Systematic evaluation re-evaluation of Kangai injection in combination with chemotherapy for non-small cell lung cancer

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Abstract: To evaluate the methodological quality and evidence quality of the existing systematic evaluation of Kangai injection combined with chemotherapy for non-small cell lung cancer (NSCLC), the databases of China Knowledge Network (CNKI), Wanfang Database, China Biomedical Literature Database (CBM), VIP, PubMed, Embase, Cochrane Library, and Web of Science were searched for systematic evaluations of Kangai injection in combination with chemotherapy for NSCLC from database creation to April 2022. Two investigators independently screened the literature, extracted information, used the PRISMA statement to evaluate the report quality of included studies, the AMSTAR2 scale to assess the methodological quality, and the GRADE system to assess the level of evidence. A total of 10 systematic evaluations were included, with PRISMA statement evaluations showing four scores of 21.5-27, five scores of 15.5-21, and one score of 15 or less. The AMSTAR2 review indicated one study with low methodological quality and nine studies with deficient methodological quality. The GRADE evaluation showed moderate evidence for six indicators, scarce evidence for 32 indicators, and deficient evidence for 31 indicators. The efficacy and safety of Kangai injection combined with chemotherapy for non-small cell lung cancer are superior to chemotherapy alone; however, the methodological quality of the current systematic evaluations and the quality of evidence is low.

1. Introduction

Non small cell lung cancer (NSCLC) belongs to the class of lung cancer, which accounts for approximately 85% of all lung cancers [1], and NSCLC has a slow onset relative to small cell lung cancer and a slow spread rate, but it is generally found to be advanced stage, so it is very difficult to control and treat. At present, clinical treatment is still dominated by chemotherapy, but single chemotherapy modality is gradually replaced by drug assisted systemic chemotherapy [2]. In clinical application, multi-use chemotherapy combined with Kangai injection improves patient survival quality [3]; Improved patient cell immune function and reduced serum tumor marker content [4], among others. Several studies have conducted a systematic review on the combination of Kangai injection and chemotherapy for the treatment of NSCLC, but there is still a lack of studies to evaluate the methodological quality and evidence quality grade of the systematic review, so this study conducted a systematic review on the analysis of the published systematic review on the combination of Kangai Injection and chemotherapy for the treatment of NSCLC to verify its clinically guiding role, Provide a more systematic evidence-based basis for clinical treatment.

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2. Methods

2.1. Search strategy

All literatures were obtained from China National Knowledge Infrastructure (CNKI), Wanfang, VIP, CBM, PubMed, web of science, EMBASE and Cochrane library electronic databases.The search time was limited to build the library until April 2022, and the specific search strategies are shown in Figure 1 (using PubMed as an example). Flow diagram of literature screening (See Figure 2).

Steps	Search terms
#1	((Lung Neoplasms) OR (Carcinoma， Non - Small - Cell Lung)) [MeSH]
#2	Lung Neoplasm* [Title/Abstract]
#3	lung cancer* [Title/Abstract]
#4	pulmonary neoplasm* [Title/Abstract]
#5	Pulmonary Cancer* [Title/Abstract]
#6	Non-Small-Cell Lung Carcinoma [Title/Abstract]
#7	Non-Small-Cell Lung Cancer [Title/Abstract]
#8	NSCLC [Title/Abstract]
#9	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8
#10	Kangai injection [Title/Abstract]
#11	Kang Ai injection [Title/Abstract]
#12	Kang'ai injection [Title/Abstract]
#13	#10 OR #11 OR #12
#14	Meta-Analysis [MeSH]
#15	Meta-analysis [Title/Abstract]
#16	systematic review [Title/Abstract]
#17	#14 OR #15 OR #16
#18	#9 AND #13 AND #17

