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Review Article

Efficacy of multimodal symptom management strategies for chemotherapy-induced nausea and vomiting in gynecologic cancer: a meta-analysis

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Abstract: This meta-analysis aimed to evaluate whether multimodal symptom management improves chemotherapy-induced nausea and vomiting (CINV) among patients with gynecologic cancer across acute, delayed, and overall treatment phases. We systematically searched major electronic databases and trial registries for eligible English-language studies from database inception to the final search date. Included studies enrolled female patients with gynecologic malignancies receiving chemotherapy and evaluated multimodal symptom management strategies for CINV control. Two independent researchers screened literature records and extracted data using a standardized form. Risk of bias of included studies were evaluated based on standard evaluation domains. All quantitative analyses were performed with a random-effects model. Dichotomous outcome data were pooled to calculate risk ratios (RRs) and 95% confidence intervals (CIs). Predefined subgroup analyses were conducted for acute, delayed, and overall phases. We assessed statistical heterogeneity via Cochran's Q test and I^2 statistics, and evaluated publication bias through visual inspection of funnel plots. Multimodal symptom management strategies yielded no significant improvements in overall complete CINV control (RR 1.02, 95% CI: 0.86-1.21), acute complete CINV control (RR 0.96, 95% CI: 0.80-1.15), or delayed complete CINV control (RR 0.94, 95% CI: 0.77-1.14), with low to no statistical heterogeneity across these analyses. Likewise, no significant benefit was observed for overall no-vomiting events (RR 1.46, 95% CI: 0.75-2.83) or overall no-significant-nausea events (RR 1.59, 95% CI: 0.71-3.54), with substantial heterogeneity detected for both outcomes. Notably, multimodal interventions significantly increased the rates of acute no-vomiting events (RR 1.99, 95% CI: 1.42-2.80) and acute no-significant-nausea events (RR 2.05, 95% CI: 1.43-2.94), with no detectable heterogeneity. Conclusion: Multimodal symptom management strategies offer tangible clinical benefits for acute CINV control in gynecologic cancer patients, especially in the prevention of vomiting and clinically significant nausea. These strategies show no obvious superiority for delayed and overall CINV comprehensive control.

Keywords: Gynecologic cancer, chemotherapy-induced nausea and vomiting, multimodal symptom management, meta-analysis, supportive cancer care

Introduction

Despite substantial advances in antiemetic prophylaxis over the past two decades, chemotherapy-induced nausea and vomiting (CINV) remains one of the most common and unpleasant side effects of systemic antitumor chemotherapy [1-3]. Uncontrolled CINV impairs patients' dietary intake, daily functioning, and overall quality of life. It also reduces patient adherence to scheduled chemotherapy regimens, ultimately compromising treatment response [4, 5]. As an essential component of comprehensive oncology treatment, symptom management is critical to optimizing clinical outcomes and patient quality of life in supportive cancer care.

Patients with gynecologic malignancies are a high-risk population susceptible to CINV [6-8].

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Their high susceptibility stems from multiple inherent and treatment-related risk factors. Female gender is an established individual risk factor for CINV, and gynecologic cancer patients frequently receive platinum-based chemotherapy regimens (cisplatin or carboplatin), often combined with paclitaxel, further elevating CINV risk. Although current international clinical guidelines recommend standard prophylactic regimens combining 5-hydroxytryptamine-3 receptor antagonists, neurokinin-1 receptor antagonists, dexamethasone, and the newly recommended olanzapine to prevent CINV, the management of nausea - particularly delayed nausea - remains challenging. Effective interventions for delayed CINV are still an unmet clinical need in this patient group [9].

In clinical practice, CINV management for gynecologic cancer is no longer limited to conventional pharmacological prophylaxis. A growing number of studies have focused on multimodal symptom management interventions. These interventions include optimized combined antiemetic regimens and integrative non-pharmacological approaches such as acupuncture, acupressure, and auricular acupressure, as well as other supportive care measures [13-18]. Multimodal strategies target multiple biological and behavioral pathways associated with CINV, which may produce incremental therapeutic benefits compared with single conventional antiemetic treatment. However, existing studies vary greatly in study design, intervention types, chemotherapy treatment settings, and outcome definitions. The clinical value of multimodal interventions in improving CINV-related outcomes has not been systematically clarified.

Existing clinical studies focusing on gynecologic cancer have yielded inconsistent findings regarding multimodal CINV management. Several small studies have confirmed favorable effects of multimodal interventions, especially in controlling acute vomiting and improving patient-reported nausea symptoms [10, 11]. In addition, other study have only observed marginal or non-reproducible benefits [12]. The available evidence is derived from diverse study types, including randomized controlled trials, prospective cohort studies, and retrospective comparative studies, and thus, it is hard to draw definitive conclusions. To date, no systematic meta-analysis has quantitatively evaluated the efficacy of multimodal symptom management for acute, delayed, and overall CINV control in gynecologic cancer patients.

Against this background, we conducted a systematic review and meta-analysis to comprehensively assess the clinical efficacy of multimodal symptom management interventions for CINV in gynecologic cancer. We synthesized evidence from published studies focusing on important clinical outcomes, such as complete CINV control, no vomiting, and no major nausea at acute, delayed, and overall treatment stages. We also systematically evaluated the methodological quality and consistency of the current evidence base.

Methods

Search strategy

Extensive literature search was conducted to identify studies evaluating multimodal symptom management strategies for CINV in gynecologic cancer patients. We searched major electronic bibliographic databases and clinical trial registries from database inception to the final search date. The search terms combined controlled vocabulary and free-text terms, covering gynecologic cancer, chemotherapy-induced nausea and vomiting, CINV, multimodal symptom management, antiemetic therapy, acupuncture, acupressure, and other supportive care interventions. Search strategies were adaptively optimized for each database, with the full search list presented in **Appendix S1**. We also manually screened the reference lists of eligible original articles and relevant reviews to retrieve additional qualified studies.

All retrieved records were imported into reference management software, and duplicates were eliminated before screening. We only included English-language studies. This systematic review was conducted in strict accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines and was prospectively registered with the International Prospective Register of Systematic Reviews (PROSPERO; Registration No. CRD420261444259).

Table 1. Inclusion criteria (PICO)

Domain	Criteria
Population	Women with gynecologic cancer undergoing chemotherapy
Intervention	Multimodal symptom management strategies for CINV
Comparator	Standard care, placebo, single-modality therapy, or alternative intervention
Outcomes	Complete response, complete control, no vomiting, no significant nausea, acute/delayed CINV incidence, nausea severity, rescue antiemetic use, quality of life
Study design	Randomized and non-randomized primary clinical studies with extractable data

Inclusion and exclusion criteria

Inclusion criteria: (1) study participants were female patients with pathologically confirmed gynecologic malignancies undergoing chemotherapy; (2) the primary outcome focused on acute or delayed CINV control for supportive cancer care; (3) the intervention was a multimodal symptom management strategy, defined as combined pharmacological antiemetic prophylaxis, integrated non-pharmacological interventions, single or combined conventional antiemetic care, or other multimodal supportive care regimens; (4) the study reported extractable quantitative data for at least one clinical outcome, such as complete CINV response, complete CINV control, no vomiting, no significant nausea, nausea severity, rescue antiemetic usage, or quality of life; (5) the study was an original English-language clinical research article. (6) the study designs included randomized and non-randomized comparative studies, prospective and retrospective clinical studies with sufficient available outcome data (**Table 1**).

Exclusion criteria: studies focusing on non-gynecologic cancer populations, studies unrelated to CINV, studies adopting single-model interventions rather than multimodal strategies, non-original research (eg, reviews, editorials, conference commentaries, or guidelines), studies with insufficient data for quantitative synthesis, duplicate reports, non-English articles, and studies focusing on postoperative nausea and vomiting rather than CINV.

Data extraction

A standardized, piloted form created a priori to conduct this review was used to extract data. The information collected on each of the eligible studies was: first author, publication year, study country, study design, sample size, patient baseline characteristics, chemotherapy regimen, details of interventions and control measures, outcome definitions, and quantitative data of all predefined endpoints.

We prioritized the extraction of CINV-related outcomes assessed at acute, delayed, and overall stages, including complete response, complete control, no vomiting, no severe nausea, nausea severity, rescue antiemetics, anorexia, and quality of life. For studies reporting multiple outcome types, dichotomous data were prioritized for quantitative synthesis, and continuous outcomes were supplemented when available.

Two independent researchers completed data extraction. Any discrepancies were resolved through group discussion, and a third senior researcher was consulted for final adjudication when necessary to ensure the accuracy and consistency of the final analytical dataset.

Statistical analysis

All quantitative synthesis analyses were performed based on dichotomous outcome data. We calculated pooled RRs with 95% CIs to evaluate the efficacy of interventions. Considering the inherent clinical and methodological heterogeneity across included studies, a random-effects model was adopted for all pooled analyses.

The predefined efficacy outcomes covered acute, delayed, and overall indicators, including complete CINV control, no-vomiting events, and no-significant-nausea events. Cochran's Q test and I^2 statistics were used to assess statistical heterogeneity; a higher I^2 value indicated greater inter-study inconsistency. Forest plots were created to show individual study effects and pooled estimates. Funnel plot symmetry was visually inspected to evaluate potential publication bias.

