

Acupuncture therapies on radiotherapy-induced radiation enteritis: A systematic review and meta-analysis

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ABSTRACT

Background: To assess the efficacy of various acupuncture therapies for treating radiotherapy-induced radiation enteritis (RE). **Materials and Methods:** Relevant studies on RE treatment through acupuncture and moxibustion were collected from medical databases. These studies were meticulously screened based on stringent inclusion and exclusion criteria. Their methodological quality was evaluated, and data were meta-analysed using Revman 5.3 software. **Results:** Six studies were included in this analysis. The fixed effect (FE) model revealed a statistically significant difference in the distribution of apparent efficacy between the experimental and control groups [OR = -0.18, 95% CI (-0.25, -0.11), $P < 0.00001$], as well as in the distribution of cure rates [OR = 0.35, 95% CI (0.20, 0.62), $P = 0.0003$]. The FE model also showed a significant difference in Karnofsky Performance Scale (KPS) scores [OR = -6.94, 95% CI (-10.39, -3.48), $P < 0.0001$]. Subgroup analysis for age and gender revealed no significant differences. **Conclusion:** This research model's robustness suggests that acupuncture and moxibustion, when used in combination, are more effective in treating patients with RE than control treatments. This effectiveness is evident in terms of significant effect proportion, cure rates, and KPS scores. These conclusions are consistent across different genders and ages.

INTRODUCTION

According to 2020 statistics, there were 19.3 million new cancer cases and nearly 10 million cancer deaths globally ⁽¹⁾. Radiation therapy (RT), which destroys the structure and function of cells, particularly cancer cells, is used in over 50% of cancer treatments and accounts for 40% of curative treatments ⁽²⁾. However, RT can cause toxic side effects to healthy tissues, such as radiation enteritis (RE) ⁽³⁾. The incidence of RE in patients receiving pelvic radiation therapy (for cancers such as cervical, endometrial, ovarian, prostate, rectal, and bladder) ranges from 50-70%. Despite this, studies on safe radiation doses for RE are scarce, making its prevention challenging ^(4, 5). Patients with RE often experience intestinal mucosal epithelial cell damage, leading to pathophysiological changes like edema, capillary dilatation, and inflammatory infiltration ⁽⁶⁾. The rise in radiotherapy for malignant tumors has consequently increased the incidence of RE ⁽⁷⁾. Early RE symptoms, typically appearing within three months' post-treatment, include nausea, abdominal pain, distension, and bloody stools ⁽⁸⁾. Late-onset RE,

occurring three months or more after radiotherapy, is characterized by irreversible intestinal histopathologies such as mucosal atrophy, vascular sclerosis and progressive intestinal wall fibrosis ⁽⁹⁾. Severe delayed RE can lead to complications like intestinal obstruction, tube formation, or perforation ⁽¹⁰⁾. RE not only affects patients' quality of life but may also necessitate alterations or interruptions in treatment plans, thereby impeding effective tumor control. Thus, selecting suitable and effective RE treatment modalities is an urgent clinical need.

Modern RE treatments include drug therapy, nutritional support, physiotherapy, and surgical intervention ⁽¹¹⁾. Pharmacological treatments aim to reduce inflammation, control diarrhea, and promote tissue repair ^(11, 12). Nutritional support through oral or intravenous nutrient supplementation plays a crucial role in treating patients with RE, aiding in reducing malabsorption and ameliorating weight loss. In cases of complex or severe RE, surgical interventions, such as the removal of necrotic tissue and repair of intestinal structures, may be necessary ⁽¹³⁾. Acupuncture, as a physical therapy modality, promotes the healing and repair of intestinal tissues

and mitigates the inflammatory response ⁽¹⁴⁾. Moreover, compared to drug therapy, acupuncture is often considered safer, attributable to its potential to minimize drug-induced side effects ⁽¹⁵⁾. Recent years have seen a surge in Chinese medicine studies on RE. However, the majority of these studies are descriptive, with a notable dearth of clinical randomized controlled trials (RCTs) featuring rigorous standardization. The limited sample sizes in existing RCTs hinder effective demonstration of acupuncture's efficacy in treating RE. This study addresses this gap by reviewing published RCTs on acupuncture for RE, following the systematic evaluation methodology of the Cochrane Collaboration. A meta-analysis using Revman5.3 software was conducted to objectively evaluate the efficacy of acupuncture for RE. This study is pioneering in verifying the efficacy and safety of acupuncture in treating RE patients through literature analysis. It aims to compare treatment protocols most likely to improve patient prognoses, thereby offering clinical treatment protocol references.

