FARMACIA, 2026, Vol. 74, 4

https://doi.org/10.31925/farmacia.2026.4.3 **REVIEW**

META-ANALYSIS OF EFFICACY OF APREPITANT IN PREVENTING CHEMOTHERAPY-INDUCED NAUSEA AND VOMITING IN COLORECTAL CANCER PATIENTS

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Manuscript received: June 2026

Abstract

This meta-analysis systematically evaluated efficacy of aprepitant (Apr) in preventing Chemotherapy-induced nausea and vomiting (CINV) in colorectal cancer (CRC) patients receiving moderately to highly emetogenic chemotherapy (MHEC). A search was performed in various databases for randomized controlled trials published between January 2003 and June 2024. The focus was on the adoption of Apr for preventing CINV in CRC patients. The control group received only a 5-HT3 receptor antagonist and dexamethasone. Two researchers implemented the selection, quality evaluation, and data extraction processes. The analysis was conducted using RevMan5.3. This meta-analysis included seven high-quality studies comprising 1812 patients. The results indicated that in CRC patients receiving chemotherapy, Apr group demonstrated dramatically higher overall phase complete response rates for CINV (odds ratio (OR) = 1.95, 95%CI = 1.53–2.49, $p < 0.00001$), complete protection rates (OR = 1.73, 95%CI = 1.27–2.36, $p = 0.0005$), no vomiting rates (OR = 4.06, 95%CI = 2.53–6.52, $Z = 5.80$, $p < 0.00001$), and no nausea rates (OR = 1.26, 95%CI = 1.01–1.57, $p = 0.04$) *versus* Control group. Additionally, there was no difference in adverse reactions between the two groups ($p > 0.05$). Apr notably enhances the complete response rate of CINV in CRC patients receiving MHEC, demonstrating a favourable safety profile.

Rezumat

Meta-analiza a evaluat eficacitatea aprepitantului (Apr) în prevenirea grețurilor și vărsăturilor induse de chimioterapie (CINV) la pacienții cu cancer colorectal (CRC) care urmează chimioterapie cu potențial emetogen moderat până la ridicat (MHEC). S-au consultat studiile clinice randomizate controlate, publicate între ianuarie 2003 și iunie 2024. Analiza s-a concentrat asupra utilizării Apr pentru prevenirea CINV la pacienții cu CRC. Grupul de control a primit doar un antagonist al receptorilor 5-HT3 și dexametazonă. Analiza statistică a fost realizată utilizând RevMan 5.3. Studiul a inclus șapte studii, care au cuprins un total de 1.812 pacienți. Rezultatele au arătat că, la pacienții cu CRC tratați prin chimioterapie, grupul care a primit Apr a prezentat rate semnificativ mai mari ale răspunsului complet în faza globală pentru CINV (raportul șanselor [OR] = 1,95, interval de încredere 95% [IC 95%] = 1,53–2,49, $p < 0,00001$), rate de protecție completă (OR = 1,73, IC 95% = 1,27–2,36, $p = 0,0005$), rate de absență a vărsăturilor (OR = 4,06, IC 95% = 2,53–6,52, $Z = 5,80$, $p < 0,00001$) și rate de absență a grețurilor (OR = 1,26, IC 95% = 1,01–1,57, $p = 0,04$), comparativ cu grupul de control. În plus, nu au fost observate diferențe semnificative în ceea ce privește reacțiile adverse între cele două grupuri ($p > 0,05$). Administrarea Apr îmbunătățește semnificativ rata răspunsului complet în CINV la pacienții cu CRC tratați cu chimioterapie cu potențial emetogen moderat până la ridicat, demonstrând totodată un profil de siguranță favorabil.

Keywords: aprepitant, meta-analysis, clinical trials, oxaliplatin, colorectal cancer, CINV

Introduction

Common chemotherapy regimens for patients with colorectal cancer (CRC) include folinic acid, fluorouracil and oxaliplatin (FOLFOX), Folinic acid, fluorouracil and irinotecan (FOLFIRI), as well as capecitabine and oxaliplatin (CAPOX), which consist of chemotherapeutic agents such as oxaliplatin, fluorouracil, leucovorin, and irinotecan (1). These chemotherapeutic agents primarily exert their cytotoxic effects by disrupting cellular proliferation and division. Nevertheless, vomiting is a common adverse reaction following chemotherapy, with the emetogenic risk associated with type, dosage, and timing of chemotherapy drugs. During chemotherapy for CRC, chemotherapy-induced nausea and vomiting (CINV) significantly impact patients' treatment adherence and quality of life (2, 3).

The most adopted antiemetic regimen during chemotherapy is the combination of 5-HT3 receptor antagonists and dexamethasone (Dex), which greatly enhances acute nausea and vomiting (acute phase, defined as 0 - 24 hours post-chemotherapy). Nevertheless, its efficacy against delayed nausea and vomiting (delayed phase, defined as 24 - 120 hours post-chemotherapy) is suboptimal (4). The use of neurokinin-1 (NK-1) receptor antagonists plus 5-HT3 receptor antagonists is recommended to prevent delayed nausea and vomiting (5, 6). Substance P is an important neuro-

transmitter that has the capacity to contract smooth muscle and blood vessels and can induce vomiting upon binding to NK-1 receptors (7). Aprepitant (Apr), the first oral NK-1 receptor antagonist approved for clinical use (initially in the United States in 2003), specifically targets this pathway. It competitively blocks the binding of substance P to NK-1 receptors within the central nervous system, particularly in the brainstem nuclei critical for the emetic reflex (*e.g.*, nucleus tractus solitarius, area postrema), thereby inhibiting the transmission of emetic signals (8).

The pharmacokinetic profile of aprepitant is particularly advantageous for CINV prevention, especially against delayed symptoms which are a significant challenge with conventional antiemetics. Its long elimination half-life (approximately 9 - 13 hours) allows for sustained receptor blockade over multiple days following chemotherapy administration. High plasma protein binding (> 95%) contributes to its prolonged presence in circulation. Crucially, aprepitant readily crosses the blood-brain barrier, enabling effective central blockade of NK-1 receptors located in key emetic control centres (9). These properties collectively underpin its efficacy, particularly in the critical 24 - 120 hour delayed phase following chemotherapy. The standard regimen for aprepitant in CINV prophylaxis is a 3-day oral regimen: 125 mg administered 1 hour prior to chemotherapy on Day 1, followed by 80 mg once daily on Days 2 and 3 (10). This regimen is designed to provide coverage throughout the acute and delayed phases of emesis risk associated with moderately to highly emetogenic chemotherapy (MHEC). Nevertheless, despite its established role and favourable properties, clinical research data specifically evaluating the adoption of Apr for prevention of CINV in CRC patients undergoing common regimens like FOLFOX, mFOLFOX6, FOLFIRI, CAPOX, and SOX remains relatively limited and merits systematic evaluation. Clinical research data on the adoption of Apr for prevention of CINV in CRC patients is limited.

