Effect of integrated traditional Chinese medicine and western medicine on the treatment of severe acute respiratory syndrome: A meta-analysis

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Original Research

Effect of integrated traditional Chinese medicine and western medicine on the treatment of severe acute respiratory syndrome: A meta-analysis

Yan CHEN, Jeff J. GUO, Daniel P HEALY, Siyan ZHAN.

ABSTRACT[*]

Background: Data regarding the treatment efficacy of integrative treatment of Traditional Chinese Medicine (TCM) and Western Medicine (WM) in treating patients with (SARS) are conflicting. The effects of integrative TCM/WM treatment have not been fully quantified.

Objectives: To systematically asses the treatment effects of integrated TCM with WM versus WM alone in patients with SARS, incorporating data from recently published studies.

Methods: A meta-analysis was conducted, using published randomized and nonrandomized controlled clinical studies that compared the treatment effects of integrative TCM/WM with WM alone from 2002 to 2006.The outcome measurements included mortality rate, cure rate, resolution of pulmonary infiltrate, use of corticosteroid, and time to defervescence. The effect sizes were presented as risk ratio (RR), rate difference (RD), and weighted mean difference (WMD).The pooled effect sizes were calculated by both fixed-effects and random-effects models.

Results: A total of 1,678 patients with a diagnosis of SARS were identified, including 866 patients from 16 randomized controlled studies and 812 patients from 8 nonrandomized controlled studies. There were no differences detected in mortality rate or cure rate between treatments. Compared with patients receiving WM treatment alone, patients receiving integrative treatment were more likely to have complete or partial resolution of pulmonary infiltrate (RD=0.18, 95%CI; 0.07 to 0.30), lower average daily dosage (mg) of corticosteroid (WMD=-60.27, 95% CI; -70.58 to -49.96), higher CD4+ counts (cells/uL) (WMD=167.96, 95% CI; 109.68 to 226.24), and shorter time to defervescence (days) (WMD= -1.06, 95%CI;-1.60 to -0.53).

Conclusions: The experience of integrative TCM/WM in the treatment of SARS is encouraging. The use of TCM as an adjunctive therapy in the treatment of SARS should be further investigated.

Keywords: Severe Acute Respiratory Syndrome. Medicine, Chinese Traditional. Meta-Analysis.

RESUMEN

Antecedentes: Los datos sobre la eficacia del tratamiento integrado de medicina tradicional china (MTC) y de tratamiento occidental (TO) para pacientes con SRAS son controvertidos. Los efectos del tratamiento MTC/TO no han sido completamente cuantificados.

Objetivos: Evaluar sistemáticamente los efectos del tratamiento integrado de MTC con TO contra el TO solo en pacientes con SRAG, incorporando datos de estudios recientemente publicados.

Métodos: se realizó un meta-análisis utilizando los estudios clínicos controlados aleatorizados y no aleatorizados que comparaban la eficacia del tratamiento integrado MTC/TO con el TO solo desde 2002 a 2006. Las medidas de resultados incluían tasa de mortalidad, tasa de cura, resolución de infiltrados pulmonares, uso de corticoides, y tiempo a la recuperación. Los efectos fueron presentados como riesgo relativo (RR), tasa de diferencia (TD) y diferencia media ponderada (DMP). Los efectos combinados se calcularon tanto por efectos fijos como por modelos de efecto aleatorio.

Resultados: Se identificaron un total de 1678 pacientes con diagnóstico de SARS, incluyendo 866 pacientes de 16 estudios controlados aleatorizados y 812 pacientes de 8 estudios controlados no aleatorizados. No hubo diferencias detectadas en las tasad e mortalidad o tasa de cura entre los tratamientos. Comparados con los pacientes recibiendo TO solo, los pacientes que recibieron tratamiento integrado tenían más probabilidad de tener una resolución total o parcial del infiltrado pulmonar (TD=0.18, IC 95% 0.07 a 0.30), menor dosis media diaria (mg) de corticoides (DMP=-60.27, IC 95% -70.58 a -49.96), mayor recuento CD4+ (células/uL) (DMP=167.96, IC 95% 109.68 a 226.24), y menor tiempo a

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recuperación (días) (DMP= -1.06, IC 95% 1.60 a -0.53).
Conclusiones: La experiencia del tratamiento integrado MTC/TO para el SRAS anima. El uso de MTC como coadyuvante en tratamiento de SRAS debería ser más investigado.

Palabras clave: Síndrome respiratorio agudo severo. Medicina tradicional china. Meta-análisis.

(English)

INTRODUCTION

Severe acute respiratory syndrome (SARS), caused by the SARS-associated coronavirus (SARS-CoV),[1] is a newly emerged infectious disease associated with significant morbidity and mortality. Even now, much about this disease still remains poorly understood. As of April 21, 2004, a cumulative number of 8,096 cases with SARS and 774 SARS-related deaths were recorded from 29 countries and regions.

