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Clinical Efficacy of the treatment of combination of Chinese and western medicine on Systemic Lupus Erythematosus:A Meta-analysis following the PRISMA

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YL and GC are the co-first authors and contribute equal to this paper.

Abstract

Systemic lupus erythematosus(SLE),known as lupus,is a chronic autoimmune disease and there is no cure for SLE.The western medication can improve syndromes to some extent,however,severe adverse drug reactions appear at the same time.Recently,it is confirmed that Chinese medicine also can have an excellent clinical efficacy on SLE.A meta-analysis was performed by using RevMan 5.3.A total of 9 randomized controlled trials, which involved 775 participants, met the inclusion criteria in this meta-analysis.It showed that the combination of Chinese and western medicine in the treatment of systemic lupus erythematosus(SLE) clearly improved the clinical efficacy compared with the control group[OR=2.71,95%CI(1.75,4.19),P<0.00001],the levels of C3 increased[MD=0.11, 95%CI(0.04,0.17),P=0.002],the Hb levels increased [MD=7.02,95%CI(4.28,9.77),P<0.00001],

the WBC levels increased [MD = 0.88, 95% CI (0.70,1.06), $p < 0.00001$]. In this study, the treatment of combination of Chinese and western medicine on SLE achieves more excellent clinical efficacy compared with the individual western medication therapy.

Keywords: Systemic Lupus Erythematosus, combination of Chinese and western medicine, meta-analysis, systemic review

1. Introduction:

Systemic lupus erythematosus (SLE), known as lupus, is a chronic autoimmune disease that immune system mistakenly attacks healthy tissue in related organs^[1]. Mostly, it occurs in teen female and the classification of symptoms vary from mild cases to severe cases. The cause of SLE is not clearly described yet. However, most researches showed that it is linked to some risk factors, for example, genetics, endocrine dyscrasia, infections and dysimmunity, etc^[2]. There is no cure for SLE. Nowadays, the treatment of western medicine involves preventing flares and reducing their severity and duration, which concludes medications such as prednisone, mycophenolic-acid and tacrolimus, disease-modifying antirheumatic drugs, immunosuppressive drugs, and analgesia^[3]. Nevertheless, the medications may cause or burden the impair of other organs and secondary infection with low immunologic function.

Certain studies have found that SLE is main cause of death in rheumatic diseases. So far, the global average prevalence of SLE is 12~39/100 thousand, and 30~70/100 thousand in China, which takes up the second place in the world. Besides, the mean age of onset is about 29 years old for SLE in China. The first clinical manifestation was hematologic abnormality (56.1%), arthritis (54.5%), butterfly erythema (47.9%), nephrosis (47.4%) and fever (37.8%) in order.

Recently, more studies expressed that during a long term clinical practices of Chinese medicine, therapists had a pronounced understanding of pathogenesis of SLE and the treatment of combination of Chinese and western medicine achieved a great progress on SLE^[4].

Thus, we performed a Systemic review and meta-analysis to assess the clinical efficacy of the treatment of combination of Chinese and western medicine on SLE.

2. Materials and methods:

We performed this Systemic review and meta-analysis following the PRISMA (Preferred Reported Items for Systemic Review and Meta-analysis) guidelines.

2.1 Types of studies

All RCTs comparing Chinese medicine plus Western medicine versus Western medicine alone were selected and assessed for inclusion in our research.

2.2 Inclusion criteria

The inclusion criteria for this study were as follows: 1) study type: randomized controlled trials, published studies, or double-blind

trials, triple-blind trials; 2) published date: from 2008 to 2020; 3) intervention: treatment of combination of Chinese and western medicine prescription for the treatment group, individual western medicine for controlled group; 4) number of patients: over 30 patients in each recruited study.

2.3 Exclusion criteria

The exclusion criteria for this study were as follows: 1) observational studies; 2) cell or animal basic researches; 3) repetitive literature; 4) unpublished clinical studies; 5) the number of patients is less than 15; 6) data or the full text are unavailable.

2.4 Interventions

Treatment group: combination of Chinese medicine (Chinese medicine prescription) and western medicine (such as glucocorticoid-GC);

Control group: individual western medicine therapy.

2.5 Outcome measures

Total remission rate (TRR; complete plus partial remission rate) was defined to evaluate the clinical efficacy of treatment of Traditional Chinese Medicine (TCM) and western medicine on SLE as the primary outcome.

The laboratory index about C3 levels, Hb levels and WBC levels were the secondary outcomes.

2.6 Information sources

Two independent reviewers performed a comprehensive search of the Wanfang Databases, the China National Knowledge Infrastructure(CNKI),Weipu Databases,PubMed,and Google Scholar. A conventional search was also performed to find potential studies that were not indexed in the electronic databases. The last search date was February 5.2020.

