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Efficacy and safety of tongxinluo capsule for angina pectoris of coronary heart disease: an overview of systematic reviews and meta-analysis

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Background: Tongxinluo capsule (TXLC) is a common drug for treating angina pectoris of coronary heart disease (CHD). In recent years, many systematic reviews (SRs) and meta-analyses (MAs) have reported the efficacy and safety of TXLC for improving angina symptoms in patients with CHD. We aimed to comprehensively evaluate the existing SRs and MAs of TXLC in treating angina pectoris of CHD, summarize the evidence quality, and provide scientific evidence and recommendations.

Methods: We searched seven databases for relevant SRs/MAs published up to 1 June 2023. Two reviewers independently completed the literature retrieval, screening, and data extraction. We used A Measurement Tool to Assess Systematic Reviews 2 (AMSTAR 2) to evaluate the methodological quality, the Risk of Bias in Systematic Reviews (ROBIS) to assess the risk of bias, and the Grading of Recommendations Assessment, Development and Evaluation (GRADE) to determine the strength of the evidence. RevMan 5.3 was used to synthesize data. Results: We identified 15 SRs/MAs, including 329 RCTs and 33,417 patients. According to the evaluation results of AMSTAR-2, only one SR was of high methodological quality, the others were very low. ROBIS assessment showed that one SR (6.67%) had a low risk, 3 SRs (20%) had an unclear risk, and 11 SRs (73.33%) had a high risk. We assessed 42 outcomes by the GRADE, 10 (23.81%) for moderate-quality evidence, 17 (40.48%) for low-quality evidence, and 15 (35.71%) for very-low-quality evidence. Mate-analysis showed that TXLC combined with conventional western medications improved electrocardiogram efficacy (RR = 1.38, 95% CI: 1.23-1.43, P < 0.001) and angina efficacy (OR = 3.58, 95% CI: 3.02-4.24, P < 0.001), reduced angina attack frequency (SMD = -0.54, 95% CI: -0.64 to -0.44, P < 0.001) and angina duration (SMD = -0.42, 95% CI: -0.57 to -0.28, P < 0.001), with general heterogeneity. The pooled results showed that TXLC appears to have some efficacy in improving cardiac function and relieving angina symptoms, but there is limited evidence that it improves cardiovascular event rates, hemorheology, lipids, or hs-CRP. In the assessment of drug safety, TXLC was associated with different degrees of adverse drug reactions. Conclusion: Based on the evidence, TXLC may be effective as an adjuvant treatment for angina pectoris of CHD. However, the quality of the evidence is low, and the drug's safety must be carefully interpreted. In future studies, highquality randomized controlled trials are needed to confirm the effectiveness and safety of TXLC.

Systematic Review Registration: http://www.crd.york.ac.uk/PROSPERO/, identifier (CRD42022365372).

KEYWORDS

tongxinluo capsule, angina pectoris, coronary heart disease, overview, traditional Chinese medicine

1 Introduction

According to the World Health Organization reported, the number of people with cardiovascular disease (CVD) worldwide increased from 271 million in 1990 to 523 million in 2019. The number of CVD patients in China is about 330 million, including 11.39 million coronary heart disease (CHD) patients (1). CHD is the most common type of CVD and the leading cause of death globally, bringing a heavy economic burden and health threat to the world's population (2). Angina pectoris of CHD is a common clinical disease with high mortality in the acute stage.

Conventional treatment for angina pectoris of coronary heart disease mainly includes antiplatelet aggregation, plaque stabilization, risk factor reduction, antianginal drugs, and revascularization. However, some limitations exist, such as clinical resistance to drugs and long-term side effects (3-5). The individual efficacy of current treatment regimens varies greatly, and patient compliance could be better, which makes it difficult to obtain satisfactory clinical efficacy. Therefore, finding potential ways to relieve angina pectoris of CHD is necessary. TXLC is a traditional Chinese medicine preparation developed by Shijiazhuang Yiling Pharmaceutical Co., Ltd. for treating angina pectoris and chest tightness caused by myocardial ischemia. It mainly comprises ginseng, leech, scorpion, centipede, chuanxiong, and borneol. It has the effect of benefiting qi and promoting blood circulation, dreading collaterals, and relieving pain. Clinically, TXLC plays a positive role in protecting the vascular endothelium, dilating the coronary arteries, enhancing cardiac contractility, improving myocardial ischemia, lowering blood lipids, stabilizing plaques, alleviating angina pectoris and preventing coronary embolism and myocardial infarction (6, 7).

TXLC is widely used in China and has been recommended by multiple guidelines and expert consensuses for treating angina pectoris. A meta-analysis showed that TXLC has an excellent secondary prevention effect on angina pectoris of CHD (8) and has beneficial effects on preventing adverse cardiovascular events (9). However, during treatment, TXLC can also cause gastrointestinal reactions, limb weakness, dizziness, headache, and other adverse drug reactions (10). Because of this, it is necessary to comprehensively evaluate the efficacy and safety of TXLC in treating angina pectoris of CHD to provide better evidence.

2 Methods

2.1 Search strategy

We searched three international databases (PubMed, Cochrane Library, and Embase) and four Chinese databases (CNKI,

SinoMed, Wanfang, and VIP) to identify eligible SRs/MAs published up to 1 June 2023 without language restriction.

Taking the PubMed database as an example, the specific retrieval formulas are as follows. In addition, we manually searched the list of references in the included SRs. The details are shown in the Supplementary Material of the search strategy.

- #1 (((((((Angina Pectoris [MeSH Terms]) OR (Coronary Disease [MeSH Terms])) OR (Coronary heart disease[Text Word])) OR (CHD [Text Word])) OR (Coronary atherosclerotic heart disease [Text Word])) OR (coronary atherosclerotic cardiopathy [Text Word])) OR (angina [Text Word])) OR (stenocardia [Text Word])) OR (angor pectoris [Text Word])
- #2 (((((Tong-xin-luo) OR (Tong xin luo)) OR (tong xin luo)) OR (Tongxinluo)) OR (tongxinluo)) OR (tongxinluo)) OR (tongxinluo capsule) [[All Fields]
- #3 ((systematic review [Text Word]) OR (systematic evaluation [Text Word])) OR (meta-analysis [Text Word])
- #4 #1 AND #2 AND #3

2.2 Inclusion criteria

We included SRs and MAs based on RCTs of TXLC for angina pectoris of CHD. Subjects were patients with stable/unstable angina pectoris of CHD without restriction on gender, age, and course of the disease. The treatment group included TXLC or TXLC combined with conventional therapy. The control group only received conventional therapy. The primary outcome measures were ECG improvement and angina symptom relief. Secondary outcome measures included the incidence of cardiovascular events, frequency of angina attack, duration of angina, hemorheology, lipid levels, hS-CRP, and adverse reactions. At least one direct result for cardiac conditions was reported in each SR.

2.3 Exclusion criteria

We excluded an SR if it met any of the following criteria: (a) SRs or MAs not based on RCTs; (b) TXLC was not the only treatment or adjuvant treatment in the experimental group; (c) repeat publications; (d) unable to obtain the full text or incomplete data presented and (e) other types of research, such as animal experiments, protocols, conference papers, and case reports.

2.4 Study selection and data extraction

According to the comprehensive retrieval strategy, two reviewers independently retrieved and screened the literature. The opinion of a

third reviewer was sought when there was a disagreement. After identifying eligible studies, two researchers independently extracted relevant data using standardized extraction tables, such as author, publication year, sample size, diagnostic criteria, interventions, outcomes, adverse reactions, conclusions, etc. Two reviewers crosschecked the extracted content; a third reviewer was consulted to resolve discrepancies.

2.5 Assessment of SRs

SRs that met the inclusion criteria were independently assessed by two reviewers for the methodological quality of the SRs, the quality of evidence, and the risk of bias.

2.5.1 AMSTAR 2

Two reviewers used A Measurement Tool to Assess Systematic Reviews 2 (AMSTAR 2) (11) to evaluate the methodological quality of SRs. This tool includes 16 items, with items 2, 4, 7, 9, 11, 13, and 15 considered essential. Items 2, 4, 7, 8, and 9 are rated as yes, no, or partially yes. The study quality was judged as high when no or only one non-essential item did not meet the requirements; medium when more than one non-essential item did not meet the requirements; low when any of the essential items did not meet the requirements and very low when more than one essential item did not meet the requirements.

2.5.2 ROBIS

We used the ROBIS tool (12) to assess the risk of bias (RoB) for SRs, including four key areas: (a) study eligibility criteria, (b) study identification and selection, (c) data collection and study appraisal, and (d) synthesis and findings. Finally, we divided the risk level into "low risk," "high risk," and "unclear risk." One person assessed RoB, another checked this assessment, and both reviewers discussed the results. In the case of disagreement, a third party was consulted.

2.5.3 GRADE

Two researchers independently used the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) tool (13) to evaluate the quality of the evidence. The tool includes five aspects: RoB, inconsistency, indirectness, imprecision, and publication bias. We graded the quality of evidence as "high," "moderate," "low," or "very low." The two reviewers cross-checked the results, and a third reviewer resolved disputes.

2.6 Data synthesis and analysis

RevMan5.3 is used for statistical analysis of the data. Relative risk (RR) was used as the statistic for categorical variables. For continuous variables, mean difference (MD) was used as the statistic if the measurement method and units were the same. Standardized mean difference (SMD) was used as the statistic if measured by different methods or with different units, and its 95% confidence interval (CI) was calculated. Heterogeneity was tested using the I^2 quantitative method. If $I^2 \leq 50\%$, homogeneity

was considered good, and Meta-analysis was performed using a fixed-effects model; if $I^2 > 50\%$, statistical heterogeneity between studies was indicated. Meta-analysis was performed using a random-effects model and, if necessary, subgroup or sensitivity analysis. Publication bias was judged using funnel plots.

3 Results

3.1 Search results

We retrieved 168 related SRs from seven databases. Of these, we deleted 114 duplicates and then screened 34 studies, followed by a full-text evaluation. Finally, we included 15 SRs. The detailed flow chart is shown in Figure 1. The list of exclusions and reasons are shown in the Supplementary Material of excluded list.

3.2 Characteristics of included SRs

The 15 SRs (14-28) were published from 2007 to 202, four SRs (25-28) were published in English, and the other 11 SRs (14-24) were in Chinese. The SRs comprised a total of 329 RCTs and 34,398 subjects. Each SR included 9-78 RCTs, including unstable angina pectoris (14-16, 28), coronary heart disease (17, 18, 27), and angina pectoris (19-26). Eight SRs defined the diagnostic criteria: three SRs (17, 22, 25) adopted the WHO diagnostic criteria for angina pectoris of CHD, two SRs (16, 27) adopted the Nomenclature and Diagnostic Criteria for Ischemic Heart Disease developed by WHO, one SR (14) adopted the Guidelines for Clinical Research on Drugs in the Cardiovascular System, one SR (23) adopted the International Society of Cardiology and Association of Diagnostic Criteria for Coronary Heart Disease Angina Pectoris and one SR (28) adopted the International Diagnostic Guidelines. The control group usually received conventional therapy, and the treatment group included TXLC or TXLC combined with conventional therapy. The duration was usually 4-8 weeks. Adverse events were reported in 11 SRs (14, 17-20, 22-26, 28), no adverse events were observed in 3 SRs (15, 16, 19), and adverse events were not mentioned in the remaining SRs (27). Regarding the methodological quality assessment, five SRs (14, 19, 21, 22, 25) used the Jadad scale, two SRs (18, 24) did not report this information, and the remaining eight SRs (15-17, 20, 23, 26-28) used the Cochrane Collaboration's RoB assessment tool. The basic characteristics of the literature are shown in Table 1.

3.3 Methodological assessment

We used AMSTAR 2 to assess the methodological quality of the 15 SRs. Only one SR had high methodological quality, and in the remaining SRs, the methodological quality could have been much higher. Among the essential items, only two SRs reported the research protocol [item 2 (25, 28)], and only one SR reported the exclusion list [item 7 (28)]. All SRs reported in detail (100%) their database searches (entry 4), fair use of the risk of bias assessment tools (item 9), and risk of bias assessment (item 13).



86.67% of SRs adequately reported on the data synthesis (item 11), and 56.25% of SRs thoroughly investigated and discussed the possible influence of publication bias on the research results (item 15). Among the non-critical items, all SRs provided reasonable information on the inclusion criteria (item 1), literature screening and data extraction (items 5 and 6), and essential characteristics (item 8); moreover, 83.3% of SRs provided a heterogeneity discussion (item 14). However, only 13.3% of SRs reported the reasons for the inclusion of RCTs (item 3), funding sources (item 10), and conflicts of interest (item 16). The detailed results are shown in Table 2.

3.4 RoB

The combined results show that only 1 SR had a low risk, 3 SRs (20%) had an unclear risk, and the remaining 11 SRs (73.33%) had a high risk. The detailed results are shown in Figure 2 and Table 3.

3.5 Quality of evidence

We used the GRADE tool to evaluate the evidence quality of 42 outcomes. There were ten outcomes of moderate quality (23.81%), 17 of low quality (40.48%), and 15 of very low quality (35.71%). The main factors influencing demotion were risk of bias, publication bias, imprecision, and inconsistency.

