

The Efficacy and Safety of Integrated Chinese Plus Western Medicine Compared with Western Medicine Alone in the Treatment for Purpuric Nephritis: A Meta-Analysis

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Abstract: *Objective:* This research is aimed to systematically evaluate the efficacy and safety of Chinese plus Western Medicine treatment for Childhood purpuric nephritis by Meta-analysis, in order to improve the cure rate and reduce adverse reactions of this disease, then provide guidance for clinical medication. *Methods:* There are six major databases including CNKI, Pubmed, Embase, World Wide Database, Web of science and Science Direct retrieved through the Internet, and the randomized-controlled trials of the combined therapy for Childhood purpuric nephritis published both in Chinese and English from the 1999 to October 2019 were collected. Meta-analysis by R software 3.5.0 was adopted to analyze the effective index and adverse effect. *Results:* In total 92 papers of randomized-controlled clinical studies were enrolled. HSPN children treated with combined therapy demonstrated a significant increase in total effective rate ($RR=1.19$; 95%CI (1.16–1.21), $P<0.001$) when compared with Western medicine alone. Our study also found that Chinese plus Western medicine had an advantage on decreasing 24-hour urine protein ($WMD=-0.47$; 95%CI (-0.53,-0.41); $p<0.001$) and urine erythrocyte count ($WMD=-8.88$; 95%CI (-9.80,-7.96); $p<0.001$) when compared with Western medicine. Children seemed to benefit more from combined treatment in the adverse effect ($RR=0.64$; 95%CI (0.46, 0.87); $p<0.01$). *Conclusions:* Integrated Chinese plus Western medicine treatment was effective for Childhood purpuric nephritis, which may be a superior alternative for HSPN. Nevertheless, long-term, high-quality and multicenter RCTs are required to make the results more convincing.

Keywords: Chinese Plus Western Medicine, Childhood Purpuric Nephritis, Efficacy and Safety, Randomized-Controlled Trials, Meta-Analysis

1. Introduction

Henoch-Schonlein purpura nephritis (HSPN) is a disease of kidney which damage the kidney within 6 months after the onset of Henoch-Schonlein purpura (HSP) [1]. At present, the specific pathogenesis of HSPN is not completely identified. It is generally accepted that some virus, bacteria, specific substances and other factors lead to allergic reactions, the disorder of cellular and humoral immunity. Eventually, the IgA immune complex deposits in the glomerulus can be seriously damaged. As a result, those substance damage the

kidney [2, 3]. There are also domestic studies which point out that the disorder of intestinal microflora in children is also related to the pathogenesis of this disease [4]. Most children with HSPN have a good prognosis. However, the report demonstrated that around 15% to 20% of children will eventually develop chronic renal failure. Thus, it is of great importance to pay enough attention to it. There is no unified treatment plan for this disease because of the diverse clinical manifestations and complex pathological classification of HSPN. At present, the treatment mainly includes symptomatic treatment, immunosuppressant and

glucocorticoid application [5, 6]. In recent years, more and more papers revealed that the integrated treatment of children HSPN with traditional Chinese and Western medicine has achieved excellent result. They determined the treatment program of Western medicine according to the clinical manifestation and pathological classification of children. At the same time, the individualized dialectical treatment combined with Chinese medicine classification. Many academic reports showed that the traditional Chinese medicine have the function of synergistic detoxification for glucocorticoid and it can be quite favorable [7, 8]. In this paper, a meta-analysis is conducted on the randomized controlled trials (RCT) of the combined treatment for children HSPN with traditional Chinese and Western medicine. The aim of the research is to objectively evaluate the effectiveness and possible advantages of the treatment so as to provide a basis for the guidance of rational clinical medication.

2. Materials and Methods

2.1. Search Strategy

The research articles were searched on the CNKI, Pubmed, Embase, World Wide Database, Web of science and Science Direct databases (1999–October 2019; key words: “purpura nephritis” and “integrated Traditional/Chinese and/plus Western Medicine” or “combined Chinese and Western Medicine”). The academic materials was limited to the published studies that focused on RCT or clinical trials of integrated Chinese and Western Medicine therapy for Childhood/children HSPN. The publications are in both English-language and Chinese-language. In order to ensure complete literature retrieval, Chinese and English keywords were used to carry out secondary search on traditional Chinese medicine, Chinese and western medicine, integrated Chinese and western medicine. Meanwhile, retrospective research was conducted on the related literature references.

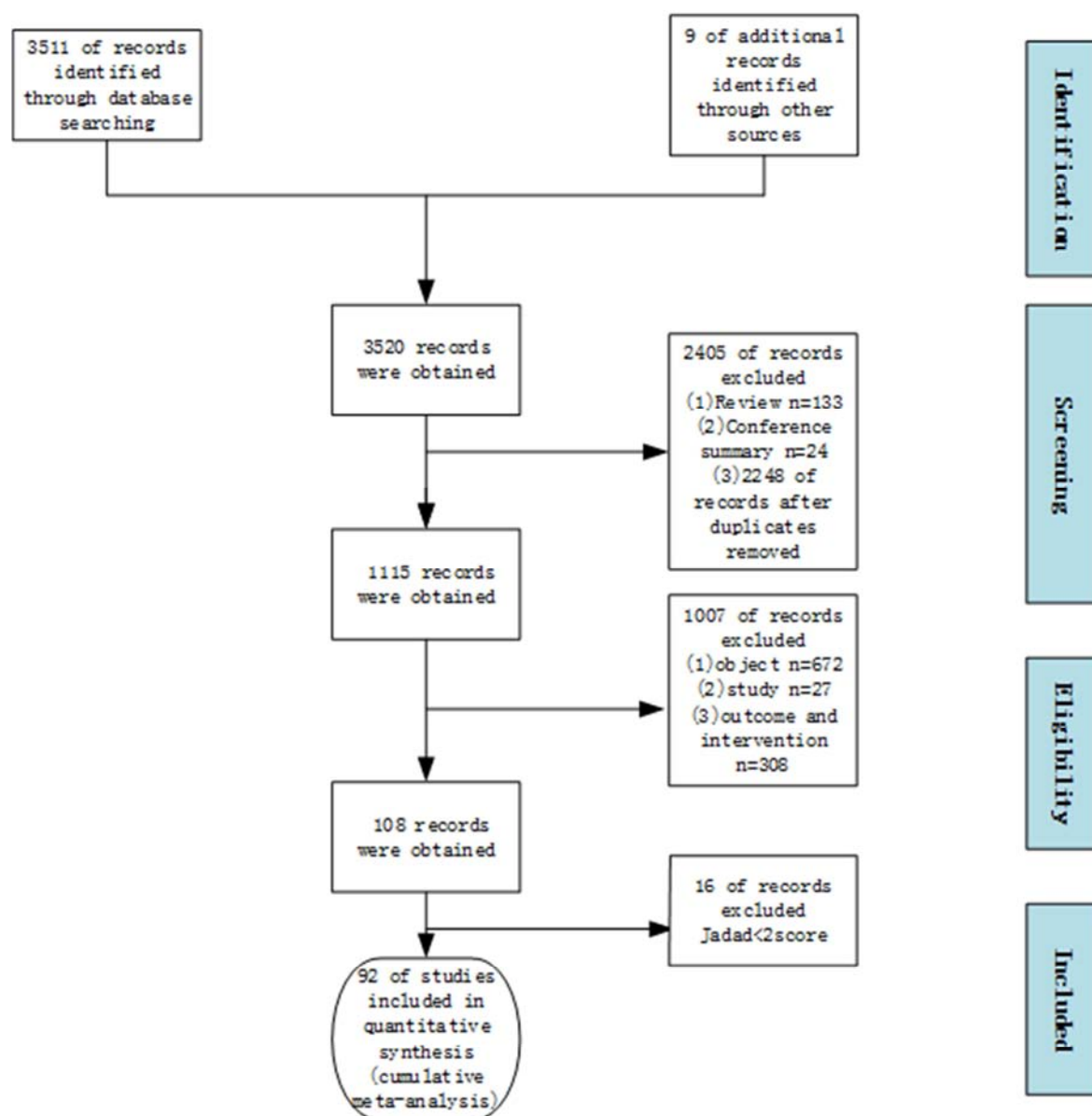


Figure 1. Flowchart illustrating the selection of studies.

2.2. Inclusion and Exclusion Criteria

The inclusion and exclusion criteria were formulated according to the PICOS features which were included in the RCT: P (patient, research object), I (intervention method), C (control, comparative intervention method), O (outcomes, measurement outcomes), S (studies, research design).

