Review Article

Acupuncture Combined with Three-Step Analgesic Drug Therapy for Treatment of Cancer Pain: A Systematic Review and Meta-Analysis of Randomised Clinical Trials

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Objective. The purpose of this study was to systematically evaluate the efficacy and safety of acupuncture combined with the WHO three-step analgesic drug ladder for cancer pain. *Methods*. The Cochrane Library, PubMed, and CNKI Database of Systematic Reviews were searched. Using the Cochrane Register for Randomized Controlled Trials, the quality of the included literature was evaluated, and the meta-analysis was carried out with RevMan 5.3 software. *Results*. Compared with three-step analgesia alone, acupuncture combined with three-step analgesia for cancer pain increased pain relief response rates (RR = 1.12, 95% CI: 1.08∼1.17, $P < 0.00001$), reduced NRS score (SMD = −1.10, 95% CI: −1.86∼−0.35, $P = 0.004$), reduced the rate of side effects (RR = 0.45, 95% CI: 0.38∼0.53, $P < 0.00001$), including nausea ($P < 0.00001$), vomiting ($P = 0.008$), constipation ($P < 0.00001$), and dizziness ($P = 0.010$), reduced the burst pain rate (SMD = −1.38; 95% CI: −2.44∼−0.32, $P = 0.01$), shortened analgesia effect onset time ($P = 0.004$), and extended the duration of response ($P < 0.0001$). *Conclusion*. For the treatment of cancer pain, acupuncture combined with three-step analgesic drugs is better than using only three-step analgesic drugs.

1. Introduction

Pain is one of the most debilitating symptoms experienced by patients with advanced cancer. According to WHO statistics, 70% of cancer patients worldwide have some degree of pain in the advanced stages of cancer [1]. Because the pain is intense and easily aggravated, it directly affects the appetite, sleep, psychological status, and treatment effect of patients, reduces their quality of life, and increases their psychological stress [2, 3]. Cancer pain has become a medical, psychological, and social issue of great concern. At present, the treatment of cancer pain mostly utilizes the three-step "ladder" treatment principle proposed by the WHO, where mild, moderate, and severe pain are treated with nonsteroidal anti-inflammatory drugs (NSAIDs), weak opioids, and strong opioids, respectively [4]. Although the analgesic effect of three-step drugs is good, their side effects,

such as liver and kidney function damage, risk of dependency and addiction, respiratory inhibition, and gastrointestinal side effects, limit their clinical application [5]. One primary reason why cancer pain is difficult to control is because cancer pain patients cannot tolerate the side effects of analgesics. Therefore, there is a consensus to seek other effective and safe analgesic methods [6]. Acupuncture is an important part of TCM. Acupuncture is to insert a needle at one of the patient's acupoints and use a specific manipulation to stimulate the patient's acupoints to achieve an effect (DE QI). Acupuncture has outstanding performance in the treatment of all kinds of pain through its principle of moving qi, dredging qi channels and collaterals, and activating blood. Various acupuncture treatments can be combined, with no risk of addiction, no side effects, convenient application and at a low cost, demonstrating the unique advantages of TCM in the treatment of cancer pain [7]. In the

last 20 years, there have been many clinical reports on the utility and safety of acupuncture for the treatment of cancer pain, and acupuncture therapy is a widely recognised alternative measure for the treatment of cancer pain. Therefore, it is necessary to use a systematic evaluation method to rigorously evaluate the randomised controlled study of acupuncture combined with three-step analgesic drugs to treat cancer pain, to assess its exact effect in the treatment of cancer pain.

2. Methods

2.1. Data Sources. The following databases were searched from their inception to January 10, 2021: the Cochrane Library, PubMed, Embase, CNKI, China Biology Medicine disc (CBMdisc), Chinese Journal of Science and Technology database (VIP), and Wanfang database. We searched MeSH (Medical Subject Headings) term trees for "acupuncture" and "pain" in PubMed, and the keywords searched included "acupuncture", "needling", "tumour", "cancer", "neoplasm", "ache", "pain", and "randomised controlled trial". The keywords were translated into Chinese and searched in the above-mentioned Chinese databases. Search terms were combined with the Boolean "AND" and "OR" terms in search strategies, for example, ("acupuncture" OR "needling") AND ("cancer" OR "tumour" OR "neoplasm" OR "ache" OR "pain") AND ("randomised controlled trial"). Comprehensive retrieval was carried out according to the characteristics of different databases. Then, the literature mentioning "randomised controlled" and "randomised grouped" was screened. In addition, we manually searched our own personal literature files. After reading the full text of the included literature and related articles, we collected the documents together in hard copy format for preservation.

2.2. Inclusion Criteria

2.2.1. Types of Studies. The included studies were all randomised controlled clinical trials. The published experiments included were mainly in the form of theses and abstracts. There were no restrictions on the language of publication.

2.2.2. Types of Participants. The subjects were patients with malignant tumours confirmed by cytology or histopathology, and all patients had cancer pain. There were no limits on age, gender, race, and nationality of the patients; however, patients had to be able to clearly describe their pain to medical staff.

2.2.3. Types of Interventions. In the literature, the intervention treatment group was treated with acupuncture augmented by three-step analgesia, including traditional acupuncture or other acupuncture methods, such as ear acupuncture and electroacupuncture. Acupuncture points included traditional acupuncture points and pain points. The control groups only received three-step analgesic treatment.

2.2.4. Types of Outcome Evaluations. The included materials had a clear evaluation standard for curative effects and at least one clinical index related to cancer pain, including the effective rate of pain relief after treatment, quality of life score, side effect rates, burst pain rate, onset time to analgesic effect, and duration of response.

2.3. Exclusion Criteria. The exclusion criteria were as follows: if patients had one or more other type(s) of pain in addition to cancer pain; if the study used moxibustion, percutaneous electrical stimulation of nerves, acupoint injection, laser irradiation, cupping, massage, herbal medicines, or other intervention measures; if the experiments were carried out on patients during or a few days after surgical therapy, radiotherapy, chemotherapy, or hyperthermia-therapy on their malignant tumours; if the trial design was not rigorous; if inappropriate statistical methods were used; if the paper was only an abstract, review, or summary of previously published literature; if the study has no result indicators; if the experimental design was unreasonable; or if the literature could not be obtained by contacting the author.

2.4. Data Extraction and Bias Risk Assessment. Two researchers independently evaluated the quality of each study meeting the inclusion criteria and extracted the data, including the baseline situation, intervention measures, and efficacy results, and cross-checked the data. Any disagreements were resolved through discussion or assessment by a third researcher. We used a "Modification of Cochrane Tool to assess the risk of bias in randomised trials," where a decision regarding bias must be made, categorised into "probably no" or "probably yes," for items that are thought to be of unclear risk [8]. We judged trials with more than 2 and more than 4 high-risk components as moderate risk and high risk, respectively [9]. The following criteria were used to assess the risk of bias: whether the study was randomised; how allocation concealment was conducted; whether the study was double-blind or triple-blind; whether the results data were complete; and whether there was selective reporting or other types of bias. The authors categorised studies into "low risk," "unclear risk," and "high risk" categories. For dropout patients, we contacted the authors of the studies twice over four weeks via e-mail for missing or unclear data. If missing data could not be found, they were recorded as high risk; if no response was received, the data were marked as unclear risk. All authors reached a consensus on the results of bias risk assessment.