2.7 Search strategy

A combination of the following English terms was used in the database searches: (Chinese medicine) and (“Systemic lupus erythematosus” or lupus or SLE) and (Western medicine). For the Chinese databases, the following keywords were used in combined ways: [“Xitongxing hongbanlangchaung” and [“Zhongyi/Zhongyao” and [“Xiyi/Xiyao”. Furthermore, the reference lists of all the related articles were reviewed to identify potential RCTs. There were no trials excluded due to their publication status or language.

2.8 Study selection

According to the inclusion criteria, two reviewers searched the titles and scanned abstracts of the included studies or read the full text to screen for possible relevant literature.Various opinions were discussed and resolved by other reviewers(Geer.Chen and X.l. Cheng). Only randomized controlled trials,or doubled-blind trials,studies with laboratory index that were linked to the treatment of TCM and western medicine on SLE were included in the analysis.

2.9 Data extraction

Three investigators (Y.H.Luo,D.H.Xu,L.Q.Wei) independently rated the included RCTs and extracted the data. We summarized the characteristics of all included RCTs in Table 1, and performed a meta-analysis using the the Review Manager (RM) 5.3 to assess the clinical efficacy of Chinese medicine plus Western medicine in the patients with SLE.

Table.1 summary of outcome measures pooled

Outcome	Studies	Patients	Statistical Methods			
			OR(M-H, fixed, 95%CI)		MD(IV, fixed, 95%CI)	
			Effect Estimate	P	Effect Estimate	P
TR	9	775	2.7[1.75,4.19] P<0.00001			
C3	6	497			0.11[0.04,0.17] P=0.002	
Hb	6	507			7.02[4.28,9.77] P<0.00001	
WBC	6	507			0.88[0.70,1.06] P<0.00001	

TR:total remission;C3:complement 3;Hb:haemoglobin;WBC:white blood cell;

OR;odds ratio;MD:mean difference;CI:confidence, intervals;

2.10 Risk of bias in individual trials

Two independent reviewers (Y.H.Luo and D.H.Xu) appraised the risk of bias in the included trials using the Cochrane Risk of Bias Tool for Randomized Controlled Trials. The following criteria were used to evaluate bias in each trial: random sequence generation; concealment of allocation; blinding of participants and personnel; blinding of outcome assessment; incomplete data; selective reporting; and other bias. The risk of bias was classified as ‘low’, ‘high’, or ‘unclear’. If there were disagreements, other reviewers repeated the extraction, analysis and interpretation of the data and the disagreements were solved by discussion until a consensus was reached.

2.11 Summary Measures and Data Synthesis

All analyses were performed using the RM 5.3. Dichotomous data were shown as the odds ratio (OR), and continuous data were shown as the weighted mean difference (WMD) with a 95% confidence intervals (CI). The I^2 statistic and Chi^2 test were used to assess statistical heterogeneity. Substantial heterogeneity was considered when $I^2 > 50\%$ or $P < 0.05$. If the hypothesis of homogeneity was not rejected, a fixed effects model was used to estimate the summary OR, WMD and 95% CI; otherwise, a random effects model was applied.

2.12 Risk of Bias across trials

Funnel plots were applied to examine the potential bias in the RCTs included in the meta-analysis.

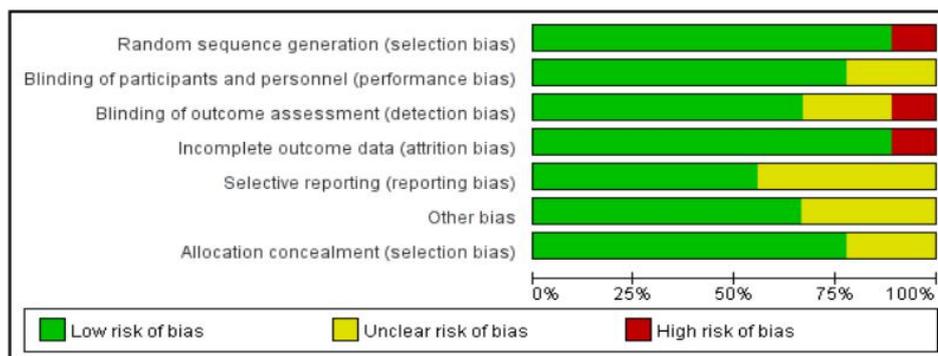


Fig.1. Risk of bias graph;