MATERIALS AND METHODS

2.1 Writing principles and registration

This study adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines and was registered with INPLASY (registration no.). The records of this study have been published on inplasy. com: INPLASY2023110067. DOI number is 10.37766/inplasy2023.11.0067.

As this study constitutes a secondary analysis, it does not require patient and public information and thus does not necessitate an ethical review. The results of this study will be disseminated through peer-reviewed publications, journals and scholarly communication.

2.2 Study population and inclusion and exclusion criteria

The literature sources for this study include publicly available RCTs or semi-randomized controlled trials (CCTs) in any language. Included clinical studies are those with abstracts providing sufficient data for analysis but lacking full publication. Studies were included if they met the following criteria: ⁽¹⁾ Randomized controlled trials published in peer-reviewed journals, ⁽²⁾ Individuals diagnosed with RE or cancer patients undergoing radiotherapy regardless of the type of cancer; ⁽³⁾ Experimental group receiving various forms of acupuncture treatment such as moxibustion, electro-acupuncture (EA), acupressure, acupressure injections (AI), acupressure poultices (AP), transcutaneous electrical stimulation (TEN) with or without medications; ⁽⁴⁾ Control group comprising

placebo, usual care, and medications; ⁽⁵⁾ Studies reporting at least one outcome such as RE cure rate, treatment efficacy rate, or specific outcome indicators (KPS scores). Exclusion criteria included: ⁽¹⁾ duplicate publications; ⁽²⁾ studies duplicating data or with incomplete data, or multiple studies from the same center with overlapping data, selecting only the most recent; ⁽³⁾ conference abstracts, case studies, or literature lacking relevant data; ⁽⁴⁾ studies on multiple treatment modalities; and ⁽⁵⁾ literature not available in its original form.

2.3 Interventions

The interventions for the treatment group included acupuncture treatment alone, acupuncture and drug combination treatment, and acupuncture combined with other modalities. The control group received blank, placebo, or basic western medicine treatment exclusively. In cases where the treatment group received a combination of acupuncture and conventional basic western medicine, the control group was administered the same dosage, method of use, and duration of basic western medicine treatment.

2.4 Outcome indicators

Outcomes must encompass the primary measure: clinical efficacy; and may include secondary indicators: symptom scores, incidence of adverse reactions, recurrence rate, etc.

2.5 Retrieval and data organization

2.5.1 Search strategy

As of February 2023, we searched PubMed, Embase, and Web of science databases with no language restrictions. We searched the databases for a combination of indexed and free text terms, including "radiation enteritis" "acupuncture therapy". We modified the limitations of the search terms each database. We also browsed references to classic review articles and the World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP; apps.who.int/trial search/) in an attempt to supplement the studies. Literature management was carried out using endnote software.

2.5.2 Literature screening and data extraction

Literature titles and abstracts were first read by 2 researchers to eliminate literature that did not meet the criteria, and the full text was read independently, and literature that might meet the criteria was included after the initial screening; uncertain literature was discussed and a decision was made to include it or not. If disagreement remained, a third researcher adjudicated. Extracts included: time of publication and authors of the included studies, basic clinical characteristics of the included subjects, parameter settings of the test and control groups, outcome indicators, and adverse reactions or adverse events. In the case of multi-arm studies, only data

that met the inclusion criteria and were relevant to the purpose of this study were extracted. If there was disagreement on data extraction, the extraction was discussed again until the opinions were united, and if disagreement still existed, a third investigator adjudicated.