2.5. Data Synthesis. The effect of acupuncture combined with three-step analgesic drug therapy for treatment of cancer pain was analyzed in terms of response rate, numerical rating scale (NRS), side effect rates, times of burst pain, onset time, and duration of response (DOR). If the information included in the study was insufficient, we communicated with the main author to obtain accurate data. RevMan 5.3 software provided by the Cochrane Collaboration Network was used for the

meta-analysis. The relative risk (RR) was used for the enumeration data, the mean difference (MD) was used for the measurement data, and the 95% confidence interval (CI) was used for each effect quantity. When the heterogeneity of test results was not statistically significant ($P > 0.05$), a fixed effects model was selected; when the heterogeneity of test results was statistically significant ($P < 0.05$), a random effects model was selected. A funnel plot was used to analyse and detect publication bias.

3. Results

3.1. Study Description. The first search found 115 potentially relevant articles. After reading and screening, 19 articles met our inclusion criteria (Figure 1). The critical data from all the included RCTs are shown in Table 1 [10–28]. In total, 1502 cancer pain cases were included. The numbers of cases of acupuncture combined with three-step analgesic drug therapy (treatment group) and three-step analgesic drug therapy (control group) were 751 and 751, respectively. All patients' cancers were confirmed by cell histology or pathology, and pain was their main symptom. The baseline was comparable between the two groups. Almost all of the research was on the use of manual acupuncture (AT), which is guided by the theory of TCM for acupuncture interventions. Two studies used electroacupuncture (EA) [11, 28]. One study used floating acupuncture (FA) [12]. Two studies used fire needle (FN) [13, 14]. Three studies used wrist-ankle acupuncture (WA) [17–19]. Among them, the two acupuncture methods were all included in Fu Yang et al.'s report [17], in which morphine hydrochloride sustained-release tablets and acupuncture or wrist-ankle acupuncture were used in the treatment of cancer pain. All studies provided patients with a semistandardised acupuncture programme, that is, the use of a predefined set of acupoints combined with a set of acupoints according to the location of the tumour. The Ashi point, Zusanli (ST36), Hegu (LI4), Sanyinjiao (SP6), and Taichong (LR3) points were most frequently used. For most studies, patients received acupuncture treatment for 1 to 3 weeks, for durations of 20 to 60 min per session. The evaluation criteria for the curative effect were similar across studies. The objective outcome measures were treatment response rate, NRS, side effect rates (nausea, vomiting, constipation, hiccups, dizziness, itching, palpitation, and abdominal distention), times of burst pain, onset time to analgesic effect (min), DOR (h), quality of life (QOL), Karnofsky performance status (KPS), and quality of life questionnaires (QLQ-C30). The minimal important difference (MID) refers to the change in the score of the smallest efficacy evaluation questionnaire recognised by the patient. MID indicates an important improvement in symptoms and signs; the intervention has achieved the minimal important difference.

3.2. Risk of Bias. Most included RCTs had a high risk of bias. Nineteen RCTs [10–28] described their randomisation methods. Among them, 9 RCTs [10, 12–14, 16–18, 22, 24] used a random number table, 1 study [15] used a computer-generated random number sequence for randomisation, and 3 RCTs [20, 21, 26] randomly numbered cases according to the order of hospitalization. Three RCTs [10, 15, 17] described incomplete outcome methods, and these three studies had cases of dropouts. Two studies reported details about allocation concealment [15, 16]. Fourteen RCTs described adverse events from acupuncture combined with three-step analgesic drugs [10, 11, 13–23, 26]. Table 2 presents the Cochrane risk of bias assessment of the included articles. There were 2 trials with high risks of bias [10, 17], 5 trials with moderate risk of bias [12, 15, 18, 23, 25], and 12 trials with low risk of bias [11, 13, 14, 16, 19–22, 24, 26–28]. A high risk of bias resulted from lack of blinding of participants and personnel and lack of blinding among outcome assessors. A moderate risk resulted from selective reporting bias and incomplete outcome data, and a low risk of bias resulted from randomisation sequence generation and allocation concealment (see Figure 2).

3.3. Response Rates. Eighteen studies reported the response rates to pain relief after treatment [10–14, 16–28]. In the treatment group, 621 out of the 679 cases had effective responses; in the control group, among the 672 cases, 548 had effective responses. The heterogeneity test in the meta-analysis showed that $\chi^2 = 22.19$, $P = 0.22$, $I^2 = 19\%$, and there was no significant difference between the studies, so a fixed effects model was used. The total response rate of the treatment group was better than that of the control group, and the difference was statistically significant ($n = 1351$, RR = 1.12; 95% CI: 1.08~1.17, $P < 0.00001$; see Figure 3).

3.4. NRS Score. Seven studies reported NRS scores after treatment [10, 11, 14, 17, 19, 22, 24]. Overall, 282 cases were in the treatment group, and 281 were in the control group. The heterogeneity test of the meta-analysis showed that $\chi^2 = 158.90$, $P < 0.00001$, $I^2 = 96\%$, and the differences between the studies were statistically significant, so a random effects model was used. The NRS score of the treatment group was lower than that of the control group, and the difference was statistically significant ($n = 563$, SMD = −1.10, 95% CI: −1.86~−0.35, $Z = 2.87$, $P = 0.004$; see Figure 4).

3.5. Side Effect Rates. Side effects mainly included nausea, vomiting, constipation, and dizziness. Eight studies reported the number of cases of nausea [10, 13, 16, 18, 21–23, 26], 7 studies reported the number of cases of vomiting [10, 13, 16, 18, 21, 22, 26], 11 studies reported the number of cases of constipation [10, 11, 13, 16–18, 20–23, 26], and 5 studies reported the number of cases of dizziness [11, 13, 17, 20, 22]. The consolidated statistics results demonstrated that, compared to the control group, in the treatment group, the incidence of nausea ($n = 659$, RR = 0.48, 95% CI: 0.34~0.66, $P < 0.00001$), vomiting ($n = 452$, RR = 0.56, 95% CI: 0.37~0.86, $P = 0.008$), constipation ($n = 843$, RR = 0.38, 95% CI: 0.29~0.49, $P < 0.00001$), and
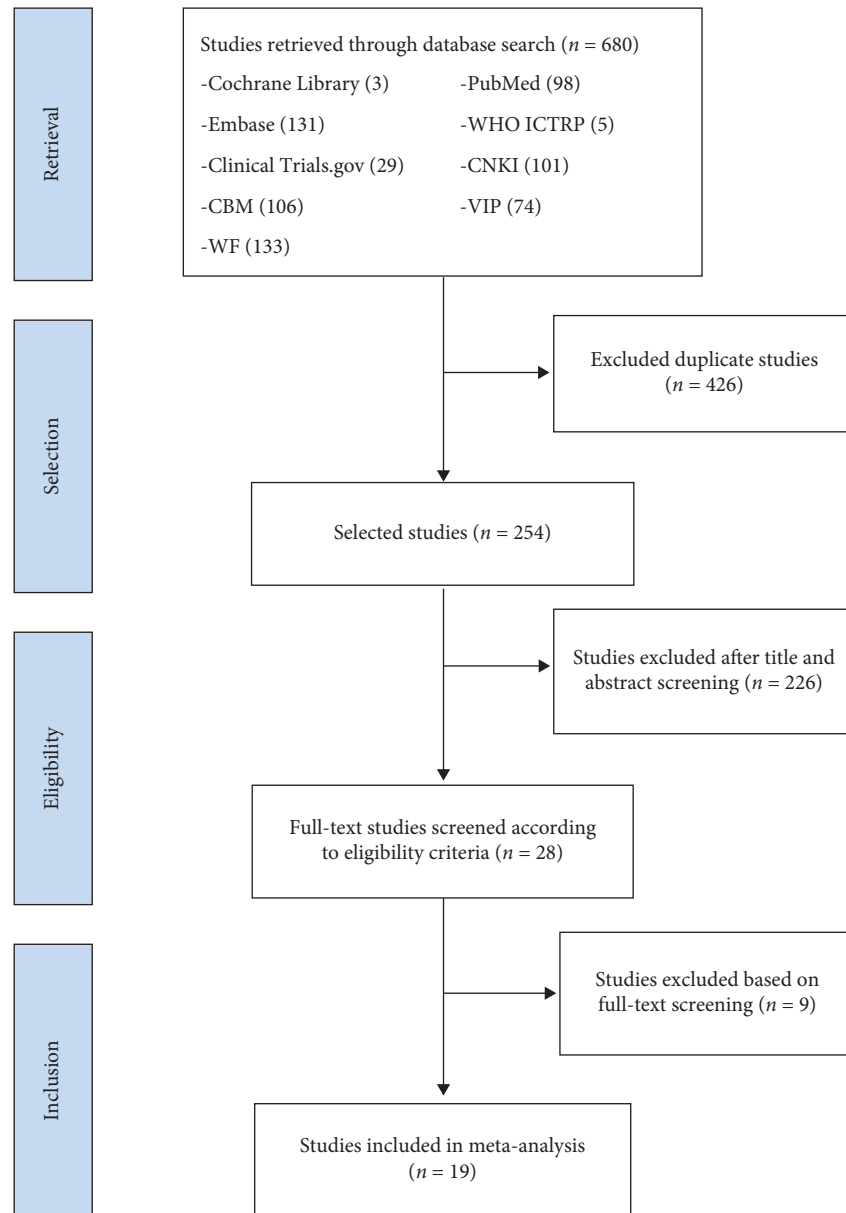
Figure 1: Flowchart of the literature review and selection process.