The urgency of a global outbreak did not allow sufficient time for conducting well-designed efficacy studies. As a result, there is currently no consensus on the optimal treatment of SARS. Many management strategies, including antiviral agents, immune-modulating agents, convalescent plasma, had been employed based on different rationales, and remained largely empiric.

In China, at the time of SARS epidemic, Traditional Chinese Medicine (TCM), as an auxiliary therapy to Western Medicine (WM), was extensively employed for the treatment of SARS. In April, 2003, several anti-SARS formulae were recommended by Ministry of Health (MOH) of China to use with WM, which consisted of more than twenty different herbal medicines (Table 1). In China, 3,104 of 5,327 clinically confirmed patients with SARS (58.27%) received TCM treatment. According to the official reports, the mortality rate in China was approximately 6.5%, which was apparently lower than that reported worldwide (9.6 %).[2]

In parallel with the TCM use, a series of studies were conducted to evaluate the effectiveness of integrative TCM/WM treatment versus WM alone. To date, a few randomized controlled (RC) studies have investigated the beneficial effects of integrated TCM/WM treatments in the reduction of case-fatality rate, improvement of clinical symptoms, and shortening the course of illness. However, the findings have largely been inconsistent due to differences in study design and outcome measures. Meanwhile, the limited number of RC studies and inherent limitations (e.g. limited sample size, inadequate statistical analyses) prevented a critical assessment of efficacy. Although there have been three published meta-analyses evaluating the effectiveness of integrative TCM/WM treatments,[3-5] no firm conclusion can be drawn due to the methodological limitations. Those three studies do not include updated data. The literature included in the Zhang MM et al. study[3] and Liu et al.[4] study was limited information available through 2003, excluding a number of more recent studies. None of them presented the sensitivity and subgroup analyses to test the robustness of findings.

With these considerations in mind, we conducted a meta-analysis using updated literature searches to asses the treatment effects of integrated TCM with WM in patients with SARS and to determine whether integrative treatment was more efficacious than WM alone in reducing mortality rate, increasing cure rate, and improving other clinical outcomes.

METHODS

Literature Search and Inclusion Criteria

A literature search was performed using MEDLINE (2002-August 2006), PubMed (2002- August 2006), EMBASE (2002 to August 2006),Cochrane library (2002 to August 2006) in English by 2 reviewers (YC and JJG) and using Chinese National Knowledge Infrastructure (CNKI) (2002- August 2006), and Chinese Biomedical Database (2002 to August 2006) in Chinese by 2 reviewers (YC and SZ). Key words used in the search were SARS or severe acute respiratory syndrome, treatment, effectiveness, Traditional Chinese Medicine, Chinese Herbal medicines, and Western Medicine. Various combinations of the search terms were used depending on the database searched. The type of publication searched was clinical study. The retrieved articles were also searched for additional references.

Two reviewers of the English literature and Chinese literature independently reviewed the studies for inclusion. Any disagreements on inclusion were resolved through discussion. Qualified studies were selected if they met the following inclusion criteria: (1) patients with a diagnosis of SARS, (2) studies had either RC design or nonrandomized controlled (NRC) design, (3) studies compared the treatment effects between integrated TCM/WM treatments and WM alone. The studied TCM included either raw herbs or refined herbal products. They could be single herb, mixtures of different herbs, or herbal extraction. The integrative TCM/WM treatment was defined as combined use of any type of TCM with WM. There was no restriction of inclusion on patients' and study characteristics, such as age, sex, medications and duration of study.

During outbreak period, there was no validated, or widely available rapid test for diagnosis of SARS Cov infection. Therefore, the diagnosis of SARS in China mainly relied on the clinical and epidemiological basis as suggested by the WHO.[6]

Data Extraction

For the included studies, data were extracted by 2 reviewers (YC and SZ). Once completed, any disagreements on data extraction and study evaluation were resolved through discussion. Recorded data included study design, patient characteristics, and medication use.

Table 1. Characteristic of identified studies with studied patients, methods, treatment durations, and medication.