2.5.3 Literature quality assessment

Two independent researchers used the Cochrane Collaboration risk of bias tool to evaluate the quality of the articles in the included RCTs. The Cochrane risk of bias was mainly evaluated in the following aspects: blinding of investigators and subjects, blinding of study outcomes, generation of randomized sequences, concealment of the allocation scheme, completeness of the outcome data, selective reporting of findings, and other biases, etc. The results of the evaluation included: low risk of bias, low risk of bias, low risk of bias, low risk of bias, low risk of bias. Outcomes included: low risk of bias, unclear risk of bias, and high risk of bias. Again, if two investigators disagreed on the quality assessment, a third investigator adjudicated.

2.5.4 Statistical analyses

Data were analyzed using RevMan software (version 5.4, Cochrane Collaboration). Pain scores (VAS or NRS) as continuous variables were expressed as Mean Difference (MD) and 95% confidence intervals (CI). Data of the same type were pooled using Standardized Mean Difference (SMD). When the literature data existed only in graphical form, we first sent an email to the original authors to request the data, and if no valid response was received, the data were extracted using the Getdata graph digitizer software. The extraction process was repeated three times and the mean value was taken for inclusion in the final analysis. When the literature data were in the form of non-standard mean (standard deviation), we converted them to mean (standard deviation) by using the "calculator" function of RevMan software and the online website (<https://www.math.hkbu.edu.hk/~tongt/papers/median2mean.html>) for the conversion⁽¹²⁾. The median (range)-mean (SD) data were converted by checking whether the data were skewed or not, and if there was no obvious skewness in the distribution.

Data were analyzed using RevMan software (version 5.4, Cochrane Collaboration). KPS was expressed as a continuous variable using Mean Difference (MD), and the incidence of adverse reactions was expressed as a dichotomous variable using Relative Ratios (RR), which were statistically assessed using 95% Confidence Interval (CI), with $P < 0.05$ being statistically significant. Statistically significant. Heterogeneity was tested using the chi-square test at a level of $P = 0.1$; if $P \leq 0.1$ and $I^2 > 50\%$ indicated that there was significant heterogeneity among the data, the random effects model was used; on the contrary, if $P > 0.1$ and $I^2 \leq$

50% indicated that the heterogeneity was not significant or there was no heterogeneity, the fixed effects model was used. On the other hand, if $P > 0.1$ and $I^2 \leq 50\%$ indicating insignificant heterogeneity or no heterogeneity, the fixed effects model was used.

2.5.5 Sensitivity analyses and subgroup analyses

Sensitivity analyses allow the researcher to assess the stability of the results by trying different methods of analysis. This may include the use of different effects models (fixed effects models and random effects models). Where there is significant heterogeneity in the study data, subgroup analyses should be conducted to explore the sources or causes of heterogeneity, and where there are no obvious reasons for heterogeneity, random effects models are used for the analyses. Further analyses may be conducted to test whether the results of meta-analysis are stable and reliable.

2.5.6 Publication bias

In this study, an inverted funnel plot was used to analyze the publication bias of the included studies. The sample size was taken as the vertical coordinate of the funnel plot and the effect size was taken as the horizontal coordinate to draw the plot; when the left and right sides of the funnel plot were basically symmetrical, it indicated that there was no obvious publication bias, while left and right sides were asymmetrical, it indicated that there might be publication bias, and it was requested that the funnel plots be drawn to analyze the literature of the meta-analyses when it equaled to 8 articles, and no analysis was done when there were less than 8 articles. When the number of documents required for meta-analysis is equal to 8, the funnel plot should be drawn for analysis.

RESULTS

3.1 Results of literature search

A total of 1,449 articles were obtained from the initial review, and by reading the references of clinical studies and classic high-scoring reviews, we included 14 additional studies. After removing 897 duplicates, abstracts and titles were read for the remaining 552 articles. After excluding 477 papers that clearly did not meet the inclusion and exclusion criteria, the remaining 75 articles were read in full. Sixty-nine articles with incomplete information and data were excluded, resulting in the inclusion of six articles for this analysis.

3.2 Basic characteristics of the included studies

Of the six studies included in this analysis, publication dates ranged from 2007 to 2023 and included 415 patients. The basic characteristics of the included literature are shown in table 1. All of the literature referred to ethnicity and interventions and

had a clear basis for grouping. In all of the literature, the intervention in the trial group was acupuncture,

and the intervention in the control group included medication (Chinese or Western) and enemas.

Table 1. Basic characteristics of the included literature.

