tongue with yellowish and white fur.

Impediment of the activities of the lung syndrome: declining high fever or stable temperature, breathlessness, rapid breathing, dyspnoea, chest distress, hypodynamia, anxiety, possibly mental weariness and incoherent speech, sweating and cold limbs, purple and dark lips, accompanied by weakened tone, tiredness, tongue with speckles.

Deficiency of both qi *and* yin *syndrome*: chest distress, dizziness, shortness of breath, hypodynamia, dysphoria with feverish sensation in chest, palms and soles, reddened complexion, slight thirst, mental weariness, distrustfulness, reddened or light red tongue, swelling of the tongue, pale fur.

Stagnation of pathogenic phlegm syndrome: breathlessness that becomes more serious when patient is moving, chest distress, hypodynamia, palpitations, joint aching, hair loss, anxiety, insomnia, deep-red tongue or speckled tongue, thin fur.

Influence of the two treatment regimens on oxygen saturation

Through the observation of oxygen saturation on the seventh, thirteenth and twenty-third days, in patients with normal SARS, integrated treatment and treatment with Western medicine were both found to improve oxygen saturation. There was no obvious difference between the two treatment groups. Similar results were obtained in patients with severe SARS; both treatment regimens

improved oxygen saturation. The integrated treatment could obviously stabilize the fluctuation range of oxygen saturation that had been normalized, whereas this effect was less obvious with Western medicine alone.

Influence of the two types of treatment on case fatality rate

Of the 76 SARS patients studied, 65 (85.53%) recovered and were discharged from hospital. Of the 11 patients who died, five deaths were caused by SARS alone (6.58%); and six deaths resulted from complications of SARS (7.89%). None of the patients with normal SARS died; all of the 11 patients who died had severe SARS. Five of the patients who died were in the integrated treatment group, four of them had underlying diseases (two had coronary heart disease and one had arrythmia). The average age was 61.0 ± 15.0 years; the oldest was 83 and the youngest 48 years old. Of the six patients who died in the group treated with Western medicine, three had underlying diseases (one had ascites caused by cirrhosis, one had nephritic disease syndrome and one had aplastic anaemia and diabetes mellitus). The average age of patients in this group was 59.5 ± 10.7 years; the oldest was 72 and the youngest 45 years old.

On the basis of the above analysis, the case fatality rate in the integrated treatment group was 20%; whereas that in the group treated with Western medicine was 30%. No obvious difference between these two groups was seen. However, a tendency towards a reduction in the case fatality rate was noted in the integrated treatment group.

Discussion[21]

SARS is a new disease that belongs to the category of epidemic febrile diseases according to its clinical symptoms and evolution. The cause of the disease is the invasion of virus through the mouth and nose. The main symptom of infection is fever, accompanied by hypodynamia, dry cough, dyspnoea and other symptoms. Noxious heat, stagnation and turbidity together with deficiency of healthy-*qi* are the three kinds of pathogenesis of SARS (*3*). This is a disease characterized by a sudden onset causing serious illness and rapid deterioration, with its nidus at the lung, but having a concurrent impact on other organs such as the liver, heart, spleen, stomach and kidneys.

The results of the analysis of the evolution of SARS TCM symptomatology and pathogenesis obtained in this study are generally in conformity with the theory of epidemic febrile diseases in TCM. "When invading upward, the pathogenic fever shall impair lung first"; this is the common characteristic of both SARS and of more common epidemic febrile diseases. The difference is that the nidus of SARS is in the lung whereas that of epidemic febrile diseases is not. SARS is extremely infective; the illness does not follow the normal pattern of diseases in *wi*, *qi*, *yin* and blood, with the pathogen lingering in the *qi* system and predominating in mid-*jiao* in most cases, and symptoms of *qi* are severe and advance quickly, those involving the blood system are scarcely seen. Also,

[21] Note that parts of this discussion are aimed at explaining the pathogenesis from the perspective of Traditional Chinese medicine

manifestation of impairment of *qi* causing hypodynamia can usually be seen at the early stage of SARS whereas at the early stage of other epidemic febrile diseases, impairment of body fluid and draining of *yin* can be observed, manifestation of the impairment of *qi* can only be seen at the late stage.

The main pathogenesis of SARS is the retention of virus in the lung, stagnation of pathogenic phlegm, impediment of the activities of the lung and deficiency of both *qi* and *yin* (*4*). The pathogenic fever originates from the virus entering through the mouth and nose to invade the lung first. Lung governs *qi* and commands *wei*, the health *qi* and the pathogens compete in the lungs causing patients to experience fever with chills and aching of the body; retention of virus in the lung and impairment and decreasing function of lung, so high fever and sweating without removal of pathogens, dry cough and breathlessness are seen. Invasion of epidemic toxin into the lung causes impediment of the lung function, so patients may experience breathlessness, chest distress, gasping and coughing, and production of little or no sputum. If the lung heat transfers into the intestine, *fu-qi* will be obstructed and turbidity will not descend. Obstruction of *qi* causes abdominal distension, poor appetite, nausea and vomiting. Epidemic toxin can alter the state of mind, so that patients may feel panic-stricken, terrified and perplexed. If the body's resistance fails to overcome the pathogenic factors and the virus penetrates deeper, the patient will experience simultaneous disorders in *qi* and *yin* systems that are manifested as agitation, dizziness and incoherent speech. During the course of the disease, epidemic toxin consumes *qi* and damages *yin*, which leads to hypodynamia, weariness, disinclination to talk, thirst, spontaneous perspiration and other symptoms. The earlier the damage of *qi* and *yin* occurs, the more serious the prognosis will be.

Traditional Chinese medicine can be used to intervene in the pyretogenic, cough and gasp and convalescent stage. Comparative superiority to Western medicine alone was seen at all stages (eliminating pathogenic factors, strengthening body resistance and preventing pathogenic transformation). Through clinical observation, physicians can identify the pathogenesis and provide treatment appropriate to each of the stages of the disease. The key point of pathogenesis in the pyretogenic stage is toxin and heat; stagnancy and turbidity are the key points in the cough and gasp stage; and asthenia is the key point in the convalescent stage. Pathological manifestations were the first to occur in most patients followed by clinical symptoms; symptoms may overlap in these stages. Therefore, with an understanding of the evolution rule of the disease, curative drugs for prospective treatment can be used at the next stage (*5*).

It is not appropriate to use hormone treatment at the pyretogenic stage. During the aggravated cough and gasp stage (emission process), hormone should be administered at a sufficient dose; 40 mg/day may be adequate, but it is possible to raise the dose up to 80–320 mg/day. Reduction of use of hormone and termination of treatment should be conducted with caution. The principle for dose reduction should be based on the standard criteria as judged by stable condition of illness, commencement of absorption of inflammation in the lung and alleviation of clinical symptoms. The intention should be to reduce the dose by one third in 3–5 days. Traditional Chinese medicine should be adjusted accordingly during the whole course of dose reduction and termination of hormone treatment; intravenous drips can be terminated first and replaced by small doses administered orally, which can then be stopped gradually.

This research demonstrates that even when a complete and thorough knowledge of pathogenesis, pathological change and rule of evolution of SARS is not available, TCM, with its unique theoretical system, can "observe pulse syndromes to understand which pathogen invaded". A reasonable TCM analysis of the etiology and pathogenesis of the disease can be made, and appropriate TCM treatment can be provided based on overall analysis of a patient's condition in order to stabilize oxygen saturation and reduce the abnormal fluctuation range. It can reduce the case fatality rate of severe cases. The results of this study therefore indicate that TCM has advantages in treatment of SARS.

Acknowledgements

This paper is dedicated to those medical professionals in Tianjin who lost their lives in the campaign against SARS, and we acknowledge our indebtedness to the State Administration of Traditional Chinese Medicine, Tianjin Science and Technology Commission and Tianjin Municipal Bureau of Health, for their assistance and support.

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Annex
Questionnaire for severe acute respiratory syndrome — Traditional Chinese medicine symptomatology

Date of filling out the form:

Name:

Sex: male □ female □

Age:

Inpatient No. or ward/bed No.:

Profession: student □ teacher □ medical professional □ manual labourer (except agricultural) □ government employee □ soldier or police officer □ farmer □ individual worker □ researcher □ business person □ unemployed □ retired □ other □

Home address or work address:
Tel:
Date of onset of disease: **Date of admission to hospital:**
Date of discharge from hospital:
Diagnostic classification: normal case □ serious case □
Number of days since onset (upon filling out the form):
Observation hospital:

TCM Diagnosis: early stage □ intermediate stage □ fastigium □ convalescent stage □

Scoring instructions: A, never; B, occasionally; C, sometimes; D, often; E, always
1. Do you have fever? yes □ no □
1.1 Quality of fever
1) Fever with aversion to cold □ 2) strong fever □ 3) intense fever in the afternoon □
4) intense fever at night □ 5) hectic fever □ 6) low fever □ 7) recessive fever □ 8) cold shivers □ 9) dysphoria with feverish sensation in chest, palms and soles □

2. Do you sweat? yes □ no □
2.1 Quality of sweat
1) slight sweat □ 2) little sweat □ 3) excessive perspiration □ 4) cold sweat □ 5) morbid perspiration only over the head □ 6) excessive perspiration all over □

3. Do you have the following symptoms? 1) cough □ 2) dry cough □ 3) expectoration □
3.1 Quality of expectoration
1) expectoration with blood streaks □ 2) little sputum □ 3) copious sputum □ 4) rale in the throat □ 5) thick sputum hard to expectorate □ 6) yellow sputum □

7) white sputum □

4. Do you have the following symptoms?
1) chest stuffiness □ 2) shortness of breath □ 3) breathlessness 4) gasping □ 5) dyspnoea □ 6) great difficulty with breathing □ 7) palpitations □

5. Do you have the following symptoms?
1) aching all over □ 2) headache □ 3) dizziness □ 4) head feels like it is tightly bound □ 5) tiredness and heaviness of limbs □ 6) heavy body □ 7) chest pain □ 8) sore throat □ 9) dry throat □

6. Do you have the following symptoms?
1) mental weariness □ 2) hypodynamia □ 3) deficiency of *qi* □ 4) disinclination to speak □ 5) inclination to yawn □ 6) inclination to sleep □ 7) susceptibility to sighing □ 8) vexation □

7. Do you suffer from insomnia? yes □ no □
7.1 Characteristics of insomnia: 1) difficulty falling asleep □ 2) dreamful sleep □ 3) easily awakened □ 4) wake early □ 5) others □

8. Do you have the following symptoms?
1) dry mouth □ 2) bitter taste □ 3) stickiness in the mouth □ 4) thirst □5) nausea □ 6) vomiting □ 7) constipation □ 8) loose stool □ 9) sticky stool □ 10) deep-coloured urine □ 11) poor appetite □ 12) normal appetite □ 13) abdominal distension □ 14) flatulence from bowels □
8.1 Type of thirst:
1) slight thirst □ 2) fond of hot drinks □ 3) fond of cold drinks □ 4) thirsty but want no drinks □ 5) want to gargle but not swallow □

9. Do you experience one or more of the following feelings?
1) terror □ 2) anxiety □ 3) irritability □ 4) panic □ 5) melancholy □ 6) sorrow □ 7) doubt □ 8) impetuosity □ 9) over-meditative □

10. Have you any of the following symptoms?
1) involuntary movement □ 2) fondness for sleep □ 3) delirium □ 4) coma □

11. Have you any of the following convulsion symptoms?
1) involuntary movement of fingers □ 2) convulsion of extremities □ 3) eyes looking upwards □ 4) clenched teeth □ 5) stiff neck □ 6) opisthotonos □

12. Have you any of the following syncope symptoms? 1) chilly extremities □ 2) faintness □

13. Mental condition: 1) normal □ 2) lassitude □ 3) fatigue □ 4) listless □ 5) over active

14. Voice: 1) normal □ 2) loud □ 3) low and timid (weak) □ 4) deep and vague □ 5) hoarse □

15. Complexion:
1) red □ 2) flushed □ 3) flush on cheeks □ 4) yellow □ 5) sallow □ 6) pale □ 7) white □ 8) darkish □

16. Facial lustre:
1) lustre □ 2) slight lustre □ 3) dim (no lustre) □

17. Lip colour:
1) reddish □ 2) red □ 3) cyanotic □

18. Tongue:
1) with teeth prints □ 2) swollen □ 3) thin □ 4) bristly □ 5) fissured □
6) ecchymosis □

19. Tongue tinge:
1) pale □ 2) pale red □ 3) red □ 4) deep red at the tongue tip □ 5) red at tongue edges □ 6) entire tongue deep red □ 7) dark red □ 8) crimson □ 9) purple (deep) □ 10) pale purple □ 11) cyanosis □

20. Coating (A):
1) thin □ 2) slight coating □ 3) no coating □ 4) thick □ 5) greasy □ 6) curdy (deposit) □

21. Coating (B):
1) even (normal) □ 2) complete coating □ 3) partial coating □ 4) lingua geographica □ 5) mirror-like tongue, smooth coating □

22. Coating (C):
1) moist □ 2) slippery □ 3) little saliva □ 4) dry □

23. Coating (D) — colour:
1) white □ 2) yellow □ 3) yellowish □ 4) yellow with white □ 5) grey (slightly grey) □ 6) carbon black □ 7) as mouldy paste □ 8) black (as soot) □

24. Physical examination:
1) body temperature
2) respiration (times/min)
3) pulse (times/min)
4) blood pressure

25. Laboratory tests:
1) haemoglobin (g/dl)
2) white blood cell count
3) blood platelet count
4) PaO_2 (kPa)
5) oxygen saturation (SpO_2) (%)

26. Chest X-ray manifestation:

Signature of observer:……..

Report 4
Clinical study on 103 inpatients undergoing therapy with integrated Traditional Chinese medicine and Western medicine

Lin Lin[22], Han Yun[22], Yang Zhimin[22], Liu Weisheng[22], Zhang Minzhou[22], Tang Guanghua[22] and Xu Yinji[22]

Abstract The objective of this study was to investigate the law of dynamic change of the state of patients with atypical pneumonia, also known as severe acute respiratory syndrome (SARS), and the clinical curative effects of therapy with integrated Traditional Chinese medicine (TCM) and Western medicine. The subjects of this study were 103 patients who had been diagnosed with SARS between January and April 2003, who were all treated with a therapeutic regimen of integrated traditional Chinese and Western medicine. In a retrospective study, information was collected on the general conditions, symptoms, results of laboratory examinations, and therapeutic effects, for all the patients when they were admitted to hospital. Emphasis was placed on the dynamic data collected at regular intervals from 77 patients with severe conditions. Data included information on clinical symptoms, body temperatures, results of routine blood tests and chest radiographs. Data were used to establish the database to conduct statistical analyses such as the χ^2 test, *t*-test, descriptive analysis and so on. Of the 103 patients, 77 had severe SARS and 26 had normal SARS: 7 (6.97%) died during the course of the study and 96 (93.21%) were cured and discharged. The defervescence time of the 103 patients after treatment in the hospital was 6.72 ± 3.95 days. Of the 77 severe cases, 29 (37.66%) were transferred to the intensive care unit for further treatment, 40 patients (51.95%) underwent non-invasive ventilation, whereas eight patients (10.39%) required invasive ventilation. The defervescence time of the 77 severe cases after treatment in the hospital was 8.34 ± 5.06 days. Unlike the patients with normal SARS, the 29 patients with severe SARS (37.66%) had lesions over the whole lung, and patchy images and a misty image on the chest radiograph were more common in these patients ($p < 0.05$). There are some recognizable patterns in the changes of clinical symptoms, laboratory examination results and chest radiographs of SARS patients. The patient with serious SARS had a more rapid clinical course and a poorer prognosis. A therapeutic regimen of integrated TCM and Western medicine had obvious curative effects on SARS patients.

Introduction

The World Health Organization (WHO) termed the atypical pneumonia, first seen in 2003, as severe acute respiratory syndrome (SARS) (*1*). SARS has been reported from 32 countries and regions around the world. From January to April

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2003, 103 SARS patients were admitted to the Guangdong Provincial Hospital of Traditional Chinese Medicine, including 77 severe cases. All inpatients were treated with a therapeutic regimen of integrated traditional and Western medicine. A retrospective study was conducted to determine the patterns of dynamic variation in the condition of SARS patients and learn about the clinical curative effect of treatment of SARS patients with integrated Traditional Chinese medicine and Western medicine.

Subjects and methods

Study design

The study was conducted by retrospective research on clinical cases of SARS.

Subjects

One hundred and three patients were included in the study; they were all inpatients at the Guangdong Provincial Hospital of Traditional Chinese Medicine.

Diagnostic criteria

The diagnostic criteria adopted were the "Diagnosis criteria of SARS clinical case" in the *Guideline for clinical diagnosis of severe acute respiratory syndrome* issued by Health Department of Guangdong Province on 9 March 2003 (*2*).

Inclusion criteria

Inpatients were eligible for inclusion if their clinical diagnosis was in accordance with the above-mentioned diagnostic criteria for SARS.

Exclusion criteria

Subjects who did not meet the diagnostic criteria were not eligible for inclusion in the study.

Therapeutic regimen

Treatment with Western medicine was based on the *Guideline for clinical diagnosis of severe acute respiratory syndrome* issued by the Health Department of Guangdong Province (*2*). Treatment with integrated traditional and Western medicine was based on the clinical stages and types into which SARS is classified by applying the theories of TCM on epidemic febrile disease of the four systems (*wei*, *qi*, *ying* and *xue*) and differentiation according to the tri-*jiao*.

Western medicine regimen

The main components of the Western medicine regimen included prescription of medicine specific for the illness, oxygen inhalation or assisted ventilation with breathing apparatus, hormone administration, nutritional support, administration of antibiotics, antiviral treatment and immune regulation.

Symptomatic treatment
Patients with a body temperature higher than 38.5 °C were treated with non-steroidal anti-inflammatory drugs. Patients with a cough were treated with drugs such as carberapentane citrate or codeine.

Oxygen inhalation or assisted ventilation with breathing apparatus
Oxygen inhalation was supplied through a nasal tube if indicated by the oxygen saturation of haemoglobin, the respiratory rate and the arterial blood gas analysis. Non-invasive inhalation of oxygen through a face mask as well as invasive ventilation was supplied to those patients in whom this was indicated. Non-invasive positive-pressure ventilation was chosen if the patient's respiratory rate was more than 30 times per minute or the oxygen saturation of haemoglobin was less than 93% even when oxygen was being inhaled at 3–5 litres per minute; nose-cup CPAP was the first option at a pressure level of 4–10 cmH_2O, and was administered continuously until the condition of the patient improved. Invasive positive pressure ventilation was chosen if the oxygen saturation of the patient's haemoglobin was still less than 90% even when inhaling oxygen at 5 litres/minute or if the oxygenate index was less than 200 mmHg after treatment with non-invasive positive-pressure ventilation, or if the patient could not tolerate the treatment with non-invasive positive-pressure ventilation.

Administration of glucocorticoids
Glucocorticoids were administered only to patients who had serious toxicity symptoms or to those who met the criteria for severe illness (i.e. those who had had a high fever for more than 3 days or whose chest radiographs had shown a trend of progressive aggravation). The usual dosage of methylprednisolone was in the range from 40 to 240 mg per day, but for the severe cases, a dosage of 500 mg per day could be administered. The dosage was regulated on a case-by-case basis.

Nutritional support
Nutrient mixture, compound amino acids and vitamins were administered through an intravenous drip. A fatty emulsion was also added to the drip fluid if the patient had a poor appetite, and albumin was supplied intravenously when the patient had a low level of albumin.

Administration of antibiotics
Regimen 1 adopted during the early stage of illness: azithromycin plus one type of beta-lactam.

Details of usage: azithromycin 0.5 g per day in intravenous drip on day 1, then azithromycin 0.25 g per day in intravenous drip on days 2–7, plus one type of beta-lactam simultaneously. The main beta-lactams included cefotaxime sodium at a dosage of 2–4 g per day administered twice daily in an intravenous drip, ceftazidime at a dosage of 2–6 g per day, administered twice or three times daily by intravenous drip, ceftriazone, 2–4 g per day once or twice daily by intravenous drip; cefepime, 2–4 g per day administered twice daily by intravenous drip; cefoperazone sodium and sulbactam sodium: 2–4 g per day administered twice daily by intravenous drip.

Regimen 2 adopted during the early stage of illness: levofloxacin 0.3 g per day by intravenous drip, plus tetracycline 2 g per day in four daily doses, administered orally. Vancomycin or norvancomycin was the treatment of choice if the results

of sputum culture or the clinical symptoms suggested the presence of infection with drug-resistant cocci. Tienam was administered at a dosage of 1.5 g per day three times a day by intravenous drip.

Administration of antiviral drugs
Oseltamivir, a neuraminidase inhibitor, was administered to 34 patients at a dosage of 150 mg twice per day for the first three days and then 75 mg per day until the end of the course of treatment (a course lasted 7–14 days if begun during the early stage of SARS).

Immunomodulator
Usually, gamma globulin at a dosage of 5 g per day was administered in an intravenous drip for 3 days. When the lymphocyte count was low, thymosin was injected at a dose of 160 mg once per 3 days.

Regimen of traditional Chinese medicine
According to the theories of Traditional Chinese medicine on the four systems (*wei*, *qi*, *yin* and *xue*) and differentiation according to the tri-*jiao*, the course of this disease can be divided into four parts: early stage, middle stage, fastigium stage (climax) and convalescent stage.

Early stage
This stage is defined as the period of 1–5 days or so after onset of illness. According to the differentiation of symptoms and signs, it should be treated by drainage of the moist heat and with *sanren* decoction in combination with *shengjiang san* powder and other drugs if appropriate. If the disease belongs to the moist heat and damages the defences of the lung, it should be treated by dispelling wind and relieving exterior syndrome (superficial or mild illness chiefly manifested by a chilly sensation, fever, headache, generalized aching and aching limbs) and by facilitating the flow of the lung-*qi* and clearing away heat with a recipe of *yingqiao* powder, *maxin ganshi* decoction in combination with *shengjiang san* powder and other drugs, if the disease belongs to the exterior cold and interior heat with dampness.

If heat pathogen was more serious in the early stage, one of the following injections was chosen and administered during a treatment course of 7 days or so until fever subsided or weakened body resistance was strengthened. The injections were:

- cordate houttuynia; 50–100 ml per day in an intravenous drip.
- *Qingkailing*, 40 ml with 5% glucose; 250 ml per day in an intravenous drip.
- Double coptis root injection, 3.6 g with 5% glucose; 500 ml per day in an intravenous drip.

Middle stage
This stage was defined as the period 3–10 days after onset of illness. If the disease belongs to the moist heat and containing toxin, it should be treated by clearing away heat and the wetness pathogen and by detoxification with or without *ganluxiaodu dan*. If the disease belongs to pathogenic factor which damages *shaoyang*, it should be treated by dissipating and discharging *shaoyang* and by clearing away heat and wetness pathogen with or without a *gaocenqingdan tang* decoction. If the disease sits in the half-superficies and half-interior position, it should be treated by leading off the pathogen with or without a *dayuan* drink.

If heat pathogen is serious or if the symptoms presented indicate the state of "containing toxin", one of the injections listed above for the early stage could be used. If fatigue is obvious or if there is a feeble pulse with little strength, *shenmai* injection can be administered at a dosage of 50–100 ml per day in an intravenous drip until the symptoms abate.

Fastigium stage (climax)
The clinical pathogenesis is characterized by abundant wet heat and toxin that dissipates *qi* and damages *yin*, and the stasis of wet heat and toxin in the lung is the main feature. The main manifestations include obvious polypnoea and dyspnoea, which may be accompanied by cyanosis, abdominal distension, constipation or loose stool. It should be treated by clearing away heat and eliminating dampness, facilitating the flow of the lung-*qi*, regulating the flow of *qi*, and removing *yong*, while paying attention to strengthening the body's resistance.

During the early phase of this stage, the stasis of wet heat and toxin in the lung is the main manifestation, and treatment is directed towards clearing away heat and toxins, regulating *qi*, invigorating the blood and eliminating dampness, as well as facilitating the flow of the lung-*qi* and removing *yong*. Medicine for supplementing *qi* and nourishing *yin* can be added when necessary. The treatment can include *ganluxiaodu dan* and *wuhu tang* decoction, plus tuber of aromatic turmeric, raw cattail pollen, *Leonurus heterophyllus, chuanlian*, British inulaflower, seed of peppergrass, balloonflower root, as well as bitter orange. The recipe for supplementing *qi* and nourishing *yin* is pseudostellaria root, plus gypsum and powder of antelope horn or buffalo horn if fever is serious.

At the advanced stage, phlegm dampness and toxin exacerbate the stasis of the lung-*qi*, which decreases the functional activities of the lung; the weakness of spleen-*qi* and lung-*qi* are the main manifestations. The patients may suffer from dyspnoea, asthma and feeling of suffocation, thin and white sputum, weakness of limbs, fatigue, loose stools, diarrhoea, a pale, enlarged and dark tongue, white and muddy *tai*, and slippery and weak pulse.

Treatment of these patients should aim at replenishing *qi* to invigorate the spleen, regulating *qi* and invigorating the blood, dispersing phlegm and eliminating dampness, as well as purging the heat accumulated in the lung and eliminating the *yong* in the lung. The treatment can comprise *buzhong yiqi tang* and *wuhu tang* decoction, accompanied by *xiefei tang* decoction with whitlow grass and Chinese date, plus *ercheng tang* decoction, *sanziyangqing tang* decoction, *pingwei* powder and *xiaochengqi tang* decoction to enhance the function of regulating the flow of *qi* and eliminating dampness and clearing away the *yong*, plus lycopus herb, raw cattail pollen, *Leonurus heterophyllus*, peach kernel and safflower to stimulate circulation to end stasis.

If the patient presents with ice-cold limbs, pale and enlarged tongue and weak pulse, it means that the patient is in a state of weak *qi* and *yang*. *Shufuzi*, common fennel fruit and cassia twig should be added.

If the patient is suffering from dropsy, *wu lin san* and *zhen wu tang* should be added to the prescription.

A few patients can show pathogenic factor in blood, vigorous heat of *qi* and *ying*, and exhausted *qi* and asthma. According to the differentiation of syndromes, symptoms and signs, treatment should be focused on clearing away heat located at *yingfen* and detoxification, as well as on supplementing *qi* and nourishing *yin*, with *qingying tang* and pulse-activating powder if the patient's symptoms result from invasion of the *ying* system by pathogenic heat and from dissipating *qi* and damaging *yin*.

Injections
According to the differentiation of syndromes, symptoms and signs, patients whose symptoms result from excessive pathogenic factor and weakened body resistance, or from loss of consciousness and collapse could be grouped into five categories.

For patients deficient in yin-qi *and who exhibit prostration syndrome: Shenmai* injection at a dosage of 100 ml to 200 ml per day was administered intravenously or in an intravenous drip in several daily doses in addition to a decoction of American ginseng and pulp of dogwood fruit.

For patients deficient in yang-qi: *Shenfu* injection at a dosage of 20–100 ml per day intravenously or in an intravenous drip in several daily doses in addition to a decoction of red ginseng and *Paofuzi*.

For patients with heat blockage: half pill of cow-bezoar bolus once or twice a day.

For those suffering from impairment by turbid pathogen: a half pill of storax should be taken once or twice a day. If the patient has no obvious haemorrhagic tendency, 30 ml *xiangdan* injection with 250 ml 5% glucose can be administered once a day in an intravenous drip. Patients with digestive problems received *huoxiangzhengqi* water at a dosage of 30 ml three times per day and berberine at a dosage of 0.9 g/day three times daily.

Convalescent stage
This stage is usually defined as the period 10–14 days after the onset of illness, with the main pathogenesis of weakened body resistance and invasive pathogenic factor as well as an inclination towards dampness and stasis. The treatment of patients at this stage should focus on eliminating the pathogenic factor and strengthening the body resistance with attention being paid to eliminating dampness and to activating blood circulation. According to the differentiation of syndromes, symptoms and signs, if the patient's symptoms result from weakness of *qi* and *yin*, the treatment should focus on supplementing *qi* and nourishing *yin* with a *shenmai* powder or *shashengmaidong tang* decoction. If the patient's symptoms result from weakened *qi* with dampness and stasis, the treatment should focus on supplementing *qi* and clearing away the wetness-pathogen, as well as on activating blood circulation and expelling the obstruction from the branches of the meridians, with *lishiqingshuyiqi tang* decoction, *shenlinbaishu* powder or *xuefuzhuyu tang* decoction adjusted according to the needs of the individual patient.

The patients at this stage of the illness who had suffered from deficiency of *qi* and *yin* were treated with *shenmai* injection at a dosage of 50 ml in an intravenous drip for one or two 7-day courses. Alternatively, a solution of pulse-activation

decoction was given orally, at a dosage of 30 ml three times per day for two or three 7-days courses. Patients at this stage of illness who had suffered from obvious deficiency of *qi* were treated with a 30-ml injection of astragalus root added to 250 ml 5% glucose or 0.9% normal saline in an intravenous drip once a day for one or two courses of 7 days. For those patients who had stasis of blood, a 30-ml injection of *xiangdan* was added to 250 ml 5% glucose or 0.9% normal saline once a day for one or two courses of 7 days, accompanied by an orally administered solution of *xuefuzhuyu* at a dosage of 10 ml three times a day and for one or two courses of 7 days.

Observations

Clinical symptoms such as fever, cough, panting, joint and muscular aching, nausea and vomiting, diarrhoea, as well as the appearance of the tongue and the strength of the pulse; signs such as body temperature and respiration; results of routine blood tests, tests of renal function and liver function, chest X-ray and chest spiral CT.

Quality control

The following quality control measures were implemented.

- All doctors who worked with SARS patients in isolation wards were trained in the diagnosis and treatment of SARS.
- The 103 patients were all confirmed as clinically diagnosed cases after consultation with the Guangdong group of SARS experts.
- Data management protocols were implemented and original material checked.
- All herbal decoction pieces to be used had to comply with the requirements specified in the *Chinese Pharmacopoeia* (2000 Edition, Part I) and the patent medicines used were prescription drugs for which market approval had been obtained from the Chinese drug administration.

Statistical treatment

The database was set up and statistical analysis carried out using the SPSS10.0 statistical package. Tests for normality and homogeneity were followed by the χ^2 test, rank-sum test and *t*-test, $\alpha = 0.05$.

Results

Status of patients admitted to hospital

General data

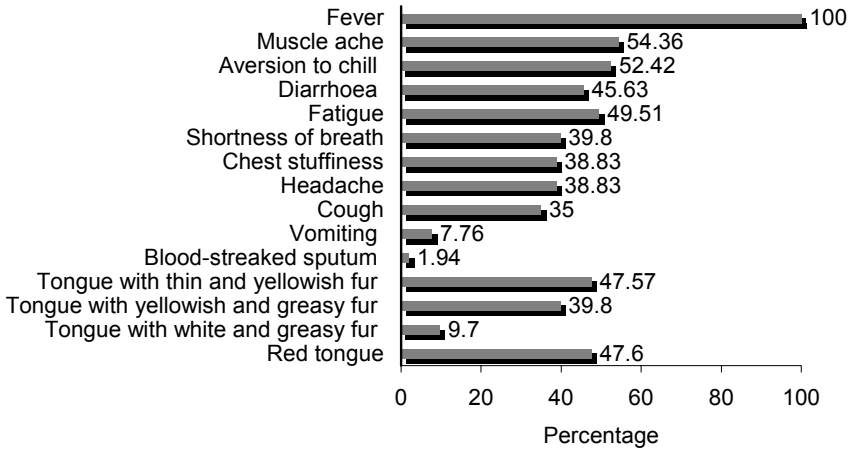
Of the 103 patients who participated in this study, 44 were male and 59 were female. The oldest patient was 79 years old and the youngest was 19 years old. The mean age was 34.64 ± 12.69 years. Ninety-three patients (90.29%) had a history of contact with SARS, whereas 10 had an unknown contact history. The average age of the 77 patients with severe SARS was 35.52 ± 13.38. Of these,

92.21% patients had a history of contact with SARS. The time between onset of illness and admission to hospital was 3.56 ± 2.67 days.

Symptoms, signs and appearance of tongue and characteristics of pulse at the time of admission

Fever was the common symptom of onset in all 103 patients. The major symptoms included: fever, muscular stiffness, aversion to cold, diarrhoea, fatigue, shortness of breath, chest distress, headache, cough, blood-streaked sputum, nausea and vomiting, red tongue, thin and yellowish tongue fur, yellowish and greasy tongue fur, and white and greasy tongue fur (Fig. 1).

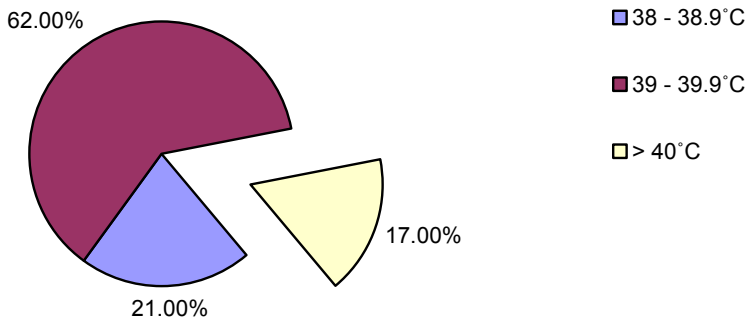
Fig. 1. Clinical symptoms of 103 patients with SARS



Body temperature at the time of admission

The highest temperature in the 103 patients was 39.11 ˚C ± 0.98. Eighty-one patients (78.64%) had a body temperature higher than 39 ˚C. The period of time for which body temperature was higher than 39 ˚C ranged from 1 day to 11 days with a mean value of 3.05 ± 2.21 days (Fig. 2).

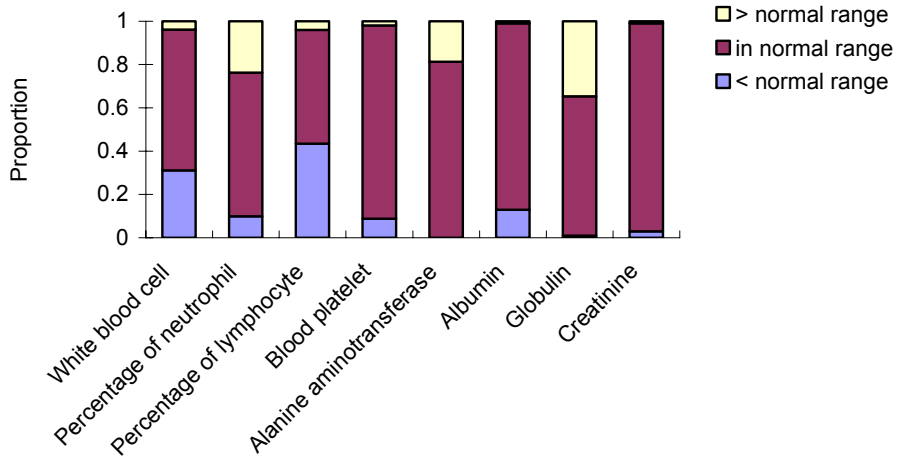
Fig. 2. The highest body temperature measured in 103 patients with severe acute respiratory syndrome



Results of laboratory tests at the time of admission

The results of peripheral blood tests and major indices of liver and kidney functions of the 103 SARS patients at the time of their admission to hospital are summarized in Fig. 3.