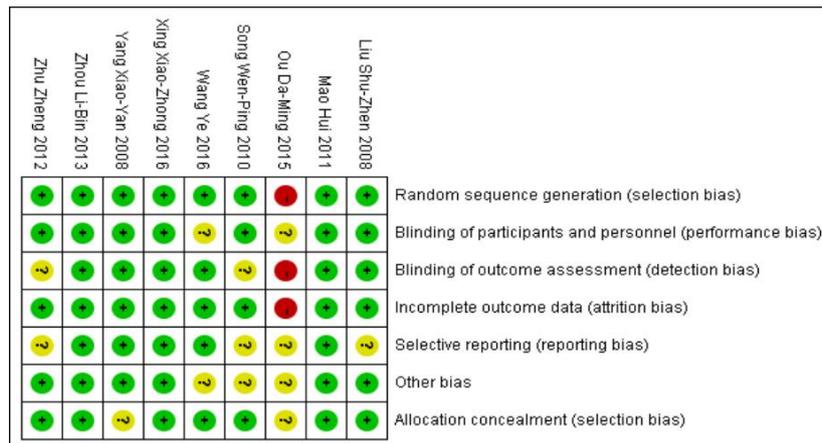


Fig.2. Risk of bias summary;

3. Results

3.1 Study selection

In this meta-analysis, a total of 512 records were identified in the initial search. Then using Endnote 7 software to eliminate duplicate literatures, 446 articles were obtained, of these, 354 articles of case reports, reviews, animal experiments were excluded after analyzing the title and the abstract. Then, 83 articles were excluded because of following reasons: non-RCT design (n=18); intervention included radiotherapy or other physical treatments (n=10); lack of laboratory index (n=55) (Fig.3). Finally, 9 trials were in this meta-analysis, a total of 775 patients was included. They all met the inclusion criteria. (Table.3)

Table.3. Principal characteristics of the studies included in the meta-analysis.

Included studies	Design	Sample size (TG/CG)	Outcome measures	Interventions	
				TG	CG
Ou Da-Ming(2015)	RCT	23/19	TR+C3+Hb+WBC	TCM+WM	WM
Liu Shu-Zhen(2008)	RCT	60/50	TR+C3+Hb+WBC	TCM+WM	WM
Zhou Li-Bin(2013)	RCT	18/15	TR+C3+Hb+WBC	TCM+WM	WM
Mao Hui(2011)	RCT	55/55	TR+Hb+WBC	TCM+WM	WM
Wang Ye(2016)	RCT	56/52	TR+C3+Hb+WBC	TCM+WM	WM
Song Wen-Ping(2010)	RCT	34/30	TR	TCM+WM	WM
Zhu Zheng(2012)	RCT	32/28	TR+C3	TCM+WM	WM
Yang Xiao-Yan(2008)	RCT	72/72	TR+C3	TCM+WM	WM
Xing Xiao-Zhong(2016)	RCT	54/50	TR+Hb+WBC	TCM+WM	WM

RCT:randomized controlled trial;TG/CG:treatment group/control group;

TR:total remission;C3:complement 3;Hb:haemoglobin;WBC:white blood cell;

TCM:Traditional Chinese Medicine;WM:western medicine;