Study ID[10-33]	Study Design	No .of Patients	Male /Female	severity Mild/Critical	Sample Size estimation	Methods of Randomization	Blind	Dropout/ withdraw	Treatment duration	TCM
Jiang[10]	RC	20/20	NR	NR	No	NR	NR	NR	NR	Compound herbs of anti-SARS formulae [a]
Ren[11]	RC	31/29	29/31	29/31	No	Random table	Single	NR	10 days	Other combinations
Bian[12]	RC	20/20	14/26	40/0	No	Computer list	Not reported	NR	3 weeks	Compound herbs of anti-SARS formulae
Huang[13]	RC	31/31	32/30	26/36	No	NR	NR	NR	NR	Other combinations
Huang[14]	RC	19/22	26/15	0/41	No	NR	NR	NR	NR	Other combinations
Kang[15]	RC	43/20	29/34	NR	No	NR	NR	NR	NR	Other combinations
Lei[16]	RC	50/41	36/55	NR	No	NR	NR	NR	NR	Herb Extracts
Li H[17]	RC	1/11	10/12	NR	No	Random classification	NR	NR	13 days	Other combinations
Li J[18]	RC	24/24	32/16	45/3	No	Random table	NR	NR	NR	Compound herbs of anti-SARS formulae
Li X[19]	RC	20/20	14/26	NR	No	NR	NR	NR	3 weeks	Other combinations
Li ZJ[20]	RC	14/14	17/11	NR	No	NR	NR	NR	NR	Herb Extracts
Wang RB[21]	RC	35/30	19/46	12/53	No	Random table	NR	NR	NR	Compound herbs of anti-SARS formulae [a]
Zhang SN[22]	RC	32/29	NR	NR	No	NR	NR	NR	NR	Other combinations
Zhang XM[23]	RC	31/32	34/29	16/47	No	Random classification	NR	NR	NR	Compound herbs of anti-SARS formulae
Zhang YL[24]	RC	32/33	36/29	20/45	No	Random classification	NR	NR	3 weeks	Compound herbs of anti-SARS formulae
Zhao CH[25]	NRC	37/40	31/46	51/26	No	NR	NR	NR	2-3 weeks	Compound herbs of anti-SARS formulae
Zhang YP[26]	NRC	54/27	NR	55/22	No	No	No	NR	NR	Compound herbs of anti-SARS formulae
Li XH[27]	NRC	73/39	39/73	80/32	No	No	No	NR	NR	Other combinations
Zhang RL[28]	NRC	22/30	16/36	45/7	No	No	No	NR	NR	Compound herbs of anti-SARS formulae
Sun[29]	NRC	8/18	19/7	NR	No	No	No	NR	NR	Herb extracts
Wang YY[30]	NRC	67/66	50/83	23/110	No	No	No	NR	NR	Other combinations
Li Hui[31]	NRC	40/40	40/40	52/28	No	No	No	NR	3 weeks	Other combinations
Tong[32]	NRC	122/115	127/110	NR	No	No	No	NR	NR	Compound herbs of anti-SARS formulae
He[33]	NRC	48/43	52/39	53/38	No	No	No	NR	NR	Other combinations

Abbreviation: TCM: Traditional Chinese Medicine; RC: randomized controlled studies; NRC: nonrandomized controlled studies; NR: not reported.

[a]Anti-SARS formulae mainly include: gypsum, anemarrhena, atractylodes , aspidum, artemisia/ sweet wormwood herb, bupleurum, peony, scute, antelope horn powder, rhizaoma copitidis, golden thread, curcuma, red-rooted sage, fritillaria, coptis.

The Jadad scale was used to assess the quality of the included RC studies, including method of randomization, double blinding, and reporting of withdrawal and dropouts.[7] One point is given for each 'yes' and 0 point for each 'no'. Besides, other individual markers, including estimation of sample size, Intention-To-Treat (ITT) analysis, were also examined for each included study.

The measurements of outcomes in this study included mortality rate, cure rate, resolution of lung infiltrates, dosage of corticosteroid (the average daily dosage, cumulative dosage of corticosteroid and course of corticosteroid treatment), CD4+ counts, and time to defervescence. The mortality rate was defined as the proportion of death among the patients with SARS who received the treatments. The cure rate was defined as the proportion of patients who simultaneously satisfied all three following conditions[6]: (1) patient's fever remained normal (37.5°C) for at least seven days without using any anti-fever medications, (2) symptoms of respiratory systems disappeared, (3) partial or complete resolution of the pulmonary infiltrates as demonstrated by chest radiographs. The time to defervescence was defined as the time period from the day of hospital admission to the date when the temperature of patients recovered to the normal range and stayed normal for at least seven days.

Data Synthesis

Data were analyzed using RevMan 4.27 (Cochrane Collaboration, Oxford, UK). Statistical significant level was predetermined at the 0.05 level. The effects of integrative treatments were presented as risk ratio (RR), rate difference (RD) for dichotomous outcomes, and weighted mean difference (WMD) for continuous outcomes. The RD was defined as the difference of occurrence rate of events between integrative treatment group and WM alone group.