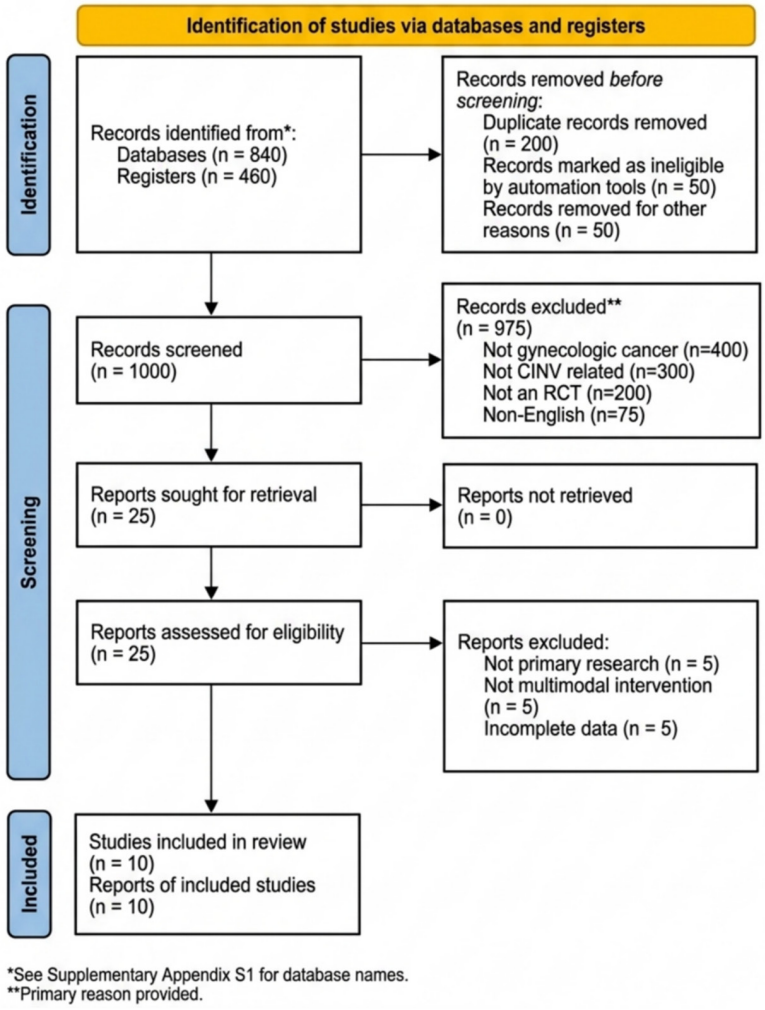

Figure 1. Flow chart.

Results

Study selection

The study selection process is summarized in the PRISMA flow diagram (**Figure 1**). The initial systematic search identified 1,300 records, including 840 records from electronic databases and 460 from clinical trial registers. Before title and abstract screening, 300 records were removed, including 200 duplicates, 50 ineligible records screened by automated tools, and 50 removed for other reasons. A total of 1,000 records proceeded to preliminary screening.

Of these 1,000 records, 975 were excluded during title and abstract screening. The primary exclusion reasons were irrelevant gynecologic cancer populations (n = 400), non-CINV-related research (n = 300), non-randomized controlled study designs (n = 200), and non-English publications (n = 75). The remaining 25 full-text articles were retrieved and assessed for eligibility. After full-text evaluation, 15 reports were further excluded due to non-original research types (n = 5), irrelevant multimodal interventions (n = 5), and incomplete extractable outcome data (n = 5). Ultimately, 10 eligible studies were included in the final meta-analysis.

Study characteristics

The 10 included studies [19-28] were published between 2015 and 2023, with cross-regional study settings covering Serbia, Italy, Japan, China, Thailand, and Turkey. The overall evidence base presented obvious methodological heterogeneity, including randomized controlled trials, phase II randomized studies, multinational double-blind randomized trials, prospective observational studies, multi-institutional single-arm phase II studies, pooled prospective cohort analyses, and retrospective comparative studies.

Most studies enrolled female patients with gynecologic malignancies who received platinum-based chemotherapy. The mainstream regimens contained cisplatin or carboplatin, frequently combined with paclitaxel. One study focused on postoperative nausea and vomiting after gynecologic surgery rather than CINV. The included multimodal interventions covered two major categories: pharmacological combined antiemetic regimens and non-pharmacological integrative supportive care. Pharmacological strategies included NEPA combined with dexamethasone, olanzapine-based quadruple antiemetic prophylaxis, and aprepitant/palonosetron/dexamethasone combination regimens. Non-pharmacological interventions involved acupuncture, P6 acupressure, Jiangxia powder

Table 2. Study characteristics

Study	Year	Country	Chemotherapy drugs	Sample size (Treatment/ Control group	Intervention methods	Outcome measure	Study design
Bošnjak 2018 [19]	2018	Serbia	Cisplatin, Carboplatin, Paclitaxel, Epirubicin	97/34	Oral NEPA + Dexamethasone	Complete Response (CR), No Significant Nausea (NSN)	Phase 2/3, Multinational, Randomized, Double-blind
Di Mattei 2020 [20]	2020	Italy	Paclitaxel + Carboplatin (± Bevacizumab)	41/40	Ondansetron + Idrocortisone	Acute & Delayed Nausea (MASCC tool)	Prospective Observational Study
Iihara 2020 [21]	2020	Japan	Carboplatin-based	37/20	Olanzapine 5 mg + NK1RA + 5-HT3RA + DEX	CR, Acute & Delayed CINV	Phase II, Multi-institution, Single-arm
Lin 2022 [22]	2022	China	Platinum + Paclitaxel	50/50	Jiangxia Powder Navel Therapy ± Auricular Point Seed Embedding	Acute & Delayed CINV incidence, KPS, FLIE	Randomized Controlled Trial (RCT)
Ongel 2023 [23]	2023	Turkey	Gynecologic surgery patients	50/52	P6 Acupressure vs. IV Ondansetron	Early PONV scores, Rescue antiemetic use	Prospective, Randomized, Single-center
Rithirangsriroj 2015 [24]	2015	Thailand	Cisplatin-based	30/30	Acupuncture + Standard antiemetics	Delayed CINV CR, Nausea scores	Phase II, Randomized
Shimokawa 2019 [25]	2019	Japan	Paclitaxel + Carboplatin (TC)	153/29	2 vs. 3 antiemetics (5-HT3RA, DEX, ± NK1RA)	Delayed CINV incidence	Prospective Cohort Study, Pooled analysis
Sugimori 2017 [26]	2017	Japan	Cisplatin-based	44/34	Aprepitant + Palonosetron + DEX vs. Palonosetron + DEX	Delayed-phase CR	Phase II, Randomized
Watanabe 2021 [27]	2021	Japan	Paclitaxel + Carboplatin (AUC5-6)	54/52	Aprepitant + Palonosetron + DEX vs. Palonosetron + DEX	CR, Severity of nausea, Anorexia	Retrospective Comparative Study
Liu 2023 [28]	2023	China	Cisplatin-based	50/50	acupuncture + acupoint application vs. acupoint applicatio	Delayed CINV CR, Nausea scores	Retrospective Comparative Study

umbilical therapy (with or without auricular point seed embedding), and acupuncture combined with acupoint application.

Study outcomes varied across eligible articles. The most commonly reported endpoints were complete treatment response, acute and delayed CINV incidence, nausea severity, and absence of significant nausea. Several studies additionally assessed rescue antiemetic usage, anorexia severity, functional status, quality of life, and patient-reported indicators including Karnofsky Performance Status and Functional Living Index-Emesis (**Table 2**).

Risk of bias

The overall risk of bias of included studies was moderate. Most methodological domains were rated as low risk, while several key domains presented notable methodological limitations (**Figure 2**). For randomized study designs, random sequence generation was mostly assessed as low risk, indicating reliable randomization procedures. However, allocation concealment was poorly reported in most studies, leading to a large proportion of unclear risk ratings (**Figure 2A**).

The primary source of high bias risk was the blinding of participants and researchers. Most non-pharmacological interventions (e.g., acupuncture, acupressure) cannot achieve effective blinding, resulting in widespread high performance bias. The blinding of outcome assessment yielded mixed results with both low and unclear risk across studies, suggesting potential inconsistent detection bias. Domains of incomplete outcome data and selective outcome reporting were generally low risk. Residual unclear or high bias mainly originated from observational, retrospective, and single-arm study designs (**Figure 2B**).

Collectively, the included evidence is methodologically acceptable for quantitative synthesis. Nevertheless, study findings should be interpreted with caution, particularly for subjective CINV outcomes susceptible to performance and detection bias.

Overall complete control rate

Among the 10 included studies, only 4 provided comparable two-arm dichotomous data for overall complete CINV control [19, 23, 27] (**Figure 3**). The remaining studies were exclud-

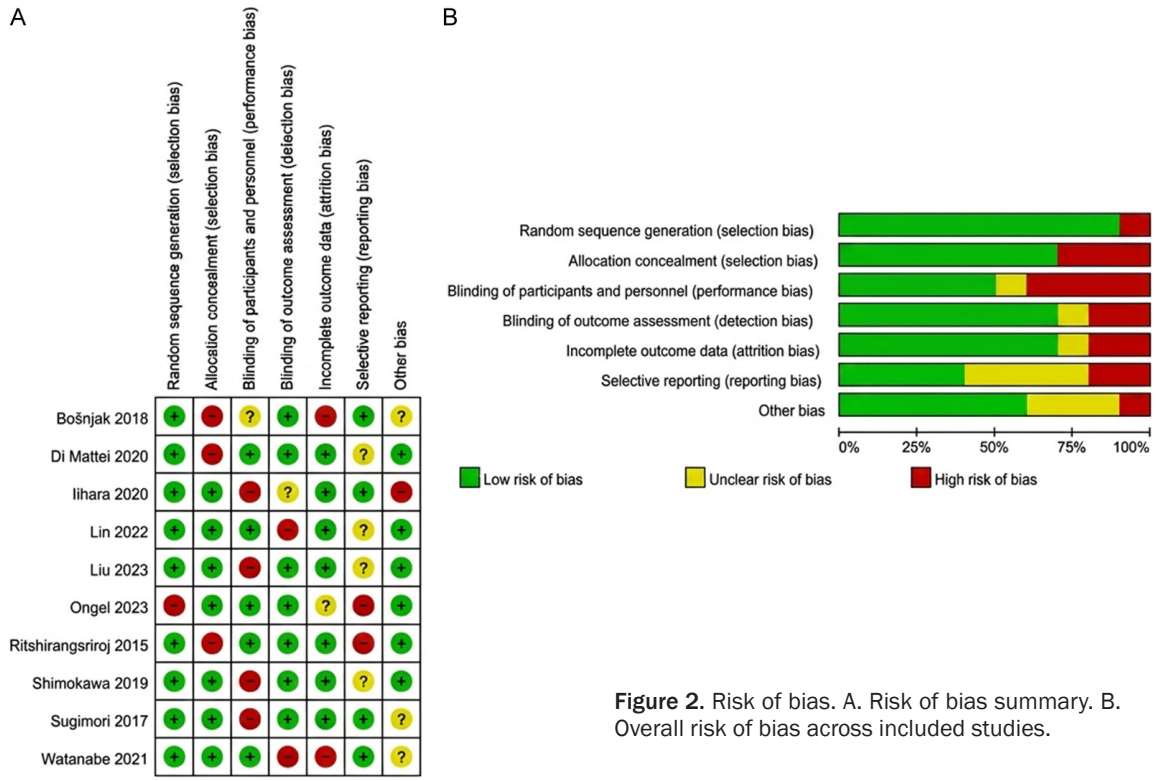

Figure 2. Risk of bias. A. Risk of bias summary. B. Overall risk of bias across included studies.