Item	Radiotherapy information	Tumor types	Experimental group	Control group	Treatment time (wk.)	Acupuncture points	Acupuncture time (min)
Sun 2023 ⁽¹⁷⁾	/	Cervix cancer Rectum cancer	Acupuncture + Drug Retention Enema	Medicated Retained Enema	8	ST25 ST39 BL21 BL20 CV4 ST36	5
Dong 2020 ⁽¹⁸⁾	Cumulative absorbed dose to intestine $\geq 40\text{Gy}$	Lower Ab-dominal Tumor	Acupuncture + Drug Retention Enema + Chinese Herbs	Medicated Retained Enema + Chinese Herbs	2	ST25 CV4 ST39 ST36 BL20 BL21	5
Ji 2008 ⁽¹⁹⁾	External radiotherapy + intracavitary treatment, whole pelvic field 25~30Gy, four fields 20~25Gy, 5 times/week, intracavitary treatment point A total dose 3540Gy, 1 time/week	Cervical cancer	Acupuncture + Drug Retention Enema	Drug Retention Enema	2	ST25 CV4 ST39 ST36 BL20 BL21	5
Li 2007 ⁽²⁰⁾	Intracavitary radiation (extracorporeal irradiation), each dose 5~8 Gy, 2 times/week, the total amount of intracavitary radiation is 50~70 Gy	Rectal cancer	Acupuncture + Em-munition	Emmunion	2	ST25 CV4 ST39 ST36 BL20 BL21	5
Pan 2021 ⁽²¹⁾	/	Cervix cancer Endometrial cancer Prostate cancer Bladder cancer	Acupuncture + Western Medicine	Western medicine	2	CV6 CV6 ST36 ST36 SP12 SP12	10
Lin 2013 ⁽²²⁾	/	Rectal cancer Colon Cancer Bladder Cancer Gynaecological Tumors	Acupuncture + conventional treatment	conventional treatment	4	RN12 CV6 CV4 BL25 BL27	20

3.3 Literature quality assessment

One of the six included studies did not mention the random sequence generation method and the remaining studies mentioned the random sequence generation method. Four studies mentioned allocation scheme concealment and two studies did not explicitly mention it. Three studies reported full study results. One study indicated other outcome bias and the remaining 5 studies did not mention other outcome bias. The risk of bias evaluation of the included literature is shown in figure 1 (a, b).

Comparison of outcome indicators and sensitivity analyses

Effective events (cure + improvement)

Comparing the distribution of the number of apparent efficacy in the experimental and control groups, the FE results showed that there was a statistically significant difference between the distribution of the number of apparent efficacy in the experimental and control groups [OR = -0.18, 95% CI (-0.25, -0.11), $I^2 = 0 \leq 50\%$, $P < 0.00001$] (figure 2a). RE results showed that there was a statistically significant difference between the distribution of the number of apparent efficacy in the experimental and control groups [OR = -0.17, 95% CI (-0.24, -0.10), $I^2 = 0 \leq 50\%$, $P < 0.00001$] (figure 3a), statistically

significant difference [OR = -0.17, 95% CI (-0.24, -0.10), $I^2 = 0 \leq 50\%$, $P < 0.00001$] (figure 2b). We used a fixed-effects model (FE) and a random-effects model (RE) for sensitivity testing of meta-analysis, respectively. The results of the two models were consistent in terms of broad trends, indicating that our main findings are relatively robust.

Cure Events

Comparing the distribution of the number of cures in the experimental and control groups, the FE results showed a statistically significant difference in the distribution of the number of cures in the experimental and control groups [OR = 0.35, 95% CI (0.20, 0.62), $I^2 = 0 \leq 50\%$, $P = 0.0003$] (figure 3a). The RE results showed a statistically significant statistical difference [OR = 0.35, 95% CI (0.20, 0.63), $I^2 = 0 \leq 50\%$, $P = 0.0004$] (figure 3b). We used a fixed-effects model (FE) and a random-effects model (RE) for sensitivity testing of meta-analyses, respectively. The results of the two models were consistent in terms of broad trends, indicating that our main findings are relatively robust.