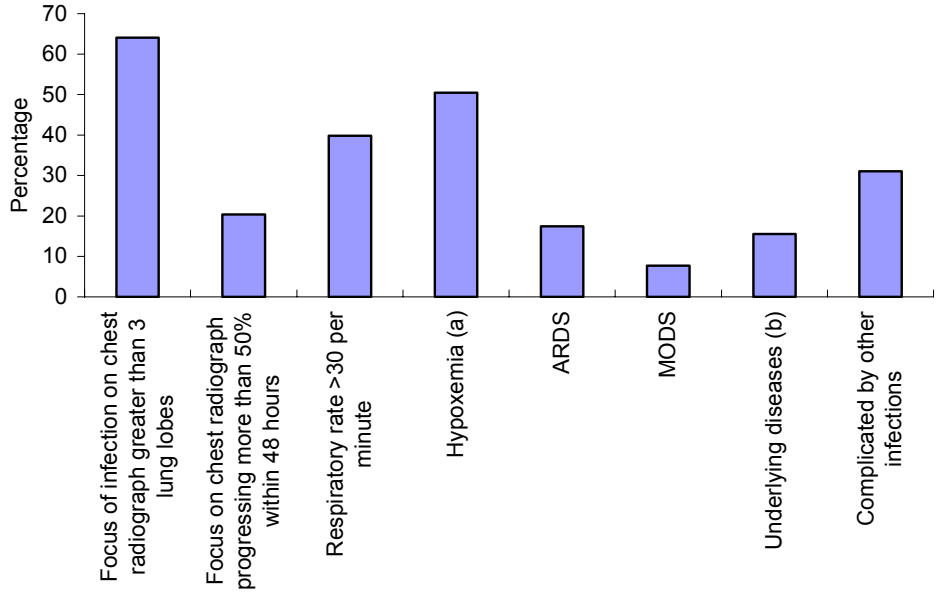
Fig. 3. Results of laboratory tests on 103 patients with severe acute respiratory syndrome at the time of their admission to hospital



Evaluation and classification of severity

Seventy-seven cases met the standard of "*Clinical diagnostic criteria of infectious SARS*"; the others were all normal cases. Patients with severe SARS all had lesions in multiple lung lobes, sometimes accompanied by underlying disease. The lesions progressed relatively rapidly and there were sometimes complications such as hypoxaemia, acute respiratory distress syndrome (ARDS) or multiple organ dysfunction syndrome (MODS). Of the patients with severe SARS, 40 received non-invasive ventilation, eight received invasive ventilation and 29 were transferred to the intensive care unit (Fig. 4).

Fig. 4. Evaluation of severity and major complications in 77 patients with severe cases of disease



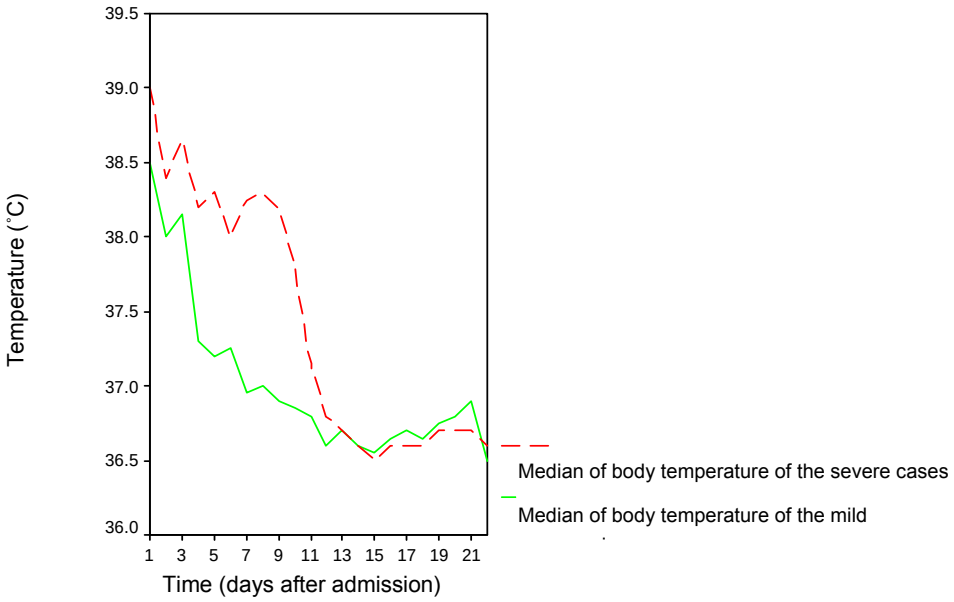
ARDS, Acute respiratory distress syndrome; MODS, multiple organ dysfunction syndrome.
(a) Hypoxaemia was defined as SaO_2 < 93% or oxygenation index < 300 mmHg when 3–5L/min oxygen was supplied.
(b) Underlying diseases: these included three patients with diabetes mellitus, one of whom had undergone amputation because of diabetic gangrene; three patients with coronary heart disease, one of whom had had a mitral valve replacement because of rheumatic heart disease; two patients with chronic renal failure; one patient with Crohn disease complicated by partial resection of the jejunum because of intestinal obstruction; and five patients with hypertensive disease.

Dynamic course of patient's condition

Changes in body temperature

The dynamic variations of body temperature in the patients after their admission to hospital are shown in Fig. 5.

Fig. 5. Day-by-day changes of body temperature (median) in patients with serious and normal severe acute respiratory syndrome



Dynamic course of clinical symptoms of 77 patients with severe SARS

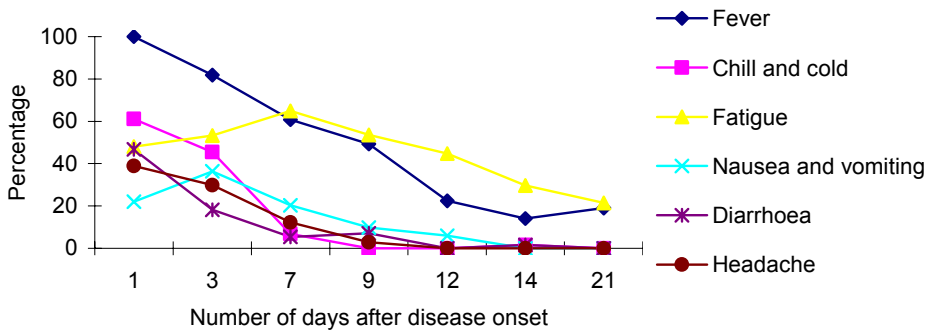
Symptoms such as aversion to cold, chills, headache, arthralgia and muscular aching, nausea and vomiting and diarrhoea were seen more frequently in the early stages of the illness. Symptoms in the respiratory tract such as cough, chest distress, and shortness of breath were aggravated between the seventh and ninth days after onset of illness, and general symptoms such as fatigue and inertia were also aggravated between the seventh and ninth days (Fig. 6a and Fig. 6b).

Results of dynamic routine blood tests of 77 patients with severe disease

At the onset of SARS, 46 patients (75.41%) had a normal white blood cell count and 13 patients had a decreased white blood cell count. The proportion of patients with an increased white blood cell count increased from the seventh day after onset and reached 29 cases (59.18%) on the twenty-first day. At the onset of illness, 23 patients (37.7%) had a decreased lymphocyte count. On the fourteenth day, the number of patients with a decreased lymphocyte count reached its peak (32 cases, 47.76%). During the initial stages of SARS, 58 cases (95.08%) had a normal or decreased neutrophilic granulocyte count. Seven days later the proportion of patients with an elevated neutrophilic granulocyte count increased significantly and reached 32 cases (65.30%) on the twenty-first day. During the early stages of SARS, 64 cases (84.21%) had a normal blood platelet count, and the proportion of patients with an increased platelet count rose from the fourteenth day. Only 2–6 patients (3.94–7.89%) had a decreased blood platelet count. All these counts had returned to a normal level by the time of follow-up (Figs 7 and 8).

Fig. 6. Dynamic course of clinical symptoms of 77 patients with severe disease

(a)



(b)

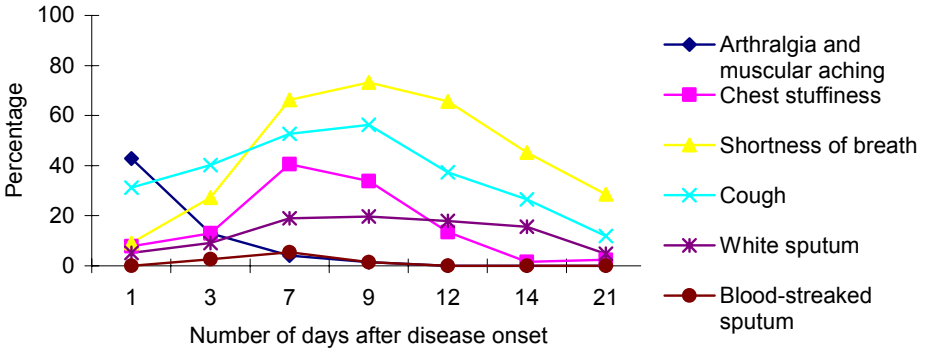
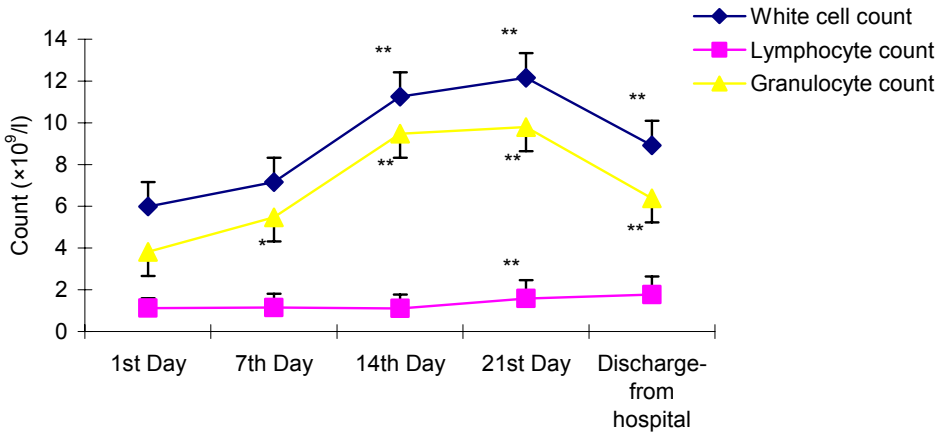
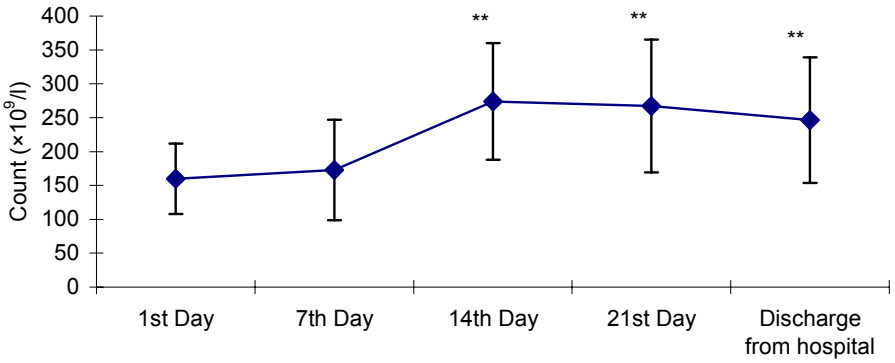


Fig 7. Dynamic course of white cell count of peripheral blood for 77 patients with severe illness ($x \pm s$)



A pair-matching *t*-test was used.
**Comparison with the first day $p < 0.01$.

Fig. 8. Dynamic course of platelet count of peripheral blood for 77 patients with severe illness ($x \pm s$)



A pair-matching *t*-test was used.
**Comparison to the first day, $p < 0.01$.

Features of chest radiograph at image fastigium stage

All 77 patients with severe SARS underwent chest radiography and 29 of them had lesions over the whole lung. The main manifestations of severe SARS seen on radiographs were patchy shadow, large patches of shadow and misty images. The images of large patches of shadow and misty appearance were more common on the chest radiographs of patients with severe SARS than in patients with normal SARS and the difference was statistically significant ($p < 0.05$) (see Table 1). (Note: image fastigium stage was defined as the time when the maximum focus was steady and would not expand any further.)

The results indicated that patients with severe SARS had a significantly higher proportion of large patches and misty images of parenchyma and mesenchyma than patients with normal SARS.

Table 1. Comparison of features of chest radiograph on image fastigium stage between patients with severe and normal SARS

Severity of illness	Small patch image	Patchy shadow	Large patches	Misty image	Exudation	Consolidation	Alteration of parenchyma	Mixed alteration of parenchyma and mesenchyma
Severe $n = 77$	2	47	24	14	41	42	38	36
Normal $n = 26$	6	16	2	0	17	9	15	4

Outcome of treatment

Gross effect

Of 103 patients, 96 (93.21%) were clinically cured and discharged and seven patients (6.79%) died. Two patients had a focus of fibrosis on their chest radiographs and one patient had diminution of eyesight after discharge. After

admission and treatment, defervescence time was 6.72 ± 3.95 days and few patients relapsed.

Of the 77 patients with severe SARS, two had infective shock, three had disseminated intravascular coagulation, seven had impaired renal function, eight had impaired liver function, eight had arrhythmia, six had haemorrhage of upper digestive tract, 18 had ARDS, eight had MODS, and one suffered from pneumothorax after endotracheal intubation. After the treatment, 70 (90.91%) of the patients who had had severe illness were clinically cured and discharged and seven (9.09%) had died. After admission and treatment, defervescence time was 8.34 ± 5.06 days. Twenty-nine patients were transferred to the intensive care unit. During their treatment, 40 patients (51.95%) received non-invasive ventilation and eight patients (10.39%) received invasive ventilation.

Results of examination of further chest radiographs
In 94 out of 96 patients (97.91%) the lung focus had completely disappeared. The time taken for focus absorption was 18.13 ± 8.99 days. Two patients had a focus of fibrosis on their chest radiographs.

Analysis of patients who died
The average age of the seven patients who died, all of whom had severe SARS, was 51.57 ± 13.36 years; the oldest was 75 years old and the youngest was 35 years old. Three of the patients who died had serious underlying cardiovascular disease. One patient's condition deteriorated quickly and this patient died within 72 hours after admission to hospital. All these patients developed ARDS and progressed to MODS and death.

Results of sputum culture
Secondary bacterial infection was detected in 38 SARS patients and 55 separate bacterial strains were identified, including 25 strains of Gram-negative bacillus (20 strains of non-zymogen), 20 strains of Gram-positive cocci (13 strains of staphylococci with negative coagulase) and 10 strains of *Candida albicans*.

Administration of glucocorticoids
Of the 103 SARS patients, 69 had been administered glucocorticoids whereas 34 had not. The intravenous glucocorticoid used was generally methylprednisolone except for three cases in which decasterolone (5–10 mg/day, 1–3 days) was administered in the initial stages of illness. In the later stages of the disease, the doses of glucocorticoid were decreased and oral preparations of prednisone and methylprednisolone were chosen (all dosages were converted to equivalent dosages of methylprednisolone). Those patients who had not been treated with glucocorticoids all recovered and were subsequently discharged (Table 2).

Table 2. Administration of glucocorticoids

Severity of illness	No glucocorticoids administered	Glucocorticoid administered	Maximum dosage per day (mg)	Minimum dosage per day (mg	Mean dosage (mg) ± standard deviation	Course of treatment (days) ± standard deviation
Normal *n* = 26	14 (54)	12 (46)	160	40	83.33 ± 39.85	8.83 ± 5.69
Severe *n* = 77	20 (26)	57 (74)	500	10	166.83 ± 116.06	18.80 ± 2.23

Discussion and conclusion

Dynamic analysis of clinical data from patients with severe illness

All 103 patients had a rapid onset of illness. The majority of them were adults with a mean age of 35.52 ± 13.38 years and 92.21% of patients had a history of contact with the disease. Fever was the common symptom of onset, and 66 patients had a body temperature exceeding 39 °C. Patients with severe SARS had a higher body temperature and longer duration of fever than patients with normal SARS. Fluctuation of body temperature was noted in the course of defervescence, but body temperature returned to normal rapidly when it was lower than 38 °C. During the early stage of SARS, common symptoms included fever, aversion to cold, chills, headache, muscle and joint pain, nausea and vomiting, and diarrhoea. These symptoms were considered to be the presentation of viraemia. As the illness progressed, respiratory tract symptoms such as cough, chest distress and shortness of breath, and general symptoms such as fatigue were gradually aggravated during days 7–12 of the illness; this period coincided with radiological manifestation at the image fastigium stage (9.91 ± 3.58 days) of severe SARS. Autopsy of patients who had died from SARS revealed acute diffuse whole-lobule interstitial pneumonia and formation of transparent membrane in the alveoli that could lead to hypoxaemia or to ARDS and was the main reason for aggravation of symptoms at the fastigium stage.

Patients with severe SARS usually had a normal or lowered white blood cell count at the onset of illness and an increased white blood cell count during the middle and final stages of the disease which peaked on day 21. Twenty-five patients (32.46%) still had an increased white blood cell count when they were discharged from hospital. At the onset of SARS, 23 patients (37.7%) had a decreased lymphocyte count. On the fourteenth day, the number of patients with a decreased lymphocyte count reached its peak (32 cases, 47.76%) and the lymphocyte count decreased to its lowest point ($1.11 \pm 0.66 \times 10^9$/l). Few patients had a decreased blood platelet count; of these three suffered from disseminated intravascular coagulation and died. Twenty-six patients (38.80%) had an increased platelet count during the middle and last stages of the disease. Abnormal blood counts had returned to the normal level by the time the patients were followed up. These results indicated that the SARS virus could impair immunological function at the onset of illness, and caused lymphocytopenia. The

serious decrease in the number of lymphocytes at the middle stage of the disease could be the result of double immunosuppression caused by glucocorticoids; this was a reversible impairment and the count was restored to normal when the patient's condition improved. The results of autopsies of SARS patients revealed that the lymphatic and haematopoietic system outside the lungs was impaired, particularly the production of T lymphocytes. Visceral bleeding, necrosis and vasculitis constituted the morphological features of acute SARS (*4*). The observations noted from the autopsies were in accordance with changes in the numbers of lymphocytes and platelets noted in our patients. The increased blood platelet count that occurred in the middle and final stages of SARS was considered to be the result of the administration of high doses of glucocorticoids, and its influence on the condition of the patients was unclear. During the middle and final stages of the disease, immunological function was depressed because of virus infection and administration of glucocorticoids, which led to secondary infections that accounted for the significant increases in the counts of white blood cells and neutrophils. Non-zymogen bacteria were responsible for most of the secondary bacterial infections, and infections caused by staphylococci with negative coagulase were second most common. Infection with *Candida albicans* or simultaneous infections with two or three different types of bacteria were seen in patients with serious SARS. *Candida albicans* infection was seen in those who had a flora imbalance.

The chest radiographs of patients with severe SARS presented a large focus that progressed rapidly. Twenty-nine patients had lesions over the whole lung. At the fastigium stage, large patchy shadow and misty shadow were the main manifestations of lung lesions. Relative to the radiographs of patients with normal SARS, serious SARS had a larger focus and longer absorption time, and residual lung lesions were seen in some patients who had severe SARS.

Analysis of results of treatment with integrated Traditional Chinese medicine

All 103 patients with SARS in this study had a rapid onset of illness and most had a history of contact with the disease and were seriously ill. Of the 103 cases, 77 met the diagnostic criteria for severe SARS. After treatment with integrated Chinese medicine and Western medicine, 96 (93.21%) of the 103 SARS patients had been cured clinically and seven had died (6.79%). Those who were cured had a defervescence time of 6.72 ± 3.95 days after admission and no relapse of fever. The chest radiographs of ninety-four of the patients showed complete absorption. Of the patients with severe SARS, 70 (90.91%) had been clinically cured and discharged and seven had died (9.09%), a rate lower than that for patients with severe "typical" pneumonia. In addition, the absorption of lung focus in these patients was good. Therapy with integrated traditional and Western medicine was adopted to treat this group of SARS patients, and emphasis was put on strengthening the body resistance to eliminate pathogenic factors in combination with reinforcement of protection and elimination of disease. Modern medicine places emphasis on support and monitoring. The results of the combination of support and monitoring indicate that therapy with integrated Chinese medicine and Western medicine has a good curative effect on SARS.

Administration of hormone

A major symptom of SARS was hypoxaemia, and patients with severe SARS were liable to progress to ARDS. SARS virus and administration of glucocorticoids inhibited immunological function, especially cellular immunity, making SARS patients susceptible to secondary bacterial infections during the last stage of disease. Certain "modern" medical treatments, notably effective oxygen therapy and assisted ventilation with breathing apparatus had an important impact on prognosis. For patients with severe SARS, timely administration of glucocorticoids was helpful in ameliorating toxicity symptoms and alleviating inflammation of the lung. But it must be noted that glucocorticoids were a double-edged sword in the treatment of SARS. In this study, 54% of patients with normal SARS and 26% of the patients with severe SARS had not been treated with glucocorticoids, and in other patients the dosage of glucocorticoids was low, which might be the result of the treatment with TCM. Further research is needed to determine whether there was a difference in prognosis between patients who were not given glucocorticoids and those who were. Previous studies have shown that a lower dosage of glucocorticoids leading to fewer side-effects could be used if TCM was added to the treatment regime. The interaction of glucocorticoids and TCM in SARS patients merits further research.

In conclusion, for the management of SARS, treatment that integrates traditional Chinese and Western medicine can incorporate the merits of both. Modern medicine is excellent for supporting, monitoring, reducing inflammation and so on, whereas Traditional Chinese medicine can ameliorate symptoms and improve curative effect by strengthening the body's resistance enabling it to eliminate pathogenic factors, and by adjusting body condition through individual diagnosis and treatment on the basis of an overall analysis of the illness and the patient's condition. Further research will be needed to clarify the mechanism of action of TCM on SARS and the interaction between TCM and Western medicine, as well as the impact of TCM on prognosis of SARS.

Acknowledgements

In the process of developing the TCM regimen for SARS control, the following experts in TCM gave us useful guidance: Professor Deng Tietao and Professor Peng Shengquan, Guangzhou University of Traditional Chinese Medicine; Professor Ren Jixue, Changchun College of Traditional Chinese Medicine; Professor Jiao Shude and Professor Chao Enxiang, Beijing China-Japan Friendship Hospital; Professor Lu Zhizheng and Professor Lu Guangshen, China Academy of TCM; Professor Yan Dexin, Medical College of Shanghai Tongji University and Professor Zhou Zhongying, Nanjing, University of Traditional Chinese Medicine. We hereby express our thanks.

We are grateful for funding received from Special Funds for SARS of the State Administration of Traditional Chinese Medicine, People's Republic of China (GZYKFDZX No. 08).

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Report 5
Clinical observations of 11 patients with SARS treated with Traditional Chinese medicine

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Abstract Through clinical observation of 11 patients with severe acute respiratory syndrome (SARS) admitted to the Ministry of Health China–Japan Friendship Hospital and treated with Traditional Chinese medicine (TCM), this study examined the feasibility and effectiveness of treating SARS with TCM. TCM prescriptions and TCM preparations for intravenous drips were used to treat 11 patients with SARS, instead of treating them with glucocorticoid, antiviral drugs, immunomodulator and other conventional Western medicines. Antibiotics were not used unless there was clear evidence of bacterial infection. The curative effects were evaluated by measuring factors such as fever-abatement time, time taken for changes to be seen on the chest X-ray, length of hospitalization period and cost of hospitalization. The fever-abatement time was between 2 and 7 days; chest radiographs showed that the shadow in the lungs of nine patients was almost absorbed, with an average absorption time of 14.56 ± 6.71 days; two of the patients showed less improvement. The average duration of hospitalization was 20.45 ± 6.04 days; the per capita cost of hospitalization was 7024.41 yuan and the per capita cost of medications was 3874.83 yuan. None of the cases included in this study was severe. Patients with normal SARS can be treated successfully by TCM alone.

Introduction

SARS is a new and highly infectious respiratory disease on which knowledge is still being gathered. In the past, TCM has been used effectively to treat influenza, viral pneumonia, encephalitis B, epidemic haemorrhagic fever, measles, epidemic parotiditis and other viral infections. Based on these successful experiences together with observations on approximately 60 patients with SARS admitted to the China–Japan Friendship Hospital (under the Ministry of Health) in early April 2003, we developed a therapeutic regimen, by using the TCM theory on pestilence, which was administered to 11 patients with SARS admitted to the same hospital. The following is a preliminary clinical treatment report, which is expected to provide the basis for an effective approach to the clinical treatment of SARS with TCM.

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Research subjects and method

Research subjects

Research subjects

- *Source of cases*: SARS patients admitted to China–Japan Friendship Hospital (under the Ministry of Health) after 8 May 2003.
- The diagnostic criteria were those formulated by the Ministry of Health of the People's Republic of China in the document entitled *Clinical diagnosis criteria for infectious SARS* (proposed) (amended on 3 May 2003).

All the patients who participated in this study were referred to the hospital after the diagnosis of SARS had been confirmed by the Beijing Centre for Disease Control (CDC).

Case inclusion criteria
Patients included in the study were:
- those that complied with the criteria for diagnosis of SARS;
- those infected by SARS not more than 10 days before admission to hospital; and
- those who had not systematically been treated with hormones and antiviral drugs before being hospitalized.

Exclusion criteria
Patients excluded from the study were:
- those with severe SARS;
- those infected by SARS more than 10 days before admission to hospital; and
- those who had been systematically treated with hormones and antiviral drugs before being hospitalized.

General information
Gender distribution: of the 11 patients, nine were male and two were female.
Age distribution: the youngest patient was 22 years old and the eldest 52 years old. The average age was 34.91 ± 11.67 years.
Underlying disease: two of the patients suffered concurrently from underlying disease; one had hypertension and one type 2 diabetes.

Main clinical symptoms
The main clinical symptoms are summarized in Table 1.

Table 1. Main clinical symptoms manifested in patients

Symptoms	Initial diagnosis No of cases	At the time of hospitalization No of cases
Cough	7	6
Fever	11	4
Headache	1	3
Inertia	1	3
Shortness of breath	0	3
Aversion to cold	3	2
Dyspnoea	0	2
Feeling of oppression in chest	3	2
Diarrhoea	1	1
Myalgia	1	1

Therapeutic regimen

The development process of SARS was divided into five stages, namely:

- incubation;
- pyretogenic;
- cough and gasp;
- collapse; and
- convalescent.

The pyretogenic stage is subdivided into three substages: onset, strong fever and toxic heat. Overlap of two or even three stages was possible in patients with severe SARS. Based on the above divisions, 12 TCM prescriptions for oral administration were developed (for the purposes of this paper the prescriptions are referred to as SARS prescriptions 1–12). Prescription 4 was developed specifically for treating patients who had received glucocorticoid. Thus none of the participants in this study were treated with SARS prescription 4. These preparations were used in combination with an intravenous drip of TCM. All the Chinese patent medicines were prescription drugs approved by State Drug Administration and are available commercially, and all the decoction pieces conformed to the *Chinese Pharmacopoeia* (2000 Edition).

Pyretogenic stage

Onset substage

The onset substage is characterized by retention of pathogenic factor in the superficial defensive system. The onset of fever was 1–3 days previously; symptoms manifested include fever, cough, headache, muscular stiffness, reddened tongue with white or greasy fur, and slippery pulse. The principles of treatment are to dispel the wind and heat, and remove toxins and dampness.

The herbal decoction for oral administration is SARS prescription 1 (Rhizoma Phragmitis 30 g, Lonicera japonica 30 g, periostracum cicadae (cicada slough) 6 g, bombyx batryticatus (stiff silkworm) 6 g, almond 10 g, unprepared Semen Coicis 30 g, and Herba Eupatorii 6 g). This prescription is used in combination with an intravenous drip containing *shuanghuanglian* powder for injection and houttuynia injection.

Strong fever substage (retention of pathogenic heat in lung)
The onset of fever was 3–5 days previously; symptoms include high fever, cough, thirst, hyperhidrosis, reddened tongue with thick or greasy and yellowish fur, and slippery pulse. The principles of treatment are to clear away heat to ventilate the lung and remove toxins to promote blood circulation. The herbal decoction for oral administration is SARS prescription 2 (including stir-fried ephedra 6 g, unprepared gypsum 30 g, almond 10 g, Lonicera japonica 30 g, Rhizoma Phragmitis 30 g, Radices Scutellariae 10 g, Cortex Mori Radicis 30 g and Radices Paeoniae Rubra 30 g), which is used in combination with an intravenous drip of *qingkailing* injection, houttuynia injection, and Salvia miltiorrhiza injection.

Toxic heat substage
The toxic heat substage is characterized by intense heat in both *qi* and *ying* systems; accumulation of toxins and stagnant heat in lung). Fever has lasted for more than 5 days; symptoms include persistent high fever, flushed face, cough, shortness of breath, dark reddened or deep red tongue, yellow thick dry or dark fur, with slippery or deep pulse. The principles of treatment are to clear *qi* and remove heat from *ying*, and remove toxins to promote blood circulation.

The herbal decoction for oral administration is SARS prescription 3 (unprepared gypsum 60 g, Rhizoma Phragmitis 60 g, Radices Scutellariae 15 g, dried rehmannia root 30 g, buffalo horn (to be decocted first) 60 g, unprepared Radices Rhei 6 g, Radices Paeoniae Rubra 30 g and Flores Carthami 10 g used in combination with an intravenous drip of *xingnaojing* injection, houttuynia injection and Salvia miltiorrhiza injection.

Cough and gasp stage
For patients who have been treated with hormones (deficiency in *yin* induces vigorous fire, stagnation of water and pathogenic heat).

Symptoms manifested include gasping and dyspnoea, cough, shortness of breath, feverish sensation in the palms and soles, hyperhidrosis, dry mouth and tongue, reddened tongue with little fur, and slippery pulse. The principles of treatment are to nourish *yin* to clear away the fire; activate blood circulation and promote the circulation of water.

The herbal decoction for oral administration is SARS prescription 4 (unprepared Radices Rehmanniae 30 g, Cortex Phellodendri 15 g, Rhizoma Anemarrhenae 15 g, unprepared licorice 10 g, pberetima 10 g, Radices Paeoniae Rubra 30 g, Herba Lycopi 30 g, and pseudostellaria root 15 g). The prescription is used in combination with an intravenous drip containing Salvia miltiorrhiza injection.

For patients who have not been treated with hormones (excessive heat in the lung, stagnation of pathogenic phlegm).

Symptoms manifested include the fever that has been allayed or not yet completely allayed, dyspnoea, cough, breathlessness, shortness of breath, reddened tongue with white or yellowish and sticky fur, and strong pulse. The principles of treatment are to remove heat from the lungs to relieve asthma, and clear the hollow viscera to promote blood circulation.

The herbal decoction for oral administration is SARS prescription 5 (including Radices Scutellariae 15 g, Cortex Mori Radicis 30 g, whole Mongolian snakegourd 30 g, Semen Lepidii 15 g, almond 15 g, pberetima 10 g, Radices Paeoniae 30 g and unprepared rhubarb 6 g). This prescription is used in combination with an intravenous drip of Salvia miltiorrhiza injection.

Collapse stage

Consumption of pectoral qi: symptoms manifested include rapid breathing, increased heart rate, profuse perspiration, mental weariness, reddened or reddish tongue, thin and white fur, with thready and weak pulse. The principles of treatment are to nourish *qi* and stop collapse, and to promote blood circulation by removing blood stasis.

The herbal decoction for oral administration is SARS prescription 6 (pseudostellaria root 30 g, Radix Astragali 30 g, pulp of dogwood fruit 15 g, Radix Ophiopogonis 30 g, pberetima 10 g and safflower 10 g). The prescription is used in combination with an intravenous drip of Salvia miltiorrhiza injection and *shenmai* injection.

Consumption of primordial qi: symptoms manifested include shortness of breath, increased heart rate, hidrorrhoea, coldness in the four limbs, reddish or light purple tongue, with rapid and weak pulse. The principles of treatment are to warm *yang* and stop depletion and to promote blood circulation by removing blood stasis.

The herbal decoction for oral administration is SARS prescription 7 (Jilin Radix Ginseng 15 g, *danfu pian* 10 g, Radix Astragali 30 g, pulp of dogwood fruit 30 g, Semen Persicae 10 g and safflower 10 g). This prescription is used in combination with an intravenous drip of Salvia miltiorrhiza injection and *shenfu* injection.

Convalescence stage

Deficiency of qi *and blood in the heart and spleen*: symptoms manifested include palpitations, mental confusion, shortness of breath, inertia, excessive sweating, mental weariness, poor appetite, reddish tongue with thin and white fur, and weak pulse. The principles of treatment are to replenish *qi* to invigorate the spleen, and nourish the heart to calm the mind.

The herbal decoction for oral administration is SARS prescription 8 (Radix Astragali 30 g, pseudostellaria root 15 g, tuckahoe 15 g, parched Atractylodes macrocephala 10 g, Radices Polygalae 10 g, lilyturf root 30 g, dried rehmannia root 15 g, amethyst (to be decocted first) 30 g, Fructus Schizandrae 10 g and Radices Salviae Miltiorrhizae 15 g). This prescription is used in combination with an intravenous drip of Salvia miltiorrhiza injection and *Shenmai* injection.

Disharmony between the heart and kidney: symptoms manifested include insomnia, hypochondriac discomfort, restlessness, irascibility, palpitations and inquietude, feverish sensation in palms and soles, dry mouth (more obvious at night),

hidrosis, reddened tongue, white and dry fur, with weak pulse. The principles of treatment are to keep the heart fire and the kidney *yin* in balance; nourish the blood and soothe the nerves.

The herbal decoction for oral administration is SARS prescription 9 (rhizoma coptidis 3 g, donkey-hide gelatine (to be melted by heating) 10 g, Radices Scutellariae 10 g, Radices Paeoniae Alba 30 g, unprepared lily 30 g, dried rehmannia root 20 g, parched date kernel 30 g, and Fructus Schizandrae 10 g). The prescription is used in combination with an intravenous drip of Salvia miltiorrhiza injection and *shenmai* injection.

