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Systematic evaluation and meta-analysis of the efficacy and safety of cinobufagin injection combined with western medicine in the treatment of liver cancer

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ABSTRACT

Objective: To evaluate the clinical efficacy and safety of cinobufagin injection in the treatment of liver cancer. **Methods:** PubMed database, Embase database and Cochrane Library database, CNKI, Wanfang database, VIP database and Sinomed database were used to search for the randomized controlled trials of cinobufagin injection combined with Western medicine in the treatment of primary liver cancer. The retrieval time was from the establishment to December 15, 2020. Two independent researchers conducted systematic screening, literature inclusion and quality assessment of the articles according to the inclusion criteria, respectively. Meta-analysis of the data was performed using RevMan 5.4 software. **Results:** A total of 30 studies with a total of 2 355 patients were included. Compared with conventional western medicine treatment, the clinical effective rate of Hububutin injection combined with western medicine was significantly higher [*RR*=1.16, 95%*CI*=(1.11,1.22), *P*<0.000 01]. It could effectively reduce the tumor size [*RR*=1.33, 95%*CI*=(1.17,1.51), *P*<0.000 01], prolong the survival time of patients [*RR*=1.41, 95%*CI*=(1.31,1.52), *P*<0.000 01], improve the quality of life [*RR*=1.37, 95%*CI*=(1.19,1.57), *P*<0.000 01], improve the liver function of patients [*RR*=-14.52, 95%*CI*=(-16.15,-12.88), *P*<0.000 01], and reduce the occurrence of adverse reactions [*RR*=0.94, 95%*CI*=(0.85,1.42), *P*=0.25] such as bone marrow suppression [*RR*=0.44, 95%*CI*=(0.31,0.62), *P*<0.000 01]. **Conclusion:** Cinobufagin injection combined with western medicine therapy can effectively improve the clinical symptoms of primary liver cancer, and the safety is good. However, the methodological quality of the included literature is low, which affects the objectivity of the outcome, and it still needs to be verified by multi-sample, multi-center, randomized double-blind controlled trial.

1. Introduction

Primary liver cancer (PLC) is one of the most common causes of cancer-related death worldwide, and its incidence and mortality are on the rise. In China, primary liver cancer is the fourth most common malignant tumor and the third leading cause of tumor-related death, so it is a major public health threat[1]. Surgical resection is the first choice for domestic clinical used in the treatment of primary liver cancer, but since the onset of more complex hidden, it is difficult to detect and patient are in the early progress rapidly, most have entered middle-late stage, missed the best period of surgical resection of liver cancer treatment, so the poor treatment effect[2]. At present, intermediate and advanced hepatocellular carcinoma patients often go through Transcatheter arterial chemoembolization (TACE), targeted chemotherapy, radiotherapy and other methods for treatment, although this technology can effectively improve the survival rate of patients with liver cancer, but the gastrointestinal reaction, strong side effects, liver damage, high recurrence risk, adverse reactions such as bone marrow suppression, has become the influence the main factors of

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health and living quality for patients with primary liver cancer[3,4].

Traditional Chinese medicine is a precious resource of Chinese civilization. In the treatment of malignant tumors, due to its advantages of good curative effect, less adverse reactions, improving human immunity and improving quality of life, the combined treatment of traditional Chinese and western medicine for primary liver cancer has become a common means of clinical treatment and research hotspot. Huabusin injection is an anticancer traditional Chinese medicine preparation independently researched and developed in China. Studies have shown that in the treatment of primary liver cancer, Huabusin injection alone or in combination with ulbenmex, TACE, Gamma knife and other western medicine treatments have significant efficacy[7,12,21]. The mechanism of action is closely related to the inhibition of DNA and RNA synthesis in tumor cells, the enhancement of humoral immunity, cellular immunity and non-specific immune function of the body, the inhibition of replication of hepatitis B virus, and the protection of liver function, which can effectively improve the recurrence of patients′ disease and alleviate the pain of disease[5]. But about HuaChan element injection combined with western medicine treatment of primary liver cancer was applied to evaluate the safety and effectiveness of research are rarely reported, this study adopts the method of Meta analysis summarizes domestic and foreign related research, system evaluation HuaChan element injection combined western medicine efficacy and safety of the treatment of primary liver cancer, provide a basis for objective effective evidence-based medicine in clinical,To guide clinical application.

2. Materials and methods

2.1 Literature search

Chinese and English databases such as Cochrane Library, Embase, PubMed, Sinomed, CNKI, VIP and Wangfang were searched by computer, and the retrieval time was set as from the establishment to June 4, 2021. The search terms were combined with subject words and free words. The Chinese search terms included: "华蟾素注射液""华蟾素注射剂""原发性肝癌""肝脏肿瘤""肝细胞瘤", etc. English search terms include: "Cinobufagin", "Bufanolides", "Liver Neoplasms", "Neoplasms, Hepatic", "Cancer of Liver", "Hepatocellular Cancer", *etc*. The literature is in Chinese and English, and the publication type is not limited.

2.2 Inclusion criteria

In this study, a randomized controlled trial (RCT) was selected, whether blind or not. The subjects were patients diagnosed with primary liver cancer by pathological examination, regardless of race, age, or gender. Intervention measures: The control group was treated with western medicine therapy, such as hepatic artery chemoembolization (TACE), gamma knife, ubenmex, and supportive therapy, etc. The experimental group was treated with hububutin injection combined with western medicine, which was consistent with the western medicine treatment in the same paper, and the course of treatment was not limited. Outcome measures include two aspects: effectiveness outcome measures (clinical efficacy, survival time, laboratory tests, quality of life, tumor size) and safety outcome measures (adverse reactions).

2.3 Exclusion criteria

Literature review, laboratory animals, republication and data similarity study; Literature whose research content is inconsistent with inclusion criteria; Documents where all valid information and data cannot be obtained; Randomized control was not used in the trial group, and the literature with incorrect or missing statistical data was not used.

2.4 Literature screening and data extraction

The two researchers screened the literature and extracted the data according to the determined screening criteria respectively, and cross-verified the results. In case of disagreement, the two parties discussed with each other or decided by a third party. The Endnote literature management software was used to remove all the repetitious literatures. The researchers carefully read the titles, years, secondary de-duplication of authors, and screened the titles, abstracts and other contents of literatures. The articles that did not meet the standards of this research were excluded. After preliminary screening, the full text of the articles were downloaded and read in detail, and finally the articles that met the requirements of this topic were included.