3.6 Clinical efficacy of TXLC

Among the 13 SRs that assessed ECG improvement, 6 SRs with outcome measures of moderate quality suggested that TXLC improved cardiac function, but 7 SRs had low-quality evidence. 9 SRs evaluated the time to angina symptom relief, 3 SRs with outcome measures of moderate quality suggested that TXLC shortened the time to angina relief, and the rest were of low/very

x_{0} ct, et al. (14) 12 (72/363) 0 $TXLC + CT$ CT 0	Author, year (Country)	Trials (subjects)	Diagnostic criteria	Treatment intervention	Control intervention	Adverse reaction	Primary outcomes	Methodological evaluation tool	Main conclusion
Turdit Lunder TXLC+CT CT None 0.0300000 Centure TN Vu X Qr e1 (i) 1.107) 1.107) 2 TXLC+CT CT None 0.020000000 Centure TX Vu X Qr e1 (i) 1.107) 3 7YY600 Centure TX TX Centure TX Clinese) 2 YU X Qr e1 (i) 1.1070/X00000 Centure TX TX Clinese) 2 YU X Cr e1 (i) 1.1070/X00000 Centure TX Clinese) 10 1.107/X0000 Centure TX TX Clinese) 10 1.107/X00000 Centure TX TX Clinese) 10 1.107/X00000000000000000000000000000000000	Xu GL et al. (14) (Chinese)	15 (727/653)	Θ	TXLC + CT	CT	Θ	03	Jadad	TXLC was superior to CT in relieving AP and improving electrocardiogram.
W. M. M. Ge tail (16) [16] (16) [16] (16) [16] (16) [16] (16) [16] (16) [16] (16) [16] (16) [16] (16) [16] (16) [16] (16) [16] (16) [16] (16) [17] (17) [16] (17) [17] (17) [16] (16) <td>Yang J et al. (15) (Chinese)</td> <td>30 (1,188/ 1,107)</td> <td>Unclear</td> <td>TXLC + CT</td> <td>CT</td> <td>None</td> <td>D2345678900</td> <td>Cochrane</td> <td>The effect of TXLC on UAP was definite.</td>	Yang J et al. (15) (Chinese)	30 (1,188/ 1,107)	Unclear	TXLC + CT	CT	None	D2345678900	Cochrane	The effect of TXLC on UAP was definite.
Zhou ZR et al. (1)13 (73)(69)(2)TXLCCT(0.26)(0)CoheneTX(Chines)19 (1,05)(86)UnclearTXLCCT0.26.3(4)UnclearMatTX(Chines)19 (1,05)(86)UnclearTXLCCT0.26.3(4)UnclearTXTX(Chines)10 (1)20 (1,194)20 (1,195)UnclearTXLCCT0.26.3(4)UnclearTX(Chines)10 (1)20 (1,194)UnclearTXLCCT0.300.2DateTX(Chines)10 (1)10 (1)10 (1)10 (1)0.20.2DateTX(Chines)10 (1)10 (1)10 (1)0.20.2DateTX(Chines)10 (1)9 (570)UnclearTXLCCT0.30.2DateTX(Chines)10 (1)9 (570)UnclearTXLCCT0.05(6)0.2DateTX(Chines)10 (1)9 (570)UnclearUnclear0.20.2DateTX(Chines)10 (1)10 (1)10 (1)Unclear10 (1)UnclearTX(Chines)10 (1)10 (1)10 (1)0.20.2DateDateDate(Chines)10 (1)10 (1)10 (1)0.20.2DateDateDate(Chines)10 (1)10 (1)10 (1)0.20.2DateDateDate(Chines)10 (1)10 (1)10 (1)10 (1	Wu XQ et al. (16) (Chinese)	14 (661/605)	6	TXLC + CT	CT	None	03	Cochrane	TXLC combined with CT improved clinical symptoms and electrocardiogram of UAP was better than CT.
He HZ et al. (18) $9 (1,005/86)$ UnclearTXLC CT $(0^{2})^{2}(0)$ $(0^{2})^{2}(0)$ $(10^{2}0)^{2}(0)$ $(10^{2}0)^{2}(0)$ $(10^{2}0)^{2}(0)^{2}(0)^{2}(0)$ $(10^{2}0)^{2}($	Zhou ZR et al. (17) (Chinese)	13 (797/699)	0	TXLC	CT	033	Θ	Cochrane	TXLC was superior to CT in treating AP of CHD.
Hao CH et al. (19) $20(1.198')$ UnclearTXLCCT 0 <	He HZ et al. (18) (Chinese)	19 (1,005/869)	Unclear	TXLC	CT	0.234	Θ	Unclear	TXLC had better clinical efficacy and electrocardiogram efficacy than CT.
Wang Y et al. (20) 21 (1,157/ Unclear TXL + CT CT 0.3 0 Cohrane TX Chinese) $1,0300$ Unclear TXL C + CT CT None 0.3 10300 TX 113 10300 TX 113 10301 TX TX 113 10301 TX 113 110 1134433 110 110 113 110	Hao CH et al. (19) (Chinese)	20 (1,198/ 1,026)	Unclear	TXLC	CT	Θ	00	Jadad	TXLC was effective and safe in treating angina pectoris.
Xu GL et al. (1)9 (570/492)UnclearTXLCCTNone 0^{20} 0^{20} 124 123 $126/4433$ $126/44333$ $126/44333$ $126/44333$ $126/44333$ $126/44333$ $126/44333$ $126/44333$ $126/44333$ $126/44333$ $126/44333$ $126/44333$ $126/44333$ $126/44333$ $126/44333$ $126/44333$ $126/44333$ $126/44333$ $126/44333$ $126/443333$ $126/443333$ $126/443333$ $126/443333$ $126/443333$ $126/443333$ $126/443333$ $126/4433333$ $126/4433333$ $126/4433333$ $126/44333333$ $126/44333333$ $126/44333333$ $126/44333333$ $126/44333333$ $126/44333333333333333126/443333333333333333333333333126/4433333333333333333333333333333333333$	Wang Y et al. (20) (Chinese)	21 (1,157/ 1,030)	Unclear	TXLC + CT	CT	03	Θ	Cochrane	TXLC combined with CT is more efficient than CT.
Peng R et al. (22) $10 (434/43)$ 2 $TXLC+CT$ CT $0 = 3 = 6 = 6$ $13 = 44$ TX Chinese) $12 (685/460)$ 4 $TXLC$ $10 = 36 = 6 = 6 = 6 = 6 = 6 = 6 = 6 = 6 = $	Xu GL et al. (21) (Chinese)	9 (570/492)	Unclear	TXLC	CT	None	00	Jadad	TXLC was better than CT in relieving AP and improving electrocardiogram.
Chen J et al. (23)I2 (685)460)(\oplus TXLCIsosorbide dinitrate(\square (\square)($\square)$ ($\square)$	Peng R et al. (22) (Chinese)	10 (434/433)	8	TXLC + CT	CT	D4567	03	Jadad	TXLC combined with CT could effectively improve AP
Fan R et al. (24) I1 (645/617) Unclear TXLC + CT CT U U Unclear TX (Chinese) 1 (1,062/874) 20 (1,062/	Chen J et al. (23) (Chinese)	12 (685/460)	4	TXLC	Isosorbide dinitrate	033	03	Cochrane	TXLC is more effective than isosorbide nitrate in treating AP of CHD, and has higher safety.
	Fan R et al. (24) (Chinese)	11 (645/617)	Unclear	TXLC + CT	CT	Θ	00	Unclear	TXLC combined with CT was better than CT
Jia YL et al. (26) 78 (3,444) Unclear TXLC Betloc ①②③ ① Cochrane TX (English) 3,980) 3,980) TXLC Betloc ①③③ ① Cochrane TX Liu Q et al. (27) 15 (789/789) ③ TXLC + Atorvastatin Atorvastatin Unclear ④⑤①③④ XL Liu Q et al. (28) 42 (2,867) ⑤ TXLC + CT CT ①③⑧④ Cochrane XL Li PQ et al. (28) 42 (2,867) ⑤ TXLC + CT CT ①③⑧④ Cochrane TX- Li PQ et al. (28) 25:34) ⑤ ①③⑧④ ①③⑧ Cochrane TX-	Jia YL et al. (25) (English)	20 (1,062/874)	8	TXLC	Isosorbide dinitrate	D 234	Θ	Jadad	TXLC combined with CT was better than CT
Liu Q et al. (27) 15 (789/789) ③ TXLC + Atorvastatin Atorvastatorvastin Atorvastatorvastin	Jia YL et al. (26) (English)	78 (3,444/ 3,980)	Unclear	TXLC	Betloc	033	Θ	Cochrane	TXLC combined with CT was better than CT
Li PQ et al. (28) 42 (2,867) ⑤ TXLC + CT CT ①⑤⑧⑨ ①③⑧ Cochrane TX (English) 2.554) ⑥ TXLC + CT CT ①③⑧ Cochrane TX	Liu Q et al. (27) (English)	15 (789/789)	0	TXLC + Atorvastatin	Atorvastatin	Unclear	45678900	Cochrane	XLC combined with atorvastatin was more effective in treating CHD.
	Li PQ et al. (28) (English)	42 (2,867/ 2,554)	6	TXLC + CT	CT	0080	000	Cochrane	TXLC is effective and safe for AP.

developed by WHO. (a) International Society of Cardiology and Association of Diagnostic Criteria for coronary heart disease angina pectoria. (a) International diagnostic guidelines are acceptable.

Adverse reaction: ③ Digestive reaction. ③ Headache. ③Fushing. ④ Dizziness. ⑤ Bleeding. ⑥ Palpitation. ⑦ Chest tightness. ⑥ Hypotension. ⑥ Bradycardia. Primary outcomes: ⑥ ECG improvement. ② Angina symptoms relief. ③ Incidence of cardiovascular events. ④ Angina attack frequency. ⑤ Duration of angina. ⑥ Hypersensitivity-CRP. ⑦ Total cholesterol. ⑧ Triglyceride. ⑥ High-density lipoprotein cholesterol. ⑩ Low-density lipoprotein cholesterol. ⑪ Adverse reaction. AP, angina pectoris; UAP, unstable angina pectoris; CHD, coronary heart disease; I, intervention; C, comparison; d, day: w, week; Y, year; TXLC, tongxinluo capsule; CT, conventional therapy.9.

TABLE 2 The detail	ed results	of AMSTAF	R-2.														
References								A	MSTAR-2								Quality
	ltem1	ltem2	ltem3	ltem4	ltem5	ltem6	ltem7	ltem8	ltem9	ltem10	ltem11	ltem12	ltem13	ltem14	ltem15	ltem16	
Xu GL et al. (14)	Υ	z	z	ΡΥ	Υ	Y	z	ΡΥ	Y	z	Y	z	Y	Υ	z	z	Critically low
Yang J et al. (15)	Υ	z	z	ΡΥ	Υ	Y	z	ΡΥ	Y	Y	Y	Y	Y	Υ	Y	Y	Critically low
Wu XQ et al. (16)	Υ	z	z	ΡΥ	Υ	Y	z	ΡΥ	ΡΥ	z	Y	Y	Y	Υ	Y	z	Critically low
Zhou ZR et al. (17)	Υ	z	z	ΡΥ	Υ	Y	z	Υ	Y	z	Y	z	Y	Υ	Y	z	Critically low
He HZ et al. (18)	Υ	z	Υ	Υ	Υ	Y	z	ΡΥ	Y	z	Y	Y	Y	Υ	Y	z	Critically low
Hao CH et al. (19)	Υ	z	z	ΡΥ	Υ	Y	z	ΡΥ	ΡY	z	Y	Y	Y	Υ	Y	z	Critically low
Wang Y et al. (20)	Υ	z	z	ΡΥ	Υ	Y	z	ΡΥ	Y	z	Y	z	Y	Z	z	z	Critically low
Xu GL et al. (21)	Υ	z	z	ΡΥ	Υ	Y	z	ΡΥ	Υ	z	Υ	z	Υ	Υ	z	z	Critically low
Peng R et al. (22)	Υ	z	Υ	ΡΥ	Υ	Y	z	ΡΥ	Y	z	Y	z	Y	Υ	z	z	Critically low
Chen J et al. (23)	Υ	z	z	ΡΥ	Υ	Y	z	ΡΥ	Y	z	Y	Y	Υ	Υ	Y	z	Critically low
Fan R et al. (24)	Υ	z	z	ΡΥ	Υ	Y	z	ΡΥ	Y	z	Y	Y	Y	Υ	Y	z	Critically low
Jia YL et al. (25)	Υ	Y	z	ΡΥ	Υ	Y	z	ΡΥ	Y	z	z	z	Y	Υ	z	z	Critically low
Jia YL et al. (26)	Υ	z	z	ΡΥ	Υ	Y	z	ΡΥ	Y	z	z	z	Y	Υ	Z	z	Critically low
Liu Q et al. (27)	Υ	Z	Z	ΡΥ	Υ	Y	z	ΡΥ	Υ	z	Υ	Υ	Y	Υ	Y	Y	Critically low
Li PQ et al. (28)	Υ	Υ	Z	ΡΥ	Υ	Y	Υ	ΡΥ	Υ	Υ	Υ	Υ	Y	Υ	Y	Y	High
Y + PY/total (%)	100	13.3	13.3	100	100	100	6.67	100	100	13.3	86.67	53.3	100	83.3	60	13.3	

low quality. In addition, there is limited evidence that TXLC improves the incidence of cardiovascular events, hemorheology, lipid levels, and hs-CRP levels. Thus, TXLC appears to have some efficacy in improving cardiac function and relieving angina pectoris, but the overall efficacy in angina pectoris of CHD should be interpreted with caution.

Eight SRs reported the effectiveness of TXLC in treating AP (14, 19, 20, 22–26), and all of them suggested that the TXLC group had better cardiac function recovery than the control group. Only four SRs had a moderate quality of evidence (19, 20, 24, 25), and the rest of the items were of low quality or very low quality. Five SRs showed that the improvement of angina symptoms in the TXLC group was better than that in the control group (14, 19, 22–24). The evidence quality of only two SRs was moderate (19, 24), and that of the rest was low.

Four SRs reported the effectiveness of TXLC in treating UAP (15, 16, 21, 28). All of them reported electrocardiogram results with TXLC in UAP patients, and the results suggested that TXLC was better than Western medical treatment. Only one SR was rated as moderate quality (15), and the rest of the evidence was low quality. Three SRs suggested that the TXLC group had more significant relief of angina symptoms than the control group (15, 16, 21), and only one had moderate quality of evidence (15). Two SRs suggested that cardiovascular events and hs-CRP incidence were lower in the TXLC group than in the control group. One study reported a significant reduction in the frequency and duration of angina attacks in the TXLC group [SMD = -1.00, 95% CI (-1.58, -0.42), P = 0.0007; SMD = -2.25, 95% CI (-3.31, -1.19), P < 0.0001]. In addition, there was very-low-quality evidence that TXLC has some efficacy in improving lipid levels in UAP.

3.7 Adverse events

12 SRs reported adverse events, mainly gastrointestinal discomfort, such as loss of appetite, nausea, abdominal pain, and abdominal distension, and other adverse events, such as facial flushing, chest tightness, dizziness, headache, and gingival bleeding. A meta-analysis was performed on three SRs for adverse reactions, and two SRs showed no significant difference between the experimental and control groups (15, 27). Another SR (17) showed that the incidence of adverse reactions to TXLC was lower than that of conventional western drugs [RR = 0.33, 95% CI (0.20, 0.53), P < 0.00001], but the quality of evidence was low.