Dampness and heat in the liver channel: symptoms manifested include fullness in both costal regions, distension and fullness in gastric cavity, poor appetite, lassitude and listlessness, sticky and greasy perspiration, reddish tongue, yellow thick and greasy fur, with deep and slippery pulse. The principles of treatment are to remove heat from the liver, and remove toxins and dampness.

The herbal decoction for oral administration is SARS prescription 10 (Paris polyphylla Sm. Rhizoma Bistortae 20 g, Rhizoma Smilacis Glabrae 30 g, Herba Hedyotidis 15 g, herba of stringy stonecrop 15 g, Herba Artemisiae 15 g, Fructus Schizandrae 10 g, parched Atractylodes macrocephala 10 g, and three scorched herbs (scorched germinating barley, hawthorn fruit and medicated leaven) 30g) used in combination with intravenous drip of *kuhuang* injection or *yinzhihuang* injection.

Deficiency of yin *due to excess fire and toxic substances*: symptoms manifested include flushed face and red eyes, feverish sensation in palms and soles, hypochondriac discomfort and uneasiness, dry throat and thirst, constipation and yellow urine, dark red tongue, little fur or white, thick and dry fur, with weak pulse. The principles of treatment are to clear away pathogenic heat and remove the toxin, and nourish *yin* to reduce pathogenic fire.

The herbal decoction for oral administration is SARS prescription 11 (Cortex Phellodendri 10 g, Rhizoma Anemarrhenae 10 g, dried rehmannia root 20 g, unprepared licorice 10 g, Rhizoma Coptidis 3 g, Radices Trichosanthis 20 g, adenophora root 30 g, and Cortex Granati 20 g).

Accumulation of phlegm in pulmonary vessels: symptoms manifested include cough and asthma that is especially obvious after movement, chest distress, lassitude and listlessness, dark red tongue, white fur, deep and weak pulse. The principles of treatment are to nourish *qi* and moisten the lung; disperse phlegm and activate the channels.

The herbal decoction for oral administration is SARS prescription 12 (pseudostellaria root 20 g, Radices Glehniae 30 g, Fructus Schizandrae 10 g, Thunberg fritillary bulb 10 g, earthworm 10 g, leech 30 g, Radices Pseudoginseng 3 g, and tabasheer 10 g).

Observations

Types of observation
Observations on the following aspects of illness were recorded: clinical symptoms, change in physical signs, routine blood and biochemical assays, chest X-ray, duration and cost of hospitalization.

Period of observation
The period of observation started from the time when the patient was admitted to the hospital and ended at the time when he or she was discharged from hospital or died.

The criteria for discharging a patient from hospital were based on the *Reference standard for the discharge of cases of infectious SARS* issued by the Ministry of Health of the People's Republic of China and on meeting the following requirements:

- Body temperature had returned to normal for at least 7 days.
- Respiratory symptoms had been obviously improved.
- X-ray showed clearly that the lung shadow had been absorbed.
- Course of the illness had lasted up to 21 days.

Results

None of the 11 SARS patients treated with Traditional Chinese medicines became severely ill.

In four of the patients (those who had fever when they were admitted to hospital; Nos 4, 5, 8 and 11), the fever abated on days 3, 6, 7 and 2, respectively. Continuous observations were made and there was no recurrence of fever before these patients were discharged (Table 2 and Fig. 1).

Fig. 1. Change of body temperature

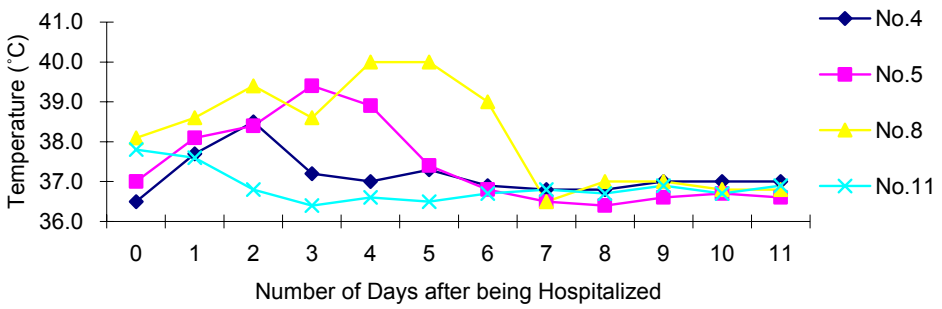


Table 2. Characteristics of fever in 11 study subjects[a]

Patient No	Date of onset	Date of admission to hospital	Highest body temperature before admission (°C)	Body temperature at time of admission (°C)	Highest body temperature after admission	Date on which fever abated
1	8 May	13 May	39.0	<37.0	<37.0	–
2	8 May	12 May	40.0	<37.0	<37.0	–
3	13 May	16 May	39.0	37.3	37.3	–
4	3 May	13 May	39.7	37.7	38.5	May 16
5	3 May	9 May	38.6	37.0	39.4	May 15
6	7 May	12 May	39.4	<37.0	<37.0	–
7	6 May	13 May	38.4	<37.0	<37.0	–
8	5 May	9 May	39.0	38.2	40.0	May 16
9	7 May	12 May	39.0	<37.0	<37.0	–
10	28 April	8 May	38.3	<37.0	<37.0	–
11	11 May	13 May	39.3	37.8	37.8	May 15

[a]The average time for between onset of SARS and admission to the hospital was 5.5 ± 2.6 days (ranging from 2 days at the shortest to 10 days at the longest).

The lymphocyte counts of three of the patients at the time of hospitalization were lower than 1.0×10^9/l, and those of the remaining eight patients were all lower than 1.5×10^9/l. After the treatment, nine patients had a lymphocyte count higher than 1.5×10^9/l, and the other two had counts higher than 1.0×10^9/l, but lower than 1.5×10^9/l. The total white blood cell counts (lymphocyte percentage and neutrophil granulocyte percentage) after treatment were all within the normal range (Figs 2–7 and Table 3).

Fig. 2. Change in lymphocyte count before and after treatment

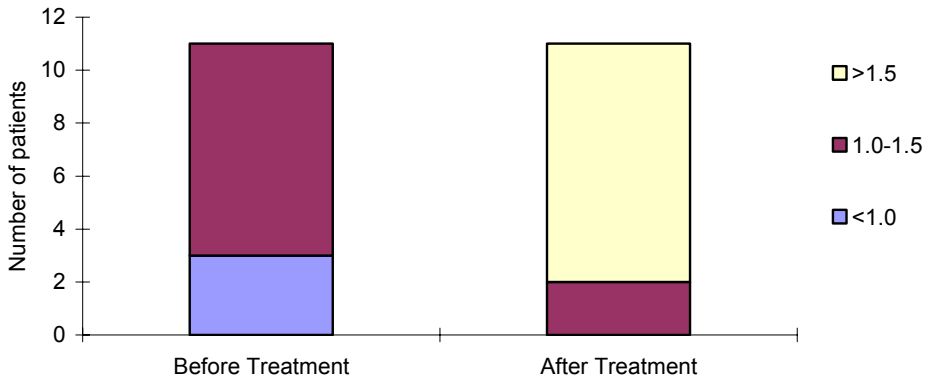


Table 3. Results of routine blood tests before and after the treatment

	WBC (× 10⁹/l)		GRAN %		LYM (× 10⁹/l)		LYM (%)		PLT	
	Before	After	Before	After	Before	After	Before	After	Before	After
1	2.9	4.9	52.9	68.8	0.9	1.2	33.0	23.7	141.0	165.0
2	4.2	6.3	59.8	64.8	0.9	1.6	22.0	25.5	151.0	179.0
3	4.4	5.6	63.7	66.2	1.2	1.5	26.5	25.8	117.0	186.0
4	8.0	5.6	72.3	49.6	1.1	2.3	14.3	41.1	279.0	224.0
5	3.7	4.8	61.8	48.5	1.0	1.9	28.1	40.1	108.0	359.0
6	4.7	5.9	61.7	44.5	1.3	2.9	28.2	49.4	182.0	260.0
7	7.5	5.3	78.6	57.7	1.4	2.0	18.4	37.5	248.0	183.0
8	4.3	5.7	77.1	48.7	0.6	2.2	14.8	38.5	159.0	234.0
9	3.6	5.6	47.7	46.5	1.1	1.9	28.9	34.0	193.0	215.0
11	5.9	8.3	73.9	50.8	1.3	3.1	21.3	37.3	194.0	305.0
Average	4.9	5.8	65.0	54.6	1.1	2.1	23.6	35.3	177.2	231.0

WBC, White blood cell count; GRAN, granulocyte count; LYM, lymphocyte count; PLT, platelet count.

Fig. 3. Change of lymphocyte count

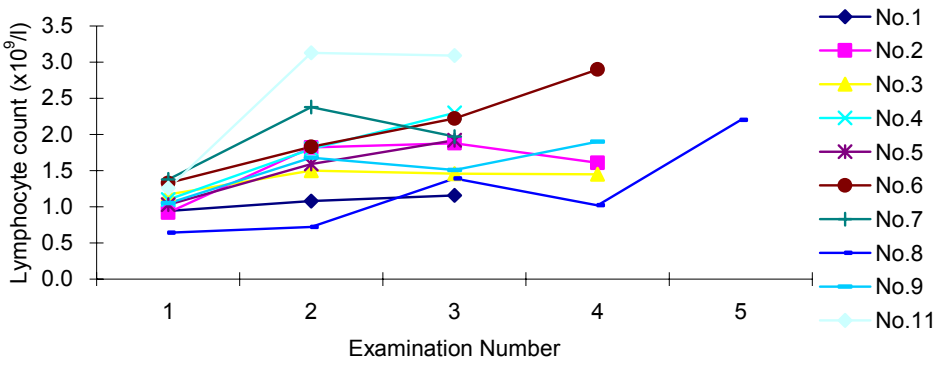


Fig. 4. Change of total white blood cell count

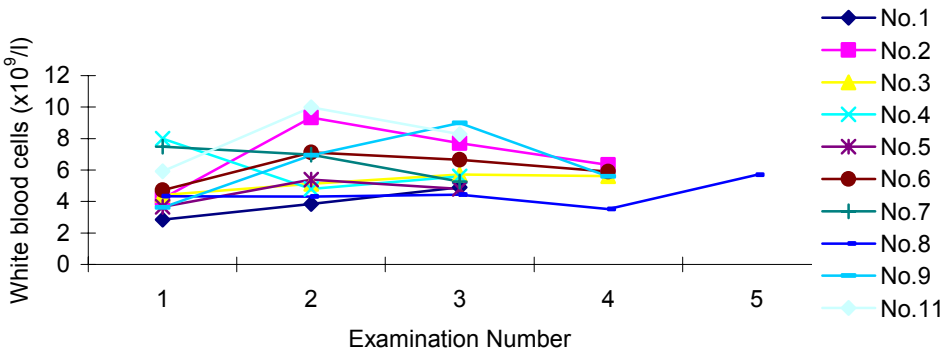


Fig. 5. Change of neutrophil granulocyte percentage

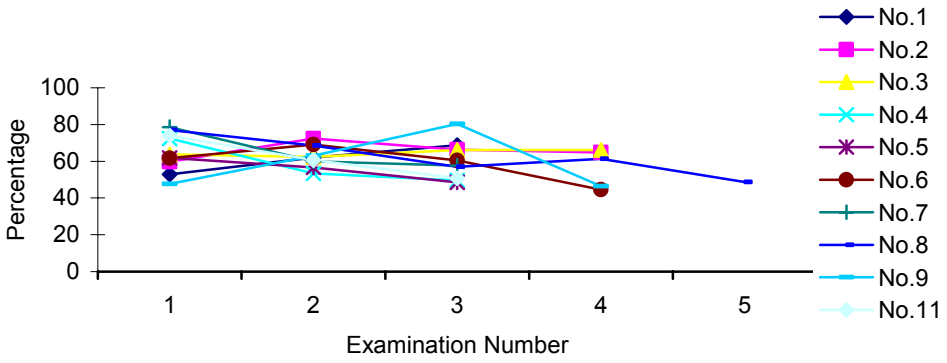


Fig. 6. Change of lymphocyte percentage

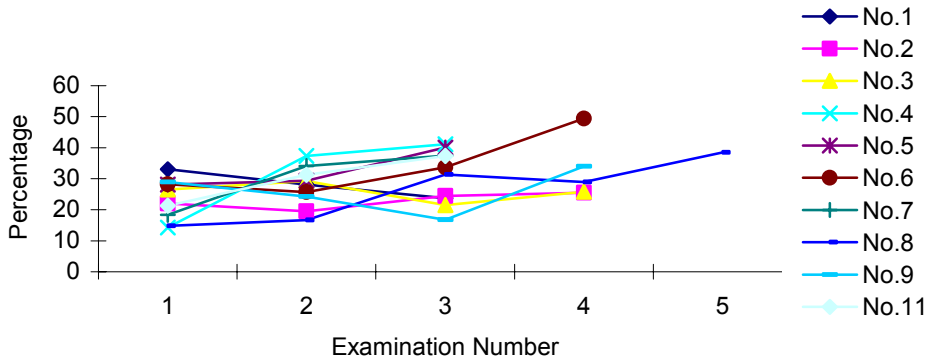
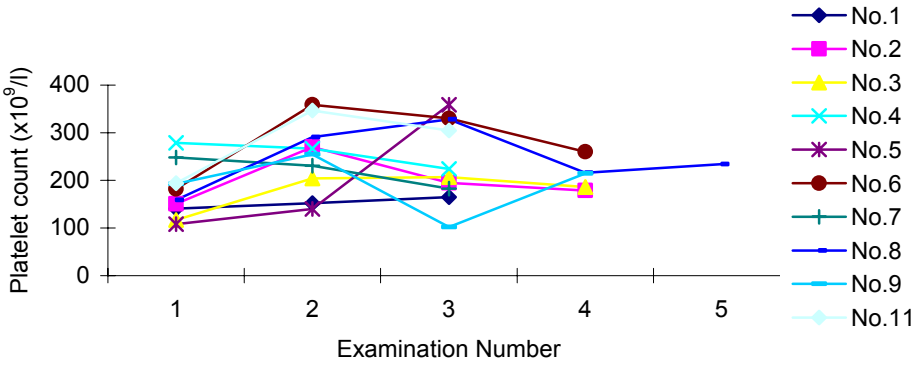


Fig. 7. Change of platelet count



From the chest radiographs of the 11 patients, it could be seen that the lung shadow in nine of them had almost been absorbed after a mean of 14.56 ± 6.71 days, and the two remaining patients had shown an improvement. (Note: The basic absorption criterion was that no abnormality was visible on the chest radiograph. The criterion for improvement was that the chest radiograph showed that the infiltration range had been reduced by over 50%, or from bilateral

pathological change to unilateral pathological change, or from unilateral multi-lobular lesions to single-lobular or local lesions.)

Three patients were found to have increased alanine aminotransferase (ALT) when they were admitted to the hospital, but they improved to a varying extent after treatment (Table 4, Fig. 8). The ALT of four other patients started to rise on days 7, 11, 8 and 9, respectively, after being hospitalized (i.e. days 10, 16, 12 and 11 after being attacked by SARS). One patient had a normal level of ALT when he left the hospital. None of the 11 patients showed abnormalities of renal function after the treatment. Two patients had a high blood sugar level when they were admitted to the hospital but it returned to normal after the treatment, whereas the remaining nine patients showed no increase in blood sugar level. The changes in concentration of aspartate transaminase, blood urea nitrogen, creatinine and glutamic acid are shown in Figs 9–12.

Table 4. Liver and renal function before and after treatment

Patient	ALT		AST		BUN		CRE		GLU	
no	Before	After	Before	After	Before	After	Before	After	Before	After
1	24	35	22	28	9.8		0.5		71	
2	95	89	44	37	12.0	11.8	1.1	1.1	85	83
3	35	88	26	33	10.8	14.4	1.1	1.3	102	86
4	141	70	126	37	32.6	21.2	1.2	1.2	164	74
5	14		16		6.2		0.9			
6	41	19	49	20	8.1	8.0	1.1	0.9	99	81
7	20	26	16	19	14.9	11.6	1.2	1.0	92	73
8	26	179	33	80	8.2	11.8	0.9	1.1	134	88
9	65	35	37	21	11.0	10.1	1.3	1.3	98	83
11	44	116	44	45	9.4	13.6	1.2	1.2	105	96
Average	51	73	41	36	12.3	12.8	1.1	1.1	106	83

ALT, Alanine aminotransferase; AST, aspartate transaminase; BUN, blood urea nitrogen; CRE, creatinine; GLU, glutamic acid

Fig. 8. Change in concentration of alanine aminotransferase

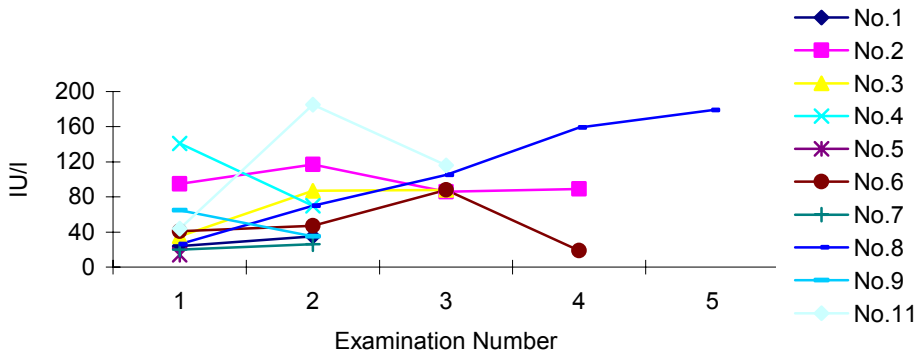


Fig. 9. Change in concentration of aspartate transaminase

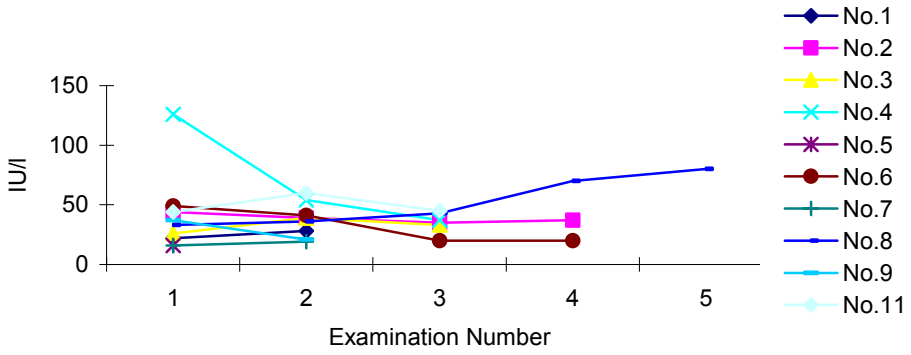


Fig. 10. Change in concentration of blood urea nitrogen

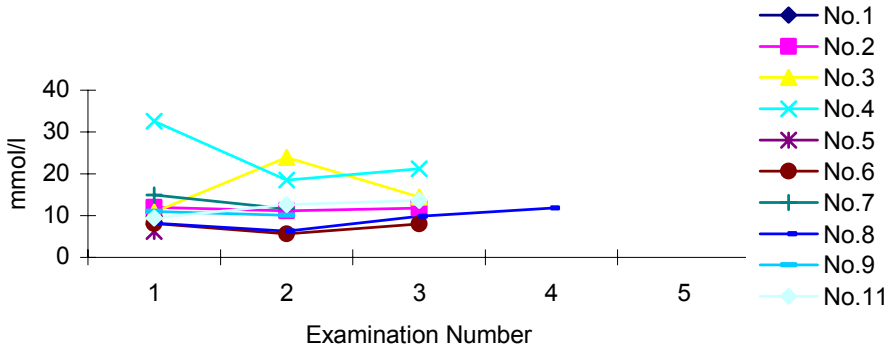


Fig. 11. Change in concentration of creatinine

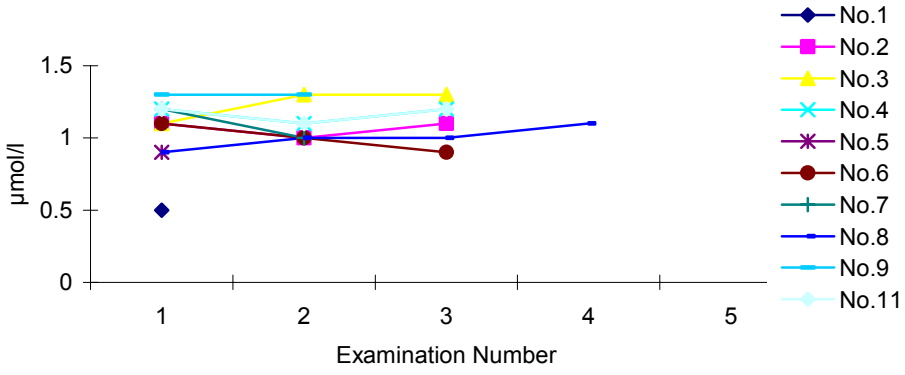
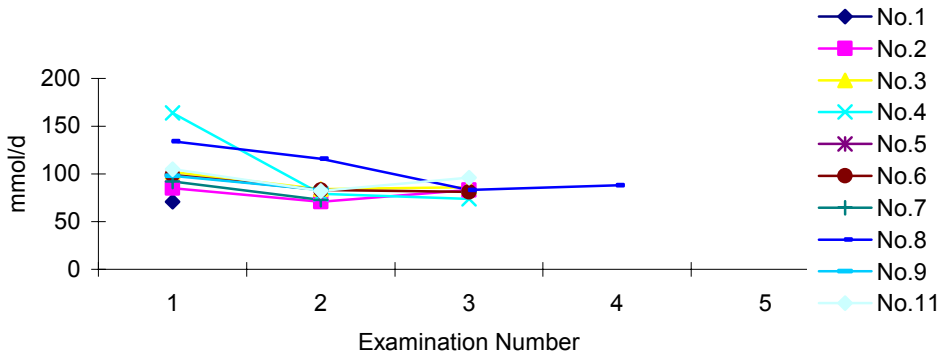


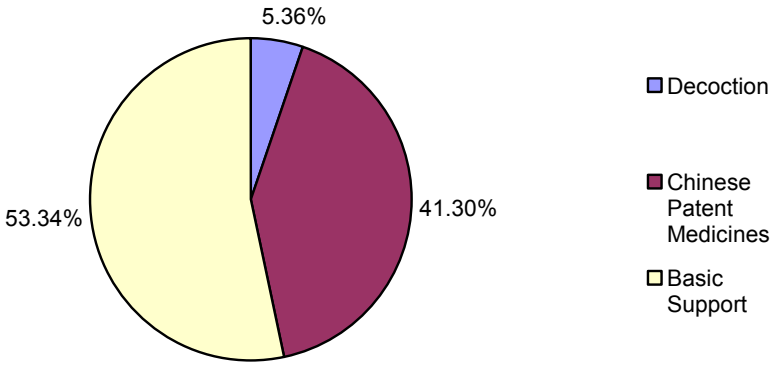
Fig. 12. Change of concentration of glutamic acid



Duration of hospitalization and costs

The average length of stay in hospital was 20.45 ± 6.04 days. The per capita cost of hospitalization was 7024.41 yuan, and the per capita medication expenses were 3874.83 yuan. The per capita cost of hospitalization for the control group was 18 867.36 yuan (Fig. 13). The control group consisted of 11 patients with normal SARS with a similar distribution of age, sex and state of illness, who were treated with Western medicine alone.

Fig. 13. Composition of the medical expenses



Discussion

Fever

All the 11 SARS patients had fever, and had received various treatments before being hospitalized. The body temperature of the four patients who still had a fever after being hospitalized returned to normal after 2, 3, 6 and 7 days, respectively, and none had a relapse, which indicates that TCMs have certain curative effects in terms of allaying fever.

Liver function

Three patients had abnormal liver function at the time of their admission to hospital, which had returned to normal by the time they left hospital. However, four other patients showed abnormal liver function only after being hospitalized. To find out whether this finding was related to the treatment with TCM or not, we looked at the liver functions of another 198 patients who had been hospitalized during the same period, and found that 104 of them had abnormal liver functions (52.5% of the total). The period from the ninth to the twelfth day after the onset of SARS was the peak time for signs of abnormal liver function; this period of time coincided with duplication of the SARS virus and the peak concentration of live virus. Therefore there is support for suggesting that the abnormal liver functions observed in four patients during the treatment may not have been directly related to the TCMs used.

Avoidance of harmful side-effects

As can be seen from the clinical observations, the use of TCM for the treatment of the 11 patients in this study is likely to have avoided the toxic effects and side-effects that may be caused by using large amounts of glucocorticoid, antiviral drugs and other Western medicines.

Absorption of shadow on lung

Chest radiographs showed that in nine out of the 11 patients with middle lung shadow, the shadow had been almost absorbed after a mean of 14.56 ± 6.71 days, and the remaining two cases showed improvement.

Conclusions

- Patients with normal SARS can be treated successfully with TCM alone.
- TCMs have good curative effects in allaying fever, restoring lymphocyte levels and improving absorption of inflammation.
- In terms of liver functions, renal functions and routine blood tests, the TCMs showed no obvious toxic effects or side-effects.
- Treatment with TCMs can avoid the toxic effects and side-effects that may be associated with the use of large amounts of glucocorticoid and antiviral drugs.
- Treatment with TCM can significantly reduce the cost of hospital treatment and shorten the number of days of hospitalization needed.

Acknowledgements

We would like to express our appreciation to the State Administration of Traditional Chinese Medicine of the People's Republic of China, which earmarked funds for this project. Our grateful thanks also go to the directors and medical staff of the China–Japan Friendship Hospital (under the Ministry of Health) who fought with us against SARS, and also to the leaders of the hospital and those working in the Department of Medical Affairs, Department of Science

and Education, Department of Radiation, the laboratories and the Office of Medical Cases of the hospital, who gave us their full support with the collection of clinical data.

Report 6
Effects of applying integrated therapy with Traditional Chinese medicine and Western medicine on liver and kidney functions in patients with SARS

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Abstract The objective was to investigate the effectiveness and safety of treatment for severe acute respiratory syndrome (SARS) applying an integrated therapeutic regimen of Traditional Chinese medicine (TCM) and Western medicine. Forty-seven patients with confirmed SARS were randomly allocated to either the integrated treatment group or the Western medicine-treated group for a treatment course of 3 weeks. Serum alanine aminotransferase (ALT), aspartate aminotransferase (AST) , total bilirubin (Tbil) and creatinine (CRE) and blood urea nitrogen (BUN) were measured every week throughout the treatment period. Hepatic dysfunction occurred in all patients. The total numbers of patients with hepatic dysfunction were 23 in the integrated treatment group and 21 in the group treated with Western medicine, and the numbers had decreased to 13 and 20 after treatment (p = 0.00441). The effect of TCM on ALT was the most marked: before treatment there were 20 and 8 patients with abnormal ALT in the integrated treatment group and the group treated with Western medicine, respectively, whereas the numbers were 13 and 19 after treatment. The highest level of ALT in the integrated treatment group was 81.54 ± 49.25 IU/l reached on day 7, and after treatment, it had decreased to 46.92 ± 29.25 IU/l ($p < 0.05$). In the group treated with Western medicine, the value before treatment was 53.96 ± 48.59 IU/l, and it had risen to 80.80 ± 56.26 IU/l after treatment ($p < 0.05$). There were nine and six patients with abnormal AST before treatment in the integrated treatment group and the group treated with Western medicine, respectively; the numbers had decreased to one and three cases, respectively after treatment. Fifteen patients in the integrated treatment group and 10 in the group treated with Western medicine had renal dysfunction. After treatment there were still six and four cases in the two groups, respectively. Dysfunction in liver and kidney appeared in SARS patients during the onset and later stages of the disease (particularly in ALT). It was shown that the integrated therapy with TCM and Western medicine was effective in alleviating damage to liver and kidneys, promoting improvement of hepatic function, protecting renal function and accelerating patients' recovery from illness, and the TCM regimen proved safe when applied in the treatment of SARS.

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Introduction

SARS is a respiratory system disease with strong infectivity and a high case fatality rate caused by a corona virus subtype (SARS virus) (*1*). The illness progresses very fast; acute respiratory distress syndrome (ARDS) may occur in some patients and many will suffer from impairment of liver and kidney functions (*2*–*4*). Because there is as yet no specific treatment for SARS, the present study used the general clinical characteristics of SARS patients and a prospective case–control study design to investigate the effects of therapy with integrated traditional and Western medicine on liver and kidney functions. The investigation considered the effectiveness and safety of TCM when used in the treatment of patients with SARS.

Methods

Study subjects

Source of case history

Medical histories were obtained from 47 patients with confirmed SARS admitted to our hospital. The histories of the patients were in compliance with the inclusion criteria for this study. The study subjects were randomly allocated to either the integrated treatment group (the experiment group) (24 cases) or the group treated with Western medicine (the control group) (23 cases). General information on the 47 cases is given in Table 1 and the distribution of symptoms is shown in Fig. 1.

The steroid, methylprednisolone, was used to treat patients in both groups, and the average accumulated dose was 5278.33 ± 4032.20 mg in the integrated treatment group and 6266.70 ± 4137.25 mg in the group treated with Western medicine (*t*-test; $p = 0.4113$) and there was no significant difference between the two groups with respect to sex, age, stage of illness, clinical classification and use of hormone ($p > 0.05$).

Fig. 1. Main symptoms of 47 cases at time of admission to hospital

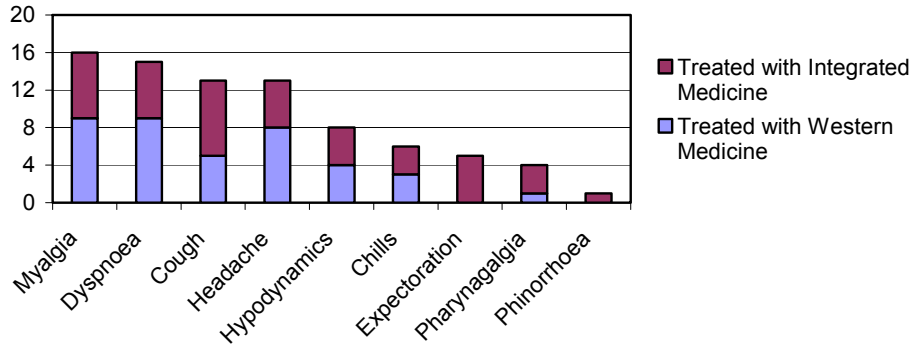


Table 1. Case distribution of patients at the time of their inclusion into the treatment groups

	Control group	Experiment group	Total
Number of subjects	23	24	47
Sex			
Male	18	14	32
Female	5	10	15
Age (years)			
18-20	2	3	5
21-30	7	11	18
31-40	9	6	15
41-50	2	3	5
51-60	2	1	3
61-65	1	0	1
Profession			
Health care workers	10	9	19
Others	13	15	28
Days after onset when patient was included in treatment group			
< 7 days	5	8	13
8-14 days	6	5	11
> 15 days	12	11	23
Body temperature (°C)			
38.1-39.0	12	13	25
39.1-40.0	6	5	11
37.1-38.0	3	6	9
> 40.0	2	0	2

Diagnostic criteria

Diagnoses were made according to the criteria in *Clinical diagnosis criteria for infectious SARS* (proposed) promulgated by the State Ministry of Health on 3 May 2003. Forty-seven patients were clinically classified as follows: 44 common cases (23 cases in the integrated treatment group); three serious cases (one case in the integrated treatment group); no very serious cases were included.

Case inclusion criteria

Patients were included if they met the diagnostic criteria for SARS and were aged between 18 and 65 years. Patients were classified as normal cases, serious cases and very serious cases according to the *Guide to clinical work in respect of infectious SARS* issued by the Beijing SARS Treatment and Command Centre on 27 April 2003.

Case exclusion criteria

Patients were excluded if they had severe cardiovascular or cerebrovascular diseases, liver and kidney diseases, blood diseases, endocrine diseases, pulmonary diseases, neuropsychosis or serious diseases such as tumours or

acquired immunodeficiency syndrome that affected their quality of life before contracting SARS.

Allocation to treatment group

The SAS 6.12 software kit was used to allocate the patients randomly to one or other of the treatment groups.

Therapeutic regimens

Therapeutic regimen for Western medicine
The treatment regimen for Western medicine recommended by the Ministry of Health on 3 May 2003 was adopted. The basic components of this treatment are: antiviral agent, antibiotics, immunopotentiator and hormone.

Therapeutic regimens for integrated treatment
The therapeutic regimens for integrated traditional and Western medicine were based on the above regimen for Western medicine treatment together with a combination of the treatment regimens appropriate to the types and stages of diseases in accordance with the theories of TCM.

Normal cases
Mixture of honeysuckle flower and isatis leaf including Flos Lonicerae (20 g), Folium Isalipis (20 g), Radix Purariae (15 g) and Folium Perilla (12 g) used to remove heat and ventilate the lung, relieve exterior syndrome and regulate channels, and to remove dampness heat and expel pathogens.

Serious and very serious cases
Compound mixture of cordate houttuynia including Herba Houttuyniae (45 g), Radix Scutellariae (15 g), Semen Armeniacae Amarum (15 g), Radix Bupleuri (15 g), Fossilia Chitonis (30 g) and Radix Pseudostellariae (20 g). This preparation is used to ventilate the lung and subdue adversity, regulate *shaoyang*, replenish *qi* and nourish *yin*.

Patients at the stage of recovery from disease (reduced dose of hormone)
Mixture of licorice and astragalus root consisting of Radix Astragali *seu hey sar* (45 g), Radix Glycyrrhizae (30 g), Semen Persicae (30 g). This preparation is used to replenish *qi* and nourish *yin*, tonify lung and promote digestion, remove dampness and regulate channels. Changes in the ingredients based on the above three prescriptions may be made during clinical treatment in response to a patient's actual symptoms. All regimens were administered as one dose per day to be decocted and taken orally.

No. 1 SARS granules: consist of Rhizome Cyrtomium (20 g), Radix Bupleuri (10 g), fibrous root of American Ginseng (5 g) and Fructus Schisandrae (10 g). They were used to remove heat and toxin, replenish *qi* and nourish *yin*; they were also used against dominance of pathogenic heat and deficiency of both *qi* and *yin*.

No. 2 SARS granules: consist of Chinese globeflower (10 g), Rhizome Cyrtomium (10 g) and Folium Isalidis (10 g), used to remove heat, toxin and pathogens in patients with excess pathogenic heat.

One or other of the above prescriptions were administered for a 3-week course of treatment.