To address this, this meta-analysis included published randomized controlled trials investigating the efficacy of Apr in preventing CINV in CRC patients accepting MHEC regimens such as FOLFOX, mFOLFOX6, FOLFIRI, CAPOX and S-1 and oxaliplatin (SOX). This systematic review aimed to evaluate Apr's efficacy and safety, providing valuable references for guiding the management of nausea and vomiting in CRC chemotherapy.

Materials and Methods

Search strategy

The search was conducted in the databases PubMed, Embase and the Cochrane Library. For PubMed, the search terms included "aprepitant", "colorectal cancer", "chemotherapy-induced nausea and vomiting", along with their synonyms and related terms, combined using Boolean operators such as "aprepitant AND (colorectal cancer) AND (chemotherapy-induced nausea and vomiting)". Additionally, truncation symbols were applied to expand the search scope, for example, "colorectal cancer*" to retrieve terms like "colorectal cancer" and "colorectal cancers." A similar search strategy was applied to the Embase database, adjusting the syntax of the search terms according to the database's specific characteristics to ensure comprehensive and accurate retrieval. For the Cochrane Library, the proprietary search tools and syntax were utilized, inputting search term combinations similar to those mentioned above, to retrieve relevant Cochrane systematic reviews and original research studies. The search was limited to publicly published randomized controlled trials from January 2003 (the year Apr was approved for use in the United States) to May 2025.

Criteria

Inclusion criteria: (i) randomized controlled trial; (ii) participants were patients diagnosed with CRC through pathological examination and treated with MHEC; (iii) the intervention group received Apr alone or with 5-HT3 receptor antagonists and dexamethasone (Dex), while Control group received 5-HT3 receptor antagonists and Dex; (iv) outcome measures include CINV complete response, CINV complete protection, no nausea, no vomiting, and adverse reactions.

Exclusion criteria: (i) duplicated publications; (ii) non-randomized controlled trials; (iii) participants without clear clinical pathological diagnoses or who had not received MHEC; (iv) studies with protocols that did not meet the standards; (v) case reports, reviews, and conference abstracts; (vi) incorrect or incomplete data; (vii) inability to obtain full texts.

Quality evaluation

Independently, two researchers conducted quality assessment. In the event of discrepancies, discussions or consultations with a third researcher were conducted to reach a consensus. The quality evaluation utilized the Jadad scale (11), which examines aspects of random sequence generation, allocation concealment, blinding, and handling of withdrawals or dropouts. The Jadad scale primarily evaluates random sequence generation (2 points), allocation concealment (2 points), blinding (2 points) and the description of withdrawals and dropouts (1 point), with a total score ranging from 1 to 7. Studies scoring 1 - 3 are considered low quality, while those scoring 4 - 7 are classified as high quality. Papers were classified as low quality with scores ranging from 1 to 3, and high quality with scores from 4 to 7. Furthermore, the Cochrane Reviewer's Handbook 5.0.1 bias risk assessment tool (12) was employed, focusing on random sequence generation, allocation concealment,

blinding, completeness of outcome data, selective reporting, and other relevant criteria. The risk assessment outcomes were categorized as low, high, or unclear risk.

Data extraction

Study data extraction was implemented by two researchers independently, who verified their findings against each other upon completion. In instances of disagreement, discussions or consultation with a third researcher were utilized to achieve a consensus. The extracted information encompassed the first author's name, publication year, study population, chemotherapy regimen, treatment protocols for both Apr group and Control group, sample size, complete response rates for CINV, complete protection rates for CINV, rates of no nausea, and rates of no vomiting in acute, delayed, and overall phases, as well as adverse reactions.

Statistical analysis

Statistical analyses for the included studies were performed employing RevMan5.3. The odds ratio (OR) was utilized as the statistical metric for efficacy analysis of count data, with all effect sizes presented alongside a 95%CI. I2 statistic was employed to assess heterogeneity among the study results. If $p \geq 0.10$ and $I2 \leq 50\%$, the results were considered to show neglectable heterogeneity, allowing for the adoption of a fixed-effect model (FEM) in the meta-analysis. Conversely, if $p < 0.10$ and $I2 > 50\%$, significant heterogeneity was identified, necessitating the application of a random-effects model for the meta-analysis. A Z-test was conducted, with $p \leq 0.05$ implying statistical significance.

Results and Discussion

Search results

Three hundred eighty-one articles were sourced from databases. After duplicates were eliminated, 208 articles were retained for a preliminary review of titles and abstracts. Following the above criteria, 179 papers were excluded for various reasons, including 42 non-randomized controlled trials, 43 studies of differing types, 28 studies on different species, 55 review articles, and 11 conference abstracts. The full texts of 29 initially suitable articles were downloaded, but 22 were excluded due to various criteria: 10 were inaccessible, 5 lacked extractable data, 5 were cohort studies, and 2 had ambiguous designs. In the end, 7 articles (13-19) were included in this meta-analysis (Figure 1).

