Effectiveness of Bailing capsules in the treatment of lupus nephritis: A meta-analysis

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Abstract. Previous studies have explored the treatment of lupus nephritis with Bailing capsules; however, due to limited sample sizes and inconsistent results across these studies, no definitive conclusions have been drawn. Thus, the present study aimed to provide evidence for the effectiveness of Bailing capsules in the treatment of lupus nephritis. To obtain relevant clinical studies (published before 20 July 2019), PubMed, Embase, Cochrane Library, China National Knowledge Infrastructure, WanFang and the Chinese Biomedical Literature Database were searched, and relevant studies concerning the use of Bailing capsules for treating lupus nephritis were selected. The extracted data were general characteristics such as the first author, publication year, study year, follow-up time, age, sex, course of the disease and a number of outcome indicators. These included systemic lupus erythematosus disease activity index (SLEDAI) score, serum albumin (Alb), 24-h urinary protein, serum creatinine, anti-ds-DNAIgM, complement component 3 (C3), and the number of effective treatments and complications. Meta-analysis was performed using R-3.12 software. Publication bias was assessed using Egger's test. A total of 14 studies comprising 1,301 participants were combined for analysis in the present study. The results demonstrated that with the exception of anti-ds-DNAIgM and complement C3, other indicators, such as SLEDAI score, Alb, 24-h urinary protein, serum creatinine, and the number of effective treatments and complications) in the Bailing capsule treatment group were improved compared with those in the control group. The results of the present meta-analysis suggested that Bailing capsules may be effective in the treatment of lupus nephritis.

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Introduction

Lupus nephritis is a kidney inflammation caused by systemic lupus erythematosus (SLE) (1). SLE is characterized by persistent and severe inflammation that damages multiple organs (2). In particular, 60-80% of patients with SLE develop renal or urinary function abnormalities (3). It has been estimated that in North America, the annual prevalence of SLE is 23.2/100,000 and 241/100,000 for males and female, respectively (4). In addition, >50% of patients with SLE have lupus nephritis (5); thus, it is necessary to find effective methods for the treatment of lupus nephritis.

The main treatment regimen for lupus nephritis are immunosuppressants, such as corticosteroids and cyclophosphamide (6,7); however, the use of immunosuppressants increases the risk of infections in patients (8). In view of the limitations of immunosuppressants, the use of Bailing capsules, which are prepared from the dry powder of *Ophiocordyceps sinensis* mycelium, has been explored previously in lupus nephritis therapy (9). Bailing capsules possess antihypoxic, anti-inflammatory and antitumor effects, regulate the endocrine system and enhance the immune function (10). Bailing capsules have been widely used in adjuvant therapy of glomerulonephritis, pyelonephritis, nephrotic syndrome and other diseases without adverse effects (11). Studies have reported the treatment of lupus nephritis with Bailing capsules. For example, Zhou *et al* (12) indicated that treatment with Bailing capsules regulated cellular immunity levels in patients with lupus nephritis. A previous study in patients with lupus nephritis indicated that the 24-h urinary protein, serum creatinine and urea nitrogen levels after treatment were markedly lower in the treatment group (Bailing capsules with cyclophosphamide) compared with those in the control group (13). In a similar study, the serum creatinine, 24-h urinary protein, β_2 microglobulin and SLE Disease Activity Index (SLEDAI) scores in the treatment group (Bailing capsules + Leflunomide + Prednisone acetate) were lower compared with those in the control group, whereas the albumin (Alb), complement C3 and red blood cell (RBC) levels were higher compared with those of the control group (14). Despite the existence of multiple studies, no definitive conclusions has been drawn on the effectiveness of Bailing capsules in the treatment of lupus nephritis due to limited sample sizes and inconsistent results across these studies.

The present study conducted a meta-analysis of studies which explored the use of Bailing capsules to treat lupus nephritis.

Materials and methods

Data source. Relevant clinical studies were obtained from PubMed (ncbi.nlm.nih.gov/pubmed/), Embase (embase.com), Cochrane Library (cochranelibrary.com/), China National Knowledge Infrastructure (cnki.net/), WanFang database (wanfangdata.com.cn/) and the Chinese Biomedical Literature Database (sinomed.ac.cn/). A literature search was performed using the following search strategy: Sources published between July 2004 and 2019 were searched, without language limitations, using the keywords including 'Bailing capsule', AND 'lupus nephritis' OR 'lupus erythematosus nephritis'.