A data extraction table was designed, and Excel 2020 was used to extract the data to be analyzed, including the following: ①Basic information of the included study: first author, publication year, age of included patients, gender ratio, sample size, *etc*. ②Treatment plan: intervention and control method, course of treatment, route of administration, *etc*. ③Outcome indicators: quality of life, clinical efficacy, adverse reactions, survival time, *etc*. ④Quality assessment criteria: whether it is RCT, whether blind method is used, *etc*.

2.5 Quality assessment

In this study, Cochrane bias quality risk assessment tool[6] was used to evaluate the quality of the included articles from the following seven aspects: random sequence assignment; Distribution mode is hidden; Blind the experimenter and the researcher; Implement blind method in outcome evaluation; Outcome indicators are incomplete; Selective reporting of experimental results; Other biases. The statistical data in the above aspects were evaluated at three different levels of "low risk bias", "uncertain risk bias" and "high risk

bias″ respectively, and were graphically displayed by RevMan 5.4 software.

2.6 Statistical analysis

RevMan 5.4 software was used for further statistical analysis of the included literature data. In counting data, relative risk (*RR*) index was used to represent effect statistics.However, in the measurement data, the units of measurement results for the same index among different types of studies are the same and the mean difference is small, so mean difference (*MD*) is adopted. Standardized mean difference (*SMD*) was adopted for different measurement units and large mean differences, and the combined results were both expressed with 95% confidence interval (*CI*) and effect value. The included articles were tested for clinical, statistical and methodological heterogeneity, respectively. The clinical heterogeneity was tested according to the study objects, intervention and treatment measures, outcome diagnostic indicators, etc, to determine whether the indicators included in the study had specific differences, and subgroup analysis could be carried out if the differences were large. Methodological heterogeneity is mainly based on the relevant experimental model design and research data in the selected literature to determine whether there are differences. Statistical heterogeneity is determined by Q statistics combined with I2 statistics analysis results. If $P>0.1$, $I^2\leqslant 50\%$, it indicates a small heterogeneity. Fixe-effect model (FEM) is used to analyze the data. If $P\leqslant 0.1$, $I^2>50\%$, it indicates greater heterogeneity. When the source of heterogeneity data could not be explained by clinical heterogeneity and methodological heterogeneity, the random effect model (REM) was selected to analyze the data. When the heterogeneity is large, sensitivity analysis can be conducted on the included research results. If the inclusion criteria are changed and the heterogeneity and effect value of each excluded article change, then the article is the source of sensitivity. When a certain outcome index was included in more than 10 articles, funnel plots were drawn to observe whether bias occurred. Descriptive analysis is mainly used to describe articles that are not completely consistent with Meta analysis.

3. Results

3.1 Basic information of the included literature

A total of 1 237 articles were obtained by preliminary retrieval, including 1 142 articles in Chinese and 95 articles in English.All included in the articles imported Endnote software, according to the inclusion criteria were screened, out of 1 207 articles: duplicate entry research 672, title, summary, 462 articles of discrepancies without access to the original text, 21 non randomized controlled with 42 references, data incomplete 10 articles, eventually into a total of 30 articles, are all Chinese. The retrieval process is shown in Figure 1.

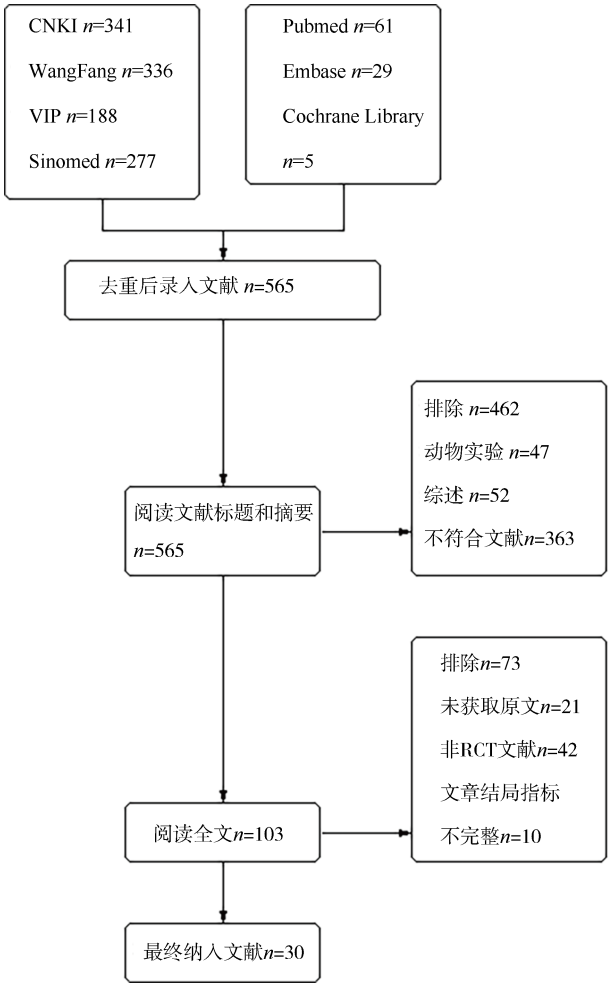

Fig 1 Flow chart of literature screening

3.2 Basic characteristics of the included literature

Thirty articles[7-36] on the treatment of PLC with Hububutin injection combined with Western medicine were included, all of which were published Chinese literature on combined Chinese and Western medicine therapy, including 2 355 patients, including 1 185 cases in the experimental group and 1 170 cases in the control group. Thirteen studies had a Child-Pugh scale, while the others were not described in detail. Intervention measures: the experimental group was treated with hububutin injection combined with western medicine therapy, while the control group was treated with western medicine therapy, such as hepatic artery chemoembolization (TACE), gamma knife, ubenmex, and supportive therapy, which were consistent with the western medicine therapy in the same article (Table 1).