The inclusion criteria were as follows. (a) P: children with HSPN and all met the diagnostic criteria of the evidence-based guidelines for the diagnosis and treatment of HSPN in the kidney disease group of the Chinese Medical Association in 2009 [9] or in 2000. (b) I: Chinese medicine (self-designed prescription, traditional medicine) plus hormones and/or immunosuppressants. TCM compounds include traditional decoction, tablets made with modern technology, injection, capsule. Administration may include oral, intravenous, enema, or combination therapy. Chinese medicine compound refers to a group of drugs which are made up of appropriate dosage and proper compatibility according to the composition principle after the treatment is decided by the reason of syndrome differentiation. (c) C: 24-hour urine protein ration > 250mg, need to be treated with hormone and/or immunosuppressant. (d) O: The outcome measures should be included total effective rate and/or 24-hour urine protein ration and/or Urine erythrocyte count, the safety index was side-effect. (e) S: Randomized controlled trial (random number table, computer random arrangement, coin toss, lottery, etc.). Semi-randomized controlled trial (grouped by visit order, parity of birth date, etc.). (f) Basic treatment: All groups should include basic treatment, such as, look for allergens and avoid allergenic foods and medications. Rest and keep warm. Give antihistamines to fight allergies. Take vitamin C and vitamin P to improve the fragility of capillary wall, hemostasis, anti-infection and other symptomatic treatment.

Following are the exclusion criteria. (a) No parallel or animal studies. (b) Patients have serious complication, infection and other acute and chronic serious heart and lung disease. (c) The control group also used Chinese medicine decoction, compound Chinese patent medicine, single Chinese medicine and so on. (d) The observation indicators did not include clinical total effective rate/ 24-hour urine protein quantitative / Urine erythrocyte count and other indicators reflecting the efficacy. (e) Retrospective study, experience summary, case report, etc. (f) Summary and only abstract without full text and data.

2.3. Study Selection and Data Extraction

A unified table was developed by two evaluators to extract data from the included literature, based on the inclusive and exclusive criteria through titles and abstracts. The parts expressed in tabular form were the first author, publication year, study design, demographic characteristics, number and intervention measures of patients enrolled in trial and control group, duration of intervention and follow-up, main outcome measures (the total effective rate/24-hour urine protein

ration/Urine erythrocyte count), side-effects. The consensus was reached by consulting the third investigator when disagreements happened.

2.4. Outcome Measurements

To evaluate the efficacy and safety of Chinese plus Western medicine, the ratio of recovery significant effect, effective rate is called total effective rate.

(1) Recovery: clinical symptoms and signs decreased $\geq 90\%$, urine sediment erythrocyte and/or 24h urine protein quantitative normal.

Significant effect: clinical symptoms and signs were reduced by $75\% \sim 90\%$, urine sediment erythrocyte decreased by ≥ 3 /HP and/or 24-hour urine protein ration decreased by $\geq 50\%$.

Effective: clinical symptoms and signs decreased in $50\% \sim 75\%$, urine sediment erythrocyte decreased ≥ 2 /HP and/or 24-hour urine protein ration decreased by 25% to 50% . Different studies had their own definition of complete and partial remission, but all of them used the reduction of urinary protein as the indicator.

(2) 24-hour urine protein ration and Urine erythrocyte count.

(3) The safety index were the incidence of adverse reactions during treatment and follow-up.

2.5. Quality Assessment and Data Synthesis

Since the selected articles were all involved Chinese medicine, the JADAD Scale, which considered the randomization, blinding, follow-up, was used to assess the quality of studies that was scored from 0 to 5 by two investigators. At the same time, the Distribution of hidden is evaluated. 0-2 was classified as low quality, 3-5 were classified as high quality studies. All scores were over 2, suggesting that their outcomes were convictive.

Risk ratios (RR) with its 95% confidence interval (CI) were analyzed for dichotomous outcomes, while the mean difference (MD) was chosen for continuous variables, described with a 95%CI. R version 3.5.0 was used to conduct meta-analysis. We applied a random-effect model or a fixed-effect analysis depending on I^2 and P which was to measure the heterogeneity. The effective and adverse rate are combined and tested with the escale and rma. uni functions of the R metafor. 24-hour urine protein ration and Urine erythrocyte count mean with the metacont function of the R metafor. If the results show a statistical difference, the potential publication bias will be analyzed by "funnel plot". Funnel plot are tested by regtest function. If the graph is symmetrical, there will be no effect of publication bias. If the graph is asymmetric, there is publication bias. At last, mixed effect models were used to analyze heterogeneity in studies with high heterogeneity. Studies with high heterogeneity were analyzed for heterogeneity.

3. Results

3.1. Basic Characteristics of Included Studies

A total of 7,394 children in the 92 studies were included in the systematic evaluation, all of whom were aged from 2 to 15 years old. All studies described and compared the baseline conditions of children in the experimental group and the control group in terms of age, sex ratio, disease course, with statistical significance between the two groups ($P>0.05$). On

the whole, the study showed good inter-group equilibrium and comparability ($P>0.05$). The experimental group of 44 studies was treated with proprietary Chinese medicine capsules, tablets and injections, and the remaining 48 studies were treated with traditional Chinese medicine decoction. Western medicine in the control group was treated with glucocorticoids, including 11 studies that added CTX and other immunosuppressor, with the basic treatment measures in all studies were basically the same.

Table 1. Basic characteristics of included studies.

Study	Baseline: M/F (n), age (Y)		Interventions	outcome							Jadad
	Trial	control		Trial	control	randomization	hidden	blinding	Withdrawal	score	
Lu XD 2019 [10]	27/17 8.04±1.81	24/20 6.16±1.59	Bupi Liangxue Huoxue Decoction 3 months + prednisone 1mg/(kg.d) 7days	prednisone 1mg/(kg.d) 7 days	(1)(4)	random number table	unclear the exact allocation	unclear	No one	3	
Yi HL 2019 [11]	39/21 9.23±2.45	38/22 9.35±2.17	Huoxue Huayu Decoction +prednisone 0.5mg/(kg.d) 4 weeks	prednisone 0.5mg/(kg.d) 4 weeks	(1)(4)	random number table	unclear the exact allocation	unclear	No one	3	
Qin YF 2019 [12]	37/29 8.49±5.78	38/30 6.25±3.78	Jiawei Xijiao Dihuang Decoction 3 months+ Prednisone acetate tablets1.5-2mg/(kg.d) 3 months	Prednisone acetate tablets1.5-2mg/(kg. d) 3 month	(1)(2)	random number table	unclear the exact allocation	unclear	specify	3	
Niu DC 2019 [13]	28/18 8.42±2.05	27/19 8.73±1.96	TWP 0.5mg/kg.bid/d 2months + Methyl prednisolone 15~20mg/kg iv.dirp 7days	Methyl prednisolone 15~20mg/kg iv.dirp 7days	(1)(4)	random number table	unclear the exact allocation	unclear	No one	3	
Zhu W 2019 [14]	27/13 7.25±1.23	25/15 7.32±1.25	TWP2.0mg/(kg.d) 3months +Prednisone acetate tablets 1mg/(kg.d) 7days	Prednisone acetate tablets 1mg/(kg.d) 7days	(1)(4)	random number table	unclear the exact allocation	unclear	No one	3	
Ma L 2019 [15]	26/17 7.01±1.28	26/16 7.24±1.09	Qingre Liangxue Huayu Decoction 3~6months+ prednisone 1~2mg/(kg.d) 3months	prednisone 1~2mg/(kg.d) 3months	(1)	random number table	unclear the exact allocation	unclear	No one	3	
Huo LJ 2019 [16]	22/19 8.25±2.34	21/18 8.85±1.94	Shenyankangfupian 6 weeks + prednisone	prednisone	(1)(4)	random number table	unclear the exact allocation	unclear	No one	3	
Ding LJ 2019 [17]	25/13 8.5±3.3	24/14 8.4±3.1	Qingre liangxue Jiedu Decoction + prednisone 1mg/(kg.d) 2weeks	prednisone 1mg/(kg.d) 2weeks	(1)	random number table	unclear the exact allocation	unclear	No one	3	
Li Y 2018 [18]	18/12 7.50±0.07	17/13 7.02±0.10	Corbrin Capsule 0.4-0.6g tid/d + prednisone 1.5mg/(kg.d) 4weeks	prednisone 1.5mg/(kg.d) 4weeks	(2)(4)	random number table	unclear the exact allocation	unclear	No one	3	
Hunag GC 2018 [19]	46/32 8.6±2.3	44/34 9.6±2.4	TWP 1.5mg/(kg.d)+Qingre Zhixue Decoction 12weeks+Xiangdan injection 0.5ml/(kg.d) 2weeks+prednisone 1.0mg/(kg.d) 12weeks	prednisone 1.0mg/(kg.d) 12weeks	(1)(2)(3)	random number table	unclear the exact allocation	unclear	No one	3	
Liu XS 2018 [20]	47/21 9.2±2.11	45/23 9.3±2.24	Shipyin Decoction+prednisone 0.5~1.0mg/(kg.d) 16weeks	prednisone 0.5~1.0mg/(kg.d) 16weeks	(1)(2)(3)(4)	random number table	unclear the exact allocation	unclear	No one	3	
Wu HJ 2018 [21]	28/21 6.80±2.15	30/19 6.82±2.06	TWP+prednisone	prednisone	(1)(4)	random number table	unclear the exact allocation	unclear	No one	3	
Huang XH 2018 [22]	24/17 6.9±1.6	22/19 6.7±1.5	Yupingfeng granules5g.tid/d+1-20mg/kg methylprednisolone iv.dirp + CTX 10mg/(kg.d) iv.dirp 6months	1-20mg/kg methylprednisolone iv.dirp + CTX 10mg/(kg.d) iv.dirp 6months	(1)(2)(4)	random number table	unclear the exact allocation	unclear	No one	3	
Yang QY 2017 [23]	24/14 6.79±1.42	22/16 6.85±1.53	TWP1.5mg/(kg.d) 12weeks+Prednisolone 1.5mg/(kg.d) a week	Prednisolone 1.5mg/(kg.d) a week	(1)	random number table	unclear the exact allocation	unclear	No one	3	
Wang HN 2017 [24]	22/21 7.34±2.04	23/20 7.13±2.12	TWP1.0mg/(kg.d)+Prednisolone acetate tablet 1.5-2mg/(kg.d)	Prednisolone acetate tablet	(1)	random number table	unclear the exact	unclear	No one	3	