Inclusion and exclusion criteria. The selected studies involved the use of Bailing capsules for the treatment of lupus nephritis. For repeated publications or when the same dataset was used for multiple studies, only the latest or the most comprehensive article was included. Reviews, reports, letters, comments and studies without complete data which could be used for statistical analysis were excluded.

Data extraction and quality assessment. The following data from each study: First author, publication year, study year, follow-up time, number of Bailing capsule and control (non-Bailing capsule) groups, medication, age, sex, course of the disease and outcome indicators including SLEDAI score, Alb levels, 24-h urinary protein, serum creatinine, anti-ds-DNAIg, C3 and the number of effective treatments and complications were extracted by two independent researchers. Quality assessment of the included studies was based on the guidelines recommended by the Cochrane Collaboration (15).

Statistical analysis. Meta-analysis was performed using R-3.12 software, and the odds ratio (OR) or standardized mean differences (SMD) and 95% confidence interval (95% CI) (16) were used for the effect index. Heterogeneity was analysed using the Cochran's Q test (17) and the I^2 test. If $P<0.05$ or $I^2>50\%$, indicating that all the studies were heterogeneous, the random effects model was applied. If not, the fixed effect model was used (18). Sensitivity analysis was conducted by trimming one study at a time (19). The pooled effect differences before and after the trim were compared. A reversal of the pooled results after the trim was indicative of unstable results. Publication bias was evaluated using Egger's test (20).

Results

Characteristics of the included studies. A total of 98 articles were obtained after excluding 49 duplicates. Then, 66 obvious irrelevant articles were eliminated. Two animal studies, six reviews, eight studies without useable data and two studies with duplicated populations were subsequently removed after abstract and full-text review. 14 articles (11,13,14,21-31) were included in the present meta-analysis; the flow diagram of the search and selection process is presented in Fig. 1.

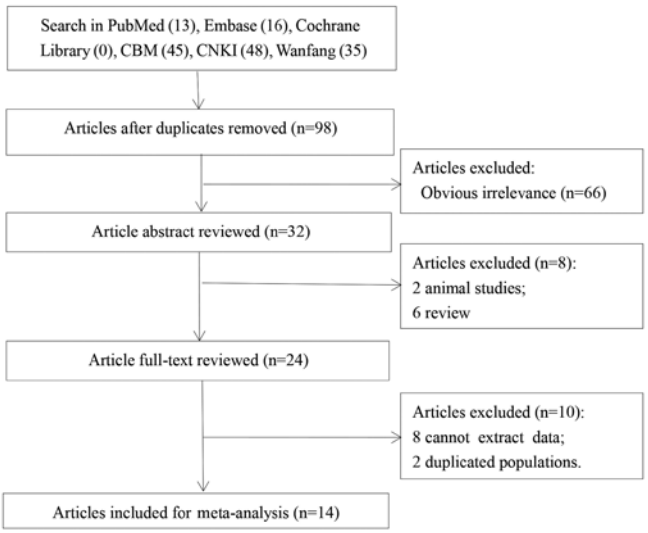

Figure 1. Flow diagram of the search and selection process. CBM, China Biology Medicine; CNKI, China National Knowledge Infrastructure.

The included studies were published between 2006 and 2019 and performed between 2000 and 2018. The follow-up time was 1-12 months. The studies comprised 1,301 participants, including 654 patients with lupus nephritis and 647 controls. The Bailing capsule group were treated with Bailing capsule combined with cortisone, prednisone, prednisolone, low molecular weight heparin, tacrolimus, methyprednisolone cyclophosphamide, methylprednisolone or leflunomide. No significant differences were observed in sex, age or course of the disease between the Bailing capsule and control groups in each publication (Table I). The outcome indicators, including SLEDAI score, complications (such as respiratory infection, fatigue, drowsiness, gastrointestinal symptoms, rash and leukocytopenia), Albumin, 24-h urinary protein, serum creatinine, C3 and the number of effective treatments and were recorded (Table II). The results of the quality assessment demonstrated high or unclear risk of bias (Fig. 2), indicating that the literature was of average quality.

Meta-analysis. The heterogeneity test demonstrated $P<0.05$ and $I^2>50\%$ for SLEDAI score, Alb, 24-h urinary protein, complement C3 and serum creatinine. The random effects model was thus applied for these indicators. The fixed effect model was used for the other results.