3.3 Risk assessment of bias in included studies

All the 30 included studies were randomized controls. Among them, 2 studies were grouped by random number table[8,21], 2 studies were randomized by envelope method[30,32], and the other studies only mentioned randomness in text without specific description. In

Tab 1

Basic information of the included literatureInclusive criteria

	Sample size (men/woman)		Average age/year		Intervention measures	Period of treatment/month	Outcome indicators
	T	C	T	C			
Huang XY 2020[7]	30(18/12)	30(19/11)	53.02±6.01	52.26±5.98	Cinobufagin+TACE	18	①⑥⑤④
Wang L 2020[8]	42	42	58.3±13.5		Cinobufagin+TACE	30	①②⑯⑤⑥⑮
Sun DX 2019[9]	28(19/9)	28(21/7)	65.4	63.6	Cinobufagin+TACE	17	①⑨②⑤
Li J 2019[10]	45(38/7)	45(34/11)	54±8	50±10	Cinobufagin+TACE	24	①②③④⑤
Tian SY 2016[11]	30(17/13)	30(18/12)	55.8±5.4	56.3±4.8	Cinobufagin+FOLFOX4	24	①⑤②
Jia JY 2016[12]	49(29/20)	46(27/19)	58.4±8.3	58.1±8.7	Cinobufagin+Ubenimex	29	①②⑮
Deng ZY 2015[13]	26(14/11)	27(15/9)	48.65±16.12	48.3±16.24	Cinobufagin+TACE	25	③⑬②⑭⑤
Zhao ZG 2015[14]	22	18	41-75		Cinobufagin+Supporting treatment	11	②⑬⑯③
Yang GH 2014[15]	45(24/21)	45(23/22)	61.9±5.4	62.3±7.2	Cinobufagin+Western medicine therapy	36	①⑪⑧
Long D 2014[16]	60(35/25)	60(36/24)	48.05±1.61	47.86±1.48	Cinobufagin+Supporting treatment	36	⑬⑥②⑰⑫⑤
Sun Y 2013[17]	33(27/6)	30(26/4)	53.2±8.7	52.7±7.9	Cinobufagin+TACE	48	①②⑤
Yu JG 2013[18]	30(14/6)	30(15/5)	49.7	50.8	Cinobufagin+TACE	87	③⑥⑭①
He SL2012[19]	26(20/6)	25(18/7)	58.8		Cinobufagin+TACE	41	①④③⑧②⑤
Feng XM2012[20]	38(23/9)	32(21/17)	53.2±10.4	52.6±11.7	Cinobufagin+FOLFOX4	24	①②③
Zhang XY 2011[21]	30(22/8)	30(20/10)	58.81±14.45	57.29±12.87	Cinobufagin+Gamma knife	5-36	③⑥⑨②⑩④⑤
Fu ZL2010[22]	78(60/18)	78(59/19)	58	56	Cinobufagin+TACE	40	①②⑤
Zhou XB 2010[23]	29(20/9)	29(17/12)	48		Cinobufagin+Supporting treatment	12	⑦②⑬③④
Liu YQ 2010[24]	38(34/4)	44(38/6)	54.2±10.32	55.32±11.62	Cinobufagin+TACE	31	①⑬⑤
Xue Q 2010[25]	32(21/11)	30(24/6)	45.75±11.4	45.45±10.7	Cinobufagin+TACE	33	①④②⑭⑤
Ma YJ 2010[26]	40(31/9)	40(29/11)	49.3	49.7	Cinobufagin+Supporting treatment	57	⑦②⑬③④
Liu XH 2009[27]	42	42	48.5		Cinobufagin+TACE	48	①④⑮⑥⑤
Huang ZF 2009[28]	30(25/5)	30(27/3)	42.2±5.3	41.1±4.6	Cinobufagin+Supporting treatment	18	①②⑭⑮④
Shen ZJ 2009[29]	23	24	52.2±7.4		Cinobufagin+TACE	36	⑤③②⑬
Ni BQ 2009[30]	33	32	52		Cinobufagin+Supporting treatment	60	②⑭⑯⑬⑥④
Li Y 2008[31]	48	48	44.5		Cinobufagin+TACE	24	①②④⑤
Li Q 2008[32]	50	46	50.2		Cinobufagin+TACE	36	①②④③⑮
Li WH 2006[33]	19	19	45		Cinobufagin+TACE		②⑬③④⑤
Zhou JS 2006[34]	21(17/4)	22(17/5)	60.8		Cinobufagin+TACE	36	①⑥②④③⑭
Chen J 2003[35]	50(39/11)	50(37/13)	49.3	46.9	Cinobufagin+Supporting treatment	48	⑦②⑬③④
Sun ZJ 2002[36]	118	118	51.4		Cinobufagin+TACE	72	①④⑥⑤

Note: T: Experimental group; C: The control group; The control group: western medicine treatment plan (TACE, Supporting treatment, Gamma knife, FOLFOX4, *etc.*); ①Clinical curative effect/Disease control rate; ②Quality of life Karnofsky score; ③Laboratory examination WBC, AFP, CA199; ④Follow-up PFS (survival time); ⑤Adverse reactions; ⑥Liver function; ⑦Period of treatment; ⑧VEGF; ⑨VAS score (pain relief); ⑩CT; ⑪PA value; ⑫The long-term curative effect; ⑬Objective changes of solid tumors; ⑭Clinical syndrome changes; ⑮Immune function T cells, NK cells; ⑯Weight; ⑰HBV-DNA.

one study[8], patients' conditions and grouping were blinded, which was not explicitly mentioned in other articles. None of the included literatures mentioned the blind method and selective reporting of experimental results in outcome assessment. 3 articles did not describe whether there was statistical difference, while other articles did not[14,16,29] (Figure 2).

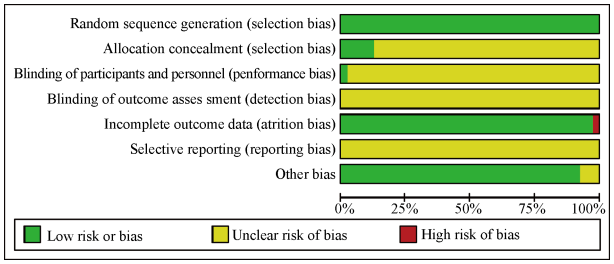

Fig 2 Percentage of bias risk assessment in the included studies

3.4 meta-analysis

3.4.1 Clinical efficiency

A total of 20 articles reported the clinical efficacy of huabatin injection[7-12,15,17-21,23,25,27,28,31,32,34,37], including 1 694 patients, and the combined data showed good homogeneity(P=0.01, I^2=46%). The results of meta-data analysis using fixed effect model showed that Huabamin injection had better clinical efficacy compared with western medicine [RR=1.16, 95%CI=(1.11,1.22), P<0.000 01]. The difference was statistically significant (Figure 3).