Figure 1. PubMed search strategy

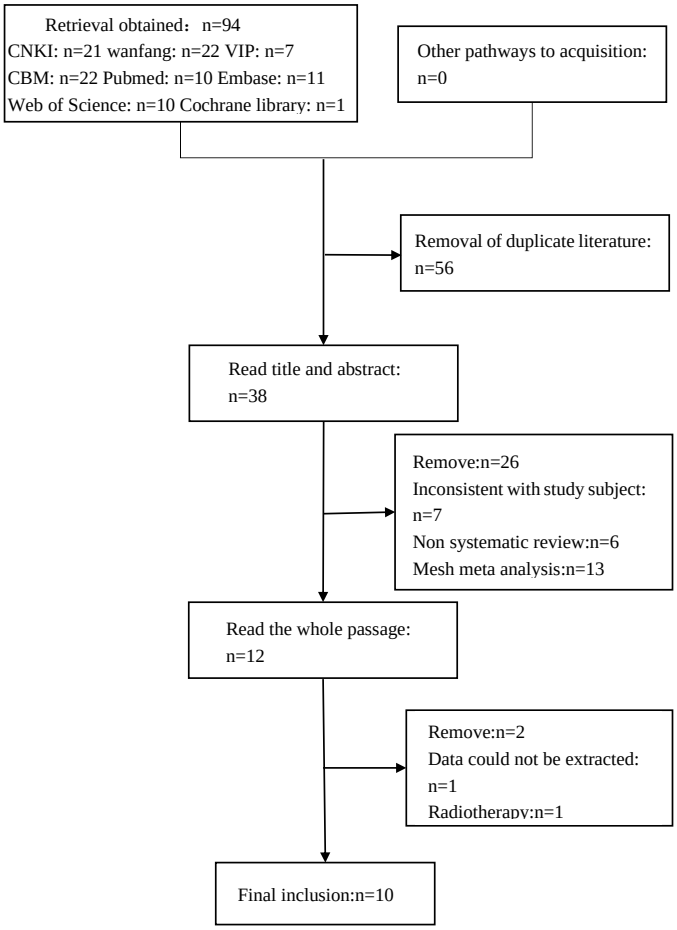

Figure 2. Flow diagram of literature screening.

2.2. Study selection

The inclusion criteria were: (1) A systematic review and analysis of Kangai injection combined with chemotherapy for non-small cell lung cancer based on randomized controlled experiments (RCTs) with limited language in Chinese and English; (2) Patients with a pathological diagnosis of non-small cell lung cancer (NSCLC), irrespective of sex, age, disease duration; (3) The intervention of the treatment group was Kangai injection combined with chemotherapy, the intervention of the control group was chemotherapy alone, and the chemotherapy regimen was not limited; (4) Primary outcome measures included objective response rate (ORR), disease control rate (DCR), quality of life improvement (QOL), secondary outcome measures included phlebitis, alopecia, etc., and safety measures included immune function (percentage of CD3 +, CD4 +, CD8 +, and NK and the ratio of CD4 + / CD8 +), gastrointestinal reactions / nausea and vomiting Myelosuppression (symptoms of Erythropenia, leukopenia, thrombocytopenia).

The exclusion criteria included: (1) Duplicate published literature; (2) Incomplete data or inability to obtain full-text literature; (3) The interventions in the treatment group contained other TCM formulations; (4) A systematic review plan; (5) Meeting abstract.

2.3. Data extraction

Two reviewers performed "" back-to-back "" independent screening with data extraction and cross checked, in case of controversy, with a third investigator to assist in the adjudication. Data extraction content included first author, publication year, type of study, the number of included original studies (literature size), sample size, chemotherapy regimen, outcome measures, assessment method of risk of bias and funding support. The evaluation process was performed independently by two investigators and cross checked, with disagreements resolved in consultation with a third investigator.

2.4. Quality evaluation

The literature was evaluated for methodological quality using the amstar2 scale [5] and the grade system was used to assess the level of evidence[6-7].

3. Results

3.1. Study selection

A total of 94 relevant articles was obtained after searching, and 39 remained after removing duplicates, 26 were removed after primary screening of reading the title and abstract, and 3 were removed after reading the full text, and finally included in 10 [8-17] systematic review analyses .

3.2. Characteristics of the included studies

Of the 10 included systematic review analyses, six [8-12,16] were in Chinese and four [13-15,17] were in English, published in 2011-2022, and the amount of included original studies ranged from 5 to 35; The sample size ranged from 356 to 2618 patients, of which five literatures were financially supported.

3.3. Quality evaluation

3.3.1. Methodological quality assessment of included studies

Only 1 study was of low methodological quality and 9 studies were of very low methodological quality as assessed by the amstar2 scale; The specific evaluation results are shown in Table 1.

Table 1 Methodological quality assessment of included studies.