KPS score

Comparing the distribution of KPS scores in the experimental and control groups, the FE results

showed that there was a statistically significant difference in the distribution of KPS scores in the experimental and control groups [OR = -6.94, 95% CI (-10.39, -3.48), $I^2 = 0 \leq 50\%$, $P < 0.0001$] (figure 4a). The RE results showed that the KPS scores in the experimental and control groups There was a statistically significant difference in the distribution [OR = -6.94, 95% CI (-10.39, -3.48), $I^2 = 0 \leq 50\%$, $P < 0.0001$] (figure 4b). We used a fixed-effects model (FE) and a random-effects model (RE) for sensitivity testing of meta-analysis, respectively. The results of the two models were consistent in terms of general trends, indicating that our main findings were relatively robust.

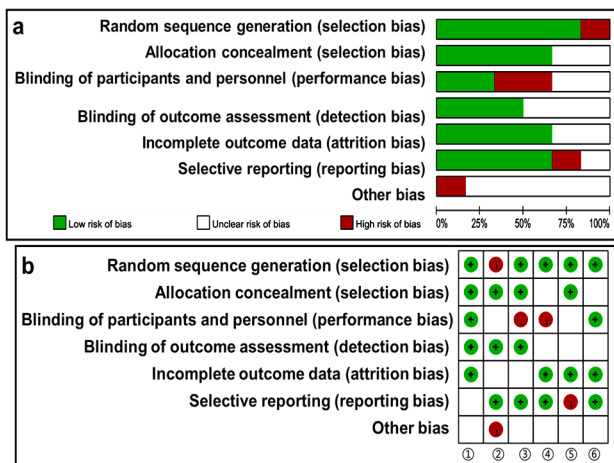


Figure 1. Article quality assessment charts (a. Risk of bias chart: review authors' judgment of the risk of bias for each item, expressed as a percentage of all included studies; b. Risk of bias summary: review authors' judgment of the risk of bias for each included study).

Note: Random sequence generation (selection bias): random sequence generation (selection bias); Allocation concealment (selection bias): allocation concealment (selection bias); Blinding of participants and personnel (performance bias): blinding of patients, trial personnel (implementation bias); Blinding of outcome assessment (detection bias): blinding of outcome assessors (measurement bias); Incomplete outcome data (attrition bias): Incomplete outcome data (follow-up bias); Selective reporting (reporting bias): selective reporting (reporting bias); Other bias: other bias; Low risk of bias; Unclear risk of bias (Low risk of bias; Unclear risk of bias; High risk of bias. ①: 17Sun 2023; ②: 21Pan 2021; ③: 22Lin 2013; ④: 20Li 2007; ⑤: 19Ji 2008; ⑥: 18Dong 2020

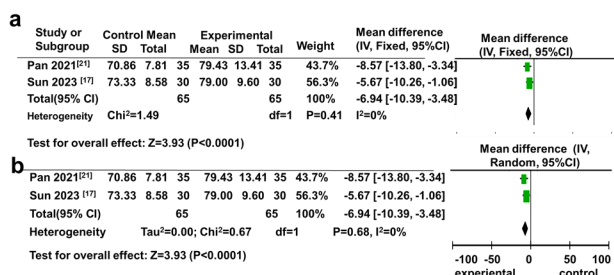


Figure 4. Forest plot of KPS scores in RE and FE (a. Forest plot of KPS scores in FE; b. Forest plot of KPS scores in RE) (CI, Confidence Interval; RE, Fixed Effects; RE, random effects).

3.5 Subgroup analysis

The results of subgroup analysis of age (FX) showed that there was no statistically significant difference in the distribution of age in the experimental and control groups [OR = 1.04, 95% CI (-0.57, 2.64), $I^2 = 0 \leq 50\%$, $P = 0.21$] (figure 5a). The results of the subgroup analysis (FX) of gender showed that there was no statistically significant difference in the distribution of gender in the experimental and control groups [OR = 0.89, 95% CI (0.56, 1.41), $I^2 = 0 \leq 50\%$, $P = 0.62$] (figure 5b). This suggests that our main conclusions remain consistent across these subgroups, both across age levels and across gender.