3.4.2 Quality of life

Article 17 reported quality of life, in total 1 169 patients[8,9,13,14,16,17,19,20,23,26,28,30-35], patients with combined data analysis shows that using Huabenin injection and the control group to improve the quality of life has a statistically significant [RR=1.37, 95%CI=(1.19,1.57), P<0.000 01], heterogeneity test I^2=70%, by using the random effects model, the article one by one, after screening, ruled out after a study[13] I^2=51%. It may be sources of heterogeneity. At the same time, different drugs were used in different papers, which may be the source of sensitivity (Figure 4).

3.4.3 Follow-up survival time

Survival time after follow-up was used as an outcome indicator in 14 articles[7,10,21,23,25-28,30-36], and 6 months survival time was

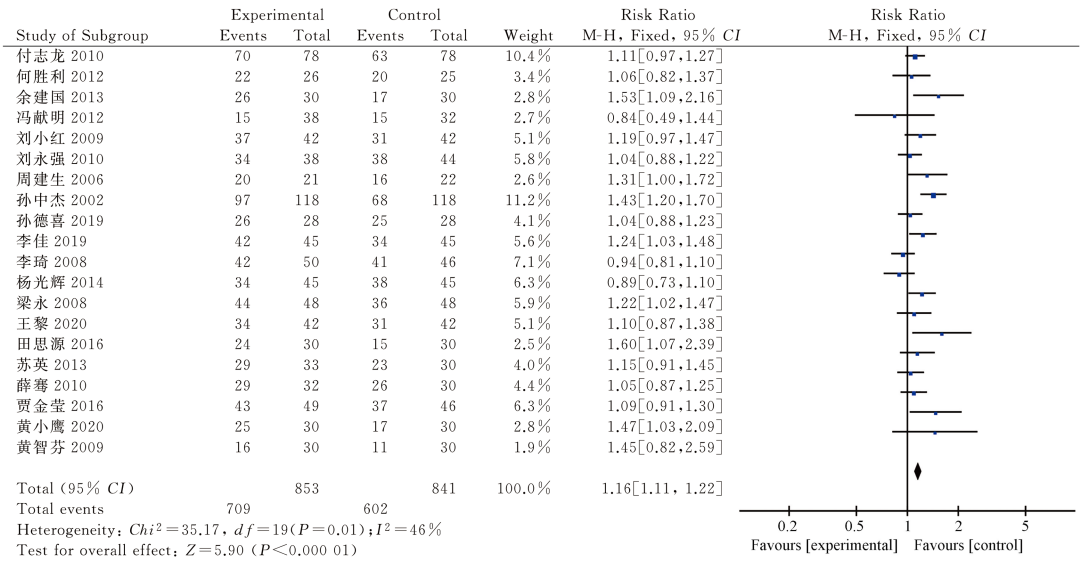

Fig 3 Meta-analysis of clinical response rate

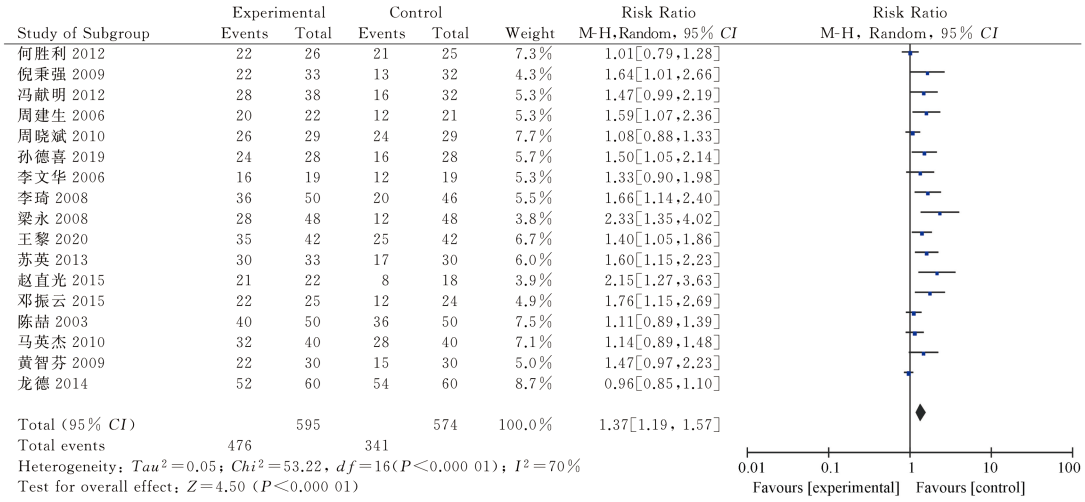

Fig 4 Meta-analysis of quality of life

counted in 7 articles[23,25,26,28,31,32,35] with good homogeneity (P=0.48, I^2=0%) and fixed effect model was used for analysis. In 13 studies[7,10,21,23,25-27,30-33,35,36], the survival time after 12 months was recorded. Compared with the western medicine group, the survival time of patients in the huabamin combined with western medicine group was significantly prolonged [RR=1.50, 95%CI=(1.35,1.68), P<0.000 01], and the difference was statistically significant with good homogeneity (P=0.04, I^2=44%). At 24 months, the 6 studies recorded[25,27,32-34,36] that the treatment group was significantly better than the control group, and the survival time of patients was prolonged [RR=1.93, 95%CI=(1.55,2.39), P<0.000 01]. The difference was statistically significant and the homogeneity was good (P=0.66, I^2=0%). According to the combined data analysis, compared with the control group, the survival time in the huabamin injection group was prolonged, with a statistical difference [RR=1.41, 95%CI=(1.31,1.52), P<0.000 01] (Figure 5).