Outcome indicators and evaluation criteria

Outcome indicators were indices of hepatic function and renal function, including ALT, AST, Tbil, CRE and BUN. The range of normal values is as follows: ALT, 0–40 IU/l; AST, 0–40 IU/l; Tbil, 0–17.1 μmol/l; CRE, 44–106 μmol/l; BUN, 2.9–8.2 μmol/l.

Observations

Changes in the clinical conditions of patients were noted and ALT, AST, Tbil, CRE and BUN were measured before treatment and on days 7, 14 and 21 after commencement of treatment in all patients. A fully automatic biochemical analyser was adopted for testing and analysing functions of liver and kidney. An observation cycle lasted 3 weeks.

Quality control

To ensure the quality of this research and avoid errors in gathering case information, the following quality control measures were taken during research. The head of the subject group and the coordinator were appointed to coordinate matters relevant to data gathering in the hospital under the leadership of the chief official of the Centre. Centralized training was provided to physicians participating in the clinical research so that each understood and had mastered the treatment proposals, the requirements and precautions for filling out case report forms. Standardization of data gathering, data management and counterchecking of original documents were also strengthened by the training programme.

Data management and statistical treatment

The responsible physician filled in the required details on the state of illness and on the treatment measures in the case report form without delay. The details were entered into the database after they had been examined and certified to be true and correct by higher-ranking physicians. The data were then examined, errors in the database were corrected and the database made read-only for statistical analysis. The database was established using ACCESS, the Wilcoxon rank-sum test and Fisher's exact test were also used for the statistical analysis. Measurements were expressed as mean value ± standard deviation.

Research results

Serum hepatic function tests — overall findings

The classification of abnormality in ALT, AST and Tbil conformed to that given in *Preventive and curative regimens for virus hepatitis* (2000) (5). Hepatic dysfunction occurred in all patients after admission to hospital. The total numbers of patients with hepatic dysfunction (abnormal levels of any one of ALT, AST or TBil) in the integrated treatment group and the group treated with Western medicine were

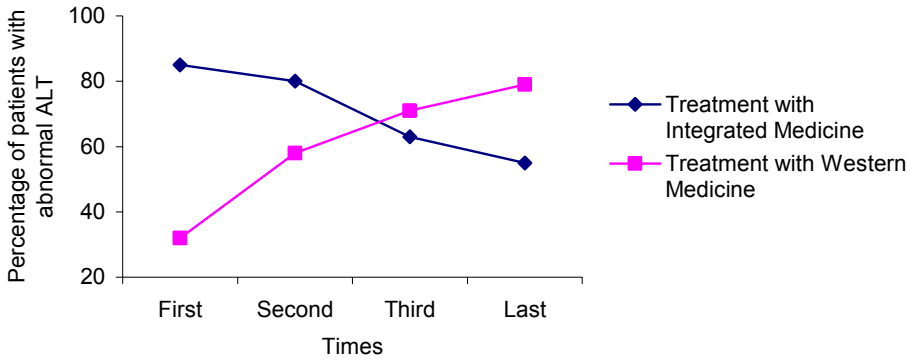
23 and 21, respectively, and, after treatment, the numbers of patients with abnormal results were 13 and 20, respectively. The result of Fisher's exact test (p = 0.00441) showed that the differences were statistically significant, especially that for ALT. The numbers of patients with abnormal ALT in the two treatment groups are shown in Table 2.

Table 2 Patients with abnormal serum ALT in the two treatment groups

Treatment group	**Abnormality of ALT**	**Number of cases**			
		Day 1	Day 7	Day 14	Day 21
Integrated treatment (n = 24)	Minor	17	13	10	11
	Above moderate	3	6	5	2
Total		20	19	15	13
Western medicine (n = 23)	Minor	6	12	11	11
	Above moderate	2	2	6	8
Total		8	14	17	19

There were 12 patients more with abnormal ALT before treatment in the integrated treatment group than in the group treated with Western medicine (20 cases and eight cases, respectively). After treatment, the numbers were 13 and 19 cases, respectively (i.e. six fewer abnormal cases in the integrated treatment group than in the group treated with Western medicine). Fig. 2 is a trend chart showing the percentages of patients with abnormal ALT tests in patients of both groups at four time points. The percentage of patients with abnormal ALT levels in the group treated with Western medicine increased over time, while that of the patients in the integrated treatment group gradually decreased. AST was measured before and during the treatment. Nine patients in the integrated treatment group showed minor abnormality (40–120 IU/l) and none had moderate abnormality or above (>120 IU/l). In the group treated with Western medicine alone, six patients had minor abnormality of AST levels and none had any moderate or severe abnormality. After treatment, only one patient in the

Fig. 2. Changes in abnormal serum alanine aminotransferase (ALT) in patients of both groups



integrated treatment group showed abnormal AST, whereas in the group treated with Western medicine there were still three patients with abnormal AST.

TBil was measured before and during the treatment, and eight patients in the integrated treatment group showed slight abnormality (17.1–34.2 μmol/l) and three patients had moderate abnormality or above (>34.2 μmol/l). The corresponding figures for the group treated with Western medicine alone were five and one, respectively. TBil was also measured at the end of the course of treatment, and both the treatment groups had one patient with minor abnormality. From the test results of ALT, AST and TBil of patients in both groups and the trend of abnormality in ALT, it is apparent that the therapeutic regimen of integrated treatment with TCM and Western medicine has certain advantages over the treatment with Western medicine alone in facilitating the restoration of liver function.

Change in serum ALT of patients in the two treatment groups

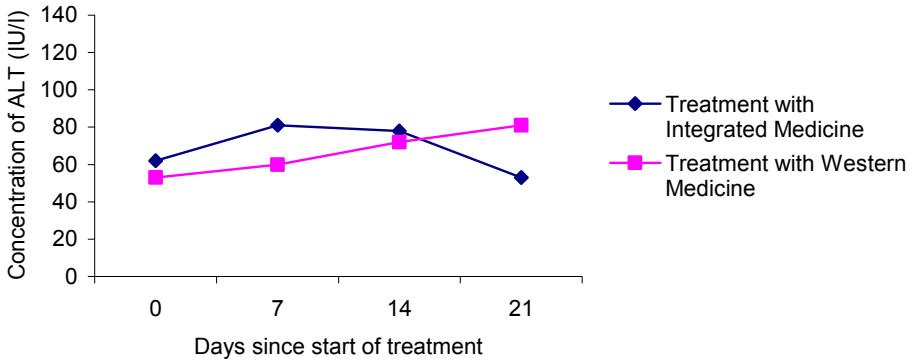
All the 47 SARS patients experienced hepatic dysfunction in the course of their treatment, and the abnormality of ALT was especially obvious. ALT was measured four times during the course of treatment, and the mean values in the integrated treatment group and the group treated with Western medicine alone were not significantly different ($p > 0.05$). In patients in the integrated treatment group ALT reached its highest level on day 7 and gradually decreased to reach the lowest level at the time of the last test; comparison of the value on day 7 with that on day 21 showed a significant difference ($p = 0.0465$). In the group treated with Western medicine, ALT continued to increase throughout the treatment and peaked at the end of treatment. The ALT values before and after treatment showed a statistically significant difference ($p = 0.0394$). From the trend of the mean values of ALT in both treatment groups, it was apparent that the integrated treatment was superior to treatment with Western medicine alone in alleviating lung inflammation and facilitating the restoration of hepatic function (Table 3, Fig. 3), which indicated that integrated therapy with TCM and Western medicine not only had better curative effects, but also greater clinical safety.

Table 3 Changes in the results of testing serum alanine aminotransferase (ALT) in patients in the two treatment groups ($\bar{x} \pm SD$ ***IU/l)***

Treatment group	ALT (IU/l)			
	Day 1 Mean ± SD	**Day 7 Mean ± SD**	**Day 14 Mean ± SD**	**Day 21 Mean ± SD**
Traditional Chinese plus Western medicine ($n = 24$)	61.54 ± 46.02	81.54 ± 49.25	77.13 ± 63.99	49.91 ± 29.00*
Western medicine only ($n = 23$)	53.33 ± 48.95	62.78 ± 47.34	72.85 ± 44.42	82.68 ± 57.15**
P	0.5023	0.1799	0.5876	0.1106

Note: Results on day 21 compared with the results on day 7 in the same treatment group, *$p < 0.05$; when results on day 21 were compared with the results of the same group obtained on the first day, **$p < 0.05$.

Fig. 3 Change trend of mean serum alanine aminotransferase (ALT) of patients in both groups



Note: Results compared with the results on day 7 in the same treatment group, $*p < 0.05$; when compared with the results from the same group obtained on the first day. ($p < 0.05$).

Change of hepatic dysfunction ratio in patients with normal hepatic function in the two treatment groups

For patients in both treatment groups with normal hepatic function indices before treatment or tested at the end of the treatment period, an analysis was conducted of the percentage change of any one parameter with an abnormal index (ALT, AST or Tbil) measured on the subsequent test day (Table 4).

Table 4. Change of hepatic dysfunction ratio in patients who started with normal hepatic function in both treatment groups

Treatment group	Abnormal cases/normal cases			
	Day 1	Day 7	Day 14	Day 21
Integrated (Chinese traditional plus Western medicine)	0/4	3/4	1/2	3/9
Western medicine alone	0/13	7/1	5/9	3/6
p		0.6030	1.0000	0.6220

Changes of serum creatinine (CRE) and blood urea nitrogen (BUN) of patients in both treatment groups

Renal dysfunction occurred in some of the 47 SARS patients, including 15 cases in the integrated treatment group and 10 in the group treated with Western medicine alone. After treatment there were six cases and four cases in the integrated treatment group and the group treated with Western medicine, respectively. However, no significant difference was found between the mean values for the two treatment groups when CRE and BUN were measured at four different times during the course of treatment ($p > 0.05$) (Table 5), the change trend in the mean values is shown in Figs 4 and 5. No significant differences were seen in CRE and BUN between patients at the same stage of illness in the two groups or between different stages in the same group ($p > 0.05$).

Table 5. Change of serum creatinine (CRE) and blood urea nitrogen (BUN) ($\bar{x} \pm SD$ IU/l)

Item measured	Treatment group	Day 1	Day 7	Day 14	Day 21
CRE (μmol/l)	Integrated (TCM plus Western medicine) (n = 24)	84.58 ± 16.49	85.38 ± 15.96	82.90 ± 18.76	85.22 ± 15.77
	Western medicine alone (n = 23)	82.65 ± 11.11	82.35 ± 16.65	80.45 ± 19.47	82.74 ± 11.58
BUN(mmol/l)	Integrated (TCM plus Western medicine) (n = 24)	6.48 ± 2.18	6.80 ± 1.72	6.89 ± 1.73	6.74 ± 2.19
	Western medicine alone (n = 23)	6.15 ± 1.50	7.16 ± 1.82	7.50 ± 1.86	7.58 ± 1.82

TCM, Traditional Chinese medicine; SD, standard deviation.

Fig. 4. Change trend of mean serum creatinine in patients in the two treatment groups

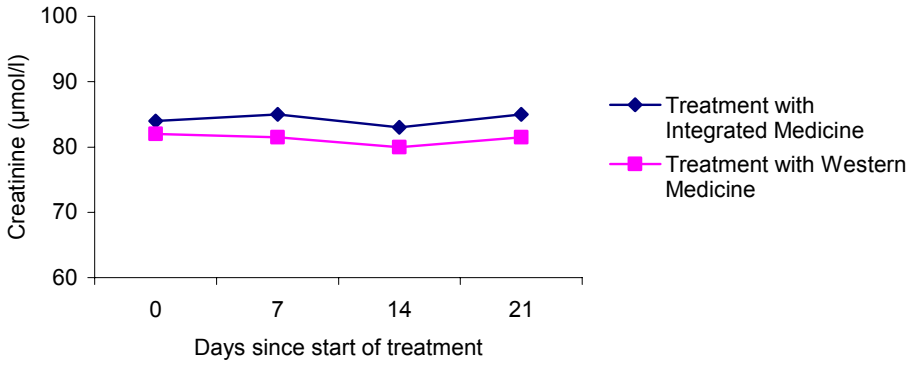
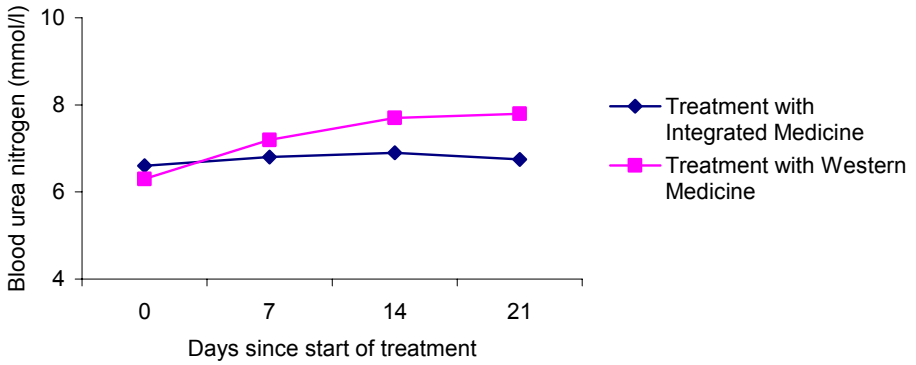


Fig. 5. Change trend of mean serum blood urea nitrogen in patients in the two treatment groups



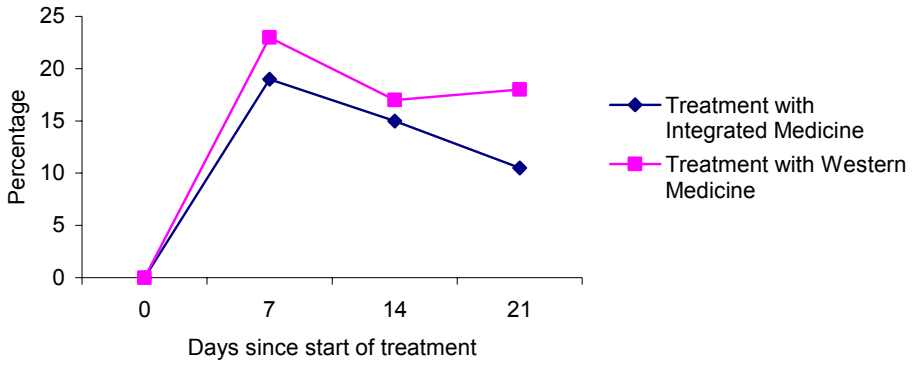
Change of renal dysfunction ratio in patients with normal renal function in the two treatment groups

For patients with normal renal function indices in both groups before treatment or when previously measured, an analysis was made of the percentage change in CRE and BUN tested at the end of the treatment period (Table 6 and Fig. 6).

Table 6. Change of renal dysfunction ratio in patients with normal renal function in the two treatment groups

Treatment group	Percentage (abnormal cases/normal cases)			
	Day 1	**Day 7**	**Day 14**	**Day 21**
Integrated treatment (Chinese plus Western medicine)	0 (0/16)	18.75 (3/16)	15.00 (3/20)	10.53 (2/19)
Western medicine only	0 (0/22)	22.73 (5/22)	16.67 (3/18)	17.65 (3/17)
p		1.0000	1.0000	0.6500

Fig. 6. Change trend of renal dysfunction ratio in patients with normal renal function in the two treatment groups



Discussion and conclusion

The present treatment for SARS includes antiviral agents such as ribavirin and oseltamivir; hormone to suppress immune reaction, avoid damage to the lung and allay fever; and antibiotics to prevent potential bacterial infections. Treatment with TCM is based on an overall analysis of symptoms and signs, the cause, nature and location of the illness, and the patient's physical condition according to the basic theories of TCM, and the provision of appropriate treatment based on the specific symptoms.

It has been reported that the SARS virus may cause serious infection of the lower respiratory tract and damage to several systems in the body. Clinical workers from mainland China, Hong Kong SAR and other countries have noted

impairment of the functions of liver and kidney in many patients. This dysfunction is mainly demonstrated as an abnormality of ALT, AST, Tbil, CRE and BUN; changes in ALT were especially significant (*2–4*). These findings suggest that damage to the parenchyma cells of the liver and kidney probably occur in SARS patients during the onset and progression of the disease. The results of the present study support this suggestion.

As a relatively sensitive index, ALT might reflect the scale of liver inflammation in SARS patients, and the status of liver function could be determined directly through measurement of ALT. Hepatic dysfunction probably occurs at the early stage in most patients, as indicated by the autopsy results of one patient who died from SARS in our hospital. Hepatic damage was mainly due to secondary anoxia caused by infection and other factors, which could be related to SARS itself. It is also possible that the use of antivirals, hormone and other drugs caused impairment of liver function during the treatment. Because the liver is the central organ for metabolizing medicine to enable it to perform its curative function, a knowledge of how to alleviate liver inflammation and protect the parenchyma cells of the liver from damage so as to facilitate the restoration of liver function would also be a critical step in the successful treatment of SARS.

From the changes of the mean values of ALT in both groups, the integrated treatment was shown to be better than the treatment with Western medicine alone, demonstrating that integrated therapy was effective in treating SARS.

The kidney is a target organ in SARS virus infection. Although renal dysfunction was seen in some patients, the rate of abnormality was lower than that for hepatic function, and no significant differences between the mean values of CRE and BUN between the two treatment groups were found. As seen in the change trend of the ratio of hepatic dysfunction and renal dysfunction in patients in both groups who had normal hepatic and renal function at the start of treatment, the integrated treatment was superior to the treatment with Western medicine alone. This finding suggests that treatment with integrated TCM and Western medicine was safe.

It has been reported that treatment of SARS patients with integrated traditional and Western medicine can significantly enhance the overall recovery of patients from illness (*6*). We also found that this treatment could significantly shorten the duration of clinical symptoms, speed up the usage of hormone, promote absorption of lung inflammation and accelerate recovery of patients from illness. Based on the integrative concept, theory and principles of overall analysis of symptoms and signs, the cause, nature and location of the illness and the patient's physical condition in TCM together with the general law regarding the progress of epidemic febrile diseases, we chose appropriate herbal remedies. These included Flos Lonicerae, Folium Isalidis, Herba Houttuynia and Radix Isatidis for clearing away heat and toxin, Radix Astragali and Radix Panalis Quinquefolii for replenishing *qi* and nourishing *yin*, also large Fructus Scutellariae, Radix Bupleuri and Carapax Trionycis for clearing, regulating, nourishing the liver and replenishing the kidney. The TCM curative regimens, recognized the integrative concept of TCM, i.e. to regulate *yin* and *yang* in order to achieve an equilibrium and to strengthen body resistance and expel pathogens so as to reach the goal of overcoming pathogens and promoting recovery.

As was shown from the results of this study, the adoption of the therapeutic regimen of integrated traditional and Western medicine had significant advantages over Western medicine in promoting hepatic function, protecting renal function and further accelerating recovery of patients from illness. The results also indicate that the therapeutic regimen of integrated traditional and Western medicine is safe for the treatment of SARS. These findings should be taken into consideration in choosing appropriate treatment for SARS patients.

Acknowledgements

The State Ministry of Science and Technology and State Administration of Traditional Chinese Medicine offered great support in terms of funding during the campaign against SARS and our research work. The China Institute of Traditional Chinese Medicine provided us with training and guidance so as to ensure the quality of this research, and the leaders in our hospital and the Institute of Infectious Diseases were also most helpful. We herewith express our thanks to them.

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Report 7
Clinical research on 63 patients with SARS treated with integrated Traditional Chinese medicine and Western medicine

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Abstract The objective was to evaluate the clinical curative effects of Traditional Chinese medicine (TCM) regimens 1, 2 and 3 integrated with basic Western medicine in treatment of severe acute respiratory syndrome (SARS). In line with the diagnostic criteria for SARS issued by the Chinese Centre for Disease Control and Prevention, criteria for inclusion and exclusion of cases were decided upon. Sixty-three patients with clinically confirmed SARS were selected and divided into normal cases and serious cases according to the severity of their illness, and were randomly assigned either to the integrated treatment group (31 cases) or the group treated with Western medicine (32 cases). The course of the illness was divided into three stages in accordance with the natural progression and clinical manifestations of SARS (namely, the high fever stage, the dyspnoea and cough stage, and the absorption stage). In the integrated treatment group, in addition to standard treatment, patients were instructed to take oral preparations of SARS regimens 1, 2 or 3, for the high fever stage, the dyspnoea and cough stage, and the absorption stage, respectively. Patients in the group treated with Western medicine received standard treatment. Monitoring of general symptoms and signs caused by fever, chest X-ray films, the results of routine blood examinations and blood biochemical tests, hormone doses and other indicators was carried out for 21 days. Therapy with the integrated treatment can obviously alleviate general toxic symptoms and promote absorption of pulmonary inflammation; when compared with the effects in the group treated with Western medicine alone the differences were significant. Clinical curative effects were achieved through the administration of integrated TCM and Western medicine and no obvious side-effects were observed.

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Introduction

Beijing was one of the areas hardest hit by the epidemic of SARS accounting for over 50% of the total morbidity recorded for the whole country. After the end of April 2003, the rapid spread of SARS had led to about 100 new cases in Beijing every day.

After full consultation and advice from a number of experts in TCM and according to the clinical features and the different pathological stages of SARS, a preliminary explanation of the pathogenesis and etiology of SARS from the point of view of TCM was put forward, and SARS regimens 1, 2 and 3 were developed. In accordance with the principles for clinical research design, prospective clinical observation proposals were made and 63 eligible confirmed cases were studied.

Methods

Study subjects

Case sources
All participants were patients with clinically confirmed SARS from Beijing Changxindian Hospital, a specially designated hospital for SARS patients, and all the patients had been reported to the China Centre for Disease Prevention and Control as required by the relevant regulations. The observation period was from 21 April to 20 May 2003. Of the 63 cases, 29 were female and 34 were male, with an average age of 41 ± 8.3 years; 16 of the patients had normal SARS and 47 serious SARS.

Criteria for diagnosis
The criteria given in the *Guide to clinical work in respect of infectious SARS* were adopted. They were developed by the China Centre for Disease Prevention and Control and published by Beijing SARS Treatment and Command Centre on 27 April 2003.

Criteria for inclusion
Patients were included in the study if:
- they met the diagnostic criteria;
- were aged between 18 and 65 years old;
- the onset of disease was no more than 5 days before the start of the study; and
- they could be categorized as being normal or serious cases.

Criteria for exclusion
Patients were not eligible to participate in the study if they:
- had extremely severe disease, were suffering from shock, acute respiratory distress syndrome (ARDS) or multiple organ dysfunction (MODS);
- had severe cardiovascular diseases with serious complications, cerebrovascular diseases, liver diseases, kidney diseases, blood system diseases, endocrine system diseases, nervous system diseases or neuropsychosis;
- were aged less than 18 years or more than 65 years;

- were pregnant or lactating; or
- had a history of food or drug allergy.

Allocation to the treatment groups
The patients included in the study were grouped by means of a hierarchical random grouping method. The serious cases and normal cases were grouped separately, and then lots were drawn. Twenty-four pairs of patients were divided into lot 1 and lot 2 for the serious cases and eight pairs of patients divided into lot 1 and lot 2 for the normal cases, giving a total of 32 pairs. Cases drawn with serious case lot 1 or normal case lot 1 formed the integrated treatment group, whereas those with serious case lot 2 or common case lot 2 comprised the group treated with Western medicine. The integrated treatment group consisted of 31 patients of whom 24 had serious and seven had normal SARS. The group treated with Western medicine consisted of 32 cases of whom 23 had severe illness and nine normal disease. There were 63 patients in total. No obvious differences between the two groups in terms of distribution of sex, age or severity of their conditions were found.

Therapeutic regimens
The integrated treatment group received standard treatment with Western medicine plus treatment with TCM (either regimen 1, 2 or 3 according to the different syndromes and pathological stages of the illness; appropriate changes were made as the illness progressed.

The group treated with Western medicine received standard treatment alone.

Standard treatment
The standard treatment included the following components: hormone, antiviral agents, antibiotics and immunopotentiators.

- *Hormone*: dosages were prescribed according to the severity of syndromes (80 mg, 160 mg, 320 mg or 640 mg per day in an intravenous drip).
- *Antivirals*: 5% glucose 250 ml + canciclovir 250 mg in intravenous drip, twice per day.
- *Antibiotics*: one treatment regime was selected from the following:
    - levofloxacin 0.2 iv drip, twice per day + azithromycin 0.5 iv drip once per day (Qd)
    - rocephin 2.0 iv drip per day + azithromycin 0.5 iv drip per day
    - sulperazon 2.0 iv drip twice daily + azithromycin 0.5 iv drip per day
- *Immunopotentiator*: thymopolypeptides 20 mg intravenously (in small bottle) per day
- *Other medications*: appropriate doses of medicines to relieve fever, ease pain and repel sputum, soothe cough and asthma and suppress acid.

Therapy with traditional Chinese medicine
High-fever stage: 1 to 7 days after onset of the disease with high fever as the first and the most prominent symptom.

Treatment focused on removing heat, repelling toxin and dispelling dampness and turbidity.

Regimen 1: Fossilia Chitonis (45 g) (put in first), Rhizoma Anemarrhenae (15 g), Fructus Scutellariae (15 g), Rhizoma Atractylodis (10 g), Herba Artemisiae Annuae (15 g), Radix Paeoniae Rubra (15 g), Radix Bupleuri (10 g).

Dyspnoea and cough stage: 8 to 14 days after onset, characterized by severe dyspnoea and cough, fever and increasing shadows on lungs.

Treatment focused on relieving dampness and fever and ventilating the lungs to relieve symptoms.

Regimen 2: Fructus Scutellariae (20 g), Diosoreae gracillimae (10 g), Rhizoma Coptidis (15 g), Faeces Bombycis (10 g), Trichosanthes Kirilowii (30 g), Herba Artemisiae Annuae (15 g), Semen Coicis (30 g), Flos Inulae (10 g, wrapped), Radix Curcumae (15 g), Radix Salviae Miltiorrhizae (30 g).

Absorption stage: 15 days after onset of the disease, temperature returning to normal level, dyspnoea and cough occurring occasionally (worse after physical exertion), and the shadows in the lungs being absorbed.

Treatment focused on tonifying *qi* and replenishing *yin*, repelling phlegm, promoting blood circulation and removing dampness and turbidity.

Regimen 3: Radix Panacis Quinquefolii (45 g), Fructus Corni (30 g), Radix Astragali (30 g), Trichosanthes Kirilowii (30 g), Herba Coelogynes Punctulatae (15 g), Rhizoma Coptidis (15 g), Herba Patriniae cum Radice (30 g), umbellate pore/Poris Cocos (15 g each) and Radix Salviae Miltiorrhizae (30 g).

The above regimens were decocted regularly, 300 ml each time, taken orally in three 100 ml doses.

Evaluation indices

Traditional Chinese medicine symptoms

Semiquantitative evaluation criteria centrally developed by the researchers were adopted. The scoring system was as follows:

- none = 0 points
- slight = 1 point
- medium = 2 points
- serious = 3 points

During the course of treatment, scores were assigned once a day; statistical analyses were carried out on days 7, 14 and 21.

Routine examination of chest X-rays was done on days 1, 3, 5, 7 and 21 (additional examinations were made when there was a change in the patient's condition). A statistical analysis was made at the end of the treatment to compare the percentage of patients whose radiographs showed absorption of shadow and those with shadow residues between the two groups. The routine blood examination included counts of leukocytes, neutrophilic granulocytes, lymphocytes and blood platelets to allow comparisons of the counts before and after treatment and between the treatment groups. The blood biochemical indices measured included creatinine kinase (CK), creatinine kinase-isoenzyme (CK-MB), lactate dehydrogenase (LDH), hydroxybutyric acid-dehydrocortisone

(HBDH), alanine aminotransferase (ALT) and aspartate aminotransferase (AST) to allow comparisons of the values before and after treatment and between treatment groups.

Observations
Observations were recorded on the following: TCM symptoms, fever stages (temperature, time of fever abatement), lung X-ray, routine blood examination and blood biochemical indices, use of hormone, and the administration of regimens 1, 2 and 3. The observation period lasted 21 days.

Quality control
The investigators were qualified physicians who were given the necessary training. A report was made on every case participating in the study every day, the relevant case report form was filled out every day by the physician in-charge and submitted to the head of subject for examination and inspection of original data, and signature after it had been verified. The herbal pieces used conformed to the standards of the *Chinese Pharmacopoeia* (2000 Edition, Volume I).

Data management and statistical treatment
The data on each participant were faxed to the clean area every day. Upon completion of observations on all the 63 cases, the Department of Science and Education in the Oriental Hospital established the database. After the test for normality and the homogeneity test for variance had been carried out the *t*-test was applied to the interblock mean and a χ^2 test to rate comparison.

Results

Changes of general concomitant syndromes (total value of symptoms) over three weeks

The results of the analysis of general changes in symptoms are shown in Table 1.

Table 1. Comparison of the changes of general concomitant syndromes (general value of symptoms) over 3 weeks (mean ± standard deviation)

Treatment group	Days 1-7	Days 8-14	Days 15-21
	mean ± SD	mean ± SD	mean ± SD
Integrated treatment (TCM plus Western medicine) (31 cases)	22.32 ± 6.09	9.79 ± 4.83*	2.08 ± 1.70*
Treatment with Western medicine (32 cases)	24.30 ± 7.60	15.74 ± 5.83	7.51 ± 4.72

SD, Standard deviation; TCM, Traditional Chinese medicine.
*$p < 0.001$.

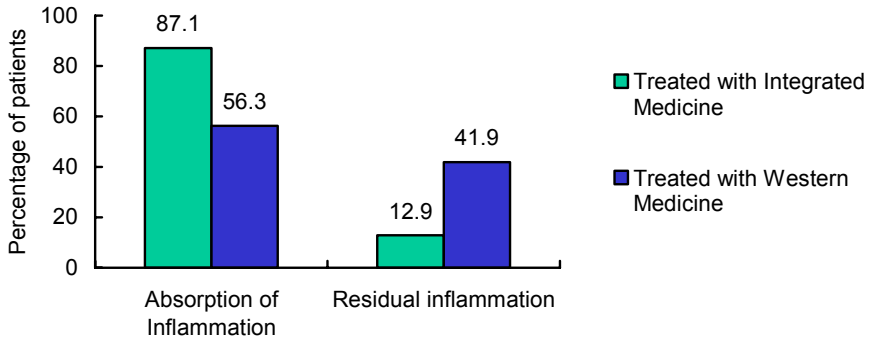
Relative to the control group, the integrated treatment group showed a significant decline in the general value of toxicosis symptoms, especially in the second and third weeks of treatment ($p < 0.001$).

The integrated treatment group also showed radical improvement in alleviation of headaches, arthralgia, pantalgia, cough, expectoration and haemoptysis, chest pain, poor appetite, nausea, sweating and cardio palmus in comparison with the group treated with Western medicine.

Comparison of the absorption of pulmonary inflammation on chest radiographs

As shown in Fig. 1, after the 21-day period of treatment, 27 patients in the integrated treatment group (87.1%) and 18 patients in the group treated with Western medicine (56.3%) showed absorption of shadow. Four patients in the integrated treatment group (12.9%) and 14 (43.8%) in the group treated with Western medicine had residual inflammation. The integrated treatment resulted in better alleviation of lung inflammation than treatment with Western medicine alone at the end of the treatment period ($p < 0.05$).

Fig. 1. Comparison of absorption of pulmonary inflammation on chest radiographs



Routine blood examination

Table 2 shows the changes in the results of routine blood examinations in the two treatment groups before and after treatment.

Table 2. Changes in results of routine blood examinations before and after treatment in the two treatment groups (mean ± standard deviation)

Blood parameter	Integrated treatment group		Western medicine-treated group	
	Pre-treatment	Post-treatment	Pre-treatment	Post-treatment
White blood cells ($x10^9$/l)	6.46 ± 3.58	9.82 ± 3.29**	7.29 ± 2.87	10.51 ± 3.85••
Neutrophils (%)	78.16 ± 14.31	80.19 ± 17.80*	79.71 ± 11.57	83.84 ± 7.33•
Lymphocytes (%)	15.41 ± 11.73	15.42 ± 16.33	15.68 ± 10.34	12.21 ± 8.39
Platelet count ($x10^9$/l)	161.44 ± 61.76	186.00 ± 75.36	187.46 ± 101.85	174.33 ± 70.07

The difference in the white blood cell count of the integrated treatment group before and after treatment was ** $p < 0.001$, neutrophil (%) *$p < 0.05$.
The difference in the white blood cell count of the control group before and after treatment was •• $p < 0.001$, neutrophil (%) • $p < 0.05$.

There was no statistically significant difference between the two groups either before or after the treatment.

Changes in blood biochemistry

The changes in the blood biochemistry in the two treatment groups before and after treatment are summarized in Table 3.

Table 3. Changes in blood biochemistry before and after treatment

Item measured	Integrated treatment group		Western medicine-treated group	
	Pre-treatment	Post-treatment	Pre-treatment	Post-treatment
CK (U/l)	163.7 ± 140.33	64.00 ± 66.92	152.17 ± 187.32	96.33 ± 121.81
CK-MB	39.64 ± 33.97	26.71 ± 7.97	35.11 ± 23.22	28.56 ± 9.91
LDH (U/l)	274.29 ± 119.85	174.45 ± 38.34*	248.33 ± 185.93	203.6 ± 97.46
HBDH	148.75 ± 50.55	137.25 ± 35.14	283.60 ± 154.67	227.6 ± 105.95
ALT (IU/l)	100.79 ± 85.68	91.38 ± 55.38	69.36 ± 94.16	71.16 ± 54.80
AST (IU/l)	53.85 ± 39.95	24.23 ± 7.76**	58.37 ±41.72	29.25 ± 17.73•

CK, Creatinine kinase; CK-MB; LDH, lactate dehydrogenase; HBDH; ALT, alanine aminotransferase; AST, aspartate aminotransferase.
The difference in LDH of the integrated treatment group before and after the treatment was *$p < 0.05$, AST **$p < 0.05$.
The difference of AST of the control group before and after treatment was • $p < 0.05$.

There was no statistically significant difference between the two groups either before or after the treatment.

Of the 63 study participants, seven died (11.1%). Of the 31 patients in the integrated treatment group, three died (9.67%); average age 53.33 years. One of these patients had hypertension with complications and one had coronary heart disease. Of the 32 patients in the group treated with Western medicine, four

patients died (12.5%); average age was 55.5 years. One patient had hypertension with complications and one had type-2 diabetes.