Study	Baseline: M/F (n), age (Y)		Interventions	outcome						Jadad
	Trial	control	Trial	control		randomization	hidden	blinding	Withdrawal	score
			12weeks	1.5-2mg/(kg.d)			allocation			
Zhang L 2017 [25]	20/15 6.92±1.48	19/16 7.08±1.54	TWP1.0mg/(kg.d)+Prednisolone 1.5-2mg/(kg.d) 8weeks	Prednisolone 1.5-2mg/(kg.d) 8weeks	(1)	random number table	unclear the exact allocation	unclear	No one	3
Liu DF 2017 [26]	25/20 6.81±2.14	26/19 6.31±2.05	TWP1.0mg/(kg.d) 3~6months+Prednisolone 1.5-2mg/(kg.d) 8weeks	Prednisolone 1.5-2mg/(kg.d) 8weeks	(1)(4)	random number table	unclear the exact allocation	unclear	No one	3
Liu XG 2016 [27]	18/14 8.03±4.29	17/15 7.98±3.60	Corbrin Capsule 0.4-0.6 tid/d + prednisone 1.5mg/(kg.d) 4weeks	prednisone 1.5mg/(kg.d) 4weeks	(2)	random number table	unclear the exact allocation	unclear	No one	3
Li J 2016 [28]	18/14 7.7±1.3	19/12 8.3±2.1	TWP1.0~1.5mg/(kg.d)+prednisone 12weeks	prednisone 12weeks	(1)(4)	random number table	unclear the exact allocation	unclear	No one	3
Sun ZH 2016 [29]	16/20 9.1±3.8	17/19 9.2±3.7	Fushen Decoction + prednisone 0.5mg~2mg/(kg.d) 2months	prednisone 0.5mg~2mg/(kg.d) 2months	(1)(2)	random number table	unclear the exact allocation	unclear	No one	3
Zhao QW 2016 [30]	62/28 6.8±0.4		Abelmosk capsule tid/d+prednisone+CTX 8 weeks	prednisone+CTX 8 weeks	(1)	random number table	unclear the exact allocation	unclear	No one	3
He JM 2016 [31]	21/15 7.2±2.1	19/18 7.6±2.6	Liangxue Shenyu Decoction p.o+Prednisolone 30mg/(kg.d) iv.dirp 3weeks	Prednisolone 30mg/(kg.d) iv.dirp 3weeks	(1)(2)(3)	random number table	unclear the exact allocation	unclear	No one	3
Gu MM 2016 [32]	19/15 7.15±1.86	18/16 7.24±1.92	Liangxue Xiaoban granules 4 weeks+ Prednisolone	Prednisolone	(1)(4)	random number table	unclear the exact allocation	unclear	No one	3
Liu XY 2016 [33]	23/27 6.5±2.4		TWP1.0mg/(kg.d)+Prednisolone 3 months	Prednisolone 3 months	(1)(4)	random number table	unclear the exact allocation	unclear	No one	3
Yin HW 2016 [34]	35/39 6.2±1.1		TWP1.0mg/(kg.d)+Prednisolone 0.5-2mg/(kg.d) 3months	Prednisolone 0.5-2mg/(kg.d) 3months	(1)(4)	random number table	unclear the exact allocation	unclear	No one	3
Zhang XP 2016 [35]	18/12 7.8±3.32	16/14 8.19±3.36	Xiaodian Decoction+Prednisolone 0.5-1.0mg/(kg.d) 6weeks	Prednisolone 0.5-1.0mg/(kg.d) 6weeks	(1)(2)(3)(4)	random number table	unclear the exact allocation	unclear	No one	3
Liu FJ 2015 [36]	68/40 10.1±3.5	44/40 10.3±3.7	Chinese herbs +prednisone 0.4-1mg/(kg.d) 10 weeks	prednisone 0.4-1mg/(kg.d) 10 weeks	(1)(2)(4)	random number table	unclear the exact allocation	unclear	No one	3
Lu W 2015 [37]	12/8 8.71±5.02	9/11 8.12±4.35	Huaiqihaung granules+prednisone 1 month	prednisone 1 month	(1)(4)	random number table	unclear the exact allocation	unclear	No one	3
§Zhang SS 2015 [38]	26/14 9.2	24/16 9.0	TWP1.0mg/(kg.d)+prednisone 0.5-1mg/(kg.d) 3months	prednisone 0.5-1mg/(kg.d) 3months	(1)(3)	random number table	unclear the exact allocation	unclear	No one	3
	27/13 9.7		TWP1.0mg/(kg.d)+Chinese herbs 3 months							
Sun ZM 2015 [39]	25/17 8.6±2.4	26/15 8.5±2.2	TWP1.0mg/(kg.d)+prednisone 3months	prednisone 3months	(1)(2)(3)(4)	random number table	unclear the exact allocation	unclear	No one	3
Zhao F 2015 [40]	21/19 5.2±3.1	23/17 6.2±2.1	TWP1.0mg/(kg.d)+prednisone 1.5-2.0mg/(kg.d) 3months	prednisone 1.5-2.0mg/(kg.d) 3months	(1)	random number table	unclear the exact allocation	unclear	No one	3
Liu BZ 2015 [41]	18/22 8.1±2.5	16/24 7.8±3.2	Taohong Siwu Decoction methylprednisolone 1.5mg/(kg.d) 2 weeks	methylprednisolone 1.5mg/(kg.d) 2weeks	(1)	random number table	unclear the exact allocation	unclear	No one	3
Wu HM 2015 [42]	60/36 8.2		Qiong Danshen injection triazine 2.5~5ml/d+prednisolone acetate 1.5-2.0mg/(kg.d) 8 weeks	prednisolone acetate 1.5-2.0mg/(kg.d) 8 weeks	(1)(2)(3)	random number table	unclear the exact allocation	unclear	No one	3
Lin SX 2015 [43]	161/42 4.2±0.6		Yishen Jianpi Huoxue Decoction+prednisone 1.8-8.0mg/(kg.d) 4 weeks	prednisone 1.8-8.0mg/(kg.d) 4 weeks	(1)(2)	random number table	unclear the exact allocation	unclear	No one	3
Mao GR 2014 [44]	19/13 4~14	20/12 4~14	Shengyang Yiwei Decoction + prednisone 0.5-2.0mg/(kg.d) 3	prednisone 0.5-2.0mg/(kg.d) 3	(1)	random number table	unclear the exact	unclear	No one	3