3.8 Results of the data synthesis and quantitative analysis

The outcome index of electrocardiogram efficacy was evaluated in 50 original RCTs screened from 15 SRs. The TXLC group was superior to the traditional therapy group (RR = 1.38, 95% CI: 1.23–1.43, P < 0.001), with moderate heterogeneity ($I^2 = 42\%$) and high confidence. According to the outcome index of 52 original RCTs selected from 15 SRs, TXLC combined with Western medicine can effectively improve angina pectoris with high confidence (OR = 3.58, 95% CI:

ġ.

PY, partial yes; N,

Y, yes;



3.02–4.24, P < 0.001, $I^2 = 34\%$). According to the outcome index of 15 original RCTs selected from 15 SRs, TXLC combined with Western medicine was superior to conventional therapy in reducing the frequency of angina attacks (SMD = -0.54, 95% CI: -0.64 to -0.44, P < 0.001). Heterogeneity and reliability are moderate ($I^2 = 48\%$). Eight original RCTs selected from 15 SRs were evaluated as an outcome of angina duration. Compared with traditional therapy, the TXLC group can significantly reduce the angina duration (SMD = -0.42, 95% CI: -0.57 to -0.28, P < 0.001), with low heterogeneity ($I^2 = 17\%$) and high confidence. Funnel plot analysis of four outcome indexes of RCTs, including electrocardiogram therapy, angina efficacy, angina duration, and angina attack frequency, showed that the visual graph was symmetrical, indicating no obvious publication bias. The detailed results are shown in Figures 3–10.

4 Discussion

4.1 Summary of the main results

This systematic review summarizes the data from 15 TXLC SRs for angina pectoris in coronary heart disease, including 329 RCTs and 33,417 patients. The results showed that TXLC effectively

TABLE 3 The detailed results of RoB.

improved cardiac function and relieved angina pectoris. However, there was insufficient evidence to support the role of TXLC in improving the incidence of cardiovascular events, hemorheology, and lipid levels. The adverse drug effects of TXLC did not appear to be statistically significant compared with those in the control group. The methodological quality of 14 SRs could have been higher, with only 26% of the evidence being of medium quality and over 90% of SRs having unclear or high risk. The results of a single SR confirmed the efficacy of TXLC in relieving angina pectoris of coronary heart disease. However, the results of ROBs evaluation showed that the risk of bias of the SRs was high, which reduced the credibility of their conclusions.

4.2 Results-based discussion

Regarding the AMSTER 2 methodological evaluation, 86.67% of SRs did not indicate whether they had pre-registered for the study protocol. A detailed research plan is necessary for a systematic review, and following the plan can reduce the risk of bias in the systematic review process. Almost all SRS did not include a list of exclusions and reasons for exclusion. We could not determine whether researchers purposefully excluded some original studies that affected the SR results, which may have increased selection bias. Nearly 50% of the SR authors did not evaluate the possible impact of the risk of bias in the included studies on the meta-analysis results in detail and did not thoroughly investigate the possibility of publication bias in the quantitative synthesis, which may affect the stability of the results. When conducting a qualitative analysis, the possible influence of the risk of bias on the results of a single study should be discussed, and the publication bias should be reasonably analyzed; for example, the funnel plot and Egger's test should be used to evaluate the publication bias and sensitivity analysis should be used to verify the stability of the results.

Regarding the GRADE evidence quality assessment, only 23.81% of the outcome measures were rated as medium quality.

Reference	Study eligibility criteria	Identifification and selection of studies	Data collection and study appraisal	Synthesis and fifindings	Risk of bias in the review
Xu GL et al. (14)	high risk	low risk	low risk	low risk	high risk
Yang J et al. (15)	high risk	high risk	high risk	low risk	high risk
Wu XQ et al. (16)	high risk	high risk	high risk	high risk	high risk
Zhou ZR et al. (17)	low risk	unclear risk	low risk	low risk	unclear risk
He HZ et al. (18)	low risk	high risk	low risk	low risk	high risk
Hao CH et al. (19)	high risk	high risk	high risk	low risk	high risk
Wang Y et al. (20)	high risk	high risk	high risk	low risk	high risk
Xu GL et al. (21)	high risk	low risk	high risk	unclear risk	unclear risk
Peng R et al. (22)	high risk	high risk	high risk	high risk	high risk
Chen J et al. (23)	high risk	high risk	high risk	high risk	high risk
Fan R et al. (24)	low risk	low risk	unclear risk	high risk	unclear risk
Jia YL et al. (25)	low risk	low risk	low risk	low risk	low risk
Jia YL et al. (26)	low risk	high risk	high risk	low risk	high risk
Liu Q et al. (27)	high risk	high risk	low risk	high risk	high risk
Li PQ et al. (28)	low risk	high risk	low risk	low risk	high risk

tudu or Cubaroun	Experim	Total	Evente	Tatal	Walaht	M H Bandom OFV CL	M H Bandom OF% Cl
Study of Subgroup	Events	10(a)	Events	Total	weight	M-H, Kaliuolii, 93% Cl	
Lai 2004	29	40	20	40	1.4%	1.45 [1.01, 2.09]	
Lao 2009	29	35	23	35	2.0%	1.26 [0.95, 1.67]	
Chen 2010	26	29	22	29	2.5%	1.18 [0.93, 1.50]	
Cheng 2010	52	60	41	58	3.0%	1.23 [1.01, 1.49]	-
Chen RX 2009	64	94	38	96	2.0%	1.72 [1.30, 2.28]	
Du 2005	37	50	24	50	1.6%	1.54 [1.11, 2.15]	
Du 2016	32	40	12	40	0.9%	2.67 [1.62, 4.39]	
Fu 2004	47	60	15	24	1.6%	1.25 [0.89, 1.76]	
Guo 2010	48	52	24	50	1.9%	1.92 [1.43, 2.59]	
Hao 2015	50	55	40	55	3.2%	1.25 [1.04, 1.50]	-
Hui 2018	47	50	38	50	3.4%	1.24 [1.04, 1.47]	-
Jiang 2010	30	43	19	43	1.3%	1.58 [1.07, 2.33]	
Kang 2008	34	50	27	48	1.8%	1.21 [0.88, 1.65]	<u>+-</u>
Li 2010	38	40	30	40	3.0%	1.27 [1.04, 1.54]	-
Li 2013	77	80	62	80	4.1%	1.24 [1.10, 1.41]	-
Liao 2013	38	55	22	55	1.4%	1.73 [1.19, 2.50]	
Liu 2011	25	40	7	20	0.6%	1.79 [0.94, 3.40]	
Liu 2017	21	30	14	30	1.0%	1.50 [0.96, 2.35]	
Liu CH 2006	37	60	36	57	2.0%	0.98 [0.74, 1.29]	+
Li YY 2003	46	53	37	53	2.9%	1.24 [1.01, 1.53]	
Luo 2007	27	30	24	30	2.8%	1.13 [0.91, 1.39]	-
Luo 2010	20	28	12	26	0.9%	1.55 [0.96, 2.49]	
Peng 2010	28	34	17	34	1.4%	1.65 [1.14, 2.39]	
Pi 2011	31	36	23	30	2.5%	1.12 [0.89, 1.42]	+-
Qiao 2006	26	30	11	30	0.9%	2.36 [1.45, 3.86]	
Qu 2011	50	60	31	52	2.3%	1.40 [1.09, 1.80]	
Ren 2018	34	50	26	50	1.7%	1.31 [0.94, 1.81]	
Rui 2010	37	50	24	50	1.6%	1.54 [1.11, 2.15]	
Shen 2006	25	38	15	36	1.0%	1.58 [1.01, 2.47]	
Shi CI 2013	50	62	36	58	2.5%	1.30 [1.03, 1.64]	
Shi CO 2013	100	134	66	134	3.0%	1.52 [1.24, 1.85]	-
Song 2008	50	56	41	56	3.2%	1.22 [1.02, 1.46]	
Sun 2015	29	40	19	40	1.4%	1.53 [1.05, 2.23]	
Tao 2007	19	30	16	30	1.1%	1.19 [0.77, 1.83]	_
Wang 2014	52	60	46	60	3.4%	1 13 [0 95 1 34]	-
Wang EL 2011	36	45	28	45	2.1%	1 29 [0 98 1 69]	L
Wang FS 2011	23	30	14	30	1 1%	1.64 [1.07, 2.53]	
Wang 71 2006	51	00	47	00	3.4%	1.09 [0.92, 1.29]	L .
Wally 20 2000	111	194	52	160	2.4%	1.09 [0.92, 1.29]	
Wu 2009 Viana 2009	20	104	12	22	2.5%	1.00 [1.44, 2.39]	
Xi011g 2009	25	25	10	25	1.0%	1.45 [0.91, 2.31]	
Xiu 2008 Xang 2010	20	55	10	55	1.4%	1.44 [0.99, 2.10]	
Tang 2019	29	50	20	50	2.4%	1.04 [0.71, 1.51]	
rang G 2005	40	50	39	50	3.4%	1.18 [1.00, 1.40]	·
Yao 2012	20	34	19	34	1.5%	1.37 [0.96, 1.95]	
Yu 2007	/4	120	22	60	1.5%	1.68 [1.17, 2.41]	
znan 2011 Zhana 2001	21	30	16	30	1.2%	1.31 [0.87, 1.97]	T
Zhang 2004	26	33	27	35	2.3%	1.02 [0.79, 1.31]	T
Zhang 2011	35	43	25	43	2.0%	1.40 [1.05, 1.87]	
Zhang 2015	40	45	33	45	2.9%	1.21 [0.99, 1.49]	-
Zheng 2014	28	40	16	40	1.1%	1.75 [1.14, 2.69]	
Fotal (95% CI)		2629		2428	100.0%	1.33 [1.27, 1.40]	1
Total events	1996		1355				
Heterogeneity: Tau ² =	= 0.01; Ch	$i^2 = 84.$	31, df = ·	49 (P =	0.001); I	² = 42%	
Test for overall effect	: Z = 11.0	2 (P < 0	.00001)				Eavours [experimental] Eavours [control]
			,				ravours (experimental) ravours (control)

Because of the reasons for the degradation of evidence quality, we summarize the following points: First, the risk of bias was high, mainly due to the methodological quality of the included original research, including various biases in the design, implementation, and measurement of the study. Second, the publication bias was high. The number of RCTs was small, the results were positive, or the funnel plot was asymmetric, which may lead to the biased publication of the outcome indicators. Publication bias is used to determine whether the inclusion of relevant literature meeting the inclusion criteria of a systematic review is comprehensive (such as whether to search grey literature, search research trials, impose language or database restrictions Etc). Commonly used test methods include the funnel plot and Begg and Egger's tests. Third was imprecision, as most of the results of this performance evaluation were degraded due to the small sample size or the small number of RCTs, which resulted in a wide pooled 95% confidence interval. Last is inconsistency. Inconsistency refers to the differences among the original studies included in the systematic review, mainly manifested in the poor overlap of credibility intervals between different studies, significant