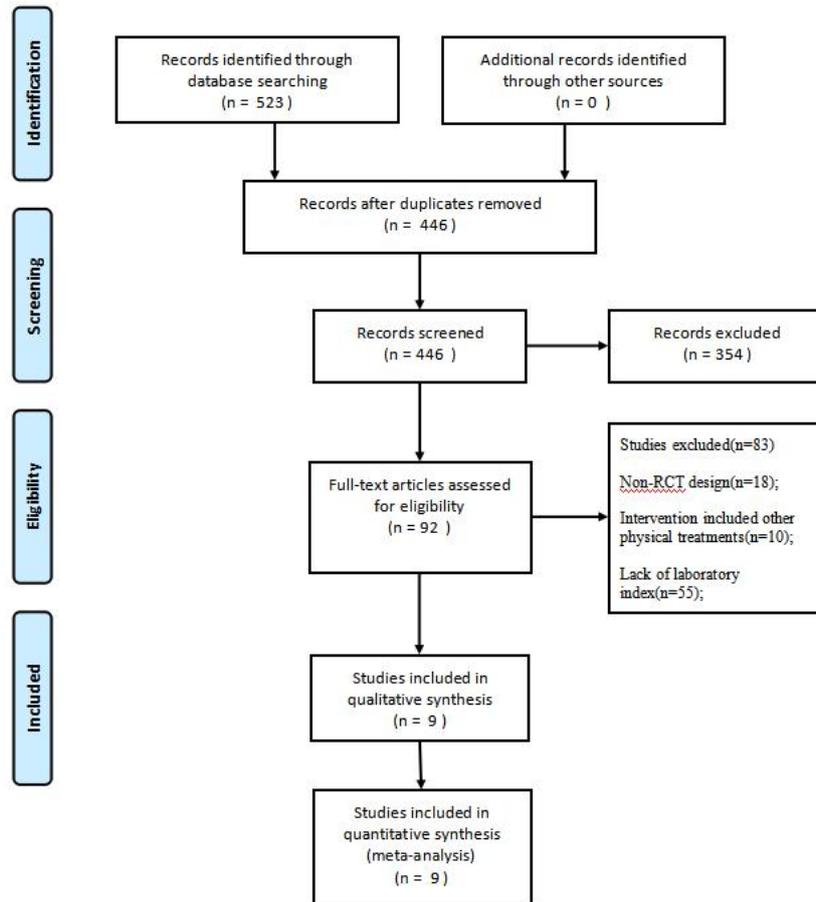


Fig.3. Preferred Reporting Items for Systematic Reviews and Meta-Analyses diagram of searching.RCT=randomized controlled trial;

3.2 Study Characteristics

The 9 RCTs comprising of 775 patients were included (Table.3). (Liu,et al,2018;Mao.et al,2011;Ou.et al.2015;Song.et al.2010;Wang.et al.2016;Xing.et al.2016;Yang.et al.2008;Zhou.et al.2013;Zhu.et al.2012) All included RCTs were implemented in China, and the articles were published from 2008 to 2018. There were 404 and 371 patients in the experimental and control groups, respectively. The number of subjects in each RCT varied from 33 to 144.

All RCTs included compared Chinese medicine combined with Western medicine versus Western medicine alone. Nine trials for TRR, six trials for C3, six trials for HB levels and six for WBC levels. The characteristics of the 27 trials are shown in Table 3.

3.3 Methodologic quality

The risk of bias and methodologic quality of all included RCTs were evaluated and presented in Tables. The Randomization was used in the 9 trials; however, only 4 trials distinctly reported the random methods. In most trials, the concealment of allocation, blinding of participants, personnel, outcome assessment, and selective report were unclear. In all included trials, the data were complete. Any other bias was not clear. (Table 2)

Studies	Random Sequence Generation	Allocation Concealment	Blinding of Participants and personnel	Blinding of Outcome assessment data	Incomplete Outcome Reporting	Selective Reporting bias	other
Ou Da-Ming(2015)	-	?	?	-	-	?	?
Liu Shu-Zhen(2008)	+	+	+	?	+	?	+
Zhou Li-Bin(2013)	+	+	+	+	+	+	+
Mao Hui(2011)	+	+	+	+	+	+	+
Wang Ye(2016)	+	+	?	+	+	+	?
Song Wen-Ping(2010)	+	+	+	?	+	?	?
Zhu Zheng(2012)	+	+	+	?	+	?	+
Yang Xiao-Yan(2008)	+	?	+	+	+	+	+
Xing Xiao-Zhong(2016)	+	+	+	+	+	+	+

“-”=“low risk”,“+”=“high risk”, “?” =“unclear risk”

3.4 Outcome measures

The findings of the meta-analyses are summarized in Table 1 and 4.

Studies	Patients(No.)		TRR(%)		P
	Male	Female	TG	CG	
Ou Da-Ming	4	38	82.61	78.95	P<0.05
Liu Shu-Zhen	13	97	93.3	80	P<0.05
Zhou Li-Bin	8	25	94.4	80	P<0.05
Mao Hui	3	107	85.45	70.91	P<0.05
Wang Ye	12	96	89.3	73.1	P<0.05
Song Wen-Ye	18	46	94.12	76.67	P<0.05
Zhu Zheng	5	55	90.63	89.28	P<0.05
Yang Xiao-Yan	9	135	94.33	93.06	P<0.05
Xing Xiao-Zhong	58	46	96.3	78	P<0.05

TG: treatment group;CG: control group;TRR:total remission rate;No.:the number of patients;

3.4.1 Study of TRR:

There are nine studies included into the meta-analysis to assess the clinical efficacy of the treatment of combination of Chinese and western medicine on SLE compared with only western medicine therapy, and TRR is performed to be representative of the clinical efficacy. A summary of the data of nine studies of TRR pooled in Table.4. Furthermore, summary estimates of 9 trials indicated a significant improvement of TRR [OR=2.71, 95%CI(1.75,4.19), P<0.00001]. (Fig.4)

The forest plots (Fig.4) expressed that the treatment group had a higher value of clinical efficacy compared with the control group.

