SUPPLEMENTARY MATERIAL

The systemic lupus erythematosus interventional trials in mainland China: a continuous challenge

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Appendix 1 Objectives and specific aims

The objective of the proposed study is to provide an overview of randomized clinical trials (RCTs) of Systemic lupus erythematosus (SLE) in China by systematically reviewing all published or registered RCTs of LE during the past three decades.

Aim 1: to provide overall information of LE RCTs in mainland China such as numbers and percentages of RCTs using different interventions, numbers of RCTs started in each year, and the geographical distribution of primary investigator, et al. and to describe specific trial characteristics such as sample size, masking status, intervention duration, loss to follow-up, et al.

Aim 2: to determine various affecting participant loss to uncover the potential bias of SLE RCTs conducted in mainland China.

Aim 3: to identify limitations in SLE RCTs conducted in mainland China to inform future research and improve trial quality.

Significance and Background

China has huge number of SLE RCTs, while Chinese guidelines for the management of SLE patients are similar to international guidelines partly due to the lack of evidence from high-quality RCTs involving ethnic Chinese patients that could provide evidence for clinical practice. To comprehensively analyze clinical trials conducted in mainland China and to prevent unnecessary bias in the future, we systematically searched for published articles and for records of registered trials in clinical trial registries for SLE RCTs performed in China over the past three decades.
Appendix 2 Detailed methods

a. Search strategy

Two investigators (JR.T and H.Z) searched published articles and clinical trial registry records, appraised studies on eligibility, and extracted data independently. Discrepancies were discussed and agreed by consensus.

The search for RCTs included published articles from peer-reviewed English-language journals and registered trials in clinical trials registries, both up to May 4, 2021 and without start date restriction. The published articles were searched in literature databases including the PubMed, EMBASE, and Cochrane Library Central Register of Controlled Trials (CENTRAL). The MeSH and keyword search terms associated with lupus were used in each database. In order not to miss out on potentially useful articles, references cited in relevant reviews were also searched manually. RCTs published in Chinese medical journals were also included.

Records of registered RCTs were collected from 4 publicly available web-based clinical trials registries, including the ClinicalTrials.gov of the US National Library of Medicine, the International Standard Randomised Controlled Trial Number Register (ISRCTN), the Australian and New Zealand Clinical Trials Registry (ANZCTR), and the Chinese Clinical Trial Register. The keyword search term “lupus” was entered combined with other specific filtering options in advanced search function for ‘Country’, ‘Study type’, and ‘Current status’ et al. in searching for eligible RCTs.

b. Study selection

We evaluated published articles at the title or abstract level, with divergences resolved after consensus by two independent investigators. If potentially relevant, we evaluated them as complete reports according to prespecified selection criteria. For both published articles and registered records, trials were included if they enrolled subjects with lupus patients, and randomly assigned patients to different intervention groups. We excluded studies which are: 1) non-human studies; 2) observational studies; 3) studies without randomization or intervention groups; 4) studies not conducted in patients with lupus; 5) studies without ethics committee approval. In addition, published articles which are: 1) not in the English language or not in Chinese full text; 2) without full text (i.e. abstracts and conference proceedings) or not reporting original studies (i.e. narrative reviews, meta-analyses, editorials, commentaries, protocols, guidelines, or perspectives); or 3) duplicate reports and registration were also excluded. The search
process of literature from published articles and records from clinical trial registries are shown below.

c. Data extraction

Two investigators independently extracted information on characteristics of each included studies, including general information (author, publication year, registration ID, year of start, domestic or multinational, single- or multi-center, affiliations of primary investigators), participant characteristics (subject type, number of participants, loss to follow-up), study intervention (measures of intervention or control, duration, blinding), and primary outcomes. Some information of participant characteristics was not available for multinational trials because they did not provide information separately for participants in individual countries. Extracted data from published articles and records from clinical trials registries were entered separately into two piloted spreadsheets, and then combined together matched by the registration ID or other information if the registration ID was unavailable. For studies with data available from both sources, data from published articles were used. Potential duplicate registry entries were searched for by matching on important trial characteristics including year of start, affiliation of primary investigator, subject category, number of participants, interventions, and primary outcome. Published trials which did not include a trial registration ID was considered not registered.

The following information will be extracted from each included trial.