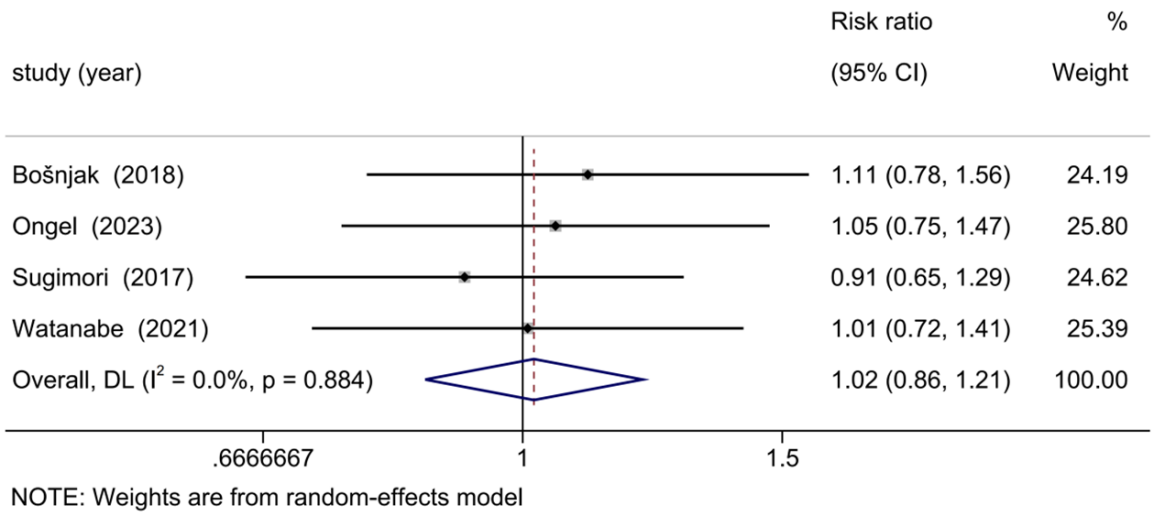

Figure 3. Forest plot of overall complete control rate.

ed from this subgroup analysis because they only reported single-phase outcomes, other efficacy endpoints, or lacked extractable comparative data.

The pooled analysis demonstrated no significant difference in overall complete CINV control between multimodal symptom management and conventional control regimens (RR = 1.02, 95% CI: 0.86-1.21). No measurable between-study heterogeneity was detected (I^2 = 0.0%, P = 0.884). Individual study effect sizes were all close to the null value (RR: 0.91-1.11), and no single study showed statistically significant between-group differences.

Acute complete control rate

Three eligible studies [19, 22, 27] provided extractable two-arm dichotomous data for

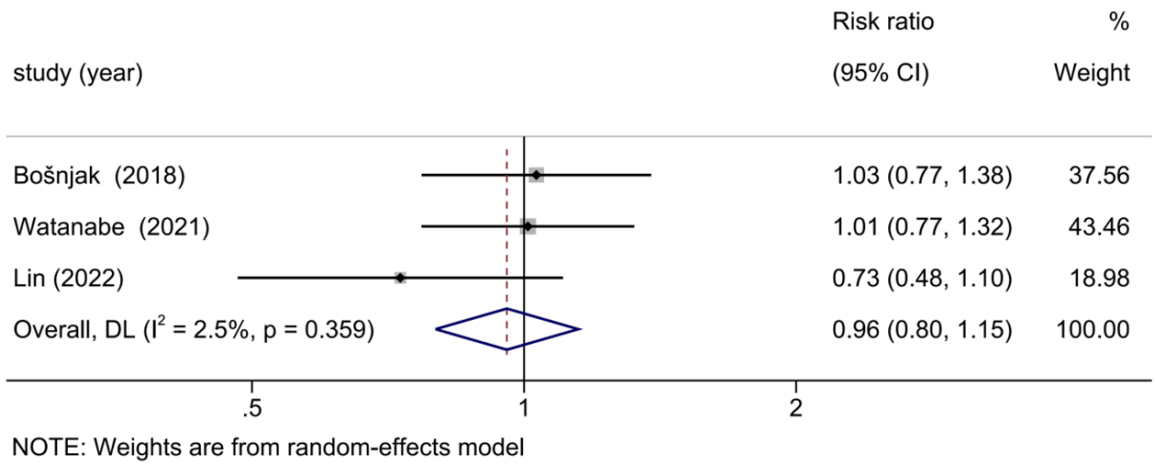

Figure 4. Forest plot of acute complete control rate.

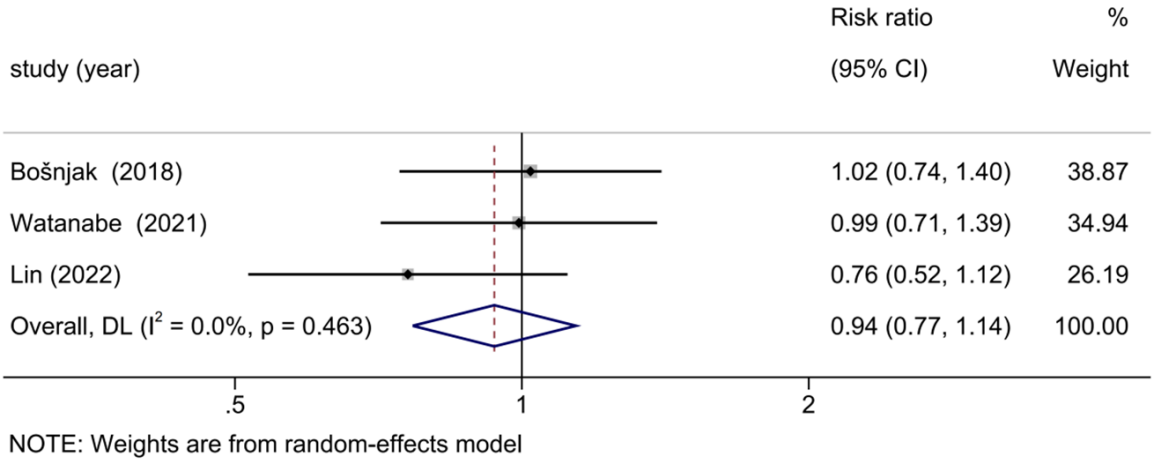

Figure 5. Forest plot of delay complete control rate.

acute complete CINV control (**Figure 4**). Other studies were excluded due to missing acute-phase data, exclusive reporting of other endpoints, or insufficient comparative data for pooling.

The pooled result showed no significant improvement in acute complete CINV control with multimodal interventions (RR = 0.96, 95% CI: 0.80-1.15). Statistical heterogeneity was low (I^2 = 3.5%, P = 0.355), suggesting that the treatment effects were generally consistent across included studies. Individual trial effect sizes ranged from 0.73 to 1.03, with no independent statistically significant results.

Delayed complete control rate

Three studies [19, 22, 27] were included in the meta-analysis of delayed complete CINV control (**Figure 5**). No significant difference was observed between multimodal intervention and control groups (RR = 0.94, 95% CI: 0.77-1.14). No between-study heterogeneity was identified (I^2 = 0.0%, P = 0.462), reflecting highly consistent findings across studies despite varied intervention modalities and clinical settings.

All individual study effect estimates clustered near the null value (RR: 0.76-1.02), with no single study reporting a significant improvement in delayed complete CINV control.

Overall no-vomiting events

Three studies [22, 23, 25] reported valid two-arm data for overall no-vomiting events (**Figure 6**). The pooled analysis indicated that multimodal interventions did not significantly

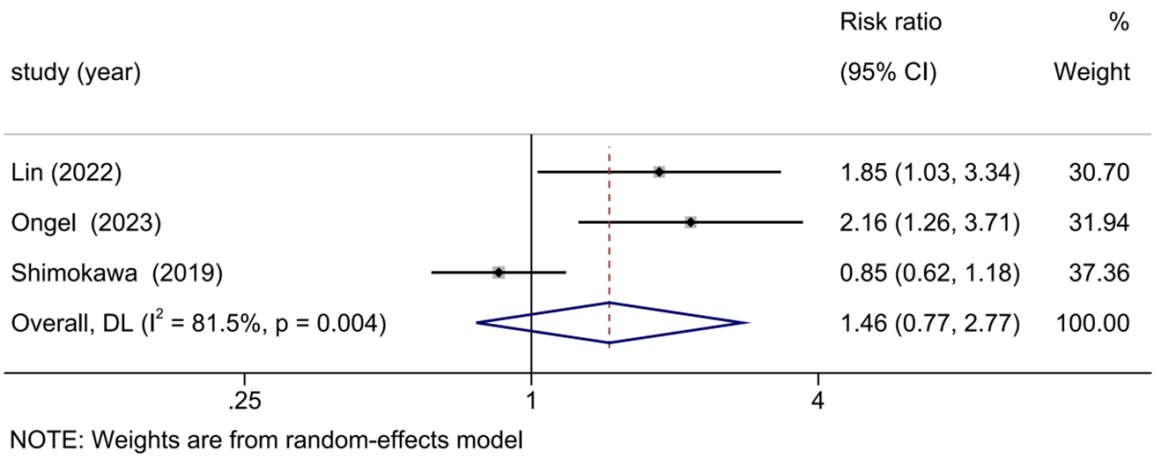

Figure 6. Forest plot of overall no vomiting events.