Study or Subgroup Events Total Events Total Weight M-H, Fixed, 95% CI M-H, Cai 2010 40 43 32 43 1.5% 4.58 [1.18, 17.83] Cai 2010 40 45 32 1.5% 4.58 [1.18, 17.83] Cao 2009 32 35 2.68 3.51 [1.66, 20.53] 1.56 [0.45, 5.34] Chen 2002 40 45 36 43 2.7% 1.56 [0.45, 5.34] Chen 2003 33 40 13 40 1.5% 9.79 [3.43, 27.99] Du 2016 48 50 35 50 0.7% 9.15 [1.51, 43.90] Cao 2014 48 51 32 51 1.2% 9.50 [2.60, 34.76] Cuo 2010 49 52 38 50 1.5% 5.16 [1.36, 19.58] Cuo 2010 49 52 38 50 1.2% 3.51 [1.08, 34, 3.31] J 2010 76 80 67 80 2.2% 3.69 [1.15, 11.85] </th <th></th> <th>Experim</th> <th>ental</th> <th>Contr</th> <th>ol</th> <th></th> <th>Odds Ratio</th> <th>Odds Ratio</th>		Experim	ental	Contr	ol		Odds Ratio	Odds Ratio
$ \begin{array}{c} \begin{tabular}{ c c c c c c c c c c c c c c c c c c c$	Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
Cal 2010 40 43 32 43 1.5% 4.58 [1.18, 1.7.83] Chen 2002 40 45 36 43 2.7% 1.56 [0.63, 11.31] Chen 2008 28 30 23 28 1.0% 3.04 (0.54, 17.77) Chen 2005 33 40 13 40 1.5% 9.79 [3.43, 27.99] Du 2016 48 50 35 50 0.9% 10.29 [2.21, 47.90] Gao 2014 48 51 32 51 [1.36, 1.9.58] [1.10, 8.94] Gao 2014 48 51 35 50 2.7% 3.69 [1.15, 11.85] Gao 2014 48 51 35 50 2.7% 3.16 [1.22, 19.31] [1.2013] Gao 2014 48 51 32 35 1.2% 5.05 [1.22, 19.31] [1.2013] Gao 2014 48 51 32 36 [1.20, 17.5, 38.37] [1.2016] [1.2013] [1.2016] [1.2016] [1.2016] [1.2016] [1.2016] [1.2016]	Cai 2004	37	40	28	40	1.4%	5.29 [1.36, 20.53]	
Cao 2009 32 35 28 35 1.6% 2.67 (0.63, 11.31) Chen 2002 40 45 36 43 2.7% 1.56 (0.45, 5.34) Chen 2008 28 30 23 28 1.0% 3.04 (0.54, 17.17) Cheng 2010 91 94 67 96 1.4% 13.13 (3.84, 44.91] Du 2005 33 40 13 40 1.5% 9.79 [3.43, 27.99] Du 2016 48 50 35 50 0.9% 10.29 [2.21, 47.90] Feng 2003 38 40 27 40 0.9% 9.15 [1.91, 43.90] Cao 2014 48 51 32 51 1.2% 9.50 [2.60, 34.76] Cao 2014 48 51 32 51 1.2% 9.50 [2.60, 34.76] Cao 2010 49 52 38 50 1.5% 5.16 [1.36, 1.958] Hui 2018 44 50 35 50 2.7% 3.14 [1.10, 8.94] Jang 2019 76 80 67 80 2.2% 3.69 [1.5, 11.85] Kang 2008 46 50 43 48 2.3% 1.34 (0.34, 5.31] — U 2003 36 40 13 20 1.1% 4.85 [1.22, 19.31] Li 2010 76 80 51 80 1.7% 10.80 [3.58, 32.69] Li 2013 53 55 42 55 1.0% 8.20 [1.75, 38.37] Li 2010 76 80 51 80 1.7% 10.80 [3.58, 32.59] Li 2013 53 55 42 55 1.0% 8.20 [1.75, 38.37] Li 2010 76 80 51 80 1.7% 10.80 [3.58, 32.59] Li 2013 28 30 24 30 1.0% 4.26 [0.81, 22, 13] Li 2010 76 80 52 57 4.0% 0.77 [0.22, 2.44] — Uu 2011 28 30 23 30 1.0% 4.26 [0.81, 22, 53] Li 2013 46 60 56 60 8.5% 0.22 [0.95, 0.63] Li 2017 49 53 42 53 2.1% 3.21 [0.95, 10.83] Li 2010 72 72 82 21 26 0.5% 6.43 [0.79, 59.28] Li 20207 27 28 21 26 0.5% 6.43 [0.79, 59.28] Li 20207 27 28 21 26 0.5% 6.43 [0.70, 59.28] Li 20207 27 28 21 26 0.5% 6.43 [0.70, 59.28] Li 20207 27 28 21 26 0.5% 6.43 [0.70, 59.28] Li 20207 27 28 21 26 0.5% 6.43 [0.70, 59.28] Li 20207 27 28 21 26 0.5% 6.43 [0.70, 59.28] Li 20207 27 28 21 26 0.5% 6.43 [0.70, 59.28] Li 20207 27 28 21 26 0.5% 6.43 [0.70, 71, 78] Ma 2015 50 52 39 51 1.0% 7.69 [1.63, 36.40] Ma 2015 50 52 39 51 1.0% 7.69 [1.63, 36.40] Ma 2015 50 52 39 51 1.0% 7.69 [1.63, 36.40] Ma 2015 50 52 39 51 1.0% 7.69 [1.63, 36.40] Ma 2017 46 50 46 50 2.4% 1.00 [0.24, 1.24] Mu 2010 35 88 2.53 61 1.3% 5.50 [1.65, 71, 74] Sun 2013 49 56 40 56 3.3% 2.80 [1.05, 7.17] Sun 2013 49 56 40 56 3.3% 2.80 [1.05, 7.17] Sun 2015 38 82 36 [1.2%, 1.2% [1.57, 1.48] Wang 2020 55 30 40 27 40 0.4% 18.78 [2.32, 71] Wang 2020 55 30 60 51 60 3.4% 5.50 [1.46, 20.76] Wang 2015 48 50 41 50 1	Cai 2010	40	43	32	43	1.5%	4.58 [1.18, 17.83]	
Chen 2002 40 45 36 43 2.7% 1.56 [0.45, 5.34] Chen 2008 28 30 23 28 1.0% 3.04 [0.54, 17.17] Chen 2008 33 40 13 40 1.5% 9.79 [3.43, 27.99] Du 2016 48 50 35 50 0.9% 10.29 [2.21, 47.90] Gao 2014 48 51 32 51 1.2% 9.50 [2.60, 34.76] Guo 2010 49 52 38 50 1.5% 5.16 [1.36, 19.58] Hui 2018 44 50 35 50 2.7% 3.16 [1.10, 8.94] Jaag 2019 76 80 67 80 2.2% 3.69 [1.15, 11.85] Li 2003 36 40 13 20 1.1% 4.85 [1.22, 19.31]	Cao 2009	32	35	28	35	1.6%	2.67 [0.63, 11.31]	
Chen 2008 28 30 23 28 1.0% 3.04 (0.54, 17.17) Cheng 2010 91 94 67 96 1.4% 13.13 (3.84, 4.4.91) Du 2005 33 40 13 40 1.5% 9.79 [3.43, 27.99] Du 2016 48 50 35 50 0.9% 10.29 [2.21, 47.90] Feng 2003 38 40 27 40 0.9% 9.15 [1.91, 43.90] Cao 2014 48 51 32 51 1.2% 9.50 [2.60, 34.76] Cao 2014 48 51 32 51 1.2% 9.50 [2.60, 34.76] Cao 2014 48 51 32 51 1.2% 9.50 [2.60, 34.76] Cao 2010 49 52 38 50 1.5% 5.16 [1.36, 19.58] Hui 2018 44 50 35 50 2.7% 3.14 [1.10, 8.94] Jang 2019 76 80 67 80 2.2% 3.69 [1.15, 11.85] Cao 2010 76 80 51 80 1.7% 10.80 [3.58, 32.59] Li 2013 36 40 13 20 1.1% 4.85 [1.22, 19.31] Li 2013 53 55 42 55 1.0% 8.20 [1.75, 38.37] Li 2013 53 55 42 55 1.0% 8.20 [1.75, 38.37] Li 2016 30 40 23 40 3.7% 2.22 [0.86, 5.74] Liu 2011 28 30 23 30 1.0% 4.26 [0.81, 22.53] Liu 2011 28 30 23 30 1.0% 4.26 [0.81, 22.53] Liu 2011 28 30 23 30 1.0% 4.26 [0.81, 22.53] Liu 2011 28 30 23 30 1.0% 4.26 [0.81, 22.53] Liu 2011 28 30 23 30 1.0% 4.26 [0.81, 22.53] Liu 2017 49 53 42 53 2.1% 3.21 [0.95, 10.83] Liu 2017 49 53 42 53 2.1% 3.21 [0.97, 0.76] Ma 2015 50 52 39 51 1.0% 7.69 [1.63, 36.40] Nan 2018 33 39 24 39 2.4% 1.00 [0.51, 7.88] Qiao 2017 46 50 46 50 2.4% 1.00 [0.54, 4.24] Ma 2015 50 52 39 51 1.3% 7.52 [0.67, 1.78] Qiao 2017 46 50 46 50 2.4% 1.00 [0.54, 4.24] Ma 2015 30 46 27 40 0.4% 18.78 [2.32, 122.17] Tao 2007 26 30 17 30 1.5% 4.97 [1.42, 32.37] Kui 2010 35 38 25 36 1.3% 5.13 [1.30, 20.32] Shen 2006 60 62 54 58 1.3% 5.13 [1.30, 20.32] Shen 2016 60 25 60 48 60 2.4% 1.00 [0.54, 4.24] Mang 2015 48 50 43 50 1.1% 3.91 [0.77, 19.83] Mang 2015 48 50 43 50 1.1% 3.91 [0.77, 19.83] Mang 2015 48 50 43 50 1.1% 3.51 [1.40, 1.57] Mang 50.11 39 45 32 45 2.8% 2.64 (0.90, 7.73] Mang 2015 48 50 41 50 1.1% 3.57 [1.06, 25.78] Yang 2019 48 50 41 50 1.1% 5.57 [1.07, 7.13.83] Mang 2015 48 50 41 50 1.1% 5.57 [1.07, 7.13.83] Mang 2015 48 50 41 50 1.1% 5.57 [1.07, 7.13.83] Mang 2015 48 50 41 50 1.1% 5.57 [1.06, 35.83] Yang 2019 48 50 41 50 1.1% 5.57 [1.06, 35.83] Yang 2019 48 50 41 50 1.1% 5.57 [1.06, 35.83] Yang	Chen 2002	40	45	36	43	2.7%	1.56 [0.45, 5.34]	
Cheng 2010 91 94 67 96 1.4% 13.13 [3.8, 44.91] Du 2015 33 40 13 40 0.5% 9.79 [3.4], 27.99] Du 2016 48 50 35 50 0.9% 10.29 [2.21, 47.90] Feng 2003 38 40 27 40 0.9% 91.51 [1.91, 43.90] Gao 2010 49 52 38 50 1.5% 5.16 [1.36, 19.58] Hui 2018 44 50 35 50 2.7% 3.14 [1.10, 8.94] Jiang 2019 76 80 67 80 2.2% 3.69 [1.15, 11.85] Kang 2008 46 50 43 48 2.3% 1.34 [0.34, 5.31] — Li 2013 36 40 13 20 1.1% 4.85 [1.22, 19.31] Li 2010 76 80 51 80 1.7% 10.86 [3.58, 3.25.9] Li 2013 53 55 42 55 1.0% 8.20 [1.75, 38.87] Li 2016 30 40 23 40 3.7% 2.22 [0.86, 5.74] Liao 2013 28 30 24 30 1.0% 4.26 [0.81, 22, 2.44] Li 2016 30 40 23 40 3.7% 2.22 [0.86, 5.74] Li 2011 28 30 22 30 1.0% 4.26 [0.81, 22, 2.53] Li 2011 28 30 22 30 1.0% 4.26 [0.81, 22, 2.53] Li 2011 28 30 22 30 1.0% 4.26 [0.81, 22, 2.53] Li 2011 28 30 22 30 1.0% 4.26 [0.81, 22, 2.53] Li 2017 49 53 42 53 2.1% 3.21 [0.95, 10.83] Luo 2007 27 28 21 26 0.5% 6.43 [0.70, 5.0, 2.8] Luo 2013 46 60 56 60 8.5% 0.23 [0.07, 0.76] Ma 2015 50 52 39 51 1.0% 7.69 [1.63, 36.40] Nan 2018 33 39 24 39 2.4% 3.44 [1.16, 1.05] Peng 2010 32 36 24 30 1.9% 2.00 [0.51, 7.88] Qua 2011 47 50 36 50 1.4% 6.09 [1.63, 22.82] Ren 2018 48 50 39 50 1.0% 6.77 [1.42, 32.37] Rui 2010 35 38 25 36 1.3% 5.13 [1.30, 20.32] Shen 2006 60 62 54 58 1.2% 2.22 [0.39, 12.62] - Shen 2016 48 50 39 50 1.4% 6.09 [1.63, 22.82] Wang 2015 33 39 40 27 40 0.4% 18.78 [2.32, 152.17] Tao 2007 26 30 17 30 1.5% 4.97 [1.39, 17.82] Wang 2015 48 50 43 50 1.1% 3.91 [0.77, 19.83] Wang 2015 48 50 43 50 1.1% 3.91 [0.77, 19.83] Wang 2015 48 50 43 50 1.4% 5.05 [1.46, 20.76] Wang 10.1 47 50 37 50 1.4% 5.05 [1.46, 20.76] Wang 2015 48 50 41 50 1.1% 5.27 [1.08, 25.78] Yang 2005 55 60 48 60 2.6% 2.75 [0.90, 8.37] Wang 2018 47 50 37 50 1.4% 5.05 [1.46, 20.76] Wang 12.01 56 30 42 23 4.2% 3.4% 5.01 [1.6, 1.57] Wang 2015 42 45 245 2.8% 3.66 [1.57] Wang 2015 43 26 41 50 1.1% 5.27 [1.08, 25.78] Yang 2005 53 60 51 60 3.9% 50 1.4% 5.05 [1.46, 20.76] Wang 2005 53 60 51 60 3.9% 50 1.4% 5.05 [1.46, 1.57] Yang 2005 53 60 51 60 3.9	Chen 2008	28	30	23	28	1.0%	3.04 [0.54, 17.17]	
Du 2005 33 40 13 40 1.5% 9.79 [3.43, 27.99] Du 2016 48 50 35 50 0.9% 10.29 [2.21, 47.90] Feng 2003 38 40 27 40 0.9% 9.15 [1.91, 43.90] Gao 2014 48 51 32 51 1.2% 9.50 [2.60, 34.76] Guo 2010 49 52 38 50 1.5% 5.16 [1.36, 19.58] Hui 2018 44 50 35 50 2.7% 3.14 [1.10, 8.94] Jiang 2019 76 80 67 80 2.2% 3.69 [1.15, 11.85] Kang 2008 46 50 43 48 2.3% 1.34 [0.34, 5.31] — Li 2010 76 80 51 80 1.7% 10.80 [3.58, 32.59] Li 2013 53 55 42 55 1.0% 8.20 [1.75, 38.37] Li 2013 53 55 42 55 1.0% 8.20 [1.75, 38.37] Li 2013 33 65 40 13 20 1.0% 3.50 [0.65, 18.98] Li 2013 53 60 52 57 4.0% 0.73 [0.22, 2.44] — Li 2011 28 30 24 30 1.0% 4.26 [0.81, 22.53] Lu 2017 49 53 42 53 2.1% 3.21 [0.95, 10.83] Lu 2017 27 28 21 26 0.5% 6.43 [0.70, 59.28] Lu 2013 46 60 56 60 8.5% 0.23 [0.07, 0.76] — Ma 2015 50 52 39 51 1.0% 7.69 [1.63, 36.40] Nan 2018 33 39 24 39 2.4% 3.44 [1.16, 10.15] Peng 2010 32 36 24 30 1.9% 2.00 [0.51, 7.88] Qia 2017 46 50 46 50 2.4% 1.00 [0.24, 4.24] — Qu 2011 47 50 36 50 1.4% 6.09 [1.63, 22.82] Ren 2018 48 50 39 50 1.0% 6.77 [1.42, 32.37] Rui 2010 35 38 25 36 1.3% 5.13 [1.30, 20.32] Shen 2006 60 62 24 58 1.3% 5.13 [1.30, 20.32] Shen 2006 60 62 24 58 1.3% 5.22 [0.39, 1.76, 2] Mang 2015 39 40 27 40 0.4% [8.78 [2.32, 152.17] Ta 2007 26 30 17 30 1.5% 4.97 [1.39, 17.82] Wang 2014 27 30 22 30 1.4% 3.27 [1.07, 7.18, 8] Wang 2015 48 50 43 50 1.1% 3.91 [0.77, 19.83] Wang 2015 48 50 43 50 1.1% 3.91 [0.77, 13.83] Wang 2015 48 50 43 50 1.1% 3.91 [0.77, 13.83] Wang 2015 48 50 43 50 1.1% 3.91 [0.77, 13.83] Wang 2015 48 50 43 50 1.1% 3.91 [0.77, 13.83] Wang 2015 48 50 43 50 1.1% 3.91 [0.77, 13.83] Wang 2015 48 50 43 50 1.1% 3.91 [0.77, 13.83] Wang 2015 48 50 43 50 1.1% 3.91 [0.77, 13.83] Wang 2015 48 50 43 50 1.1% 3.50 [1.46, 1.57] Wang 52011 39 45 22 45 2.3% 2.64 [0.90, 7.73] Xia 2015 33 38 25 38 2.1% 3.36 [1.09, 7.73] Xia 2015 33 38 25 33 2.1% 3.45 [1.32, 1.75] Yang 2019 48 50 41 50 1.1% 5.57 [1.46, 1] Xiu 2008 31 35 22 357 100.0% 3.58 [3.02, 4.24] Ta 2010 22 9 34 22 34 2.1% 3.36 [0.97, 1.03] Yang 201	Cheng 2010	91	94	67	96	1.4%	13.13 [3.84, 44.91]	