1 General information

1.1 Data source: ‘clinical trial registry’, ‘published articles’, or ‘published articles in Chinese’.

1.2 Author, year of publication: the first author and publication year of the trial from published articles. For trials in the registries, name of the registers including ‘ClinicalTrials.gov’, ‘International Standard Randomised Controlled Trial Number Register’, Australian New Zealand Clinical Trials Registry’, and ‘Chinese Clinical Trial Registry’ will be used.

1.3 Registration ID: the registered number of the trial. For trials without registration ID, ‘not available’ will be used.

2 Trial information

2.1 Year of start: the start year of the trial if it is available, otherwise ‘not mentioned’ will be used.
2.2 **Multinational study:** ‘Yes’ if the trial is a multinational study, or ‘No’ if the trial was conducted entirely in one country.

2.3 **Affiliation of primary investigator:** The affiliation of the primary investigator can be found in registries. For published articles, the affiliation of the corresponding author will be used. The last corresponding author will be chosen if there are multiple corresponding authors.

2.4 **Single or Multicenter:** ‘Single center’ if it is a single-center study, ‘Multicenter’ if the trial is conducted at ≥2 centers, or ‘Not mentioned’ if it is not recorded.

2.5 **Primary outcome:** the primary outcome identified in the included trial. For trials which list several outcomes without identification of the primary outcome, all the reported outcomes will be extracted and ‘primary outcome not identified’ will be noted.

3 **Participant characteristics**

3.1 **Subjects:** ‘SLE’ if subjects are patients with systemic lupus erythematosus; ‘JSLE’ if subjects are patients with juvenile-onset systemic lupus erythematosus; ‘SCLE’ if subjects are patients with subacute cutaneous lupus erythematosus; ‘LN’ if subjects are patients with lupus nephritis; ‘MLN’ if subjects are patients with membranous lupus nephritis; ‘DPSLE’ if subjects are patients with diffuse proliferative lupus nephritis; ‘NPSLE’ if subjects are patients with neuropsychiatric Lupus Erythematosus.

3.2 **Number of participants:** the number of randomized subjects in published articles, or the number of estimated enrollments for ongoing trials and the number of actual enrollments for completed trials in the registries.

3.3 **Number of participants loss to follow-up:** the number of participants who did not complete the follow-up. ‘not available’ will be used for registered ongoing trials.

3.4 **Percentage of loss-to-follow-up (%):** calculated by ‘Number of participants loss to follow-up’ divided by ‘Number of participants’. ‘not available’ will be used for registered ongoing trials.

3.5 **Age duration (years):** the age duration in years of participants. ‘Not mentioned’ if it is not recorded or only has average age.
3.6 **Country and area:** the country and area where the clinical trial is located. For trials which are multinational studies, all the reported locations will be extracted.

4 **Study intervention**

4.1 **Intervention categories:** including ‘Pharmacological treatment’, ‘Behavioral intervention’, ‘Dietary supplement’, ‘Biological therapy’, ‘Device’, ‘Procedure’, and ‘Others’.

4.2 **Intervention:** interventions (control) in the included trial.

4.3 **Intervention duration (months):** the intervention duration in months for completed trials. ‘not available’ will be used for ongoing registered trials or if information is not provided.

4.4 **Blinding:** including ‘Single-blind’, ‘Double-blind’, ‘Open-label’, or other types of blinding (triple-blind or quadruple-blind) if it is available. ‘Not mentioned’ if information on blinding is not provided.

5 **Reference:** the reference for published articles and URL for registered trials.

d. **Study categorization**

We included RCTs conducted in subjects with SLE. We further classified included RCTs according to interventions. We referred classifications adapted from the ClinicalTrials.gov registry, which has 7 categories of intervention including pharmacological treatment, behavioral intervention, dietary supplement, biological therapy, procedure, device, and others. We also adopted care as an independent intervention category. The following table 2 listed the detail information.