The computations of RR, RD and WMD were given by the following standard formulas: $RR_i = (a_i / n_{1i}) / (c_i / n_{2i})$ with standard error $se\{\ln(RR_i)\} = \sqrt{1/a_i + 1/c_i - 1/n_{1i} - 1/n_{2i}}$ and $RD_i = (a_i / n_{1i}) - (c_i / n_{2i})$ with standard error $se(RD_i) = \sqrt{a_i b_i / n_{1i}^3 + c_i d_i / n_{2i}^3}$, where a_i and c_i are the events, b_i and d_i are non-event, n_{1i} and n_{2i} are the group size, for two studied groups in study i, respectively. $WMD_i = m_{1i} - m_{2i}$ with standard error $se(WMD_i) = \sqrt{sd_{1i}^2 / n_{1i} + sd_{2i}^2 n_{2i}}$, where m_{1i} and m_{2i} are the mean response, sd_{1i} and sd_{2i} are the standard deviation, for the two studied group in the study i, respectively.

The pooled RR, RD and WMD were calculated by using both fixed-effects[8] and random-effects model.[9] If the test of heterogeneity (chi square

statistic) was significant ($p<0.05$), we presented the results of the random-effect models; otherwise, estimated results of fixed-effect models were presented.

In order to exclude the bias brought by those nonrandomized controlled clinical studies (NRC), sensitivity analysis was performed to reassess the treatment effects by including randomized controlled clinical studies (RC) only. In addition, subset analyses were performed, where the robustness of the pooled estimates were further assessed by repeating the meta-analysis on the basis of sample sizes and the presence of adequate information about randomization.

RESULTS

Identified Studies and Characteristics

The English and Chinese-language literature search yielded a total of 182 published studies, of which the abstracts were reviewed. Then, 52 full articles that were potentially relevant were further reviewed, of which 25 studies were excluded because of lack of controls, 3 because of the duplicate publications. Finally, 24 studies met the inclusion criteria, including 16 RC studies,[10-25] and 8 NRC studies.[26-33] A total of 1,678 patients with a diagnosis of SARS were included, where 866 patients came from 16 RC studies and 812 patients from 8 NRC studies (Table 1).

Of the 24 included studies, WM treatment mainly consisted of empiric antibiotics (e.g. azithromycin: 0.5g/d, Levofloxacin: 0.4g/d, Ceftriaxone: 2-4g/d), antiviral drugs (e.g. ribavirin: 0.5-1g/d), corticosteroid (e.g. Methylprednisolone: 80-320mg/d), and/or thymosin (50-200 mg/d). The use of TCM is shown in Table 1, where anti-SARS formulae were evaluated in ten studies, herb extracts were evaluated in three studies, and other combinations of herbal medicines were evaluated in eleven studies.

Of the 24 studies, only three studies reported the outcomes based on the severity of diseases[14,27,33] Of the 16 RC studies, most of them did not provide adequate information about the methods of blinding, and ITT. According to the Jadad scoring method, of the 16 RC studies, 7 studies scored 2 points[11,12,17,18,21,23,24] and the remaining studies each scored 1 point.

Mortality Rate

Ten of 24 studies reported the mortality rate.[11,13,14,21,23,25,27,29,32,33] The pooled mortality rates attributed to SARS in the integrated TCM/WM group and WM alone group were 3.7% (16/430) and 10.9% (44/403), respectively (RR=0.38, 95%CI:0.22 to 0.63). Based on the sensitivity analysis, when NRC studies were excluded[27,29,32,33], the conclusion was not affected (RR=0.33, 95%CI: 0.14 to 0.77) (Figure 1). However, no significant difference in mortality rate between treatments was detected in further subset analysis (RR=0.35, 95%CI: 0.12 to 1.10), where only those RC studies with larger sample sizes and adequate information of randomization were included (Table 2).