Bailing capsule application was demonstrated to be more effective compared with treatment without the use of Bailing capsule for lupus nephritis (OR, 3.62; 95% CI: 2.55, 5.13; Z=7.22; P<0.001; Fig. 3A). Sensitivity analysis demonstrated that the results were reliable; there was a publication bias for the effectiveness of treatment Egger's test, t=2.76; P<0.001).

No significant differences were observed in the anti-ds-DNAIg levels between the Bailing capsule and control groups (OR, 0.84; 95% CI: 0.56, 1.27; Z=0.83; P=0.400; Fig. 3B). Sensitivity analysis demonstrated that the results were reliable. There was a publication bias for anti-ds-DNAIg (t=33.40; P=0.0001).

The number of complications in the Bailing Capsule group was lower compared with that in the control group (OR, 0.48; 95% CI: 0.31, 0.75; Z=3.22; P=0.0013; Fig. 3C). Sensitivity

Table I. Characteristics of the included studies.

Author, year	Study year	Follow-up, months	Group	N	Drugs	Sex (male/female)	Age, years	Course of the disease, months	(Refs.)
Bai *et al*, 2019	2017.01-2018.06	6	Bailing capsule	30	Cyclophosphamide + Bailing capsule	7/23	31.42±12.39	13.91±6.17	(13)
			Control	30	Cyclophosphamide	15/15	35.17±14.21	13.54±7.48	
He *et al*, 2013	2010.03-2012.03	2	Bailing capsule	21	Methylprednisolone + heparin + Bailing capsule	2/19	31.80±4.40	12±10.8 (year)	(21)
			Control	21	Methylprednisolone + heparin	3/17	30.20±5.30	0.9±1.2 (year)	
Li and Wang, 2017	2010.06-2016.06	NA	Bailing capsule	45	Prednisone + Bailing capsule	4/41	35.26±10.89	59.50±17.21	(11)
			Control	45	Prednisone	5/40	36.21±9.32	60.89±23.24	
Li *et al*, 2019	2012.12-2017.03	6	Bailing capsule	63	Leflunomide + prednisone acetate + Bailing capsule	29/34	38.92±12.75	30.70±8.67	(14)
			Control	63	Leflunomide + prednisone acetate	28/35	38.20±9.16	31.28±9.30	
Liu *et al*, 2006	2000-2005	1	Bailing capsule	65	Prednisone + Bailing capsule	NA	15-55	12-180	(16)
			Control	61	Prednisone				
Shu *et al*, 2019	2016.01-2017.06	12	Bailing capsule	24	Cyclophosphamide + Bailing capsule	7/17	31.80±9.40	12±9.6 y	(31)
			Control	23	Cyclophosphamide	6/17	30.60±10.50	10.8±12 y	
Wang *et al*, 2018	2012.06-2017.08	6	Bailing capsule	56	Prednisone acetate + Bailing capsule	8/48	45.06±3.71	22.98±5.63	(23)
			Control	56	Prednisone acetate	10/46	46.01±3.80	23.58±5.71	
Wang 2019	2013.05-2018.03	6	Bailing capsule	55	Prednisone acetate + Bailing capsule	32/23	45.18±9.46	20.36±12.61	(24)
			Control	55	Prednisone acetate	30/25	44.88±9.60	23.07±12.45	
Wang 2018	2016.05-2017.05	6	Bailing capsule	26	Tacrolimus + Bailing capsule	13/13	41.54±7.21	20.21±6.21	(30)
			Control	26	Tacrolimus	14/12	40.21±7.21	20.21±6.21	
Wang *et al*, 2017	2014.09-2016.02	12	Bailing capsule	59	Tacrolimus + Bailing capsule	11/48	22.03±12.08	20.59±12.13	(25)
			Control	59	Tacrolimus	9/50	29.96±8.02	22.03±12.08	
Wu 2007	2003.05-2005.02	2	Bailing capsule	22	Prednisone + Bailing capsule	14/28	34.30±12.20	56.4±19.2	(26)
			Control	20	Prednisone		32.60±11.80	50.4±20.4	
Xu 2018	2016.01-2017.02	12	Bailing capsule	60	Tacrolimus + Bailing capsule	5/55	46.95±10.62	13.17±3.25	(29)
			Control	60	Tacrolimus	6/54	47.84±11.56	12.87±3.43	
Zhu *et al*, 2015	2010.12-2013.12	12	Bailing capsule	60	Cyclophosphamide + Bailing capsule	6/54	49.87±16.34	NA	(28)
			Control	60	Cyclophosphamide	7/53	50.03±16.40	NA	
Yang *et al*, 2015	2013.05-2014.05	12	Bailing capsule	68	Cyclophosphamide + Bailing capsule	10/58	51.37±17.53	NA	(27)
			Control	68	Cyclophosphamide	12/56	50.89±17.48	NA	

NA, no data available; N, number.