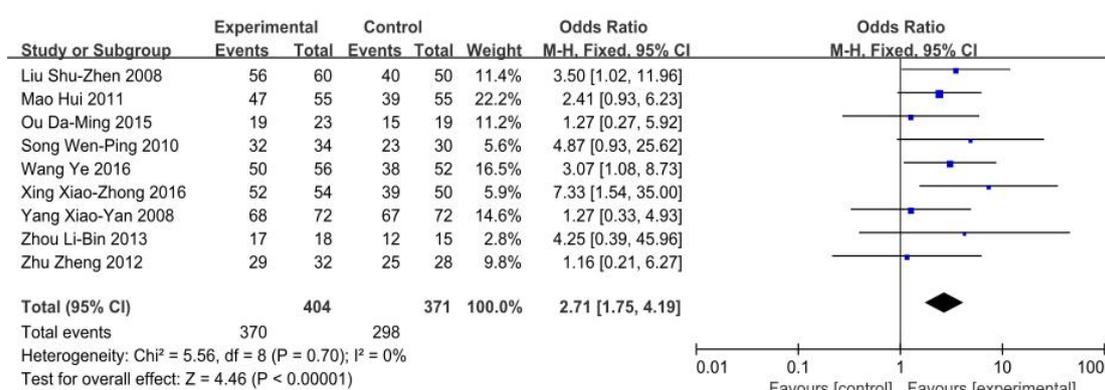


Fig.4. Forest plots showing a significant improvement of TRR in treatment group compared with control group;

3.4.2 Study of C3

With regard to C3, the data of 6 trials were collected to evaluate the clinical efficacy of the treatment of combination of Chinese and western medicine on SLE compared with only western medicine therapy, which was presented in Fig.5. From the forest plots graph (Fig.5), it showed that the experimental group increased the levels of C3 after three-month treatment when compared with the control group obviously.

[MD=0.11, 95%CI(0.04, 0.17), P=0.002]

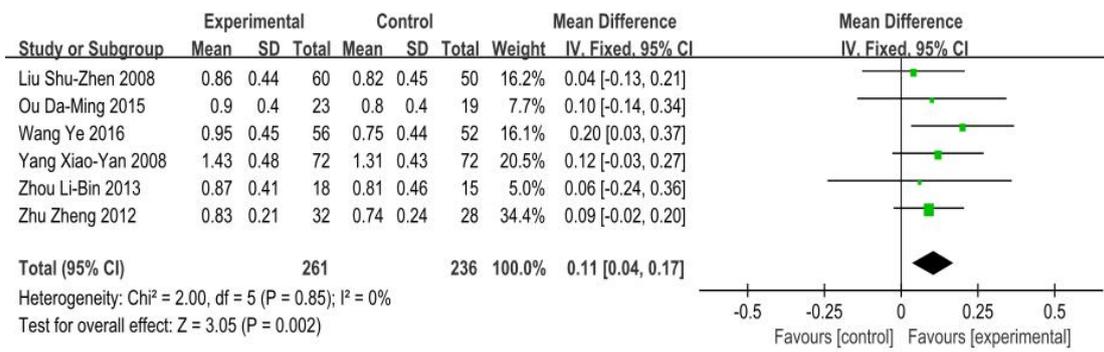


Fig.5. Forest plots showing a significant difference of the C3 levels between the treatment group and the control group;

3.4.3 Study of Hb*

In aspect of Hb levels, statistics of 6 studies were collected to show the difference between the treatment group and control group to describe the the clinical efficacy of the treatment of combination of Chinese and western medicine on SLE compared with only western medicine therapy (Fig.6 and Fig.7). The figure expressed that the Hb levels of the treatment group were higher than that of control group notably (except for the study Ou Da-Ming*,) (the data of Ou Da-Ming 2015 was doubtful.)

As the graph (Fig.7) showed, all data of six studies was extracted to analyze by Revman 5.3. According to the principle of statistical analysis, I² = 82% > 50%, which regarded that the test of heterogeneity existed, a random-effects model was applied. The result was presented in the diagram. [MD = 4.98, 95% CI (0.38, 9.58), P = 0.03].