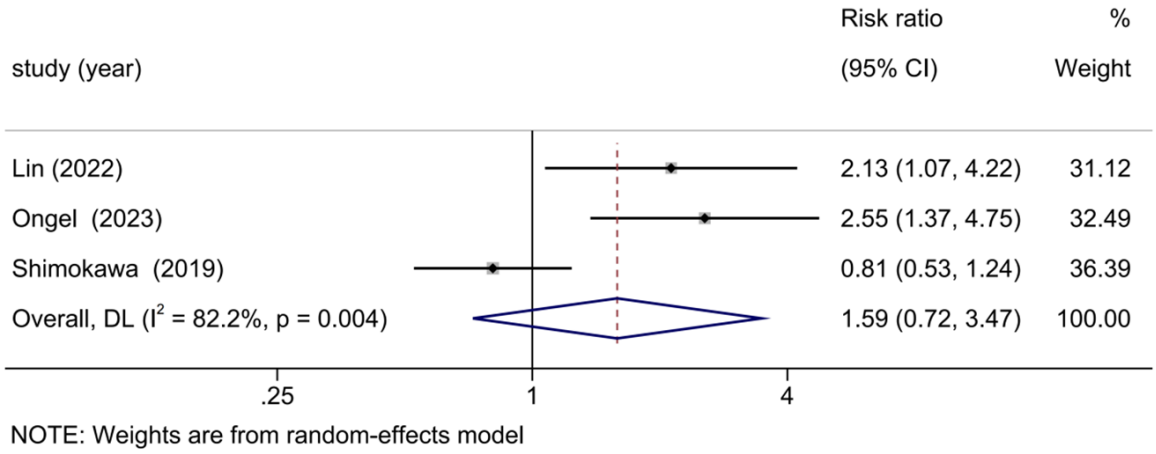

Figure 7. Forest plot of overall no significant nausea events.

increase the rate of overall no-vomiting events (RR = 1.46, 95% CI: 0.75-2.83). Substantial between-study heterogeneity was detected (I^2 = 82.5%, P = 0.003).

Heterogeneity was mainly attributed to inconsistent individual study results. Lin et al. [22] and Ongel et al. [23] favored multimodal interventions with higher overall no-vomiting rates, while Shimokawa 2019 showed no clinical benefit, resulting in a wide confidence interval for the pooled estimate.

Overall no-significant-nausea events

Three studies [22, 23, 25] were analyzed for overall no-significant-nausea events (**Figure 7**). The pooled result showed no significant difference between multimodal and control groups (RR = 1.59, 95% CI: 0.71-3.54). Substantial statistical heterogeneity was present (I^2 = 82.9%, P = 0.003).

Consistent with overall vomiting outcomes, Lin et al. [22] and Ongel et al. [23] demonstrated favorable effects of multimodal interventions, whereas Shimokawa 2019 yielded neutral results. This inter-study discrepancy accounted for the high heterogeneity and non-significant pooled outcome.

Acute no-vomiting events

As shown in **Figure 8**, 3 studies [22, 23, 28] provided acute-phase no-vomiting outcome data. The pooled analysis confirmed that multimodal symptom management significantly elevated the rate of acute no-vomiting events (RR

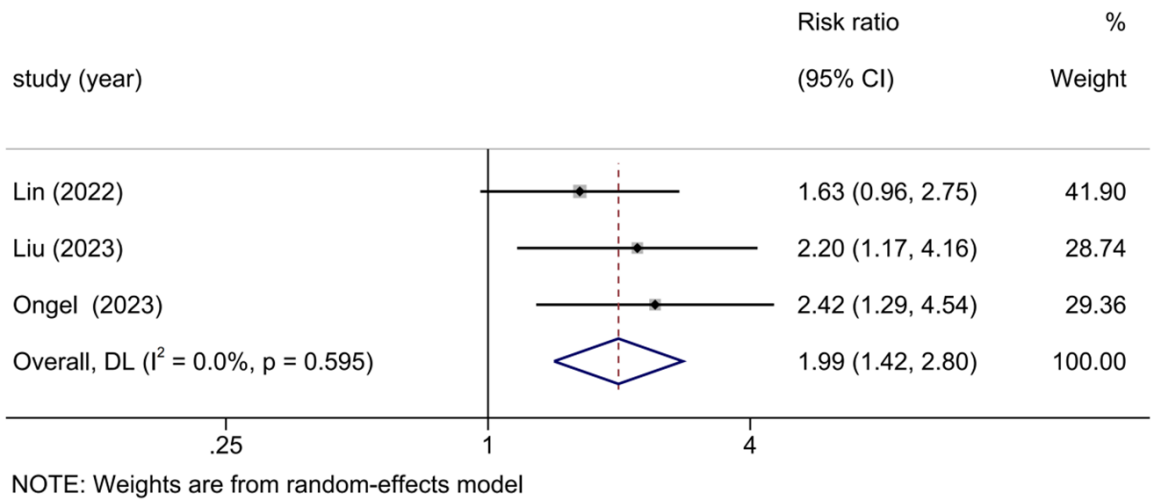

Figure 8. Forest plot of acute no vomiting events.

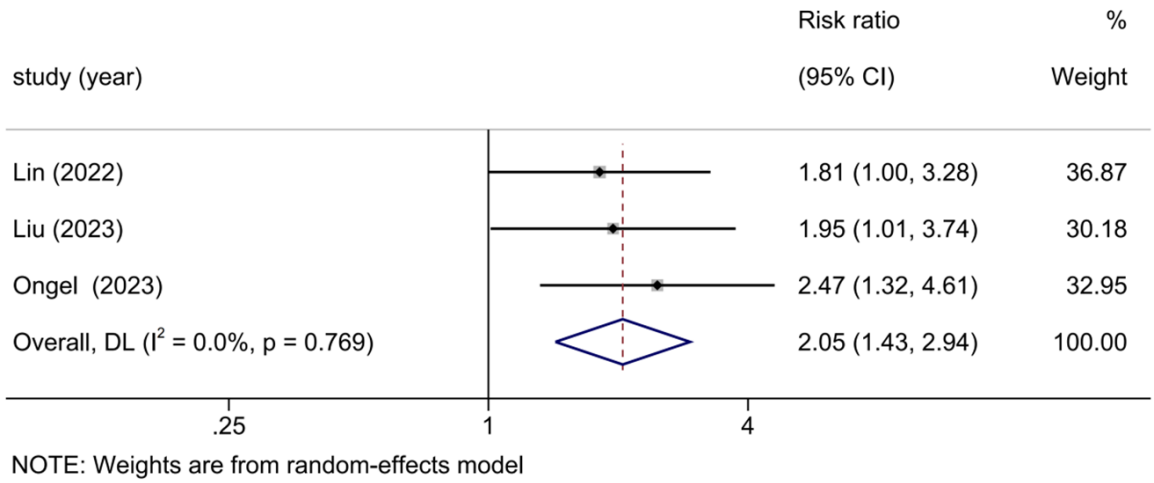

Figure 9. Forest plot of acute no significant nausea events.

= 1.99, 95% CI: 1.42-2.80). No between-study heterogeneity was found (I^2 = 0.0%, P = 0.593), indicating highly stable treatment effects.

All individual studies favored the multimodal intervention strategy. Two trials reported statistically significant benefits, and the third showed a consistent favorable trend, verifying the robustness of acute-phase anti-vomiting efficacy.

Acute no-significant-nausea events

As shown in **Figure 9**, 3 studies [22, 23, 28] were included in the analysis of acute no-significant-nausea events. Multimodal interventions significantly improved acute no-significant-nausea outcomes compared with conventional care (RR = 2.05, 95% CI: 1.43-2.94), with zero between-study heterogeneity (I^2 = 0.0%, P = 0.769).

All individual studies supported the efficacy of multimodal strategies. Two studies showed significant clinical benefits, and the remaining one presented a borderline favorable effect, further validating the consistent acute-phase therapeutic advantage.

Delayed no-vomiting events

Three studies [22, 23, 25] reported delayed-phase no-vomiting data (**Figure 10**). The pooled estimate showed no significant benefit of multi-

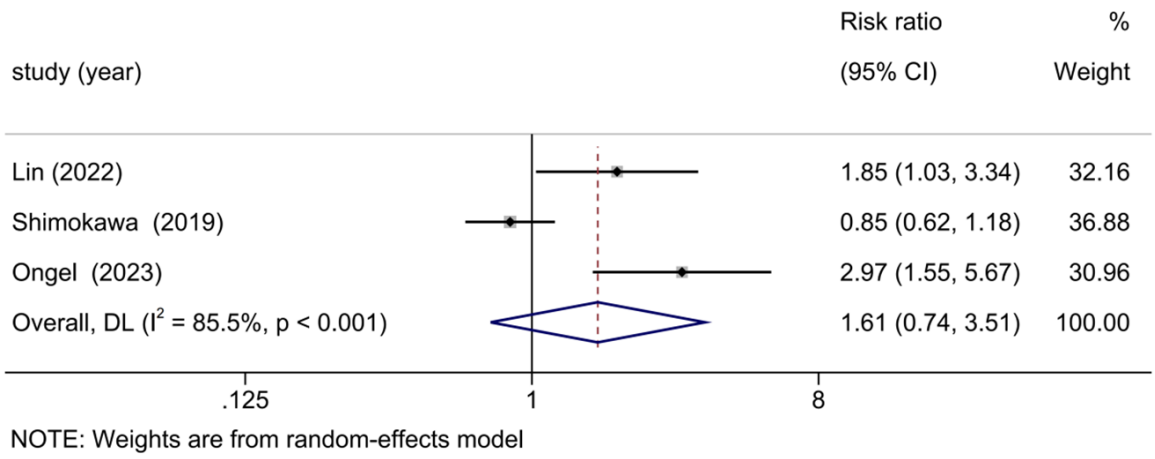

Figure 10. Forest plot of delay no vomiting events.