3.4.4 Tumor size

Tumor size was reported in 8 studies[13,14,16,23,26,30,33,35]. A total of 550 patients were included, including 278 in the experimental group and 272 in the control group. Meta-analysis of combined data showed that compared with the control group, the tumor size of the patients could be effectively controlled in the combination group [RR=1.33, 95%CI=(1.17,1.51), P<0.000 01] with a statistically significant difference, and the fixed-effect model was adopted (P=0.46, I^2=0%) (Figure 6).

3.4.5 Laboratory examination

Laboratory tests were reported in 11 articles[10,14,19,20,21,23,26,29,32,34,35], and subgroup analysis was performed for different results. Among them, 7 studies[14,20,21,23,26,32,35] described the detection indicators of WBC, and the treatment effects of the warbufin treatment group and the control group were basically the same [MD=0.29, 95%CI=(-0.13,0.71), P=0.18]. There was no statistical difference in the results, and the heterogeneity was large (P<0.000 01, I^2=90%). The random effects model was used. After sensitivity analysis, one study[14] was removed (I^2=13%), indicating that the literature was a source of heterogeneity. The AFP value of 9 studi

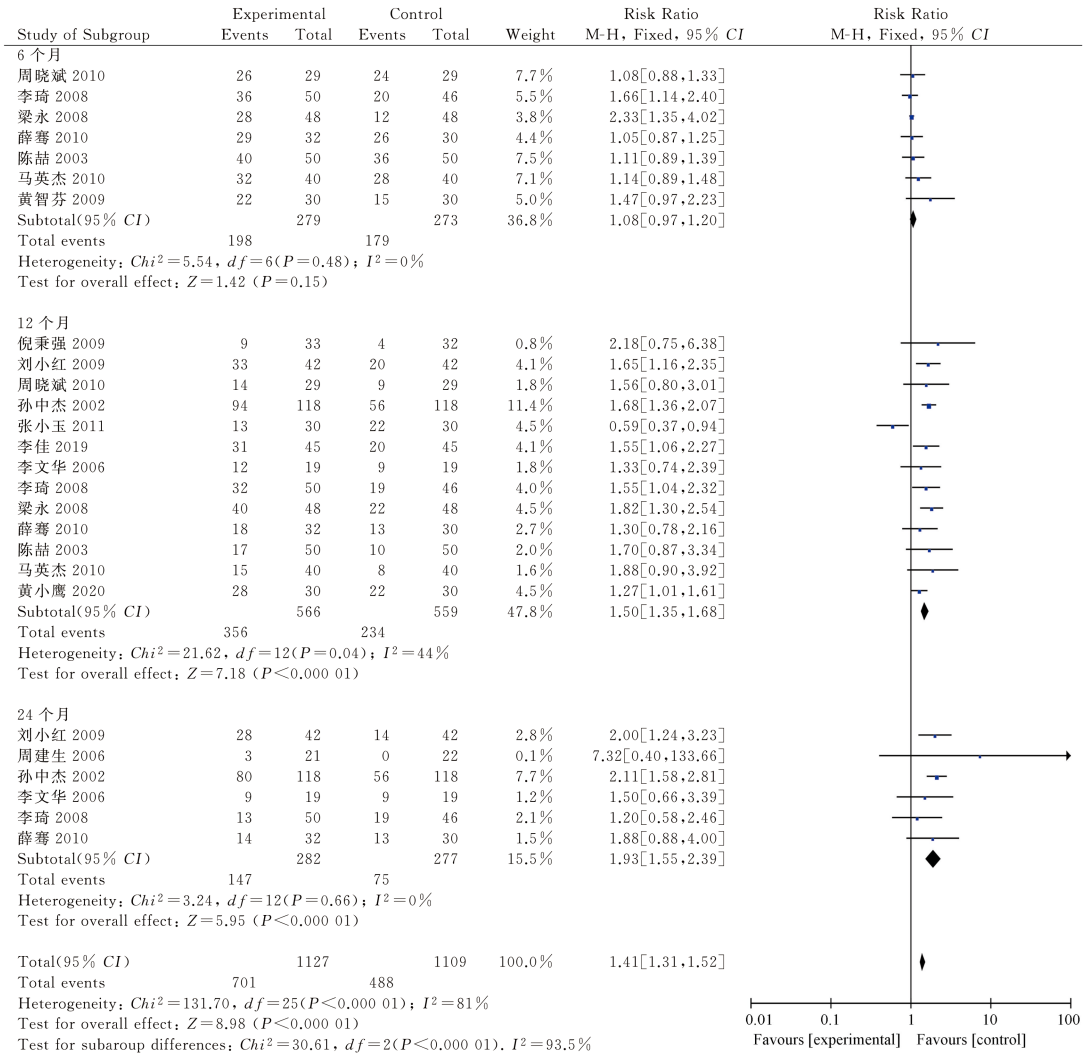

Fig 5 Meta-analysis of follow-up survival time

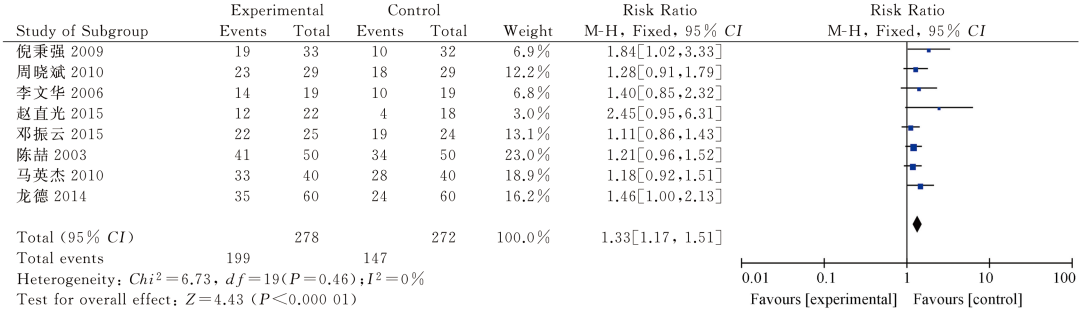

Fig 6 Meta-analysis of tumor size

es[10,14,19,21,23,26,29,34,35] was described, and there was a statistical difference between the group treated with hububutin and western medicine and the group treated with western medicine [*MD*=-216.89, 95%*CI*=(-284.28,-149.50), *P*<0.000 01]. Heterogeneity is great (*P*<0.000 01, I^2=97%). ALT values of 8 studies[14,21,23,26,29,32,34,35] were reported. The treatment group was significantly better than the control group [*MD*=-33.77, 95%*CI*=[-43.55,-24.00], *P*<0.00001], and the difference was statistically significant with great heterogeneity (*P*<0.000 01, I^2=93%). Eight studies[14,21,23,26,29,31,34,35] described the TBIL value, and the treatment group was significantly better than the control group [*MD*=-14.52, 95%*CI*=(-20.11,-8.68), *P*<0.000 01], the difference was statistically significant and the heterogeneity was large (*P*<0.000 01, I^2=94%). According to the combined data analysis, compared with the control group, the huabamin injection group could effectively reduce the indicators of laboratory examination, with statistical difference [*RR*=-14.52, 95%*CI*=(-16.15,-12.88), *P*<0.000 01] (Figure 7).