Study	Baseline: M/F (n), age (Y)		Interventions	outcome							Jadad
	Trial	control	Trial	control		randomization	hidden	blinding	Withdrawal	score	
Guo WG 2014 [45]	17/15 7.9	14/18 8.1	months Qiong Danshen injection triazine 2.5~5ml/d +prednisolone acetate 0.5-2.0mg/(kg.d) 8 weeks	months prednisolone acetate 0.5-2.0mg/(kg.d) 8 weeks	(1)(2)(3)	random number table	unclear the exact allocation	unclear	No one	3	
§Qiu XY 2014 [46]	18/13 8.5±3.9	17/14 8.3±3.7	Compound Danshen injection+glucocorticoids 3months	glucocorticoids 3months	(1)(2)(3)	random number table	unclear the exact allocation	unclear	No one	3	
	17/14 8.2±4.0		Compound Danshen injection+nadroparin calcium+glucocorticoids 3months								
Peng YH 2014 [47]	16/12 7.10±5.12	15/11 7.15±4.79	Huaiqihaung granules+ prednisone 1.0-2.0mg/(kg.d) 3 months	prednisone 1.0-2.0mg/(kg.d) 3 months	(1)	random number table	unclear the exact allocation	unclear	No one	3	
Xiang M 2014 [48]	12/9 6.36±3.21	10/11 6.82±3.36	TWP1.0mg/(kg.d)+glucocorticoids 3months	glucocorticoids 3months	(1)(4)	random number table	unclear the exact allocation	unclear	No one	3	
Li BN 2014 [49]	45/40 2~14		TWP1.0~1.5mg/(kg.d)+prednisone 2.0mg/(kg.d) 12weeks	prednisone 2.0mg/(kg.d) 12weeks	(2)	random number table	unclear the exact allocation	unclear	No one	3	
Li P 2014 [50]	19/13 6.8±3.3	21/14 7.1±3.6	TWP1.0mg/(kg.d)+prednisolone acetate 1.0mg/(kg.d) 3months	prednisolone acetate 1.0mg/(kg.d) 3months	(1)	random number table	unclear the exact allocation	unclear	No one	3	
Wang P 2014 [51]	15/13 10.78±2.05	14/14 11.22±1.98	Xiaodian Shenfu Decoction+ glucocorticoids 4weeks	glucocorticoids 4weeks	(1)(2)(3)	random number table	unclear the exact allocation	unclear	No one	3	
Wu H 2014 [52]	22/18 6.4±3.2	20/18 6.6±3.3	TWP1.0mg/(kg.d)+prednisone 0.5-2mg/(kg.d) 3months	prednisone 0.5-2mg/(kg.d) 3months	(1)(4)	random number table	unclear the exact allocation	unclear	No one	3	
Wang J 2014 [53]	19/17 8.6±2.7	21/15 8.7±2.8	Yishen Jianpi Qushi Huoxue Decoction+ prednisone 0.5-2mg/(kg.d) 3months	prednisone 0.5-2mg/(kg.d) 3months	(1)(2)(3)(4)	random number table	unclear the exact allocation	unclear	No one	3	
Wu YH 2014 [54]	34/21 5~14		Zidian Shenyan Decoction+prednisone 3months	prednisone 3months	(1)	random number table	unclear the exact allocation	single-blind	specify	4	
Han DX 2014 [55]	42/31 7.3±2.4		Huaiqihaung granules+ prednisone 1.0mg/(kg.d) +CTX 6 weeks	prednisone 1.0mg/(kg.d) +CTX 6 weeks	(1)(2)(3)(4)	random number table	unclear the exact allocation	unclear	No one	3	
Gong BX 2014 [56]	35/24 8.6±4.2	33/26 9.0±4.8	Huoxue Huayu Decoction +methylprednisolone 1.0mg/(kg.d) +CTX 8 weeks	methylprednisolone 1.0mg/(kg.d) +CTX 8 weeks	(1)(2)(3)(4)	random number table	unclear the exact allocation	unclear	No one	3	
Cheng L 2014 [57]	23/15 8.84±4.23	22/16 8.19±5.03	Yishen Jianpi Huoxue Decoction+prednisone 1.5mg/(kg.d) 4 weeks	prednisone 1.5mg/(kg.d) 4 weeks	(1)(2)(3)	random number table	unclear the exact allocation	unclear	No one	3	
Liu YZ 2014 [58]	15/15 7.4±2.4	18/12 6.8±2.6	Yishen Jianpi Huoxue Decoction+ prednisone 1.5~2.0mg/(kg.d) 4 weeks	prednisone 1.5~2.0mg/(kg.d) 4 weeks	(1)(2)	random number table	unclear the exact allocation	unclear	No one	3	
Shi ZM 2014 [59]	15/15 8.0±0.5	12/18 7.0±1.5	Huoxue Huayu Decoction +prednisone 1.0~2.0mg/(kg.d) 4 weeks	prednisone 1.0~2.0mg/(kg.d) 4 weeks	(1)	random number table	unclear the exact allocation	unclear	No one	3	
			Bupi Yiqi Liangxue Huoxue								
Zhao YX 2013 [60]	20/12 12.9	18/14 11.7	Decoction+ hexadecadrol 1.0~2.0mg/(kg.d) 4 weeks	hexadecadrol 1.0~2.0mg/(kg.d) 4 weeks	(1)	random number table	unclear the exact allocation	unclear	No one	3	
Huang T 2013 [61]	35/33 6.32±2.18		Tanshinone IIA iv.dirp+prednisone 2.0mg/(kg.d) 3 months	prednisone 2.0mg/(kg.d) 3 months	(1)(2)(3)(4)	random number table	unclear the exact allocation	unclear	No one	3	
He GX 2013 [62]	32/24 3.5±2.5		Kangmin Xiaoban Decoction+prednisone 2.0mg/(kg.d) 4 weeks	prednisone 2.0mg/(kg.d) 4 weeks	(1)(2)(3)	random number table	unclear the exact allocation	unclear	No one	3	
Zeng LL 2013 [63]	33/41 6.1±2.6		TWP1.5~2.0mg/(kg.d)+prednisone 1.5~2.0mg/(kg.d) 3months	prednisone 1.5~2.0mg/(kg.d) 3months	(1)	random number table	unclear the exact allocation	unclear	No one	3	

Study	Baseline: M/F (n), age (Y)		Interventions	outcome							Jadad
	Trial	control	Trial	control		randomization	hidden	blinding	Withdrawal	score	
Yan HQ 2013 [64]	24/21 7.32±2.08	25/20 6.98±2.18	TWP1.0mg/(kg.d)+prednisone 0.5~2.0mg/(kg.d) 3months	prednisone0.5~2.0 mg/(kg.d) 3months	(1)(4)	random number table	unclear the exact allocation	unclear	No one	3	
Jiang JP 2013[65]	20/14 7.23±3.53	19/14 7.09±3.84	Qingre Zhuyu Decoction+prednisone0.5~2.0 mg/(kg.d) 3months	prednisone 0.5~2.0mg/(kg.d) 3months	(1)	random number table	unclear the exact allocation	unclear	No one	3	
Deng BZ 2013[66]	10/6 13.8	9/7 13.3	Xiaodian Decoction+prednisone 8 weeks	prednisone 8 weeks	(1)(2)(4)	random number table	unclear the exact allocation	unclear	No one	3	
Li MY 2013 [67]	14/12 6.2	13/7 7.5	Chinese herbs +prednisone 1.0~2.0mg/(kg.d) 8 weeks	prednisone 1.0~2.0mg/(kg.d) 8 weeks	(1)	random number table	unclear the exact allocation	unclear	No one	3	
Jin JW 2013 [68]	22/20 9.0±1.8	21/20 9.1±1.8	Yuduqing Decoction+glucocorticoids+CT X 12weeks	glucocorticoids+CT X 12weeks	(1)	random number table	unclear the exact allocation	unclear	No one	3	
Yuan PZ 2013 [69]	19/15 4~15	20/15 5~14	Zidian Shengkang Decoction+glucocorticoids 8weeks	glucocorticoids 8weeks	(1)	random number table	unclear the exact allocation	unclear	No one	3	
Wang YJ 2012 [70]	30/20 6.36±3.21	26/28 6.82±3.36	TWP1.0mg/(kg.d)+prednisone 0.5~2.0mg/(kg.d) 3 months	prednisone0.5~2.0 mg/(kg.d) 3 months	(1)	random number table	unclear the exact allocation	unclear	No one	3	
Ji RW 2012 [71]	21/14 10.8	20/15 9.6	Yiqi Yangyang Huoxue Decoction+ prednisone1.0mg/(kg.d) 4 weeks	prednisone1.0mg/(k g.d) 4 weeks	(1)	random number table	unclear the exact allocation	unclear	No one	3	
Li YE 2011 [72]	18/12 15	19/11 14	Qingshen liangxue Decoction+ prednisone 1.0~2.0mg/(kg.d) 4 weeks	prednisone 1.0~2.0mg/(kg.d) 4 weeks	(1)	random number table	unclear the exact allocation	unclear	No one	3	
Chen CL 2011 [73]	19/14 8.1±3.7	18/13 8.7±2.9	Compound Danshen injection+nadroparin calcium+glucocorticoids 3months	glucocorticoids 3months	(1)	random number table	unclear the exact allocation	unclear	No one	3	
Pang FM 2011[74]	25/9 7.5	23/7 8.0	TWP1.0mg/(kg.d)+prednisone0 .5~2.0mg/(kg.d) 3 months	prednisone0.5~2.0 mg/(kg.d) 3 months	(1)	random number table	unclear the exact allocation	unclear	No one	3	
Pei HB 2011 [75]	20/17 7.0±1.0	20/15 7.2±1.2	Shenggyang Sanhuo Decoction+prednisone1.0mg/(k g.d) 4weeks	prednisone1.0mg/(k g.d) 4 weeks	(1)(2)(4)	random number table	unclear the exact allocation	unclear	No one	3	
Wang CF 2011 [76]	128/84 10.1±3.27	114/98 9.5±3.87	Yishen granules+glucocorticoids+CTX 6 months	glucocorticoids+CT X 6 months	(1)	random number table	unclear the exact allocation	unclear	No one	3	
Guo YH 2011 [77]	27/33 4~14		Zidian Shenyan Decoction+prednisone 0.5~2.0mg/(kg.d) 3 months	prednisone 0.5~2.0mg/(kg.d) 3months	(1)	random number table	unclear the exact allocation	unclear	No one	3	
Li JC 2011 [78]	18/12 5~14	16/14 5~14	Chinese herbs +glucocorticoids 1month	glucocorticoids 1month	(1)	random number table	unclear the exact allocation	unclear	No one	3	
Zhao ZY 2011 [79]	26/14 8.2	12/8 8.1	Yishen Decoction+glucocorticoids+CT X 12weeks	glucocorticoids+CT X 12weeks	(1)(2)(3)	random number table	unclear the exact allocation	unclear	No one	3	
Peng HP 2011 [80]	17/33 2~15		Chinese herbs +glucocorticoids+CTX 4weeks	glucocorticoids+CT X 4weeks	(1)	random number table	unclear the exact allocation	unclear	No one	3	
Zhao YD 2011 [81]	16/14 3~16	19/11 3~16	Chinese herbs +prednisone 1.0mg/(kg.d) 2 months	prednisone 1.0mg/(kg.d) 2 months	(1)(4)	random number table	unclear the exact allocation	unclear	No one	3	
Hao JJ 2011 [82]	60/24 9.7±3.9	54/24 8.9±4.8	TWP1.5mg/(kg.d)+prednisone 0.5~2.0mg/(kg.d) 4 months	prednisone0.5~2.0 mg/(kg.d) 4 months	(1)(2)(3)	random number table	unclear the exact allocation	unclear	No one	3	
Lu J 2010 [83]	25/17 8.5	23/17 9.1	Liangxue Huoxue Huayu Decoction+ glucocorticoids 4weeks	glucocorticoids 4weeks	(1)	random number table	unclear the exact allocation	unclear	No one	3	
Chen ZH 2010 [84]	22/16 8.3±2.6	18/14 8.2±2.8	Chinese herbs +prednisone 1.0~2.0mg/(kg.d) 4 weeks	prednisone 1.0~2.0mg/(kg.d) 4 weeks	(1)(2)(3)(4)	random number table	unclear the exact allocation	unclear	No one	3	

