Efficacy of opioids in combination with gabapentin vs. opioids alone in the treatment of patients with cancer-related pain due to bone metastases from malignant neoplasms: A meta-analysis

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Abstract. Cancer pain seriously affects the quality of life of patients with malignant tumors, especially the pain caused by bone metastases. In recent years, gabapentin has demonstrated potential value in the treatment of cancer pain from bone metastases, providing promising new ideas for clinical treatment. The aim of the present study was to systematically evaluate the efficacy of opioids combined with gabapentin compared with opioids alone in the treatment of cancer-related pain due to bone metastases of malignant tumors based on meta-analysis. PubMed, Embase, Web of Science, China National Knowledge Infrastructure, VIP, Wanfang Data and other databases were searched to collect randomized controlled trials and non-randomized controlled trials of opioids combined with gabapentin compared with opioids alone for the treatment of cancer pain due to malignant bone metastases. The quality of the included studies was evaluated using the Cochrane Risk of Bias Assessment 2.0 tool and the Newcastle-Ottawa Scale. Subsequent meta-analyses were performed using the R language. A total of 25 studies including 1,805 patients were included. Meta-analysis results showed that gabapentin in combination with opioids exhibited a notable advantage in reducing pain scores compared with opioids alone (mean difference=1.26; 95% CI, 0.88-1.65). Subgroup analyses by study type, sample size and treatment regimen revealed that heterogeneity was influenced by a number of factors. Sensitivity analyses demonstrated the robustness of the findings. However, limited data on adverse effects precluded comprehensive safety analysis. Gabapentin in combination with opioids may be an effective regimen for the treatment of cancer-related pain associated with bone metastases from malignant tumors. However, due to the heterogeneity of the included studies and limited safety data, clinical application requires caution and individualized treatment regimens based on patient-specific conditions.

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Introduction

Cancer pain is a common and challenging complication in patients with malignant tumors, which seriously affects their quality of life. Bone metastasis is one of the most notable causes of cancer pain (1). Epidemiological studies have demonstrated that bone metastases occur in 65-75% of patients with advanced breast cancer and prostate cancer, and in 30-40% of patients with lung cancer (2). Furthermore, ~70% of patients with bone metastases experience moderate-to-severe pain, making it a notable clinical burden (3). The majority of patients with advanced tumors experience cancer pain, and the pain caused by bone metastases is particularly severe, which has a notable impact on the quality of life of the patients and their survival (4). In China, the incidence of cancer pain ranges from 40-90%, reaching >80% in patients with advanced malignant tumors. Approximately one-third of these patients suffer from moderate-to-severe pain, with some patients experiencing persistent pain until mortality (5).

Opioids are currently the first-line drugs for the treatment of moderate-to-severe cancer pain and common opioids include oxycodone hydrochloride controlled-release tablets, morphine, oxycodone and fentanyl. Morphine, as a representative of opioids, is a potent analgesic that can effectively relieve all types of severe pain, but long-term use is prone to tolerance and dependence, with risk of additional adverse effects, including constipation, nausea, vomiting and respiratory depression (6). Oxycodone is a semi-synthetic opioid with dual receptor agonism, precise analgesic effect and good relief for moderate-severe pain (7). Oxycodone hydrochloride controlled-release tablets utilize unique controlled-release technology that allows the drug to be released slowly in vivo, maintaining a stable blood concentration and prolonging the duration of analgesia (8,9). Fentanyl, on the other hand, is a

potent opioid analgesic with a rapid onset and short duration of analgesic action and is commonly used for anesthesia-assisted analgesia and the management of breakthrough pain (10). Studies have shown that long-term use of opioids is prone to drug resistance and multiple adverse effects, such as constipation, nausea, vomiting and respiratory depression, thereby reducing the treatment compliance of the patient and their overall quality of life (11,12). Therefore, how to reduce the dosage and adverse effects of opioids while effectively controlling pain is a key issue in the field of cancer pain management for bone metastases that needs to be urgently addressed.

Gabapentin is a γ-aminobutyric acid analogue with an analgesic mechanism that inhibits neurotransmitter release, primarily by binding to the α2δ subunit in neuronal voltage-gated Ca2+ channels (13). Although gabapentin has a unique analgesic mechanism and good drug metabolism properties, it does not bind to plasma proteins, but instead crosses the blood-brain barrier using the L-type amino acid transporter protein 1 (14). Furthermore, gabapentin does not undergo hepatic metabolism, which avoids any effect on the hepatic cytochrome P450 system and reduces interactions with other drugs (15). However, gabapentin needs to enter the neuronal cytoplasm through a neutral amino acid transporter in order to be effective (16) and the limited transport capacity of this transporter results in an oral bioavailability of only 33-66% (17). Therefore, gabapentin is often used in combination with analgesic drugs with different mechanisms of action in order to optimize the analgesic effect. For example, in clinical practice, gabapentin has been found to have a synergistic analgesic effect when used in combination with opioids, potentially reducing the required dose of opioids (18,19).

A number of clinical studies (20-23) have been conducted on the efficacy of opioids combined with gabapentin compared with opioids alone in the treatment of cancer-related pain due to bone metastases from malignant tumors, but the results of these studies are not yet fully consistent. These differences may stem from numerous factors including study design, sample size, interventions and characteristics of the study population. Therefore, it is necessary to conduct a systematic evaluation and meta-analysis of the existing studies to comprehensively assess the differences in efficacy between the two treatment regimens and to provide more reliable evidence for the clinical treatment of cancer pain from bone metastases.

Materials and methods

Inclusion and exclusion criteria

Inclusion criteria. Inclusion criteria ensured the type of study was: i) A randomized controlled trial (RCT) or non-randomized controlled trial (NRCT); ii) the study population consisted of patients with a definitive diagnosis of cancer pain due to bone metastases from malignant tumors, regardless of cancer type or stage; iii) the intervention was gabapentin in combination with opioid regimen; iv) the control group was treated with opioids alone; and v) the outcome metrics needed to include the numerical rating scale (NRS) for assessing pain intensity. No restrictions were placed on publication language or year.