Conclusion and discussion

SARS can be categorized as an epidemic febrile disease on the basis of TCM theory. It is caused by exogenous pathogens that trigger the inner pathogens. There is characteristically a sudden and fierce outbreak and rapid spread. With the aggravating toxicosis and inner dampness, high fever is usually the first and most prominent symptom, rapidly followed by lung or visceral damage resulting in cough and breathing difficulties. In some patients the condition worsened further giving rise to fever in *yin* and blood and over-consumption of the *yin* of liver and kidney, which was manifested by cyanosis, purple tongue and decreased oxygen saturation. In serious cases, patients died from sudden failure of the heart-*yang*. Death was caused by direct damage to visceral organs in some severe cases. Taking a comprehensive view of the onset, development process and main clinical features of SARS, it can be concluded that the treatment should be administered in a timely manner; most importantly in the early stage. The therapeutic approach should be focused on relieving fever and toxin, dispelling inner dampness and turbidity, reinvigorating *qi* and improving *yin*. The therapeutic regimen comprises several different phases appropriate to the stage of development of the disease and a series of regimens should be administered in large dosages.

Therefore, we propose that the treatment should be divided into three stages.

- *High-fever stage*: 1–7 days after onset of the disease, when high fever and a thick yellow tongue coating are prominent features. The treatment at this stage should focus on eliminating the fever and toxin and removing the inner dampness and turbid pathogens through administration of SARS regimen 1.
- *Dyspnoea and cough stage*: 8–14 days after onset of the disease, when the affliction develops rather fast and patients suffer from breathing difficulty and fever which should be controlled. The shadow over the lung is expanding during this stage. The treatment should focus on removing the internal dampness and ventilating lung to relieve symptoms through administration of SARS regimen 2.
- *Absorption stage*: 15 days after onset of the disease, when the fever can be sensed by the patient, difficulty in breathing occurs occasionally, especially after physical exertion, the tongue has a red or reddish colour, and the shadows over the lungs begin to shrink gradually. The therapeutics should focus on tonifying *qi* and replenishing *yin*, reducing phlegm, promoting blood circulation, and removing internal dampness and turbidity through administration of SARS regimen 3.

The results of this study indicate that prescriptions 1, 2 and 3 can effectively alleviate symptoms of general toxicosis caused by fever, especially in the second and third weeks after the onset of disease. Radical alleviation of headaches, arthralgia, myalgia, cough, and hemoptysis, chest pain, poor appetite, nausea, sweating, and cardio palmus were observed. The alleviation of lung inflammation was clearly better in the integrated treatment group than in the group treated with Western medicine alone. At the end of the treatment, there

were more patients whose lung shadows had shrunk in the group treated with integrated TCM and Western medicine than in the group treated with Western medicine alone.

In conclusion, the integrated therapy with TCM and Western medicine can be effective in treatment of SARS and has no obvious side-effects. Further research on TCM is planned in the areas of recovery therapy and recuperation nutrition.

Acknowledgements

The research was supported by a special fund from the State Administration of Traditional Chinese medicine. We are indebted to Mr Wang Yongyan, of the Chinese Academy of Sciences, Professor Zhang Boli, Professor Sun Sulun, Professor Jiang Liangduo and Professor Zhou Ping'an for their help and instruction starting from the establishment of the project through to its implementation. We are also grateful to the leaders of the State Administration of Traditional Chinese Medicine, Beijing Traditional Chinese Medicine University, Fengtai District Bureau of Health, and the Oriental Hospital for their support.

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Report 8
Influence of integrated therapy with Traditional Chinese medicine and Western medicine on lymphocytes and T-lymphocyte subpopulations of patients with SARS

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Abstract The objective was to study how integrated therapy with Traditional Chinese medicine (TCM) and Western medicine regulated the immune function of the body by analysing its effects on lymphocytes and T-lymphocyte subpopulations in patients with severe acute respiratory syndrome (SARS). Forty-seven patients with SARS were randomly allocated to either the integrated treatment group or the group treated with Western medicine for a treatment course of 3 weeks. Levels of lymphocytes and subpopulations of T-lymphocytes, CD3, CD4/CD8, were measured in peripheral blood before and after treatment. Before treatment, the absolute level of lymphocytes in the peripheral blood of 38 of the patients was low, and a decrease in percentages of CD3, CD4/CD8 was observed in 19 cases. Comparison of the difference in the absolute value of peripheral lymphocytes in the two treatment groups before and after treatment showed a statistically significant difference ($p < 0.01$), and the integrated treatment was superior to the treatment with Western medicine alone in this respect. Before treatment, there were 19 patients with extremely low CD3 levels (9 in the integrated treatment group and 10 in the group treated with Western medicine alone). After treatment there were two and eight cases in the integrated treatment group and the group treated with Western medicine alone, respectively. The numbers of patients with extremely low levels of CD4/CD8 before treatment were 15 and 13 in the integrated treatment group and the group treated with Western medicine, respectively and the numbers after treatment were 5 and 10, respectively. Fisher's exact test was used for statistical analysis. The integrated treatment was obviously superior to the treatment with Western medicine alone in promoting recovery of T-lymphocyte subpopulations ($p < 0.05$). The integrated treatment was obviously superior to the treatment with Western medicine alone in alleviating inhibition of lymphocyte activity, raising the level of T-lymphocyte subpopulations and enhancing immune function.

Introduction

SARS is a disease of the respiratory system with strong infectivity and a high mortality rate caused by a corona virus subtype (SARS virus) (*1*). There is currently no specific treatment available for this disease. Based on a summary of the general clinical characteristics of SARS patients and a prospective study design in which subjects were randomly allocated to either the "experiment" group or the control group, we studied integrated treatment with TCM and

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Western medicine and its ability to alleviate inhibition of lymphocyte activity and raise the level of T-lymphocyte subpopulations to improve immune function.

Methods

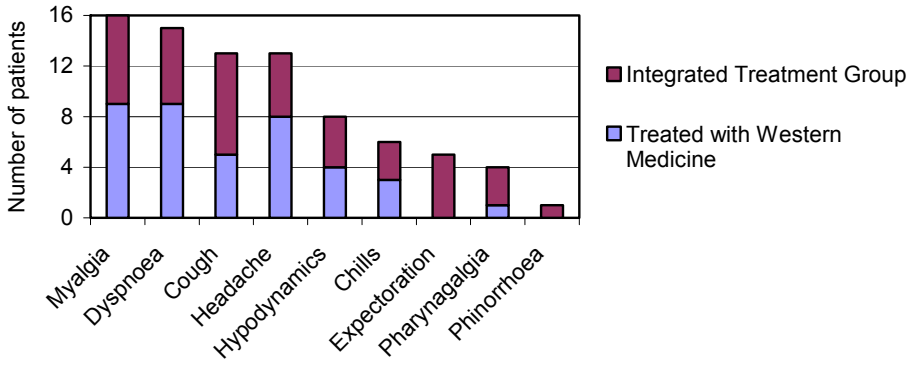
Source of cases

Forty-seven of the patients admitted for treatment in our hospital had case histories that conformed with the criteria for inclusion in the study and were randomly allocated either to the integrated treatment group (24 cases) or the group treated with Western medicine (23 cases). The general characteristics of the 47 patients upon inclusion into the treatment groups are shown in Table 1 and the main symptoms are shown in Fig. 1.

Table 1. Characteristics of 47 patients upon inclusion into one of the two treatment groups

	Control group (Western medicine only)	Experiment group (integrated TCM plus Western medicine)	Total
Number of patients	23	24	47
Sex			
Male	18	14	32
Female	5	10	15
Age (years)			
18-20	2	3	5
21-30	7	11	18
31-40	9	6	15
41-50	2	3	5
51-60	2	1	3
61-65	1	0	1
Profession			
Medical personnel	10	9	19
Others	13	15	28
Days after onset at time of inclusion in treatment group			
< 7 days	5	8	13
8-14 days	6	5	11
> 15 days	12	11	23
Body temperature (°C)			
38.1-39.0	12	13	25
39.1-40.0	6	5	11
37.1-38.0	3	6	9
> 40.0	2	0	2

Fig. 1. Main symptoms of 47 cases at the time of their admission to hospital



Methylprednisolone was administered to patients in both treatment groups and the average cumulative dose was 5278.33 ± 4032.20 mg in the integrated treatment group and 6266.70 ± 4137.25 mg in the group treated with Western medicine. A *t*-test (p = 0.4113) showed that there was no significant difference between the two groups ($p > 0.05$) and no significant differences were seen between the two groups with respect to sex, age, course of illness, diagnostic classification and use of hormone.

Diagnostic criteria

The diagnostic criteria used conformed to the *Clinical diagnosis criteria for infectious SARS* (proposed) issued by the Ministry of Health of the People's Republic of China on 3 May 2003. The disease severity of forty-seven patients was classified as follows: 44 normal cases (23 in the integrated treatment group); three serious cases (one in the integrated treatment group) and no very serious cases.

Case inclusion criteria

Patients were eligible for inclusion in the study if they had symptoms that conformed with the criteria for the diagnosis of SARS and were aged between 18 and 65 years. The severity of SARS was classified as normal, serious and very serious (according to the criteria in the *Guide to clinic work of severe acute respiratory syndrome* issued by the Beijing Treatment and Command Centre on 27 April 2003).

Case exclusion criteria

Patients who were not eligible to participate in this study included those suffering from severe cardiovascular and cerebrovascular diseases, liver and kidney diseases, blood diseases, endocrine diseases, pulmonary diseases, neuropsychosis or serious diseases such as tumours or acquired immunodeficiency syndrome (AIDS) that affected the quality of life.

Allocation to treatment groups

A block random method was adopted. The block length was set to 4 which was divided into 15 blocks. The SAS 6.12 software kit was utilized to generate 60 random numbers. Patients were randomly allocated either to the experiment

group (TCM plus Western medicine) or to the control group (Western medicine only) according to their serial number.

Clinical therapeutics

Treatment with Western medicine
The Western medicine regimen adopted was that recommended by the Ministry of Health of the People's Republic of China on 3 May 2003. The basic components of treatment were antiviral agent, antibiotic, immunopotentiator and hormone.

Treatment with integrated traditional Chinese medicine and Western medicine
Integrated therapy with integrated Traditional Chinese medicine and Western medicine was based on the Western medicine regimen described above in combination with the TCM therapy specific to the different types and stages of disease.

Normal cases
Patients with normal SARS received a mixture of honeysuckle flower and isatis leaf prepared with Flos Lonicerae (20 g), Folium Isalipis (20 g), Radix Purariae (15 g) and Folium Perilla (12 g) used to remove heat and ventilate the lung, and regulate channels, and also to remove damp heat and expel pathogens.

Serious and very serious cases
Patients with serious and very serious SARS received a compound mixture of Cordate Houttuynia prepared with Herba Houttuyniae (45 g), Radix Scutellariae (15 g), Semen Armeniacae Amarum (15 g), Radix Bupleuri (15 g), Fossilia Chitonis (30 g) and Radix Pseudostellariae (20 g) to ventilate the lung and subdue adversity, regulate *shaoyang*, replenish *qi* and nourish *yin*.

Recovery stage
Patients at the stage of recovery from disease (reduced dose of hormone) received a mixture of licorice and astragalus root consisting of Radix Astragali Seu Hedysari (45 g), Radix Glycyrrhizae (30 g) and Semen Persicae (30 g) to replenish *qi* and nourish *yin*, tonify lung and promote digestion, remove damp heat and regulate channels.

Changes in the ingredients in the above three prescriptions, when used in clinical treatment, were made according to the patient's actual symptoms. Treatment was with one freshly prepared dose per day decocted and taken orally.

No. 1 SARS granules consisting of Rhizome Cyrtomium (20 g), Radix Bupleuri (10 g), fibrous root of American Ginseng (5 g), Fructus Schisandrae (10 g) was used to remove heat and toxin, replenish *qi* and nourish *yin*, and also used against dominance of pathogenic heat and deficiency of both *qi* and *yin*.

No. 2 SARS granules which contained Chinese globeflower (10 g), Rhizome Cyrtomium (10 g) and Folium Isalidis (10 g) were used to remove heat, toxin and pathogens and were suitable for patients with excess pathogenic heat.

According to the patients symptoms the appropriate prescriptions were administered for a 3-week treatment course.

Evaluation indices

The evaluation indices included peripheral lymphocytes and T-lymphocyte subpopulations, CD3, CD4/CD8. The normal range of the absolute value of lymphocytes in the peripheral blood was 1.3–3.0 × 10^9/l, the normal range for CD3 was 66.1–77% and for CD4/CD8, the range of normal values was 0.98–1.94%.

Observations

Patients were observed for clinical symptoms and changes in peripheral blood lymphocytes and T-lymphocyte subpopulations before and after treatment. Peripheral blood lymphocytes were counted before and after treatment, followed by classification of T-lymphocyte subpopulations into CD3, CD4/CD8. Peripheral blood lymphocytes were counted with a fully automatic blood cell analyser; CD3, CD4/CD8 T-lymphocyte subpopulations were analysed using a laser induced fluorescence technique and flow cytometry. The observation cycle lasted for 3 weeks.

Quality control

To ensure the appropriate quality of this research and to avoid errors in gathering information, the following measures were taken to strengthen quality control during research. The head of the subject group and a coordinator were specifically appointed to coordinate the strategy for data collection in the hospital under the guidance of the official in charge of the centre. Centralized training was provided to the physicians participating in the clinical research so that they all understood and had mastered the treatment proposals and the requirements and precautions for filling out case report forms. They were also instructed in standardization of data gathering; data management and counterchecking of original documents. All herbal pieces used conformed to the criteria of the *Chinese Pharmacopoeia* (2000 Edition, Volume I) and the patent medicines were all prescription medicines approved by the state administration and available commercially.

Data management and statistical treatment

The authorized physician filled in details of the state of illness and treatment measures in the case report form promptly. After they had been checked and certified as being true and correct by physicians at a higher level, data were entered into the database, then examined and errors in the database were corrected. The database was made read-only for statistical analysis. The database was established using ACCESS, and statistical analysis using *t*-test and Fisher's exact test was performed. Measurement data were expressed as mean value ± standard deviation.

Results

Measurement of the absolute value of peripheral blood lymphocytes

The changes in the overall concentrations of peripheral blood lymphocytes in patients before and after treatment are summarized in Table 2. The first measurement of the absolute value of peripheral blood lymphocytes was made at the time of the patient's admission to the hospital. The mean value was 1.00 ± 0.46 $\times 10^9$/l in the integrated treatment group and 1.30 ± 0.58 × 10^9/l in the group treated with Western medicine. The levels in both groups were below normal. No significant difference was found between the two groups ($p > 0.05$). The mean values in the two treatment groups generally returned to normal after treatment and significant differences were observed when compared with the levels measured before treatment ($p < 0.01$), which demonstrated the curative effects of the therapy adopted for both treatment groups. However, the difference between the two groups before and after treatment was highly significant ($p < 0.01$), showing that the integrated therapy with TCM and Western medicine was superior to that with Western medicine alone in raising the level of blood lymphocytes.

Table 2. Changes in concentrations of blood lymphocytes (× 10^9/l) in patients of both groups before and after treatment

Treatment group	No of cases	Before treatment (mean ± SD)	After treatment (mean ± SD)	Difference (mean ± SD)
Integrated (TCM plus Western medicine)	24	1.00 ± 0.46	1.92 ± 0.74*	0.92 ± 0.61
Western medicine only	23	1.30 ± 0.58	1.80 ± 0.51*	0.49 ± 0.40
p - value		0.0616	0.5044	0.0068

SD, Standard deviation; TCM, Traditional Chinese medicine
*p <0.01, compared with values in the same group before treatment

The change in absolute value before and after treatment in patients of both groups who had abnormal levels of peripheral blood lymphocytes before treatment is summarized in Table 3.

There were 35 patients with an extremely low absolute level of blood lymphocytes among the 47 cases included in the study. Twenty of these patients were in the integrated treatment group and 15 in the group treated with Western medicine. The mean value at the time when the patients were first included in the treatment groups was 0.85 ± 0.22 $\times 10^9$/l in the integrated treatment group, and 0.97 ± 0.30 × 10^9/l in the group treated with Western medicine. No significant difference was seen between the two treatment groups ($p > 0.05$). After treatment with the different therapeutic regimens there were still 10 patients with abnormal lymphocyte counts; five in each group. Both therapeutic

regimens had obvious curative effects and there was a significant difference when the results obtained after treatment were compared with those before treatment ($p < 0.01$). Comparison before and after treatment of patients from the two groups who had had abnormal blood lymphocyte counts before treatment revealed significant differences ($p < 0.05$). This comparison showed that integrated therapy with TCM and Western medicine was superior to that of Western medicine alone in restoring blood lymphocyte counts to normal.

Table 3. Changes in concentrations of blood lymphocytes (×10⁹/l) before and after treatment in patients who had abnormal blood lymphocyte counts before treatment

Treatment group	No of cases	Before treatment (mean ± SD)	After treatment (mean ± SD)	Difference (mean ± SD)
Integrated treatment	20	0.85 ± 0.22	1.83 ± 0.71* (5)[a]	0.98 ± 0.65
Western medicine only	15	0.97 ± 0.30	1.61 ± 0.41*	0.59 ± 0.34
p - value		0.1953	0.3111	0.0332

SD, Standard deviation

[a] The value in parentheses was the number of patients who still had an abnormal blood lymphocyte count after treatment.

*$p < 0.01$, as compared with values in the same group before treatment

Measurement of blood T-lymphocyte subpopulations CD3, CD4/CD8

Table 4 shows the changes in T-lymphocyte subpopulations before and after treatment.

Table 4. Changes before and after treatment in patients who had abnormal subpopulations of CD3, CD4/CD8 before treatment

Treatment group	Item measured	Before treatment (%) (mean ± SD)	After treatment (%) (mean ± SD)	Normal range (%) (mean ± SD)
Integrated (TCM plus Western medicine)	CD3	55.56 ± 7.70 (9)[a]	69.44 ± 6.19 (2)[a]	66.1–77.0
Western medicine only	CD4/CD8	0.80 ± 0.11 (15)[a]	1.26 ± 0.36 (5)[a]	0.98–1.94
	CD3	53.80 ± 10.00 (10)[a]	63.2 ± 8.04 (8)[a]	66.1–77
	CD4/CD8	0.70 ± 0.16 (13)[a]	0.97 ± 0.20 (10)[a]	0.98–1.94

TCM, Traditional Chinese medicine; SD, standard deviation

[a]The numbers in parentheses are the numbers of patients with abnormal lymphocyte subpopulations

In total, 38 patients were tested for the classification of their T-lymphocyte subpopulations; 18 were in the integrated treatment group, and 20 in the group treated with Western medicine. Nineteen patients had extremely low CD3 levels before treatment (nine cases in the integrated treatment group and 10 in the group treated with Western medicine). After treatment, two patients in the integrated treatment group had levels that were below normal, yet the overall mean value had returned to within the normal range. In the group treated with Western medicine, the levels in eight patients had still not returned to normal and the overall mean value was below the normal range. In total there were 28 patients with extremely low CD4/CD8 levels before treatment; 15 and 13 patients in the integrated treatment group and the group treated with Western medicine, respectively. The numbers of cases whose levels had normalized after treatment were 10 in the integrated treatment group and three in the group treated with Western medicine, and the overall mean value for patients in the integrated treatment group had normalized, but that of the group treated with Western medicine was still below normal.

Comparison of curative effects of both therapies in restoring the levels of T-lymphocyte subpopulations

The effects of the two treatment regimens on the T-lymphocyte subpopulations are summarized in Table 5.

Table 5. Curative effects of the two therapeutic regimens in restoring the level of T-lymphocyte subpopulations

Treatment group	Number of cases							
	CD3				CD4/CD8			
	Normal	Abnormal	Total	*p*-value	Normal	Abnormal	Total	*p*-value
Integrated treatment (TCM plus Western medicine)	7	2	9	0.023	10	5	15	0.030
Western medicine alone	2	8	10		3	10	13	
Total	9	10	19		13	15	28	

TCM, Traditional Chinese medicine

Of the nine patients in the integrated treatment group and 10 patients in the group treated with Western medicine who had an extremely low CD3 level before treatment, there were seven and two patients in the two groups, respectively whose levels had normalized after treatment. Of the 15 patients in the integrated treatment group and 13 patients in the group treated with Western medicine alone in whom the CD4/CD8 subpopulation was extremely low before treatment, there were 10 cases in the former group and three in the latter group, respectively, in whom the levels had normalized after treatment. Treatment with integrated TCM and Western medicine was more effective than Western

medicine alone in restoring T-lymphocyte subpopulations; the *p*-values were 0.023 and 0.03, respectively (Fisher's exact test). Both *p*-values were less than 0.05, showing that there was a significant difference between the two therapeutic regimens. Therefore, the treatment with integrated Traditional Chinese medicine and Western medicine was significantly superior to treatment with Western medicine alone in restoring normal levels of T-lymphocyte subpopulations.

Discussion and conclusion

SARS is a new disease in humans and a continuing endeavour is being made by medical professionals to achieve a thorough understanding of it. The current treatment for SARS includes an antiviral agent such as ribavirin or oseltamivir; hormone to inhibit damage to the lung and allay the fever; and antibiotics to prevent potential bacterial infections. Treatment with TCM is based on an overall analysis of symptoms and signs, the cause, nature and location of the illness and the patient's physical condition according to the basic theories of TCM and relevant treatment based on specific symptoms.

It is known that the SARS virus may cause serious infection in the lower respiratory tract and damage to multiple systems in the patient's body. Clinical workers from mainland China, Hong Kong SAR and other countries have noted that a decrease in absolute value of lymphocytes occurred in most SARS patients, and an effect on T-lymphocyte subpopulations was demonstrated by a decrease in CD3, CD4, CD8 as well as CD4/CD8 (*2–5*) which shows that damage to the patient's cellular immune system leads to decreased immune function during the onset and progress of the disease, as demonstrated by the results of this study. Therefore, improving patient's immune function is critical to the success of treatment.

TCM has accumulated rich clinical experience and rational knowledge relating to the treatment of acute virus infectious diseases. The outbreak of SARS in the winter and spring was due to seasonal epidemic wind-heat pathogens; the disease was highly infectious and characterized by abrupt onset and rapid pathogenic progress, showing the feature of "migratory and variable pathogenic wind". The main symptoms include fever, myalgia, chest distress and cough. Patients with severe illness may suffer from dyspnoea and cyanotic lips caused by asthma; depletion of *yin* and *yang* may occur at the end and the patient may die. Therefore, SARS fits into the category of epidemic febrile diseases with the characteristics of epidemic diseases and epidemic lung diseases. In treating SARS patients with integrated therapeutic regimens of TCM and Western medicine, treatments were prepared based on the integrative concept and the theory of overall analysis of symptoms and signs, the cause, nature and location of the illness and the patient's physical condition in TCM. The therapy can significantly improve the recovery of patients from illness when used to supplement treatment with Western medicine (*2*). The data from this study show that the integrated therapy with TCM and Western medicine is superior to treatment with Western medicine alone in promoting the restoration of blood lymphocytes to normal concentrations and raising the level of T-lymphocytes provided that there is no significant difference in the average cumulative dose of hormone between the two groups.

Many herbal medicines such as Radix Astragali Seu Hedysari and Radix Panacis Quinquefolii can help regulate the immune system. This finding reflects the overall therapeutic concept of TCM which is to adjust *yin* and *yang* so as to achieve an equilibrium of the two, and to strengthen the body's resistance and eliminate pathogens so that the patient recovers. In the present study, we found that treatment with integrated TCM and Western medicine can alleviate reduction of lymphocyte activity, raise the levels of T-lymphocyte subpopulations and strengthen the body's immunity which would further speed up patients' recovery from illness.

Acknowledgements

Thanks are due to the State Ministry of Science and Technology and State Administration of Traditional Chinese Medicine for providing funding during the campaign against SARS and support for our research work. Thanks are also due to the China Institute of Traditional Chinese Medicine which provided us with training and guidance regarding our study to ensure the high quality of the research, and to the leaders in our hospital and the Institute of Infectious Diseases who also gave us their help.

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Report 9
Analysis of the clinical curative effects on patients with SARS of treatment with Traditional Chinese medicine and Western medicine

Wang Rongbing[34], Liu Junmin[34], Jiang Yuyong[34], Wu Yunzhong[34], Wang Xiaojing[34], Chi Pinpin[34], Sun Fengxia[34] and Gao Lianyi[34]

Abstract The objective was to observe how integrated treatment with Traditional Chinese medicine (TCM) and Western medicine affects major indices of the progress of severe acute respiratory syndrome (SARS), and to evaluate the curative effects of the integrated treatment with TCM and Western medicine. The study included 135 patients with clinically confirmed SARS of whom 68 were in the integrated treatment group and 67 in the control group. Patients in the control group received basic treatment with Western medicine, whereas patients in the integrated treatment group received herbal decoctions for relieving fever, removing toxins and eliminating dampness in addition to the same basic Western medicines as used in the control group. Both groups received a course of treatment of more than 2 weeks. Fever relief, cellular immunity, pulmonary inflammation, secondary infection and other curative effects were compared between the two groups after treatment. On days 2 and 3 after the start of treatment, the body temperature of patients in the control group was higher than that in patients in the integrated treatment group and the difference was significant ($p < 0.01$). The curve of decline in body temperature against time for patients in the group that received integrated treatment was relatively smooth; on day 20 after start of treatment, better cellular immunity and improvement in absorption of pulmonary inflammation were observed in the integrated treatment group. The statistical comparison between the two treatment groups revealed no significant differences in the time taken to absorb inflammation, cumulative dose of methylprednisolone, timing of administration and daily dose per person ($p > 0.05$). A decreasing tendency in the occurrence of secondary infection was seen in the integrated treatment group. Curative effects in the integrated treatment group were superior to those noted in the group treated with Western medicine alone in terms of gradual reduction of body temperature, mitigation of inhibition of cellular immunity and promotion of absorption of pulmonary inflammation.

Introduction

SARS is an acute infectious disease, caused by a newly found corona virus, with strong infectivity and a high mortality rate. Human beings are vulnerable to this disease and it presents a severe threat to health as well as affecting productivity. At present, studies on the microbiological characteristics and pathogenic mechanism of the SARS virus are still ongoing and no specific treatment is available. For the purposes of improving clinical curative effects, alleviating symptoms and mitigating the suppression of cellular immunity and severe

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inflammatory reaction during the course of disease, we treated 68 SARS patients with integrated TCM and Western medicine and set up a control group of 67 cases treated concurrently with Western medicine alone. Satisfactory curative effects were obtained with both treatments, but treatment with the integrated therapy was more effective.

Methods

Study subjects

All the participants were patients with clinically confirmed SARS admitted to our hospital from 10 April 2003 to 26 May 2003. Twenty-seven male and 41 female patients, aged 18–56 years with an average age of 35 years, were included in the group treated with integrated traditional and Western medicine (treatment group). Thirty-six patients were classified as normal cases and 32 as serious cases. Twenty-three male and 44 female patients, aged 20–65 years with an average age of 38 years, were included in the group treated with Western medicine alone (the control group); 39 patients in this group were classified as normal cases and 28 as serious cases.

The criteria for clinical diagnosis, case classification and discharge from hospital were in conformity with the criteria for infectious atypical pneumonia promulgated by the Ministry of Health of the People's Republic of China. The general clinical data and grouping of the patients are shown in Table 1.

Criteria for inclusion

The criteria conformed with those given in *Clinical diagnosis criteria for infectious SARS* (proposed) issued by the Ministry of Health; the patients included were aged 18–65 years and showed no sensitivity or allergic reactions to any of the medicines used.

Criteria for exclusion

Patients were not eligible for participation in the study if they:

- were aged < 18 years or > 65 years;
- had serious underlying diseases; or
- were pregnant or lactating.

Therapeutic regimens

The study subjects were allocated to seven different treatment zones according to the order of admission, and assigned to either the integrated treatment group or the group treated with Western medicine alone.

The basic treatment given to patients in both groups was identical to the therapeutic regimens recommended by experts from the SARS Command Centre of the Ministry of Health of the People's Republic of China. In our hospital, the usual dosage of methylprednisolone was 80–160 mg/day and the dose of ribavirin was 0.75 g–1.5 g/day for a course of 2 weeks. Other drugs administered

were: azithromycin 0.5 g per day for 5 days; levofloxacin 0.4 g per day for 7 days; thymosin 100–200 mg per day; no limits were imposed on supportive treatment. All patients received oxygen through a nasal tube and ventilators were used when necessary.

Therapeutic regimens of TCM were administered in accordance with the recommendations of experts from the State Administration of Traditional Chinese Medicine.

In our hospital, *Guoyao* No. 2 was administered during the acute stage of disease. The main ingredients were Sypsum Fibrosum 30 g, Semen Armeniacae Amarum 10 g, Radix Scutellariae 10 g, Rhizoma Atractylodis 10 g, Rhizoma Pinelliae 10 g and Radix Arnebiae seu Lithospermi 15 g.

Guoyao No. 3 was used in the critical stage. The main ingredients were Cornu Bubali 30 g, Radix Rehmanniae 15 g, Radix Scrophulariae 15 g and Flos Chrysanthemi Indici 15 g.

For patients in whom the course of disease had exceeded 3 weeks, or patients in the convalescent stage, *Guoyao* No. 4 was administered. The main ingredients included Radix Adenophorae Strictae 15 g, Radix Ophiopogonis 15 g, Radix Salviae Miltiorrizae 15 g, Radix Paeoniae Rubra 10 g and Radix Panacis Quinquefolii 10 g, taken separately.

Each dose was decocted in 200 ml, and taken twice daily, 100 ml in the morning and 100 ml at night; i.e. one dose per day. The treatment period for the entire course of TCM was more than 2 weeks and the observation period was 3 weeks.

Criteria for discharge from hospital conformed to the *Reference standard for the discharge of cases of infectious SARS* issued by the Ministry of Health of the People's Republic of China.

Observations

In the course of treatment, symptoms and signs of all patients were recorded and physiochemical analysis was carried out before and after the treatment. The observations recorded included body temperature, results of routine blood tests, serum enzymogram, T-lymphocyte subpopulations, and results of examination of chest X-rays. Some of the patients were tested for SARS RNA and IgG in pharyngeal aspirate, blood and urine. These special tests were conducted by the national or Beijing Centre for Disease Control; the RNA test was carried out using the polymerase chain-reaction method, and an enzyme-linked immunosorbent assay method was employed for antibody tests; for the analysis of T-lymphocyte subpopulations, a flow cytometry method was used. All experiments were conducted by our hospital.

Statistical analysis

All data were subjected to statistical analysis, and the normal distribution, *t*-test, rank-sum test and χ^2 test were conducted.

Quality control

To ensure appropriate quality of clinical research, the researchers and physicians recording the observations were trained and suitably qualified. For each district, a professor was responsible for the implementation of the clinical research protocol. Two suitably qualified persons were elected to gather data which were delivered to the medical statistical department of the hospital for statistical analysis. The database and case research documents were checked by the research management staff of the hospital. All the herbal pieces used conformed to the standards in the *Chinese Pharmacopoeia*, (2000 Edition, Volume I), and the patent medicines used were all commercially available prescription drugs.

Results

General clinical information on patients

The distribution of age, sex and stage of disease of the patients in the two treatment groups and the clinical classification of the two groups was comparable, with no statistically significant difference. There were no statistically significant differences between the integrated treatment and the treatment with Western medicine alone with respect to positive rate of pathogenic inspection at the time of admission to the hospital and after 20 days, or in the lymphocyte counts and T-lymphocyte subpopulations (Tables 1–3).

Table 1. General clinical information on patients in the two treatment groups (mean ± SE)

Treatment group	Sex		Age (mean ± SE)	Clinical type		Case distribution at each stage			Stage when patients were included in the groups (mean ± SE)
	M	F		Serious	Normal				
Integrated (TCM plus Western)	26	42	35.06 ± 1.27	32	36	37	29	2	6.46 ± 0.56
Western medicine	23	44	38.43±1.43	28	39	30	33	4	7.43 ± 0.50
p	0.721		0.129	0.605		0.439			0.252

M, Male; F, female; SE, standard error; TCM, Traditional Chinese medicine

Table 2. Results of test for SARS RNA in pharyngeal aspirate upon admission to hospital, and for SARS-corona virus-IgG in blood, and RNA in urine 20 days after hospitalization

Treatment group	Pharyngeal aspirate RNA		Blood IgG	Urine RNA
Integrated TCM plus Western medicine	No. tested	29	53	23
	Positive (%)	18 (62.07)	39 (73.58)	1 (4.35)
Western medicine only	No. tested	25	17	8
	Positive (%)	18 (72.00)	13 (76.47)	0
p		0.368	0.261	0.261

Table 3. Comparison of abnormal lymphocyte count and T-lymphocyte subpopulations of patients upon inclusion in a treatment group (mean ± SE)

	Lymphocyte (x 10^9/l)	CD3 (/µl)	CD4 (/µl)	CD8 (/µl)
Normal value	1-5	1032-2086	706-1125	323-886
Integrated treatment group	*n* = 40 0.67 ± 0.19	*n* = 63 451.68 ± 218.39	*n* = 66 256.97 ± 155.12	*n* = 55 163.75 ± 71.72
Western medicine alone	*n* = 42 0.65 ± 0.20	*n* = 56 491.39 ± 222.35	*n* = 60 283.72 ± 159.77	*n* = 48 188.52 ± 77.44
p	0.683	0.365	0.261	0.136

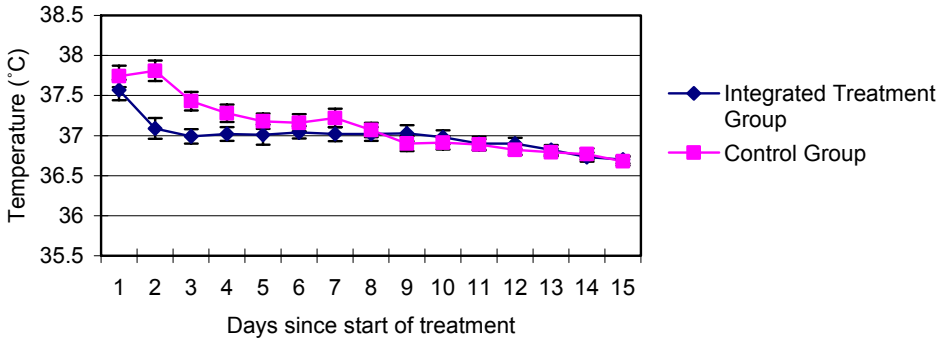
SE, Standard error

There was good comparability between patients in terms of lymphocyte count and T-lymphocyte subpopulation at the time of their inclusion in one of the treatment groups.

Influence on pyretolysis

Fever was the main manifestation of SARS; it lasted up to 2 weeks and was therefore one of the main targets of treatment. No significant difference between the treatment groups in terms of decrease in body temperature was seen before or after treatment, although the body temperature of patients in the control group was higher than that in the integrated treatment group 2 or 3 days after the start of treatment, and this difference was statistically significant ($p < 0.01$). A smooth curve for the decrease in temperature was observed in the integrated treatment group (Fig. 1).