Study	Baseline: M/F (n), age (Y)		Interventions	outcome							Jadad
	Trial	control	Trial	control		randomization	hidden	blinding	Withdrawal	score	
Yu FM 2010 [85]	12/16 14	17/11 14	Zidian Decoction+prednisone 1.0mg/(kg.d) 4 weeks	prednisone 1.0mg/(kg.d) 4 weeks	(1)	random number table	unclear the exact allocation	unclear	No one	3	
Zhang TD 2010 [86]	18/12 15	19/11 14	Xijiao Dihaung Decoction +prednisone 1.0~2.0mg/(kg.d) 4 weeks	prednisone 1.0~2.0mg/(kg.d) 4 weeks	(1)	random number table	unclear the exact allocation	unclear	No one	3	
Guo QY 2009 [87]	30/12 9.7±3.9	27/12 8.9±4.8	TWP+Chinese herbs +prednisone 2.0mg/(kg.d) 4 months	prednisone 2.0mg/(kg.d) 4 months	(1)(2)(3)	random number table	unclear the exact allocation	unclear	No one	3	
Huang QY 2009[88]	18/13 7.9±2.4	13/17 8.5±2.3	TWP+nadroparin calcium+glucocorticoids 2 weeks	glucocorticoids 2 weeks	(1)	random number table	unclear the exact allocation	unclear	No one	3	
Chen CB 2009 [89]	10/7 8.2	10/9 8.0	TWP+glucocorticoids+CTX 3 months	glucocorticoids+CT X 3 months	(1)(4)	random number table	unclear the exact allocation	unclear	No one	3	
Ma XC 2009 [90]	17/13 2~15	10/10 2~15	Shenyankang granule+glucocorticoids 4 weeks	glucocorticoids 4 weeks	(1)	random number table	unclear the exact allocation	unclear	No one	3	
Li G 2009 [91]	17/7 10		Chinese herbs+glucocorticoids 4 weeks	glucocorticoids 4 weeks	(1)	random number table	unclear the exact allocation	unclear	No one	3	
Huang WY 2009 [92]	21/14 5~15	18/12 4~14	Chinese herbs+glucocorticoids 4 weeks	glucocorticoids 4 weeks	(1)	random number table	unclear the exact allocation	unclear	No one	3	
Wu ZC 2009 [93]	50/42 9.2		Chinese herbs+prednisone 2.0mg/(kg.d) 10 days	prednisone 2.0mg/(kg.d) 10 days	(1)	random number table	unclear the exact allocation	unclear	No one	3	
Wang J 2009 [94]	17/11 7.8±2.6	18/12 8.2±2.8	Yishen Jianpi Huoxue Decoction+ prednisone 1.5~2.0mg/(kg.d) 4 weeks	prednisone 1.5~2.0mg/(kg.d) 4 weeks	(1)(2)(3)	random number table	unclear the exact allocation	unclear	No one	3	
Wang JL 2007 [95]	21/15 9.5	19/14 9.7	Chinese herbs+prednisone 0.5~2.0mg/(kg.d) 8 weeks	prednisone 0.5~2.0mg/(kg.d) 8 weeks	(1)(2)(3)	random number table	unclear the exact allocation	unclear	No one	3	
Wang YL 2007 [96]	33/23 7.20±3.92	29/21 7.90±3.58	TWP1.0mg/(kg.d)+prednisone 0.5~2.0mg/(kg.d) 12 weeks	prednisone0.5~2.0 mg/(kg.d) 12 weeks	(1)	random number table	unclear the exact allocation	unclear	No one	3	
Fan WW 2007 [97]	15/8 8.2	13/8 9.1	Qingre Huayu Shufeng Decoction+prednisone 0.8~1.0mg/(kg.d) 3 months	prednisone 0.8~1.0mg/(kg.d) 3 months	(1)(2)(3)	random number table	unclear the exact allocation	unclear	No one	3	
Zhang JP 2006 [98]	15/11 7.4	14/13 7.6	TWP1.0mg/(kg.d)+prednisone 1.5~2.0mg/(kg.d) 12 weeks	prednisone1.5~2.0 mg/(kg.d) 12 weeks	(1)	random number table	unclear the exact allocation	unclear	No one	3	
Chang WJ 2006 [99]	46/14 4~15	22/8 5~16	Yiqi Tonglin granules+glucocorticoids 3 months	glucocorticoids 3 months	(1)(2)(3)	random number table	unclear the exact allocation	unclear	No one	3	
Song MS 2005 [100]	18/12 9~13	19/11 8~14	Xiere Xiaoban Decoction+glucocorticoids	glucocorticoids	(1)(2)	random number table	unclear the exact allocation	unclear	No one	3	
Mao YY 2004 [101]	7/10 8.3	6/9 8.6	Zidian Shenyang Decoction+prednisone 1.5~2.0mg/(kg.d)+CTX 4 weeks	prednisone 1.5~2.0mg/(kg.d)+ CTX 4 weeks	(1)(2)(3)	random number table	unclear the exact allocation	unclear	No one	3	

(1): total effective rate (2): 24-hour urine protein ration (3): Urine erythrocyte count (4): adverse effects rate.

§ three arms trial.

3.2. Meta-Analysis

3.2.1. Effect of Combine Therapy on Total Effective Rates

89 studies described efficiency, we combined and tested the results by the escalc functions of the R metafor. As presented in figure 2, the forestplot showed the heterogeneity of each study ($P<0.01$, $I^2=38.98\%$), and the random effect model was used for analysis. Children treated with Chinese

plus Western medicine demonstrated a significant increase in total effective rates [Figure 2 RR=1.19; 95%CI (1.16–1.21), $P<0.001$] when compared with Western medicine alone. Taking total effective rate as an evaluation index, children seemed to benefit more from combined therapy. Then the 91 studies were analyzed by funnel plot with regtest function, as presented in Figure 3, $P<0.01$, the plot is not completely symmetrical, indicating publication bias.