**Table S1. The classification of intervention categories**

| Categories                     | Interventions                                                                 |
|-------------------------------|-------------------------------------------------------------------------------|
| **Pharmacological treatment** |                                                                               |
| Chemical drugs and biologicals| This includes trials which evaluate the effects of monotherapy of glucocorticoids, immunosuppressants, antimalarial drugs, biologicals, combination therapy of glucocorticoids and/or antimalarial drugs and other immunosuppressants and/or biologicals, and other chemical drugs such as docosahexaenoic acid, etc. |
| Traditional Chinese medicine  | This includes trials which evaluate the effects of herbal compound formula and herbal concentrate-granules. |
| Antibodies                    | This includes trials which evaluate the effects of humanized monoclonal antibody against different targets. |
| Category             | Description                                                                                                                                 |
|----------------------|---------------------------------------------------------------------------------------------------------------------------------------------|
| Vaccines             | This includes trials which evaluate the effects or safety of vaccines, such as herpes zoster vaccine, etc.                                   |
| **Behavioral intervention** |                                                                                                                                 |
| Diet intervention    | Intervention using diet such as the low glycemic index diet, the low carbohydrate diet, the calorie restriction diet, etc.                |
| Exercise intervention| Intervention using exercise such as the aerobic and resistance exercise, high-intensity interval exercise, motion/muscle strengthening, etc. |
| Education            | Intervention using group-based or individualized health educational program for LE management such as drug usage, telephone counseling intervention, cognitive behavioral intervention, lifestyle modification, etc. |
| **Dietary supplement** |                                                                                                                                 |
|                      | Intervention using dietary supplement such as health products, fish oil, vitamins, etc.                                                    |
| **Biological therapy** |                                                                                                                                 |
|                      | Intervention using stem cell therapy.                                                                                                     |
| **Device**           | Intervention using high-intensity laser device, needle-free injectors, autoinjector, foot orthoses, intrauterine device, etc.               |
| **Procedure**        | Intervention using plasmapheresis, acupuncture, laser coagulation, laser photocoagulation, surgery, etc.                                   |
| Care                 | Intervention using different kind of care.                                                                                                  |
| **Others**           | Interventions not belong to any of the above categories are categorized as 'others' such as motivational interviewing, sleep intervention, digital therapeutic intervention, mobile/web-based intervention, genetic, sunscreens, etc. |
### Appendix 3 Search strategies

#### Table S2. The search strategy in PubMed (Medline)

| #  | Terms                                                                 | Quotes     |
|----|----------------------------------------------------------------------|------------|
| 4  | #1 AND #2 AND #3                                                     | 2,367      |
| 3  | (randomized controlled trial [pt] OR controlled clinical trial [pt] | 1,343,564  |
|    | OR randomized [tiab] OR placebo [tiab] OR clinical trials as topic   |            |
|    | [mesh: noexp] OR randomly [tiab] OR trial [ti]) NOT (animals [mh]     |            |
|    | NOT humans [mh])                                                    |            |
| 2  | (“Therapeutics” [Mesh] OR “therapy” [Subheading] OR “prevention and  | 15,006,631 |
|    | control” [Subheading] | OR “Intervention” |            |
|    | OR “prevention” OR “prevention and control” OR “Intervention” OR     |            |
|    | “prevention” OR prevention)                                          |            |
| 1  | (((((“Lupus Erythematosus, Systemic” [Mesh] OR Systemic Lupus       | 83,756     |
|    | Erythematosus OR Lupus Erythematosus Disseminatus OR Libman-Sacks    |            |
|    | Disease OR Disease, Libman-Sacks OR Libman Sacks Disease) OR (“Lupus |            |
|    | Nephritis”[Mesh] OR Lupus Glomerulonephritis OR Nephritis, Lupus OR  |            |
|    | Lupus Nephritides OR Nephritides, Lupus OR Glomerulonephritis, Lupus |            |
|    | OR Glomerulonephritides, Lupus OR Lupus Glomerulonephritides)) OR    |            |
|    | (“Lupus Vasculitis, Central Nervous System”[Mesh] OR Central Nervous |            |
|    | System Lupus Vasculitis OR Systemic Lupus Erythematosis, Central     |            |
|    | Nervous System OR Central Nervous System Lupus OR central nervous    |            |
|    | system systemic lupus erythematosus OR Neuropsychiatric Systemic     |            |
|    | Lupus Erythematosus OR Lupus Meningoencephalitis OR Lupus             |            |
|    | Meningoencephalitides OR Meningoencephalitides, Lupus OR             |            |
|    | Meningoencephalitides, Lupus) OR (systemic lupus erythematosus) OR    |            |
|    | (lupus erythematosus) OR (systemic lupus)) OR (Lupus Erythematosus,   |            |
|    | Discoid[MeSH Terms])) OR (Lupus Erythematosus, Cutaneous[MeSH Terms])|            |