Fig. 1. Changes in body temperature of patients in the two treatment groups



Influence on cellular immunity

After the onset of illness, concentrations of lymphocytes and T-lymphocyte subpopulations were seen to decrease significantly, and those patients who experienced a continuous decrease were generally seriously ill. The levels of lymphocytes recovered naturally during the convalescent stage. There was good comparability between the groups before the start of treatment, whereas 20 days after start of treatment, the integrated treatment showed better effects in protecting cellular immunity and promoting recovery (Fig. 2).

Fig. 2a. Change in lymphocyte concentration in patients in the two treatment groups before and after treatment

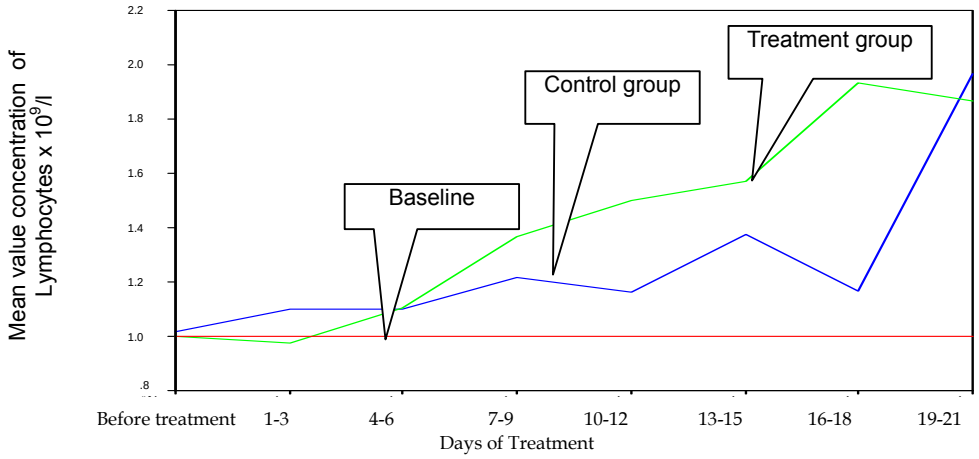


Fig. 2b. Change in concentration of CD3 cells in patients in the two treatment groups before and after treatment

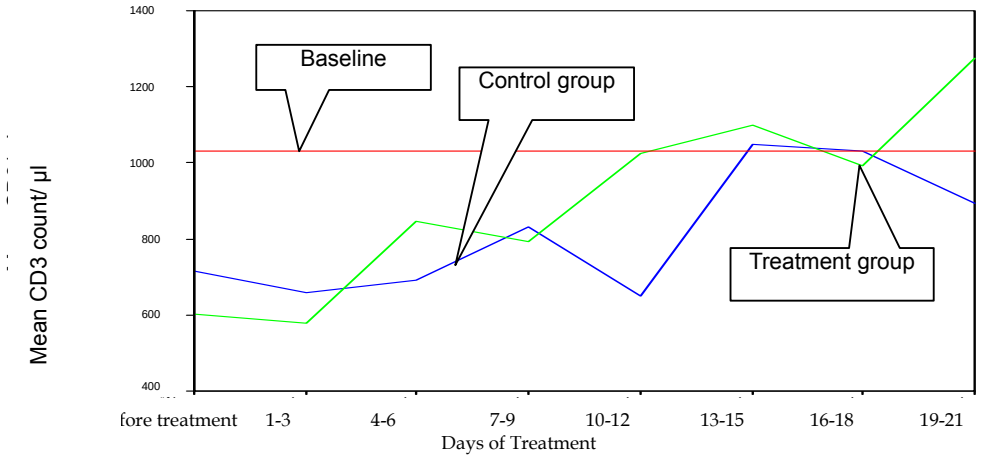


Fig. 2c. Change in concentration of CD4 cells in patients in the two treatment groups before and after treatment

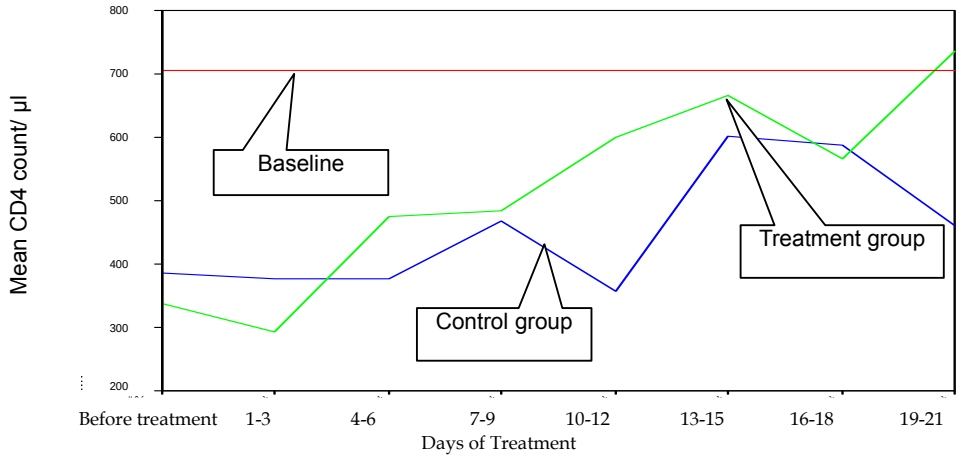
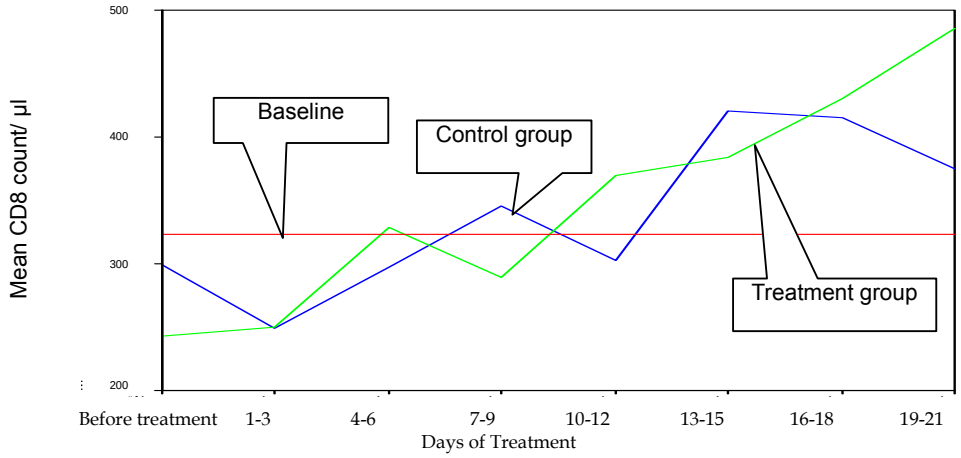


Fig. 2d. Change in concentration of CD8 cells in patients in the two treatment groups before and after treatment



Influence on the absorption of lung inflammation

A different extent of inflammation was seen in the lungs of individual patients, and various degrees of improvement or nearly total absorption of inflammation (as seen from X-ray examination), were observed 3 weeks after the start of treatment. There was good comparability between the states of illness of patients in the two groups as seen from X-rays obtained before treatment, yet the number of patients in the treatment group in whom inflammation was absorbed was obviously larger than that in the group treated with Western medicine 3 weeks after treatment, and no significant difference in the number of days needed for absorption of inflammation was observed (Table 4).

Table 4. Comparison of chest X-ray examination of patients in the two treatment groups

Treatment group	Pathogenic change in single lung lobe (*n*)	Pathogenic change in multiple lung lobes (*n*)	Complete absorption (*n*)	Incomplete absorption (*n*)	Days of absorption (mean ± SE)
Integrated treatment (TCM plus Western medicine)	12	56	48	20	18.58 ± 1.00
Western medicine only	13	52	33	34	17.00 ± 1.08
p		0.825		0.014	0.153

SE, standard error; TCM, Traditional Chinese medicine

The absorption of pulmonary inflammation in the treatment group was better than that in the group treated with Western medicine.

Methylprednisolone treatment

The doses of methylprednisolone and number of days of administration to the study subjects are summarized in Table 5.

The cumulative dosage, number of days of administration and per capita daily dose of methylprednisolone for patients in the two treatment groups were relatively low, and no significant differences between the two treatment groups were observed (Table 5).

Table 5. Dose and number of days of administration of methylprednisolone in the two treatment groups (mean ± SE)

Treatment group	No of patients treated with methylprednisolone	Total dose of methylprednisolone (mg)	No of days of administration per patient (mg)	Daily dose of methylprednisolone (mg)
Integrated treatment (TCM plus Western medicine)	51 (75%)	1466.86 ± 624.97	15.98 ± 4.69	91.79 ± 30.78
Western medicine only	48 (71.65%)	1823.54 ± 836.61	17.81 ± 7.20	102.39 ± 41.96
p	0.700	0.080	0.168	0.257

SE, Standard error; TCM, Traditional Chinese medicine

Secondary infection and complications

The course of SARS lasted for 4 weeks, during which impairment of the cellular immune system and administration of immunosuppressant led to secondary infection. The occurrence of secondary infection in the integrated treatment group was lower than that in the group treated with Western medicine alone (Table 6). As secondary infection was one of the causes of death in patients with SARS, reducing and controlling it would help to lower the case fatality rate.

Table 6. Secondary infection and outcome in the two treatment groups

Treatment group	Bacterial infection *n* (%)	Fungal infection *n* (%)	Haemorrhage in digestive tract *n* (%)	Discharge criteria satisfied *n* (%)	Deterioration	Death
Integrated (TCM plus Western medicine	5 (7.4)	2 (2.9)	0 (0)	66 (97.1)	1	1
Western medicine only	9 (13.4)	5 (7.5)	4 (6.0)	58 (86.6)	2	7
p	0.191	0.274	0.058	0.031		

Secondary infections and complications were fewer in the integrated treatment group, and the prognosis for patients in this group was superior to that for the patients who received treatment with Western medicine alone.

Discussion

Therapy with integrated traditional and Western medicine is a unique form of clinical medicine used in the People's Republic of China. At present, the Chinese medicines that are usually combined with Western medicine to treat SARS are the TCMs for relieving heat, toxin and dampness and clearing away lung-heat, which have resulted in definite curative effects.

Because there is as yet no specific and effective treatment for infection with the SARS virus and the pathogenic mechanism of the disease has not yet been elucidated, medical treatment should be specific to the symptoms, and control the excessively strong immune reactions and potential complications. The TCM should be based upon an overall analysis of symptoms and signs, the cause, nature and location of the illness and the patient's physical condition according to the basic theories of TCM. Successful treatment necessitates the integration of experience in treating epidemic febrile diseases in both ancient and modern times to develop prescription principles for different stages of the disease, taking the methods of relieving heat, toxin and dampness and clearing away lung-heat as the main basis for all stages of treatment. Suitable therapy with integrated traditional and Western medicine can combine the advantages of both TCM and Western medicine, overcome adverse drug reactions and promote overall curative effects.

Fever is the major manifestation of the disease. Adrenal cortical hormone was used in the treatment of most of the patients in both treatment groups. Because it brought down body temperature quickly, the antipyretic effect of pure herbal medicine could not be demonstrated. The smooth curve representing decrease in temperature over time in the integrated treatment group suggested that traditional herbal medicines were likely to inhibit the impairment of the immune system caused by the virus, alleviate inflammatory reactions and facilitate a smooth decrease in body temperature by means of an unknown mechanism. So far, treatment that includes TCM has been found safe and effective.

A significant decrease in lymphocyte concentration results from damage to the immune system that has a bearing not only on diagnostic significance but also on the prognosis of the disease. In our study, it was observed that the scale of the reduction in lymphocyte concentration was decreased and the increase in concentration during the convalescent period was enhanced by treatment with integrated traditional and Western medicine. This demonstrates the protective effects of TCM on lymphocytes and immune function, and against the suppressive effects of antagonistic hormone on cellular immunity. Our study also demonstrated the effects of TCM in maintaining stability of the internal environment of the organism, expelling pathogenic factors, strengthening body resistance and improving the stress reaction and immune function.

Comprehensive research on the pathogenic mechanism of SARS is being conducted. Blocking the progress of pathogenic change in the lung and promoting the absorption of inflammation are important therapeutic goals. Effectiveness in promoting absorption of lung inflammation was observed in the patients who received the integrated treatment. This was possibly due to the action of TCM in alleviating impairment of the immune system and in

suppression of fibrosis and the effects on the restoration of tissues of using large doses of antagonistic hormone.

There are many causes of mortality in SARS patients, among which serious immune damage and secondary infection related to the use of hormone are important. Fungal infection, septicaemia, disseminated intravascular coagulation and other infectious syndromes may appear in patients at the advanced stage of the disease. In our study, the rate of occurrence of secondary infection and adverse reactions to hormone administration in the treatment group was observed to be lower than in the group treated with Western medicine alone. This showed that treatment with TCM did have certain effects in protecting the function of immune cells and in promoting the body's ability to fight infection.

Traditional Chinese medicine has accumulated rich clinical experience and rational knowledge relevant to treating diseases caused by viral infection, reinforcing the idea that medical advice should be sought as quickly as possible to prevent pathogenic progress. The prescriptions used in our research, which were prepared by several specialists in TCM, were based on the experience accumulated since ancient times. They included medicinal ingredients to expel pathogens and toxin so as to strengthen and replenish *qi* and *yin*. We believe that the methods and curative effects of therapy with integrated traditional and Western medicine would be further improved by extending the research and developing a deeper knowledge of the disease together with optimization of therapeutic regimens.

Conclusion

Treatment with integrated TCM and Western medicine was found to be superior to that with Western medicine alone in alleviating inhibition of cellular immunity and ameliorating absorption of pulmonary inflammation. Its positive effects in reducing adverse reactions to hormone treatment, and the rates of secondary infection and complications were also indicated.

Acknowledgements

This paper is dedicated to clinical researchers working at the forefront of the fight against SARS, and thanks are due to the specialists who offered guidance on this research. Thanks are also due to the State Administration of Traditional Chinese Medicine and the Beijing Administration of Traditional Chinese Medicine for their valuable support.

Report 10

Evaluation of clinical curative effects of Traditional Chinese medicine in treatment of patients convalescing from SARS

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Abstract The objective was to evaluate the efficacy and safety of integrated treatment with Traditional Chinese medicine (TCM) and Western medicine in patients convalescing from SARS. Eighty-five SARS patients were selected for clinical research, 62 received the integrated treatment with TCM and Western medicine, and 23 were in the control group. Patients received an orally administered TCM regimen daily and were observed for 2–3 weeks. Observations recorded included clinical symptoms, serology, lung X-rays and self-rated quality-of-life scores. SPSS 10.0 software was used for the statistical analysis. The database was established and after data had been entered they were made read-only for the analysis. The total score of symptoms decreased more obviously in patients in the integrated treatment group than that in those in the control group (p = 0.04). There was a significant difference in both treatment groups before and after treatment, but compared with the control group, the number of patients with hepatic dysfunction in the integrated treatment group decreased more after treatment (p = 0.002). There were significant differences between the two groups in the level of improvement seen on the lung X-rays after treatment (p = 0.04); in the total score on the quality-of-life questionnaire (p = 0.04) and in the score of mental sentiment factors (p = 0.02). The results of integrated treatment were superior to those obtained in the control group. TCM was superior to treatment with Western medicine alone in improving the total score of symptoms, lung X-rays, hepatic function, total score for the quality of life and mental sentiment factors in SARS patients at the convalescent stage.

Introduction

SARS is a new and serious infectious disease. It was observed that the absorption of lung inflammation in some patients was rather slow and there were signs of pulmonary interstitial fibrosis to different degrees after recovery from SARS. Most of the patients suffered from various types of discomfort, yet modern medicine offers no effective treatment for SARS at this stage. The study reported here focused on evaluating the clinical curative effects of therapy with integrated

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TCM and Western medicine in treating SARS patients at the convalescent stage. The research method adopted was that of differentiating diseases in combination with differentiating symptoms and signs, so as to evaluate the efficacy and safety of TCM in treating patients convalescing from SARS.

Design of Study

A prospective, concurrent control, study design was adopted.

Subjects

Source of cases
All the cases were from Beijing Ditan Hospital, and 85 patients hospitalized during the period from 22 May to early June 2003 were selected; 62 cases were included in the integrated treatment group and the remaining 23 in the control group.

General information
Seven male and 16 female patients were included in the control group and 19 male and 43 female patients were included in the integrated treatment group. The average age of the patients in the control group was 39.43 ± 15.32 years old and that of the patients in the integrated treatment group was 36.26 ± 11.40 (p = 0.30). The average duration of disease of the patients in the control group was 33.00 ± 8.93 days whereas that of the patients in the integrated treatment group was 34.02 ± 8.23 days (p = 0.62). Sixteen of the patients in the control group were treated with glucocorticoid as were 49 patients in the integrated treatment group. There was no significant difference between the two groups (p = 0.40).

Symptoms
No statistically significant difference was apparent between the integrated treatment group and the control group in the distribution of any of the symptoms before treatment. These findings showed that the two groups were comparable with regard to sex, age, course of illness and distribution of symptoms.

Case selection criteria

Inclusion criteria
Patients who met the following requirements simultaneously were eligible for inclusion in the study.

- Patients who met the *Clinical diagnosis criteria for infectious SARS* (proposed) issued by the Ministry of Health of the People's Republic of China on 3 May 2003 (*1*).
- Patients who met the diagnostic criteria of the SARS convalescent stage:
  The following three conditions had to be met at the same time:
  - obvious improvement shown on chest radiograph;
  - obvious improvement in symptoms in the respiratory system; and
  - body temperature had returned to normal for at least 7 days, or there had been low fever (temperature ≤37.5 °C) for more than 2 weeks.

- Patients who were allowed to leave hospital after 1 week.
- Patients aged between 18 and 70 years old.

Exclusion criteria
Patients with any one of the following were not eligible for inclusion in the study:
- those patients who, before being infected by SARS, had underlying severe cardiovascular diseases, liver and kidney diseases, blood diseases, internal secretion diseases, lung diseases, neuropsychosis or other severe diseases such as tumours or acquired immunodeficiency syndrome;
- women who were gestating or lactating; and
- patients with a history of allergies.

Criteria for terminating the treatment
The criteria for terminating the treatment were as follows:
- Disappearance of symptoms;
- No obvious damage to lung or other viscera; the immunological functions had returned to normal; and
- SARS antibodies had been produced.

Criteria for the termination of treatment had to include at least the first two items.

Case distribution
Twenty-three patients formed the control group and 62 patients formed the integrated treatment group.

Treatment Method

Therapeutic regimen

Standard treatment
The principles of the standard treatment were as follows.
- The patients were advised to restrict their movement and to avoid fatigue or physical exertion.
- Mental irritation was avoided and patients who had cough with phlegm were given antitussives and apophlegmatics.
- Appropriate treatment was given to patients with functional damage to organs including the heart, liver and kidneys.
- Nutritional support was given.

Therapeutic regimen for traditional Chinese medicine
The TCM therapeutic regimen was developed by referring to the *TCM prevention and treatment regimen of SARS in Beijing Area* developed and recommended by specialists and organized by the Beijing Municipal Administration of Traditional Chinese Medicine (*2*); the *Routine therapeutics of integrated traditional and Western medicine for treatment of SARS* developed by the Guang'anmen Hospital which is affiliated to the China Academy of TCM; and by drawing on recent practical experience in the prevention and treatment of SARS as well as using the recent experience of fever experts together with information dating back to the Qing

Dynasty regarding recuperation from febrile diseases. The therapeutic regimens are specific to three types of illness:

- deficiency of both *qi* and *yin*;
- deficiency of *qi* in the lung and spleen; and
- lingering of pathogenic factor leading to deficiency of *yin*.

Based on this classification, three agreed prescriptions, adjusted to individual needs, were developed. The herbal decoction was taken orally, one dose per day. Details of the regimens are provided below.

Prescriptions

Prescription 1 for supplementing *qi* and nourishing *yin*, used against the deficiency of both *qi* and *yin*:

Radix Panacis Quinquefolii (6 g), Radix Ophiopogonis (12 g), Fructus Shisandrae (6 g), Radix Astragali (18 g), Rhizoma Polygonati Officinalis (12 g), pollen (12 g), Atractylodes macrocephala (15 g), Poria cocos (12 g), mulberry leaf (12 g), Radix Angelica Sinensis (9 g), Radix Paeoniae Lactiflorae (12 g), Rhizoma Ligustici Wallichii (12 g), lotus leaf (10 g) and *liu yi san* (10 g).

Prescription 2 for tonifying the lung and strengthening the spleen, used against the deficiency of *qi* in the lung and spleen:

Radix Astragali seu Hedysari (raw, 30 g), Radix Codonopsis Pilosula (15 g), Rhizoma Atractylodes Macrocephala (15 g), Yunnan tuckahoe (15 g), Radix Bupleuri (9 g), Radix Paeoniae Alba (12 g), Radix Angelicae Sinensis (9 g), Rhizoma Agustici Chuanxiong (12 g), Radix Auklandiae (12 g), Fructus Amomi (add later when preparing the decoction, 6 g), tangerine peel (12 g), Rhizoma Pinelliae (9 g), Herb Agastachis (10 g) and charred triplet (10 g each).

(Charred triplet is a mixture of equal parts of the following: charred medicated leaven, charred hawthorn fruit and charred germinated barley for improving digestion.)

Prescription 3 For replenishing the vital essence and removing heat, used against deficiency of *yin* caused by the lingering of pathogenic factor:

American ginseng (3 g), Radix Adenophorae Strictae (15 g), Radix Ophiopognis (12 g), Radix Bupleuri (9 g), Radix Scutellariae (12 g), mulberry leaf (15 g), Cortex Lycii Radicis (12 g), Herba Artemisiae (15 g), Rhizoma Phragmitis (15 g), Radix Angelicae Sinensis (9 g), Radix Paeoniae Alba (12 g), Rhizoma Pinelliae (9 g), roasted malt (15 g) and *liu yi san* (10 g).

Adjustment to individual symptoms

The following adjustments were made in response to specific symptoms.

- Plus Herba Artemisiae and chicken-bone herb for those with damaged liver functions or accompanied with increased level of cholerythrin;
- Plus tendril-leaved fritillary bulb and steamed stenona root for those who had cough without phlegm;
- Plus fritillaria bulb and perilla fruit for those who had cough with profuse sputum;

- Plus Rhizoma Anemerrhenae and yellow corktree bark for those who had dysphoria with feverish sensation in chest, palms and soles as well as those with yellow urine;
- Plus jade-screen powder and calcined dragon's bone and oyster shell for those who were prone to sweating;
- Plus pulp of dogwood fruit and prepared rehmannia root for those who suffered from deficiency of *yin*, which in turn affected the kidney, and those with reddened tongue and little fur, hot palms and soles, deficiency of *qi* and feebleness of the knees.
- Plus scutellaria root, Fructus Gardeniae and Herba Pogostemi for those who had damp-heat pathogen and greasy fur on tongue;
- Plus *Trichosanthes kirilowii* maxim and Semen Cannabis for those who suffered from constipation;
- Plus baked ginger and parched Semen Dolichoris for those who had loose stools;
- Plus mother-of-pearl and jujube kernel for those who suffered from insomnia.

Course of treatment

The course of treatment, which began at the time the patient had reached the convalescent stage, had the following three components:

- administration of herbal decoction and hospitalization for observation for 1 week;
- administration of herbal decoction for 2 weeks after leaving hospital; and
- follow-up visits which were continued until the termination of at least the first two indicators listed above under "Criteria for terminating the treatment".

Observations

General information

The general information collected included: name, sex, age, profession, home addresses, postcode, contact phone number, date of disease onset, dates of hospitalization and discharge, main symptoms at time of inclusion in the treatment groups, past medical history, diagnosis by Western medicine and differentiation of TCM. These details were entered after the patients had been included in one of the treatment groups.

Symptoms and signs

Observations recorded included hypodynamia, shortness of breath, sweating, palpitations, poor appetite, insomnia, characteristics of urine and stools, appearance of tongue, and characteristics of pulse. A quantitative method was adopted for recording the severity of the symptoms: none, light, moderate and severe were scored as 0, 1, 2 and 3, respectively. This information was collected once every three days for hospitalized patients, once a week during follow-up and at the last return visit by patients who had left hospital.

Laboratory examinations

The results of routine blood tests, myocardial enzymograms, tests of liver and kidney function, chest radiography and antibody detection were first recorded at the time the patients were included in one of the treatment groups and again at the time the course of treatment ended.

Rating of the quality of life
Quality of life was assessed by means of a self-rating scale questionnaire. The scale was prepared by referring to the contents and formats of the St. George's questionnaire on respiratory diseases, a questionnaire on the quality of life for adult asthma patients (*1*) and the health investigation questionnaire, and by noting the comments of specialists in pneumology, experts on clinical epidemic diseases and statisticians, as well as the physical symptoms of the patients. The scale consists of 16 questions on three aspects of life: restriction of day-to-day activities (*1–5*), symptoms of dyspnoea (*6–10*) and mental health (*11–16*). There were five options ranging from poor to very good, which were scored on a scale of 1 to 5; the option representing the best quality of life was scored as 5, and that representing the worst was scored as 1. The rating was ascertained first when the patients were included in one of the treatment groups and again when the course of treatment ended.

Indices and criteria for evaluation of curative effects

The curative effects were evaluated on the basis of the criteria described below.

Change of symptoms: the change in the total score was noted.

Quality of life: this was assessed by evaluation of the self-rated quality-of-life scale completed for the SARS patients.

Chest radiograph: absorption of inflammation as seen on the chest radiograph was evaluated using a scoring system.

This scoring system was based on *Clinical studies on the treatment of SARS cases with therapeutics integrating traditional and Western medicine*, one of the key national projects — an 863 key project — developed under the tenth Five-Year Plan developed by the State Ministry of Science and Technology. The scoring principles are based on the density and size of the shadow on the chest radiograph. There are 12 evaluation spots distributed in the upper, middle and lower parts as well as the inner and outer zones of the left and right lungs, and three levels (high, low and cord strip) for the density of the pathological changes; attention is also paid to heart size and complications in the pleura and other factors. The scores were assigned by designated radiologists blinded as to the identity of the patients; the standard normal chest radiograph was scored as 0, and the score for the greatest possible lung damage was 38.

Damage to liver functions
Improvement of liver function was assessed in patients who had abnormal alanine aminotransferase (ALT) levels before treatment.

Quality control

Management and coordination
A task group leader responsibility system was established, head specialists were appointed and personnel for quality supervision, logistic support and follow-up visits were suitably equipped.

Training
Centralized and rapid training was provided for the research team following its formation, so that the researchers would fully understand the clinical research plan and its indicators and implications.

Key points for quality control
The personnel involved in this research were required to:

- strictly observe the criteria for the inclusion and exclusion of cases;
- truthfully and carefully record all items in the case report form according to the standard requirements so as to ensure an accurate and reliable record;
- check all observation results and findings to ensure that data were reliable and that all conclusions from the research came from original data;
- record all symptoms as per the quantitative standard with no omission of any important examination indicators with clinical significance, such as hepatic function and chest radiograph;
- try to adopt the TCM prescription designed for this study with appropriate adjustments to meet special situations; and
- record the correct contact information and address, conduct regular follow-up visits, ensure that patients made return visits to a fixed location and communicate and coordinate with patients early on to improve the adherence of patients and avoid any negligence or omission.

The quality of all the decoction pieces used complied with the standards in the *Chinese Pharmacopoeia*, (2000 Edition, Volume I), and all the Chinese patent drugs used had been approved by the State Drug Administration of China and were commercially available.

Ethics and informed consent

This research was conducted with the approval of the Ethics Commission of Guang'anmen Hospital, and the proposed treatment was discussed with the patients and their consent obtained.

Statistical analysis

Data were analysed by use of SPSS 10.0 software. After the database was set up, the data were entered and verified and then made read-only for analysis. All the quantitative indicators were expressed as mean ± standard deviation, and tested using a *t*-test and a chi-squared test. A *p*-value <0.05 indicated that the results were statistically significant (two-tailed test).

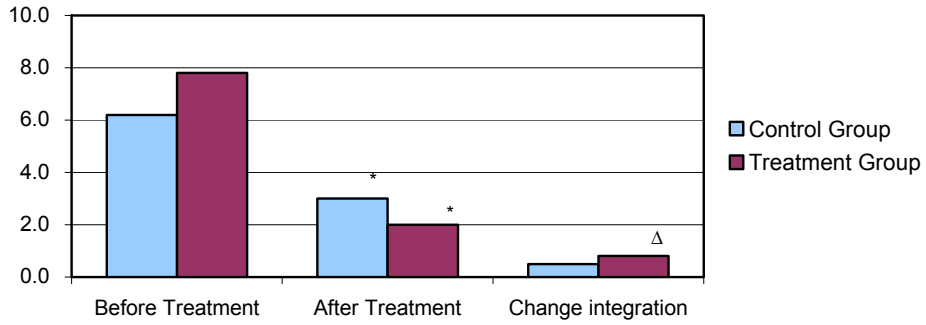
Results

Comparison of symptom scores before and after treatment

The total symptom scores in the two treatment groups before and after treatment were not significantly different, but the scores for each of the symptoms after treatment were significantly different ($p < 0.01$) from those before the treatment in both groups. In terms of improvement in symptom scores, the integrated

treatment group was superior to the control group, and the difference was significant ($p < 0.05$) (Fig. 1).

Fig. 1. Comparison of symptom scores before and after treatment

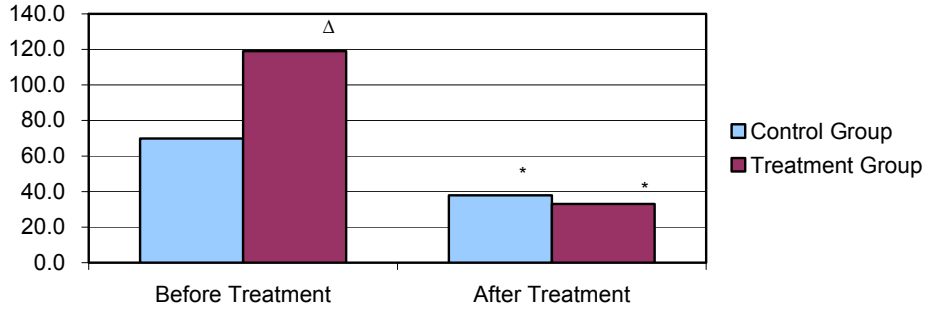


*$p < 0.01$, compared with score before treatment; △ $p < 0.05$, compared with score in control group.

Comparison of alanine aminotransferase before and after treatment

For patients who had abnormal levels of ALT at the time they were assigned to a treatment group, the mean ALT of the patients in the integrated treatment group before treatment was higher than that of patients in the control group ($p < 0.01$). After treatment the ALT levels of both groups had returned to normal, and the difference was not significant ($p > 0.05$). The ALT level of patients in both groups was significantly different before and after the treatment ($p < 0.01$) (Fig. 2).

Fig. 2. Comparison of levels of alanine aminotransferase before and after treatment

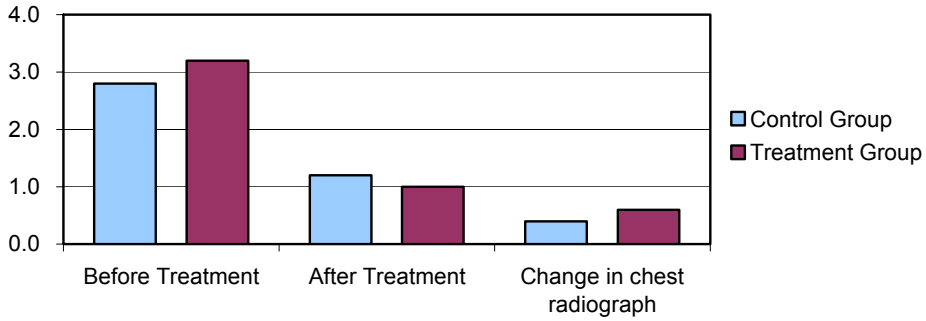


* $p < 0.01$, compared with levels before treatment; △$p < 0.01$, compared with levels in control group

Comparison of chest radiographs before and after treatment

The scores for the chest radiographs before and after treatment were not significantly different between the two groups, but the scores after treatment were significantly different ($p < 0.01$) from those before treatment. In terms of improvement after treatment, the scores of the treatment group were better than those in the control group and the difference was statistically significant ($p < 0.05$) (Fig. 3).

Figure 3. Comparison of change in chest radiograph before and after treatment



Assessment of the quality of life before and after treatment

Altogether 85 self-rated quality-of-life questionnaires were distributed before the treatment and 81 usable questionnaires were returned. Six out of the 85 questionnaires were excluded after treatment, therefore the number of usable questionnaires finally analysed was 79. The total scores and scores in the three aspects (restricted day-to-day activities, symptoms of dyspnoea and mental health) of the two groups before treatment were not significantly different ($p > 0.05$). The differences in total scores and the scores for mental health of both groups before and after treatment were significantly different ($p < 0.05$). The differences in total scores, and those for mental health and dyspnoea in the integrated treatment group before and after treatment were highly significant ($p < 0.01$), and the score for restricted activities in the integrated treatment group before and after treatment was also significantly different ($p < 0.05$). The total scores and the scores for each individual factor before and after treatment in the control group were significantly different ($p < 0.05$) (Table 1).

Table 1. Comparison of quality-of-life rating of patients in the two treatment groups before and after treatment

Sub-scale	Treatment group	Time of rating (*n*)	Score after treatment (mean ± standard deviation)
Restricted activities	Treatment group	Before treatment (61)	7.54 ± 0.34
		After treatment (59)	5.54 ± 0.16*
	Control group	Before treatment (20)	8.00 ± 0.70
		After treatment (20)	5.95 ± 0.34*
Dyspnoea	Treatment group	Before treatment (61)	9.57 ± 0.57
		After treatment (59)	6.44 ± 0.23**
	Control grop	Before treatment (20)	9.20 ± 0.92
		After treatment (20)	6.80 ± 0.57*
Mental affection	Treatment group	Before treatment (61)	12.43 ± 0.61
		After treatment (59)	7.95 ± 0.27**△
	Control group	Before treatment (20)	12.70 ± 0.97
		After treatment (20)	9.35 ± 0.56*
Total scores	Treatment group	Before treatment (61)	29.54 ± 1.29
		After treatment (59)	19.93 ± 0.48**△
	Control group	Before treatment (20)	29.90 ± 2.25
		After treatment (20)	22.10 ± 1.10*

* $p < 0.05$, ** $p < 0.01$, compared with score before treatment; △$p < 0.05$, compared with score of control group.