Du 2016 48 50 35 50 0.9% 10.29 [2.21, 47.90] Feng 2003 38 40 27 40 0.9% 9.15 [1.91, 43.90] Gao 2014 48 51 32 51 1.2% 9.50 [2.60, 34.76] Guo 2010 49 52 38 50 1.5% 5.16 [1.36, 19.58] Hui 2018 44 50 35 50 2.7% 3.14 [1.10, 8.94] Jiang 2019 76 80 67 80 2.2% 3.69 [1.15, 11.85] Kang 2008 46 50 43 48 2.3% 1.34 [0.34, 5.31] Li 2003 36 40 13 20 1.1% 4.85 [1.22, 19.31] Li 2010 76 80 51 80 1.7% 10.80 [3.58, 32.59] Li 2016 30 40 23 40 3.7% 2.22 [0.86, 5.74] Liao 2013 28 30 24 30 1.0% 3.50 [0.65, 18.98] Liu 2006 53 60 52 57 4.0% 0.73 [0.22, 2.44] Liu 2011 28 30 23 30 1.0% 4.26 [0.81, 22.53] Liu 2017 49 53 42 53 2.1% 3.21 [0.95, 10.83] Luo 2007 27 28 21 26 0.5% 6.43 [0.70, 59.28] Luo 2013 46 60 56 60 8.5% 0.23 [0.07, 0.76] Ma 2015 50 52 39 51 1.0% 7.69 [1.63, 36.40] Ma 2015 50 52 39 51 1.0% 7.69 [1.63, 36.40] Ma 2015 50 52 39 51 1.0% 6.77 [1.42, 32.37] Rui 2010 32 36 24 30 1.9% 2.00 [0.51, 7.88] Qua 2017 46 50 46 50 2.4% 1.00 [0.24, 4.24] Qu 2011 47 50 36 50 1.4% 6.09 [1.63, 22.82] Ren 2018 48 50 39 50 1.0% 6.77 [1.42, 32.37] Rui 2010 35 38 25 36 1.3% 5.13 [1.30, 20.32] Shen 2006 60 62 54 58 1.2% 2.22 [0.39, 12.62] Shu 2013 49 56 40 56 3.3% 2.20 [1.05, 7.47] Shu 2013 49 56 40 56 3.3% 2.20 [1.05, 7.47] Shu 2013 49 56 40 56 3.3% 2.80 [1.05, 7.47] Shu 2013 49 56 40 56 3.3% 2.80 [1.05, 7.47] Shu 2013 49 56 40 56 3.3% 2.80 [1.05, 7.47] Shu 2013 49 56 40 56 3.3% 2.80 [1.05, 7.47] Shu 2013 49 56 40 56 3.3% 2.80 [1.05, 7.47] Shu 2013 49 56 40 56 3.3% 2.80 [1.05, 7.47] Shu 2013 49 56 40 56 3.3% 2.80 [1.05, 7.47] Shu 2013 49 56 40 56 3.3% 2.80 [1.05, 7.47] Shu 2013 49 56 40 56 3.3% 2.80 [1.05, 7.47] Shu 2013 49 56 40 56 3.3% 2.80 [1.05, 7.47] Shu 2013 49 56 40 56 3.3% 2.80 [1.05, 7.47] Shu 2006 53 60 51 60 3.9% 1.34 [0.46, 3.86] Yang 2015 48 50 41 50 1.1% 3.57 [1.46, 1.57] Wang 505 53 60 51 60 3.9% 1.34 [0.46, 5.86] Yang 2014 27 30 22 30 1.4% 3.35 [1.02, 7.73] Xia 2015 33 88 25 38 2.1% 3.45 [1.17, 7.55] Zhua 2011 27 30 23 30 0.2% 19.47 [1.06, 58.38] Total (95% C1) 2435 2357 100	Du 2005	33	40	13	40	1.5%	9.79 [3.43, 27.99]	
Feng 2003 38 40 27 40 0.9% 9.15 [1.9, 1, 43.90] Gao 2014 48 51 32 51 1.2% 9.50 [2.60, 3.476] Guo 2010 49 52 38 50 1.5% 5.16 [1.36, 19.58] Hui 2018 44 50 35 50 2.7% 3.14 [1.10, 8.94] Jang 2019 76 80 67 80 2.2% 3.69 [1.15, 11.85] — Li 2010 76 80 51 80 1.7% 10.80 [3.58, 32.59] Li 2016 30 40 2.3% 1.34 [0.34, 5.31] — Li 2016 30 40 2.3 40 3.7% 2.22 [0.86, 5.74] — — Lia 2013 28 30 23 30 1.0% 3.50 [0.65, 18.98] …	Du 2016	48	50	35	50	0.9%	10.29 [2.21, 47.90]	
Gao 2014 48 51 32 51 1.2% 9.50 [2.60, 34.76] Hui 2018 44 50 35 50 2.7% 3.14 [1.10, 8.94] Jiang 2019 76 80 67 80 2.2% 3.69 [1.15, 11.85] Kang 2008 46 50 43 48 2.3% 1.34 [0.34, 5.31] — Li 2003 36 40 13 20 1.1% 4.85 [1.22, 19.31] Li 2010 76 80 51 80 1.7% 1.0.80 [3.58, 32.59] Li 2013 53 55 42 55 1.0% 8.20 [1.75, 38.37] Li 2016 30 40 23 40 3.7% 2.22 [0.86, 5.74] Liao 2013 28 30 24 30 1.0% 4.26 [0.81, 22.53] Li 2016 23 60 52 57 4.0% 0.73 [0.22, 2.44] — Li 2016 23 0.10% 4.26 [0.81, 22.53] Liu 2006 53 60 52 57 4.0% 0.73 [0.22, 2.44] — Liu 2006 53 60 52 57 4.0% 0.73 [0.22, 2.44] — Liu 2011 28 30 23 30 1.0% 4.26 [0.81, 22.53] Liu 2017 49 53 42 53 2.1% 3.21 [0.95, 10.83] Luo 2017 27 28 21 26 0.5% 6.43 [0.70, 59.28] Luo 2013 46 60 56 60 8.5% 0.23 [0.07, 0.76] — Ma 2015 50 52 39 51 1.0% 7.69 [1.63, 36.40] Nan 2018 33 39 24 39 2.4% 3.44 [1.16, 10.15] Peng 2010 32 36 24 30 1.9% 2.00 [0.51, 7.88] Qiao 2017 46 50 46 50 2.4% 1.00 [0.24, 4.24] — Qu 2011 47 50 36 50 1.4% 6.09 [1.63, 22.82] Ren 2018 48 50 39 50 1.0% 6.77 [1.42, 32.37] Ren 2018 48 50 39 50 1.0% 6.77 [1.42, 32.37] Ren 2018 48 50 39 50 1.0% 6.77 [1.42, 32.37] Shen 2006 60 62 54 58 1.2% 2.22 [0.39, 12.62] — Shen 2006 60 62 54 63 3.3% 2.80 [1.05, 7.47] Sun 2015 39 40 27 40 0.4% 18.78 [2.32, 152, 17] Ta 0 2007 26 30 17 30 1.5% 4.97 [1.39, 17.82] Wang 2014 27 30 22 30 1.4% 5.50 [1.46, 20.76] Wang 2015 48 50 43 50 1.1% 3.91 [0.77, 19.83] Wang 2015 48 50 43 50 1.1% 3.91 [0.77, 19.83] Wang 2015 48 50 43 50 1.1% 3.50 [1.46, 20.76] Wang F2 011 39 45 2.45 2.8% 2.46 [0.09, 7.73] Xia 2015 33 38 25 38 2.1% 3.43 [1.08, 10.89] Wang 2015 48 50 43 50 1.1% 3.50 [1.46, 20.76] Wang F2 011 39 45 2.45 2.8% 2.46 [0.09, 7.73] Xia 2015 43 50 51 1.60 3.9% 1.34 [0.46, 3.86] Yang 2019 44 50 37 50 1.4% 5.50 [1.46, 20.76] Wang F2 011 39 45 2.45 2.8% 2.46 [0.09, 7.73] Xia 2015 53 60 51 60 3.9% 1.34 [0.46, 3.86] Yang 2019 44 50 43 2.64 3 2.8% 3.36 [1.22, 15.93] Yang 2019 44 50 43 50 1.1% 5.57 [1.46, 1] Xia 208 31 35 22 35 1.60% 4.58 [1.32, 15.93] Yang 201	Feng 2003	38	40	27	40	0.9%	9.15 [1.91, 43.90]	
Guo 2010 49 52 38 50 1.5% 5.16 1.36 19.58 Haing 2019 76 80 67 80 2.2% 3.69 1.15 1.8.894 Jiang 2019 76 80 67 80 2.2% 3.69 1.15 1.18 5.314 [1.10, 8.94] Li 2010 76 80 51 80 1.7% 1.0.80 [3.58, 32.59] 1.15 1.135 4.85 [1.22, 19.31]	Gao 2014	48	51	32	51	1.2%	9.50 [2.60, 34.76]	
Hui 2018 44 50 35 50 2.7% 3.14 [1.10, 8.94] Jang 2019 76 80 67 80 2.2% 3.69 [1.15, 11.85] Kang 2008 46 50 43 48 2.3% 1.34 [0.34, 5.31] — Li 2003 36 40 13 20 1.1% 4.85 [1.22, 19.31] … Li 2010 76 80 51 80 1.7% 10.80 [3.58, 32.59] … … Li 2016 30 40 23 40 3.7% 2.22 [0.86, 5.74] … Liao 2013 28 30 24 30 1.0% 4.26 [0.81, 22.53] … … … Liu 2017 49 53 42 53 2.1% 3.21 [0.95, 10.83] … <td>Guo 2010</td> <td>49</td> <td>52</td> <td>38</td> <td>50</td> <td>1.5%</td> <td>5.16 [1.36, 19.58]</td> <td></td>	Guo 2010	49	52	38	50	1.5%	5.16 [1.36, 19.58]	
$ \begin{aligned} ang 2019 76 & 80 & 67 & 80 & 2.2\% & 3.69 1.15, 11.85 $	Hui 2018	44	50	35	50	2.7%	3.14 [1.10, 8.94]	
Kang 2008 46 50 43 48 2.3% 1.34 0.34, 5.31	Jiang 2019	76	80	67	80	2.2%	3.69 [1.15, 11.85]	
$ \begin{aligned} 12003 & 36 & 40 & 13 & 20 & 1.1\% & 4.85 [1.22, 19.31] \\ 112010 & 76 & 80 & 51 & 80 & 1.7\% & 10.80 [3.58, 32.59] \\ 112013 & 53 & 55 & 42 & 55 & 1.0\% & 8.20 [1.75, 38.37] \\ 112016 & 30 & 40 & 23 & 40 & 3.7\% & 2.22 [0.86, 5.74] \\ 112016 & 30 & 40 & 23 & 40 & 3.7\% & 2.22 [0.86, 5.74] \\ 112016 & 30 & 40 & 23 & 40 & 3.7\% & 2.22 [0.86, 5.74] \\ 112016 & 23 & 60 & 52 & 57 & 4.0\% & 0.73 [0.22, 2.44] &$	Kang 2008	46	50	43	48	2.3%	1.34 [0.34, 5.31]	
$ \begin{aligned} L2010 & 76 & 80 & 51 & 80 & 1.76 & 10.80 & [3.58, 32.59] \\ Li 2013 & 53 & 55 & 42 & 55 & 1.06 & 8.20 & [1.75, 38.37] \\ Li 2016 & 30 & 40 & 23 & 40 & 3.76 & 2.22 & [0.86, 5.74] \\ Liao 2013 & 28 & 30 & 24 & 30 & 1.06 & 3.50 & [0.65, 18.98] \\ Liu 2016 & 53 & 60 & 52 & 57 & 4.06 & 0.73 & [0.22, 2.44] &$	LI 2003	36	40	13	20	1.1%	4.85 [1.22, 19.31]	
$ \begin{array}{c c c c c c c c c c c c c c c c c c c $	Li 2010	76	80	51	80	1.7%	10.80 [3.58, 32.59]	
$ \begin{aligned} Li 2010 & 30 & 40 & 23 & 40 & 3.7\% & 2.22 (0.86, 5.74) \\ Li 2011 & 28 & 30 & 24 & 30 & 1.0\% & 3.50 [0.65, 18.98] \\ Li 2006 & 53 & 60 & 52 & 57 & 4.0\% & 0.73 [0.22, 2.44] &$	LI 2013	20	22	42	>>	1.0%	8.20 [1.75, 38.37]	
$ \begin{aligned} \begin{aligned} & Lab 2015 & 20 & 30 & 2^4 & 30 & 1.0\% & 3.30 & [0.05, 16.95] \\ & Liu 2006 & 53 & 60 & 52 & 57 & 4.0\% & 0.73 & [0.22, 2.44] \\ & Liu 2011 & 28 & 30 & 23 & 30 & 1.0\% & 4.26 & [0.81, 22.53] \\ & Liu 2017 & 49 & 53 & 42 & 53 & 2.1\% & 3.21 & [0.95, 10.83] \\ & Luo 2007 & 27 & 28 & 21 & 26 & 0.5\% & 6.43 & [0.70, 59.28] \\ & Luo 2013 & 46 & 60 & 56 & 60 & 8.5\% & 0.23 & [0.07, 0.76] \\ & Ma 2015 & 50 & 52 & 39 & 51 & 1.0\% & 7.69 & [1.63, 36.40] \\ & Nan 2018 & 33 & 39 & 24 & 39 & 2.4\% & 3.44 & [1.61, 10.15] \\ & Peng 2010 & 32 & 36 & 24 & 30 & 1.9\% & 2.00 & [0.51, 7.88] \\ & Qia 2017 & 46 & 50 & 46 & 50 & 2.4\% & 1.00 & [0.24, 4.24] & \\ & Qi 2011 & 47 & 50 & 36 & 50 & 1.4\% & 6.09 & [1.63, 22.82] \\ & Ren 2018 & 48 & 50 & 39 & 50 & 1.0\% & 6.77 & [1.42, 32.37] \\ & Rui 2010 & 35 & 38 & 25 & 36 & 1.3\% & 5.13 & [1.30, 20.32] \\ & Shen 2006 & 60 & 62 & 54 & 58 & 1.2\% & 2.22 & [0.9, 12.62] & \\ & Shi 2013 & 49 & 56 & 40 & 56 & 3.3\% & 2.80 & [1.05, 7.47] \\ & Sun 2015 & 39 & 40 & 27 & 40 & 0.4\% & 18.78 & [2.32, 152.17] \\ & Tao 2007 & 26 & 30 & 17 & 30 & 1.5\% & 4.97 & [1.9, 17.82] \\ & Wang 2066 & 55 & 60 & 48 & 60 & 2.6\% & 2.75 & [0.90, 8.37] \\ & Wang 2014 & 27 & 30 & 22 & 30 & 1.4\% & 3.50 & [1.06, 1.77, 19.83] \\ & Wang 2015 & 48 & 50 & 43 & 50 & 1.1\% & 3.91 & [0.77, 19.83] \\ & Wang 2018 & 47 & 50 & 37 & 50 & 1.4\% & 5.50 & [1.46, 20.76] \\ & Wang F2 & 2011 & 56 & 60 & 48 & 60 & 2.1\% & 3.50 & [1.06, 1.157] \\ & Wang 5020 & 53 & 60 & 51 & 60 & 3.9\% & 1.34 & [0.46, 3.86] \\ & Yang 2005 & 53 & 60 & 51 & 60 & 3.9\% & 1.34 & [0.46, 3.86] \\ & Yang 2019 & 48 & 50 & 41 & 50 & 1.1\% & 5.27 & [1.08, 25.78] \\ & Yang 2019 & 48 & 50 & 41 & 50 & 1.1\% & 5.27 & [1.08, 25.78] \\ & Yang 2011 & 20 & 30 & 23 & 30 & 0.2\% & 3.36 & [1.27, 1.755] \\ & Zhang 2011 & 36 & 43 & 26 & 43 & 2.8\% & 3.36 & [1.27, 1.755] \\ & Zhang 2011 & 36 & 43 & 26 & 43 & 2.8\% & 3.36 & [1.27, 9.27] \\ & Zhang 2011 & 26 & 30 & 23 & 30 & 0.2\% & 1.9.47 & [1.06, 358.38] \\ & Total events & 2221 & 1760 \\ \\ & Heterogeneity: Chi^2 = 7.67, df = 51 (P = 0.01); I^2 = 34\% \\ \end{aligned}$	Li 2016	30	40	23	40	3.7%	2.22 [0.86, 5.74]	