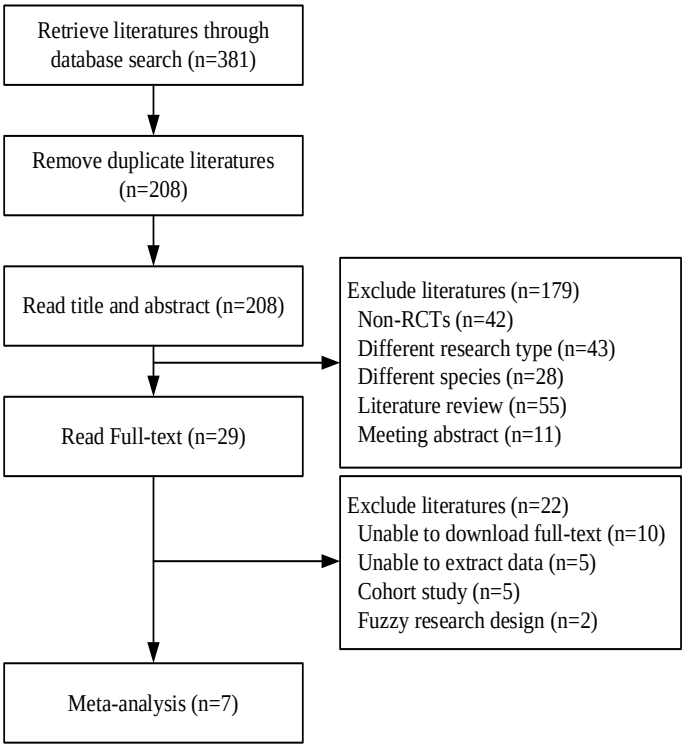

Figure 1.
Literature screening process

Basic literature characteristics and quality evaluation

Seven studies were included (13-19), encompassing a total of 1,812 patients, with 882 participants in Control group and 930 in Apr group. The fundamental characteristics of these studies are summarized in Table I. Utilizing the Jadad scoring system, all seven studies were categorized as high-quality research. Utilizing the Jadad scoring system, all seven studies were categorized as high-quality research (scores ranging from 4 to 6). Detailed assessment of the

Jadad scale items revealed the following: all seven studies (100%) reported using a randomization method. Among these, five studies (13-15, 18, 19) explicitly described the specific method of random sequence generation (*e.g.*, random number table, computer-generated). Three studies (13-15) adequately reported the method of allocation concealment (e.g., sealed envelopes, central randomization). Regarding blinding, one study implemented double-blinding (14) (participants and outcome assessors), while the majority (six studies (13, 15-19)) were open-label without blinding of participants or personnel; however, outcome assessment blinding status was unclear or not reported in most. All seven studies provided descriptions of withdrawals and dropouts, including the number and reasons.

Table I

Basic literature characteristics

Author	Year	Chemotherapy regimen	Intervention measures		Sample size		Jadad
			Control group	Apr group	Control group	Apr group	
Aridome (13)	2016	FOLFOX, CAPOX or FOLFIRI	Dex (9.9 mg on d 1, followed by 8 mg on d 2 and 3)	Dex (6.6 mg on d 1, 8 mg on d 2 and 3) + Apr (125 mg on d 1, 80 mg on d 2 and 3)	54	59	6
Cheng (14)	2022	mFOLFOX6	Dex (10 mg on d 1, followed by 1.5 mg on d 2 and 3)	Apr (125 mg on d 1, 80 mg on d 2 and 3)	155	160	6
Hayashi (15)	2021	FOLFOX or CAPOX	5-HT_3 receptor antagonist+ Dex	5-HT_3 RA + Dex and Apr	136	136	5
Kaneko (16)	2013	mFOLFOX6or FOLFIRI	5-HT_3 receptor antagonist (0.75 mg on d 1)	Apr (125 mg on d 1, 80 mg on d 2 and 3)	27	59	4
Nishimura (17)	2015	FOLFOX, CAPOX or SOX	5-HT_3 receptor antagonist+ Dex	5-HT_3 RA + Dex and Apr	206	207	6
Takemoto (18)	2017	FOLFOX, CAPOX or SOX	Dex (9.9 mg intravenously on d 1, followed by 4 mg orally on d 2 and 3)	Apr (125 mg) + Dex (6.6 mg) on d 1, followed by Apr (80 mg) and Dex (2 mg) on d 2 and 3	183	187	6
Wang (19)	2021	FOLFOX or FOLFIRI	5-HT_3 receptor antagonists (0.25 mg) and Dex (12 mg)	Apr (125 mg on d 1, 80 mg on d 2 and 3); 5-HT_3 receptor antagonist (0.25 mg); Dex (12 mg)	120	123	6

FOLFOX and mFOLFOX6 regimens include oxaliplatin, fluorouracil, and leucovorin; the CAPOX regimen consists of oxaliplatin and capecitabine; the FOLFIRI regimen comprises irinotecan, leucovorin, and fluorouracil; the CAPOX regimen includes oxaliplatin and capecitabine; and the SOX regimen consists of oxaliplatin and tegafur

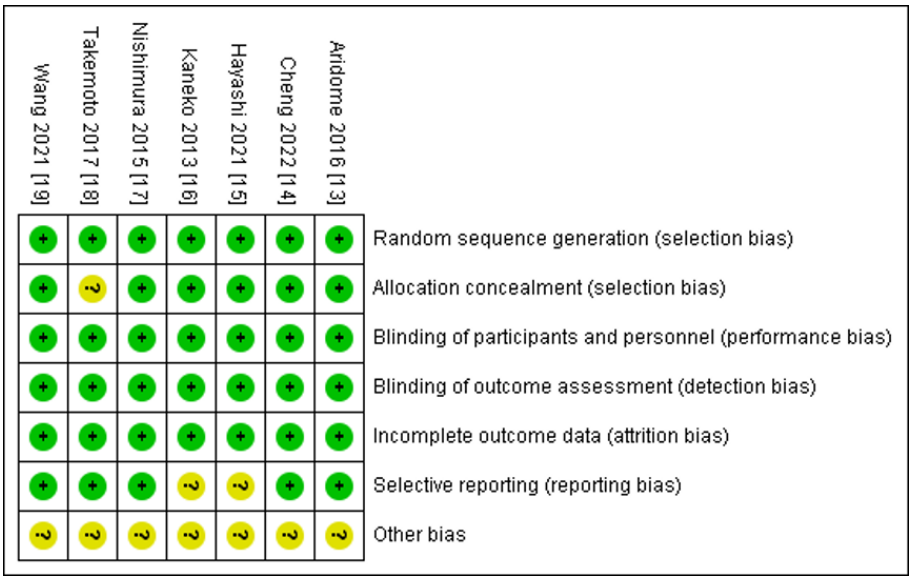

Figure 2.

Summary of quality evaluation

Regarding the bias risk assessment criteria based on the Cochrane Handbook, each study was assessed across key domains (Figure 2). The results indicated a predominantly low risk of bias associated with random sequence generation (attributed to the explicit description in 5 studies (13-15, 18, 19)) and

completeness of outcome data (all studies reported withdrawals/dropouts). However, risk associated with allocation concealment was judged as unclear in four studies (16-19) (due to insufficient reporting) and low in three (13-15). Blinding of participants and personnel was assessed as high risk in six open-label studies (13-15, 17-19) and unclear in one (16); blinding of outcome assessment risk was largely unclear (due to inadequate reporting). Selective reporting risk was low across all studies. The overall bias risk assessment outcomes for each domain per study are presented in Figure 2.