Thus, the test of heterogeneity was needed to exclude. After the data of the study Ou Da-Ming* removed, I² = 0% < 50%, the result changed by using a fixed-effects model in Fig.6. [MD = 7.02, 95% CI (4.28, 9.77), P < 0.00001]

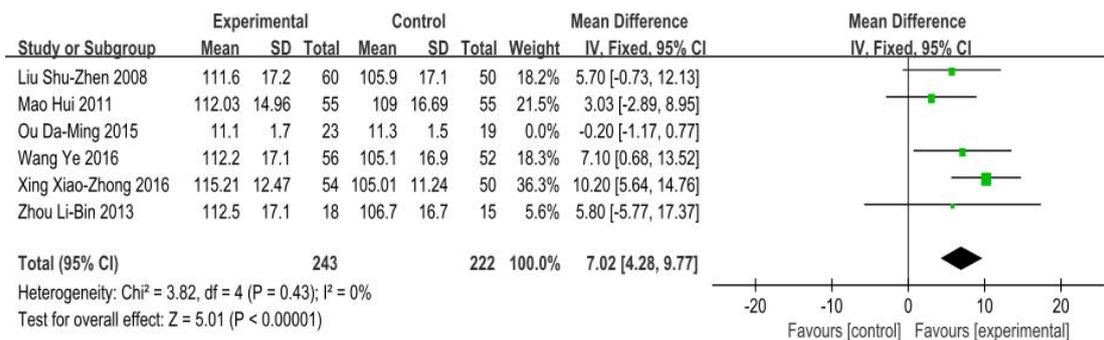


Fig.6. Forest plots showing a significant difference of the Hb levels between the treatment group and

the control group in fixed-effects model;

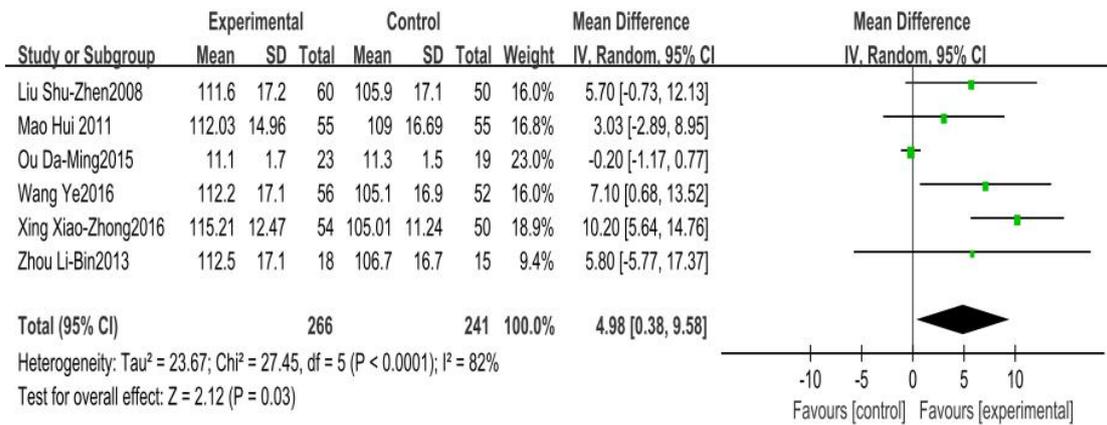


Fig.7.Forest plots showing a significant difference of the Hb levels between the treatment group and the control group in random-effects model;

3.4.4 Study of WBC

With the consideration of WBC, there are 6 studies pooled to show the WBC levels of the treatment group and control group. The comparison within two groups could be used to measure the clinical efficacy of the treatment of combination of Chinese and western medicine on SLE compared with only western medicine therapy. A summary of six records of WBC levels was presented in Fig.8. [MD=0.88, 95%CI(0.70,1.06), p<0.00001]. The graph showed clearly that the experimental group had a greater values of WBC levels than control group after therapy.

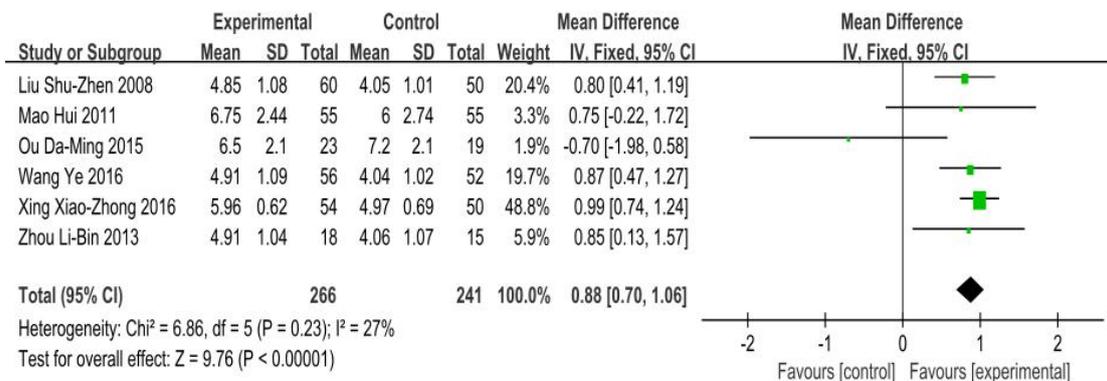


Fig.8.Forest plots showing a significant difference of the WBC levels between the treatment group and the control group;

3.5 Publication Bias

The asymmetry in the funnel plots of the TRR (Figure 9) and the C3 levels (Figure.10) indicated the publications bias existed.