Lu 2000 32 37 4.0% 0.73 [0.22, 244] Liu 2011 28 30 23 30 1.0% 4.26 [0.81, 22.53] Liu 2017 49 53 42 53 2.1% 3.21 [0.95, 10.83] Luo 2007 27 28 21 26 0.5% 6.43 [0.70, 0.76] Ma 2015 50 52 39 51 1.0% 7.69 [1.63, 36.40] Nan 2018 33 39 24 39 2.4% 3.44 [1.16, 10.15] Peng 2010 32 36 24 30 1.9% 2.00 [0.51, 7.88] Qiao 2017 46 50 46 50 2.4% 1.00 [0.24, 4.24] Qu 2011 47 50 36 50 1.4% 6.09 [1.63, 22.82] Ren 2018 48 50 39 50 1.0% 6.77 [1.42, 32.37] Rui 2010 35 38 25 36 1.3% 5.13 [1.30, 20.32] Shen 2006 60 62 54 58 1.2% 2.22 [0.39, 12.62] Shi 2013 49 56 40 56 3.3% 2.80 [1.05, 7.47] Sun 2015 39 40 27 40 0.4% 18.78 [2.32, 152, 17] Tao 2007 26 30 17 30 1.5% 4.97 [1.39, 17.82] Wang 2015 48 50 43 50 1.1% 3.91 [0.77, 19.83] Wang 2015 48 50 43 50 1.1% 3.91 [0.77, 19.83] Wang 2014 27 30 22 30 1.4% 5.50 [1.46, 2.76] Wang 2018 47 50 37 50 1.4% 5.50 [1.46, 2.76] Wang 2018 47 50 37 50 1.4% 5.50 [1.46, 2.76] Wang 2018 47 50 37 50 1.4% 5.50 [1.6, 11.57] Wang 52 011 39 45 32 45 2.8% 2.64 [0.90, 7.73] Xia 2015 33 82 53 6.03 4.58 [1.32, 15.2, 15] Wang 52 011 39 45 32 45 2.8% 2.64 [0.90, 7.73] Xia 2015 33 60 51 60 3.9% 1.34 [1.08, 10.89] Xia 2015 48 50 41 50 1.1% 5.50 [1.46, 3.86] Yang 2029 59 66 20 32 1.9% 5.50 [1.6, 3.86] Yang 2029 42 23 42 2.34 2.1% 3.43 [1.08, 10.89] Xia 2018 47 50 31 60 3.9% 1.34 [0.46, 3.86] Yang 2019 48 50 41 50 1.1% 5.27 [1.88, 2.5.8] Yang 2019 48 50 41 50 1.1% 5.27 [1.88, 2.5.8] Yang 2019 48 50 41 50 1.1% 5.27 [1.88, 2.5.8] Yang 2019 48 50 41 50 1.1% 5.27 [1.88, 2.5.8] Yang 2019 48 50 41 50 1.1% 5.27 [1.88, 2.5.8] Yang 2019 48 50 41 50 1.1% 5.27 [1.88, 2.5.8] Yang 2019 48 50 41 50 1.1% 5.27 [1.88, 2.5.8] Yang 2019 48 50 41 50 1.1% 5.27 [1.88, 2.5.8] Yang 2011 20 30 23 30 0.2% 19.47 [1.06, 358.38] Total events 2221 1760 Heterogeneity: Chi ² = 76.77, df = 51 (P = 0.01); i ² = 34%	Liao 2013	28	30	24	50	1.0%	5.50 [0.65, 18.98]	
$\begin{aligned} \begin{aligned} & Lu \ 2011 & 203 & 30 & 23 & 30 & 1.0\% & 4.26 \ [0.61, 22.3] \\ Luo 2017 & 49 & 53 & 42 & 53 & 2.1\% & 3.21 \ [0.95, 10.83] \\ Luo 2013 & 46 & 60 & 56 & 60 & 8.5\% & 0.23 \ [0.07, 0.76] & & & & & & & & & & & & & & & & & & &$	Liu 2006	22	20	32	3/	4.0%	4 26 [0 91 22 52]	
$ \begin{array}{c ccccccccccccccccccccccccccccccccccc$	Liu 2011	20	50	23	50	2.1%	4.20 [0.81, 22.53]	
$ \begin{aligned} & \text{Lio} 2007 & 2.7 & 2.8 & 2.1 & 2.6 & 6.3.8 & 6.4.3 & [0.7, 0.7, 6] \\ & \text{Ma} 2015 & 50 & 52 & 39 & 51 & 1.0\% & 7.69 & [1.63, 36.40] \\ & \text{Ma} 2018 & 33 & 39 & 24 & 39 & 2.4\% & 3.44 & [1.61, 0.15] \\ & \text{Peng} 2010 & 32 & 36 & 24 & 30 & 1.9\% & 2.00 & [0.51, 7, 88] \\ & \text{Qia} 2017 & 46 & 50 & 2.4\% & 1.00 & [0.24, 4.24] & \\ & \text{Qu} 2011 & 47 & 50 & 36 & 50 & 1.4\% & 6.09 & [1.63, 22.82] \\ & \text{Ren} 2018 & 48 & 50 & 39 & 50 & 1.0\% & 6.77 & [1.42, 22.37] \\ & \text{Rei} 2010 & 35 & 38 & 25 & 36 & 1.3\% & 5.13 & [1.30, 20.32] \\ & \text{Shen} 2006 & 60 & 62 & 54 & 58 & 1.2\% & 2.22 & [0.39, 12.62] & \\ & \text{Shi} 2013 & 49 & 56 & 40 & 56 & 3.3\% & 2.80 & [1.05, 7.47] \\ & \text{Sun} 2015 & 39 & 40 & 27 & 40 & 0.4\% & [8.78 & [2.32, 152.17] \\ & \text{Tao} 2007 & 26 & 30 & 17 & 30 & 1.5\% & 4.97 & [1.39, 17.82] \\ & \text{Wang} 2006 & 55 & 60 & 48 & 60 & 2.6\% & 2.75 & [0.90, 8.37] \\ & \text{Wang} 2014 & 27 & 30 & 22 & 30 & 1.4\% & 3.27 & [0.77, 13.83] \\ & \text{Wang} 2015 & 48 & 50 & 43 & 50 & 1.1\% & 3.91 & [0.77, 19.83] \\ & \text{Wang} 2018 & 47 & 50 & 37 & 50 & 1.4\% & 5.50 & [1.46, 20.76] \\ & \text{Wang FI 2011 } 56 & 60 & 48 & 60 & 2.1\% & 3.50 & [1.66, 11.57] \\ & \text{Wang FS 2011 } 39 & 45 & 32 & 45 & 2.8\% & 2.64 & [0.90, 7.73] \\ & \text{Xia} 2005 & 53 & 36 & 21 & 60 & 3.9\% & 1.34 & [0.46, 3.86] \\ & \text{Yang 2009 } 59 & 66 & 20 & 32 & 1.9\% & 5.06 & [1.75, 14.61] \\ & \text{Xiu} 2008 & 31 & 35 & 22 & 35 & 1.6\% & 4.58 & [1.32, 15.93] \\ & \text{Yang 2019 } & 48 & 50 & 41 & 50 & 1.1\% & 5.27 & [1.08, 25.78] \\ & \text{Yang 2019 } & 48 & 50 & 41 & 50 & 1.1\% & 5.27 & [1.08, 25.78] \\ & \text{Yang 2019 } & 48 & 50 & 41 & 50 & 1.1\% & 5.27 & [1.08, 25.78] \\ & \text{Yang 2011 } & 20 & 30 & 23 & 30 & 5.0\% & 0.61 & [0.20, 1.90] \\ &\frac{1}{2hang 2011} & 26 & 30 & 23 & 30 & 0.2\% & 19.47 & [1.06, 358.38] \\ \hline \text{Total events } & 2221 & 1760 \\ & \text{Heterogeneity: Chi^2 = 76.77, df = 51 & (P = 0.01); i^2 = 34\% \\ \end{array}$	Liu 2017	49	22	42	25	2.1%	5.21 [0.95, 10.65] 6.42 [0.70, 50.28]	
Lico 2013 40 60 50 60, 53, 78 7, 63 7, 64 Ma 2015 50 52 39 51 1, 0% 7, 69 1, 63, 36, 40 Nan 2018 33 39 24 39 2,4% 3,44 [1,6,1,0,5] Peng 2010 32 36 24 30 1,9% 2,00 [0,5,1,7,8] Qiao 2017 46 50 46 50 2,4% 1,00 [0,24,4,24]	Luo 2012	27	20	56	60	0.5%	0.45 [0.70, 59.26]	
$ \begin{array}{c c c c c c c c c c c c c c c c c c c $	Ma 2015	40	52	30	51	1.0%	7 69 [1 63 36 40]	
$ \begin{array}{c c c c c c c c c c c c c c c c c c c $	Ma 2015 Nan 2018	33	30	24	30	2.4%	3 44 [1 16 10 15]	
Arrig 2010 32 30 24 30 243 30 1236 2144 306 1237 1236 1237 1236 1237 1236 1237 1236 1237 1236 1237 1236 12377 12377 12377 12377 12377 12377 12377 12377 12377 12377 12377 12377 12377 12377 12377 123777 123777 123777 123777 123777 123777 123777 1237777 1237777 1237777 1237777 1237777 1237777 1237777 12377777 12377777 123777777 123777777 $123777777777777777777777777777777777777$	Pana 2010	32	36	24	30	1 0%	2 00 [0 51 7 88]	
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Call 2012 10 30 30 50 1.0% 6.77 [1.42, 32.37] Rui 2010 35 38 25 36 1.3% 5.13 [1.30, 20.32] Shen 2006 60 62 54 58 1.2% 2.22 [0.39, 12.62] - Shi 2013 49 56 40 56 3.3% 2.80 [1.05, 7.47] - Sun 2015 39 40 27 40 0.4% 18.78 [2.32, 152.17] - Tao 2007 26 30 17 30 1.5% 4.97 [1.39, 17.82] - Wang 2006 55 60 48 60 2.6% 2.75 [0.90, 8.37] - - Wang 2014 27 30 22 30 1.4% 3.27 [0.77, 13.83] - Wang 2018 47 50 37 50 1.06, 11.57] - - Wang FS 2011 39 45 32 45 2.8% 2.64 [0.90, 7.73] - - Xia 2015 33 38 25 38 2.1% 3.43 [1.08, 10.89] - -	Quad 2017	47	50	36	50	1.4%	6.09 [1.63, 22, 82]	
Reliability	Ren 2018	48	50	39	50	1.0%	6 77 [1.42, 32, 37]	
Number of the state of th	Rui 2010	35	38	25	36	1.3%	5 13 (1 30 20 32)	
Shi 2013 49 56 40 56 3.3% 2.80 [1.05, 7.47] Sun 2015 39 40 27 40 0.4% 18.78 [2.32, 152.17] Tao 2007 26 30 17 30 1.5% 4.97 [1.39, 17.82] Wang 2006 55 60 48 60 2.6% 2.75 [0.90, 8.37] Wang 2014 27 30 22 30 1.4% 3.27 [0.77, 13.83] Wang 2015 48 50 43 50 1.1% 3.91 [0.77, 19.83] Wang 2018 47 50 37 50 1.4% 5.50 [1.46, 20.76] Wang FL 2011 56 60 48 60 2.1% 3.50 [1.06, 11.57] Wang FS 2011 39 45 32 45 2.8% 2.64 [0.90, 7.73] Xia 2015 33 38 25 38 2.1% 3.43 [1.08, 10.89] Xia 2015 53 60 51 60 3.9% 1.34 [0.46, 3.86] Yang 2009 59 66 20 32 1.9% 5.06 [1.75, 14.61] Xiu 2008 31 35 22 35 1.6% 4.58 [1.32, 15.93] Yang 2019 48 50 41 50 1.1% 5.27 [1.08, 25.78] Yao 2012 29 34 22 34 2.1% 3.16 [0.97, 10.31] Yu 2011 20 30 23 30 5.0% 0.61 [0.20, 1.90] Zhan 2011 27 30 21 30 1.4% 3.86 [0.93, 16.05] Zhang 2015 42 45 34 45 1.5% 4.53 [1.17, 17.55] Zhuo 2014 30 30 23 30 0.2% 19.47 [1.06, 358.38] Total (95% CI) 2435 2357 100.0% 3.58 [3.02, 4.24] Total events 2221 1760 Heterogeneity: Chl ² = 76.77, df = 51 (P = 0.01); l ² = 34%	Shen 2006	60	62	54	58	1.2%	2.22 [0.39, 12.62]	
Sin 2015 39 40 27 40 0.4% 18.78 [2.32, 152.17] Tao 2007 26 30 17 30 1.5% 4.97 [1.39, 17.82] Wang 2006 55 60 48 60 2.6% 2.75 [0.90, 8.37] Wang 2014 27 30 22 30 1.4% 3.27 [0.77, 13.83] Wang 2015 48 50 43 50 1.1% 3.91 [0.77, 19.83] Wang 2018 47 50 37 50 1.4% 5.50 [1.66, 20.76] Wang FL 2011 56 60 48 60 2.1% 3.50 [1.06, 11.57] Wang FS 2011 39 45 32 45 2.8% 2.64 [0.90, 7.73] Xia 2015 33 38 25 38 2.1% 3.43 [1.08, 10.89] Xiong 2009 59 66 20 32 1.9% 5.06 [1.75, 14.61] Xiu 2008 31 35 22 35 1.6% 4.58 [1.32, 15.93] <	Shi 2013	49	56	40	56	3.3%	2.80 [1.05, 7.47]	·
Tao 2007 26 30 17 30 1.5% 4.97 [1.39, 17.82] Wang 2006 55 60 48 60 2.6% 2.75 [0.90, 8.37] Wang 2014 27 30 22 30 1.4% 3.27 [0.77, 13.83] Wang 2015 48 50 43 50 1.1% 3.91 [0.77, 19.83] Wang 2018 47 50 37 50 1.4% 5.50 [1.46, 20.76] Wang FL 2011 56 60 48 60 2.1% 3.50 [1.06, 11.57] Wang FS 2011 39 45 32 45 2.8% 2.64 [0.90, 7.73] Xia 2015 33 38 25 38 2.1% 3.43 [1.08, 10.89] Xiong 2009 59 66 20 32 1.9% 5.06 [1.75, 14.61] Xiu 2008 31 35 22 35 1.6% 4.58 [1.32, 15.93] Yang 2019 48 50 41 50 1.1% 5.27 [1.08, 25.78] Yao 2012 29 34 22 34 2.1% 3.16 [0.97, 10.31] Yu 2011 20 30 23 30 5.0% 0.61 [0.20, 1.90] Zhan 2011 27 30 21 30 1.4% 3.86 [0.93, 16.05] Zhang 2015 42 45 34 45 1.5% 4.53 [1.17, 17.55] Zhuo 2014 30 30 23 30 0.2% 19.47 [1.06, 358.38] Total (95% CI) 2435 2357 100.0% 3.58 [3.02, 4.24] Total (95% CI) 2435 2357 100.0% 3.58 [3.02, 4.24]	Sun 2015	39	40	27	40	0.4%	18.78 [2.32, 152,17]	