Table II. The outcome indicators of the included studies.

Author, year	Group	N	SLEDAI	Complications	Alb, g/l	Effectiveness	24-h urinary protein, g/24 h	Serum creatinine, μmol/l	Anti-ds-DNAIg, +/-	C3, g/l	(Refs.)
Bai *et al*, 2019	Bailing Capsule	30	5.83±2.79	3	NA	29	0.71±0.16	62.49±7.13	NA	NA	(13)
	Control	30	8.64±3.84	11	NA	23	1.65±0.31	79.51±8.48	NA	NA	
He *et al*, 2013	Bailing Capsule	21	NA	NA	44.5±4.2	NA	1.02±0.42	147.3±22.5	NA	NA	(21)
	Control	21	NA	NA	36.1±3.6	NA	2.09±0.72	190.3±21.8	NA	NA	
Li and Wang, 2017	Bailing Capsule	45	NA	NA	NA	43	NA	NA	23	NA	(11)
	Control	45	NA	NA	NA	35	NA	NA	25	NA	
Li *et al*, 2019	Bailing Capsule	63	5.69±1.72	NA	36.27±6.80	58	0.58±0.16	66.52±11.80	NA	1.09±0.29	(14)
	Control	63	9.83±2.20	NA	29.10±6.15	50	1.69±0.50	77.89±11.20	NA	0.77±0.20	(16)
Liu *et al*, 2006	Bailing Capsule	65	NA	37	NA	61	NA	NA	NA	NA	
	Control	61	NA	52	NA	47	NA	NA	NA	NA	
Shu *et al*, 2019	Bailing Capsule	24	NA	NA	41.68±12.13	20	0.78±0.22	56.88±9.68	NA	0.96±0.27	(31)
	Control	23	NA	NA	35.23±10.86	15	1.05±0.42	63.64±11.07	NA	0.78±0.22	
Wang *et al*, 2018	Bailing Capsule	56	3.12±0.98	6	NA	51	0.25±0.10	62.33±8.53	NA	NA	(23)
	Control	56	5.42±1.65	4	NA	43	0.75±0.23	85.63±10.55	NA	NA	
Wang, 2019	Bailing Capsule	55	3.10±0.91	4	NA	NA	0.23±0.12	62.34±8.51	NA	NA	(24)
	Control	55	5.44±1.61	6	NA	NA	0.73±0.24	85.66±10.51	NA	NA	
Wang, 2018	Bailing Capsule	26	9.01±1.21	NA	35.21±2.54	25	0.77±0.32	NA	NA	NA	(30)
	Control	26	14.21±2.32	NA	43.21±3.25	19	1.08±0.54	NA	NA	NA	
Wang *et al*, 2017	Bailing Capsule	59	2.98±1.03	16	42.98±11.87	52	0.78±0.22	62.27±31.01	30	0.78±0.22	(25)
	Control	59	5.11±2.15	28	36.27±10.86	41	1.07±0.92	64.99±33.75	32	0.72±0.23	
Wu, 2007	Bailing Capsule	22	NA	NA	NA	NA	1.02±0.46	147.3±20.4	NA	108.8±13.7	(26)
	Control	20	NA	NA	NA	NA	1.97±0.75	185.9±21.6	NA	82.6±12.8	
Xu, 2018	Bailing Capsule	60	3.01±1.09	15	29.39±5.62	53	1.42±0.33	68.95±9.87	NA	0.76±0.24	(29)
	Control	60	5.26±2.45	28	25.47±4.54	41	1.75±0.44	56.06±8.07	NA	0.61±0.16	
Zhu *et al*, 2015	Bailing Capsule	60	5.12±3.21	23	39.74±9.12	53	NA	80.86±20.78	10	1.36±0.38	(28)
	Control	60	6.64±3.43	22	36.28±8.23	43	NA	86.49±22.94	12	1.22±0.28	
Yang *et al*, 2015	Bailing Capsule	68	5.09±3.18	18	39.95±9.21	61	1.11±0.62	78.97±20.56	13	1.38±0.36	(27)
	Control	68	6.64±3.43	30	36.54±8.27	50	1.43±0.78	86.49±22.94	15	1.24±0.25	

NA, data not available; N, number.