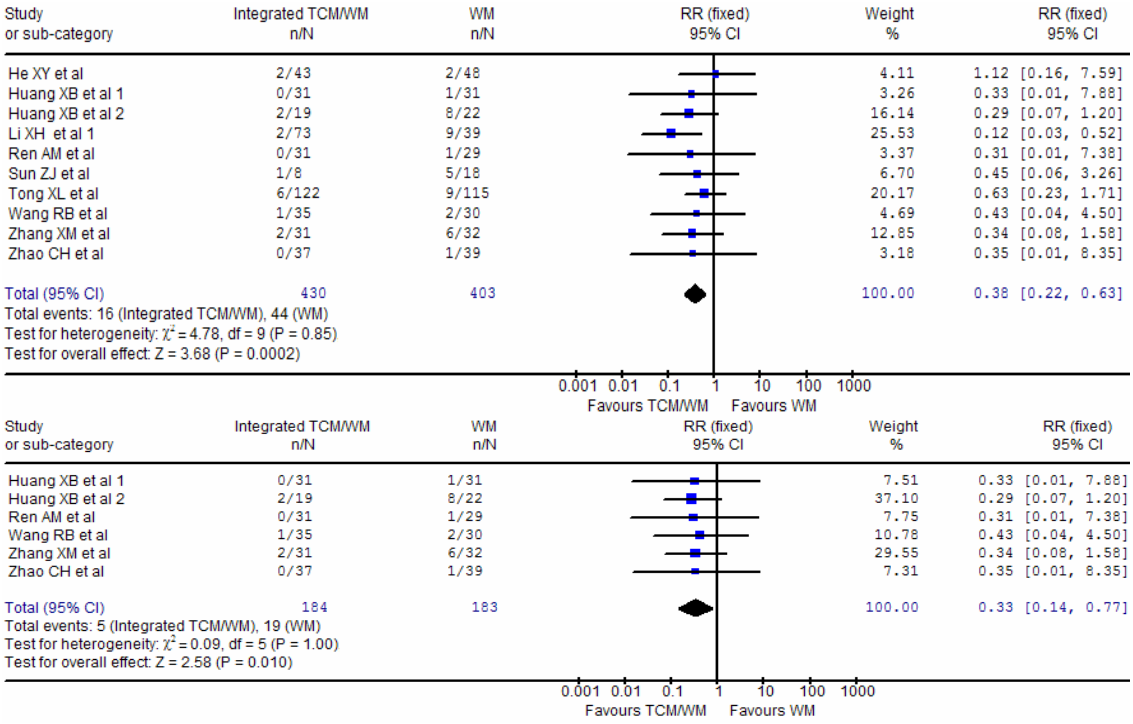

Figure 1. Relative risk of mortality rate between patients with integrative TCM/WM treatment and WM alone. The first part showed the comparisons of mortality rate between two groups including both RC studies and NRC studies. The second part showed the comparisons of mortality rates with the inclusion of RC studies only. Abbreviation: SARS: severe acute respiratory syndrome; TCM: traditional Chinese medicine; WM: western medicine; RC studies: randomized controlled studies; NRC studies: nonrandomized controlled studies; RR: risk ratio; CI: confidence interval; Fixed: fix-effects model.

Table 2. Subgroup analyses on the RC studies to assess effectiveness of integrative treatments based on sample sizes, and adequate information of randomization.

Criteria	Mortality rate		Cure rate		Resolution of lung infiltrate		Time to defervescence	
	Study ID	Pooled RR (95% CI)	Study ID	Pooled RD (95% CI)	Study ID	Pooled RD (95% CI)	Study ID	Pooled WMD (95% CI)
Sample sizes								
≥50	Huang[13] Ren[11] Wang[21] Zhang[23] Zhao[25]	0.35 (0.12 to 1.10)	Huang[13] Wang[21] Zhang[23] Zhao[25]	0.10 (-0.02 to 0.22)[a]	Kang[15] Ren[11] Wang[21] Zhang[23] Zhang YL[24]	0.26 (0.11 to 0.41)	Huang[13] Zhang[23]	-1.58 (-2.86 to -0.31)
<50	Huang[14]	0.29 (0.07 to 1.20)	Huang[14] Li ZJ[20]	0.16 (-0.32 to 0.64)[a]			Huang[14] Li ZJ[20] Li J[18]	-0.44 (-2.97 to 2.10)
Randomization								
Adequate information	Ren[11] Wang[21] Zhang[23]	0.36 (0.11 to 1.17)	Wang[21] Zhang[23]	0.12 (-0.13 to 0.37)[a]	Ren[11] Wang[21] Zhang[23]	0.23 (0.01 to 0.45)[a]	Zhang[23] Li J[18]	-1.58 (-2.98 to -0.19)
Inadequate information	Huang[13] Huang[14] Zhao[25]	0.30 (0.09 to 1.01)	Huang[13] Huang[14] Li ZJ[20] Zhao[25]	0.12 (-0.04 to 0.27)[a]	Kang[15] Zhang YL[24]	0.33 (0.17 to 0.48)	Huang[13] Huang[14] Li ZJ[20]	-0.88 (-2.86 to 1.09)

[a]: random-effects model.
Abbreviation: CI: confidence interval; RR: risk ratio; pooled RR: average effects based on individual RR; RD: rate difference; pooled RD: average effects based on individual RD; WMD: weighted mean difference; pooled WMD: average effects based on individual WMD;