Discussion and conclusions

Effects of Traditional Chinese medicine prescription series in improving the symptoms of patients at the convalescent stage

The symptoms of the 85 SARS patients at the convalescent stage could be ranked from most severe to least severe as follows: hypodynamia; palpitations; shortness of breath; sweating; low fever; yellowish urine; dysphoria with feverish sensation in chest, palms and soles; insomnia; anorexia; cough; dry mouth; constipation; diarrhoea; and bitter taste in mouth. In terms of symptom improvement, the scores before and after treatment were significantly different, and the TCM prescriptions were especially effective in improving the main symptoms, such as hypodynamia and palpitations, and other symptoms were also improved to a certain extent.

SARS is a disease caused by strong pathogens that have a severe impact on the body's resistance and patients have been treated with various medicines at different doses. In view of the fact that any drug may be toxic to certain extent,

continued use and high doses will result in impairment to the vital functions of the human body. In addition, although at the later stage of the disease the high fever has been allayed, the residual heat still remains and the body has not yet returned to normal; the pathogens may therefore continue to impair the vital-*qi* of the body, which results in deficiency of *qi*, deficiency of *yin* or deficiency of both *qi* and *yin*. The TCM prescriptions used to treat patients in this study were mainly aimed at supplementing *qi* and nourishing the *yin*, and are based on *shengmaiyin* (ginseng + lilyturf root) and *sijunzitang* decoctions, which can be added to other drugs that can be used to reduce fever, remove dampness, promote blood circulation, remove toxic substances, improve appetite and digestion, and discharge mucus through the urethra. Such decoctions have certain effects in restoring the immunological functions of the patients, balancing *yin* and *yang*, enhancing the healthy-*qi* and coordinating the functions of the visceral organs.

In terms of the evolution of the symptoms in the course of treatment, based on Traditional Chinese knowledge, only two patients experienced conversion from weakened health *qi* and body resistance, to domination of the pathogen (damp-heat and stagnated blood). These two patients were treated with *ganluxiaodudan* and *shengjiangsan* mixed with *ganluxiaodudan*, and *xuefuzhuyutang* and *shengmaiyin* mixed with *xuefuzhuyutang*, respectively, for 2 weeks, after which the domination of pathogen gradually receded. It is not yet known whether the symptoms of weakened body resistance that lead to dominance of the pathogen are due to increased viral load, and this needs to be studied further. Also, the conversion law between the deficiency of *qi*, the deficiency of *yin* and the deficiency of both *qi* and *yin* needs to be established by means of further statistical analysis.

Influence of Traditional Chinese medicine prescriptions on the liver functions of patients convalescing from SARS

The liver impairment in SARS patients at the convalescent stage may be related to the direct action of the SARS virus and endotoxaemia as well as the release and attack of inflammatory factors, and the administration of antiviral drugs, antibiotics and hormones may also damage liver cells.

The number of patients with abnormal liver functions (reflected in levels of ALT) in the integrated treatment group before treatment was greater than that in the control group before treatment. No obvious differences between the treatment group and the control group were seen after treatment but, in terms of the degree to which ALT was lowered, the integrated treatment was better than the treatment received by the control group. This indicates that the TCM prescriptions have superior effects in eliminating the negative impact on the liver of drugs such as cortical hormone, and restoring liver cell function following damage by the SARS virus.

The liver has powerful storing and compensating functions. It is not known whether the abnormal liver functions found in SARS patients resulted from the toxicity and side-effects of drugs used to treat the disease, or from transient damage to the liver caused by the virus. Alternatively, there may have been hidden chronic liver impairment factors which, in combination with some stress

factors, caused a "cell hormone storm". Long-term clinical observations are required to answer this question.

Effects of Traditional Chinese medicine prescriptions in promoting the absorption of inflammation in the lungs of patients convalescing from SARS

SARS may produce violent cellular immunoreactions in the lungs of patients, resulting in immunological injury to target organs (mainly lung tissues) and may cause violent and severe injuries to the lung tissues. The major sequelae in SARS patients are pulmonary interstitial fibrosis and pulmonary hypofunction. Pulmonary interstitial fibrosis is obvious in SARS patients who have previously had lung diseases. In spite of the normal chest radiographs obtained from some SARS patients 1 month after the onset of the disease when their clinical symptoms had completely abated, patches and bar shadows could still be detected using CT examinations. These patients showed slow absorption of pulmonary inflammation or signs of pulmonary fibrosis, which lowered the lung compliance and reduced the lung volume, manifesting as restrictive and diffuse ventilating functional disorders and progressive dyspnoea, leading to a reduced quality of life (*3, 4*).

Most patients in the integrated treatment group had abnormal pulmonary changes and two patients were particularly seriously affected. After being treated with TCM prescriptions for 3 weeks, the abnormalities in the lungs of these two patients had completely disappeared. The results of the statistical analysis also indicate that the improvement shown on the chest radiographs of the patients in the integrated treatment group was significantly better than that of the patients in the control group. This finding provided evidence that TCM, through integral regulation and treatment based on the overall analysis of symptoms and signs, has definite effects in promoting the absorption of inflammation in the lungs of the patients.

It is not known whether the abnormal changes in the lungs of SARS patients at the convalescent stage indicate that the absorption of pulmonary inflammation is not complete or that pulmonary interstitial interstitial fibrosis has occurred. Further research is needed to answer this question. Further studies are also required to determine whether pulmonary interstitial interstitial fibrosis is pathologically different from acute pulmonary diseases such as idiopathic pulmonary interstitial fibrosis.

Effects of Traditional Chinese medicine prescription series in improving the quality of life of the patients (5)

During 3–4 weeks of treatment in an isolation ward, the SARS patients were in a mental state of melancholia due to isolation. In a context in which more and more attention is paid to the overall health of patients, we recognized that the aim of clinical medicine is not only to cure "the diseases suffered by patients", but to place more emphasis on "the people suffering the diseases", so as to help patients to achieve a state of overall health from the social, physiological and psychological points of view and enable them to return successfully to life in their societies (*6*). The present study shows that the improvement in quality of life of the integrated treatment group was better than that of the control group, as

reflected in the total quality-of-life scores and the scores of mental health factors. Although the difference in the scores of restricted activities and dyspnoea was not statistically significant, the patients in the integrated treatment group showed a greater tendency towards further improvement than those in the control group. The reason that there is no statistically significant difference may be the small size of the control group; to answer this question would require further studies.

Acknowledgements

This study was funded by the Beijing Administration of Traditional Chinese Medicine. Our grateful thanks are due to the State Administration of Traditional Chinese Medicine, Beijing Bureau of Health, Beijing Administration of Traditional Chinese Medicine, China Academy of Traditional Chinese Medicine and the leaders of Ditan Hospital who have given us great support. We also wish to thank the staff of Ditan Hospital, the Radiation Department, the Health Service Office and the logistic staff of Guang'anmen Hospital, without whose efforts this research would not have been possible.

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Report A
A herbal formula for the prevention of transmission of SARS during the SARS epidemic in Hong Kong Special Administrative Region — a prospective cohort study

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Abstract. Traditional Chinese medicine (TCM) has a long history of being used to treat respiratory ailments. Many clinicians in China have used TCM to treat SARS patients with favourable outcomes as the symptoms of SARS closely resemble those of *wen bing* (feverish disease). The use of TCM for the treatment of respiratory illnesses in China has shown promise in the prevention of SARS particularly among high-risk groups SARS attack rates for two cohorts of health care workers from 11 hospitals in Hong Kong SAR, one using a herbal supplement for a 2-week period (n = 1063) and a control cohort comprising all health care workers who did not receive the supplement (n = 36 111) were compared prospectively. Changes in quality of life and influenza-like symptoms of the herbal supplement users were also examined at three time points. Results None of the health care workers who used the supplements subsequently contracted SARS as compared to 0.4% of the health care workers who did not use the supplements (p = 0.014). Improvements in influenza-like symptoms and quality of life measurements were seen among users of the herbal supplements. Fewer than 2% of supplement users reported adverse events and all such events were minor. The results of this pilot study suggest that use of the TCM preparation is a safe, efficacious and affordable SARS prevention measure. The simple, uniform formula might be considered to have violated the fundamental principles of treatment advocated by herbal experts in that only one formula was used. However, its efficacy supports the feasibility of using a uniform formula when facing an urgent need for broad prevention.

Introduction

The first outbreak of SARS occurred in the Prince of Wales Hospital in Hong Kong SAR in 12 March 2003; a total of 39 cases were reported (*1*). Health care workers were one of the groups most affected in this epidemic. As of June 2003, 338 (19.5%) of the 1755 confirmed or suspected cases of SARS reported in Hong Kong SAR had occurred in health care workers, and of these a total of six health care workers working in public hospitals had died of the disease (*2*).

The Centre for Disease Control and Prevention in China has classified SARS as a disease related to *wen bing* (meaning "feverish disease" in TCM), based on the close resemblance between the two illnesses. The Centre also advised health practitioners to refer to traditionally prescribed treatments and recommendations

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for *wen bing* in the treatment of SARS. It was reported that many SARS patients in China received a treatment regime of mainstream Western medicine supplemented with Chinese herbal medicine (*3*). A number of health practitioners have claimed that the combined treatments with Western and Chinese herbal medicine may have contributed to the relatively low mortality from SARS in China (*4*).

Chinese medicine has a favourable reputation and a long history of treating respiratory ailments that resemble influenza. In ancient China, such ailments and diseases were so prevalent that *wen bing* developed into a highly specialized and sophisticated branch of Chinese medicine that can be traced back 500 years to the late Ming Dynasty. According to the traditional precepts of *wen bing*, influenza-like diseases can be divided into four stages:

- development of fever;
- nasal symptoms;
- fever and chills (serious illness); and
- haemoptysis (*4*).

In Western medicine, the first two of the above-mentioned stages (fever and other mild symptoms) may be viewed as symptoms that usually subside even without treatment. The later stages may represent more unusual conditions when bronchitis and late pneumonia occur, possibly requiring hospitalization. There is no simple effective treatment for influenza in Western medicine. It has, however, long been noted that *wen bing* practitioners have had measurable success in controlling symptoms in the early stages, and are, thereby, presumably able to prevent the ailment from progressing to bronchitis and pneumonia. As SARS may be considered to be a viral infection related to influenza, the use of a *wen bing* formula for prevention and treatment during the early stages of illness shows great promise. Proven efficacy of this formula would have far-reaching implications for reducing the number of SARS cases.

The primary objective of the present study was to investigate the efficacy of a herbal formula in the prevention of transmission of SARS among health care workers in the hospitals in Hong Kong SAR, by comparing a cohort of herbal formula users with a control group of non-users. The secondary objectives included investigations of the differences among herbal supplement users in their quality of life and in the frequencies of self-reported influenza-like symptoms, as measured before they began to take the formula and at week 2 and week 4 after commencing intake, as well as to evaluate safety data related to the intake of the herbal formula.

Methods

The herbal formula

The formula was created by combining two herbal formulae that have commonly been used in the prevention and treatment of early-stage influenza-like symptoms. The first formula *sang ju yin* has been used widely in southern China (*5*). The second, *yu ping feng san*, has been popular in central and northern

China (*6*). Two ingredients noted in the modern herbal pharmacopoeia to have strong antiviral properties were added to the two formulae. The entire formula therefore consisted of 12 herbs: Folium Mori, Flos Chrysanthemi, Semen Armeniacae Amarum, Fructus Forsythiae, Herba Menthae, Radix Platycodonis, Radix Glycyrrhizae, Rhizoma Phragmitis, Radix Astragali, Radix Saposhnikoviae, Folium Isatidis and Radix Scutellariae. These herbs have been used traditionally for more than a thousand years and are considered safe for consumption because no noteworthy adverse effects have been recorded (*5, 6*).

The herbs were purchased from a reputable TCM supplier to ensure high quality, and the herbal preparation was manufactured according to standard good manufacturing practice (*7*). The ingredients were boiled to form a decoction which was subsequently freeze-dried into pellets that could be easily reconstituted into a tea-like drink.

Subjects and data collection methods

Volunteers who were health care workers working in 11 hospitals regulated by the Hong Kong Hospital Authority were recruited for the study. All these hospitals had been caring for SARS patients. Once informed consent had been obtained, the study subjects received 14 packets of the herbal supplement free of charge and were advised to consume the herbal drink every day for two weeks. All the health care workers recruited were free from SARS symptoms when they joined the study. Exclusion criteria included: serious illness, renal insufficiency and any history of hypersensitivity to Chinese medicine. The initiative was supported by the Hong Kong Hospital Authority. Ethical approval was obtained from the Clinical Research Ethics Committee of the Chinese University of Hong Kong. The volunteers also received three identical short questionnaires which were to be completed before commencing herbal supplement use, at the end of the 2-week period (week 2) during which the herbal supplement was taken and then, another 2 weeks after completing the treatment (week 4). The volunteers were instructed to return the three self-administered questionnaires to the research team by fax at the conclusion of the study. The herbal formula was distributed around mid-April 2003. In Hong Kong, the last SARS case was reported on 11 June 2003, and the last SARS case among health care workers was reported on 4 June 2003.

In order to achieve the primary research objective, a cohort study design was used in which a cohort using the herbal formula was compared with another control cohort that consisted of all other health care workers from the 11 participating hospitals, who did not use the herbal formula. The two cohorts were prospectively followed up to see whether any cohort members contracted SARS during the study period (17 April 2003 to 17 August 2003), by comparing the names of the herbal formula users against a registry of all SARS cases among health care workers in Hong Kong SAR maintained by the Hospital Authority. The attack rates of the two cohorts were compared statistically.

To achieve the secondary objectives, a "pre-post" study design was used. No control group was used, as the study was conducted at the peak of the SARS epidemic when the Hospital Authority wished to offer the herbal supplement to as many front-line workers as possible. A total of 2601 health care workers (out of a total of 16 437 working in these 11 hospitals) received the herbal supplement

and a total of 1063 (40.9%) returned completed questionnaires to the investigators.

Outcome measures

For the primary research objective, the outcome measure was whether the study subjects contracted the SARS virus between 17 April 2003 and 17 August 2003. The figures were cross-checked with the Hospital Authority's database on 17 August 2003 to determine whether any of the herbal supplement users had contracted SARS. In order to address the secondary objectives, the investigators measured quality of life, self-reported influenza-like symptoms and various indices of *wen bing*-related symptomatology that had been suggested by a panel of expert practitioners of Chinese medicine in the supplement users at the three time points. The mental health and vitality subscales of the Chinese version of the Short Form-36 (SF-36), which had been validated in Hong Kong SAR, were used in the study to measure two domains of quality of life (*8*). The list of influenza-like symptoms included fever, chills, muscle pain, headache and "heavy feeling", cough, fatigue, rigors and "hot feeling" (feverishness). Each of these symptoms was measured by a visual-analogue scale (with scores of 0–10). The list of TCM symptoms included: thick tongue sign (yes/no), sore and/or dry throat (yes/no), sleeping problems (yes/no), feeling "cold", "heat" or "humid"(yes/no). All adverse events were also recorded.

An understanding of the influenza-like symptoms and *wen bing* symptoms was considered necessary because these self-assessed symptoms in general might have been used by the health care workers as indicators of the possibility of having contracted SARS during the epidemic.

Statistical analysis

The difference in the attack rates of SARS between the cohort using the herbal supplement and the control cohort was tested by Fisher's exact test. Changes in the SF-36 mental health and vitality subscales and the influenza-like symptoms before and after the intake of the herbal supplement were tested for statistical significance by using a paired *t*-test and McNemar's test.

Table 1. Background characteristics of the herbal supplement users (n = 1063)

	No of subjects	Percentage
Age (years)		
20-30	184	17.3
31-40	366	34.4
41-50	377	35.5
51-60	135	12.7
> 60	1	0.1
Gender		
Female	829	78.0
Male	234	22.0
Occupation		
Nurse	485	45.6
Non-clinically trained support staff[a]	283	26.6
Physicians, allied health workers and others[b]	295	27.8
Location of work		
Accident and emergency unit	16	1.5
Intensive care unit	98	9.2
Infection ward	166	15.6
General ward	289	27.2
Orthopaedics and traumatology	48	4.5
Outpatient clinic	110	10.3
Administrative area	93	8.7
Other[c]	243	22.9
Hospital		
A	414	38.9
B	139	13.1
C	132	12.4
D	86	8.1
E	80	7.5
F	79	7.4
G	35	3.3
H	29	2.7
I	28	2.6
J	26	2.4
K	15	1.4

[a]General service assistant, health care assistant, ward assistant, manual worker, steward, operating theatre assistant and blood-taking assistant.

[b]Physician, dietitian, audiologist, radiographer, physiotherapist, occupational therapist, podiatrist, technician and research assistant.

[c]Pharmacy, endoscopy unit, electrodiagnostic unit, telemedicine unit, information technology office, laboratories, X-ray unit, occupational therapy department, physiotherapy department, radiology department, department of prosthetics and orthopaedics, central office, admission office, rehabilitation, transportation, canteen, mortuary, central sterile supply department and health information centre.

Results

Background characteristics

The background characteristics of the subjects are summarized in Table 1. The distributions of the three types of health care workers (nurses, non-clinically trained support staff, physicians/allied health workers and others) of the two cohorts were comparable (Table 2).

Table 2. Comparison of the job distribution of the two study cohorts

Job category	Supplement user cohort	Control cohort
Nurses	485 (45.6%)	19 228 (53.2%)
Non-clinically trained support staff	283 (26.6%)	7 235 (20.1%)
Physicians, allied health workers and others	295 (27.8%)	9 648 (26.7%)
Total	1063 (100%)	36 111 (100%)

Efficacy in SARS prevention

None of the 1063 herbal supplement users contracted SARS, whereas the attack rate in the control group was 0.4% (64 out of 15 374). The difference was statistically significant ($p = 0.014$, one-tailed *t*-test).

Mental health and vitality subscales

The means and standard deviations of the mental health and vitality (quality of life) scores at days 0, 14 and 28 are summarized in Table 3. It can be seen that the mental health of the subjects improved from day 0 to day 14 ($p < 0.001$), and remained more or less constant from day 14 to day 28 ($p = 0.284$); the difference between the scores on day 0 and day 28 was also statistically significant ($p < 0.001$). The vitality score also showed statistically significant improvements from day 0 to day 14 ($p < 0.001$) and from day 0 to day 28 ($p = 0.010$), although it decreased slightly from day 14 to day 28 ($p = 0.019$).

Table 3. Changes in Short Form-36 mental health and vitality quality of life subscales

	Mental health			Vitality		
Days	**Mean**	**(SD)**	**Paired *t*-test *p*-value**	**Mean**	**(SD)**	**Paired *t*-test *p*-value**
0	60.08	(9.89)		57.88	(11.89)	
14	62.14	(9.25)		59.15	(11.77)	
28	62.34	(9.38)		58.63	(11.92)	
0 - 14			< 0.001			< 0.001
14 - 28			0.284			0.019
0 - 28			< 0.001			0.010

SD, Standard deviation.

Table 4. Changes in visual-analogue scale scores referring to western medicine's "influenza-like" symptoms among herbal supplement users

	Chill symptoms			Rigor symptoms			Muscle symptoms			Headache and heaviness symptoms			Cough			Fatigue			Fever symptoms		
Days	**Mean**	**SD**	**Paired *t*-test *p*-value**	**Mean**	**SD**	**Paired *t*-test *p*-value**	**Mean**	**SD**	**Paired *t*-test *p*-value**	**Mean**	**SD**	**Paired *t*-test *p*-value**	**Mean**	**SD**	**Paired *t*-test *p*-value**	**Mean**	**SD**	**Paired *t*-test *p*-value**	**Mean**	**SD**	**Paired *t*-test *p*-value**
0	0.41	1.35	—	0.37	1.18	—	1.63	2.22	—	1.41	2.14	—	0.59	1.27	—	2.94	2.61	—	1.18	2.11	—
14	0.35	1.17	—	0.34	1.07	—	1.46	2.07	—	1.23	1.91	—	0.52	1.14	—	2.70	2.38	—	1.27	2.16	—
28	0.30	1.08	—	0.32	1.09	—	1.44	2.12	—	1.04	1.81	—	0.43	1.09	—	2.53	2.35	—	1.20	2.13	—
0–14			0.035			0.170			< 0.001			< 0.001			0.016			< 0.001			0.025
14–28			0.007			0.442			0.597			< 0.001			0.001			< 0.001			0.017
0–28			< 0.001			0.121			< 0.001			< 0.001			< 0.001			< 0.001			0.765

SD, standard deviation.

Influenza-like symptoms

The mean and standard deviations of the visual-analogue scales for various influenza-like symptoms are summarized in Table 4. It can be seen that subjects tended to have fewer symptoms on days 14 and 28 than on day 0 ($p < 0.05$), except for rigors (days 14 and 28; $p > 0.05$) and fever (day 28; $p > 0.05$). Continuous improvement from day 14 to day 28 occurred for the following symptoms: chills, cough, fatigue, headache and feelings of "heaviness" ($p < 0.05$), whereas the figures for changes in symptoms of rigors, muscle pain and feverishness on days 14 and 28 were not statistically significant ($p > 0.05$).

Traditional Chinese medicine symptoms related to *wen bing*

The percentages of subjects reporting symptoms related to wen bing are shown in Table 5. From day 0 to day 14 and from day 0 to day 28, it can be seen that each of the listed symptoms except the symptoms related to bowel habit and stool condition improved. The prevalence of sore/dry throat conditions decreased from 38.1% to 27.1%. The percentage of respondents feeling "humid" decreased from 48.4% to 37.3% ($p < 0.01$). Between day 14 and day 28, the prevalence of most symptoms continued to decrease, except for the symptoms related to irregular bowel habits and sleep.

Adverse events

Of the 1063 respondents, none reported serious adverse events and only 19 (1.8%) reported minor adverse events. These included diarrhoea, sore throat, dizziness and nausea. Of the respondents who reported adverse events, nine ceased using the supplements, three halved the dosage and the others continued to use the herbal formula as prescribed. The details of the adverse events reported are summarized in Table 6. It should be noted that the reported symptoms (e.g. dizziness and nausea), were rather non-specific, and might not have been related to the herbal drinks at all.

Table 5. Percentages of subjects having symptoms that are related to wen bing

Symptoms	Percentage			McNemar test *p*-value		
	Day 0	Day 14	Day 28	Day 0 vs Day 14	Day 14 vs 28	Day 0 vs Day 28
Thick tongue sign	47.3	42.9	40.5	< 0.001	0.008	< 0.001
Dry/sore throat condition	38.1	30.8	27.1	< 0.001	0.003	< 0.001
Irregular bowel habit	23.8	23.0	22.6	0.575	0.696	0.250
Loose/watery/hard stool condition	16.7	28.1	17.1	< 0.001	< 0.001	0.826
Not good/bad sleep condition	85.6	81.0	81.7	< 0.001	0.494	< 0.001
Feeling "cold"	19.8	16.0	14.6	< 0.001	0.044	< 0.001
Feeling "heat"	22.2	19.5	17.4	0.013	0.018	< 0.001
Feeling "humid"	48.4	39.9	37.3	< 0.001	0.028	< 0.001

Table 6. Details of adverse events reported by subjects taking supplement

Subject	Adverse event
1	Diarrhoea, headache, dizziness
2	Diarrhoea, headache, dizziness
3	Diarrhoea
4	Constipation, sore throat, cold sores
5	Diarrhoea, dizziness
6	Dizziness
7	Sore throat
8	Sore throat, fitful sleep with many dreams
9	Insomnia
10	Palpitations
11	Low-grade fever
12	Sore throat
13	Headache, nausea
14	Diarrhoea
15	Fever and sweating
16	Dizziness, nausea, shaking hands, bowel pain
17	Irregular menstruation
18	Malaise
19	Diarrhoea, stomach ache, allergic skin reaction

Discussion

To the authors' knowledge, this is the first study to explore the possibility of using TCM to prevent SARS in a high-risk population (i.e. health care workers). Despite the preliminary nature of this investigation, it has the strength of having used a prospective cohort design, and having used the actual SARS attack rates

as the primary outcome measure. A randomized controlled trial could not, however, be carried out at the time of the study (which was conducted during the middle of the SARS epidemic). During this time, health care workers in Hong Kong SAR were contracting SARS as a result of breakthrough transmissions (*9*). Due to heightened concern over SARS transmissions among health care workers, there was strong motivation to provide them all with the highest degree of protection against SARS infection. Hence, the random allocation of subjects to a control group was neither feasible nor desirable. Nevertheless, the job distribution of the two cohorts was comparable. The timing and settings of the study were also unique. The two cohorts were at a high risk of contracting SARS. The large number of nosocomial transmissions in Hong Kong SAR allowed such a comparison to be made.

The study results are encouraging and are compatible with the claim that TCM is an efficacious treatment for SARS (*10*). There is preliminary evidence that the herbal formula used in this study may have protective effects against the virus. Although serological tests were not conducted on asymptomatic health care workers in our study sample to confirm their SARS seronegativity, a recent seroprevalence survey identified no asymptomatic cases in the same population of health care workers (*11*), lending credence to the finding of differential attack rates between the two cohorts. The results of another study that documented an increase in the immune function which persisted for a 2-week period after cessation of supplement use among 37 SARS laboratory technicians using an identical herbal supplement treatment regime to the one in this study also provided evidence to support the potential efficacy of these supplements as a SARS-prevention measure (*12*). The quality-of-life data as well as the data collected on TCM and Western allopathic symptomatology, further support the beneficial effects of the herbal supplement to at-risk individuals.

Although the present study was an innovative one, using TCM to treat respiratory ailments is widespread in China. An unpublished study has reported that approximately 4% of the general population were likely to use TCM or complementary medicine for the purpose of SARS prevention in Hong Kong, SAR (Lau et al, unpublished data). Establishing the efficacy of TCM as a SARS prevention measure would be likely to result in a heightened demand for its use in Chinese populations around the world as well as in non-Chinese communities. Hence, the potential for using TCM as a SARS-preventive measure should not be underestimated.

Herbal formulas had also been reported to be effective in preventing diseases such as influenza, but few of the relevant studies were randomized clinical trials (*13*). The major limitation of the present study is that it was not a randomized study, for the reasons discussed above. There is, however, no indication that health care workers who were at lower risk of contracting SARS were more likely to volunteer to use the herbal supplement. In fact, it is expected that the reverse would be true, i.e. that those who were at higher risk would have a stronger motivation to use the herbal supplement. The direction of the participation bias should therefore not confound the results. The response rate was another limitation as only slightly more than 40% of those participants who received the herbal packets returned the completed questionnaires. By checking the SARS registry, the investigators confirmed that none of the 3160 health care workers who received the herbal supplement had contracted the virus. The 2097 non-

responders were then regarded as non-users in the statistical analysis, providing a conservative estimate of the difference in SARS prevalence between the two cohorts. This would mean that if some of the non-respondents who had actually used the herbal supplement as prescribed were moved from the control cohort to the herbal-supplement-user cohort, the actual difference in the SARS attack rates between the two cohorts should be even more marked. In the most extreme case, if all of the non-respondents were classified as supplement users, the attack rates for the supplement users and control group would be 0 and 0.46%, respectively (Fisher's exact test, $p < 0.001$). One other limitation of this study was that the absence of assessment of quality of life and symptoms in the control cohort makes interpretation of these results difficult, as other potential confounders may exist. The high consistency of the study results, however, suggests that the herbal supplement has real beneficial effects on symptom control and quality of life. Consumption of the herbal formula is apparently safe because only 1.8% of the subjects who used it reported adverse effects, and some of these may have been unrelated to the herbal drink.

Very few studies have compared the effectiveness of different measures for preventing SARS and none have examined the use of nutritional supplements in SARS prevention. As the herbal formula used in this study is safe and generally affordable (the cost is approximately US$ 8.5 for a 2-week supply), it merits consideration as a SARS prevention option. Large-scale controlled trials on the prevention of influenza in different high-risk groups, such as health care workers and elderly residents of nursing homes may be warranted.

Experts on herbal treatments might disagree with the use of a single herbal formula because they would generally prepare specific preparations tailored to fit specific groups of individuals showing different patterns of physiological characteristics. However, with the huge demand for immediate responses during the recent epidemic, the need for an instantaneous supply of the preventive drink overwhelmed any other considerations. It was also the opinion of our herbal expert that for this wide preventive need, more generalization in the herbal formula could be allowed: the appropriateness of this strategy had been demonstrated by the efficacy of the single formula when facing an urgent need for broad prevention.

Acknowledgements

Funding for this study was obtained from the Hong Kong Society of Accountants and the Institute of Chinese Medicine, Hong Kong SAR. We would like to thank those who participated in this study. We would also like to express appreciation to Dr Jean Kim for revising and editing the manuscript.

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Report B
Effects of Chinese medicine on patients convalescing from SARS in Hong Kong special administrative region — a prospective non-randomized controlled trial

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Abstract. It is unknown whether Traditional Chinese medicine (TCM) can affect the course of recovery of patients with severe acute respiratory syndrome (SARS). We studied 129 patients convalescing from SARS who chose for themselves whether to receive TCM or Western medical care. Ninety-one patients chose to receive TCM. The probabilities of normalizing laboratory test results over time were similar for patients who did and did not receive TCM treatment. Patients who participated in pulmonary rehabilitation programmes with or without TCM showed similar 6-minute-walk distance and hand-grip strength at start, interim and endpoint measurements. The Short-Form-36 (SF-36) health survey questionnaire scores were also similar at endpoints for patients who did or did not receive TCM treatment. A group of patients who experienced greater limitations on physical activities chose to receive TCM alone, but not to participate in a pulmonary rehabilitation programme. They showed improvements in 6-minute-walk distance and hand-grip strength equivalent to those seen in patients who did participate in pulmonary rehabilitation. These results suggest that TCM could provide an alternative treatment option for patients convalescing from SARS, particularly for those who experience limitations on physical activities.

Background

In May 2003, the Hospital Authority of Hong Kong SAR invited two Chinese medicine practitioners experienced in the treatment of SARS in Guangzhou to provide TCM services to SARS patients in Hong Kong SAR. In addition to caring for SARS patients during the acute phase of the disease, they also provided TCM services to patients convalescing from SARS.

This report aims to compare the effects of TCM with those of conventional treatment (Western medicine) on SARS patients who had been discharged from hospitals.

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Methods

Design

This was a prospective non-randomized controlled trial.

Source of patients

The patients were from the Wong Tai Sin Hospital (WTSH), a regional convalescence hospital that serves several general hospitals. A few SARS patients had not been admitted to WTSH but had learned of the availability of TCM through the media and volunteered to join this programme. After a face-to-face explanation by nurses, patients chose their own treatment, i.e. with or without TCM care. Those who chose TCM were not required to pay additional fees.

Patient groups

Two groups of patients, namely inpatients and outpatients, participated in the study. Inpatients were admitted to WTSH immediately after they had been discharged from acute hospitals and they participated in a pulmonary rehabilitation programme. Outpatients were those study subjects who had already been discharged from WTSH, but were participating in outpatient follow-up pulmonary rehabilitation programmes that entailed a 7-day inpatient training period at the start. Patients who chose to receive TCM care but did not want to participate in a pulmonary rehabilitation programme were followed up as outpatients in the Chinese Medicine Research and Services Centre at Kwong Wah Hospital (Table 1).

Table 1. Patient groups

	TCM (*n*)	**No TCM (*n*)**
Inpatients on pulmonary rehabilitation programme	16	28
Outpatients on pulmonary rehabilitation programme	59	10
Outpatients not on pulmonary rehabilitation programme	16	

TCM, Traditional Chinese medicine.

Treatment with Traditional Chinese medicine

TCM physicians provided a 21-day course of individualized TCM treatment to patients who chose to receive it. Decoctions of Chinese medicine were prepared at a single TCM pharmacy located at Kwong Wah Hospital.

Parameters studied (*1–4*)

In this report, we present observations on normalization of abnormal laboratory results (probability), and 6-minute-walk distance, hand-grip strength and SF-36

questionnaire scores (*5*). Nurses (Western medicine) performed tests and observations independently of the TCM physicians. For laboratory results we compared the first set of results from patients on starting this programme with their second (8–14 days) and third (15–28 days) sets of laboratory results. For 6-minute-walk and hand-grips, measurement were done at start, interim (7 days; i.e. after training) and endpoints (1 month). For patients who did not participate in pulmonary rehabilitation, there was no training and no interim measurement. For SF-36 scores, measurements were made at start and endpoints (1 month).

Source of data

Patients' laboratory data were obtained from a SARS-specific territory-wide database built by the Hospital Authority of Hong Kong SAR. Laboratory results had already been classified as normal, high or low in the corporate laboratory information system. Rehabilitation data were processed in a separate database in Kwong Wah Hospital using patients' unique Hong Kong identity numbers for indexing.

Statistical analysis

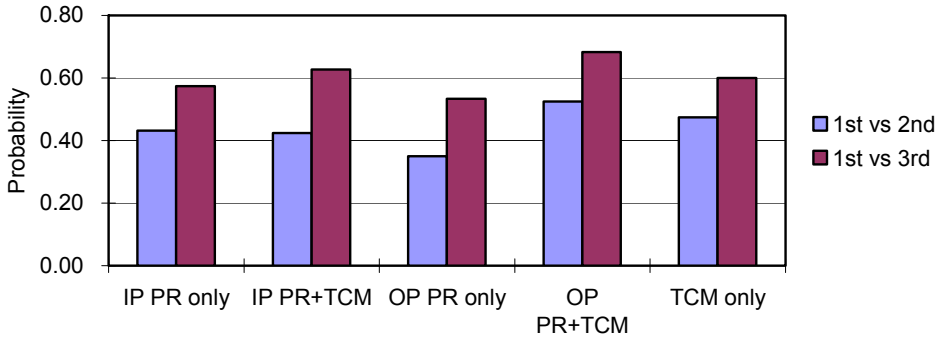
We first established benchmark values for patients who chose not to receive TCM care. For comparisons with benchmarks, we used a *t*-test for continuous data, the Wilcoxon rank-sum test for ranked data and the chi-squared test for probabilities. A statistically significant difference was defined by a p-value < 0.05. Unless specified, all p-values were two-sided.