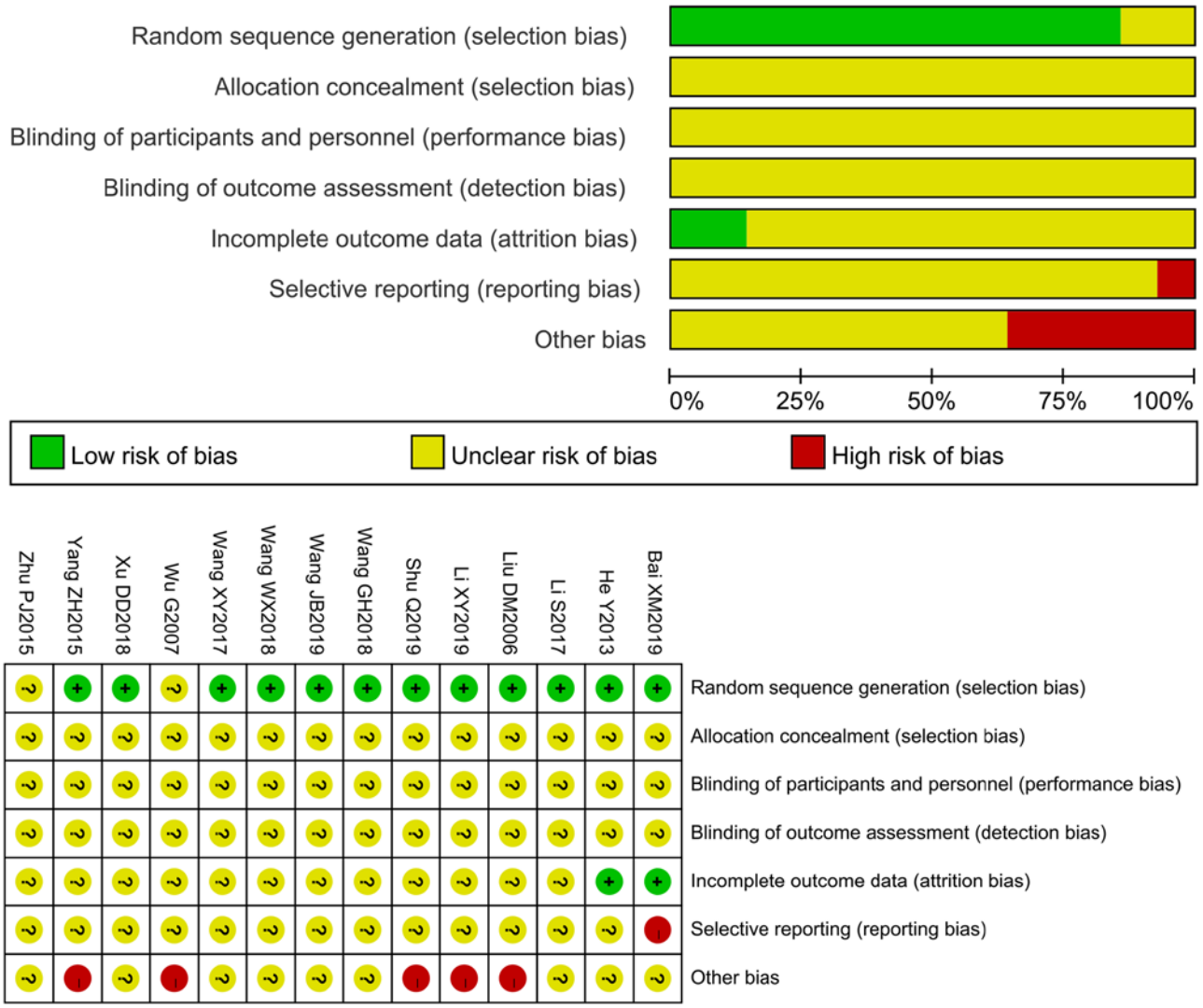

Figure 2. Quality assessment of the studies, based on the following criteria: Random sequence generation (selection bias), allocation concealment (selection bias), blinding of participants and personnel (performance bias), incomplete outcome data (attrition bias) and selective reporting (reporting bias).

analysis demonstrated that the results were reliable; there was no publication bias for complications (t=0.45; P=0.67).