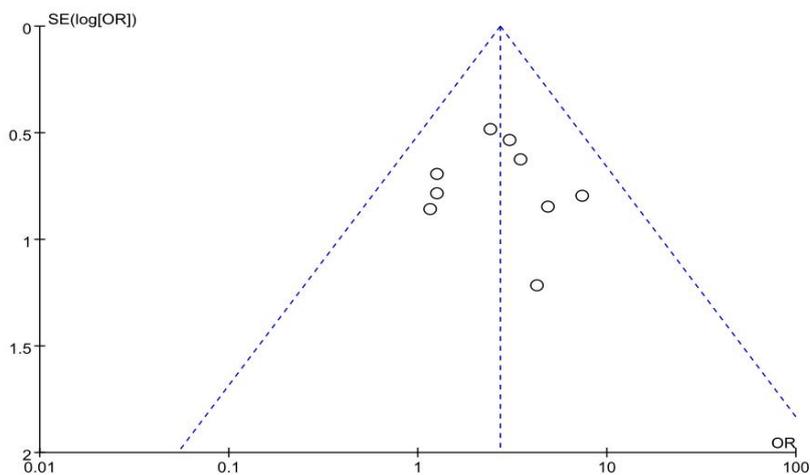


Fig.9. Funnel plots of the TRR showing that publication bias existed.

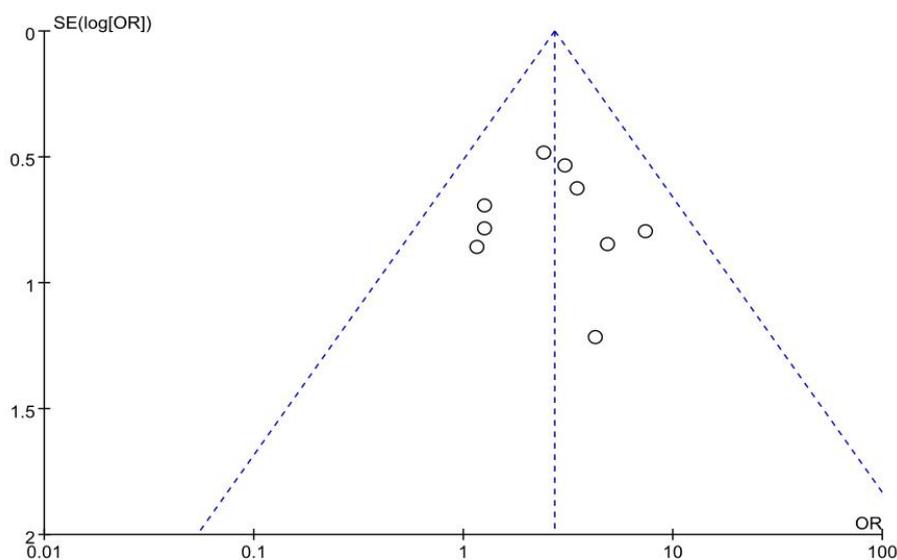


Fig.10. Funnel plots of the C3 levels showing that publication bias existed.

3.6 Sensitivity analyses

Generally, good homogeneity was found between all included clinical trials.

With regard to TRR, the primary outcome, the pooled data showed that Chinese medicine plus Western medicine increased TRR significantly [OR=2.71,95%CI(1.75,4.19),P<0.00001]. The

findings were similar when the subgroup and sensitivity analyses were performed based on the quality of the study ,C3[MD=0.11, 95%CI(0.04, 0.17),P=0.002],Hb levels[MD=7.02, 95%CI(4.28,9.77),P<0.00001],WBC levels[MD=0.88, 95%CI(0.70,1.06),p<0.00001],subject size(each study \geq 30).

4.Discussion

Systemic lupus erythematosus(SLE) is a chronic multi-system autoimmune disease of unclear etiology. The course of disease is complex. At present, Western Medicine mainly treats with glucocorticoid and immunosuppressants in order to alleviate the state of disease, however, some side effects such as bone marrow suppression, liver and kidney damage, and osteoporosis could be one of the causes of SLE mortality. As an important part of traditional medicine, traditional Chinese Medicine (TCM) is one of the effective means of comprehensive treatment of SLE, which can effectively reduce the side effects caused by Western medicine.