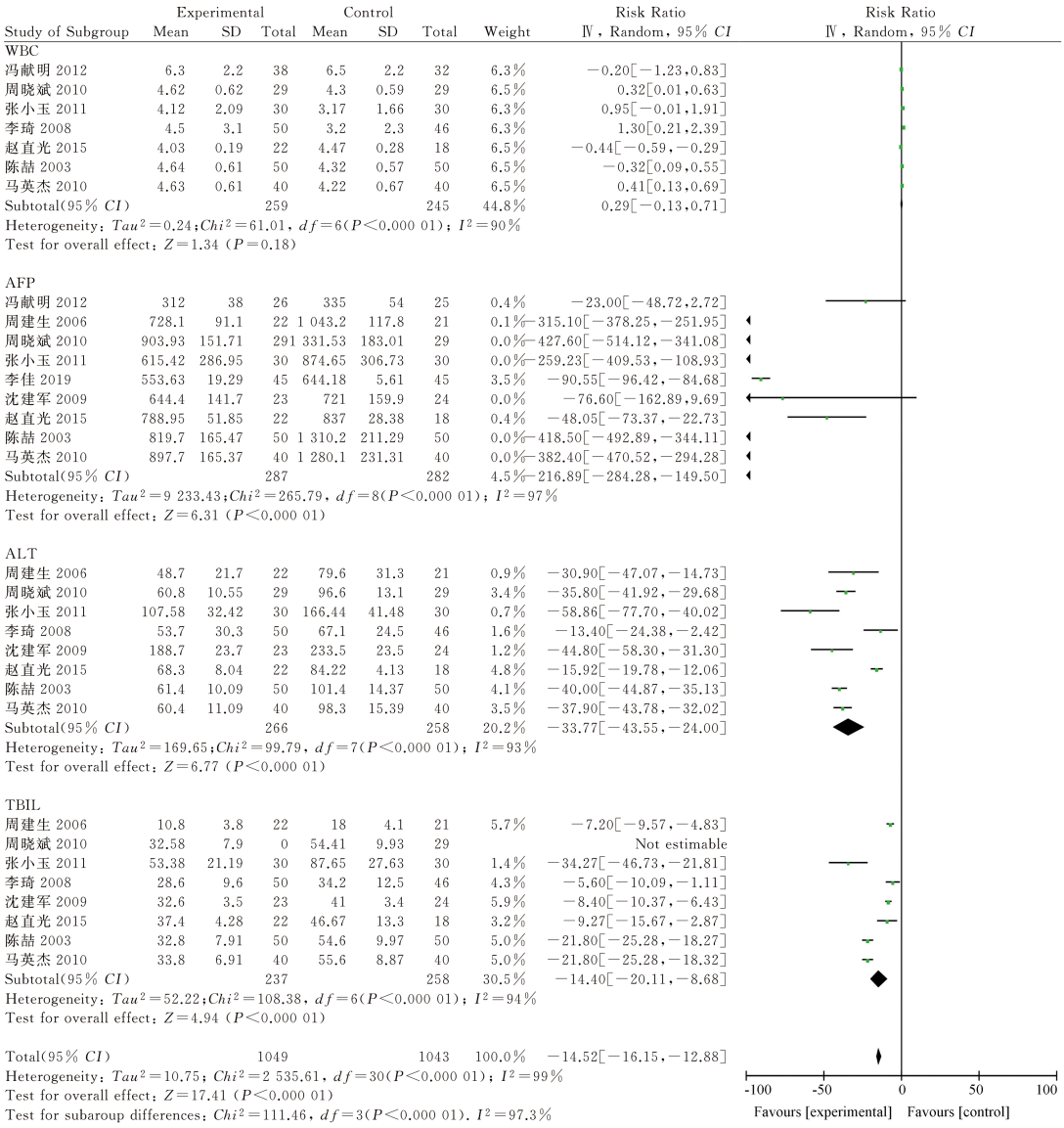

Fig 7 Meta-analysis of laboratory tests

3.5 Adverse reactions

Thirteen studies[7,8,10,11,13,17,19,21,22,24,25,29,31] reported adverse reactions from 7 aspects, including decreased WBC, fever, liver function injury, decreased PLT level, abdominal pain and diarrhea, nausea and vomiting, and bone marrow suppression, respectively. Subgroup analysis was conducted for different evaluation criteria.

Among them, 6 studies[10,11,19,21,24,31] described the WBC value with great heterogeneity (P<0.000 01, I^2=87%). The random effects model was used to analyze the data, and the results showed that there was no statistical significance between the warbufin group and the control group [RR=1.15, 95%CI=(0.80,1.64), P=0.45]. Four studies[10,11,19,24] reported the decrease of PLT, indicating that there was no statistical significance between the warbufin group and the control group [RR=0.76, 95%CI=(0.47,1.24), P=0.27], and the heterogeneity was great (P=0.009, I^2=74%). Five studies[10,19,21,24,29] reported that there was no significant difference in fever between the warbufin group and the control group [RR=1.06, 95%CI=(0.72,1.56), P=0.77], with great heterogeneity (P<0.000 1, I^2=86%). Six studies[10-12,21,24,31] described liver function injury, and the results showed that the huabamin group had no statistical significance compared with the control group [RR=0.86, 95%CI=(0.66,1.12), P=0.25], and the heterogeneity was large (P<0.000 1, I^2=82%). Five literatures[8,10,19,21,24] described the reactions of abdominal distension, abdominal pain and diarrhea. Compared with the control group, there was no statistical significance in the warbufin group [RR=1.07, 95%CI=(0.73,1.56), P=0.72], and the heterogeneity was large (P=0.004, I^2=74%). Nine literatures[7,8,10,11,13,19,21,24,29] described nausea and vomiting reactions, indicating that the huabamin group had no statistical significance compared with the control group [RR=0.82, 95%CI=(0.67,1.02), P=0.07], and the homogeneity was good (P=0.16, I^2=33%). According to the combined data, there was no statistically significant difference in adverse reactions between the warbubenin group and the control group [RR=0.94, 95%CI=(0.85,1.42), P=0.25] (Figure 8).