The decrease in the SLEDAI score in the Bailing capsule group was higher compared with that in the control group (SMD, -1.35; 95% CI: -1.80, -0.90; Z=5.89; P<0.0001; Fig. 3D). Sensitivity analysis indicated that the results were reliable; no publication bias existed for the SLEDAI score (t=2.38; P=0.05).

The decrease in 24-h urinary protein in the Bailing capsule group was greater compared with those in the control group (SMD, -1.67; 95% CI: -2.33, -1.01; Z=5.89; P<0.0001; Fig. 4A). Sensitivity analysis demonstrated that the results were reliable and stable. Publication bias was identified for 24-h urinary protein (t=2.42; P=0.04).

The decrease in serum creatinine in the Bailing capsule group was greater compared with those in the control group (SMD, -1.03; 95% CI: -1.73, -0.33; Z=2.88, P=0.004; Fig. 4B). Sensitivity analysis suggested that the results were reliable and stable; there was no publication bias for serum creatinine (t=2.06; P=0.07).

The increase in Alb in the Bailing capsule group was greater compared with those in the control group (SMD, 0.77; 95% CI: 0.42, 1.12; Z=4.32; P<0.0001; Fig. 4C). However, after eliminating the study of Wenxin W (30), the results of the pooled SMD were reversed. No publication bias was identified for Alb (t=0.70; P=0.51).

No significant differences were observed in the levels of complement C3 between the Bailing capsule and control groups (SMD, 0.42; 95% CI: -0.15, -0.99; Z=1.45; P=0.15; Fig. 4D). Sensitivity analysis demonstrated that the results were reliable and stable; there was no publication bias for complement C3 (t=1.73; P=0.15).

Discussion

In this meta-analysis, a total of 14 studies comprising 1,301 participants were included to verify the effectiveness of Bailing capsules in the treatment of lupus nephritis. The results demonstrated that, with the exception of anti-ds-DNAIg and complement C3, other indicators (SLEDAI score, Alb, 24-h urinary protein, serum creatinine, and the number of effective treatments and complications) in the Bailing capsule group were improved compared with those in the control group.