Exclusion criteria. Exclusion criteria ensured studies that did not provide complete data or were unable to extract the required information, case reports, conference abstracts, review articles and duplicate publications were excluded.

Search strategy

Scope of search. Searches were conducted using Chinese and English literature databases including China National Knowledge Infrastructure (https://www.cnki.net), VIP (https://www.cqvip.com), Wanfang Data (https://www.wanfangdata.com.cn), PubMed (https://pubmed.ncbi.nlm.nih.gov), Embase (https://www.embase.com) and Web of Science (https://www.webofscience.com). The search was conducted from the time of database construction to the 21st of November 2024.

Search terms. Chinese words for cancer pain, cancer-related pain, gabapentin, morphine, oxycodone, oxycodone hydrochloride controlled-release tablets, fentanyl, tramadol, codeine and opioids were used as search terms. In English, 'cancer pain', 'malignant pain', 'tumor pain', 'oncologic pain', 'neoplastic pain', 'gabapentin', 'neurontin', 'morphine', 'oxycodone', 'fentanyl', 'tramadol' and 'opioid' were used as search terms. The specific search strategies are detailed in Table SI.

Literature data extraction and quality assessment

Data extraction. Data screening and extraction was carried out independently by two researchers. Duplicate entries were eliminated at the initial screening stage using EndNote X9.3.3 (Clarivate) software and literature unrelated to the study topic was screened by reading the title and abstract. In cases of disagreement at the initial screening stage, a third researcher was sought to discuss and reach an agreement. Extracted information included basic information about the included studies, study population and interventions, risk of bias assessment, outcome indicators and outcome measure data.

Quality assessment. A systematic approach was used in the present study to assess the risk of bias and methodological quality of the included literature. For RCTs, the Cochrane Risk of Bias Assessment Tool (24) was applied. Furthermore, for NRCTs, the Newcastle-Ottawa Scale (25) was used. The two types of studies were carefully evaluated separately, starting with the key areas of randomization, blinding and confounding control. Evaluations were completed independently by two researchers and disagreements were resolved through a discussion or third-party arbitration. Studies were finally categorized according to the risk of bias level ('high', 'medium' or 'low').

Outcome indicator. Pain score was the main indicator of outcome and was assessed by the NRS.

Statistical processing. Meta-analysis was performed using R software (version 4.3.0; Posit Software, PBC) with the 'meta' package (26). Pain scores were described by mean difference (MD). Estimation intervals for overall parameters are expressed as 95% CIs. Random-effects models were used for all pooled analyses regardless of the I^2 values. Statistical heterogeneity was assessed using the Q test and the I^2 statistic. Z-tests were used to analyze the combined statistics. Subgroup analyses were performed based on study type (RCT vs. NRCT), sample size (small, <40 patients per group vs. large, ≥40 patients per group) and treatment regimen (specific opioid types). Sensitivity analyses using the leave-one-out