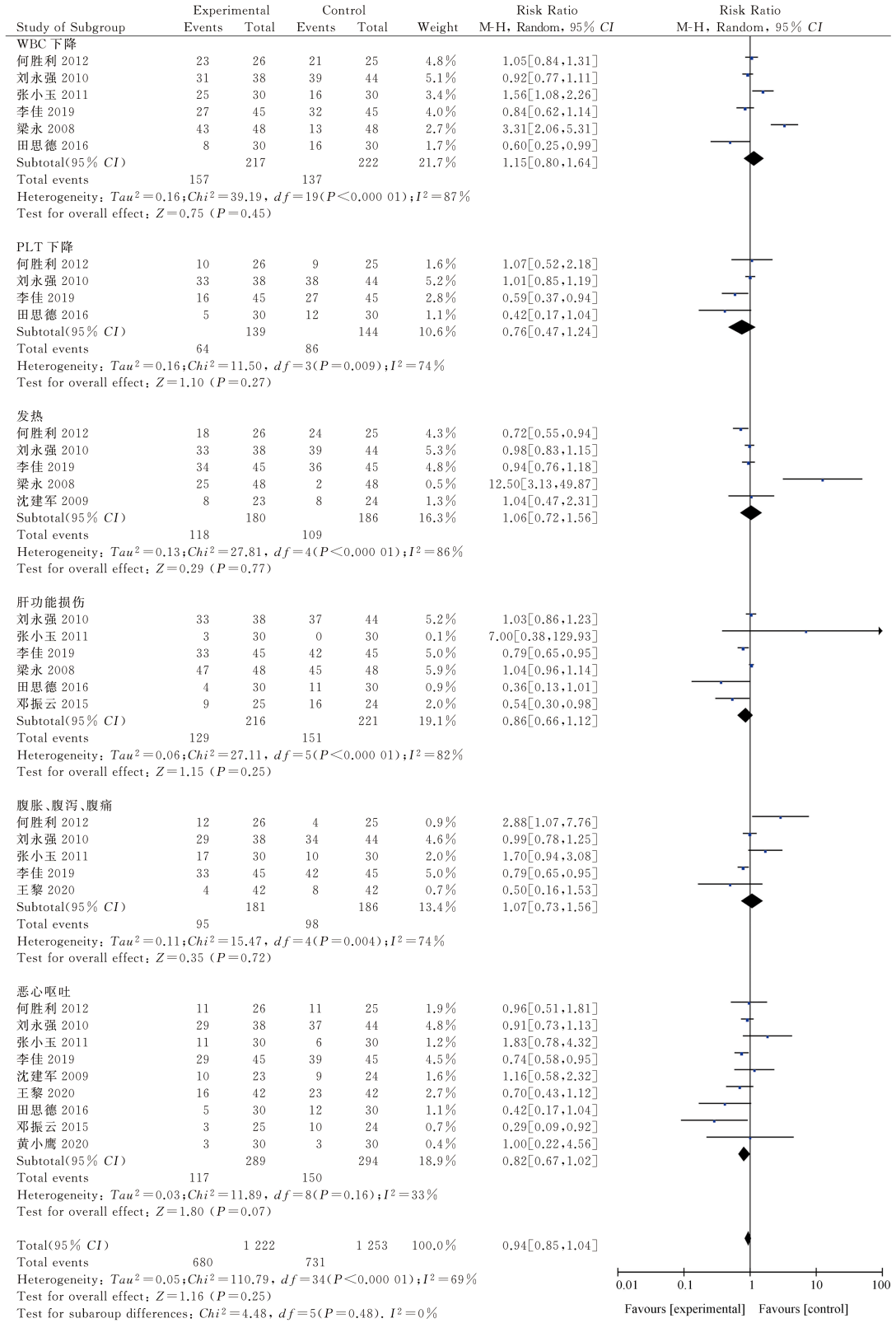

Fig 8 Meta-analysis of adverse reactions

Five articles[8,13,17,22,25] described myelosuppression, and the results showed that the myelosuppression was more obvious in the huabamin group compared with the control group [*RR*=0.44, 95%*CI*=(0.31,0.62) *P*<0.000 01], with statistical difference and small heterogeneity (*P*=0.38, I^2=5%). The fixed effect model was adopted. In summary, compared with other treatment regimens, there were no obvious adverse reactions of huabamin (Figure 9).

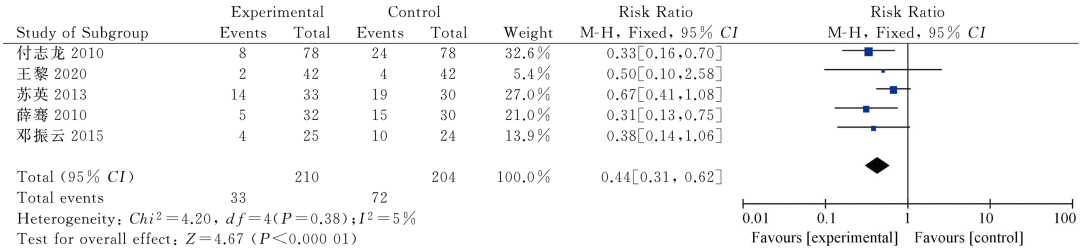

Fig 9 Meta-analysis of myelosuppression

3.6 Bias analysis

As included in the relevant literature is more, the selected results index base is more than 10 articles, and the amount of literature related to clinical efficient statistically difference, reason for efficient of related literature publication bias analysis, draw the corresponding funnel graph, as shown in Figure 10, you can see that asymmetric distribution around, prompt publication bias exists.