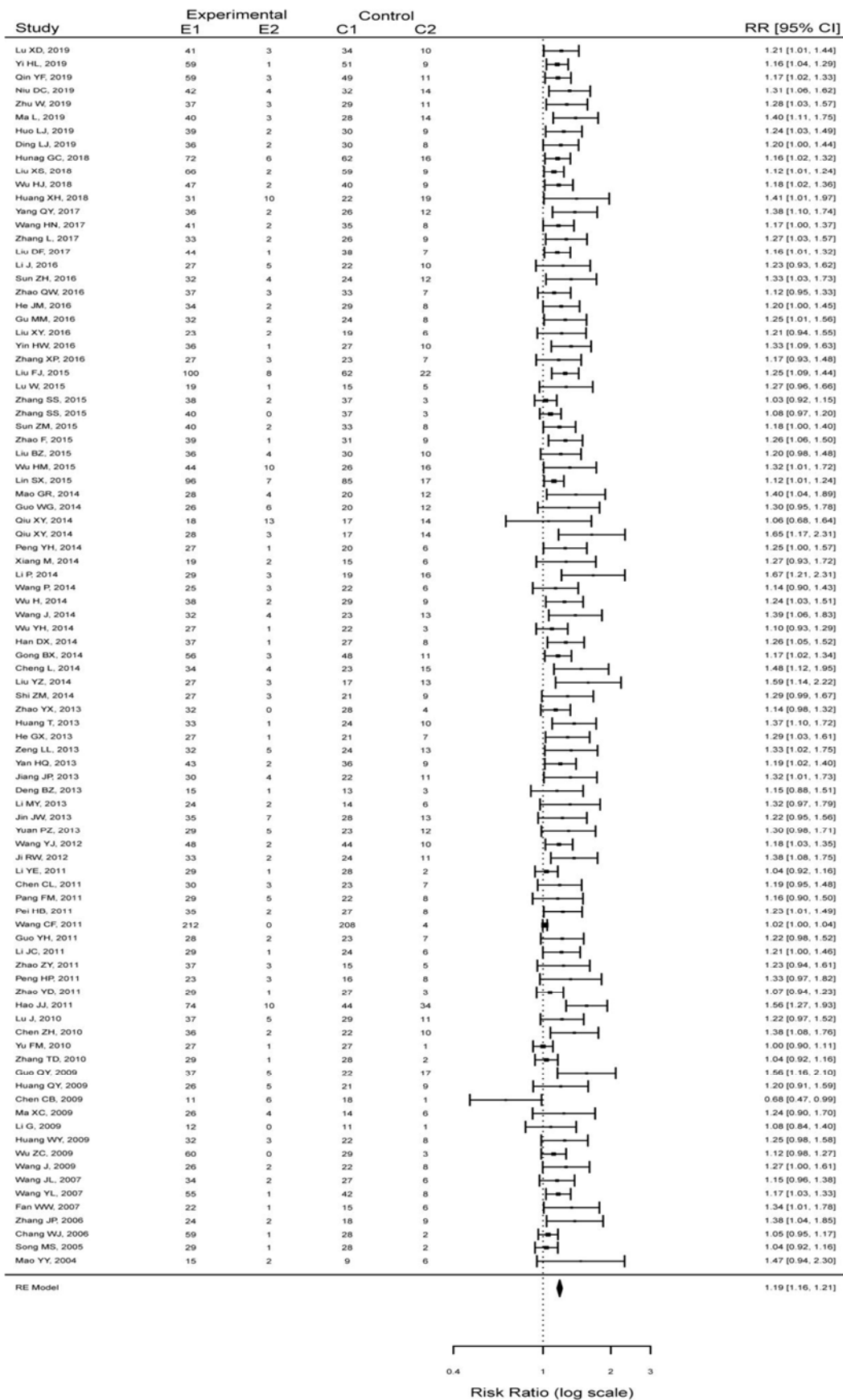


Figure 2. Forestplot for effective rate.

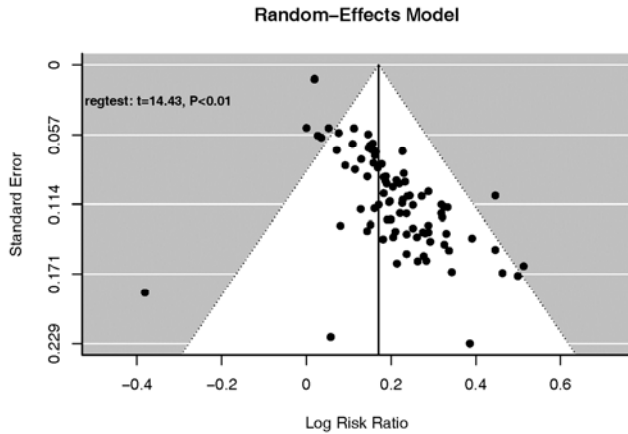


Figure 3. Funnelplot for effective rate.

3.2.2. Effect of Combined Therapy on 24-hour Urine Protein Ration Level

37 studies described 24-hour urine protein ration level, we combined and tested the results by the metacont function of the R metafor. As presented in figure 4, the forestplot showed the heterogeneity of each study ($I^2=98\%$), and the random effect model was used for analysis. Our study also found that Chinese plus Western medicine had an advantage on decreasing 24-hour urine protein [Figure 4 WMD=-0.47; 95%CI (-0.53,-0.41); $p<0.001$] when compared with Western medicine alone. We conducted funnel plot analysis of the 37 studies, as presented in Figure 5, $P<0.001$, the plot is not completely symmetrical, indicating publication bias.

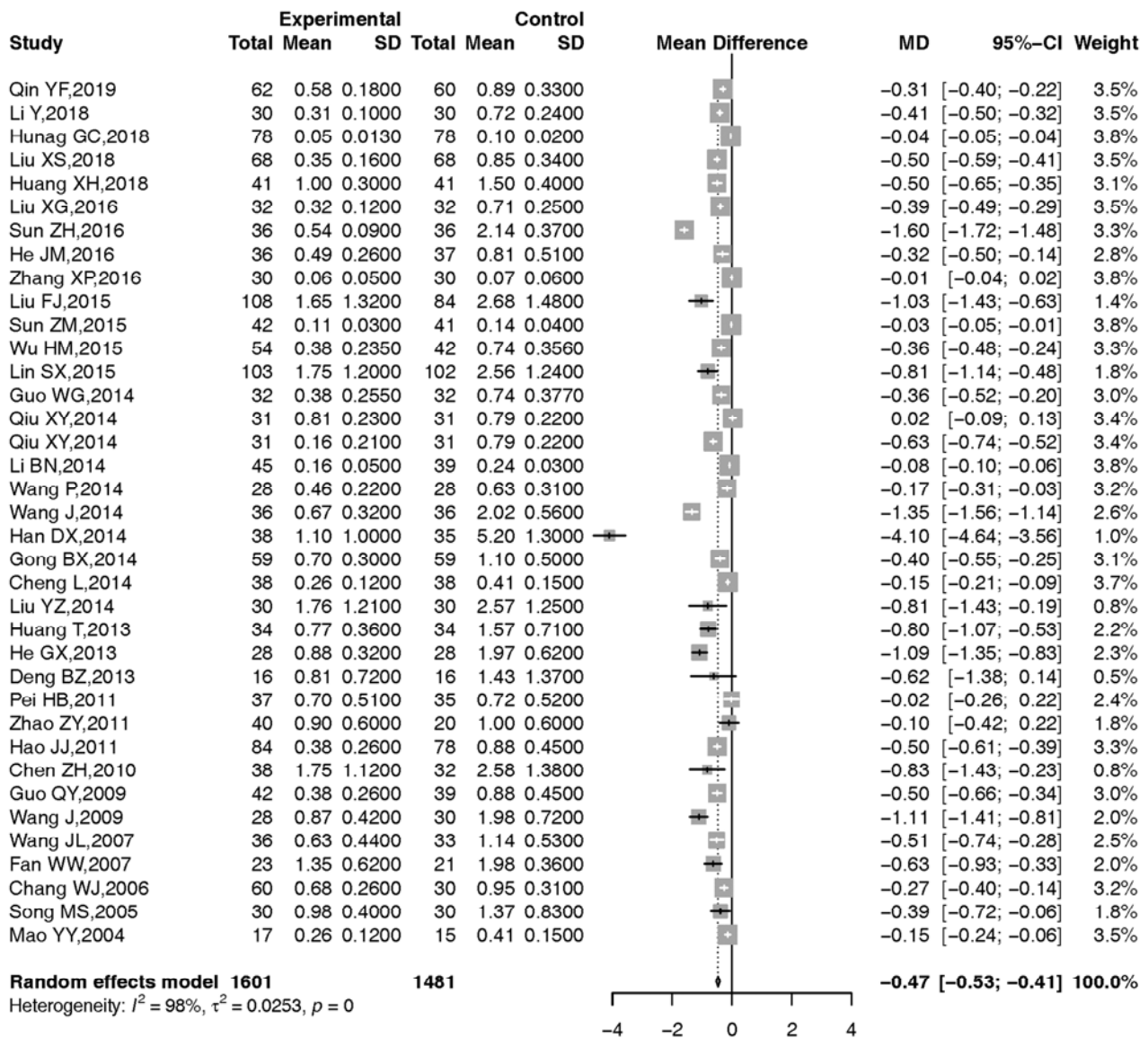


Figure 4. Forestplot for 24-hour urine protein.