Wang 2006 55 60 48 60 2.6% 2.75 [0.90, 8.37] Wang 2014 27 30 22 30 1.4% 3.27 [0.77, 13.83] Wang 2015 48 50 43 50 1.1% 3.91 [0.77, 19.83] Wang 2018 47 50 37 50 1.4% 5.50 [1.46, 20.76] Wang FL 2011 56 60 48 60 2.1% 3.50 [1.06, 11.57] Wang FS 2011 39 45 32 45 2.8% 2.64 [0.90, 7.7] Xia 2015 33 38 25 38 2.1% 3.43 [1.08, 10.89] Xia 2015 33 38 25 38 2.1% 3.44 [0.46, 3.86] Yang 2009 59 66 20 32 1.9% 5.06 [1.75, 14.61] Xiu 2008 31 35 22 35 1.6% 4.58 [1.32, 15.93] Yang 2019 48 50 41 50 1.1% 5.27 [1.08, 25.78]	Tao 2007	26	30	17	30	1.5%	4.97 [1.39, 17.82]	
Wang 2014 27 30 22 30 1.4% 3.27 [0.77, 13.83] Wang 2015 48 50 43 50 1.1% 3.91 [0.77, 19.83] Wang 2018 47 50 37 50 1.4% 5.50 [1.46, 20.76] Wang FL 2011 56 60 48 60 2.1% 3.50 [1.06, 11.57] Wang FS 2011 39 45 32 45 2.8% 2.64 [0.90, 7.73] Xia 2015 33 38 25 38 2.1% 3.43 [1.08, 10.89] Xia 2015 33 38 25 38 2.1% 3.43 [1.08, 10.89] Xia 2015 33 38 25 38 2.1% 3.43 [1.08, 10.89] Xia 2015 33 38 25 38 2.1% 3.43 [1.08, 10.89] Xia 2016 53 60 51 60 3.9% 1.34 [0.46, 3.86] Yang 2019 48 50 41 50 1.1% 5.27 [1.08, 25.78] Yaa 2011 20 30 23 30 5.0% 0.61 [0.20, 1.90] </td <td>Wang 2006</td> <td>55</td> <td>60</td> <td>48</td> <td>60</td> <td>2.6%</td> <td>2.75 [0.90, 8.37]</td> <td></td>	Wang 2006	55	60	48	60	2.6%	2.75 [0.90, 8.37]	
Wang 2015 48 50 43 50 1.1% 3.91 [0.77, 19.83] Wang 2018 47 50 37 50 1.4% 5.50 [1.46, 20.76] Wang FL 2011 56 60 48 60 2.1% 3.50 [1.06, 11.57] Wang FS 2011 39 45 32 45 2.8% 2.64 [0.90, 7.73] Xia 2015 33 38 25 38 2.1% 3.43 [1.08, 10.89] Xiong 2009 59 66 20 32 1.9% 5.06 [1.75, 14.61] Xiu 2008 31 35 22 35 1.6% 4.58 [1.32, 15.93] Yang 2019 48 50 41 50 1.1% 5.27 [1.08, 25.78] Yao 2012 29 34 22 34 2.1% 3.16 [0.97, 10.31] Yu 2011 20 30 23 30 5.0% 0.61 [0.20, 1.90] Zhan 2011 27 30 21 30 1.4% 3.86 [0.93, 16.05] Zhang 2015 42 45 34 45 1.5% 4.53 [1.17, 17.55]	Wang 2014	27	30	22	30	1.4%	3.27 [0.77, 13.83]	
Wang 2018 47 50 37 50 1.4% 5.50 [1.46, 20.76] Wang FL 2011 56 60 48 60 2.1% 3.50 [1.06, 11.57] Wang FS 2011 39 45 32 45 2.8% 2.64 [0.90, 7.73] Xia 2015 33 38 25 38 2.1% 3.43 [1.08, 10.89] Xia 2015 33 38 25 38 2.1% 3.43 [1.08, 10.89] Xia 2015 33 38 25 38 2.1% 3.43 [1.08, 10.89] Xia 2018 31 35 22 35 1.6% 4.58 [1.32, 15.93] Yang 2005 53 60 3.9% 1.34 [0.46, 3.86] - Yang 2019 48 50 1.1% 5.27 [1.08, 25.78] Yao 2012 29 34 22 34 2.1% 3.16 [0.97, 10.31] - - - - - - - - - - - - - - - - </td <td>Wang 2015</td> <td>48</td> <td>50</td> <td>43</td> <td>50</td> <td>1.1%</td> <td>3.91 [0.77, 19.83]</td> <td></td>	Wang 2015	48	50	43	50	1.1%	3.91 [0.77, 19.83]	
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Wang FS 2011 39 45 32 45 2.8% 2.64 [0.90, 7.73] Xia 2015 33 38 25 38 2.1% 3.43 [1.08, 10.89] Xiong 2009 59 66 20 32 1.9% 5.06 [1.75, 14.61] Xiu 2008 31 35 22 35 1.6% 4.58 [1.32, 15.93] Yang 2005 53 60 51 60 3.9% 1.34 [0.46, 3.86] Yang 2019 48 50 41 50 1.1% 5.27 [1.08, 25.78] Yao 2012 29 34 22 34 2.1% 3.16 [0.97, 10.31] Yu 2011 20 30 23 30 5.0% 0.61 [0.20, 1.90] Zhang 2011 36 43 2.6 43 2.8% 3.36 [1.22, 9.27] Zhang 2015 42 45 34 45 1.5% 4.53 [1.17, 17.55] Zhuo 2014 30 30 23 30 0.2% 19.47 [1.06, 358.38] Total (95% CI) 2435 2357 100.0% 3.58 [3.02, 4.24] 10.01 <td>Wang FL 2011</td> <td>56</td> <td>60</td> <td>48</td> <td>60</td> <td>2.1%</td> <td>3.50 [1.06, 11.57]</td> <td></td>	Wang FL 2011	56	60	48	60	2.1%	3.50 [1.06, 11.57]	
Xia 2015 33 38 25 38 2.1% 3.43 [1.08, 10.89] Xiong 2009 59 66 20 32 1.9% 5.06 [1.75, 14.61] Xiu 2008 31 35 22 35 1.6% 4.58 [1.32, 15.93] Yang 2005 53 60 51 60 3.9% 1.34 [0.46, 3.86] Yang 2019 48 50 41 50 1.1% 5.27 [1.08, 25.78] Yao 2012 29 34 22 34 2.1% 3.16 [0.97, 10.31] Yu 2011 20 30 23 30 5.0% 0.61 [0.20, 1.90] Zhan 2011 27 30 21 30 1.4% 3.86 [0.93, 16.05] Zhang 2011 36 43 2.6 43 2.8% 3.36 [1.22, 9.27] Zhang 2015 42 45 34 45 1.5% 4.53 [1.17, 17.55] Zhuo 2014 30 30 23 30 0.2% 19.47 [1.06, 358.38] Total (95% CI) 2435 2357 100.0% 3.58 [3.02, 4.24] 1.5%	Wang FS 2011	39	45	32	45	2.8%	2.64 [0.90, 7.73]	
Xiong 2009 59 66 20 32 1.9% 5.06 [1.75, 14.61] Xiu 2008 31 35 22 35 1.6% 4.58 [1.32, 15.93] Yang 2005 53 60 51 60 3.9% 1.34 [0.46, 3.86] Yang 2019 48 50 41 50 1.1% 5.27 [1.08, 25.78] Yao 2012 29 34 22 34 2.1% 3.16 [0.97, 10.31] Yu 2011 20 30 23 30 5.0% 0.61 [0.20, 1.90] Zhan 2011 27 30 21 30 1.4% 3.86 [0.93, 16.05] Zhang 2013 43 26 43 2.8% 3.36 [1.22, 9.27] Zhang 2015 42 45 34 45 1.5% 4.53 [1.17, 17.55] Zhuo 2014 30 30 23 30 0.2% 19.47 [1.06, 358.38] Total (95% CI) 2435 2357 100.0% 3.58 [3.02, 4.24] Total events 2221 1760 Heterogeneity: Chl ² = 76.77, df = 51 (P = 0.01); l ² = 34% 4.01 0.1 <td>Xia 2015</td> <td>33</td> <td>38</td> <td>25</td> <td>38</td> <td>2.1%</td> <td>3.43 [1.08, 10.89]</td> <td></td>	Xia 2015	33	38	25	38	2.1%	3.43 [1.08, 10.89]	
Xiu 2008 31 35 22 35 1.6% 4.58 [1.32, 15.93] Yang 2005 53 60 51 60 3.9% 1.34 [0.46, 3.86] Yang 2019 48 50 41 50 1.1% 5.27 [1.08, 25.78] Yao 2012 29 34 22 34 2.1% 3.16 [0.97, 10.31] Yu 2011 20 30 23 30 5.0% 0.61 [0.20, 1.90] Zhan 2011 27 30 21 30 1.4% 3.86 [0.93, 16.05] Zhang 2015 42 45 34 45 1.5% 4.53 [1.17, 17.55] Zhang 2015 42 45 34 45 1.5% 4.53 [1.06, 358.38] Total (95% CI) 2435 2357 100.0% 3.58 [3.02, 4.24] Total events 2221 1760 1760 1760 1760	Xiong 2009	59	66	20	32	1.9%	5.06 [1.75, 14.61]	
Yang 2005 53 60 51 60 3.9% 1.34 $[0.46, 3.86]$ Yang 2019 48 50 41 50 1.1% 5.27 $[1.08, 25.78]$ Yao 2012 29 34 22 34 2.1% 3.16 $[0.97, 10.31]$ Yu 2011 20 30 23 30 5.0% 0.61 $[0.97, 10.31]$ Zhan 2011 27 30 21 30 1.4% 3.86 $[0.93, 16.05]$ Zhang 2011 36 43 26 43 2.8% 3.36 $[1.22, 9.27]$ Zhang 2015 42 45 34 45 1.5% 4.53 $[1.17, 17.55]$ Zhuo 2014 30 30 23 30 0.2% 19.47 $[1.06, 358.38]$ Total (95% Cl) 2435 2357 100.0% 3.58 $[3.02, 4.24]$ Total events 2221 1760 1760 172 34% 10.0% 10.0%	Xiu 2008	31	35	22	35	1.6%	4.58 [1.32, 15.93]	————
Yang 2019 48 50 41 50 1.1% 5.27 [1.08, 25.78] Yao 2012 29 34 22 34 2.1% 3.16 [0.97, 10.31] Yu 2011 20 30 23 30 5.0% 0.61 [0.20, 1.90] Zhan 2011 27 30 21 30 1.4% 3.86 [0.93, 16.05] Zhang 2011 36 43 26 43 2.8% 3.36 [1.22, 9.27] Zhang 2015 42 45 34 45 1.5% 4.53 [1.17, 17.55] Zhuo 2014 30 30 23 30 0.2% 19.47 [1.06, 358.38] Total (95% CI) 2435 2357 100.0% 3.58 [3.02, 4.24] Total events 2221 1760 1760 1760 1760	Yang 2005	53	60	51	60	3.9%	1.34 [0.46, 3.86]	
Yao 2012 29 34 22 34 2.1% 3.16 [0.97, 10.31] Yu 2011 20 30 23 30 5.0% 0.61 [0.20, 1.90] Zhan 2011 27 30 21 30 1.4% 3.86 [0.93, 16.05] Zhang 2011 36 43 26 43 2.8% 3.36 [1.22, 9.27] Zhang 2015 42 45 34 45 1.5% 4.53 [1.17, 17.55] Zhuo 2014 30 30 23 30 0.2% 19.47 [1.06, 358.38] Total (95% CI) 2435 2357 100.0% 3.58 [3.02, 4.24] Total events 2221 1760 Heterogeneity: Chl ² = 76.77, df = 51 (P = 0.01); l ² = 34% 10.01 0	Yang 2019	48	50	41	50	1.1%	5.27 [1.08, 25.78]	
Yu 2011 20 30 23 30 5.0% 0.61 [0.20, 1.90] Zhan 2011 27 30 21 30 1.4% 3.86 [0.93, 16.05] Zhang 2011 36 43 26 43 2.8% 3.36 [1.22, 9.27] Zhang 2015 42 45 34 45 1.5% 4.53 [1.17, 17.55] Zhuo 2014 30 30 23 30 0.2% 19.47 [1.06, 358.38] Total (95% Cl) 2435 2357 100.0% 3.58 [3.02, 4.24] Total events 2221 1760 1760 1760 1760 Heterogeneity: Chl ² = 76.77, df = 51 (P = 0.01); l ² = 34% 10.01 0 1	Yao 2012	29	34	22	34	2.1%	3.16 [0.97, 10.31]	├ ────
Zhan 2011 27 30 21 30 1.4% 3.86 [0.93, 16.05] Zhang 2011 36 43 26 43 2.8% 3.36 [1.22, 9.27] Zhang 2015 42 45 34 45 1.5% 4.53 [1.17, 17.55] Zhuo 2014 30 30 23 30 0.2% 19.47 [1.06, 358.38] Total (95% Cl) 2435 2357 100.0% 3.58 [3.02, 4.24] Total events 2221 1760 Heterogeneity: Chl ² = 76.77, df = 51 (P = 0.01); l ² = 34% $10.01 = 0^{1}$	Yu 2011	20	30	23	30	5.0%	0.61 [0.20, 1.90]	
Zhang 2011 36 43 26 43 2.8% 3.36 [1.22, 9.27] Zhang 2015 42 45 34 45 1.5% 4.53 [1.17, 17.55] Zhuo 2014 30 30 23 30 0.2% 19.47 [1.06, 358.38] Total (95% CI) 2435 2357 100.0% 3.58 [3.02, 4.24] Total events 2221 1760 Heterogeneity: Chl ² = 76.77, df = 51 (P = 0.01); l ² = 34% 10.01 0.1	Zhan 2011	27	30	21	30	1.4%	3.86 [0.93, 16.05]	
Zhang 2015 42 45 34 45 1.5% 4.53 [1.17, 17.55] Zhuo 2014 30 30 23 30 0.2% 19.47 [1.06, 358.38] Total (95% CI) 2435 2357 100.0% 3.58 [3.02, 4.24] Total events 2221 1760 Heterogeneity: Chi ² = 76.77, df = 51 (P = 0.01); l ² = 34% 10.01 0.1	Zhang 2011	36	43	26	43	2.8%	3.36 [1.22, 9.27]	
Zhuo 2014 30 30 23 30 0.2% 19.47 [1.06, 358.38] Total (95% CI) 2435 2357 100.0% 3.58 [3.02, 4.24] Total events 2221 1760 Heterogeneity: Chi ² = 76.77, df = 51 (P = 0.01); l ² = 34% 10.01 0.1	Zhang 2015	42	45	34	45	1.5%	4.53 [1.17, 17.55]	
Total (95% CI)24352357100.0%3.58 [3.02, 4.24]Total events22211760Heterogeneity: $Chi^2 = 76.77$, df = 51 (P = 0.01); $i^2 = 34\%$ 100.01	Zhuo 2014	30	30	23	30	0.2%	19.47 [1.06, 358.38]	·
For the control (55.7 C) (55.	Cotal (95% CI)		2425		2357	100.0%	3 58 [2 02 4 24]	
Heterogeneity: $Chi^2 = 76.77$, df = 51 (P = 0.01); $I^2 = 34\%$	Total (95% CI)	2221	2433	1760	2337	100.0%	5.56 [5.02, 4.24]	
neterogeneity, cm = 70.77, d1 = 51 (F = 0.01), 1 = 54%	Heterogeneity: Chi2 -	76 77 4	- 51 /	1/00	$ ^2 = 2$	494		
Test for overall effect: $7 = 14.71 (P < 0.00001)$ 0.01 0.1	Test for overall effect	7 = 147	1 (P < 0	- 0.01)	,	1/0		0.01 0.1 i 10 10
Favours [experiment	rest for overall effect	. 2 = 14.7	I (F < 0	.00001)				Favours [experimental] Favours [control]
	est plot of angina pe	ectoris effi	cacy.					