Questions	Xiran He 2011[8]	Wei Zhuang 2011[9]	Yujiao Guo 2012[10]	Yufen Qin 2012[11]	Xiaoqing Xue 2014[12]	Xueqian Wang 2015[13]	Qiang Lu 2018[14]	Hongxiao Li 2019[15]	Xianghui Zhou 2021[16]	Dongwei Zhu 2022[17]
Q1	Y	N	Y	Y	Y	Y	Y	Y	Y	Y
Q2	N	N	N	N	N	N	N	Y	N	N
Q3	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Q4	Y	PY	PY	PY	PY	PY	PY	PY	PY	PY
Q5	Y	Y	Y	N	N	Y	Y	Y	Y	Y
Q6	Y	Y	Y	N	N	Y	Y	Y	Y	Y
Q7	N	N	N	N	N	N	N	N	N	N
Q8	PY	Y	PY	PY	PY	Y	PY	Y	PY	Y
Q9	Y	N	N	N	N	Y	Y	Y	N	Y
Q10	N	N	N	N	N	N	N	N	N	N
Q11	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Q12	Y	N	N	N	N	N	N	Y	N	N
Q13	Y	Y	N	Y	N	Y	Y	Y	N	N
Q14	Y	Y	Y	Y	Y	Y	N	N	Y	N
Q15	N	Y	Y	N	N	Y	N	Y	Y	Y
Q16	Y	N	N	N	N	Y	Y	Y	N	Y
Quality ratings	Very low	Very low	Very low	Very low	Very low	Very low	Very low	low	Very low	Very low

Notice: Y: Yes N: No PY: Partial Yes

3.3.2. Results of evidence grade of included studies

Included studies performed a meta-analysis of 69 outcome measures graded for grade, with six indicators of moderate evidence, 32 indicators of low-grade evidence, and 31 indicators of very low-grade evidence with no high-grade evidence at this time[18]. The specific evaluation results are shown in Table 2.

Table 2 Level of evidence included in the study.

First author and year of publication	Outcome indicators	Bias risk	Inconsistency	Indirectness	Imprecision	Publication bias	Level of evidence
Xiran He2011[8]	Clinical response rate	-1[a]	0	0	0	-1[f]	Low
	Effective	-1[a]	0	0	0	-1[f]	Low
	Quality of life	-1[a]	0	0	0	-1[f]	Low
	Clinical symptoms	-1[a]	0	0	0	-1[f]	Low
	Inhibiting leukopenia	-1[a]	0	0	-1[e]	-1[f]	Low
	Inhibition of red blood cell decline	-1[a]	0	0	-1[e]	-1[f]	Very Low
	Inhibition of platelet decline	-1[a]	0	0	-1[e]	-1[f]	Very Low
	Reduce nausea and vomiting	-1[a]	0	0	0	-1[f]	Very Low
	Reduce phlebitis	-1[a]	0	0	0	-1[f]	Low
Wei Zhuang 2011[9]	short-term effects	-1[a]	0	0	0	-1[f]	Low
	Quality of life improvement	-1[a]	0	0	0	-1[f]	Low
	Digestive tract reaction	-1[a]	0	0	0	-1[f]	Low
	Myelosuppression reaction	-1[a]	0	0	0	-1[f]	Low
Yujiao Guo 2012[10]	Effective	-2[b]	0	0	0	-1[f]	Very Low
	Quality of life	-2[b]	0	0	0	-1[f]	Very Low
	Clinical symptoms	-2[b]	0	0	0	-1[f]	Very Low
	Inhibiting leukopenia	-2[b]	0	0	0	-1[f]	Very Low
Yufen Qin 2012[11]	short-term effects	-2[b]	0	0	0	-1[f]	Very Low
	Quality of life	-2[b]	0	0	0	-1[f]	Very Low
Xiaoqing Xue 2014[12]	Recent efficiency	-2[b]	0	0	0	0	Low
	Quality of life improvement	-2[b]	0	0	0	0	Low
	Weight gain	-2[b]	0	0	0	0	Low
	Incidence rate of digestive tract	-2[b]	0	0	0	0	Low
	Adverse reaction of bone marrow suppression	-2[b]	0	0	0	0	Low
Xueqian Wang2015[13]	Objective tumor response	-1[a]	0	0	0	-1[f]	Low
	Quality of life	-1[a]	0	0	0	-1[f]	Low