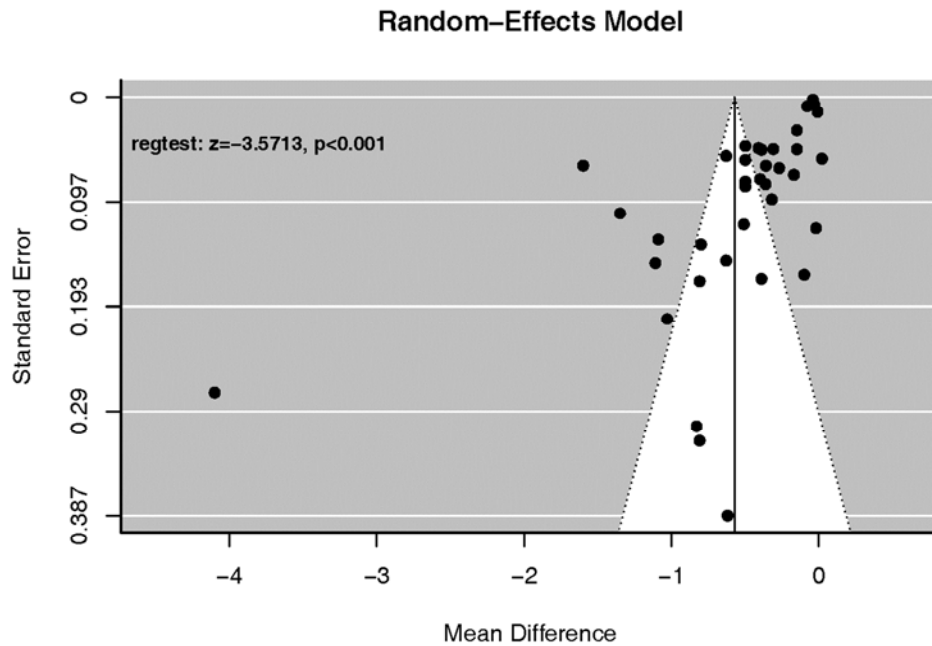


Figure 5. Funnelplot for 24-hour urine protein.

3.2.3. Effect of Combined Therapy on Urine Erythrocyte Count Level

We combined and tested the Urine erythrocyte count of 28 studies by the metacont function of the R metafor. Our study found combined therapy could significantly reduce the urine erythrocyte count [Figure 6 WMD=-8.88; 95%CI (-9.80,-7.96); $p<0.001$, random effects model] compared with the western medicine alone. Funnel plot shows that the graph is not completely symmetrical ($P=0.0119$), Figure 7, with publication bias.

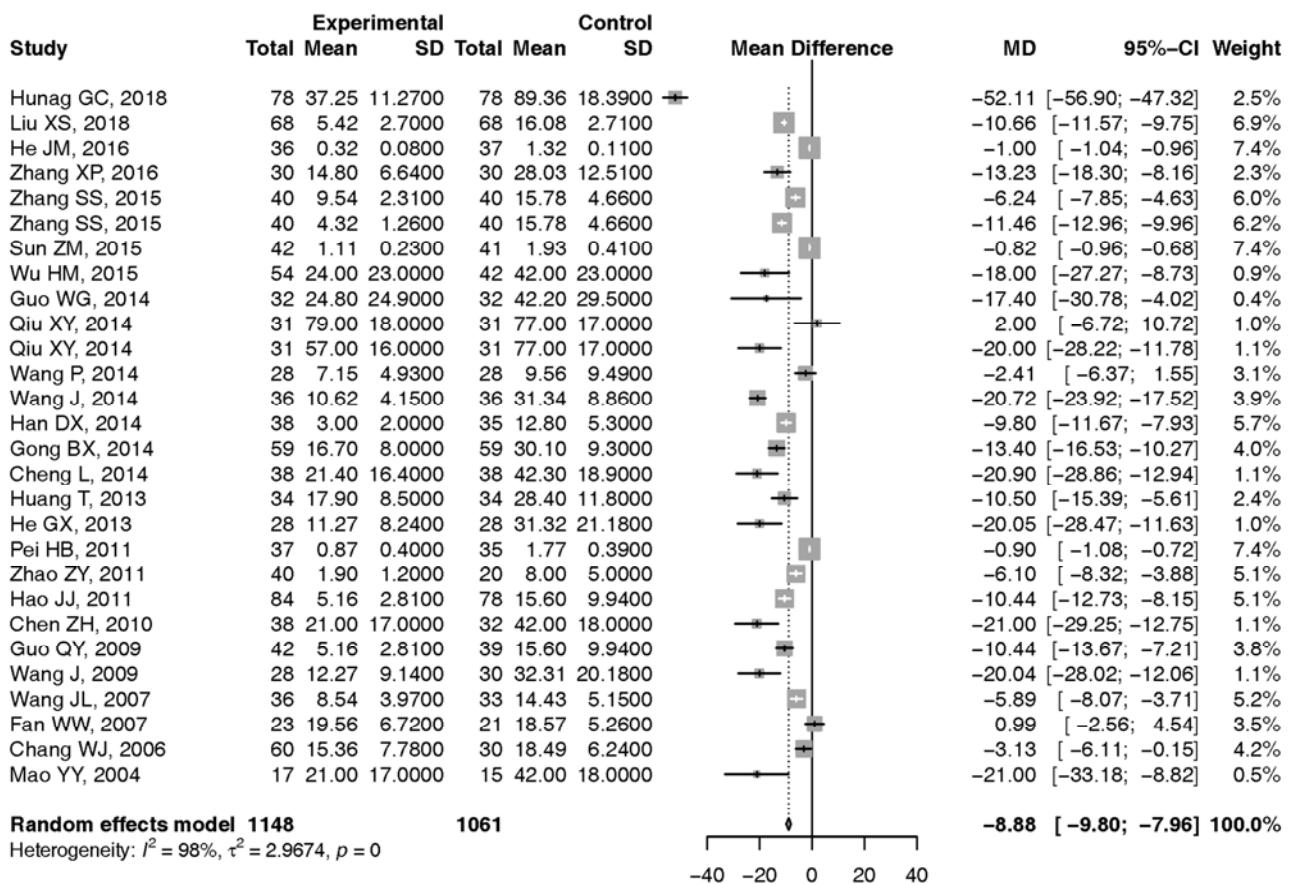


Figure 6. Forestplot for urine erythrocyte count.

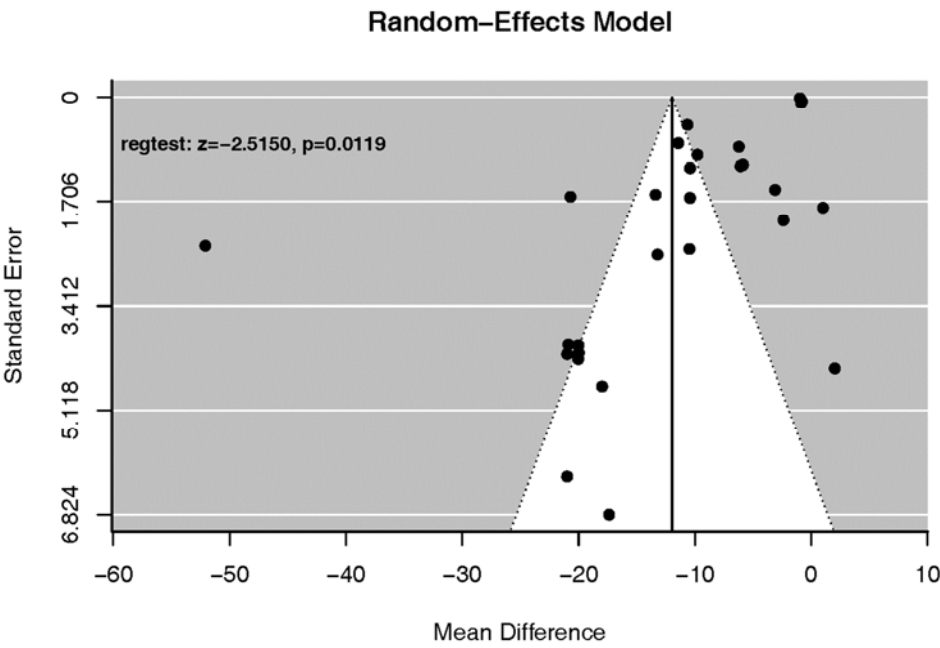


Figure 7. Funnelplot for urine erythrocyte count.

3.2.4. Adverse Effects of the Combine Therapy

30 studies reported adverse effect in the course of treatment. Heterogeneity exists in each study ($P<0.01$), the random effect model was adopted. It is proved that Chinese plus Western medicine could decrease adverse effects more effectively [Figure 8 $RR=0.64$; 95%CI (0.46, 0.87); $p<0.01$] than Western medicine alone. The funnel plot also shows the graph is basically symmetrical ($P=0.71>0.05$), figure 9, with no publication bias.