Table 1: Summary of randomised clinical studies of acupuncture combined with three-step analgesic drug therapy for the treatment of cancer pain.

Study (year)	Type of cancer	Sample sizes		Interventions		Acupuncture point selection	Session frequency and duration	Main outcomes and assessment of pain
		T	C	T	C			
Wang (2018) [10]	Various	35	35	AT + C	Drug (three-step analgesic ladder)	LI4, LR3, and Ashi point	30 min qd 6 weeks	Response rate, NRS, and side effect rate
Wang (2016) [11]	Lung cancer	30	30	EA + C	Oxycodone sustained-release tablets	LI4, PC6, ST36, and SP6	30 min qd 14 days	Response rate, NRS, side effect rate, burst pain, onset time, and DOR
Zhong (2016) [12]	Various	30	30	FA + C	Morphine sulfate sustained-release tablets	Ashi point	Once a day 14 days	Response rate, QOL, and burst pain

TABLE 1: Continued.

Study (year)	Type of cancer	Sample sizes		Interventions		Acupuncture point selection	Session frequency and duration	Main outcomes and assessment of pain
		T	C	T	C			
Mi (2010) [13]	Gastric cancer	32	30	FN + AT + C	Drug (three-step analgesic ladder)	FN: BL21, BL18, and BL17. AT: CV12, ST25, and St36	30 min qod 4 weeks	Response rate and side effect rate
Bai (2019) [14]	Various	50	50	FN + C	Drug (three-step analgesic ladder)	Ashi point, ST36, and SP6	qod 14 days	Response rate, NRS, and side effect rate
Liu (2018) [15]	Various	72	75	TEAS + C	Drug (three-step analgesic ladder)	LI4, PC6, ST36, and SP6	30 min bid 3 weeks	Response rate, BPI-S, KPS, and side effect rate
Liu (2011) [16]	Liver cancer	30	30	AT + C	Tramadol hydrochloride sustained-release tablets	SP4, PC6, GB41, TE5, SI3, BL62, LU7, KI6, LR3, and LR14	qd 14 days	Response rate, NRS, QOL, side effect rate, onset time, and DOR
Fu (2019) [17]	Various	16/16	16	AT + C WA + C	Morphine hydrochloride sustained-release tablets	PC6 and SP6	1 h qd	Response rate, NRS, KPS, side effect rate, burst pain, onset time, and DOR
Wu (2019) [18]	Various	30	30	WA + C	Drug (three-step analgesic ladder)	Based on syndrome differentiation and disease differentiation	12 h qd 10 days	Response rate, VAS, burst pain, and side effect rate
Dong (2018) [19]	Various	60	60	WA + C	Drug (three-step analgesic ladder)	Based on syndrome differentiation and disease differentiation	10–12 h qd 7 days	Response rate, NRS, QLQ-C30, and side effect rate
Sun (2016) [20]	Various	30	30	AT + C	Oxycodone	LI4, PC6, ST36, SP6, Ashi point, and others	30 min qd 14 days	Response rate, NRS, KPS, QOL, and side effect rate
Zhang (2014) [21]	Various	30	30	AT + C	Drug (three-step analgesic ladder)	LI4 and ST36. Lung cancer: PC6 and LU6. Liver cancer: GB34, LR6, and LR3. Colorectal cancer: PC6, CV12, and TE6	30 min qd 7 days	Response rate, QOL, side effect rate, onset time, and DOR
Hui (2019) [22]	Various	40	40	AT + C	Drug (three-step analgesic ladder)	Ashi point, LI4, GV14, BL11, GB34, and LR3	30 min qd 14 days	Response rate, side effect rate, onset time, and DOR
Tan (2012) [23]	Various	106	101	AT + C	Drug (three-step analgesic ladder)	LI4 and PC6. Lung cancer: LU6. Liver cancer: GB34 and LR6. Colorectal cancer: CV12, ST36, and TE6	0.5–1 h qd 3 weeks	Response rate and side effect rate
Fan (2017) [24]	Lung cancer	35	34	AT + C	Drug (three-step analgesic ladder)	PC6, LI4, ST36, GB34, and SP6	20 min qd 20 days	Response rate, NRS, onset time, and DOR
Jiang (2016) [25]	Various	25	25	AT + C	Drug (three-step analgesic ladder)	Ashi point, LR3, and LI4	30 min qd 7 days	Response rate and NRS
Li (2017) [26]	Gastric cancer	30	30	AT + C	Drug (three-step analgesic ladder)	ST36, LR3, and LI4	30 min qd 7 days	Response rate, NRS, QOL, and side effect rate
Huang (2018) [27]	Various	31	31	AT + C	Drug (three-step analgesic ladder)	PC6. Lung cancer: LI4, LU4, LU6, and ST36. Liver cancer: GB34 and LR3. Breast cancer: LI4, STI8, and CV9. Gastric cancer: CV12, ST36, and TE6	30 min qd 7 days	Response rate
Peng (2012) [28]	Various	23	24	EA + C	Drug (three-step analgesic ladder)	LI4, PC6, ST36, and SP6	30 min qd 7 days	Response rate, onset time, and DOR

T: treatment group, C: control group, AT: acupuncture, EA: electroacupuncture, FA: floating acupuncture, FN: fire needle, WA: wrist-ankle acupuncture, DOR: duration of response, NRS: numerical rating scale, BPI-S: brief pain inventory-severity, QOL: quality of life, and KPS: Karnofsky performance status.