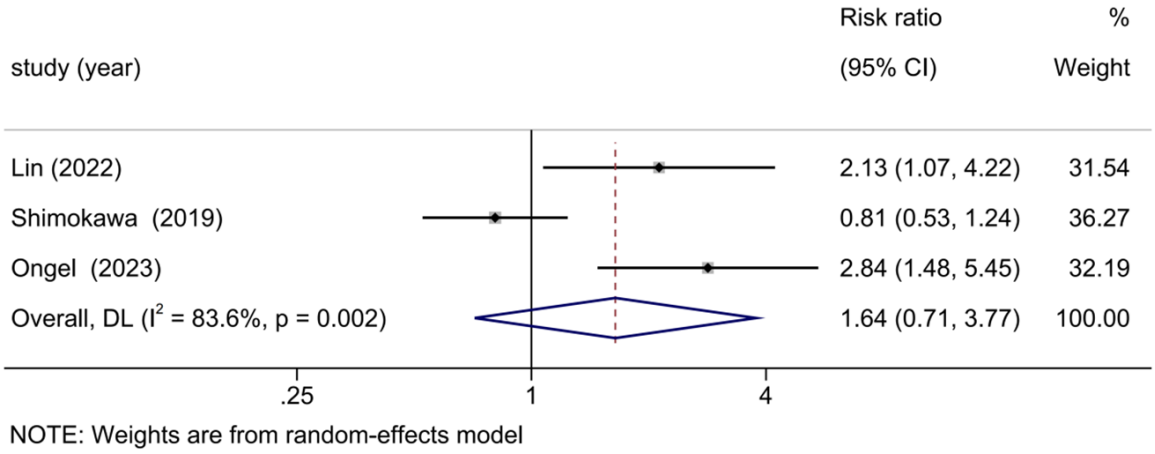

Figure 11. Forest plot of delay no significant nausea events.

modal interventions for delayed no-vomiting events (RR = 1.62, 95% CI: 0.72-3.63). Substantial between-study heterogeneity was observed (I^2 = 86.7%, P = 0.001).

Lin et al. [22] and Ongel et al. [23] reported favorable delayed-phase outcomes with multimodal treatment, while Shimokawa 2019 showed no benefit. This inconsistency was the primary cause of high heterogeneity and the non-significant pooled result.

Delayed no-significant-nausea events

Three studies [22, 23, 25] contributed data for delayed no-significant-nausea analysis (**Figure 11**). Multimodal interventions failed to significantly improve delayed-phase nausea control (RR = 1.64, 95% CI: 0.70-3.85), with substantial heterogeneity (I^2 = 84.4%, P = 0.002).

Similar to delayed vomiting outcomes, two studies [22, 23] favored multimodal interventions and one showed neutral effects, leading to unstable pooled estimates and high inter-study variability.

Quality of life

Two studies [22, 24] evaluated patient quality of life after multimodal CINV intervention (**Figure 12**). The pooled analysis based on the random-effects model showed no significant improvement in quality of life with multimodal strategies (MD = 0.19, 95% CI: -2.34 to 2.72). Individual study outcomes were inconsistent, but the overall pooled effect was close to the null value.

Extremely high between-study heterogeneity was detected (I^2 = 98.0%, P<0.001), which may

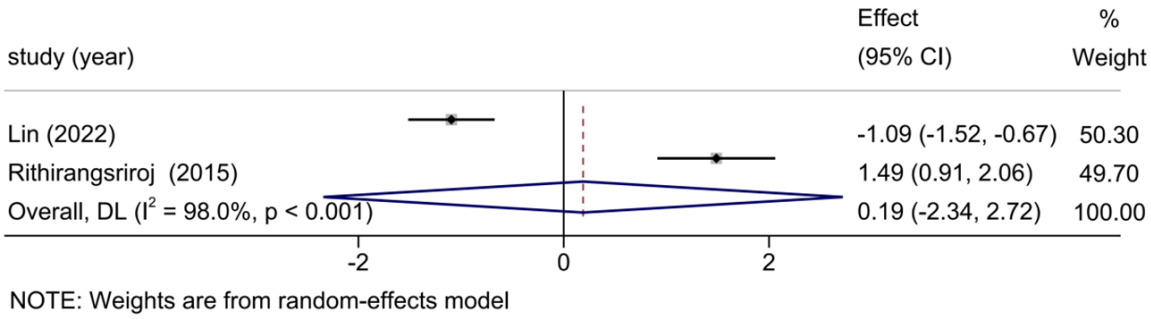

Figure 12. Forest plot of quality of life.

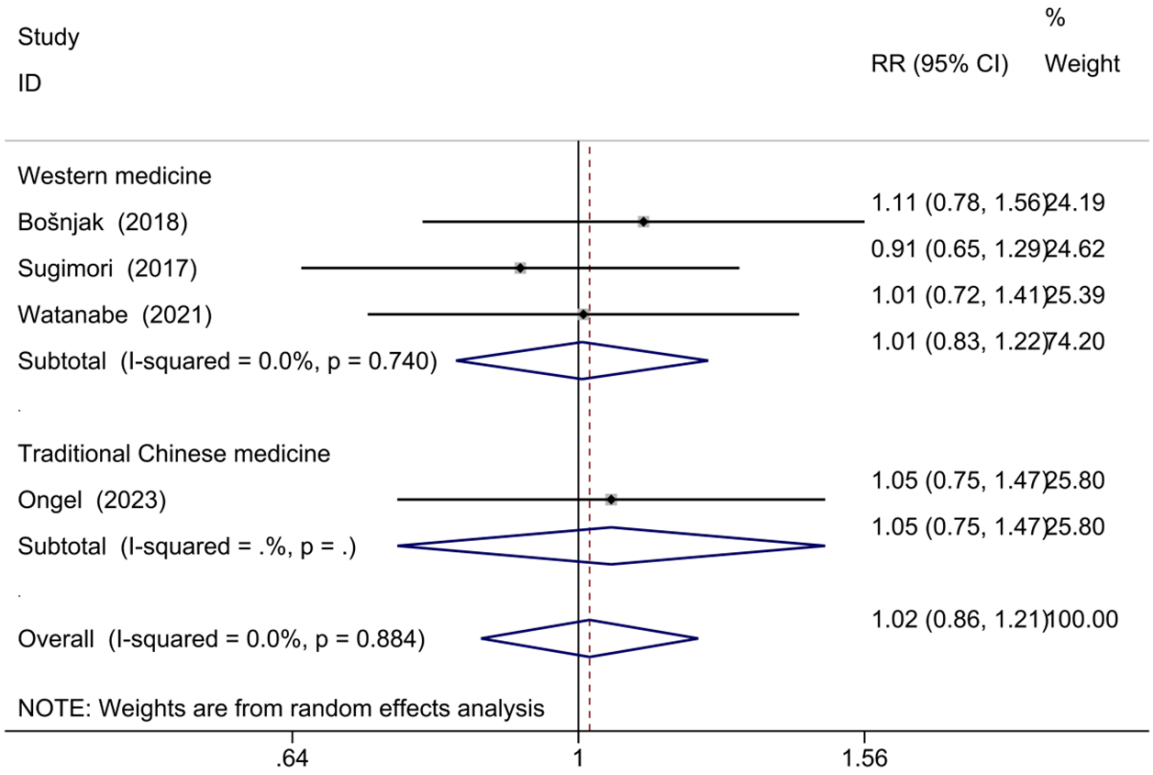

Figure 13. Subgroup analyses of overall complete control rate based on intervention type.

stem from varied clinical settings and intervention modalities. Given the limited sample size and extreme heterogeneity, the association between multimodal symptom management and quality of life remains inconclusive and requires further high-quality evidence for verification.

Subgroup analyses of overall complete control rate based on intervention type

Subgroup analysis stratified by intervention type showed consistent neutral effects on overall complete CINV control for both Western medicine and traditional Chinese medicine (TCM) multimodal strategies (**Figure 13**). The Western medicine subgroup [19, 26, 27] yielded a non-significant pooled result (RR = 1.01, 95% CI: 0.83-1.23). The single TCM-based study also presented a neutral effect (RR = 1.05, 95% CI: 0.75-1.47).