Meta-analysis results

Complete response

Five studies (13, 14, 17-19) evaluated the complete response rate for CINV. The heterogeneity analysis revealed no significant differences among the results (I^2 = 31%, p = 0.12), allowing for the use of a FEM. The meta-analysis findings indicated that the complete response rates for CINV in Apr group were notably greater than those in Control group during the acute phase (OR = 1.64, 95% CI = 0.85–3.17, Z = 1.48, p = 0.14), delayed phase (OR = 2.02, 95%CI = 1.56–2.61, Z = 5.34, p < 0.00001), and overall phase (OR = 1.95, 95%CI = 1.53–2.49, Z = 5.35, p < 0.00001).

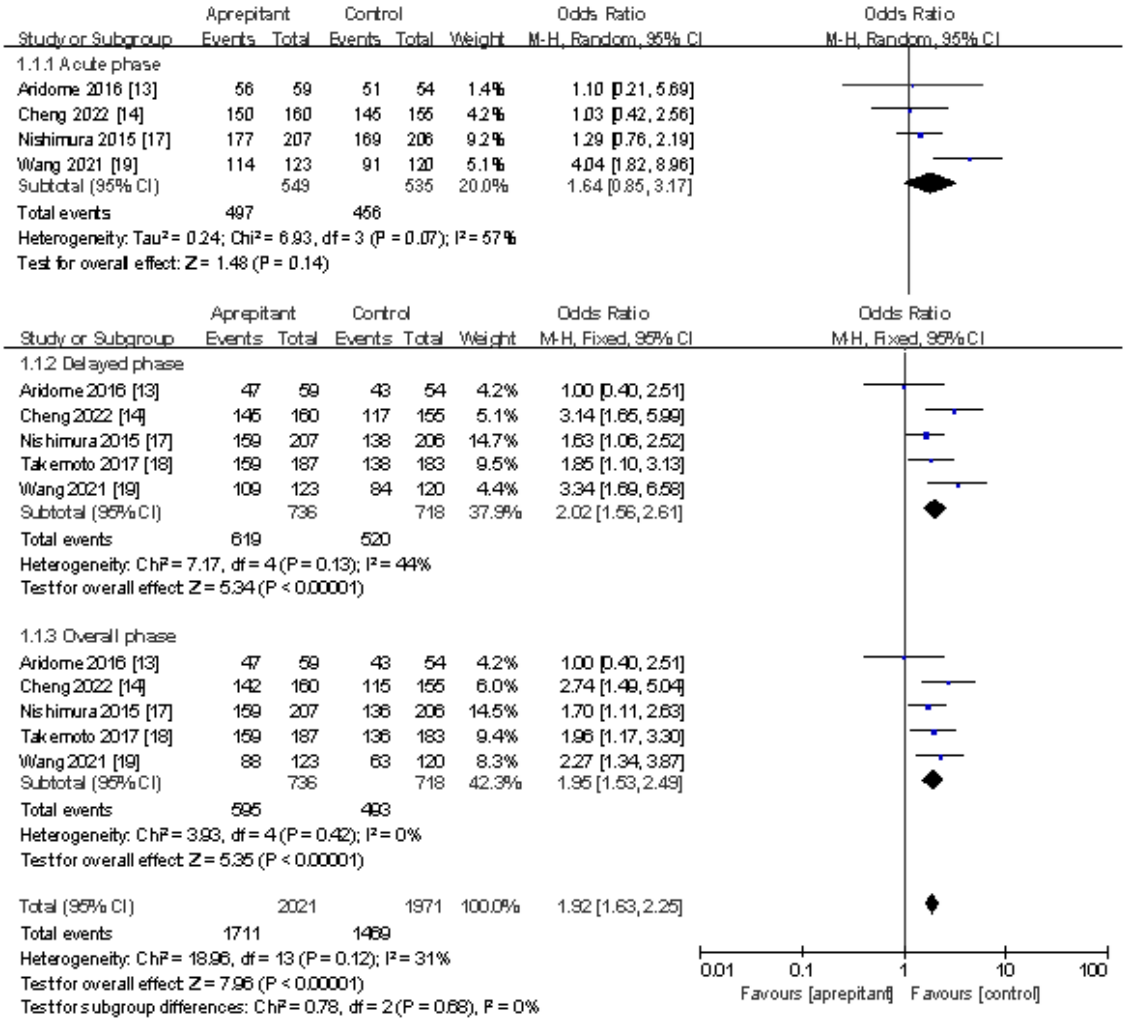

Figure 3.
Meta-analysis forest plot of CINV complete response rate

Complete protection

Three studies (13, 17, 18) assessed the complete protection rate for CINV. The heterogeneity analysis suggested slight variability among the results (I^2 = 0%, p = 0.78), allowing for the application of a FEM. The meta-analysis indicated inconsiderable difference in the CINV complete protection rate between Apr group and Control group during the acute phase (OR = 1.33, 95%CI = 0.82–2.17, Z = 1.17, p = 0.24). Nevertheless, in the delayed phase (OR = 1.55, 95%CI = 1.16–2.08, Z = 2.92, p = 0.003) and overall phase (OR = 1.73, 95%CI = 1.27–2.36, Z = 3.46, p = 0.0005), Apr group exhibited a greatly higher CINV complete protection rate versus Control group (Figure 4).