Results

Normalization of laboratory results

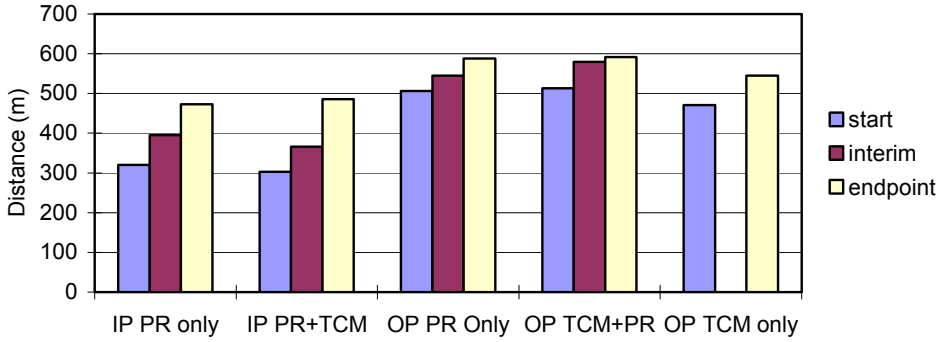
Whether or not convalescent patients received TCM treatment, their abnormal laboratory test results gradually normalized. The probabilities of normalizing abnormal laboratory results (including levels of urea, creatinine, sodium, potassium, albumin, globulin and haemoglobin; white cell count, platelet count, absolute lymphocyte count, absolute neutrophil count; aspartate amino transferase; amino alanine transferase; and lactate dehydrogenase) during convalescence were similar for all patients whether or not they received TCM treatment (Fig. 1). The probabilities of normalization of the individual test results listed above were also similar for patients who did and did not receive TCM treatment.

Fig. 1. Probability of abnormal laboratory tests becoming normalized over time



IP, Inpatients; PR, pulmonary rehabilitation; OP, outpatient; TCM, Traditional Chinese medicine.
[a]The tests included: urea, creatinine, sodium, potassium, albumin, globulin, haemoglobin, white cell count, platelet count, absolute lymphocyte count, absolute neutrophil count, aspartate amino transferase, amino alanine transferase and lactate dehydrogenase.

Fig. 2. Six-minute-walk distance of various patient groups



IP, Inpatients; PR, pulmonary rehabilitation; OP, outpatient; TCM, Traditional Chinese medicine.

For inpatients, measurements in the TCM-treated group were comparable with benchmark values at start, interim and endpoint (Table 2).

Table 2. Six-minute-walk results (metres) for outpatients convalescing from SARS

Time of test	**Benchmark pulmonary rehabilitation Metres walked (95% CI) *n* = 13**	**TCM + pulmonary rehabilitation Metres walked (95% CI) *n* = 12**
Start	320 (248-392)	303 (224-383)
Interim	395 (325-465)	366 (290-442)
Endpoint	473 (396-550)	486 (420-553)

TCM, Traditional Chinese medicine
No significant difference was found at the 5% level (*t*-test).

For outpatients, the TCM-treated groups were also comparable with benchmark values at start, interim and endpoint (Table 3). For the TCM patients who were also taking part in pulmonary rehabilitation programmes, most of the improvement had occurred by the time of the interim measurement.

Table 3. Six-minute-walk results (metres) of outpatients convalescing from SARS

Outpatients	**Benchmark pulmonary rehabilitation Metres walked (95% CI) *n* = 10**	**TCM + pulmonary rehabilitation Metres walked (95% CI) *n* = 54**
Start	506 (452-559)	513 (495-530)
Interim	545 (486-605)	580 (561-599)
Endpoint	588 (536-640)	592 (568-615)

TCM, Traditional Chinese medicine
No significant difference was found at the 5% level (*t*-test).

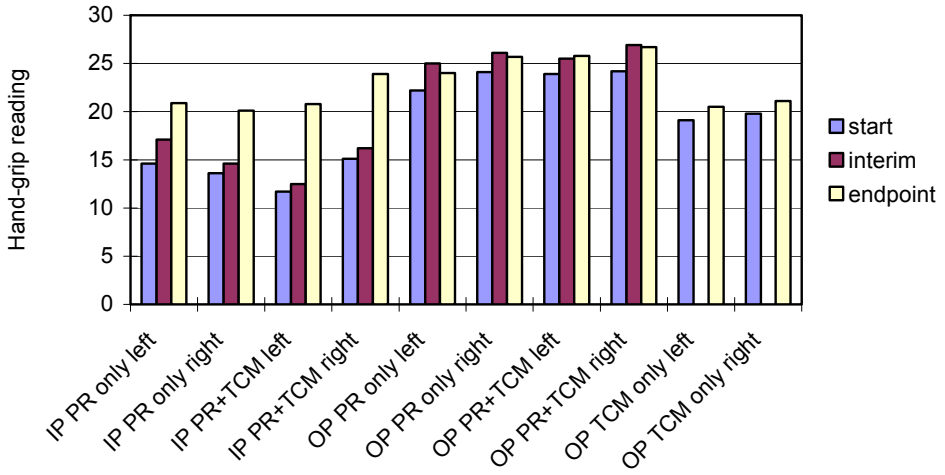
Of particular interest is that outpatients who were receiving TCM but were not taking part in the pulmonary rehabilitation programme also showed gradual improvement in the 6-minute-walk test. Performances were comparable with benchmark values at the start and endpoints (Table 4).

Table 4. Six-minute-walk results (metres) for outpatients receiving traditional Chinese medicine (TCM) compared with patients taking part in a pulmonary rehabilitation programme but not receiving TCM

Time of test	**Benchmark Pulmonary rehabilitation Metres walked (95% CI) *n* = 10**	**TCM only Metres walked (95% CI) *n* = 9**
Start	506 (452-559)	471 (396-546)
Interim	545 (486-605)	NA
Endpoint	588 (536-640)	545 (505-585)

No significant difference was found at the 5% level (*t*-test).

Fig. 3. Hand-grip strength in various patient groups



IP, inpatients; PR, pulmonary rehabilitation; OP, outpatient; TCM, Traditional Chinese medicine.

Tables 5–7 show that the hand-grip strengths of TCM patients were comparable with benchmark values in all patient groups. As for the results of the 6-minute walk, patients who were receiving TCM, but did not participate in the pulmonary rehabilitation programme, also showed gradual improvement, and their results were comparable with benchmark values at start and endpoints (Table 7). From Fig. 3, it is apparent that the improvement of hand-grip strength over time was more marked in inpatients.

Table 5. Hand-grip strength of convalescing SARS inpatients

	Benchmark Pulmonary rehabilitation Hand-grip reading (95% CI)		**TCM + pulmonary rehabilitation Hand-grip reading (95% CI)**	
	Left (*n* = 7)	**Right** (*n* = 11)	**Left** (*n* = 9)	**Right** (*n* = 15)
Start	14.6 (10.5-18.6)	13.6 (10.3-16.8)	11.7 (8.4-15.0)	15.1 (11.2-19.0)
Interim	17.1 (11.0-23.3)	14.6 (11.0-18.3)	12.5 (9.6-15.4)	16.2 (12.9-19.6)
Endpoint	20.9 (15.9-25.8)	20.1 (18.5-21.8)	20.8 (17.2-24.4)	23.9 (20.8-27.0)

TCM, Traditional Chinese medicine.
No significant difference was found at the 5% level (*t*-test).

Table 6. Hand-grip strength of outpatients convalescing from SARS

	Benchmark Pulmonary rehabilitation Hand-grip reading (95% CI) *n* = 10		**TCM + pulmonary rehabilitation Hand-grip reading (95% CI) *n* = 54**	
	Left	**Right**	**Left**	**Right**
Start	22.2 (18.1-26.2)	24.1 (20.9-27.3)	23.9 (21.0-26.8)	24.2 (21.5-26.9)
Interim	25.0 (20.8-29.2)	26.1 (22.3-29.8)	25.5 (23.0-28.1)	26.9 (24.1-29.7)
Endpoint	24.0 (20.5-27.5)	25.7 (23.0-28.4)	25.8 (23.3-28.3)	26.7 (24.1-29.4)

TCM, Traditional Chinese Medicine

Table 7. Hand-grip strength of outpatients on traditional Chinese medicine (TCM) only, compared with patients taking part in a pulmonary rehabilitation programme but not receiving TCM

	Benchmark Pulmonary rehabilitation Hand-grip reading (95% CI) *n* = 10		**TCM only Hand-grip reading (95% CI) *n* = 10**	
	Left	**Right**	**Left**	**Right**
Start	22.2 (18.1-26.2)	24.1 (20.9-27.3)	19.1 (14.4-23.8)	19.8 (15.1-24.5)
Interim	25.0 (20.8-29.2)	26.1 (22.3-29.8)	NA	NA
Endpoint	24.0 (20.5-27.5)	25.7 (23.0-28.4)	20.5 (15.3-25.7)	21.7 (16.6-26.8)

No significant difference was found at the 5% level (*t*-test).

Short-Form-36 scores

For inpatients, the SF-36 scores of patients treated with TCM were comparable with benchmark values at the endpoint despite weaker scores in vitality, social functioning and emotional orientation at the start (Table 8). (Higher scores indicated a more satisfactory quality of life than did lower scores.)

Table 8. SF-36 scores for inpatients convalescing from SARS

SF-36 Measure		Inpatients undergoing pulmonary rehabilitation		
		- TCM	+ TCM	
		Score (95% CI)	Score	Remark
Physical functioning				
	Start	51 (38.50-63.49)	38.64	NS
	End	62.76 (45.47-80.06)	59.33	NS
Physical orientation				
	Start	29 (13.32-44.67)	16.17	NS
	End	30.76 (8.4-53.13)	33.33	NS
Bodily pain				
	Start	61.48 (51.44-71.51)	55.05	NS
	End	70.58 (52.97-88.17)	79	NS
General Health				
	Start	52.36 (45.75-55.96)	46.82	NS
	End	50.15 (37.40-62.90)	55.26	NS
Vitality				
	Start	56.66 (47.88-65.44)	43.03	$p < 0.05$
	End	57.69 (45.24-75.12)	59.56	NS
Social Functioning				
	Start	71.76 (57.25-86.26)	46.01	$p < 0.05$
	End	92.30 (77.72-108.9)	78.25	NS
Emotional orientation				
	Start	45.33 (29.01-61.65)	17.64	$p < 0.05$
	End	48.71 (21.92-75.51)	55.5	NS
Mental health				
	Start	63.2 (52.8-73.6)	57.25	NS
	End	67.6 (56.5-78.7)	75.46	NS

SF-36, Short-from-36 health survey questionnaire; TCM, Traditional Chinese medicine; NS, not significant.

For outpatients, the SF-36 scores of patients receiving TCM were comparable with benchmark values for all patient groups (Tables 9 and 10).

Table 9. SF-36 scores for convalescing SARS outpatients

SF-36 Measure		Outpatients undergoing pulmonary rehabilitation		
		- TCM	+ TCM	
		Score (95% CI)	Score	Remark
Physical functioning				
	Start	64.58 (52.81-76.35)	74.14	NS
	End	72.5 (58.67-86.32)	80.11	NS
Physical orientation				
	Start	18.75 (0-43.23)	22.41	NS
	End	32.5 (5.77-59.22)	49.03	NS
Bodily pain				
	Start	65.25 (49.85-80.64)	67.47	NS
	End	72.22 (48.21-96.22)	61.33	NS
General Health				
	Start	48.16 (34.3-62.0)	48.13	NS
	End	47 (27.45-66.54)	51.98	NS
Vitality				
	Start	59.16 (48.86-69.46)	51.18	NS
	End	60 (43.13-76.86)	55.96	NS
Social Functioning				
	Start	76.45 (56.25-96.66)	75.32	NS
	End	91.12 (76.29-105.95)	86.2	NS
Emotional orientation				
	Start	33.3 (7.79-58.87)	42.52	NS
	End	30 (3.75-56.24)	46.15	NS
Mental health				
	Start	65.66 (55.13-76.19)	67.59	NS
	End	64.8 (46.96-82.63)	70.03	NS

SF-36, Short-from-36 health survey questionnaire; TCM, Traditional Chinese medicine; NS, not significant.

Table 10. SF-36 scores for outpatients receiving traditional Chinese medicine (TCM) but not pulmonary rehabilitation (PR), compared with patients undergoing PR but not receiving TCM

SF-36 Measure		**Outpatients on PR versus outpatients on TCM only**		
		On PR	**on TCM only**	
		Score (95% CI)	**Score**	**Remark**
Physical functioning				
	Start	64.58 (52.81-76.35)	54.68	NS
	End	72.5 (58.67-86.32)	66.92	NS
Physical orientation				
	Start	18.75 (0-43.23)	21.87	NS
	End	32.5 (5.77-59.22)	26.92	NS
Bodily pain				
	Start	65.25 (49.85-80.64)	51.6	NS
	End	72.22 (48.21-96.22)	69.07	NS
General Health				
	Start	48.16 (34.3-62.0)	46.81	NS
	End	47 (27.45-66.54)	44.23	NS
Vitality				
	Start	59.16 (48.86-69.46)	55	NS
	End	60 (43.13-76.86)	61.92	NS
Social Functioning				
	Start	76.45 (56.25-96.66)	64.75	NS
	End	91.12 (76.29-105.95)	79.23	NS
Emotional orientation				
	Start	33.3 (7.79-58.87)	39.58	NS
	End	30 (3.75-56.24)	35.89	NS
Mental health				
	Start	65.66 (55.13-76.19)	65.25	NS
	End	64.8 (46.96-82.63)	72.61	NS

SF-36, Short-from-36 health survey questionnaire; NS, not significant.

To analyse why some patients preferred not to undergo pulmonary rehabilitation, we looked at the scores for question 3 of the SF-36 questionnaires and found that those who chose not to participate in a pulmonary rehabilitation programme had significantly lower scores ($p < 0.05$) for strenuous and moderate physical activities, carrying weights, walking up flights of stairs and for bathing and dressing.

Discussion

Because patients chose their own programmes, it was difficult to balance the numbers of patients in the different treatment groups. It was noted that the TCM programme was less popular among inpatients than in outpatients, probably because the treatment in the former group was started earlier and time was needed for TCM to gain acceptance.

It is unknown whether TCM can influence the course of recovery in SARS patients. From our results, TCM did not appear to have any additional benefits over a period of one month. One explanation for this observation is that when patients gradually recover, their physical performance will level off at their best intrinsic ability, and additional TCM cannot lead to any additional improvement.

However, we did observe that in the outpatient group, those who received TCM showed most of the improvements in their 6-minute-walk distance between the baseline and interim measurements, although at the endpoint the distances were comparable with those measured in the non-TCM-treated comparison group. In the future, studies on whether TCM can hasten the recovery of physical strength in SARS patients, by means of more frequent tests near the start of TCM care would be useful.

During the follow-up period, we noted that a few patients complained of hip pains while performing the 6-minute-walk tests. We referred these patients for further investigations and follow-up for any avascular necrosis of the femoral head, a known complication of steroid treatment.

It was interesting to note that there were some patients who chose to receive TCM, but did not want to participate in pulmonary rehabilitation. There is evidence that their avoidance of pulmonary rehabilitation may have been related to their greater limitations in physical activities. Because patients on TCM showed only gradual improvement over time and their progress was essentially similar to that of patients on the pulmonary rehabilitation programme, we propose that TCM could be an alternative option for patients convalescing from SARS, particularly for those whose ability to perform physical activities is limited.

Conclusion

During convalescence from SARS, patients who chose to receive TCM treatment alone showed improvements in the 6-minute-walk distance and hand-grip strength comparable to those measured in patients who participated in a pulmonary rehabilitation programme. TCM could provide an effective alternative treatment for convalescing SARS patients, particularly for those whose ability to perform physical exercise is limited.

Acknowledgements

We thank the Statistics Team at the Hospital Authority Head Office for their expert advice. We are also grateful to the TCM team at the Tung Wah Group of Hospitals who organized the ward rounds and prepared Chinese medicine decoctions of the highest quality.

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Report C
Traditional Chinese medicine in the management of patients with SARS in Hong Kong Special Administrative Region — a case–control study of 24 patients

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Abstract. Traditional Chinese medicine (TCM) is not the first-line treatment for severe acute respiratory syndrome (SARS) in Hong Kong Special Administrative Region (SAR). From May 2003, 48 inpatients received individualized TCM treatment, of whom 24 were successfully matched to 107 controls with comparable age, sex, comorbidities and disease severity. Relative to the matched controls, survivors of SARS who had received complementary TCM benefited by needing a shorter hospital stay (a reduction of 4 days, $p < 0.05$), requiring less steroid (6 g less, $p < 0.05$) and shorter duration of steroid treatment (2 days fewer, $p < 0.05$). The survival rate following interventional complementary TCM care (70% of patients received TCM treatment > 21 days after onset of symptoms), was not significantly different from that in matched controls. SARS patients who received TCM treatment benefited from improvements in symptoms including fatigue, dry mouth, dyspnoea and loose stools. Shortening of hospital stay was most marked in patients who first received TCM treatment < 28 days after onset of symptoms, suggesting that early provision of TCM care in SARS patients may be most beneficial for patients. The benefit of requiring less steroid treatment was observed in all patients treated with TCM regardless of when treatment started. Our results indicate that SARS patients treated with TCM benefited from shorter hospitalization, a substantial decrease in steroid administered, and improvement of symptoms.

Background

The public hospitals of Hong Kong SAR offer no TCM service on their wards. In May 2003, two TCM physicians who were experienced in the treatment of SARS in Guangzhou, China, were invited by the Hospital Authority of Hong Kong to provide complementary TCM care to SARS inpatients in public hospitals in Hong Kong SAR.

This report describes a study that aimed to compare the effects of complementary TCM on SARS patients with matched controls who received conventional (Western) medical care only.

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Methods

Design

A case–control study design was used.

Access to Traditional Chinese medicine

SARS patients in public hospitals of Hong Kong SAR were eligible for TCM care if the following three conditions were fulfilled.
1. Patients themselves requested TCM care.
2. Attending doctors (Western medicine) endorsed such requests.
3. TCM physicians considered that patients were suitable for TCM treatment.
In fact, condition 3 was never applied. All requests for TCM care that fulfilled conditions 1 and 2 above were granted.

Source of data

Demographic data and details of treatments received by the study subjects were extracted from a SARS-specific territory-wide database constructed by the Hospital Authority of Hong Kong SAR. TCM-related data (mostly in Chinese) were collected from the hospitals where the patients were being treated. The dates were processed in a separate database in Kwong Wah Hospital using patients' unique Hong Kong identity numbers for indexing.

Patient profiles

Forty-eight SARS patients received TCM care (Table 1). The ratio of females to males was 2:1 and the mean age was 45.1 years for males and 42.5 years for females. Eighty per cent of patients received TCM 14 days or more after admission (Fig. 1). Seventy per cent of patients first received TCM 21 days or more after onset of symptoms (Fig. 2). On average, patients first received TCM care 31.6 days after admission and 34.3 days after onset of symptoms.

Table 1. Demographic profiles of SARS patients who received treatment with traditional Chinese medicine

		Comorbidities?					
		No		**Yes**		**Total**	
		Survived	**Died**	**Survived**	**Died**	***n***	**Percentage**
Sex	**Age (years)**						
Female	21-40	11	3	-	-	14	29.2
	41-60	10	2	2	3	17	35.4
	61-80	-	2	-	1	3	6.3
Male	21-40	3	2	-	-	5	10.4
	41-60	4	2	-	1	7	14.6
	61-80	1	-	1	-	2	4.2
All		29	11	3	5	48	100.0

Fig. 1. Number of days between starting TCM treatment and admission to hospital

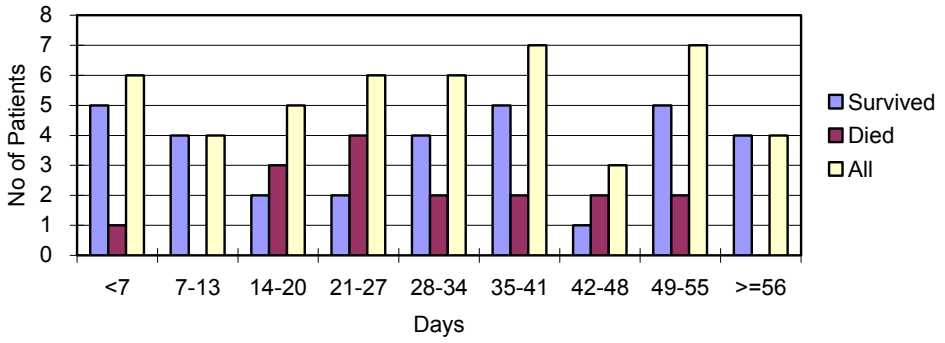


Fig. 2. Number of days between starting TCM treatment and onset of symptoms

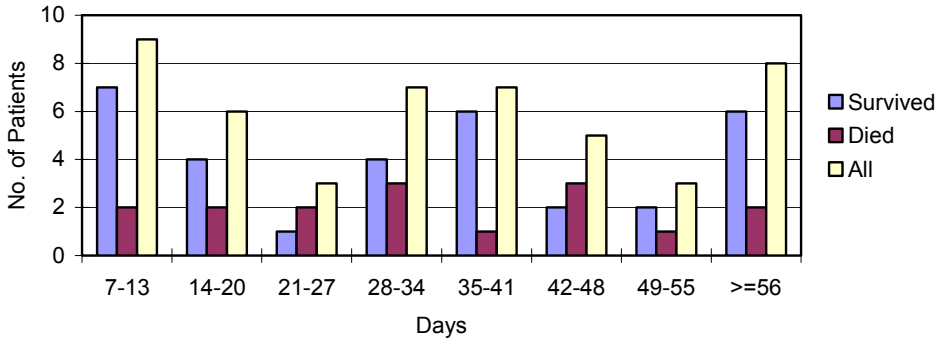
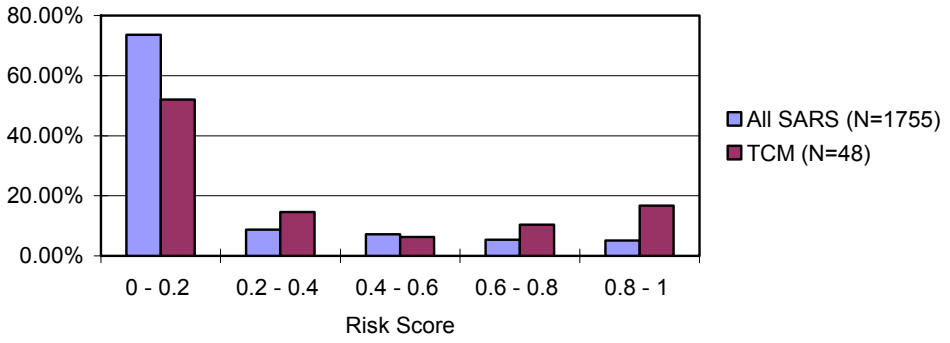


Fig. 3. Risk score distribution for SARS patients at start of treatment with traditional Chinese medicine



Risk profiles of patients

Based on gender, age, presence of comorbidities (including chronic obstructive airway disease, ischaemic heart disease, cerebrovascular disease, cancer, diabetes and chronic liver disease), serum lactate dehydrogenase (LDH) levels and respiratory status on admission (*1, 2*), we used multivariate logistic regression on risk scores equivalent to the probability of death for all SARS patients (Fig. 3). Patients who received TCM care represented a subset that had higher risk scores at the time when they first received TCM.

A risk score (equivalent to probability of death) was calculated by logistic regression using five prognostic factors (age, sex, comorbidity, lactate dehydrogenase and respiratory status) of 1755 SARS patients from Hong Kong SAR at the start of treatment.

Matching of controls

To ensure comparability, we divided start of TCM care into three phases: early (up to 14 days after onset of symptoms), delayed (14–27 days after onset) and late (≥ 28 days after onset). We used patients' gender, age, presence or absence of comorbidities, highest LDH level and worst respiratory status at the first administration of TCM as markers for identifying controls, so that the times at which the latter two markers occurred were similar in patients and controls. The comorbidities included were chronic obstructive airway disease, ischaemic heart disease, cerebrovascular disease, cancer, diabetes, chronic renal failure and chronic liver disease (*1, 2*). To minimize bias and retain the relative weighting of the case groups, we performed 1000 rounds of random one-to-one bootstrap sampling to match controls (*3–6*). A total of 107 matched controls were successfully obtained for 24 of the patients treated with TCM. The clinical profiles of the matched patients are listed in Table 2. The patients for whom no controls could be identified are listed in Table 3, with reasons for the non-availability of matched controls.

Symptoms and signs according to Traditional Chinese medicine

A list of TCM symptoms was specifically requested and ranked by the TCM physicians, as listed in Table 4.

Treatment with Traditional Chinese medicine

Treatment was individualized and independent of patients' concurrent Western medical care. Chinese medicine decoctions were prepared at a single TCM pharmacy located in Kwong Wah Hospital.

Clinical decision-making

Only the attending Western medicine physicians decided the dosage and duration of steroid treatment. These physicians also made the decisions regarding discharge of patients, admission to the intensive care unit, duration of stay in intensive care and intubations.

Table 2. Profiles of 24 patients with whom controls were matched

	Time between onset of symptoms and start of treatment with Traditional Chinese medicine (days)			
	Early (<14)	**Delayed (14-27)**	**Late (≥28)**	**Total**
Age (years)				
21-40	3	1	7	11
41-60	4	4	4	12
61-80	1	-	-	1
Sex				
Female	6	4	7	17
Male	2	1	4	7
Comorbidity[a]				
No	6	5	10	21
Yes	2	-	1	3
Acute respiratory distress syndrome	2	2	4	8
Mean lactate dehydrogenase reading	635.33	672.25	1064.4	5
Mean age (years)	43.63	43.2	37.55	40.75
Mean days from symptom onset to start of treatment with Traditional Chinese medicine	9.25	16.4	39.64	24.67
Mean days from admission to start of treatment with Traditional Chinese medicine	7.88	15.4	38.55	23.5

[a]Comorbidities included: chronic obstructive airway disease, ischaemic heart disease, cerebrovascular disease, cancer, diabetes, renal failure and chronic liver disease.

Table 3. Reasons why 24 patients treated with TCM were not matched with controls

Reasons	**No of patients**	**Deaths**
Patients were discharged within 5 days after start of TCM care. They recovered well but the duration of TCM treatment was too short. Although they had excellent outcomes, they were not included in the analysis	5	0
Incomplete records of LDH / respiratory status because patients were from different hospitals	4	0
Patients were very ill (ARDS and very high LDH levels). They were the most seriously ill SARS patients and no comparable controls were identified	7	5
Unable to match: no controls with the appropriate combination of LDH and respiratory status within the same age, sex and comorbidity group were identified. These subjects may have represented a unique clinical subgroup of SARS patient	8	2
Total	24	7

TCM, Traditional Chinese medicine; LDH, lactate dehydrogenase; ARDS, acute respiratory distress syndrome.

Table 4. Symptoms and signs recorded in traditional Chinese medicine

Q1	fever	Q19	cough
Q2[a]	sweating	Q19a	nature of cough
Q2.1	nature of sweat	Q19b	time of cough
Q3	headache	Q20[a]	sputum
Q4	dizziness	Q20a	ease of expectoration
Q5[a]	weakness	Q20b	colour of sputum
Q6[a]	tiredness of limbs	Q20c	nature of sputum
Q7[a]	tremor	Q21[a]	capacity of stomach
Q8[a]	numbness	Q21a	anorexia
Q9	muscle spasm	Q21b	eats a lot; frequent hunger
Q10	sensation of mouth	Q22	epigastric fullness
Q10a[a]	dry mouth	Q23	stool
Q10a.1	desire to drink	Q23a[a]	loose stool
Q10b[a]	thirst	Q23b	dry stool
Q10b.1	preference of drinking	Q23c	sticky stool
Q10c	tastelessness	Q24[a]	urination
Q10d	sticky sensation in mouth	Q25[a]	menstrual status
Q11[a]	palpitations	Q25a	last menstrual period
Q12[a]	dysphoria	Q25b	menstruation affected by present illness
Q13	dysphoric feverishness	Q26	body build
Q14	hotness of 5 centres	Q27	tongue texture
Q15[a]	insomnia	Q28	tongue coating
Q16[a]	sensation of oppression in chest	Q29	tongue body
Q17	shortness of breath	Q30	tongue condition
Q18[a]	dyspnoea	Q31	pulse

[a]Only these symptoms showed significant improvement after TCM treatment.

Statistical analysis

Percentages were compared by the chi-squared test, and distributions of risk scores were compared by the chi-squared test for goodness of fit. Continuous and ranked data were compared by the t-test and Wilcoxon rank-sum test, respectively. Within-subject improvement in symptoms before and after TCM treatment was compared by the Wilcoxon sign-rank test. A statistically significant difference was defined by a p-value of < 0.05. Unless specified, all p-values were two-sided. We used commercially available software (SPSS 10.0 and SAS 6) for the statistical analysis.

Results

SARS patients who received TCM were characterized by a higher risk profile than that for all SARS patients in Hong Kong SAR ($p < 0.01$). The death rate of SARS patients who received TCM was not significantly different from that in matched controls (Table 5). However it was clear (Table 5) that patients who were treated with TCM benefited from a significant decrease in the quantity of steroid used.

Table 5. Comparison of progress of illness in SARS patients with that in matched controls

	TCM+ WM Mean (SD)	WM Mean (SD)	Comment
Total stay (days)	36 (2.602)	38.8 (1.53)	NS
ICU stay (days)	15.1 (3.67)	11.03 (1.21)	*P*<0.05
Duration of intubation (days)	12 (3.01)	8.45 (1.30)	*P*<0.05
Total dose of steroid used (MG)	22 920 (1968)	30 736 (1862)	*P*<0.05
Duration of steroid treatment (days)	24.4 (2.14)	28.25 (1.09)	*P*<0.05
Duration of fever ≥ 38°C (days)	8.7 (1.89)	6.62 (0.77)	*P*<0.05
Death rate	37.5%	30.7%	NS
Intubation rate	41.7%	41.9%	NS
ICU admission rate	50.0%	51.6%	NS
Number of cases	24	107	

TCM, Traditional Chinese medicine; WM, Western medicine; SD, standard deviation; ICU, intensive care unit; NS, no significant difference.

Table 6. Comparison between survivors of SARS and matched controls

	TCM+ WM Mean (SD)	WM Mean (SD)	Probability
Total stay (days)	32.7 (3.47)	36.9 (1.53)	<0.05
ICU stay (days)	7.06 (4.49)	3.08 (0.62)	<0.05
Intubation (days)	3.66 (3.316)	2.2 (0.561)	<0.05
Total steroid use (mg)	16230 (1618.9)	22519(2398.5)	<0.05
Steroid treatment (days)	22.26 (1.93)	25.46 (1.13)	<0.05
Fever (≥ 38°C) period (days)	6.3 (3.31)	5.34 (0.408)	<0.05
Number of cases	15	83	

TCM, Traditional Chinese medicine; WM, Western medicine; ICU, intensive care unit.

The characteristics of the survivors are presented in Table 6. On average, survivors of SARS who received TCM benefited by needing a shorter hospital stay (4 days shorter, $p < 0.05$), and by requiring less steroid (a total dose of 16 000 mg versus 22 000 mg; $p < 0.05$) than the corresponding controls. Patients who received TCM also needed a shorter duration of steroid treatment than did controls. It is also noteworthy that although patients treated with TCM stayed longer in the ICU and were intubated for a longer period, they had a shorter total stay in hospital and received less steroid.

We observed that the shortening of hospitalization occurred mainly in TCM patients who first received TCM < 28 days after onset of symptoms (24.2 days for subjects in the TCM-treated group and 28.6 days for controls). For patients who received TCM treatment > 28 days after onset of symptoms, the duration of hospital stay was not significantly different from that of controls (49.9 days for the TCM-treated group and 51.2 days for controls). The benefit of requiring less steroid treatment for TCM-treated patients was observed in all patients regardless of when TCM treatment started.

Table 4 shows that after TCM treatment, patients showed a significant improvement in many TCM symptoms, including tiredness, shortness of breath, loose stools, insomnia and dry mouth.

Discussion

Up to now, Western medicine has been the conventional medicine provided in public hospitals in Hong Kong SAR. TCM is not a routine service to which patients at public hospitals can have access as of right. The provision of TCM care to inpatients in Hong Kong SAR during the SARS outbreak was therefore a special and novel arrangement.

TCM care became available to SARS patients in public hospitals 2 months after the start of the outbreak. The policy governing the access to TCM and the delayed provision of TCM care resulted in there being a group of TCM users who were more seriously ill than the average SARS patients at the time they first received TCM. Our results could not therefore be used to evaluate the effect of TCM on the full spectrum of SARS patients, and they are not strictly comparable with results from China where TCM treatment was started early on in the course of the disease.

To avoid bias, the parameters considered in this study were largely related to decisions made by the practitioners of Western medicine attending the patients. TCM physicians did not interfere with decisions on the duration of hospital stay, admission to the ICU or dosage of steroid. We consider that this arrangement ensured the objectivity of our results.

Some of the TCM patients in this study represented the most seriously ill SARS patients in Hong Kong SAR, and therefore no comparable controls were available for analysis.

Because the patients in this study were from several hospitals, there were some variations in the patterns of investigation, treatment and documentation among the TCM patients. This led to insufficient data for the matching of controls in four cases. In preparation for possible future outbreaks, a standard clinical pathway would greatly help statistical comparison between various treatment regimes, particularly for new diseases such as SARS for which there was no consensus on treatment.

The majority of patients requested TCM care at least 2 weeks after onset of their symptoms. It has been shown that SARS patients in Hong Kong harboured a high viral load mainly during the first week of the disease, whereas the later stage of the disease may be characterized by immune-mediated disorders (*7*). Therefore the timing of provision of TCM care may have an impact on the outcome of the disease. In this study, the effect of early TCM treatment could not be investigated. However, the observation that patients receiving TCM needed a shorter period of hospitalization applied to patients who first received TCM < 28 days after the onset of symptoms. This suggests that earlier provision of TCM care may be still more beneficial to SARS patients.

The decrease in the total quantity of steroid used in the patients treated with TCM is sizeable. There was also a shortening of the duration of steroid treatment for the patients treated with TCM relative to their matched controls. These observations suggest that TCM may also be useful in conditions that have conventionally required prolonged treatment with high doses of steroids.

We observed no adverse effects of treating SARS patients with TCM, but rather symptoms were improved. Some of the improvements may be related to decreased steroid usage. This observation suggests that TCM may have potential use in relieving the side-effects of steroid treatments.

The need to provide TCM care for SARS patients created the first opportunity for TCM to be used at the ward level of public hospitals in Hong Kong SAR. It also marked the first step in the official recognition of TCM and in the functional integration of Western medicine and TCM in the public hospitals of Hong Kong SAR.

Acknowledgements

We wish to thank the TCM team at the Tung Wah Group of Hospitals who organized the ward rounds and prepared Chinese medicine decoctions of the highest quality and the statistics team at the Hospital Authority Head Office who provided statistics support. We are also grateful to all physicians who referred SARS patients for TCM care.

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Annex
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