The overall pooled result remained non-significant (RR = 1.02, 95% CI: 0.86-1.21, I^2 = 0.0%, P = 0.884). Intervention types did not alter the efficacy of multimodal strategies for overall

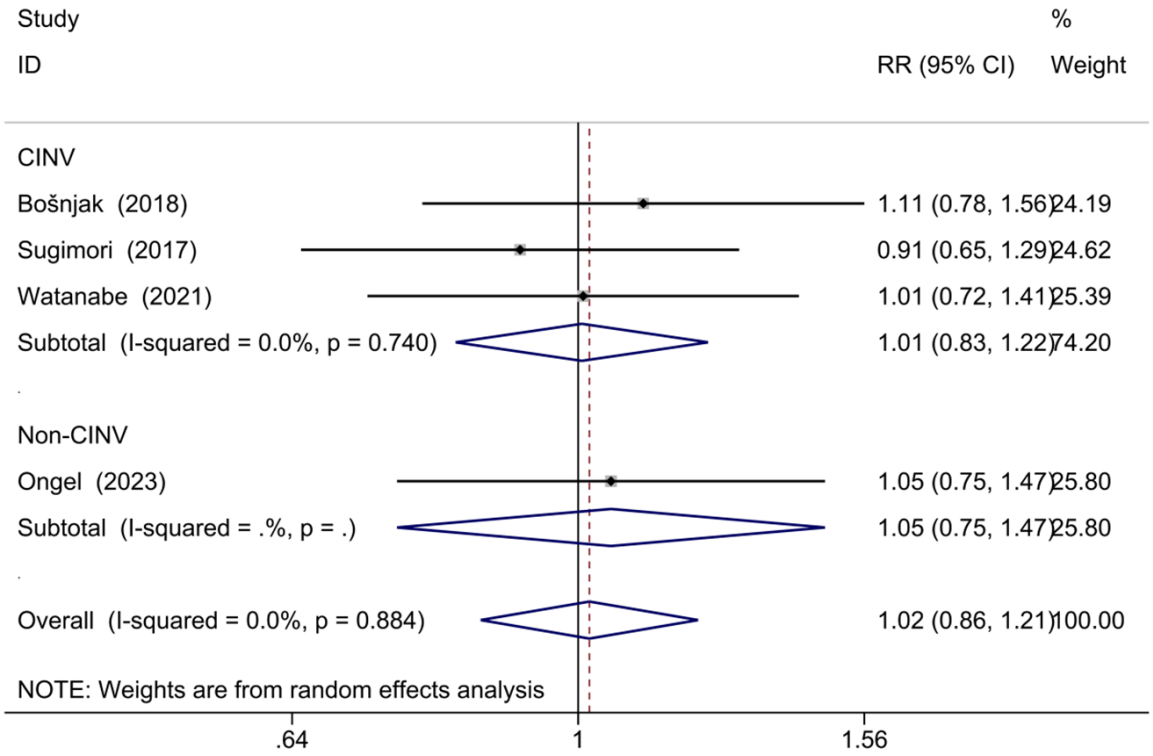

Figure 14. Subgroup analyses of overall complete control rate based on clinical setting (CINV vs. non-CINV).

complete CINV control, indicating stable neutral effects across pharmacological and integrative intervention models.

Subgroup analyses of overall complete control rate based on clinical setting

Subgroup analysis stratified by clinical setting (CINV vs. non-CINV) demonstrated consistent neutral outcomes for overall complete control (**Figure 14**). The CINV subgroup [19, 26, 27] showed no significant intervention benefit (RR = 1.01, 95% CI: 0.83-1.22, I^2 = 0.0%, P = 0.740). The single non-CINV perioperative study yielded a similar neutral result (RR = 1.05, 95% CI: 0.75-1.47). The overall pooled analysis remained non-significant (RR = 1.02, 95% CI 0.86-1.21; I^2 = 0.0%, P = 0.884), indicating that the clinical setting did not modify the therapeutic effect of multimodal interventions on overall complete CINV control. The stable neutral pooled outcome was consistent across different clinical contexts, though the non-CINV subgroup result should be interpreted cautiously due to limited study volume.

Subgroup analyses of overall complete control rate based on tumor type

Subgroup analysis by tumor subtype explored the potential modification effect of cancer type on intervention efficacy (**Figure 15**). For ovarian/fallopian tube cancer [19, 27], multimodal interventions showed no significant improvement in overall complete control (RR = 1.06, 95% CI: 0.83-1.34, I^2 = 0.0%, P = 0.703). For other gynecologic cancers [23, 26], the pooled result was also non-significant (RR = 0.98, 95% CI: 0.77-1.25, I^2 = 0.0%, P = 0.561).

The subgroup difference test showed no significant interaction between tumor type and treatment effect (P = 0.679). Tumor subtype did not affect the efficacy of multimodal symptom management for overall complete CINV control, with consistent neutral effects across all gynecologic cancer subtypes (RR = 1.02, 95% CI: 0.86-1.21; I^2 = 0.0%, P = 0.884).

Publication bias

Publication bias was assessed via funnel plot visual inspection, Egger's regression test, and

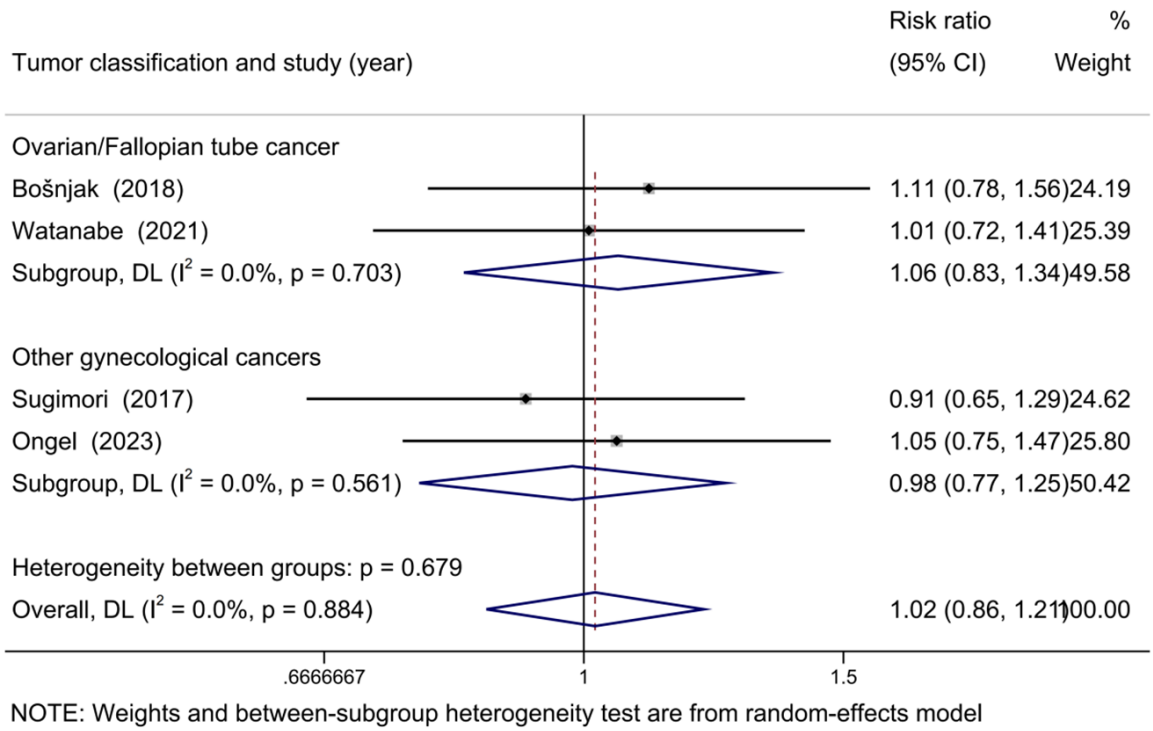

Figure 15. Subgroup analyses of overall complete control rate based on clinical setting (Ovarian/Fallopian tube cancer vs. Other gynecological cancers).

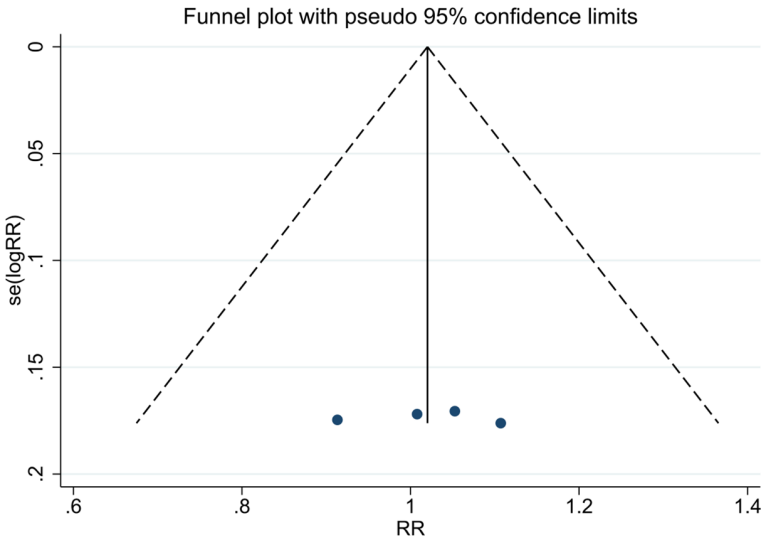

Figure 16. Funnel plot.

Begg's rank-correlation test for all primary pooled outcomes. The funnel plot showed symmetrical distribution of study effect sizes, with all data points evenly distributed within the pseudo 95% CI (**Figure 16**). Both statistical tests confirmed no significant publication bias or small-study effects (Egger's test: P = 0.984; Begg's test: P = 1.000). Collectively, no substantial publication bias was detected in the current meta-analysis.

Tabulated summary of pooled efficacy outcomes

All primary pooled efficacy outcomes are summarized in **Table 3**. Among nine quantitative analyses, multimodal interventions only produced significant benefits for acute-phase specific symptoms (acute no-vomiting and acute no-significant-nausea events). All complete control endpoints across acute, delayed, and overall phases yielded neutral results.