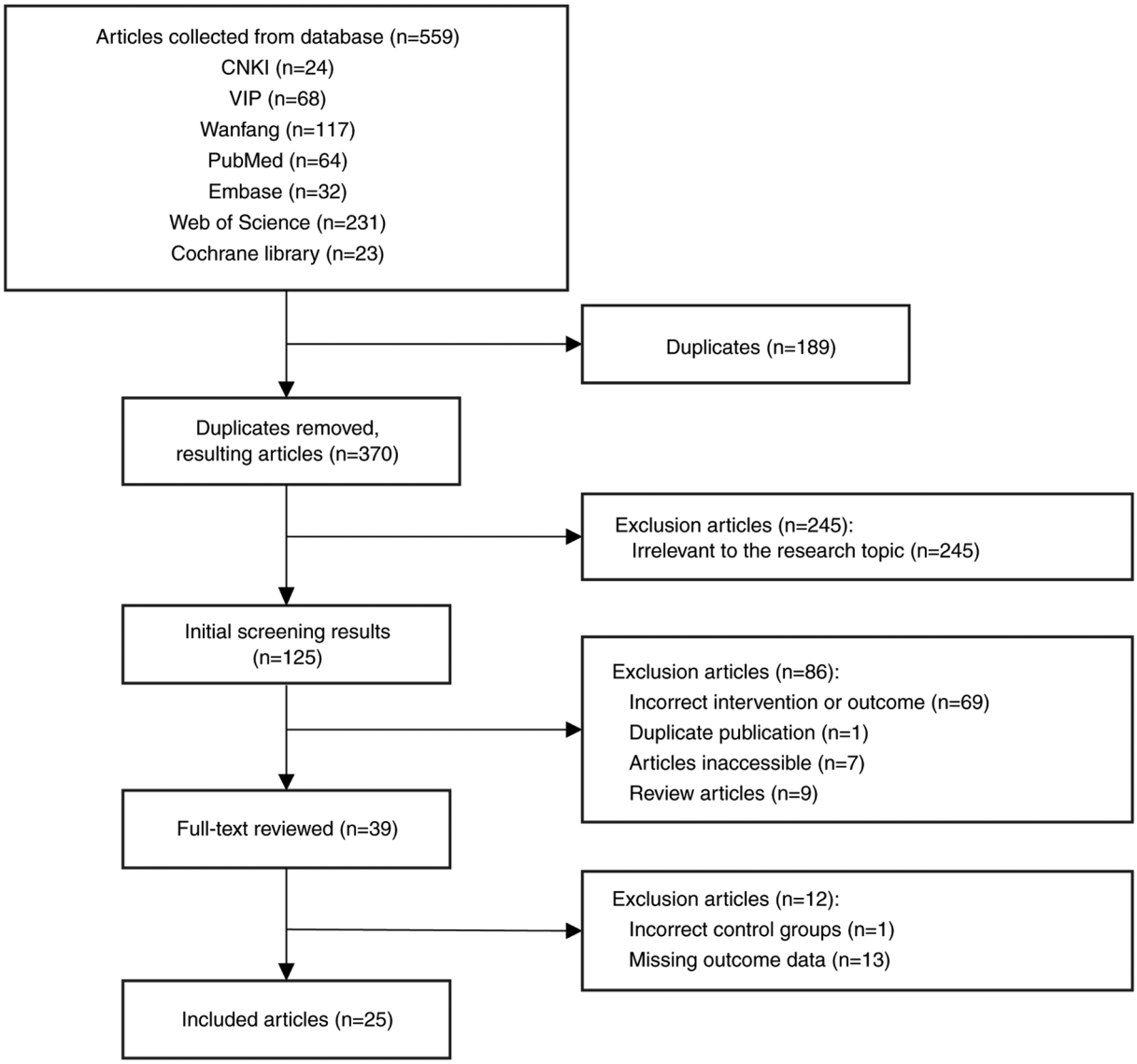

Figure 1. Literature search and screening flowchart. CNKI, China National Knowledge Infrastructure.

method (27) were conducted to assess the robustness of the findings. Funnel plots were used to determine publication bias. A test level (α) value of 0.05 was considered to indicate a statistically significant difference.

Results

Literature search results. A total of 559 relevant papers were retrieved from the present literature search and 39 papers were finally assessed in full text. Among the 39 included literature, 13 studies with missing data and 1 study with a wrong intervention were further excluded, leaving 25 studies that met the present study inclusion criteria retained for meta-analysis (Fig. 1). Among them, 6 studies were NRCTs and 19 studies were RCTs.

Basic characteristics of the included literature. A total of 1,805 patients were included in the present study with 563 patients included across six NRCTs (20,28-32) and 1,242 patients included in 19 RCTs (33-51). The mean age of patients ranged from 45-68 years. The majority of studies included patients with numerous cancer types, with lung, breast and prostate cancer being the most common primary tumors associated with bone metastases. Specific information on the included literature is outlined in Table I.

Results of the quality assessment of the included literature. Overall quality of the included literature was found to be moderate-high. The RCT quality rating scale is detailed in Figs. 2 and 3. The majority of RCTs demonstrated adequate random sequence generation and allocation concealment, though blinding procedures were not always clearly described. The overall quality scores of the NRCTs ranged from 5-7 stars, as detailed in Table II, indicating acceptable methodological quality with adequate selection of participants and comparability between groups.

Clinical efficacy

Overall analysis. In the present study, all 25 included studies used pain scores as an indicator of clinical efficacy, assessed using the NRS. The results, shown in Fig. 4, showed that

Table I. Baseline characteristics of the included literature.

First author, year	Study type	Total sample size	Sample size		Ratio of men to women		Age composition, years		Intervention		(Refs.)
			Control	Experimental	Control	Experimental	Control	Experimental	Control	Experimental	
Li *et al*, 2010	NRCT	53	32	21	18:14	9:12	57.31±13.19	57.05±12.38	Controlled release oxycodone + gabapentin	Controlled release oxycodone	(20)
Su *et al*, 2013	RCT	80	40	40	21:19	22:18	57.3±12.9	57.5±11.8	Fentanyl patch + gabapentin	Fentanyl patch	(33)
Liu *et al*, 2014	RCT	41	21	20	14:7	12:8	60.30±10.48	60.30±10.48	Morphine sulfate extended-release tablets + gabapentin	Morphine sulfate extended-release tablets	(34)
Qin *et al*, 2015	RCT	40	20	20	-	-	-	-	Oxycodone hydrochloride + gabapentin	Oxycodone hydrochloride	(35)
Chen *et al*, 2015	RCT	61	30	31	18:12	17:14	67.4±12.1	66.7±11.9	Morphine sulfate extended-release tablets + gabapentin	Morphine sulfate extended-release tablets	(36)
Zhang, 2016	RCT	90	45	45	0:21	23:22	47.0±2.9	49.6±2.5	Morphine sulfate extended-release tablets + gabapentin	Morphine sulfate extended-release tablets	(37)
Zhang *et al*, 2016	RCT	42	21	21	-	-	51	51	Morphine hydrochloride extended-release tablets + gabapentin	Morphine hydrochloride extended-release tablets	(38)
Zhao, 2016	NRCT	118	118	118	18:52	18:52	52.7±9.8	52.7±9.8	Morphine + Gabapentin	Morphine	(28)
Chen *et al*, 2017	RCT	55	28	27	15:13	14:13	54.5±7.4	54.5±7.4	Oxycodone hydrochloride + gabapentin	Oxycodone hydrochloride	(39)
Jiang, 2017	RCT	80	40	40	19:21	22:18	58.7	58.7	Oxycodone hydrochloride controlled-release tablets + gabapentin	Oxycodone hydrochloride controlled-release tablets	(40)
She *et al*, 2017	RCT	100	52	48	31:21	30:18	58	58	Morphine hydrochloride extended-release tablets + gabapentin	Morphine hydrochloride extended-release tablets	(41)

Table I. Continued.