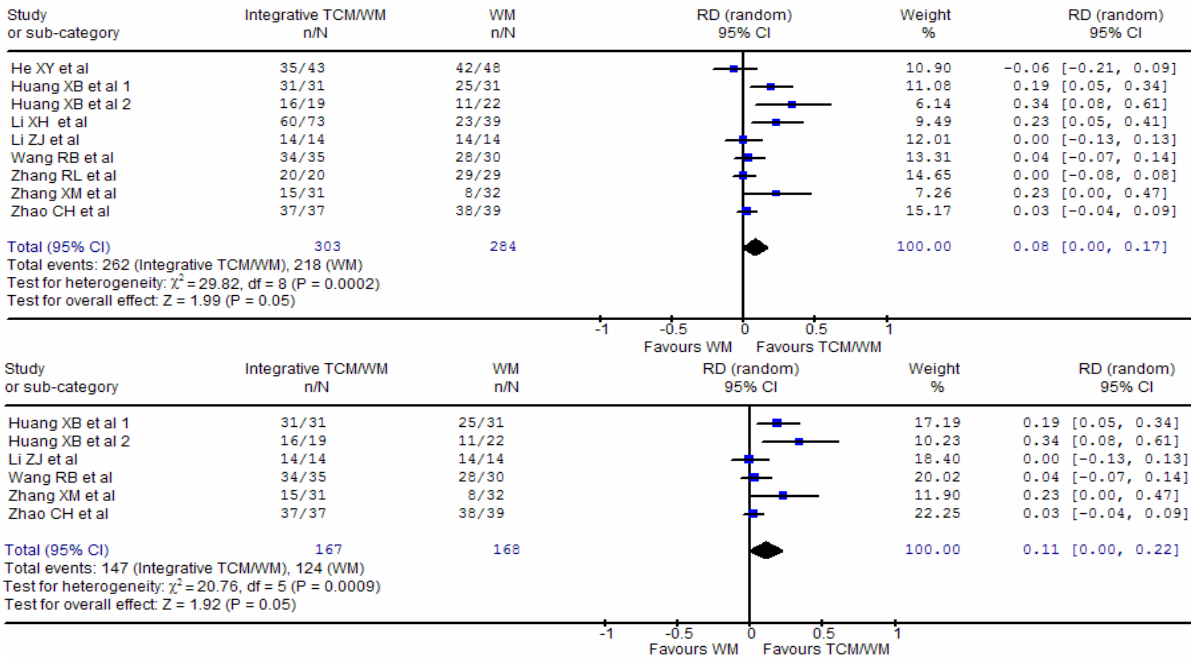

Figure 2. Comparisons of cure rate of patients with SARS. The first part showed the comparison between two groups including RC studies and NRC studies. The second part showed the comparison with the inclusion of RC studies only. Abbreviation: SARS: severe acute respiratory syndrome; TCM: traditional Chinese medicine; WM: western medicine; RC studies: randomized controlled studies; NRC studies: nonrandomized controlled studies; RD: rate difference; CI: confidence interval. Random: random-effects model.

Cure Rate

Nine studies reported the cure rate[13,14,20,21,23,25,27,28,33], of which three were NRC studies.[27,28,33] Positive effects in improving cure rate were noted with integrative treatment regardless of the inclusion of NRC studies (Figure 2), however, no significant difference was found in further subset analysis (RD=0.10 , 95%CI: -0.02 to 0.22, Table 2).

Resolution of pulmonary Infiltrate

Resolution of lung infiltrate were reported in eight studies.[11,15,17,21,23,24,26,32] As shown in Figure 3, 80.9% (292/361) patients receiving the integrative treatments had partial or complete resolution of pulmonary infiltrate, which was significantly higher than patients in WM alone group (67.8%,202/298)

(RD=0.18, 95%CI: 0.07 to 0.30). Consistent findings were noted in sensitivity and subset analyses.

Use of Corticosteroids

Ten of 24 studies reported the use of corticosteroids in terms of average daily dosage (mg),[11,23,24,33] average cumulative dosage (mg),[13,14,25] and treatment course in days.[19,20,25,28] The average daily dosage used in integrative TCM/WM treatment group was significantly lower than that in WM alone group (WMD=-60.27, 95%CI; -70.58 to -49.96). There was no significant difference between two groups either in the average cumulative dosage of corticosteroids (WMD=-229.84, 95%CI:-506.03 to 46.35) or the course of corticosteroids treatment (WMD=-1.61, 95%CI:-3.99 to 0.77).