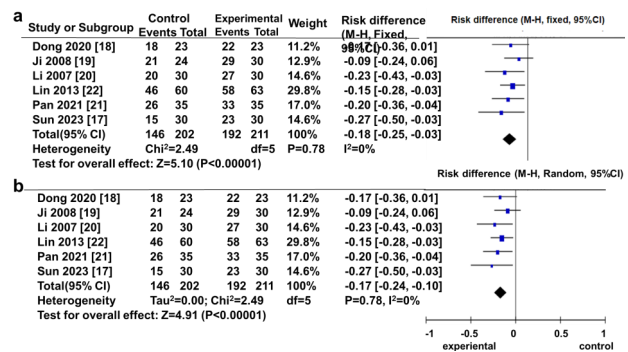


Figure 2. FE and RE forest plots for dominant events (a. Forest plot of dominant events in FE; b. Forest plot of dominant events in RE) (CI, Confidence Interval; RE, Fixed Effects; RE, random effects).

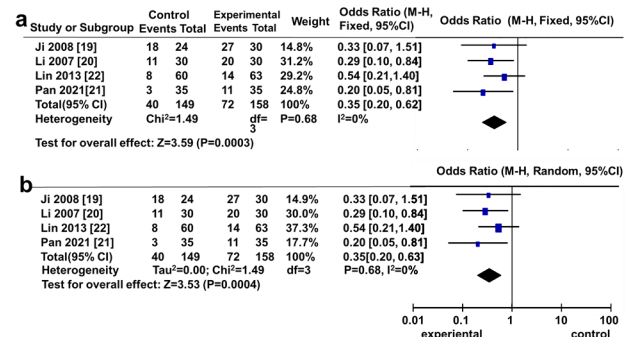


Figure 3. Forest plot of RE and FE for cure events (a. Forest plot of cure events in FE; b. Forest plot of cure events in RE) (CI, Confidence Interval; RE, Fixed Effects; RE, random effects).

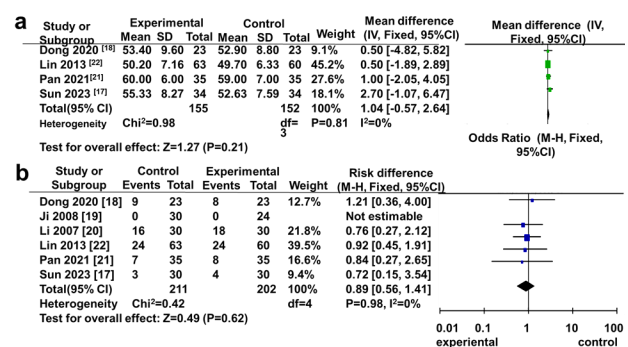


Figure 5. Forest plots for subgroup analyses (a. Age in FE model; b. Gender in FE model). (CI, Confidence Interval; RE, Fixed Effects; RE, random effects)

DISCUSSION

This study represents the first meta-analysis evaluating the effectiveness and safety of acupuncture for radiation enteritis (RE). Our results indicate that RE patients receiving acupuncture in conjunction with medication exhibit enhanced clinical efficacy and model robustness compared to control groups, with consistent findings across different genders and ages.

Our analysis reveals that acupuncture, when integrated with medication for RE treatment, significantly outperforms medication-only approaches. This underscores acupuncture's potential as a complementary therapy in the management of a specific disease or symptom. Zang *et al.* ⁽²³⁾ observed in 60 RE patients that acupuncture plus medication was more effective than medication alone, particularly in improving fecal routine tests (red blood cell count and occult blood) and reducing adverse events. In contrast, Cao *et al.* ⁽²⁴⁾ analyzed 13 radiotherapy (RT) studies and found that glutamine-based pharmacological treatment did not alleviate RE symptoms such as abdominal cramps and bloody stools. This contrasts with Zang *et al.*'s findings, suggesting the need for further clinical trials to validate the efficacy of acupuncture combined with pharmacological treatments. Given the limited research on acupuncture for RE, literature analysis remains a crucial tool for evaluating its effectiveness. Wu *et al.* ⁽²⁵⁾ concluded a network meta-analysis on post-radiation adverse effects, concluding that acupuncture combined with medication surpasses other treatments for RE. Yang *et al.* ⁽⁴⁾ assessed 60 guidelines for RE treatment, highlighting endoscopic treatment as a more established method but also pointing out the lack of comprehensive, high-quality research on RE diagnosis and treatment.