First author, year	Study type	Total sample size	Sample size		Ratio of men to women		Age composition, years		Intervention		(Refs.)
			Control	Experimental	Control	Experimental	Control	Experimental	Control	Experimental	
Yan *et al*, 2018	RCT	122	61	61	-	-	61	61	Morphine sulfate extended-release tablets + gabapentin	Morphine sulfate extended-release tablets	(42)
Ru *et al*, 2018	RCT	70	36	34	19:17	18:16	63±15	62±15	Oxycodone hydrochloride + gabapentin	Oxycodone hydrochloride	(43)
Fu, 2018	RCT	60	30	30	17:13	18:12	66.81±4.25	67.52±4.12	Morphine sulfate extended-release tablets + gabapentin	Morphine sulfate extended-release tablets	(44)
Yan, 2018	RCT	60	30	30	13:17	14:16	55.6	55.6	Oxycodone hydrochloride extended-release tablets + gabapentin	Oxycodone hydrochloride extended-release tablets	(45)
Zhou *et al*, 2019	RCT	65	32	33	17:15	18:15	-	-	Oxycodone extended-release tablets + gabapentin	Oxycodone extended-release tablets	(46)
Meng, 2019	RCT	76	39	37	23:16	22:15	56.34±6.91	56.24±6.75	Oxycodone hydrochloride + gabapentin	Oxycodone hydrochloride	(47)
Zhu, 2020	RCT	67	30	37	14:16	18:19	58.59±4.62	58.67±4.36	Morphine sulfate extended-release tablets + gabapentin	Morphine sulfate extended-release tablets	(48)
Zhao and Xia, 2020	NRCT	56	28	28	17:11	16:12	56.11±9.70	52.61±9.51	Fentanyl patch + gabapentin	Fentanyl patch	(29)
Zhang, 2021	RCT	89	44	45	24:20	26:19	58.46±4.59	58.43±4.62	Oxycodone hydrochloride + gabapentin	Oxycodone hydrochloride	(49)
Jiang *et al*, 2021	NRCT	84	42	42	27:15	26:16	58.42±5.18	58.39±5.16	Oxycodone hydrochloride + gabapentin	Oxycodone hydrochloride	(30)
Sun, 2021	NRCT	60	30	30	15:15	13:17	52.81±13.76	52.85±13.73	Morphine sulfate extended-release tablets + gabapentin	Morphine sulfate extended-release tablets	(31)

Table I. Continued.

First author, year	Study type	Total sample size	Sample size		Ratio of men to women		Age composition, years		Intervention		(Refs.)
			Control	Experimental	Control	Experimental	Control	Experimental	Control	Experimental	
Jiang *et al*, 2021	RCT	50	25	25	16:9	18:7	51.9±10.7	52.4±12.3	Oxycodone hydrochloride controlled-release tablets + gabapentin	Oxycodone hydrochloride controlled-release tablets	(50)
Teng *et al*, 2021	NRCT	74	34	40	19:15	23:17	59.00±6.20	57.13±6.09	Morphine + gabapentin	Morphine	(32)
Qi, 2024	RCT	112	56	56	10:22	11:21	56.06±14.47	56.23±14.18	Oxycodone hydrochloride + gabapentin	Oxycodone hydrochloride	(51)

RCT, randomized controlled trial; NRCT, non-randomized controlled trial.

the MD of all studies combined was 1.26 with a 95% CI of 0.88-1.65, indicating that the combination therapy (oxycodone hydrochloride controlled-release tablets combined with gabapentin, morphine combined with gabapentin, oxycodone combined with gabapentin and fentanyl combined with gabapentin) demonstrated a significant difference and the combination may be more helpful in reducing pain scores and relieving cancer pain (Z=6.45; P<0.0001). However, overall, I^2=88.7% for all studies combined, suggesting a high degree of heterogeneity among the 25 included studies.

Subgroup analysis by study type. To explore potential sources of heterogeneity, subgroup analysis was conducted based on study type (Fig. S1). For NRCTs, the pooled MD was 1.11 (95% CI, -0.15-2.37; P=0.08; I^2=96.9%), indicating no significant difference and high heterogeneity. For RCTs, the pooled MD was 1.31 (95% CI, 1.03-1.59; P<0.0001; I^2=65.0%), demonstrating a significant analgesic advantage with moderate heterogeneity. The test for subgroup differences showed no significant difference between RCTs and NRCTs (P=0.77 for random effects model), suggesting that study design may not be the primary source of heterogeneity.

Subgroup analysis by sample size. Subgroup analysis stratified by sample size revealed important differences (Fig. S2). For studies with small sample sizes (<40 patients per group), the pooled MD was 0.95 (95% CI, 0.54-1.37; P<0.0001; I^2=73.9%), showing significant efficacy with notable heterogeneity. For studies with large sample sizes (≥40 patients per group), the pooled MD was 1.57 (95% CI, 0.97-2.17; P<0.0001; I^2=92.3%), indicating even greater efficacy but with higher heterogeneity. The test for subgroup differences suggested a notable difference between small and large sample size groups (P=0.10 for random effects model), indicating that sample size may contribute to heterogeneity and affect treatment effect estimates.

Subgroup analysis by treatment regimen. Further subgroup analysis was performed based on the specific opioid used in combination with gabapentin (Fig. S3). The MD of the oxycodone hydrochloride controlled-release tablets subgroup was 0.95 (95% CI, 0.51-1.38; I^2=0.0%; P=0.76 for heterogeneity), showing significant efficacy with no heterogeneity. The MD of the oxycodone subgroup was 1.17 (95% CI, 0.79-1.55, I^2=54.8%; P=0.02), demonstrating significant efficacy with moderate heterogeneity. The MD of the morphine subgroup was 1.41 (95% CI, 0.68-2.14; I^2=94.2%; P<0.01), showing significant efficacy but with very high heterogeneity. The fentanyl subgroup MD was 1.16 (95% CI, 0.68-1.65, I^2=10.8%; P=0.29 for heterogeneity), indicating significant efficacy with low heterogeneity. The test for subgroup differences revealed a significant association (P=0.0004 for random-effects model), suggesting that the type of opioid is a significant contributor to the overall heterogeneity.

Subgroup analysis excluding morphine. Due to the high heterogeneity observed in the morphine subgroup, a sensitivity analysis was conducted excluding morphine studies (Fig. S4). The pooled MD was 1.17 (95% CI, 0.92-1.42; P=0.0449; I^2=42.8%), showing that after removing morphine studies, the overall heterogeneity notably decreased from 88.7 to 42.8%, while maintaining statistical significance. This suggests that differences in morphine studies contribute markedly to the overall heterogeneity.