TABLE 2: Risk of bias for the 19 included studies using a modified approach to the Cochrane risk of bias tool.

Source	Risk of bias							Trial characteristics		
	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessors	Infrequent loss to follow-up	Free of selective outcome reporting	Free of other types of bias	Statistical analysis (per protocol, intention to treat, etc.)	How is loss to follow-up handled?	Adverse event
Wang (2018) [10]	Definitely yes	Definitely yes	Probably no	Probably no	Definitely no	Definitely no	Definitely no	Not mentioned	Ignored	Yes
Wang (2016) [11]	Probably yes	Probably yes	Probably no	Probably no	Definitely yes	Definitely yes	Probably yes	Not mentioned	Not mentioned	Yes
Zhong (2016) [12]	Definitely yes	Definitely yes	Probably no	Probably no	Definitely yes	Definitely yes	Probably yes	Per protocol	Not mentioned	No
Mi (2010) [13]	Definitely yes	Definitely yes	Probably no	Probably no	Definitely yes	Definitely yes	Probably yes	Not mentioned	Not mentioned	Yes
Bai (2019) [14]	Definitely yes	Definitely yes	Probably no	Probably no	Definitely yes	Definitely yes	Probably yes	Not mentioned	Not mentioned	Yes
Liu (2018) [15]	Definitely yes	Definitely yes	Probably no	Probably no	Definitely no	Definitely yes	Probably yes	Not mentioned	Ignored	Yes
Liu (2011) [16]	Definitely yes	Definitely yes	Probably no	Probably no	Definitely yes	Definitely yes	Probably yes	Not mentioned	Not mentioned	Yes
Fu (2019) [17]	Definitely yes	Definitely yes	Probably no	Probably no	Definitely no	Definitely no	Definitely no	Per protocol	Ignored	Yes
Wu (2019) [18]	Definitely yes	Definitely yes	Probably no	Probably no	Definitely yes	Definitely no	Probably yes	Not mentioned	Not mentioned	Yes
Dong (2018) [19]	Probably yes	Probably yes	Probably no	Probably no	Definitely yes	Definitely yes	Probably yes	Not mentioned	Not mentioned	Yes
Sun (2016) [20]	Probably yes	Probably yes	Probably no	Probably no	Definitely yes	Definitely yes	Probably yes	Not mentioned	Not mentioned	Yes
Zhang (2014) [21]	Probably yes	Probably yes	Probably no	Probably no	Definitely yes	Definitely yes	Probably yes	Per protocol	Not mentioned	Yes
Hui (2019) [22]	Definitely yes	Definitely yes	Probably no	Probably no	Definitely yes	Definitely yes	Probably yes	Not mentioned	Not mentioned	Yes
Tan (2012) [23]	Probably yes	Probably yes	Probably no	Probably no	Definitely yes	Definitely no	Probably yes	Not mentioned	Not mentioned	Yes
Fan (2017) [24]	Definitely yes	Definitely yes	Probably no	Probably no	Definitely yes	Definitely yes	Probably yes	Per protocol	Not mentioned	No
Jiang (2016) [25]	Probably yes	Probably yes	Probably no	Probably no	Definitely yes	Definitely no	Probably yes	Per protocol	Not mentioned	No
Li (2017) [26]	Probably yes	Probably yes	Probably no	Probably no	Definitely yes	Definitely yes	Probably yes	Not mentioned	Not mentioned	Yes
Huang (2018) [27]	Probably yes	Probably yes	Probably no	Probably no	Definitely yes	Definitely yes	Probably yes	Not mentioned	Not mentioned	No
Peng (2012) [28]	Probably yes	Probably yes	Probably no	Probably no	Definitely yes	Definitely yes	Probably yes	Per protocol	Not mentioned	No

FIGURE 2: Cochrane risk of bias by trial.

dizziness ($n = 326$, RR = 0.53, 95% CI: 0.33~0.86, $P = 0.010$) decreased (see Figure 5).

3.6. Burst Pain. Four studies reported the mean number of burst pain events [11, 12, 17, 18]. The heterogeneity test in the meta-analysis showed that $\chi^2 = 78.30$, $P < 0.00001$, $I^2 = 95\%$, and the differences between the studies were statistically significant, so a random effects model was used. The combined statistical results showed that the incidence of

burst pain in the treatment group was lower than that in the control group ($n = 244$, SMD = −1.38, 95% CI: −2.44~−0.32, $P = 0.01$; see Figure 6).

3.7. Onset Time to Analgesic Effect and Duration of Response. Five studies reported the mean onset time [11, 17, 19, 24, 28]. The combined statistical results showed that the onset time in the treatment group was shorter than that in the control group ($n = 360$, SMD = −20.11, 95% CI: −33.90~−6.33,

Study or subgroup	Acupuncture + drug therapy Events	Total	Drug therapy Events	Total	Weight (%)	Risk ratio M-H, fixed, 95% CI	Year	Risk ratio M-H, fixed, 95% CI
Mi Jianping et al., 201 0	29	32	21	30	3.9	1.29 [1.00, 1.68]	2010	
Liu Jie, 2011	29	30	25	30	4.5	1.16 [0.98, 1.38]	2011	
Peng Jle et al., 2012	22	23	22	24	3.9	1.04 [0.90, 1.21]	2012	
Tan Guangsheng et al., 2012	97	106	78	101	14.5	1.18 [1.05, 1.34]	2012	
Zhang Jianwei, 2014	28	30	24	30	4.4	1.17 [0.95, 1.43]	2014	
Jiang Bin et al., 2016	22	25	19	25	3.5	1.16 [0.89, 1.51]	2016	
Wang Ying, 2016	25	30	23	30	4.2	1.09 [0.84, 1.40]	2016	
Zhong Hua, 2016	29	30	25	30	4.5	1.16 [0.98, 1.38]	2016	
Sun Ruirui, 2016	29	30	28	30	5.1	1.04 [0.92, 1.16]	2016	
Fan Liyong et al., 2017	33	35	25	34	4.6	1.28 [1.03, 1.59]	2017	
Li Dehui et al., 2017	25	30	24	30	4.4	1.04 [0.82, 1.32]	2017	
Huang Ying, 2018	30	31	27	31	4.9	1.11 [0.96, 1.29]	2018	
Dong Yumin et al., 2018	58	60	56	60	10.2	1.04 [0.95, 1.12]	2018	
Wang Daojun, 2018	27	35	33	35	6.0	0.82 [0.67, 1.00]	2018	
Fu Yang et al., 2019	12	16	11	16	2.0	1.09 [0.71, 1.69]	2019	
Hui Jianrong et al., 2019	39	40	35	40	6.4	1.11 [0.98, 1.27]	2019	
Bai Weijie et al., 2019	47	50	38	50	6.9	1.24 [1.04, 1.47]	2019	
Fu Yang., 2019	14	16	11	16	2.0	1.27 [0.87, 1.86]	2019	
Wu Qiulan et al., 2019	26	30	23	30	4.2	1.13 [0.89, 1.44]	2019	
Total (95% CI)		679		672	100.0	1.12 [1.08, 1.17]		
Total events	621		548					