#### Table S3. The search strategy in Embase

| #  | Terms                                                                 | Quotes     |
|----|----------------------------------------------------------------------|------------|
| 9  | #6 AND #7 AND #8 AND ([chinese]/lim OR [english]/lim) AND [humans]/lim| 1,645      |
| 8  | (’randomized controlled trial’/exp OR ’controlled trial, randomized’ | 687,328    |
|    | OR ’randomised controlled trial’ OR ’randomized controlled trials’ OR  |            |
|    | ’randomized controlled trials’ OR ’random controlled trials as       |            |
|    | topic’ OR ’trial, randomized controlled AND [embase]/lim) OR          |            |
|    | (’randomization’/exp OR ’random allocation’ OR ’randomisation’ AND |            |
|    | [embase]/lim) OR (’double blind procedure’/exp OR ’double-blind       |            |
|    | method’ OR ’double blind clinical trial’ OR ’double blind comparison’ |            |
|    | OR ’double blind studies’ OR ’double blind study’ OR ’double blind   |            |
|    | test2’ OR ’double blind trial’ AND [embase]/lim)                   |            |
| 7  | ’therapy’/exp OR ’prevention’/exp OR ’intervention’:ti,ab,kw OR     | 13,421,869 |
|    | ’treatment’:ti,ab,kw OR ’prevention’:ti,ab,kw                      |            |
| 6  | #1 OR #2 OR #3 OR #4 OR #5                                        | 115,502    |
| 5  | (’lupus erythematosus nephritis’/exp OR ’glomerulonephritis lupoid’ | 17,968     |
|    | OR ’lupoid nephritis’ OR ’lupus erythematosus nephritis’ OR ’lupus   |            |
|    | glomerulonephritis’ OR ’lupus kidney’ OR ’lupus nephritis’ OR ’lupus |            |
|    | nephropathy’ OR ’nephritis lupus erythematosus’ OR ’nephritis       |            |
|    | systemic lupus erythematosus OR ’systemic lupus erythematosis,       |            |
|    | nephritis’) AND [embase]/lim                                         |            |
| 4  | (’systemic lupus erythematosus’/exp OR ’dermatovisceritisis          | 99,836     |
|    | malignant’ OR ’disseminated lupus’ OR ’disseminated lupus          |            |
|    | erythematoses’ OR ’disseminated lupus erythematoses’ OR             |            |
|    | ’disseminated lupus erythematosis’ OR ’dermatovisceritis’ OR ’lupus  |            |
|    | erythematoses’ OR ’lupus erythamatoses disseminatus’ OR              |            |
|    | ’lupus erythematosus disseminatus’ OR ’lupus erythematosus           |            |
|    | visceralis’ OR ’lupus erythematoses systemic’ OR ’osler libman sacks |            |
|    | disease’ OR ’s.l.e.’ OR ’sle’ OR ’systemic lupus erythematoses’ OR  |            |
|    | ’systemic lupus erythamatoses’) AND [embase]/lim                     |            |
Table S4. The search strategy in Cochrane Library

| #  | Terms                                                                 | Quotes  |
|----|----------------------------------------------------------------------|---------|
| 1  | (therapy):ti,ab,kw                                                  | 704.834 |
| 2  | MeSH descriptor Therapeutics explode all trees                      | 143     |
| 3  | (intervention):ti,ab,kw                                            | 379.140 |
| 4  | (treatment):ti,ab,kw                                               | 782.201 |
| 5  | (prevention):ti,ab,kw                                              | 182.665 |
| 6  | MeSH descriptor Treatment Outcome explode all trees                 | 3.459   |
| 7  | (#1 OR #2 OR #3 OR #4 OR #5 OR #6)                                  | 1.219.409 |
| 8  | MeSH descriptor Lupus Erythematosus, Systemic explode all trees     | 48      |
| 9  | MeSH descriptor Lupus Nephritis explode all trees                   | 11      |
| 10 | MeSH descriptor Lupus Vasculitis, Central Nervous System explode all trees | 2      |
| 11 | MeSH descriptor Lupus Erythematosus, Cutaneous explode all trees    | 0       |
| 12 | (Lupus Erythematosus, Systemic ):ti,ab,kw                          | 2.267   |
| 13 | "Lupus":ti,ab,kw                                                   | 3.298   |
| 14 | (#8 OR #9 OR #10 OR #11 OR #12 OR #13)                              | 3.342   |
| 15 | (#7 AND #14)                                                        | 2.773   |
| 16 | pubmed:an OR embase:an                                              | 1.078.710 |
| 17 | (#15 NOT #16)                                                       | 967     |