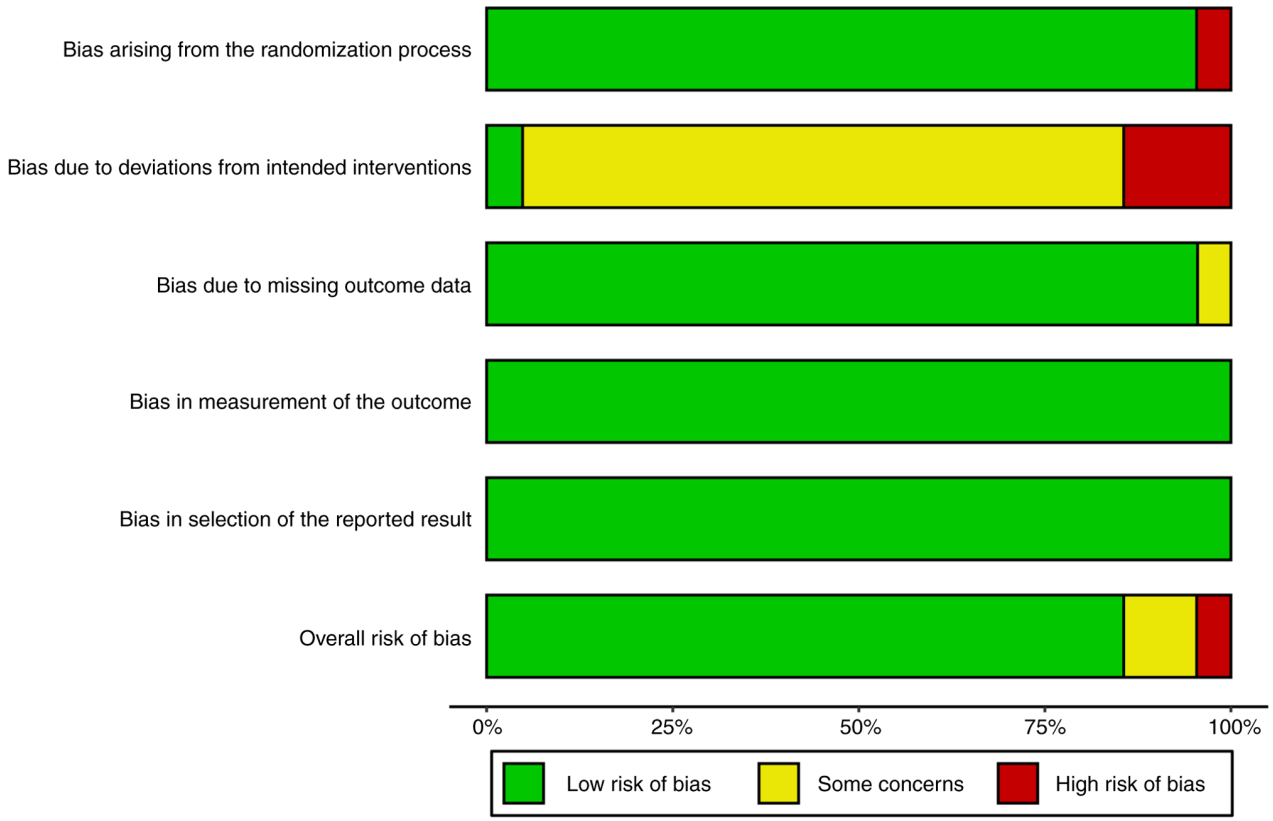

Figure 2. Quality evaluation star and bar chart of randomized controlled trials.

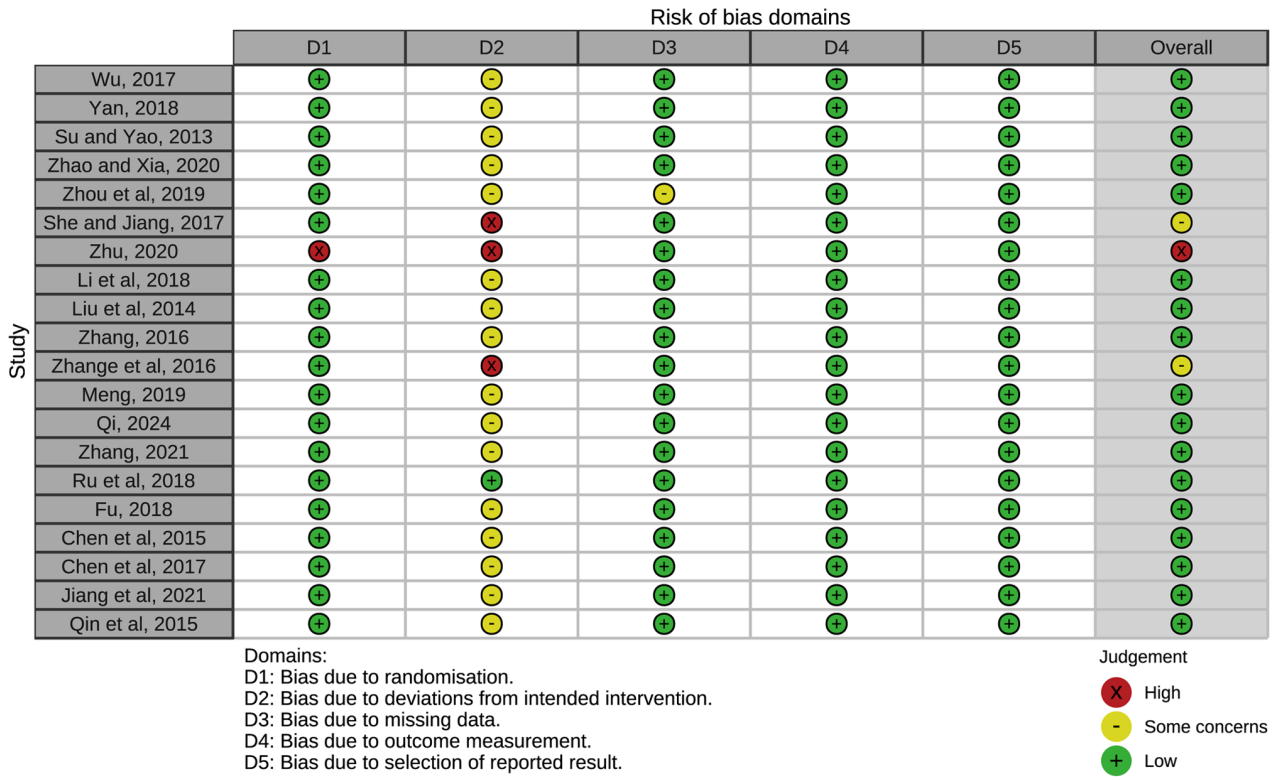

Figure 3. Quality evaluation traffic map of randomized controlled trials.