According to the theory of traditional Chinese Medicine(TCM), SLE belongs to the range of "yin-yang Toxin" , "Butterfly Sore" , "Edema" and so on. ("yin-yang Toxin" and "Butterfly Score" are special terms used in TCM). Also, it was the first time to record the symptoms of SLE by Zhang zhongjing, an outstanding Chinese Medicine practitioner born in the end of Han dynasty. Due to TCM, it is regarded that there are six aspects of etiology for SLE. Like, Congenital deficiency, deficiency of the liver and kidney, "Seven Emotions Resulting in Internal Injury", overwork , six exogenous pathogens and toxic, which induces to Yin-Yang imbalance of the whole body, even more complicated syndromes.

Most scholars consider that SLE should be treated with the treatments of combination of traditional Chinese medicine and Western medicine. Besides, treatments based on syndrome differentiation of TCM can play the advantages in different stages during the treatment of long-term SLE, so as to achieve the sustainability and safety of treatment. So far, the treatments of combination of TCM and Western Medicine applied in SLE have been widely reported, and the clinical efficiency is remarkable. For examples, a study(Si Chuan Xi ^[16]) found that systemic treatment of SLE with TCM and Western Medicine can increase the effective rate to 86.0% , moreover, improve symptoms such as fever, Erythema and joint pain during treatment, and reduce adverse reactions. The research(Jiang Yi Hui^[17]) demonstrates that hormone combined with TCM treated in SLE can not only relieve the symptoms as soon

as possible, but also control the development of the disease.

In this meta-analysis, nine eligible articles were included. Among them, prednisone was respectively combined with “Yiqi Bushen Huoxue decoction”, “Fuzheng Jiedu decoction”, “Yiqi Yangxue Jianpi Bushen decoction”, or” Liu Wei Di Huang Wan” to treat SLE, compared with the treatment of Western Medicine alone. It was found that CBC, complement C3, anti-double-stranded DNA antibody and other laboratory indicators improved significantly[4,6,9,11]. Additionally, on the basic treatment of hormone in Western medicine, treatments based on syndrome differentiation of TCM were applied. For instance, there are different types of diagnosis of SLE, so treatments corresponding to various symptoms are needed. The pattern of excessive heat toxin can be treated with clearing heat-toxin and Cooling Blood for resolving macula Chinese medicine; The yin deficiency inner heat is treated with eliminating heat by nourishing yin Chinese medicine; The deficiency of both qi and yin is treated with supplementing Qi and nourishing Yin Chinese medicine; The deficiency of spleen and kidney is treated with reinforcing kidney and spleen Chinese medicine. The symptomatic treatment can improve the clinical manifestations of fever, alopecia, Arthralgia and related experimental indexes [5,7,8,10,12]. (note: “Yiqi Bushen Huoxue decoction”, “Fuzheng Jiedu decoction”, “Yiqi Yangxue Jianpi Bushen decoction”, or” Liu Wei Di Huang Wan” are traditional Chinese herbal prescriptions.)

The results of this meta-analysis showed that the treatment of traditional Chinese medicine plus Western medicine in SLE can significantly enhance the clinical efficacy, reduce pain and skin rashes to certain extent. What's more, compared with the control group, C3, HB, WBC significantly increased in the experimental group. As an important laboratory index of SLE, the level of C3 is very helpful to the diagnosis and the judgment of disease degrees in SLE. In our study, after 3 months of treatment, the level of C3 in blood of SLE patients increased significantly, indicating that the treatment of TCM combined with Western Medicine is effective. In addition, no serious adverse drug reactions were reported in the included studies. All results have statistical significance ($P < 0.05$).

However, there are still some limitations and deficiencies in our research: 1) most of the studies with the treatment of TCM in SLE come from China, and the patients included are Chinese, thus, this meta-analysis has a certain limitation of locality; 2) the quality of the literature included in this study is medium. Majority of them do not describe the randomized method, or mention the blind method and distribution hiding, which can lead to bias easily and affect the credibility of research results; 3) The literature included in this study is limited to

clinical symptoms, signs and laboratory indicators, lack of histological evidence and more detailed description of adverse reactions, which is not conducive to explore more in-depth evaluation criteria;4) The Western medicine scheme and dose is not the same as that of TCM,which may have some influence on the result of the study; 5) The size of samples included is not enough,lack of large samples and multi-center clinical research.

5.Conclusion

In this meta-analysis,the clinical efficiency of treatment of TCM combined with Western medicine is better than that treated with Western medicine alone, which means not only reduce the side effects of Western medicine, but also improve the clinical symptoms and related laboratory indexes apparently.Furthermore, Evidence-based medicine as a whole is adequate and worthy of more clinical verification.Therefore, more large-scale, multi-center and prospective randomized clinical trials are urgently necessary in the future to obtain more reliable evidence-based medicine.

Acknowledgements

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