The therapeutic potential of acupoint stimulation for RE is not well-established, with existing clinical studies varying in quality and quantity. Further in-depth research is necessary to elucidate the mechanisms and efficacy of acupoint therapy. The acupoints selected in the studies under review are traditionally used in Chinese medicine to regulate the spleen and stomach, improve qi and blood flow, and alleviate abdominal discomfort. Some studies propose that acupoint stimulation might modulate the immune system and reduce inflammation ⁽²⁶⁻²⁹⁾, although these studies mainly address chronic inflammatory diseases rather than RE specifically. Acupoint stimulation has also been explored for pain relief ⁽³⁰⁻³²⁾ and improving the quality of life in cancer rehabilitation ^(32, 33), yet these studies don't directly pertain to RE. Our research focuses on evaluating the effectiveness of acupoint stimulation combined with other treatments in RT, thereby potentially enriching the medical evidence on its therapeutic value for RE.

The implementation and broader adoption of

acupuncture in RE treatment remain challenging. Some researchers have focused exclusively on the efficacy of drugs and surgery in treating RE, omitting acupuncture from their therapeutic regimens. L Loge *et al.* ⁽³⁴⁾ recommend maintenance nutrition and bowel resection for RE that fails to improve. Zimmerer *et al.* ⁽³⁵⁾ suggest that probiotics may reduce RT incidence to some extent. In addition, Qin *et al.* ⁽³⁶⁾ found that resveratrol could mitigate oxidative stress and apoptosis in RE by modulating antioxidant enzymes and p53 acetylation in mice, although high-quality evidence in the RE population is still lacking. Only one included study in our analysis reported that the acupuncture and drug combination group showed better symptom score improvement than the control group. Other studies focused on overall treatment effects, concluding that the combined approach of acupuncture and RT treatment merits further exploration and promotion.

Meanwhile, most current studies on radiation enteritis (RE) focus primarily on with less clarity on the radiation doses that trigger RE, making it challenging to establish safe radiation thresholds. Consequently, RE prevention becomes critically important. Wang *et al.* ⁽³⁷⁾ identified hemoglobin levels, albumin, and total T-lymphocyte count as risk factors for radiolucent enterocolitis in cervical cancer patients undergoing radiotherapy through a retrospective study. Other factors, such as excessive radiation and underlying cardiovascular disease, also predispose patients to RE. We advocate for the promotion of a healthy lifestyle and increased public awareness of these risk factors to potentially reduce RE incidence, thereby enhancing quality of life and alleviating the psychological impact on patients and their families.

This study has some limitations. The meta-analysis included only six studies, limiting the scope of the overall evaluation. Furthermore, the varying quality of these studies may affect the reliability of the synthetic results. Study heterogeneity also posed challenges to the consistency and interpretation of findings. Due to insufficient data, in-depth subgroup analyses to investigate potential influences were not feasible. Given these constraints, caution is advised in interpreting the results, and future research should aim to enlarge the sample size and enhance study quality for a more comprehensive assessment. Additionally, the inclusion of patients over 18 years in second-generation studies indicates that RE predominantly affects adults, yet there is a scarcity of research on RE outcomes in children. Considering the unique physical, psychological, and environmental characteristics of children, their response to treatment may differ from adults. Therefore, investigating the effectiveness of acupuncture in pediatric RE patients, particularly those with adverse reactions to medication or requiring personalized treatment, is clinically significant.

CONCLUSION

The robustness of this research model suggests that acupuncture and moxibustion, when combined, treat RE more effectively than the control treatment, in terms of both significant effect proportions, cure rates, and Karnofsky Performance Status (KPS) scores. Our conclusions are consistent across different genders and ages.

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Ethical consideration: Not applicable.

Author contribution: H.G and J.Z conceived and designed the study; Hq. Y and L.Y conducted the literature search and data collection; Hq. Y analyzed the data; L.Y and H.G wrote the paper. H.G and Hq. Y reviewed and edited the manuscript. All authors read and approved the final manuscript.

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