Subgroup analysis of RCTs only. To provide the highest level of evidence, only RCTs were analyzed (Fig. S5). The pooled MD for RCTs was 1.31 (95% CI, 1.03-1.59; P<0.0001; I^2=65.0%), confirming the significant benefit of combination

Table II. Newcastle-Ottawa Scale for non-randomized controlled trials.

First author, year	Representativeness of the exposed group	Selection of non-exposed groups	Determination of exposure	No observed outcome indicators occurred at study entry	Comparability of exposed and non-exposed groups	Adequacy of outcome evaluations	Sufficiently long follow-up	Adequate follow-up	Total	(Refs.)
Li *et al*, 2010	a	-	a	-	-	a	a	a	5	(20)
Zhao, 2016	a	a	a	-	b	a	-	-	6	(28)
Teng *et al*, 2021	a	a	a	a	b	a	a	a	9	(32)
Sun, 2021	a	a	a	-	b	a	a	-	7	(31)
Jiang *et al*, 2021	a	a	a	-	b	a	-	-	6	(30)

[a]Represents 1 point; [b]represents 2 points.

therapy even when restricting analysis to the most rigorous study designs. The reduced heterogeneity compared with the overall analysis (65.0 vs. 88.7%) suggested that study design does contribute to heterogeneity, though notable heterogeneity remains even among RCTs.

Sensitivity analysis. Leave-one-out sensitivity analysis was performed to assess the influence of individual studies on the overall results (Fig. S6). Analysis showed that the pooled MD ranged from 1.22 (95% CI, 0.82-1.63) to 1.36 (95% CI, 1.02-1.71) when omitting each study sequentially, with all CIs remaining >0 and statistically significant. This indicated that no single study had an excessive influence on the overall results, confirming the robustness and reliability of the present findings.

Publication bias. An analysis of publication bias was performed for all included studies. The results are shown in Fig. 5 and the funnel plot is largely symmetrical, indicating a low likelihood of publication bias. Visual inspection of the funnel plot and statistical tests suggest that the meta-analysis results are unlikely to be notably affected by unpublished negative studies.

Discussion

The present meta-analysis comprehensively evaluated the efficacy of opioids combined with gabapentin compared with opioids alone in treating cancer-related pain due to bone metastases from malignant tumors. The findings demonstrated that combination therapy provides improved pain relief compared with opioid monotherapy, with the pooled MD=1.26 points on the NRS scale, which represents a clinically meaningful improvement in pain control.

Opioids have been the primary analgesic drugs for cancer pain management, but they are more effective for nociceptive pain and have relatively limited efficacy for neuropathic pain components. In addition, long-term use of opioids is prone to drug tolerance, requiring increased dosage or shorter dosing intervals to maintain pain relief (50). Due to the more pronounced side effects of opioids, experienced clinicians tend to favor opioid-based combinations with a view to controlling cancer pain while reducing the opioid dose (39). For example, a retrospective study by Shinde *et al* (51) found that 80% of patients with cancer pain were treated with a combination of adjuvant medications.

Gabapentin is a drug with an analgesic mechanism different from that of opioids with mild and rare side effects. It is more effective in relieving chronic pain, especially neuropathic pain, and does not develop tolerance with repeated application (48). Eckhardt *et al* (52) found that gabapentin increased opioid blood concentrations after adding gabapentin to opioids used in patients with cancer pain. In patients with cancer pain and either poor pain control or on a high dose of analgesic drugs, a combination of drugs could be considered to further enhance the analgesic effect or reduce the dose of analgesic drugs, as different types of analgesic drugs exhibit different mechanisms and can enhance the analgesic effect through numerous pathways.

The present meta-analysis results are consistent with previous reports. For example, Xinlin *et al* (53) found that the