Heterogeneity: chi^2 = 22.19, df = 18 (P = 0.22); I^2 = 19%
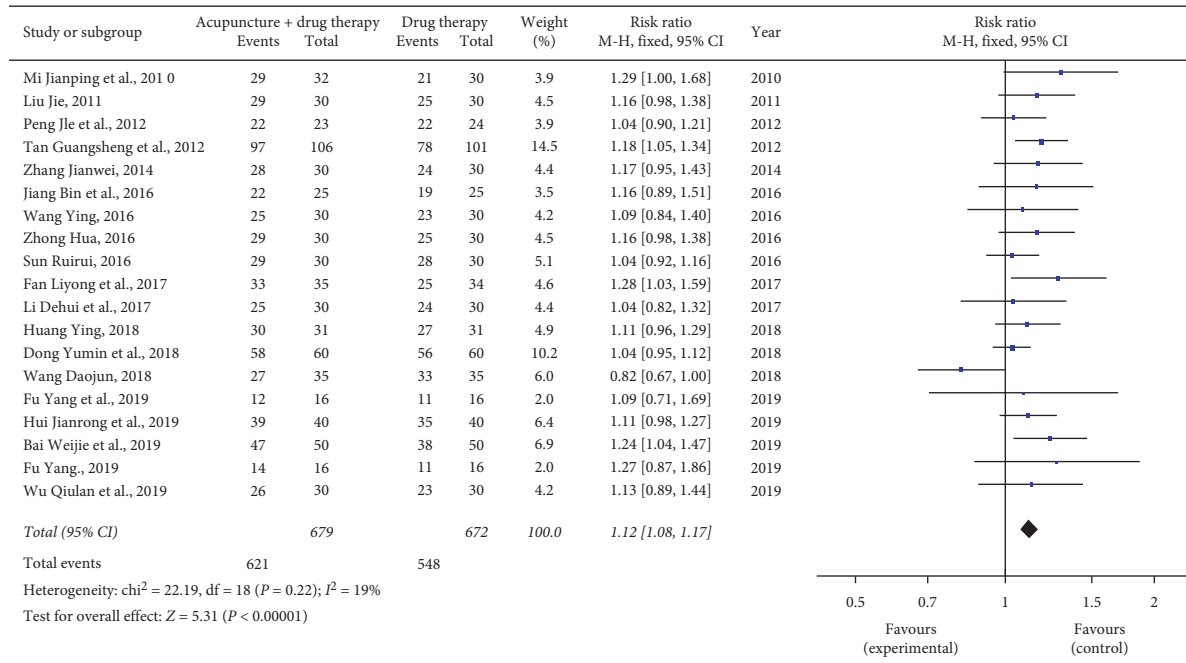Test for overall effect: Z = 5.31 (P < 0.00001)

FIGURE 3: Forest plot of the total response rates of acupuncture combined with three-step analgesic drugs versus three-step analgesic drugs alone for cancer pain.

Study or subgroup	Acupuncture + drug therapy Mean	SD	Total	Drug therapy Mean	SD	Total	Weight (%)	Mean difference IV, random, 95% CI	Year	Mean difference IV, random, 95% CI
Wang Ying, 2016	2.23	0.77	30	2.66	0.54	30	13.0	−0.43 [−0.77, −0.09]	2016	
Fan Liyong et al., 2017	4.82	1.06	35	5.43	1.11	34	12.5	−0.61 [−1.12, −0.10]	2017	
Dong Yumin et al., 2018	2.09	0.73	60	1.79	0.7	60	13.1	0.30 [0.04, 0.56]	2018	
Wang Daojun, 2018	1.94	1.26	35	2.77	0.94	35	12.5	−0.83 [−1.35, −0.31]	2018	
Fu Yang, 2019	1	1	16	5	1	16	12.0	−4.00 [−4.69, −3.31]	2019	
Bai Weijie et al., 2019	7.17	1.36	50	7.61	0.58	50	12.8	−0.44 [−0.85, −0.03]	2019	
Fu Yang et al., 2019	3	1	16	5	1	16	12.0	−2.00 [−2.69, −1.31]	2019	
Hui Jianrong et al., 2019	2.9	1.35	40	3.98	1.46	40	12.2	−1.08 [−1.70, −0.46]	2019	
Total (95% CI)			282			281	100.0	−1.10 [−1.86, −0.35]		

Heterogeneity: tau^2 = 1.11; chi^2 = 158.90, df = 7 (P < 0.00001); I^2 = 96%
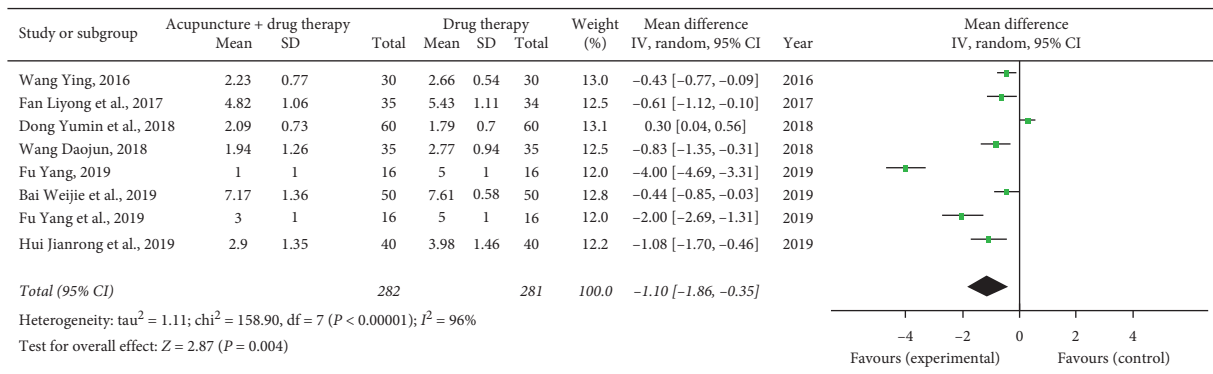Test for overall effect: Z = 2.87 (P = 0.004)

FIGURE 4: Forest plot of NRS score of acupuncture combined with three-step analgesic drugs versus three-step analgesic drugs alone for cancer pain.

P = 0.004). Six studies reported the mean duration of response [11, 17, 19, 22, 24, 28]. The combined statistical results showed that the duration of response in the treatment group was longer than that in the control group (n = 440, SMD = 3.22, 95% CI: 1.63~4.80, P < 0.0001); see Figures 7 and 8.

3.8. Publication Bias. Publication bias, which has always been a problem in meta-analysis, refers to the fact that research with positive results is easier to publish than research with negative results. The funnel chart analysis results of the main outcome indicators of the response rates of pain relief suggested that publication bias might exist and exaggerate the efficacy of acupuncture combined with three-step analgesic drugs in the treatment of cancer pain; see Figure 9.