Table S5. The search terms and specific filtering options used in the clinical trials registries

| #  | Terms                                                                 | Quotes |
|----|----------------------------------------------------------------------|--------|
| 1  | Filtering options set in advanced search function in ClinicalTrials.gov Study type: “Intervention”; Current status: “Recruiting” OR “Active, not recruiting” OR “Completed” OR “Enrolling by invitation” OR “Not yet recruiting” | 480    |
| 2  | Filtering options set in advanced search function in Chinese Clinical Trial Register Country: “China”; Study type: “Intervention” or “Prevention” or “Treatment” or “Prognosis”; Subjects recruitment: “Recruiting” OR “Completed” OR “Not recruiting” | 24     |
| 3  | Filtering options set in advanced search function in International Standard Randomised Controlled Trial Number Register (ISRCTN) Trial status: “Completed” OR “On going” Recruitment status: “Recruiting” OR “No longer recruiting” | 183    |
| 4 | Filtering options set in advanced search function in Australian and New Zealand Clinical Trials Registry (ACTR) |
|---|----------------------------------------------------------------------------------------------------------|
|   | Study type: “Intervention”;                                                                                |
|   | Registry: ANZCTR                                                                                           |
|   | Allocation to intervention: “Randomised”;                                                                |
|   | Current status: “Recruiting” OR “Active, not recruiting” OR “Completed” OR “Not yet recruiting”             |
Appendix 4 Literature search and selection

Figure S1. Literature search and selection from published articles

Records identified through database searching (n=4979)
PubMed: 2367
Embase: 1645
Cochrane library: 967

Records identified through review articles (n=102)

Records after duplicates removed (n=4342)

Records excluded (n=3792)
Full texts excluded (n=447)
not RCT: 176
full text not available: 7
not all SLE patients: 21
full text not in English or Chinese: 15
Involved same patients: 47
not in China: 181

Records full texts (n=550)

RCTs included in the systematic review (n=103)
Figure S2. Record search and selection from clinical trials registries

Records identified through websites searching (n=699)
ClinicalTrials.gov: 480
ChiCTR: 24
ISRCTN: 183
ACTR: 12

Records excluded (n=550)
not random: 63
no control group: 47
healthy participants: 21
not for LE: 274
not all SLE patients: 37
not yet approved by ethics committee: 2
not in China: 109

Records after duplicates removed
(n=88)
(61 duplicate trials)

RCTs included in the systematic review
(n=85)

The searching term “lupus” was used in each clinical trial registries.

& Records from clinical trials registries and published articles were matched using registration ID or other information if registration ID was unavailable. 61 trials were duplicated in published articles with registry entries.
## Appendix 5 Data abstraction form

### Table S6. Data abstraction form

| No. | Data Source | Author, year of publication | Registration ID | Year of start | Multinational study | Affiliation of primary investigator | Single or Multicenter | Subject categories | Number of participants |
|-----|-------------|-----------------------------|-----------------|---------------|---------------------|-------------------------------------|-----------------------|---------------------|-----------------------|
|     |             |                             |                 |               |                     |                                     |                       |                     |                       |

### Continued table 6. Data abstraction form

| Number of participants loss to follow-up | Percentage of loss-to-follow-up (%) | Intervention categories | Interventions | Intervention duration (month) | Age duration (years) | Blinding | Primary outcome | References | Country or area |
|-----------------------------------------|-------------------------------------|--------------------------|---------------|------------------------------|---------------------|----------|----------------|------------|----------------|
|                                         |                                     |                          |               |                              |                     |          |                |            |                |

| Number of participants loss to follow-up | Percentage of loss-to-follow-up (%) | Intervention categories | Interventions | Intervention duration (month) | Age duration (years) | Blinding | Primary outcome | References | Country or area |
|-----------------------------------------|-------------------------------------|--------------------------|---------------|------------------------------|---------------------|----------|----------------|------------|----------------|
|                                         |                                     |                          |               |                              |                     |          |                |            |                |
### Appendix 6. Characteristics of included RCTs