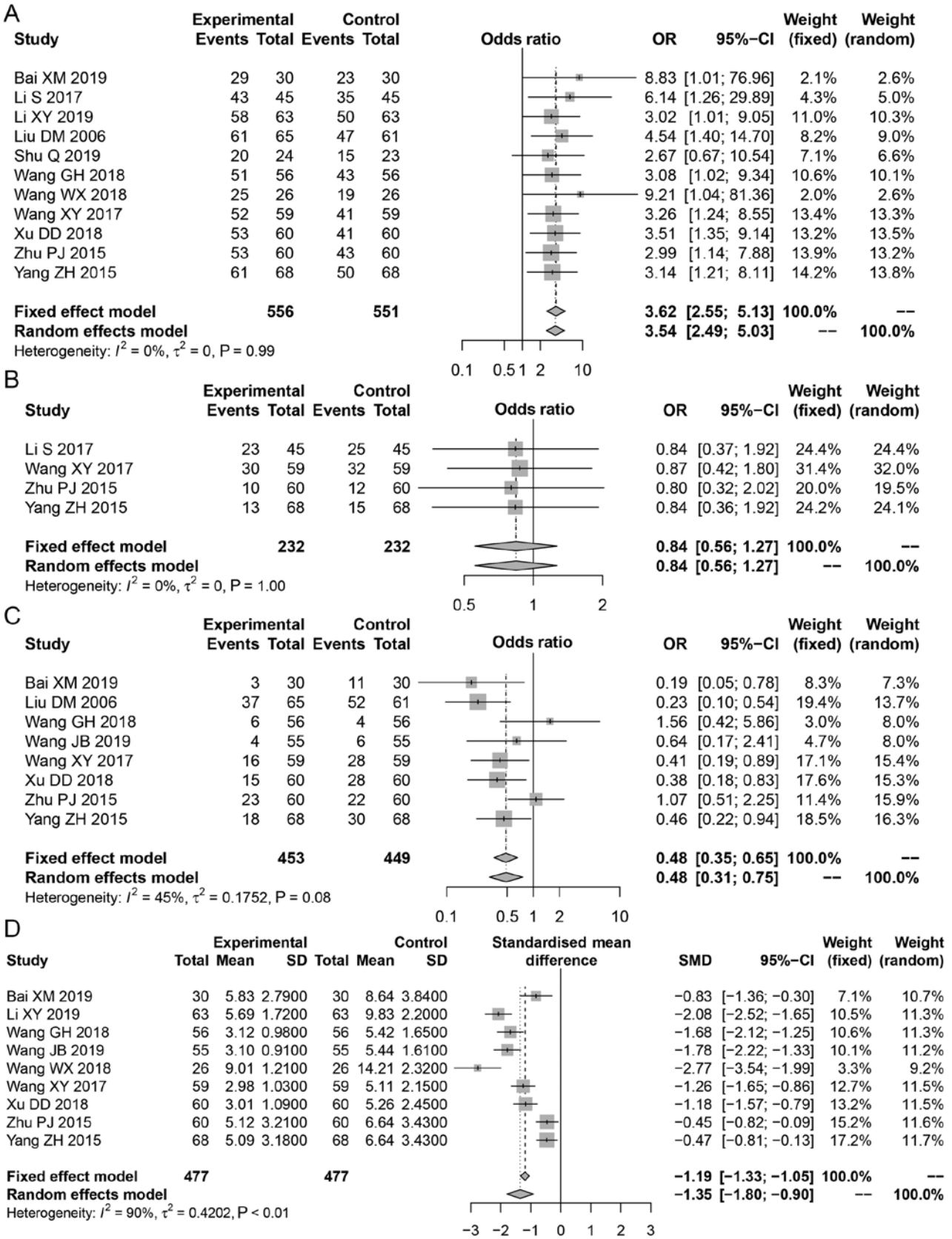

Figure 3. Forest plot of meta-analysis results of (A) effectiveness, (B) anti-ds-DNAIg, (C) complication (D) and SLEDAI score. SLEDAI, systemic lupus erythematosus disease activity index; OR, odds ratio; CI, confidence interval.

Quantitative analysis of the 24-h urinary protein levels is an important diagnostic index to assess the severity and prognosis of nephritis or kidney-related diseases (32). The SLEDAI score is an index used to assess SLE disease activity (33). Serum creatinine is positively associated with the degree of early renal injury in patients with acute glomerulonephritis (33). The