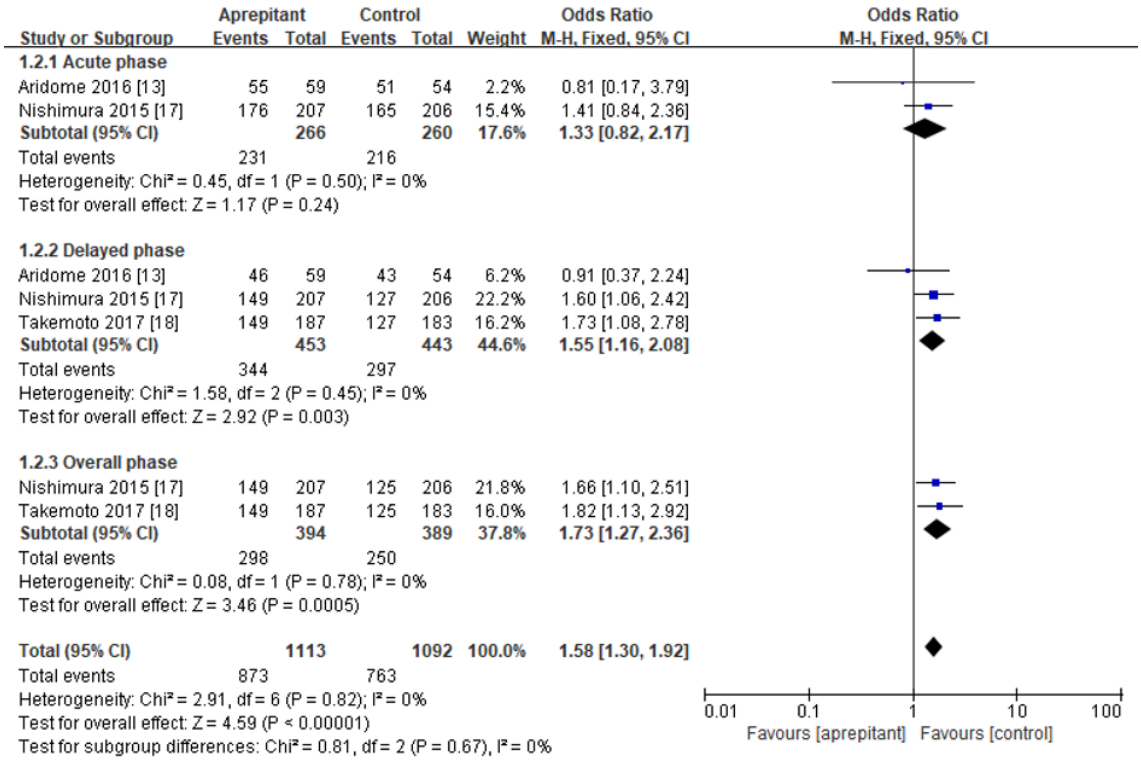

Figure 4.
Meta-analysis forest plot of CINV complete protection rate

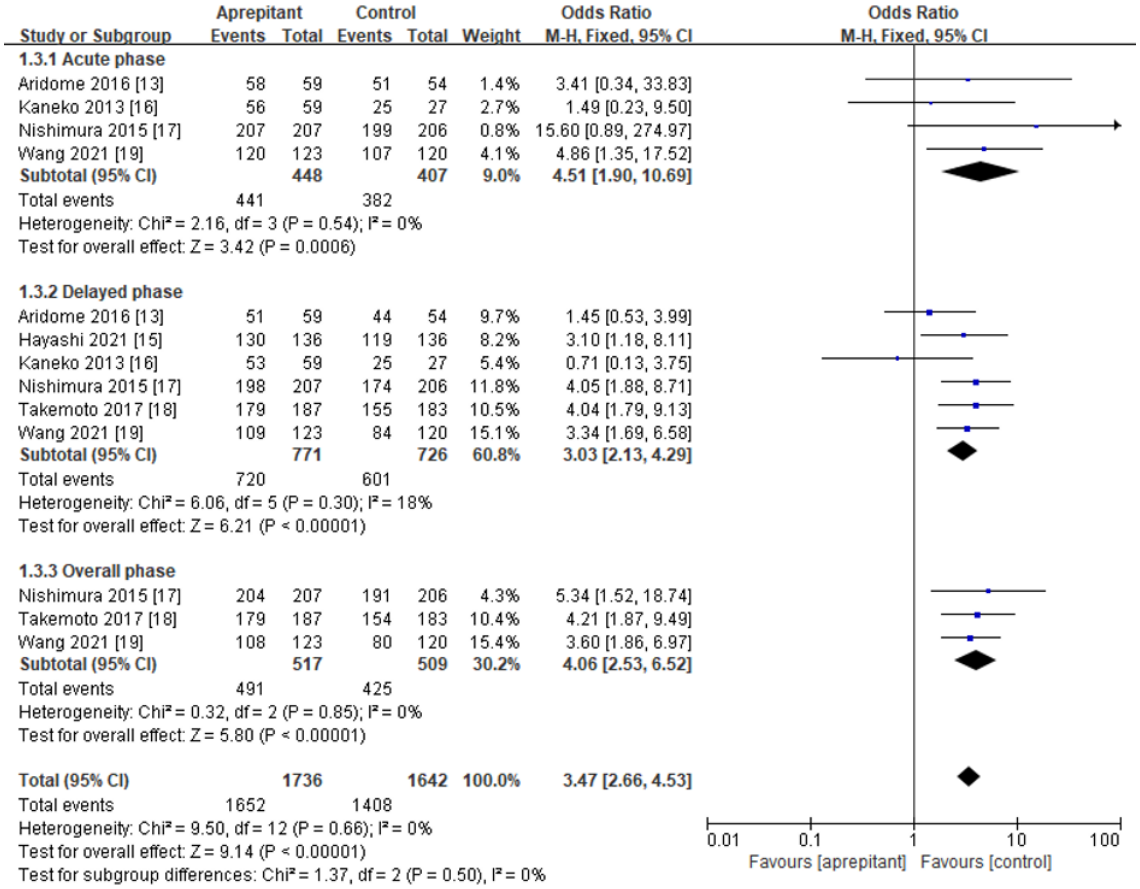

Figure 5.
Meta-analysis forest plot of no voting rate

No vomiting

Six studies (13, 15-19) evaluated the no vomiting rate. The heterogeneity analysis revealed inconsiderable variability among the results (I^2 = 0%, p = 0.66), allowing for the use of a FEM. The meta-analysis findings indicated that the no vomiting rates in Apr group were markedly superior to those in Control group during the acute phase (OR = 4.51, 95%CI = 1.90–10.69, Z = 3.42, p = 0.0006), delayed phase (OR = 3.03, 95%CI = 2.13–4.29, Z = 6.21, p < 0.00001), and overall phase (OR = 4.06, 95%CI = 2.53–6.52, Z = 5.80, p < 0.00001) (Figure 5).

No nausea

Six studies (13, 15-19) assessed the no nausea rate. The heterogeneity analysis revealed no significant differences among the results (I^2 = 12%, p = 0.32), allowing for the application of a FEM. The meta-analysis findings indicated slight differences in the no nausea rates between Apr group and Control group during the acute phase (OR = 1.20, 95%CI = 0.77–1.87, Z = 0.82, p = 0.41) and the delayed phase (OR = 1.20, 95%CI = 0.95–1.51, Z = 1.53, p = 0.13). Nevertheless, during the overall phase, the no nausea rate in Apr group was drastically greater than in Control group (OR = 1.26, 95%CI = 1.01–1.57, Z = 2.06, p = 0.04) (Figure 6).