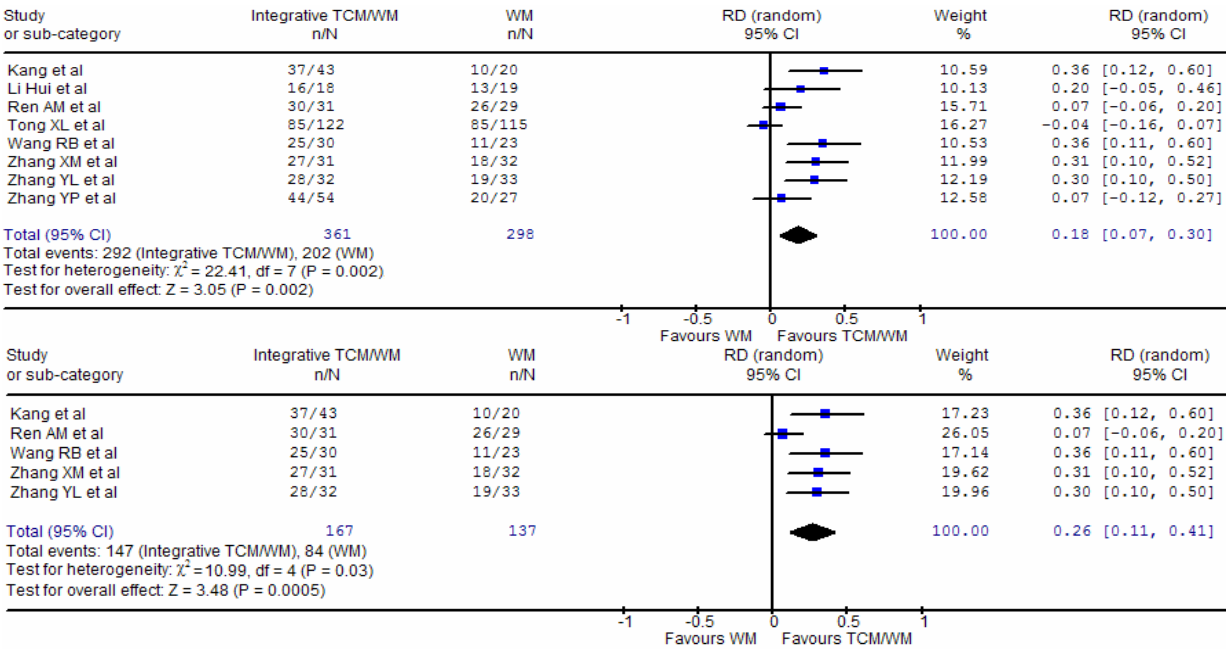

Figure 3. Comparisons of the number of patients with resolutions of lung infiltrate. The first part showed the comparison between two groups based on both RC studies and NRC studies. The second part showed the comparison with the inclusion of RC studies only. Abbreviation: SARS: severe acute respiratory syndrome; TCM: traditional Chinese medicine; WM: western medicine; RC studies: randomized controlled studies; NRC studies: nonrandomized controlled studies;RD: rate difference; CI: confidence interval. Random: random-effects model.

CD4+ Counts

Four studies reported CD4+ counts (cell/uL).[21,25,27,30] Prior to any treatments, there were no significant differences in CD4+ counts between two groups (WMD=-11.00, 95%CI: -56.02 to 34.01). After the treatments, the pooled WMD between the two groups was 167.96 (95%CI; 109.68 to 226.24) .indicating a significant difference in the recovery of CD4+ counts between integrative treatment group and WM alone group.

Time to Defervescence

Eight studies reported the time in days to fever resolution.[13,14,18,20,23,28,29,32] The pooled WMD between integrative TCM/WM treatment group and WM alone group was -1.06 (95%CI : -1.60 to -0.53, Figure 4). It suggested that integrative treatment could significantly reduce the time to defervescence in patients with SARS. Consistent findings were found in sensitivity and subset analyses.

Sensitive and Subgroup analysis

Based on the sensitivity analysis, the results were not affected with the exclusion of NRC studies (Figures 1-4). Additional subset analyses found that the previously observed differences in mortality rate and cure rate became insignificant when only RC studies with larger sample sizes and adequate randomization information were included (Table 2).

DISCUSSION

In this present study, we summarized the results of the findings from both RC studies and NPC studies using the meta-analysis. There is no convincing evidence to support that integrative TCM/WM treatment could significantly decrease the mortality rate, which contrasted from the findings from Liu et al. study.[4] Although we first noted a significant reduction in mortality rate with the integrative treatment when ten studies were included, further subgroup analyses failed to consistently find a significant difference in mortality rate in those RC studies with larger sample sizes and adequate information of randomization. This suggests that the previously observed positive effects of integrative treatment were likely due to the inclusion of those studies of poor quality.

In this study, both overall and subgroup analyses provided clear evidence to support the notion that

the integrative TCM/WM treatments might be more effective in clearing up the lung infiltrate, shortening the time to defervescence than WM treatment alone. These findings were consistent with the results from a previously published meta-analysis study.[3]