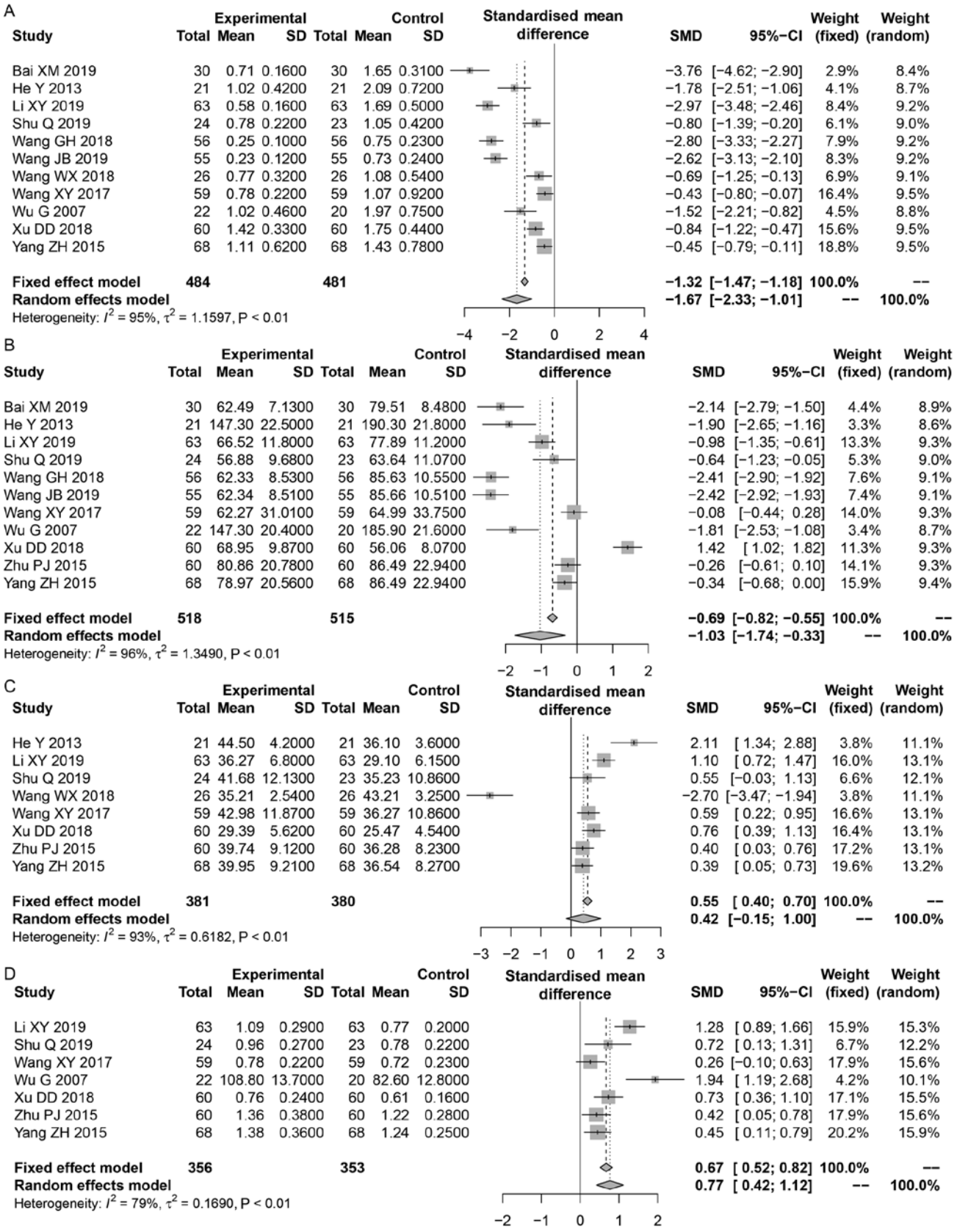

Figure 4. Forest plot of meta-analysis results of (A) 24-h urinary protein, (B) serum creatinine, (C) Alb (D) and complement C3. Alb, albumin; SMD, standardised mean difference; CI, confidence interval.

level of Alb, which reflects the nutritional status of patients, is associated with lupus nephritis development, and nephrotic syndrome is often accompanied by hypoalbuminemia (34). A significant reduction in complement C3, which is produced by liver cells, is related to the occurrence of SLE and other immune diseases, and anti-ds-DNAIg is the main immune factor

involved in the organ damage in SLE (25). In a meta-analysis by Wang *et al* (35), several indicators including serum creatinine, complement C3, 24-h urinary protein, adverse effects and SLEDAI score were improved in the Bailing capsule group compared with those in the non-Bailing capsule group for lupus nephritis therapy. In the present meta-analysis, SLEDAI score, Alb, 24-h urinary protein, serum creatinine, and the number of effective treatments and complications in the Bailing capsule group were improved compared with those in the control group. Thus, Bailing capsules may be used effectively in the treatment of lupus nephritis.

However, the present study has certain limitations; there was significant heterogeneity among the studies, likely caused by differences in habits and customs, living conditions and economic development level in different regions. In addition, the effects of other confounding factors, such as sex and age, may have contributed to this heterogeneity. In addition, due to incomplete data, correction of covariates and subgroup analysis were not performed. The number of eligible studies was further reduced due to the rigorous exclusion and inclusion criteria (36). Additionally, all the included studies were from China, which may have caused a selection bias. Publication bias was also observed for effectiveness, anti-ds-DNAIg and 24-h urinary protein. Furthermore, in the sensitivity analysis of Alb, after eliminating the study of Wang (30), the results of the pooled SMD were reversed, indicating an unreliable outcome. Lastly, since Bailing capsule was used for SLE or lupus nephritis treatment in combination with other medicines, these medicines were different in different studies, and the numbers of eligible studies for each medicine were low; thus, meta-analysis data to demonstrate the effect to Bailing Capsule therapy with other medicines was not added. Despite these limitations, the present study suggests that Bailing Capsules may be used effectively in lupus nephritis treatment. An updated meta-analysis drawing from larger scale studies and high-quality data may validate the findings of the present study.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

YL, TX and LY conceptualized and designed the study. YL, TX, XQ, BT and CB drafted and revised the manuscript. YL and TX performed the literature search, retrieved data and wrote the draft for the final manuscript. XQ performed statistical analysis. BT and CB plotted the tables and figures. YL supervised the project and approved the manuscript to be published. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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