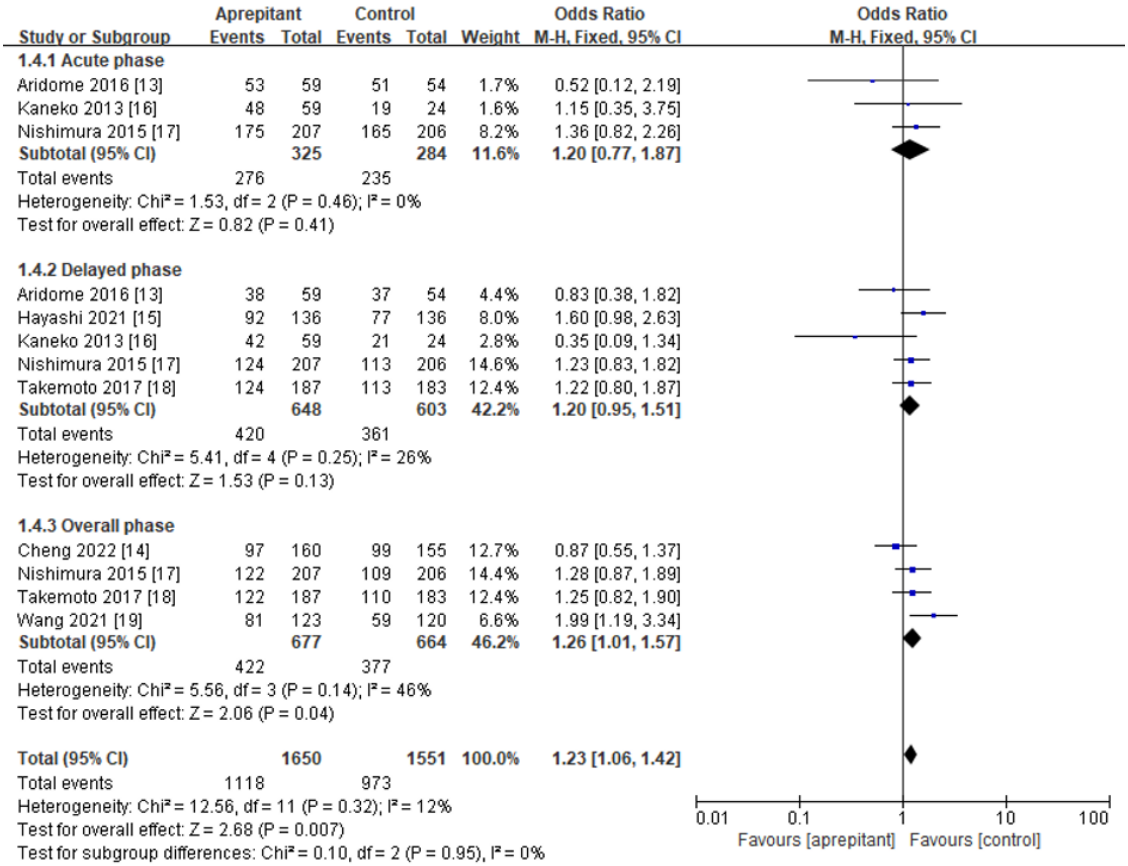

Figure 6.
Meta-analysis forest plot of no nausea rate

Adverse reactions

Four studies (13, 14, 17, 19) evaluated the adverse reactions rate. A random-effects model (REM) was employed for the analysis shown in Figure 7A (I^2 = 65%, p = 0.06). Heterogeneity analysis for the remaining comparisons revealed low variability among the studies (I^2 = 7%, p = 0.39), thereby supporting the use of a FEM for subsequent analyses. The results of the meta-analysis indicated that the overall adverse reaction rate in Apr group, encompassed skin-related reactions, anorexia, fatigue, diarrhoea, constipation, oral mucositis, leukopenia, neutropenia and thrombocytopenia (Figure 7). Figure 7 showed no significant difference in skin-related adverse events between the two groups (OR = 0.47, 95%CI = 0.14–1.59, Z = 1.22, p = 0.22); No significant difference in anorexia (OR = 1.05, 95%CI = 0.69–1.52, Z = 0.11, p = 0.92), fatigue (OR = 0.88, 95%CI = 0.43–1.81, Z = 0.34, p = 0.73), diarrhoea (OR = 0.92, 95%CI = 0.55–1.52, Z = 0.33, p = 0.74), constipation (OR = 0.70, 95%CI = 0.48–1.01, Z = 1.91, p = 0.06), oral mucositis (OR = 0.26, 95%CI = 0.05–1.28, Z = 1.65, p = 0.10), leukopenia (OR = 1.06, 95%CI = 0.72–1.56, Z = 0.31, p = 0.76), neutropenia (OR = 1.12, 95%CI = 0.78–1.60, Z = 0.61, p = 0.54) and thrombocytopenia (OR = 0.55, 95%CI = 0.29–1.02, Z = 1.91, p = 0.06).