Notably, heterogeneity patterns varied significantly by treatment phase. Complete control analyses and acute symptom analyses present-

Table 3. Summary of pooled efficacy outcomes of multimodal symptom management strategies

Domain	Phase	Studies, n	Pooled RR (95% CI)	I^2 (%)	P het	P eff	Inference
Complete control	Overall	4	1.02 (0.86-1.21)	0.0	0.884	0.820	Null
Complete control	Acute	3	0.96 (0.80-1.15)	3.5	0.355	0.659	Null
Complete control	Delayed	3	0.94 (0.77-1.14)	0.0	0.462	0.536	Null
No vomiting	Overall	3	1.46 (0.75-2.83)	82.5	0.003	0.264	NS, heterog.
No vomiting	Acute	3	1.99 (1.42-2.80)	0.0	0.593	<0.001	Benefit
No vomiting	Delayed	3	1.62 (0.72-3.63)	86.7	0.001	0.242	NS, heterog.
No significant nausea	Overall	3	1.59 (0.71-3.54)	82.9	0.003	0.258	NS, heterog.
No significant nausea	Acute	3	2.05 (1.43-2.94)	0.0	0.769	<0.001	Benefit
No significant nausea	Delayed	3	1.64 (0.70-3.85)	84.4	0.002	0.255	NS, heterog.

Table 4. Study-level effect estimates and relative weights for key symptom-control endpoints

Endpoint	Study	RR (95% CI)	Weight (%)	Direction
Overall no vomiting	Lin 2022 [22]	1.85 (1.03-3.34)	30.83	Favored multimodal
Overall no vomiting	Ongel 2023 [23]	2.16 (1.26-3.71)	32.02	Favored multimodal
Overall no vomiting	Shimokawa 2019 [25]	0.85 (0.62-1.18)	37.15	Favored control/null
Overall no significant nausea	Lin 2022 [22]	2.13 (1.07-4.22)	31.21	Favored multimodal
Overall no significant nausea	Ongel 2023 [23]	2.55 (1.37-4.75)	32.53	Favored multimodal
Overall no significant nausea	Shimokawa 2019 [25]	0.81 (0.53-1.24)	36.26	Favored control/null
Acute no vomiting	Lin 2022 [22]	1.63 (0.96-2.75)	41.90	Favored multimodal
Acute no vomiting	Liu 2023 [28]	2.20 (1.17-4.16)	28.74	Favored multimodal
Acute no vomiting	Ongel 2023 [23]	2.42 (1.29-4.54)	29.36	Favored multimodal
Acute no significant nausea	Lin 2022 [22]	1.81 (1.00-3.28)	36.87	Favored multimodal
Acute no significant nausea	Liu 2023 [28]	1.95 (1.01-3.74)	30.18	Favored multimodal
Acute no significant nausea	Ongel 2023 [23]	2.47 (1.32-4.61)	32.95	Favored multimodal
Delayed no vomiting	Lin 2022 [22]	1.85 (1.03-3.34)	32.26	Favored multimodal
Delayed no vomiting	Shimokawa 2019 [25]	0.85 (0.62-1.18)	36.59	Favored control/null
Delayed no vomiting	Ongel 2023 [23]	2.97 (1.55-5.67)	31.15	Favored multimodal
Delayed no significant nausea	Lin 2022 [22]	2.13 (1.07-4.22)	31.63	Favored multimodal
Delayed no significant nausea	Shimokawa 2019 [25]	0.81 (0.53-1.24)	36.13	Favored control/null
Delayed no significant nausea	Ongel 2023 [23]	2.84 (1.48-5.45)	32.24	Favored multimodal

ed zero or negligible heterogeneity, while overall and delayed nausea/vomiting outcomes showed substantial heterogeneity. This distinct pattern indicates a phase-specific therapeutic effect of multimodal CINV management (**Table 3**).

Study-level direction and contribution to pooled effects

Individual study contribution and effect directions are presented in **Table 4**. All included studies showed consistent favorable directions for acute no-vomiting and acute no-significant-nausea outcomes, fully supporting the acute-phase therapeutic advantage. In contrast, overall and delayed-phase outcomes presented obvious inter-study divergence. Lin 2022 and Ongel 2023 consistently favored multimodal interventions, while Shimokawa 2019 generated neutral or unfavorable results. This divergence was the core cause of high heterogeneity in overall and delayed phase analyses (**Table 4**).

Directional consistency and clinical interpretation

Directional consistency analysis revealed distinct phase-specific characteristics of multimodal intervention efficacy (**Table 5**). Complete control outcomes showed inconsistent and

Table 5. Directional consistency and robustness across pooled analyses

Outcome	Favorable studies, n/N	Study RR range	Consistency	Heterogeneity	Overall inference
Overall complete control	3/4	0.91-1.11	High	I^2 = 0.0%	Stable null effect
Acute complete control	2/3	0.73-1.03	Moderate	I^2 = 3.5%	No acute gain in composite control
Delayed complete control	1/3	0.76-1.02	Low	I^2 = 0.0%	Consistent null in delayed composite control
Overall no vomiting	2/3	0.85-2.16	Moderate	I^2 = 82.5%	Possible benefit obscured by heterogeneity
Overall no significant nausea	2/3	0.81-2.55	Moderate	I^2 = 82.9%	Possible benefit obscured by heterogeneity
Acute no vomiting	3/3	1.63-2.42	High	I^2 = 0.0%	Robust acute benefit
Acute no significant nausea	3/3	1.81-2.47	High	I^2 = 0.0%	Robust acute benefit
Delayed no vomiting	2/3	0.85-2.97	Moderate	I^2 = 86.7%	Directionally favorable but unstable
Delayed no significant nausea	2/3	0.81-2.84	Moderate	I^2 = 84.4%	Directionally favorable but unstable

clinically neutral effects across studies. By comparison, acute-phase nausea and vomiting outcomes achieved 100% directional consistency, with all individual study RRs ranging from 1.63 to 2.47 and no statistical heterogeneity.

For overall and delayed-phase symptoms, two of three studies favored multimodal interventions, but the benefit magnitude varied greatly. These findings indicate that multimodal symptom management exerts optimal efficacy in alleviating early acute CINV symptoms, rather than achieving rigorous long-term or overall CINV control.

Sensitivity analysis

Leave-one-out sensitivity analysis was performed for all pooled outcomes to verify result robustness and exclude the interference of individual studies, with focused analysis on highly heterogeneous outcomes (I^2>80%). Sensitivity results demonstrated that all core conclusions were stable and not dominated by any single study.

For acute-phase beneficial outcomes, sequential exclusion of individual studies did not alter the pooled effect size, statistical significance, or low heterogeneity, confirming the reliability of acute-phase therapeutic advantages. For highly heterogeneous overall and delayed-phase outcomes, the high variability was mainly attributed to Shimokawa et al. [25]. Exclusion of this study significantly reduced heterogeneity without changing the neutral trend of pooled results.

Notably, excluding the perioperative non-CINV study [23] did not materially change any pooled outcomes, indicating minimal clinical heterogeneity introduced by non-chemotherapy-related cases. No single study could reverse the meta-analysis core conclusions. The sensitivity analysis fully validated the stability of the phase-specific efficacy pattern: robust acute symptomatic benefits and unstable, non-significant delayed and overall CINV control effects.

Discussion

This systematic review and meta-analysis comprehensively evaluated the phase-specific efficacy of multimodal symptom management for CINV in patients with gynecologic cancer. The core findings clarify that multimodal interventions cannot improve overall, acute, or delayed complete CINV control, nor produce significant benefits for overall no-vomiting and overall no-significant-nausea outcomes with stable efficacy. Instead, multimodal strategies exert targeted, robust therapeutic effects on acute-phase nausea and vomiting prevention. These results indicate that the primary clinical value of multimodal CINV management lies in early symptomatic relief, rather than the complete control of intractable delayed CINV symptoms. The present study is the first disease-specific meta-analysis focusing exclusively on gynecologic cancer populations. It systematically integrates pharmacological and integrative non-pharmacological multimodal interventions, and elaborates phase-specific clinical efficacy across acute, delayed, and overall treatment windows.

Multimodal symptom management demonstrates better performance in improving acute symptomatic outcomes than achieving stringent composite complete control endpoints. This interpretation is strongly supported by the

pooled results: multimodal interventions significantly increased acute no-vomiting and acute no-significant-nausea event rates, while failing to improve complete CINV control in any treatment phase. These results are consistent with previous independent clinical studies [29-33]. Enhanced antiemetic regimens (olanzapine-based prophylaxis) and integrative interventions (acupuncture-related therapy) can effectively reduce acute CINV symptom burden, but cannot consistently achieve superior composite complete control outcomes. The underlying reason is that complete CINV control is a challenging composite endpoint that requires simultaneous inhibition of vomiting, elimination of nausea, and zero rescue antiemetic usage. This strict evaluation standard makes composite outcomes less susceptible to partial but clinically meaningful symptomatic improvements. Clinically, future CINV research and clinical practice should not depend solely on composite complete control indicators, as they may underestimate the patient-centered therapeutic benefits of multimodal interventions in the acute chemotherapy period.

Delayed CINV remains the most intractable clinical challenge despite the widespread application of multimodal supportive care in oncology. In the current meta-analysis, delayed complete control, delayed no-vomiting, delayed no-significant-nausea events yielded non-significant pooled results, with substantial heterogeneity for delayed symptomatic outcomes. These are consistent with previous gynecologic oncology studies confirming the poor controllability of delayed CINV [34, 35]. Patients receiving or paclitaxel/carboplatin-based chemotherapy frequently experience delayed nausea, even with aprepitant-containing prophylaxis regimens, leading to inconsistent clinical efficacy [36]. Mechanistically, delayed CINV involves more complicated biology than acute CINV, including sustained neurokinin signaling, cumulative patient vulnerability, expectancy, and persistent symptomatic discomfort after chemotherapy. This biological complexity explains the limited efficacy of current multimodal interventions for delayed CINV. Clinically, delayed-phase symptom management should remain a prominent focus of gynecologic cancer supportive care. The verified acute-phase therapeutic advantage cannot represent effective long-term CINV control throughout the entire chemotherapy risk cycle.