**Table S7. Characteristics of included RCTs of LE conducted in China**

| Categories                     | No (%)             |
|--------------------------------|--------------------|
| **Data source**                |                    |
| Published articles             | 103 (54.8)         |
| Clinical trials registries     | 85 (45.2)          |
| **Center**                     |                    |
| Single center                  | 96 (51.1)          |
| Multiple centers               | 92 (48.9)          |
| **Year of start**              |                    |
| Before 2002                    | 14 (7.4)           |
| 2002-2011                      | 61 (32.4)          |
| 2012-2021                      | 94 (50)            |
| Not available                  | 19 (10.1)          |
| **No. of participants**        |                    |
| <50                            | 44 (23.4)          |
| 50-99                          | 56 (29.8)          |
| 100-199                        | 28 (14.9)          |
| 200-499                        | 46 (24.5)          |
| ≥500                           | 14 (7.4)           |
| **Subjects**                   |                    |
| LN                             | 57 (30.3)          |
| **Blinding**                   |                    |
| Single blind                   | 7 (3.7)            |
| Double blind                   | 51 (27.1)          |
| Open label                     | 44 (23.4)          |
| Others                         | 32 (17.0)          |
| Others (Quadruple)             | 29 (15.4)          |
| Others (Triple)                | 3 (1.6)            |
| Not mentioned                  | 54 (28.7)          |
| **Intervention**               |                    |
| Pharmacological treatment      | 170 (94.1)         |
| Traditional Chinese medicine pharmacological treatment | 35 (18.6) |
| Behavioral intervention        | 1 (0.5)            |
| Biological therapy             | 9 (4.8)            |
| Procedure                      | 2 (1.1)            |
| Others                         | 3 (1.6)            |
| Care                           | 3 (1.6)            |
| **Intervention duration (months)** |                       |
| <1                             | 2 (1.1)            |
| 1-2.9                          | 10 (5.3)           |
| 3-5.9                          | 22 (11.7)          |
| Weight Range | Count (Percentage) |
|--------------|--------------------|
| 6-8.9        | 52 (27.7)          |
| 9-11.9       | 6 (3.2)            |
| 12-23.9      | 57 (30.3)          |
| 24-47.9      | 21 (11.2)          |
| ≥48          | 5 (2.7)            |
| Not mentioned| 13 (6.9)           |

**Primary outcome identification**

| Outcome | Count (Percentage) |
|---------|--------------------|
| Yes     | 143 (76.1)         |
| No      | 45 (23.9)          |

**Trial registration &**

| Registration | Count (Percentage) |
|--------------|--------------------|
| Yes          | 127 (67.6)         |
| No           | 61 (32.4)          |
## Appendix 7 Risk of bias assessments

### Figure S3. Risk of bias assessment graph: review authors’ judgements (Low, Unclear and High) for each risk of bias item