4. Discussion

Cancer is a significant global public health issue, and the disease burden is growing. Globally, there are 18.1 million new cancer cases and 9.6 million cancer deaths each year; cancer deaths are expected to exceed 13 million by 2030, and 70% of cancer deaths globally occur in low-income and middle-income countries. In China in 2018, nearly 24% (4.3 million) of global new cases and 30% (2.9 million) of deaths occurred [29, 30]. China is the largest developing country. Chinese doctors need to pay attention to promoting cancer prevention for people and treating cancer patients. Cancer pain is severe, intolerable, and intractable pain, and such pain is a main symptom in the advanced stages of malignant tumours. When the tumour body markedly enlarges, tissue necrosis, erosion, and so on result in severe compression of, damage to, and irritation of the nerve sheath, nerve fibres,

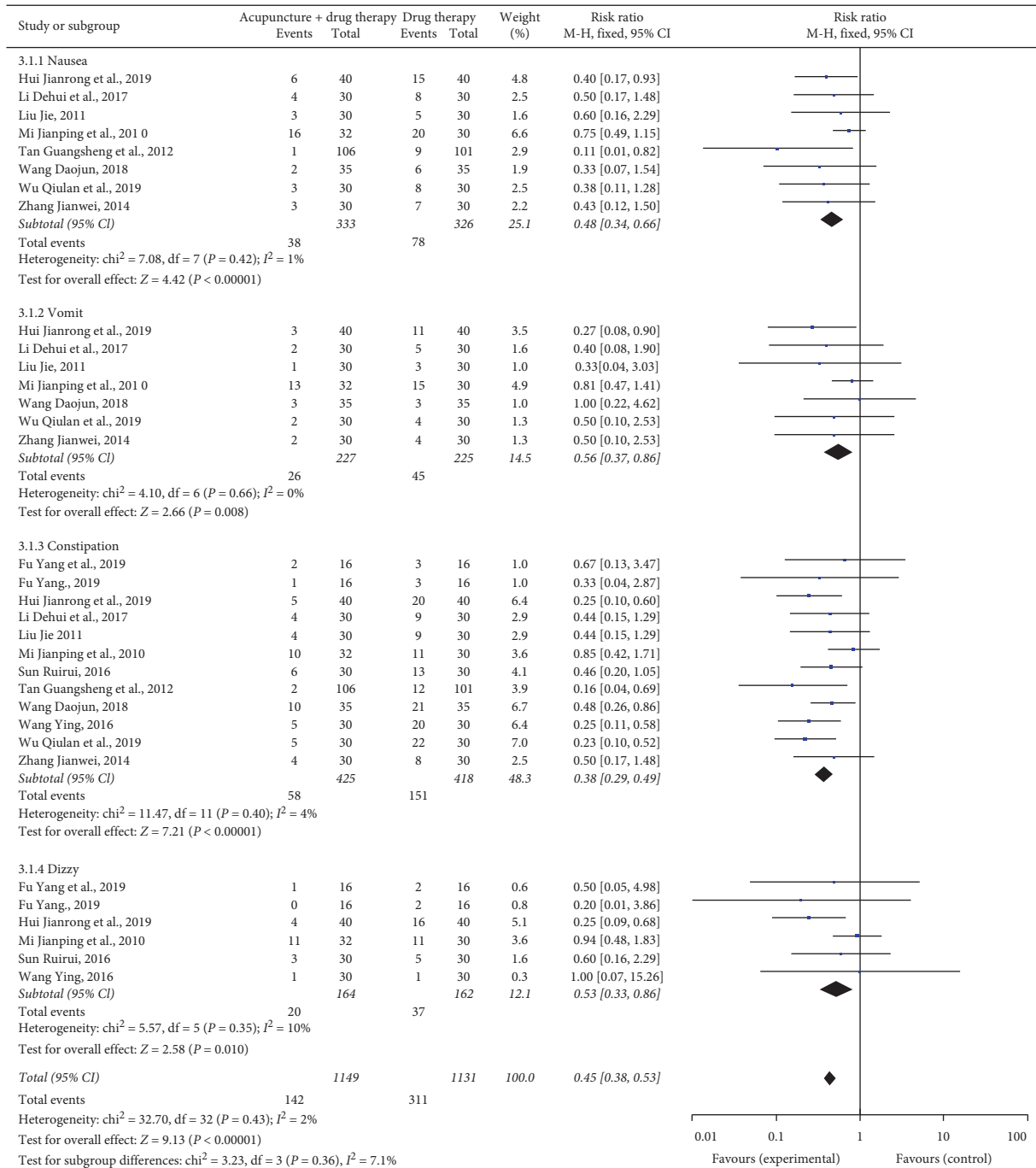| Study or subgroup	Acupuncture + drug therapy Events	Total	Drug therapy Events	Total	Weight (%)	Risk ratio M-H, fixed, 95% CI
3.1.1 Nausea						
Hui Jianrong et al., 2019	6	40	15	40	4.8	0.40 [0.17, 0.93]
Li Dehui et al., 2017	4	30	8	30	2.5	0.50 [0.17, 1.48]
Liu Jie, 2011	3	30	5	30	1.6	0.60 [0.16, 2.29]
Mi Jianping et al., 201 0	16	32	20	30	6.6	0.75 [0.49, 1.15]
Tan Guangsheng et al., 2012	1	106	9	101	2.9	0.11 [0.01, 0.82]
Wang Daojun, 2018	2	35	6	35	1.9	0.33 [0.07, 1.54]
Wu Qiulan et al., 2019	3	30	8	30	2.5	0.38 [0.11, 1.28]
Zhang Jianwei, 2014	3	30	7	30	2.2	0.43 [0.12, 1.50]
Subtotal (95% CI)		333		326	25.1	0.48 [0.34, 0.66]
Total events	38		78			
Heterogeneity: chi^2 = 7.08, df = 7 (P = 0.42); I^2 = 1%						
Test for overall effect: Z = 4.42 (P < 0.00001)						
3.1.2 Vomit						
Hui Jianrong et al., 2019	3	40	11	40	3.5	0.27 [0.08, 0.90]
Li Dehui et al., 2017	2	30	5	30	1.6	0.40 [0.08, 1.90]
Liu Jie, 2011	1	30	3	30	1.0	0.33 [0.04, 3.03]
Mi Jianping et al., 201 0	13	32	15	30	4.9	0.81 [0.47, 1.41]
Wang Daojun, 2018	3	35	3	35	1.0	1.00 [0.22, 4.62]
Wu Qiulan et al., 2019	2	30	4	30	1.3	0.50 [0.10, 2.53]
Zhang Jianwei, 2014	2	30	4	30	1.3	0.50 [0.10, 2.53]
Subtotal (95% CI)		227		225	14.5	0.56 [0.37, 0.86]
Total events	26		45			
Heterogeneity: chi^2 = 4.10, df = 6 (P = 0.66); I^2 = 0%						
Test for overall effect: Z = 2.66 (P = 0.008)						
3.1.3 Constipation						
Fu Yang et al., 2019	2	16	3	16	1.0	0.67 [0.13, 3.47]
Fu Yang., 2019	1	16	3	16	1.0	0.33 [0.04, 2.87]
Hui Jianrong et al., 2019	5	40	20	40	6.4	0.25 [0.10, 0.60]
Li Dehui et al., 2017	4	30	9	30	2.9	0.44 [0.15, 1.29]
Liu Jie 2011	4	30	9	30	2.9	0.44 [0.15, 1.29]
Mi Jianping et al., 2010	10	32	11	30	3.6	0.85 [0.42, 1.71]
Sun Ruirui, 2016	6	30	13	30	4.1	0.46 [0.20, 1.05]
Tan Guangsheng et al., 2012	2	106	12	101	3.9	0.16 [0.04, 0.69]
Wang Daojun, 2018	10	35	21	35	6.7	0.48 [0.26, 0.86]
Wang Ying, 2016	5	30	20	30	6.4	0.25 [0.11, 0.58]
Wu Qiulan et al., 2019	5	30	22	30	7.0	0.23 [0.10, 0.52]
Zhang Jianwei, 2014	4	30	8	30	2.5	0.50 [0.17, 1.48]
Subtotal (95% CI)		425		418	48.3	0.38 [0.29, 0.49]
Total events	58		151			
Heterogeneity: chi^2 = 11.47, df = 11 (P = 0.40); I^2 = 4%						
Test for overall effect: Z = 7.21 (P < 0.00001)						
3.1.4 Dizzy						
Fu Yang et al., 2019	1	16	2	16	0.6	0.50 [0.05, 4.98]
Fu Yang., 2019	0	16	2	16	0.8	0.20 [0.01, 3.86]
Hui Jianrong et al., 2019	4	40	16	40	5.1	0.25 [0.09, 0.68]
Mi Jianping et al., 2010	11	32	11	30	3.6	0.94 [0.48, 1.83]
Sun Ruirui, 2016	3	30	5	30	1.6	0.60 [0.16, 2.29]
Wang Ying, 2016	1	30	1	30	0.3	1.00 [0.07, 15.26]
Subtotal (95% CI)		164		162	12.1	0.53 [0.33, 0.86]
Total events	20		37			
Heterogeneity: chi^2 = 5.57, df = 5 (P = 0.35); I^2 = 10%						
Test for overall effect: Z = 2.58 (P = 0.010)						
Total (95% CI)		1149		1131	100.0	0.45 [0.38, 0.53]
Total events	142		311			
Heterogeneity: chi^2 = 32.70, df = 32 (P = 0.43); I^2 = 2%						
Test for overall effect: Z = 9.13 (P < 0.00001)						
Test for subgroup differences: chi^2 = 3.23, df = 3 (P = 0.36), I^2 = 7.1%						