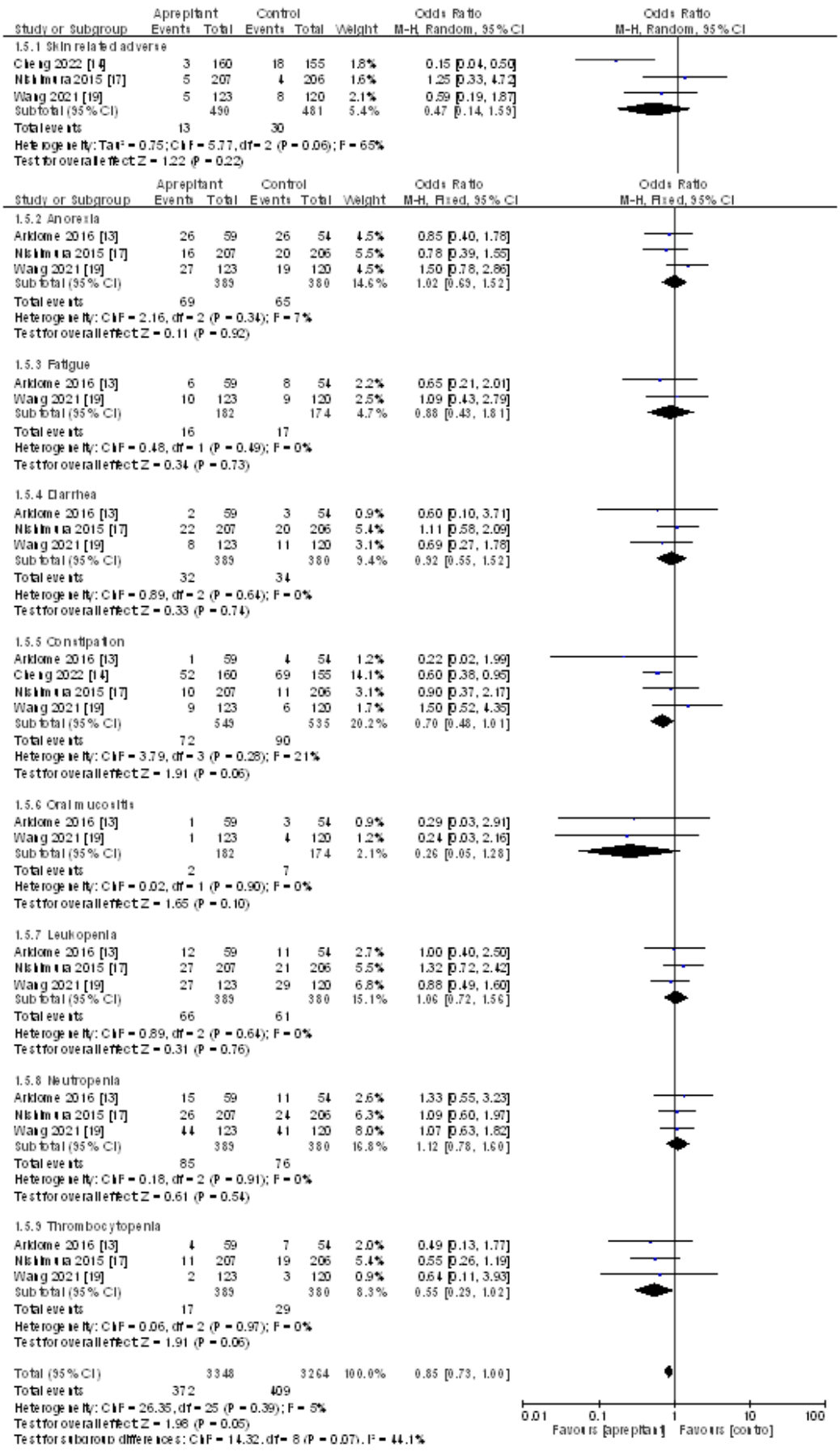

Figure 7.
Meta-analysis forest plot of adverse reactions

Bias analysis

Utilizing *RevMan5.3*, funnel plots were created for the CINV complete response rate and adverse reactions data. The plots displayed a largely symmetrical shape, suggesting a low level of variability in the study outcomes and minimal publication bias. The funnel plots depicting publication bias are presented in Figure 8 and Figure 9.

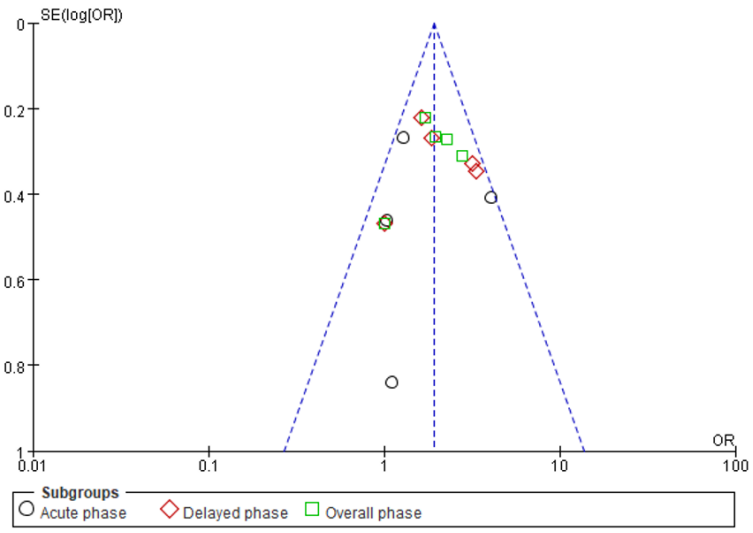

Figure 8.

Funnel plot of publication bias in CINV complete response rate

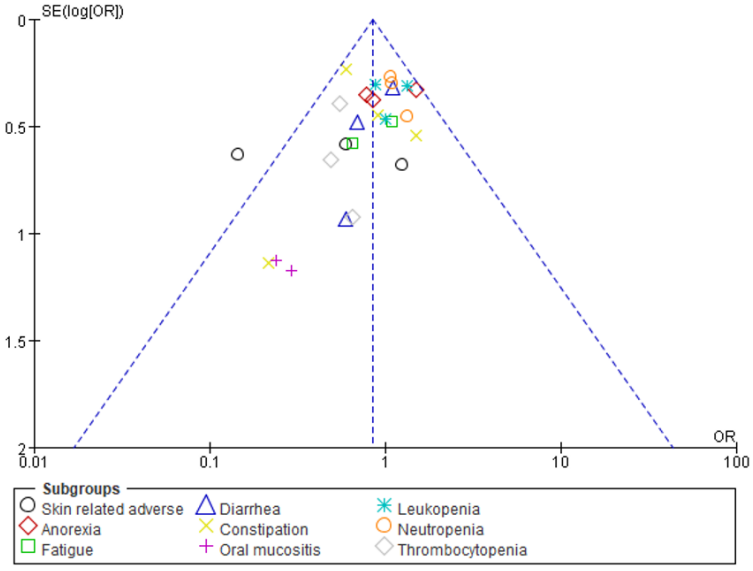

Figure 9.