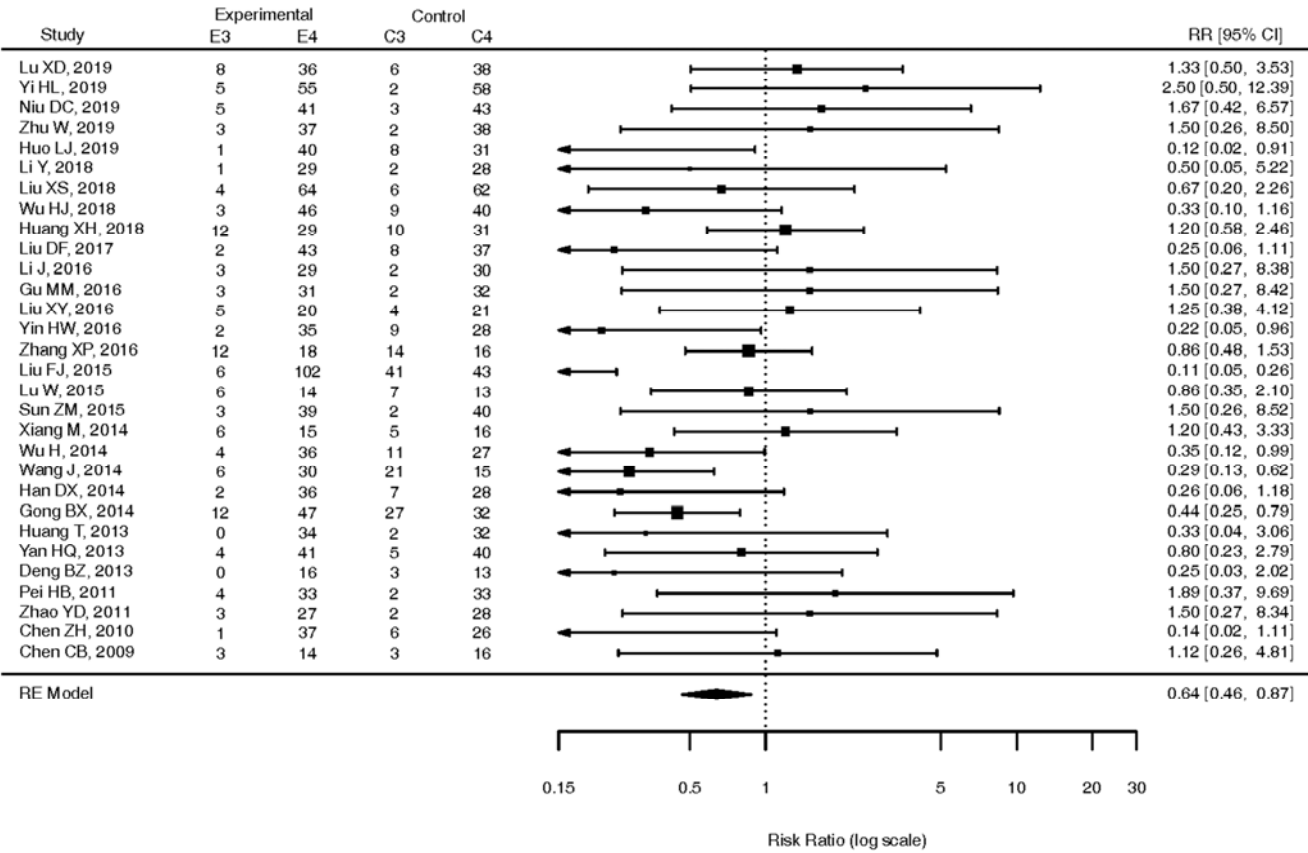


Figure 8. Forestplot for adverse rate.

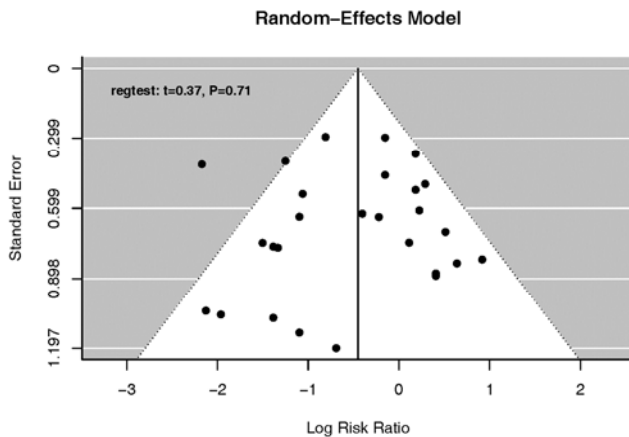


Figure 9. Funnelplot for adverse rate.

3.2.5. Heterogeneity Analysis

The main indicators, 24-hour urine protein ration, urine erythrocyte count, and adverse effect all showed high heterogeneity. We used the ratio of the number of men in the experimental group to the control group and the year of publication to fit the mixed effect model. 24-hour urine protein ration indicator shows two concomitant variables did not contribute to heterogeneity; urine erythrocyte count indicator shows two concomitant variables can explain the total heterogeneity of 5.78%, but two concomitant variable are meaningless in the model; adverse effect indicator shows two concomitant variables can explain the total heterogeneity of 4.06%, but two concomitant variables are also meaningless in the model. We tried unsuccessfully to find the source of heterogeneity. But the age and disease course of each experimental patient were basically the same between the two groups, the cause of heterogeneity is not clear, and it is preliminarily inferred that heterogeneity comes from the variation in the study.

4. Conclusion

The analysis in this study found that the integrated Chinese and Western medicine treatment for children who have HSPN was more superior in the total effective rate. Our studies also found the combined therapy could reduce the 24-hour urine protein ration level, Urine erythrocyte count and adverse rate, children could seemed to benefit more from combined treatment than the Western medicine alone. Integrated Chinese plus Western medicine treatment was effective for Childhood purpuric nephritis, which may be a superior alternative for HSPN. Nevertheless, the funnel plots of the total effective rate, 24-hour urine protein ration level and Urine erythrocyte count showed that the graphs are not completely symmetrical, with publication bias. So the long-term and high-quality RCTs are required to make the results more convincing.

At last, the main indicators, 24-hour urine protein ration, urine erythrocyte count and adverse effect all showed high heterogeneity. We performed a heterogeneity analysis from the ratio of the number of men and the year of publication

using the mixed effect model, but the cause of heterogeneity is not clear, it is preliminarily inferred that heterogeneity comes from the variation in the study.

5. Discussion

The cause of HSPN is still unknown. At present, the etiology of HSPN is mainly attributive to infection factors and genetic factors. For example, viruses, bacteria, especially streptococcus and helicobacter pylori are more inclined to cause HSPN. The rubella, hepatitis virus, mycoplasma pneumoniae and parasitic infection may cause HSPN morbidity. In addition, HLA gene, IgA are also involved in the pathogenesis of HSPN [102]. In the theory of Chinese medicine, HSPN belongs to the category of "purpura, blood disorder". The clinical physicians are intended to type the HSPN into syndrome of heat in blood, the syndrome of qi deficiency, the syndrome of yin deficiency, the syndrome of dampness-heat blocking collaterals, the syndrome of deficiency of both qi and yin, the syndrome of wind-heat hurting collaterals and so on. Blood stasis blocks collaterals, abdominal pain and joint pain, blood stasis blocks renal collaterals, urine and urine, proteinuria can be seen in renal sealing function and loss of function, and the course of pathogenesis is lingering, which suggests that blood stasis blocks collaterals can be indispensable to the pathogenesis of HSPN [103]. However, it is not enough to grasp the syndrome dynamics of children HSPN and the clinical physicians is not sufficient in the relationship between the syndromes and impact of some factors. Therefore, to some extent, the study on the children HSPN has its limitations.

At the present stage, since the pathogenesis of children HSPN has not been clearly understood, there are various kinds of drugs for clinical treatment of children HSPN, and there is insufficient in uniform standards for clinical treatment and the treatment effect is also different. Clinical medical workers have been constantly exploring and studying [104]. However, there is no recognized standard of treatment both domestically and overseas. In many oversea countries, medical researchers advocated clinical observation following up to the child with light illness but there is no consensus in China. They assume that Hormone combined with Immunosuppressor should be used. It is reported that the total effective rate of Cyclosporine A and hormone therapy for children HSPN is 97.4% [105]. Numerous studies manifested that Glucocorticoid has anti-inflammatory and anti-allergic effects are one of the first choice drugs for clinical treatment of children HSPN. However, clinical observation shows that the effect of glucocorticoid alone is limited and can easily lead to a variety of adverse reactions, such as hormone resistance, hormone dependence and so on. Therefore, the discussion of new therapeutic regimen can be crucial to the treatment of children HSPN. Along with the continuous inheritance and development of Traditional Chinese Medicine, scholars tried best to apply Traditional Chinese Medicine in the clinical treatment of children HSPN.

Individualized drug used according to TCM syndrome differentiation improves the therapeutic efficiency of children's HSPN to some extent. At present, the treatment of children HSPN is mainly based on the combination of Chinese and Western medicine in China, which is a kind of mature treatment. At present, they apply western medicine to rapidly control the deterioration of the condition and then the traditional Chinese Medicine is to treat in a safe and comprehensive way. In a sense, this can be the most safe and effective way to treat school-age children HSPN.

According to the above studies, domestic scholars have adopted RCT design in the clinical research on the combined treatment for children HSPN to be treated with traditional Chinese medicine and Western medicine. However, the implementation of operation process and matters needing attention were not rigorous enough so that there is a high possibility of implementation bias, which is also a serious problem confronted by the application of traditional Chinese medicine in clinical practice. Therefore, the research should attach great importance to the implementation of the RCT research principle in the future so that it can get more reliable, accurate and instructive data for clinical practice. What's more important, it can provide reliable evidence-based support for the treatment in children with HSPN and treated with the combination of Chinese and Western medicine to the International market. Finally, it can improve the curative effect of the treatment of diseases and benefit the general patients.

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