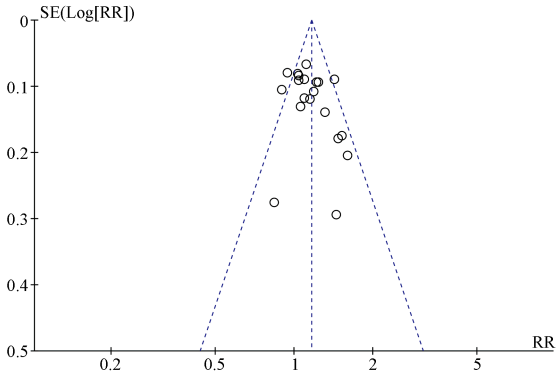

Fig 10 Funnel plot of clinical response rate

4. Discussion

Primary liver cancer with conventional western medicine treatment, radiotherapy, chemotherapy, and other treatment, which is pure western medicine treatment can effectively improve the recent curative effect, but the long-term effect is still not satisfied curative effect, and long after chemotherapy in patients with immune suppression, gastrointestinal reactions and adverse reactions such as white blood cells decline, causing poor survival quality of patients,It seriously endangers the physical and mental health of patients[4]. At present, scholars at home and abroad believe[37] that the treatment of primary liver cancer with integrated traditional Chinese and western medicine can effectively improve the survival cycle of patients, improve the quality of life, eliminate the remaining cancer cells, and the treatment effect is better than conventional treatment.

Huabusin injection is a water-soluble Chinese medicine anti-tumor preparation prepared by macroporous adsorption and separation of different polar components after the whole skin of toad was dried in the shade. Toad venom, dry toad skin belongs to the traditional Chinese medicinal herbs, which was recorded as early as in Shennong Materia Medica Classic, their sexual flavour, cool, toxic, has qingrejiedu, blood fights, detumescence hemostatic collapse nut, diuretic laxative medicinal effect, can effectively inhibit cancer cell growth in vivo, improve the body's own immune system, reduce the use of the side effects of radiation and chemotherapy radiation damage to the body[38]. Huabusin injection consists of bufo diene hydroxylolactone, small molecular organic acids, alkaloids and other active components, which are the main active compounds derived from the skin of toad. They are the marker bioactive compounds of huabetins, and the antitumor activity of huabetins may also be derived from these compounds[39]. Experimental studies have shown that Huabatin and its active compounds have significant anti-tumor activities, including inhibition of cancer cell growth and metastasis, induction of cell apoptosis and cell cycle arrest, prolongation of survival time of patients, etc., and can also interfere with Notch signaling and destroy cell proliferation[40,41]. In addition, some studies have shown that Huababin injection combined with western medicine therapy is not only widely used in the prevention and early treatment of lung cancer, nasopharyngeal cancer, stomach cancer, breast cancer, colon and rectal cancer and other malignant tumors, but also can alleviate the pain caused by radiotherapy and chemotherapy to patients and improve their quality of life[42].

In this study, 30 articles were selected and finally included, and the efficacy and safety of Huabafin injection combined with Western medicine in the treatment of liver cancer were systematically evaluated from the aspects of clinical effectiveness, quality of life, follow-up survival time, tumor size, laboratory examination and adverse reactions. The results of this study showed that: the effect of reducing the size of the tumor and the efficacy of medication in the treatment group of Huabamin combined with western medicine was significantly better than that in the western medicine treatment group, and the quality of life of patients was improved. In the follow-up survival time, the effect was not significant at 6 months, but the 12-month and 24-month follow-up of sinobufalin combined group could effectively prolong the survival time of patients. In terms of laboratory examination, compared with the control group, the AFP, ALT and TBIL levels were significantly reduced in the combined group, which could effectively control the progression of tumor and improve liver function. In terms of adverse reactions, 7 aspects were studied and analyzed respectively. In addition to the obvious bone marrow suppression, there were no other obvious adverse reactions compared with the control group, indicating that the combined group

of Huabamin injection was safe and feasible compared with the western medicine treatment group.

From methodological quality perspective, exist the problems and limitations of the following aspects: ① this study included 30 studies, only 2 study group take random number table method, 2 randomized study adopts the envelope method, other studies have failed to mention the method of the random grouping and distribution of the implementation of the hidden, easy cause selective bias. ② One study mentioned the implementation of blind method, while the others did not, which may lead to measurement bias in the process of implementation bias and outcome evaluation. ③ In this study, the maximum number of cases was 236, while the minimum number of cases was 38. The total number of cases in 27 studies was less than 100, so the sample size was limited, which may reduce the statistical efficacy of the study. ④ in the same outcome indexes between different research intervention, clinical factors may lead to deviation, these differences may cause the heterogeneity in this study, at the same time by removing article related literature on the sensitivity analysis, when the stability is good, may with different sensitivity source texts patient age, path length differences, illness weight and other factors. ⑤ The included studies were not clearly marked with missing data, and all of them were positive results. The combination of the overall analysis and the inverted funnel plot may have publication bias.

In summary, this study systematically evaluated the efficacy of Hububutin injection combined with conventional western medicine in the treatment of primary liver cancer, compared with conventional western medicine treatment, which can improve the clinical efficiency, reduce the size of the tumor, improve the quality of life, prolong the survival period of patients and reduce adverse reactions. But over the course of the study also found that the problem of clinical research should be improved in the future, a randomized controlled study should according to the current international common recognition of the CONSORT "standard of randomized controlled trials report" to repor[43], such as the random, allocation concealment and blinding to strict quality management, selection of the end of the objective and recognized as evaluation index, This makes the research results more objective, fair and accurate, which is conducive to future related research and promotion.

Description of authors' contributions: First author Ren Sisi is responsible for paper design, writing and drawing, corresponding author Professor Fan Yu is responsible for paper topic selection and revision, Guo Dongyan and Zhai Bingtao are responsible for literature screening, Li Jingtao and Shi Xiaoyan are responsible for data extraction, and Duan Lifang is responsible for the verification and correction of the paper.

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