FIGURE 5: Forest plot of side effect rates of acupuncture combined with three-step analgesic drugs versus three-step analgesic drugs alone for cancer pain.

and blood vessels. Although there are many ways to treat cancer pain, many years of clinical experience at home and abroad indicate that providers believe that drug therapy is still the most common and effective way to control cancer pain. The WHO three-step cancer pain treatment programme has become an internationally accepted cancer pain drug treatment method that can control most cancer pain; however, three-step pain drugs, especially opioids, are often accompanied by side effects such as nausea, vomiting, constipation, drowsiness, dizziness, and respiratory depression [31].

There are many ways to treat cancer, but in recent years, TCM has played an increasingly important role in cancer prevention and treatment. As an integral part of TCM, acupuncture has been used to treat pain for thousands of years. The complications of acupuncture in the treatment of pain diseases are fewer than those of drug treatment [32]. Wang Limei et al. reported that [33] complications such as
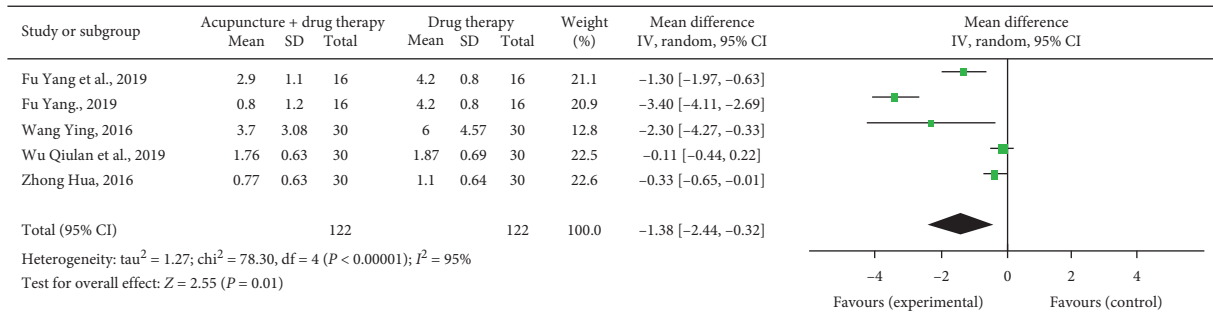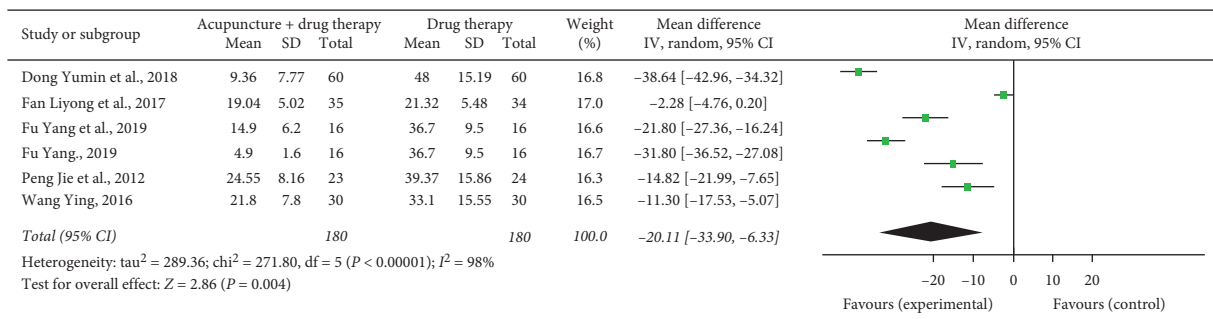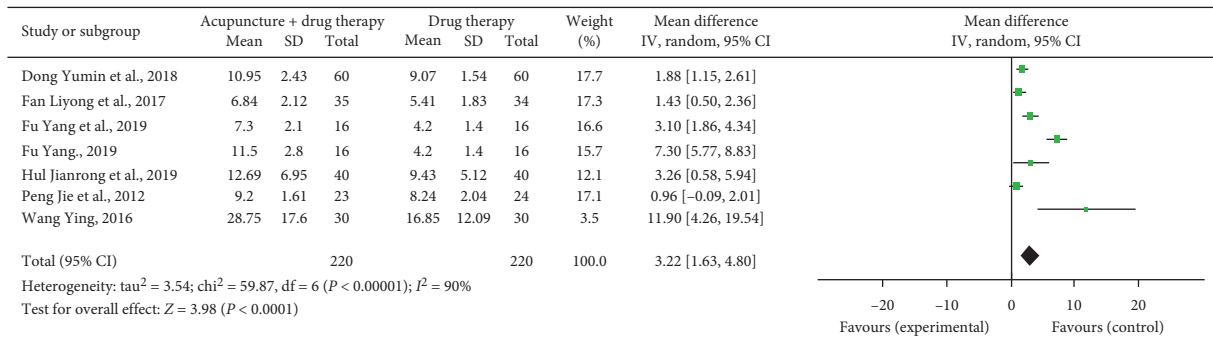
| Study or subgroup | Acupuncture + drug therapy | | | Drug therapy | | | Weight | Mean difference | Mean difference |
	Mean	SD	Total	Mean	SD	Total	(%)	IV, random, 95% CI	IV, random, 95% CI
Fu Yang et al., 2019	2.9	1.1	16	4.2	0.8	16	21.1	−1.30 [−1.97, −0.63]	
Fu Yang., 2019	0.8	1.2	16	4.2	0.8	16	20.9	−3.40 [−4.11, −2.69]	
Wang Ying, 2016	3.7	3.08	30	6	4.57	30	12.8	−2.30 [−4.27, −0.33]	
Wu Qiulan et al., 2019	1.76	0.63	30	1.87	0.69	30	22.5	−0.11 [−0.44, 0.22]	
Zhong Hua, 2016	0.77	0.63	30	1.1	0.64	30	22.6	−0.33 [−0.65, −0.01]	
Total (95% CI)			122			122	100.0	−1.38 [−2.44, −0.32]	