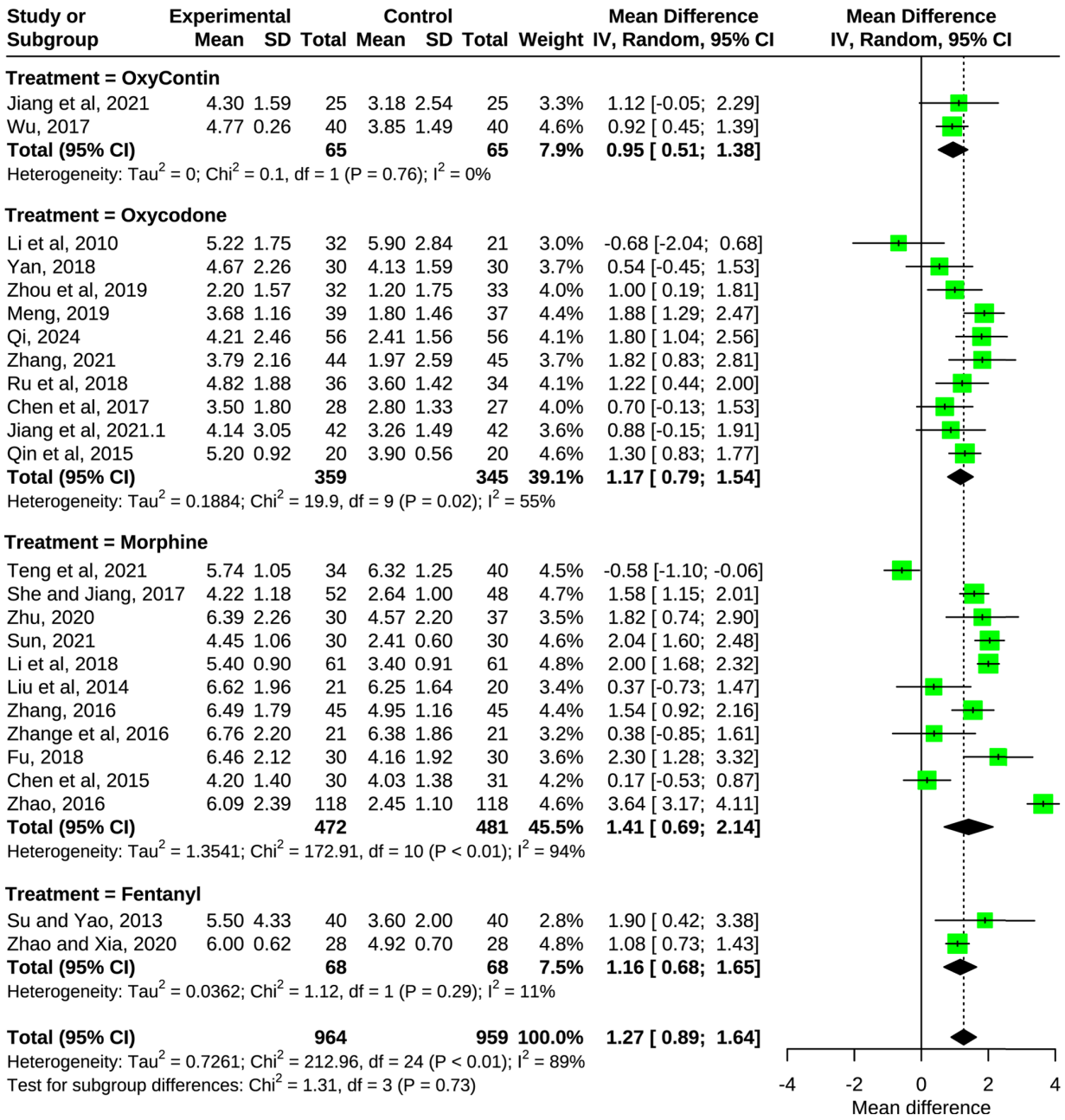

Figure 4. Forest plot of gabapentin combined with opioids compared with opioids alone for numerical rating scale score outcomes. IV, inverse-variance.

application of oxycodone hydrochloride controlled-release tablets combined with gabapentin in the treatment of neuropathic cancer pain was more effective compared with that of oxycodone hydrochloride controlled-release tablets alone (91.67 vs. 70.83%). However, it is important to note that some individual studies (20,32) have reported less pronounced benefits or no significant differences, which may be attributable to variations in study populations, treatment protocols or methodological limitations.

The high heterogeneity observed in the present analysis (I^2=88.7%) warranted comprehensive subgroup and sensitivity analyses. The present subgroup analyses revealed that sources of heterogeneity were significantly associated with multiple factors. Study type analysis showed that while both RCTs and NRCTs suggested benefit, RCTs demonstrated more consistent results with lower heterogeneity (I^2=65.0 vs. 96.9%). Sample size analysis indicated that larger studies tended to show greater treatment effects, though with higher heterogeneity, possibly reflecting more diverse patient populations or longer treatment durations in larger trials.

Most notably, treatment regimen analysis revealed marked differences among opioid types. The oxycodone hydrochloride controlled-release tablets subgroup showed the lowest heterogeneity (I^2=0%), suggesting consistent efficacy across studies. By contrast, the morphine subgroup exhibited high heterogeneity (I^2=94.2%), which may be due to several factors. First, different formulations of morphine (immediate-release vs. sustained-release) have different pharmacokinetic profiles and may interact differently with gabapentin. Second, morphine is extensively metabolized to active metabolites (morphine-3-glucuronide and morphine-6-glucuronide) and patient variability in metabolism could lead to inconsistent