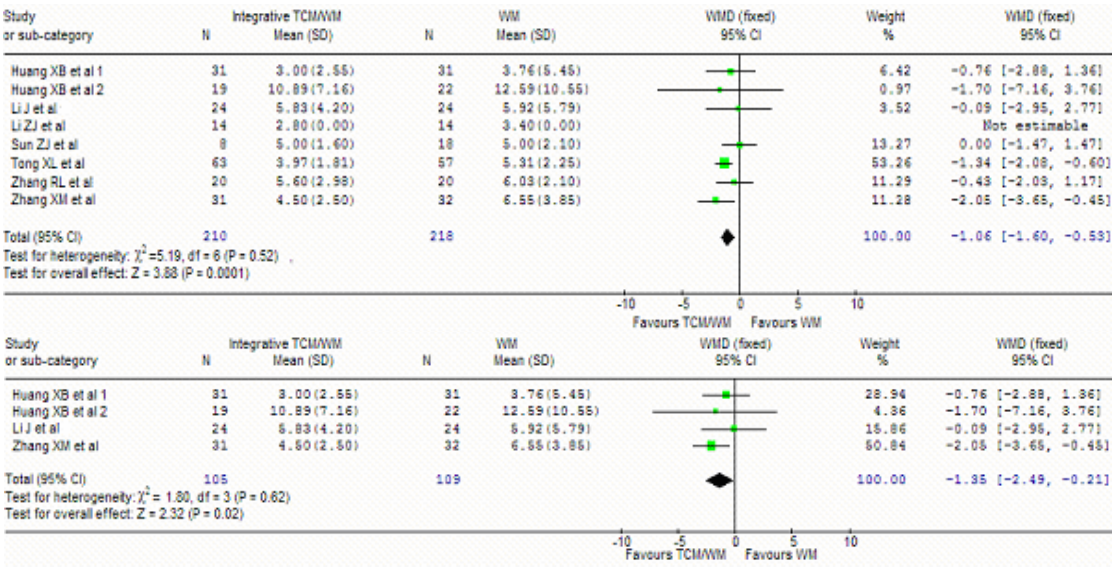

Figure 4. Comparisons of time to defervescence. The first part showed the comparison based on both RC studies and NRC studies. The second part showed the comparison with the inclusion of RC studies only. Abbreviation: SARS: severe acute respiratory syndrome; TCM: traditional Chinese medicine; WM: western medicine; RC studies: randomized controlled studies; NRC studies: nonrandomized controlled studies; WMD: weighted mean difference; CI: confidence interval; Fixed: fixed-effects model.

It has been found that a large percent of patients with SARS presented with lymphopenia.[34,35] Low counts of CD4+ and CD8+ are often associated with adverse outcome.[36] How to recover the lymphocyte cells became a critical treatment issue. In this present study, patients receiving integrative TCM/WM treatment had significantly higher CD4+ counts (uL) at the end of study (WMD=167.96, 95%CI; 109.68 to 226.24). With the limited follow-up, how well such effects could be translated into clinical outcomes were unknown. This aspect of benefits certainly warrants further investigation.

Our study suggests that adjunctive use of TCM with WM could significantly reduce the average daily use of corticosteroids. To date, use of corticosteroids for patients with SARS remains controversial. One important concern is the occurrence of adverse events associated with the use of corticosteroids, such as the development of Aspergillus, fungal infection.[37,38] Recent literature reported that some Chinese SARS survivors who had received high-dose corticosteroids treatment suffered the femoral head necrosis following therapy.[39,40] In the 24 identified studies used in this analysis, no long-term outcomes were reported. The questions of how clinically relevant the observed benefit of integrative treatment in reducing the average daily dose of corticosteroids were, and whether it could lead to a lower risk of developing corticosteroids-related adverse events, have not been answered yet in this study.

The findings of this study should be considered within the context of limitations. First, due to the limited number of published RCT studies, our analysis also included some NRC studies. However, the sudden outbreak of this new and serious disease precluded well controlled clinical studies during the epidemic. Despite twenty-four clinical studies, most of them had low methodological quality according to the Jadad scores. Second, the variation in treatment regimens, particularly the wide range of TCM in concoction constituents, dose, route of administration, and duration of therapy, became a major obstacle to a clear interpretation of the results. Third, there were only three studies that reported the outcomes on the basis of severity of disease. The data were insufficient for conducting an effective subset analysis on the severity of disease. Fourth, diagnoses of SARS during the outbreak were not confirmed by laboratory evidence of the SARS-Cov infection. As a recent study indicated, out of 28 patients, only 24 (85.71%) were eventually confirmed as having SARS according to the T-PCT detection of SARS-Cov RNA.[41] Fifth, because of the variety of TCM and WM under study, it would have been difficult to meaningfully measure the rate of adverse events related to treatments. Therefore, such an analysis of adverse events was not conducted as part of this present study.

CONCLUSION

The experience of integrative TCM/WM in the treatment of SARS is encouraging. This study demonstrated the possibility that integrated TCM/WM treatments might be a beneficial modality for the treatment of SARS, especially on quickening the resolution of lung infiltrate, increasing the CD4+

counts, and reducing the time to defervescence. Clearly, further studies are needed with any future outbreak of SARS, and the quality of studies evaluating TCM needs to be improved. Further studies should aim to standardize the TCM treatment and include long-term follow-up on major outcomes in order to strengthen the rationale of using TCM.

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