Heterogeneity observed in general and delayed-phase outcomes originates from genuine clinical variability, rather than statistical chance. The studies included differed significantly in terms of chemotherapy backbone, emetogenic risk, intervention type, comparator regimen, study design, and outcome definition. The intervention spectrum covered intensified Western pharmacological antiemetic therapy and diverse TCM integrative approaches. Chemotherapy regimens included cisplatin-based high-emetogenic schemes and carboplatin/paclitaxel-based moderate-emetogenic schemes, and one study focused on postoperative nausea and vomiting instead of CINV [37, 38]. These clinical discrepancies directly caused varied baseline event rates and differential intervention responsiveness across studies.

Furthermore, acute and delayed CINV are regulated by distinct dominant biological mechanisms: acute CINV is mainly mediated by serotonergic and vagal processes, while delayed CINV is predominantly driven by neurokinin signaling and individual patient behavioral factors. The differentiated pathological mechanisms further explain the inconsistent intervention efficacy and high inter-study heterogeneity in delayed-phase outcomes. Therefore, pooled delayed and overall results should be interpreted cautiously, and further stratified subgroup analyses and targeted clinical trials are required to optimize multimodal intervention schemes.

The verified acute-specific therapeutic advantage of multimodal interventions has solid biological and clinical rationales. Multimodal strategies combine multiple intervention pathways to target CINV-related pathological and psychological mechanisms, including emetic reflex, visceral afferent nerve modulation, autonomic nervous system adjustment, and relief of anticipatory distress and subjective symptomatic discomfort. This complementary multi-pathway intervention model is particularly suitable for gynecologic cancer patients, who have multiple inherent CINV risk factors including female gender, platinum chemotherapy exposure, and high psychological anxiety levels.

Additionally, non-pharmacological integrative interventions can optimize patient symptomatic expectancy and central symptom perception, which effectively alleviates acute CINV but has limited sustained effects on delayed symptoms

dominated by long-term neurokinin signaling [7, 39-43]. Clinically, multimodal care can be regarded as a personalized supportive care strategy that combines standardized pharmacological prophylaxis with targeted symptomatic intervention, rather than a simple increase in antiemetic drug dosage.

Multimodal symptom management serves as a beneficial adjunct rather than a substitute for evidence-based standardized antiemetic prophylaxis. The individual studies confirmed that intensified pharmacological antiemetic therapy and integrative non-pharmacological interventions only produce targeted benefits under specific clinical conditions, without universal superiority over conventional prophylaxis. This inconsistent efficacy indicates that the clinical value of multimodal strategies depends on chemotherapy regimens, treatment phase, and individual patient risk stratification. Our results indicate that a risk-adapted model where multimodal approaches are recommended for high-risk patients with severe acute CINV burden or multiple individual risk factors, while standardized guideline-concordant pharmacological prophylaxis should remain the core of care. Simultaneously, this study reminds clinicians to avoid blind expansion of multimodal intervention applications, as such strategies cannot generate incremental benefits for delayed and overall CINV control.

Several limitations should be acknowledged. First, the limited number of studies for each pooled analysis limited statistical power and reduced the robustness of publication bias assessment. Second, the evidence base had significant methodological heterogeneity, covering randomized controlled trials, observational studies, retrospective analyses, and single-arm studies. Non-randomized designs inevitably introduced selection bias and confounding factors related to baseline patient characteristics and treatment allocation.

Third, varied intervention regimens, control measures, chemotherapy backbones, and outcome definitions contributed to heterogeneity across several overall and delayed endpoints. Fourth, one included study focused on postoperative nausea and vomiting, introducing additional clinical heterogeneity. Finally, the absence of individual patient data restricted stratified analyses based on important clinical modifiers (age, motion sickness history, alcohol tolerance, anticipatory symptoms, baseline emetic risk) and dose-stratified subgroup analyses. Therefore, the findings are exploratory and hypothesis-generating, requiring further verification by high-quality clinical trials.

In conclusion, this meta-analysis indicates that the phase-specific efficacy of multimodal symptom management for CINV in gynecologic cancer patients. Multimodal interventions provide robust clinical benefits for alleviating acute vomiting and acute clinically significant nausea, but fail to improve overall and delayed complete CINV control. This evidence supports multimodal care as a valuable phase-sensitive adjunct therapy for gynecologic cancer supportive care, while highlighting the persistent unmet clinical need for delayed CINV.

Future high-quality, large-sample randomized controlled trials are warranted. Studies should target standardized outcome definitions, risk-stratified samples, and optimized combinations of pharmacological and integrative interventions. This will help refine personalized multimodal CINV management schemes and improve symptomatic supportive care for gynecologic cancer patients undergoing chemotherapy.

Disclosure of conflict of interest

None.

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Appendix S1. Electronic database and trial registry search strategies

Source	Search strategy
PubMed/MEDLINE	((“Genital Neoplasms, Female”[Mesh] OR “gynecologic cancer*”[Title/Abstract] OR “gynaecologic cancer*”[Title/Abstract] OR “gynecologic malignan*”[Title/Abstract] OR “gynaecologic malignan*”[Title/Abstract] OR “ovarian cancer*”[Title/Abstract] OR “cervical cancer*”[Title/Abstract] OR “endometrial cancer*”[Title/Abstract] OR “uterine cancer*”[Title/Abstract] OR “vulvar cancer*”[Title/Abstract] OR “vaginal cancer*”[Title/Abstract] OR “fallopian tube cancer*”[Title/Abstract]) AND (“Nausea”[Mesh] OR “Vomiting”[Mesh] OR “chemotherapy-induced nausea and vomiting”[Title/Abstract] OR “chemotherapy induced nausea and vomiting”[Title/Abstract] OR CINV[Title/Abstract] OR nausea[Title/Abstract] OR vomiting[Title/Abstract] OR emesis[Title/Abstract]) AND (“Antiemetics”[Mesh] OR multimodal[Title/Abstract] OR “multimodal symptom management”[Title/Abstract] OR antiemetic*[Title/Abstract] OR olanzapine[Title/Abstract] OR aprepitant[Title/Abstract] OR netupitant[Title/Abstract] OR palonosetron[Title/Abstract] OR ondansetron[Title/Abstract] OR acupuncture[Title/Abstract] OR acupressure[Title/Abstract] OR “auricular acupressure”[Title/Abstract] OR “acupoint application”[Title/Abstract] OR “supportive care”[Title/Abstract])) AND English[lang]
Embase	(‘female genital tract cancer’/exp OR ‘gynecologic cancer’:ti,ab OR ‘gynaecologic cancer’:ti,ab OR ‘gynecologic malignancy’:ti,ab OR ‘gynaecologic malignancy’:ti,ab OR ‘ovarian cancer’:ti,ab OR ‘cervical cancer’:ti,ab OR ‘endometrial cancer’:ti,ab OR ‘uterine cancer’:ti,ab OR ‘vulvar cancer’:ti,ab OR ‘vaginal cancer’:ti,ab OR ‘fallopian tube cancer’:ti,ab) AND (‘chemotherapy induced nausea and vomiting’/exp OR ‘chemotherapy-induced nausea and vomiting’:ti,ab OR CINV:ti,ab OR nausea:ti,ab OR vomiting:ti,ab OR emesis:ti,ab) AND (‘antiemetic agent’/exp OR multimodal:ti,ab OR ‘multimodal symptom management’:ti,ab OR antiemetic*:ti,ab OR olanzapine:ti,ab OR aprepitant:ti,ab OR netupitant:ti,ab OR palonosetron:ti,ab OR ondansetron:ti,ab OR acupuncture:ti,ab OR acupressure:ti,ab OR ‘auricular acupressure’:ti,ab OR ‘acupoint application’:ti,ab OR ‘supportive care’:ti,ab) AND [english]/lim
Web of Science Core Collection	TS=(“gynecologic cancer*” OR “gynaecologic cancer*” OR “gynecologic malignan*” OR “gynaecologic malignan*” OR “ovarian cancer*” OR “cervical cancer*” OR “endometrial cancer*” OR “uterine cancer*” OR “vulvar cancer*” OR “vaginal cancer*” OR “fallopian tube cancer*”) AND TS=(“chemotherapy-induced nausea and vomiting” OR “chemotherapy induced nausea and vomiting” OR CINV OR nausea OR vomiting OR emesis) AND TS=(multimodal OR “multimodal symptom management” OR antiemetic* OR olanzapine OR aprepitant OR netupitant OR palonosetron OR ondansetron OR acupuncture OR acupressure OR “auricular acupressure” OR “acupoint application” OR “supportive care”)
Cochrane Central Register of Controlled Trials (CENTRAL)	(“gynecologic cancer” OR “gynaecologic cancer” OR “gynecologic malignancy” OR “ovarian cancer” OR “cervical cancer” OR “endometrial cancer” OR “uterine cancer” OR “vulvar cancer” OR “vaginal cancer” OR “fallopian tube cancer”) AND (“chemotherapy-induced nausea and vomiting” OR CINV OR nausea OR vomiting OR emesis) AND (multimodal OR antiemetic OR olanzapine OR aprepitant OR netupitant OR palonosetron OR ondansetron OR acupuncture OR acupressure OR “auricular acupressure” OR “acupoint application” OR “supportive care”)
ClinicalTrials.gov	Condition/Disease: gynecologic cancer OR ovarian cancer OR cervical cancer OR endometrial cancer OR uterine cancer OR vulvar cancer OR vaginal cancer OR fallopian tube cancer. Other terms: “chemotherapy-induced nausea and vomiting” OR CINV OR antiemetic OR olanzapine OR aprepitant OR acupuncture OR acupressure OR multimodal symptom management. No restriction on recruitment status was applied.
WHO International Clinical Trials Registry Platform (ICTRP)	(“gynecologic cancer” OR “gynaecologic cancer” OR “ovarian cancer” OR “cervical cancer” OR “endometrial cancer” OR “uterine cancer”) AND (“chemotherapy-induced nausea and vomiting” OR CINV OR nausea OR vomiting) AND (antiemetic OR multimodal OR acupuncture OR acupressure OR supportive care)