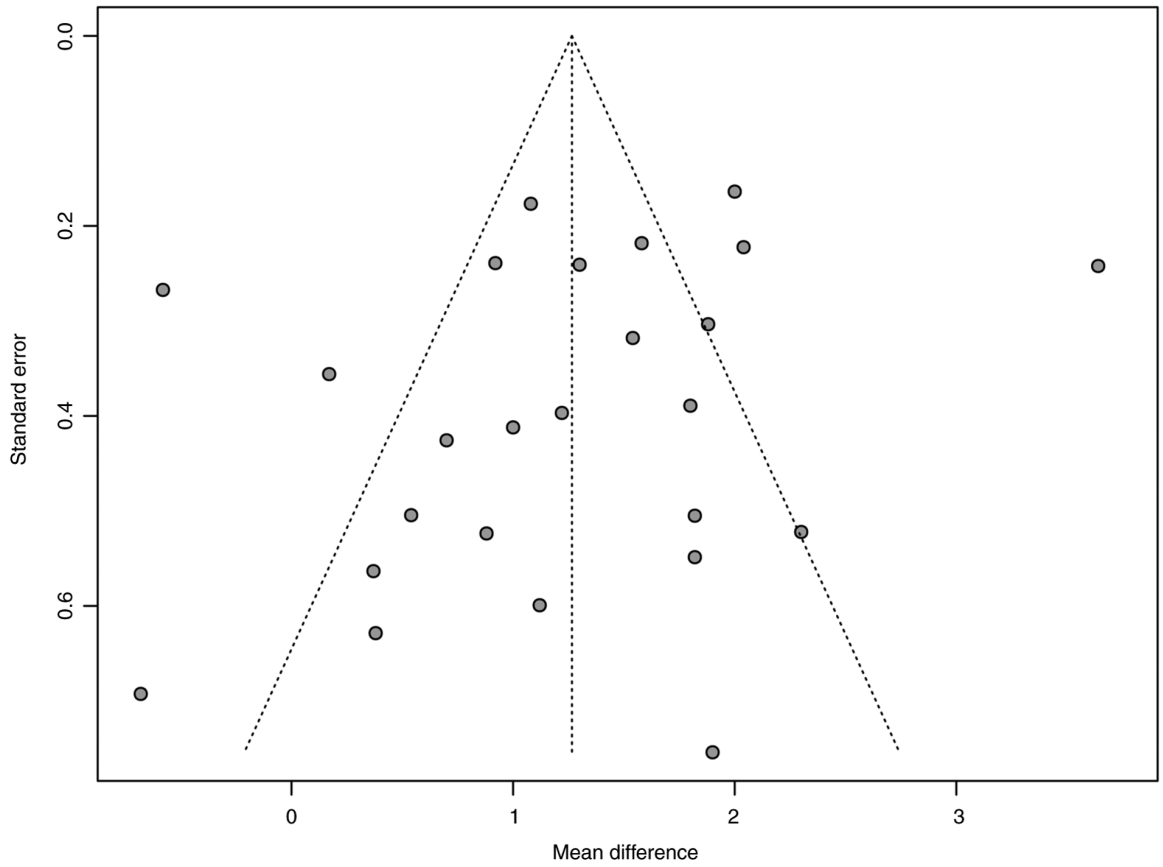

Figure 5. Funnel chart of studies related to patient satisfaction.

responses. Third, morphine studies included more heterogeneous patient populations with varying baseline pain severity and cancer types. When morphine studies were excluded in the present sensitivity analysis, overall heterogeneity notably decreased to 42.8%, while maintaining statistical significance, demonstrating that morphine studies were a notable source of heterogeneity.

The pharmacokinetic and pharmacodynamic properties of different opioids may explain these differences. Oxycodone hydrochloride controlled-release tablets provide stable drug release and consistent blood levels, potentially leading to more predictable interactions with gabapentin. Oxycodone has dual μ- and κ-opioid receptor activity, which may synergize differently with the mechanism of gabapentin. Fentanyl, being highly lipophilic and potent, may exhibit distinct interaction patterns with gabapentin (54,55). These mechanistic differences, combined with variations in study protocols, dosing regimens and patient characteristics, likely contribute to the observed heterogeneity.

The present sensitivity analyses, particularly the leave-one-out analysis, demonstrated that no single study disproportionately influenced the overall results, demonstrating the robustness of the present findings. Analysis restricted to RCTs only provided the highest level of evidence supporting combination therapy, with maintained significance and reduced heterogeneity compared with the overall analysis.

Regarding safety considerations, while the primary focus of the present study was efficacy, the limited reporting of adverse events in the included studies precluded a comprehensive meta-analysis of safety outcomes. This represents a notable limitation, as the clinical decision to use combination therapy must balance efficacy gains against potential increases in adverse effects. Gabapentin is generally well-tolerated, with common side effects including dizziness, somnolence and peripheral edema, which are typically mild and dose-dependent (56). When combined with opioids, there is a theoretical concern for additive central nervous system depression. Future studies should aim to systematically collect and report adverse event data to enable thorough safety assessments. Clinicians using combination therapy should carefully monitor patients for side effects and adjust doses accordingly.

The clinical implications of the present findings are notable. A reduction of ~1.26 points on the NRS represents a meaningful improvement for patients with severe cancer pain. This magnitude of effect may translate to improved function, quality of life and potentially reduce opioid requirements. However, the presence of heterogeneity suggests that response to combination therapy may vary among patients. Factors such as the specific opioid used, baseline pain characteristics (nociceptive vs. neuropathic components), patient age, renal function (affecting gabapentin clearance) and concurrent medications should be considered when implementing combination therapy.

Despite the clinical importance of the present study, a number of limitations should be acknowledged. First, while both RCTs and NRCTs were included to maximize available evidence, the inclusion of NRCTs may introduce selection bias and confounding. However, the present subgroup analysis by study type did not exhibit significant differences and the

RCT-only analysis confirmed the main findings. Second, the languages of the included studies were limited to Chinese and English, which may introduce language bias and miss relevant studies published in other languages. Third, safety could not be adequately assessed due to inconsistent and incomplete reporting of adverse events across studies. Fourth, variations in gabapentin dosing regimens (ranging from 300-1,800 mg daily) and treatment durations across studies may have contributed to heterogeneity, however this could not be fully explored due to insufficient data. Fifth, the mechanisms underlying the apparent differences in efficacy among different opioid types remain incompletely understood and warrant further investigation. Sixth, functional outcomes, quality of life measures and opioid dose reduction were not assessed, which are notable patient-centered outcomes. Finally, most included studies were from China, which may limit generalizability to other populations.

Future research should address these limitations through well-designed, adequately powered RCTs with standardized outcome reporting, including comprehensive adverse event monitoring, functional assessments and quality of life measures. Research should explore optimal dosing strategies for both gabapentin and opioids in combination therapy, identify patient characteristics predictive of treatment response, compare different opioid-gabapentin combinations directly, evaluate long-term efficacy and safety beyond short-term pain control and investigate mechanisms of synergy between gabapentin and specific opioids. Additionally, pharmacoeconomic analyses would help inform clinical decision-making by evaluating the cost-effectiveness of combination therapy.

In conclusion, the results of the present meta-analysis suggest that gabapentin in combination with opioids is more effective compared with opioids alone for the treatment of cancer-related pain from bone metastases, with a clinically meaningful reduction in pain scores. However, notable heterogeneity exists among studies, particularly related to the type of opioid used. In clinical application, physicians need to fully consider the specific conditions of patients, including the type and severity of pain, prior opioid exposure, renal function and potential drug interactions, to develop individualized treatment plans. Careful monitoring for adverse effects is key. The combination of oxycodone hydrochloride controlled-release tablets with gabapentin appears particularly promising due to the low heterogeneity observed in the included studies. Further research is required to optimize treatment protocols and further understand patient-specific factors that predict response to combination therapy.

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Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

HZ, JF and ZT conceived and designed the study, performed the literature review and analyzed and interpreted data. HZ and JF drafted the manuscript. HL, JF and ZT confirm the authenticity of all the raw data. All authors have read and approved the final version of the manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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