| Author and year | D1 | D2 | D3 | D4 | D5 | Overall |
|-----------------|----|----|----|----|----|---------|
| Yang et al., 1996 | 1  | 1  | 1  | 1  | 1  | Low risk |
| Fu et al., 1998  | 1  | 1  | 1  | 1  | 1  | Low risk |
| Li et al., 2014  | 1  | 1  | 1  | 1  | 1  | Low risk |
| Wang et al., 2012 | 1  | 1  | 1  | 1  | 1  | Low risk |
| Wen et al., 2007 | 1  | 1  | 1  | 1  | 1  | Low risk |
| Yang et al., 2014 | 1  | 1  | 1  | 1  | 1  | Low risk |
| Chan et al., 2000 | 1  | 1  | 1  | 1  | 1  | Low risk |
| Liu et al., 2003  | 1  | 1  | 1  | 1  | 1  | Low risk |
| Liu et al., 2009  | 1  | 1  | 1  | 1  | 1  | Low risk |
| Wang et al., 2006 | 1  | 1  | 1  | 1  | 1  | Low risk |
| Guo et al., 2002  | 1  | 1  | 1  | 1  | 1  | Low risk |
| Wen et al., 2001  | 1  | 1  | 1  | 1  | 1  | Low risk |
| Wu et al., 2019   | 1  | 1  | 1  | 1  | 1  | Low risk |
| Qi et al., 2006   | 1  | 1  | 1  | 1  | 1  | Low risk |
| Cheng et al., 2005| 1  | 1  | 1  | 1  | 1  | Low risk |
| Shi et al., 2007  | 1  | 1  | 1  | 1  | 1  | Low risk |
| Su et al., 2007   | 1  | 1  | 1  | 1  | 1  | Low risk |
| Tarn et al., 2004 | 1  | 1  | 1  | 1  | 1  | Low risk |
| Tao et al., 2007  | 1  | 1  | 1  | 1  | 1  | Low risk |
| Liu et al., 2008  | 1  | 1  | 1  | 1  | 1  | Low risk |
| Qian et al., 2015 | 1  | 1  | 1  | 1  | 1  | Low risk |
| Li et al., 2002   | 1  | 1  | 1  | 1  | 1  | Low risk |
| Wang et al., 2007 | 1  | 1  | 1  | 1  | 1  | Low risk |
| Zhang et al., 2014| 1  | 1  | 1  | 1  | 1  | Low risk |
| Appel et al., 2009| 1  | 1  | 1  | 1  | 1  | Low risk |
| Bao et al., 2008  | 1  | 1  | 1  | 1  | 1  | Low risk |
| Dooley et al., 2011| 1  | 1  | 1  | 1  | 1  | Low risk |
| Mok et al., 2019  | 1  | 1  | 1  | 1  | 1  | Low risk |
| Mok et al., 2020  | 1  | 1  | 1  | 1  | 1  | Low risk |
| Wu et al., 2003   | 1  | 1  | 1  | 1  | 1  | Low risk |
| Yap et al., 2012  | 1  | 1  | 1  | 1  | 1  | Low risk |
| Zhou et al., 2017 | 1  | 1  | 1  | 1  | 1  | Low risk |
| Chen et al., 2011 | 1  | 1  | 1  | 1  | 1  | Low risk |
| Liu et al., 2011  | 1  | 1  | 1  | 1  | 1  | Low risk |
| Chang et al., 2016| 1  | 1  | 1  | 1  | 1  | Low risk |
| Furie et al., 2014| 1  | 1  | 1  | 1  | 1  | Low risk |
| Ginzler et al., 2012| 1  | 1  | 1  | 1  | 1  | Low risk |
| Li et al., 2009   | 1  | 1  | 1  | 1  | 1  | Low risk |
| Liao et al., 2011 | 1  | 1  | 1  | 1  | 1  | Low risk |
| Ma et al., 2014   | 1  | 1  | 1  | 1  | 1  | Low risk |
| Meng et al., 2014 | 1  | 1  | 1  | 1  | 1  | Low risk |
| Navarra et al., 2011| 1  | 1  | 1  | 1  | 1  | Low risk |
| NCT00423088      | 1  | 1  | 1  | 1  | 1  | Low risk |
| Wang et al., 2015 | 1  | 1  | 1  | 1  | 1  | Low risk |
| You et al., 2009  | 1  | 1  | 1  | 1  | 1  | Low risk |
| You et al., 2010  | 1  | 1  | 1  | 1  | 1  | Low risk |
| Isenberg et al., 2015| 1  | 1  | 1  | 1  | 1  | Low risk |
| Li et al., 2012   | 1  | 1  | 1  | 1  | 1  | Low risk |
| NCT00705387      | 1  | 1  | 1  | 1  | 1  | Low risk |
| Song et al., 2013 | 1  | 1  | 1  | 1  | 1  | Low risk |
| An et al., 2019   | 1  | 1  | 1  | 1  | 1  | Low risk |
| Boedigheimer et al., 2017| 1  | 1  | 1  | 1  | 1  | Low risk |

- **D1** Randomisation process
- **D2** Deviations from the intended interventions
- **D3** Missing outcome data
- **D4** Measurement of the outcome
- **D5** Selection of the reported result