	improvement						
	Digestive tract reaction	-1[a]	0	0	0	-1[f]	Low
	Myelosuppression	-1[a]	0	0	0	-1[f]	Low
Qiang Lu2018[14]	Tumor response	-1[a]	0	0	0	0	Low
	Quality of life improvement	-1[a]	0	0	0	-1[f]	Moderate
	Immunity						
	CD3+	-1[a]	-2[d]	0	-1[e]	-1[f]	Very Low
	CD4+	-1[a]	-2[d]	0	-1[e]	-1[f]	Very Low
	CD8+	-1[a]	-2[d]	0	-1[e]	-1[f]	Very Low
	NK	-2[b]	-2[d]	0	-1[e]	-1[f]	Very Low
	CD4+/CD8+	-1[a]	-2[d]	0	0	-1[f]	Very Low
	Gastrointestinal reaction	-1[a]	0	0	0	-1[f]	Low
	Myelosuppression	-1[a]	0	0	0	-1[f]	Low
	alopecia	-1[a]	0	0	0	-1[f]	Very Low
Hongxiao Li2019[15]	Objective remission rate	-1[a]	0	0	0	0	Moderate
	Disease control rate	-1[a]	0	0	0	-1[f]	Low
	Quality of life	-1[a]	0	0	0	-1[f]	Low
	Gastrointestinal reaction	-1[a]	0	0	0	-1[f]	Low
	Inhibiting leukopenia	-1[a]	0	0	0	-1[f]	Low
	Hemoglobin decrease	-1[a]	0	0	-1[e]	-1[f]	Very Low
	platelet	-1[a]	0	0	0	-1[f]	Low
	immunity						
	NK	-1[a]	0	0	-1[e]	-1[f]	Very Low
	CD3+	-1[a]	0	0	-1[e]	-1[f]	Very Low
	CD4+	-1[a]	-2[d]	0	-1[e]	-1[f]	Very Low
	CD8+	-1[a]	-2[d]	0	-1[e]	-1[f]	Very Low
	CD4+/CD8+	-1[a]	-2[d]	0	0	-1[f]	Very Low
Xianghui Zhou 2021[16]	Total efficiency	-1[a]	0	0	0	0	Moderate
	Quality of life improvement	-1[a]	0	0	0	0	Moderate
	Incidence of myelosuppression	-1[a]	-1[c]	0	0	0	Low
	Gastrointestinal adverse reactions	-1[a]	0	0	0	0	Moderate
Dongwei Zhu2022[17]	Objective reaction rate	-1[a]	0	0	0	0	Moderate
	Disease control rate	-1[a]	0	0	0	-1[f]	Low
	Quality of life improvement	-1[a]	0	0	0	-1[f]	Low
	immunity						
	CD3+	-1[a]	-2[d]	0	0	-1[f]	Very Low
	CD4+	-1[a]	-2[d]	0	0	-1[f]	Very Low
	CD8+	-1[a]	-2[d]	0	0	-1[f]	Very Low
	CD3+/CD4+	-1[a]	-2[d]	0	0	-1[f]	Very Low
	NK	-1[a]	-2[d]	0	0	-1[f]	Very Low
	Inhibiting leukopenia	-1[a]	-1[c]	0	0	-1[f]	Very Low
	platelet	-1[a]	0	0	0	-1[f]	Low
	vomit	-1[a]	0	0	0	-1[f]	Low

Note: a: most studies come from studies with medium risk, with serious limitations; b: most information comes from studies with high bias risk, with very serious limitations; c: I2 is greater than 50%; coincidence of confidence intervals is low; d: coincidence of confidence intervals is very low; e: 95% of the total confidence interval crosses the invalid line; f: funnel chart is not symmetrical, and there may be bias risk.

4. Discussion

4.1. Systematic review quality and level of evidence

The amstar2 review results showed that the methodological quality of all studies was of low or very low grade, and the factors affecting the largest proportion of methodological quality were failure to provide a list of excluded literature and failure to report the funding sources of included studies, two aspects of the common response were that the authors of systematic reviews were not able to report the details of included studies in detail, which would increase the possibility of selection bias, And readers could not judge whether the financial support of the included studies caused bias to the study. Grade the results of this systematic review show that the quality of moderate evidence is much less than low - or very low-grade evidence, no high-grade evidence exists, and the factors contributing to the lower grade evidence grade are mainly risk of bias,

heterogeneity, imprecision, and publication bias, with the risk of bias mainly being that the original studies had major flaws in randomization methods, allocation concealment, and implementation of blinding, which can cause some degree of error and affect the authenticity of the results, The above results suggest that the systematic review authors should include more studies to elevate the sample size, original studies should make improvements in randomization methods, allocation concealment, and implementation of blinding, as well as improvements in methodological quality to provide higher evidence.

4.2. Limitations

This paper has some limitations: the included studies were of low quality, and the included original studies were at an excessive risk of bias and the reliability of the results was low; The majority of included studies did not report whether they were registered or not, making the studies less reliable and did not retrieve literatures in languages other than Chinese and English and grey literatures, with possible selection bias; And there was some subjectivity in the process of the study, which may cause bias of the results.

5. Conclusions

In summary, the efficacy and safety of Kangai injection combined with chemotherapy in the treatment of non-small cell lung cancer has some advantages compared with chemotherapy alone, but the current systematic review is of low methodological quality and evidence quality, and higher quality clinical studies should be conducted in the future to improve the methodological quality of the systematic review to improve the clinical evidence-based basis.

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