Heterogeneity: tau^2 = 1.27; chi^2 = 78.30, df = 4 ($P < 0.00001$); I^2 = 95%
Test for overall effect: Z = 2.55 (P = 0.01)

FIGURE 6: Forest plot of times of burst pain of acupuncture combined with three-step analgesic drugs versus three-step analgesic drugs alone for cancer pain.

| Study or subgroup | Acupuncture + drug therapy | | | Drug therapy | | | Weight | Mean difference | Mean difference |
	Mean	SD	Total	Mean	SD	Total	(%)	IV, random, 95% CI	IV, random, 95% CI
Dong Yumin et al., 2018	9.36	7.77	60	48	15.19	60	16.8	−38.64 [−42.96, −34.32]	
Fan Liyong et al., 2017	19.04	5.02	35	21.32	5.48	34	17.0	−2.28 [−4.76, 0.20]	
Fu Yang et al., 2019	14.9	6.2	16	36.7	9.5	16	16.6	−21.80 [−27.36, −16.24]	
Fu Yang., 2019	4.9	1.6	16	36.7	9.5	16	16.7	−31.80 [−36.52, −27.08]	
Peng Jie et al., 2012	24.55	8.16	23	39.37	15.86	24	16.3	−14.82 [−21.99, −7.65]	
Wang Ying, 2016	21.8	7.8	30	33.1	15.55	30	16.5	−11.30 [−17.53, −5.07]	
Total (95% CI)			180			180	100.0	−20.11 [−33.90, −6.33]	

Heterogeneity: tau^2 = 289.36; chi^2 = 271.80, df = 5 ($P < 0.00001$); I^2 = 98%
Test for overall effect: Z = 2.86 (P = 0.004)

FIGURE 7: Forest plot of the onset time of acupuncture combined with three-step analgesic drugs versus three-step analgesic drugs alone for cancer pain.

| Study or subgroup | Acupuncture + drug therapy | | | Drug therapy | | | Weight | Mean difference | Mean difference |
	Mean	SD	Total	Mean	SD	Total	(%)	IV, random, 95% CI	IV, random, 95% CI
Dong Yumin et al., 2018	10.95	2.43	60	9.07	1.54	60	17.7	1.88 [1.15, 2.61]	
Fan Liyong et al., 2017	6.84	2.12	35	5.41	1.83	34	17.3	1.43 [0.50, 2.36]	
Fu Yang et al., 2019	7.3	2.1	16	4.2	1.4	16	16.6	3.10 [1.86, 4.34]	
Fu Yang., 2019	11.5	2.8	16	4.2	1.4	16	15.7	7.30 [5.77, 8.83]	
Hul Jianrong et al., 2019	12.69	6.95	40	9.43	5.12	40	12.1	3.26 [0.58, 5.94]	
Peng Jie et al., 2012	9.2	1.61	23	8.24	2.04	24	17.1	0.96 [−0.09, 2.01]	
Wang Ying, 2016	28.75	17.6	30	16.85	12.09	30	3.5	11.90 [4.26, 19.54]	
Total (95% CI)			220			220	100.0	3.22 [1.63, 4.80]	

Heterogeneity: tau^2 = 3.54; chi^2 = 59.87, df = 6 ($P < 0.00001$); I^2 = 90%
Test for overall effect: Z = 3.98 ($P < 0.0001$)

FIGURE 8: Forest plot of the duration of response of acupuncture combined with three-step analgesic drugs versus three-step analgesic drugs alone for cancer pain.

pneumothorax, dizziness, pain, needle syncope, infection, and visceral puncture can occur due to improper acupuncture manipulation; however, when doctors master anatomical knowledge, perform acupuncture correctly, and sterilise needles strictly, complications are further reduced. Modern research shows that the mechanism of acupuncture analgesia may be related to regulating the self-healing of the body, changing patients' perceptions of pain, and affecting the conduction of the central nervous system [34]. Another possible acupuncture mechanism is stimulation/excitation of the endogenous pain modulation system, which induces the secretion of endogenous opioids, blocks the transmission of neurotransmitters, and regulates the perception of pain to achieve analgesia [35]. A third possibility is that the pain signals from acupuncture are modulated in the pain receptor areas, and the dorsal root ganglion cells of the outgoing primary neurons transmit the signal to the near end of the secondary neurons. The pain signal produced by acupuncture may then induce the secretion of endogenous opioids and analgesia in the periaqueductal grey matter of the midbrain, or it may induce the penetration of electric ions, stimulate neurons, and exert an inhibitory effect in the intercellular area of the periaqueductal grey matter of the midbrain [36]. The exact mechanism of acupuncture's analgesic effect has not yet been elucidated. However, this review of acupuncture treatment of cancer pain with a large number of RCT experiments demonstrated that acupuncture treatment of cancer has fewer adverse reactions such as
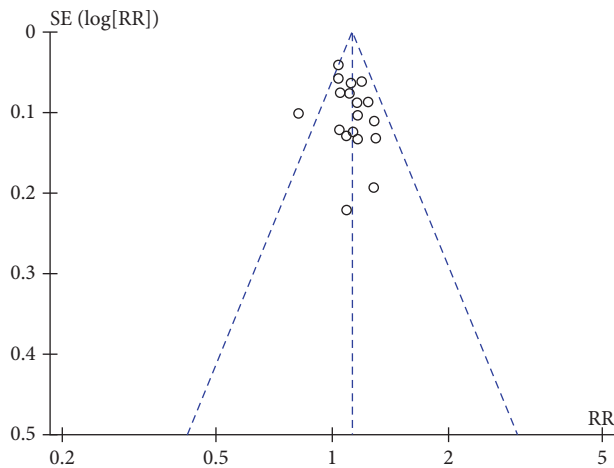
FIGURE 9: Total efficiency funnel.

nausea and vomiting than analgesic drug treatment alone. Acupuncture treatment for cancer pain is considered to have sufficient evidence to determine its effectiveness [37]; these results are encouraging and support further research on acupuncture treatment for cancer.

5. Conclusion

Based on the meta-analysis of 19 studies, compared with the treatment of cancer pain with three-step analgesic drug treatment alone, the response rates of pain relief from acupuncture combined with three-step analgesic drug treatment were higher, the NRS scores were lower, the incidence of adverse reactions such as nausea and vomiting was less frequent, the incidence of times of burst pain was also less frequent, the onset time to analgesic effect was shorter, and the duration of pain response was longer.

There were several limitations in this study. The lack of high-quality studies in the literature may limit the validity of the results. Meta-analyses generally face methodological challenges such as insufficient literature retrieval, potential selection bias for which studies are included, and inappropriate evaluation of the quality of the original research. This study only included published literature and did not search for unpublished literature; in addition, there may be publication bias in the literature.

In conclusion, this study shows that acupuncture combined with three-step analgesic drugs has specific advantages over three-step analgesic drugs alone in the treatment of cancer pain. It is hoped that, in the future, rigorous randomised controlled trials will be carried out with multicentre and large-sample studies to determine acupuncture's exact curative effect and further demonstrate the superiority of acupuncture combined with three-step analgesic drugs over the use of such drugs alone to treat cancer pain.

Data Availability

The data can be obtained from the author upon reasonable request.

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