heterogeneity of pooled results ($I^2 > 50\%$), or the failure of researchers to reasonably explain results with high heterogeneity.

4.3 Pharmacological effects of TXLC

TXLC is composed of *Panax ginseng* C.A. Mey (Ren Shen), *Hirudo nipponica* Whitman (Shui Zhi), *Buthus martensii* Karsch (Quan Xie), Paeonia lactiflora Pall. (Chi Shao), Cicadae periostracum (Chan Tui), Scolopendra subspinipes mutilans L. Koch (Wu Gong), Eupolyphaga sinensis Walker (Tu Bie Chong), Santalum album L. (Tan Xiang), Dalbergia odorifera T.C. Chen (Jiang Xiang), Boswellia carterii Birdw. (Ru Xiang), Ziziphus jujuba Mill. (Suan Zao Ren), and Cinnamomum camphora (L.) J. Presl (Bing Pian). Research shows TXLC can improve plaque stability and reduce inflammation

Mean				ntroi			Std. Mean Difference	Std. Mean Difference
	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% CI
-4	1.51	60	-2.8	1.5	58	7.7%	-0.79 [-1.17, -0.42]	
-2.2	0.8	40	-1.52	0.86	40	5.2%	-0.81 [-1.27, -0.35]	
-4.9	4.19	55	-3.1	4.89	55	7.7%	-0.39 [-0.77, -0.02]	
-2.68	1.01	50	-2.11	1.05	50	6.8%	-0.55 [-0.95, -0.15]	
-1.32	0.6	33	-0.96	0.51	32	4.4%	-0.64 [-1.14, -0.14]	
-1.9	0.9	80	-1.18	0.8	80	10.4%	-0.84 [-1.17, -0.52]	
-0.93	0.26	28	-0.54	0.62	26	3.5%	-0.82 [-1.38, -0.26]	
-3.89	1.96	39	-2.79	1.98	39	5.3%	-0.55 [-1.01, -0.10]	
-11.82	2.59	35	-10.52	2.73	35	4.8%	-0.48 [-0.96, -0.01]	
-3.4	2.8	66	-2.9	2.5	60	8.9%	-0.19 [-0.54, 0.16]	
-7.12	3.27	100	-7.04	3.21	50	9.5%	-0.02 [-0.36, 0.31]	-
-6.4	3.32	50	-3.1	3.9	50	6.4%	-0.90 [-1.32, -0.49]	
-5.28	0.81	80	-4.84	0.89	80	11.0%	-0.51 [-0.83, -0.20]	
1.01	0.98	27	1.72	0.66	27	3.5%	-0.84 [-1.40, -0.28]	
-5.28	0.69	33	-5.14	0.79	35	4.8%	-0.19 [-0.66, 0.29]	
		776			717	100.0%	-0.54 [-0.64, -0.44]	•
Wang 2005 -11.82 2.59 35 -10.52 2.73 35 4.8% -0.48 [-0.96, -0.01] Wang 2009 -3.4 2.8 66 -2.9 2.5 60 8.9% -0.19 [-0.54, 0.16] Wang 2012 -7.12 3.27 100 -7.04 3.21 50 9.5% -0.02 [-0.36, 0.31] Wang 2015 -6.4 3.32 50 -3.1 3.9 50 6.4% -0.90 [-1.32, -0.49] Xiao 2004 -5.28 0.81 80 -4.84 0.89 80 11.0% -0.51 [-0.83, -0.20] Yan 2015 1.01 0.98 27 1.72 0.66 27 3.5% -0.84 [-1.40, -0.28] Zhang 2004 -5.28 0.69 33 -5.14 0.79 35 4.8% -0.19 [-0.66, 0.29] Total (95% Cl) 776 717 100.0% -0.54 [-0.64, -0.44] Heterogeneity: Chi ² = 27.17, df = 14 (P = 0.02); l ² = 48% Total fore runcell (Fight) 7 = 10 14 (P = 0.000)								
Z = 10.1	L4 (P <	0.000	01)					Favours [experimental] Favours [control]
			-4 1.31 60 -2.2 0.8 40 -4.9 4.19 55 -2.68 1.01 50 -1.32 0.6 33 -1.9 0.9 80 -0.93 0.26 28 -3.89 1.96 39 -11.82 2.59 35 -3.4 2.8 66 -7.12 3.27 100 -6.4 3.32 50 -5.28 0.81 80 1.01 0.98 27 -5.28 0.69 33 776 27.17, df = 14 (P = 0. Z = 10.14 (P < 0.000)	$\begin{array}{cccccccccccccccccccccccccccccccccccc$	$\begin{array}{cccccccccccccccccccccccccccccccccccc$	$\begin{array}{cccccccccccccccccccccccccccccccccccc$	$\begin{array}{cccccccccccccccccccccccccccccccccccc$	$\begin{array}{cccccccccccccccccccccccccccccccccccc$



in atherosclerotic rabbits, which may be achieved by modulating intestinal flora and intestinal metabolism (29). Vitro experiments showed that TXLC significantly reduced the extent



of injury to Major cardiac adverse events by oxidizing Low-density lipoprotein (30).

Ginsenoside Rg1, the main component of Ren Shen, can inhibit myocardial apoptosis in rats with coronary heart disease by improving the scavenging capacity of oxygen free radicals and inhibiting the expression of inflammatory factors, and the myocardial protection is related to the intervention dose (31). Ginseng polysaccharide (GPS) is a bioactive ingredient with various immunomodulatory, antioxidant, and anticancer functions. GPS could improve the blood lipid abnormality in rats with coronary heart disease, had the function of anti-oxidation and anti-tumor, and had a strong protective effect on mitochondria (32). On the other hand, animal experiments have shown that the volatile oil of the Chuanxiong (Chuanxiong Rhizoma)-Suhexiang (Styrax)-Bingpian (Borneolum) formula can improve EF, FS, and other indices of myocardial damage in a rat model, thus relieving myocardial damage caused by heart hyperactivity, improving cardiac function, and protecting against myocardial damage (33).





Coronary heart disease is mainly caused by hyperlipidemia and hypercholesterolemia due to poor diet quality, too little exercise, and other life factors, which lead to the formation of coronary



atherosclerotic plaques, resulting in narrowing or even obstruction of coronary artery vascular channels. In addition, platelet aggregation, inflammation, and oxidative stress will further damage vascular endothelial cells, promote thrombosis, and accelerate coronary atherosclerosis (34). Furthermore, the enrichment results for TXLC-related pathways were mainly related to lipid metabolism, inflammatory response, vasodilation, vascular endothelial cell protection, and cardiomyocyte protection. Toll-like receptors, chemokines, MAPK, TNF, JAK-Stat, and other signaling pathways are related to inflammation (35), while the insulin signaling pathway is related to lipid metabolism. Vascular endothelial growth factor, p53, and the ErbB signaling pathway are related to angiogenesis and apoptosis (36).

In contrast, Fc epsilon RI and the calcium signaling pathway are related to cardiac function, vasodilation, and platelet aggregation (36), and each target and pathway plays a synergistic role. These results indicate that TXLC could act on multiple targets, showing the characteristics of multi-component, multitarget, and integrated regulation of a traditional Chinese medicine compound.

4.4 Advantages and limitations

In recent years, with the increase in SRs of TXLC in treating coronary heart disease angina pectoris, their quality has become controversial. Systematic overviews are a new approach to collecting different SR data sets, reassessing methodological quality, and synthesizing individual data. To our knowledge, this is the first systematic overview of TXLC for CHD angina. All SRs were rigorously assessed for methodological quality, risk of bias, and quality of evidence, and two independent reviewers performed all searches and evaluations to obtain reliable results. However, this study also has some limitations, including the limitations of the overview itself and the shortcomings of SRs. First, the system overview can only provide a quantitative synthesis and descriptive data analysis. Secondly, the methodological quality of most SRs could be higher, and the evidence quality of the results could be better, which may be related to the quality of the original research. In addition, due to the limited number of original studies, we needed more advanced data for subgroup analyses and to assess long-term efficacy. Literature reporting following the PRISMA guidelines for SR is also necessary. Finally, TXLC contains animal medicine, which is why most Western countries do not allow similar drugs for clinical use. Differences between formulations and treatment batches are an inevitable consequence of the nature of traditional Chinese medicine, although the Chinese government also sets limits for acceptable differences. These differences may contribute to any heterogeneity between the findings of different studies. In addition, it must be acknowledged that the holistic treatment philosophy of TCM differs from that of Western medicine.

For Original Research Articles, Clinical Trial Articles, and Technology Reports the introduction.

For more examples of citing other documents and general questions regarding reference style, please refer to the Chicago Manual of Style.

4.5 Health, physics and mathematics references

For articles submitted in the domain of Health or the journals Frontiers in Physics and Frontiers in Applied Mathematics and Statistics please apply the Vancouver system for in-text citations.

In-text citations should be numbered consecutively in order of appearance in the text – identified by Arabic numerals in the parenthesis (square parenthesis for Physics and Mathematics).

For some examples please click here.

For more examples of citing other documents and general questions regarding reference style, please refer to Citing Medicine.

Author contributions

LL and XZ conceived the article, drafted the research protocol, retrieved the literature, analyzed the data and wrote this manuscript. WZ and BL screened studies and evaluated methodological quality. DG and XW extracted data and gave suggestions for the discussion. ZC and LD gave suggestions on the structure of the article. PF provided data analysis and writing guidance. FZ provided methodological guidance and gave suggestions on the conception of the

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article. All authors contributed to the article and approved the submitted version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fcvm.2024. 1229299/full#supplementary-material

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