Funnel plot of publication bias in adverse reactions

Oxaliplatin is classified as a moderately emetogenic chemotherapeutic agent. In patients with CRC, CINV may persist for 3 - 4 days post-treatment, significantly impairing treatment adherence (20). The underlying mechanisms of CINV are currently understood to involve several pathways: (i) chemotherapeutic agents directly stimulate the gastrointestinal tract to release neurotransmitters, which are transmitted *via* vagal and sympathetic afferents to the central nervous system to induce emesis; (ii) chemotherapeutic agents and their metabolites directly activate the chemoreceptor trigger zone (CTZ); and (iii) neurotransmitters directly stimulate the cerebral cortex (21). Substance P, a key neurotransmitter, plays a central role in emetic signalling by binding to neurokinin-1 (NK-1) receptors widely distributed in brain regions associated with the emetic reflex, such as the nucleus tractus solitarius and the area postrema in the medulla oblongata (22). Aprepitant, the first oral NK-1 receptor antagonist, exerts its antiemetic effect by competitively blocking the binding of substance P to NK-1 receptors, thereby inhibiting central emetic signalling at its origin (23). Analysis of the present study's results demonstrates that aprepitant significantly enhances the prevention of CINV in CRC patients undergoing the MHEC regimen. The superior efficacy of aprepitant – particularly during

the delayed phase (24 - 120 hours) and the overall period – can be mechanistically attributed to its high-affinity, targeted antagonism of NK-1 receptors. In contrast to 5-HT3 receptor antagonists, which primarily act peripherally by inhibiting vagal-mediated acute-phase emesis, aprepitant centrally blocks the binding of substance P within the brainstem emetic centres, including the nucleus tractus solitarius and the area postrema (24). Substance P is released in response to cytotoxic stimuli and sustains emetic signalling during the delayed phase of CINV through activation of NK-1 receptors. Aprepitant's prolonged half-life (9 - 13 hours), high permeability across the blood-brain barrier, and sustained receptor occupancy extend the inhibition of this pathway, thereby accounting for its marked efficacy in controlling delayed-phase CINV. Specifically, aprepitant significantly improved delayed-phase complete response ($OR = 2.02$, $p < 0.00001$) and no vomiting rates ($OR = 3.03$, $p < 0.00001$). These findings are consistent with its pharmacokinetic properties and further underscore the pivotal role of the neurokinin signalling pathway in the pathophysiology of delayed emesis.

From the perspective of clinical guidelines, the findings of this study are highly consistent with the 2023 update of the MASCC/ESMO antiemetic guidelines. The updated recommendations clearly advocate for a triple antiemetic regimen – comprising an NK-1 receptor antagonist, a 5-HT3 receptor antagonist, and dexamethasone – for patients receiving MHEC, with particular emphasis on the central role of NK-1 receptor antagonists in managing delayed-phase CINV (25, 26). Common chemotherapy regimens for CRC, such as FOLFOX and CAPOX, fall within the MHEC risk category. This study demonstrates that the addition of aprepitant significantly improves CINV control in such patients, particularly in the delayed phase targeted by the guidelines (complete protection rate $OR = 1.55$), as well as in overall efficacy. These results not only validate the scientific rationale behind current guideline recommendations but also provide population-specific evidence focused on CRC patients. As such, the study contributes to the evidence base for cancer-type-specific antiemetic strategies and offers practical insights for personalized antiemetic management in clinical practice.

In this meta-analysis, certain outcome indicators exhibited moderate heterogeneity (*e.g.*, complete response in the acute phase: $I^2 = 31\%$). The potential sources of heterogeneity are primarily attributed to differences in chemotherapy regimens. The included studies encompassed various protocols such as FOLFOX, CAPOX and FOLFIRI, with FOLFIRI containing irinotecan, which may differ in emetogenic intensity and duration compared to oxaliplatin-based regimens. Additional contributing factors include variations in medication dosage and treatment schedules. For instance, the dexamethasone regimen in Aridome *et al.* (2016) was "Day 1: 9.9 mg; Days 2 - 3: 8 mg", whereas in Takemoto *et al.* (2017), it was "Day 1: 6.6 mg; Days 2 - 3: 2 mg". Such differences in corticosteroid dosing may influence the synergistic efficacy of antiemetic therapy (27, 28). Population characteristics also varied among studies, with inconsistencies in patient age, sex distribution, and comorbidity profiles. Notably, age has been identified as a potential determinant of CINV susceptibility. Furthermore, differences in outcome assessment methods represent another source of variation. Some studies did not specify the tools used to evaluate "absence of nausea" (*e.g.*, visual analogue scale *vs.* patient-reported outcomes), which could introduce bias. Although the observed heterogeneity did not exceed the threshold for statistical significance ($I^2 < 50\%$), it highlights the need for individualized antiemetic strategies in clinical practice, tailored to specific chemotherapy regimens and patient characteristics (29, 30). The findings of this study offer several concrete recommendations for clinical practice. For patients with CRC receiving MHEC regimens such as FOLFOX, CAPOX, or FOLFIRI, it is recommended to adopt a standard triple antiemetic regimen comprising aprepitant, a 5-HT3 receptor antagonist, and dexamethasone. Given aprepitant's significant efficacy in controlling delayed-phase CINV – particularly its high no-vomiting rate during the delayed phase ($OR = 3.03$) – it is especially suitable for patients with a history of delayed emesis or poor response to conventional antiemetic regimens. In terms of dosing, the standard regimen of aprepitant (125 mg on Day 1, followed by 80 mg on Days 2 and 3) is generally sufficient for most patients. Attention should also be given to dose adjustments of dexamethasone to optimize synergistic effects while minimizing potential adverse reactions (*e.g.*, dose reduction of dexamethasone when co-administered with aprepitant) (31, 32). This study also demonstrated that the overall adverse reaction rate associated with aprepitant was significantly lower than that of the control group ($OR = 0.85$), supporting its favourable safety profile. This finding substantiates its routine use in vulnerable populations, including elderly patients and those with comorbidities. Optimizing antiemetic regimens not only improves patients' quality of life and enhances adherence to chemotherapy but also ultimately contributes to better therapeutic outcomes in CRC. By specifically targeting the NK-1 receptor pathway, aprepitant demonstrates marked advantages in the prevention of CINV associated with MHEC in CRC patients. Its efficacy and safety are well supported by current evidence, reinforcing the recommendations of authoritative guide-lines and offering clear, actionable strategies for clinical implementation. These findings also underscore its translational value in clinical oncology (33, 34). Future research should further explore dose optimization of aprepitant across various chemotherapy protocols

and evaluate its efficacy in special populations, such as those with advanced or refractory CRC.

Nevertheless, this meta-analysis has certain limitations. The included studies employed varying treatment regimens, including both dual and triple therapies, which may affect the reliability of the results. The primary limitation of this study lies in the relatively small number of randomized controlled trials (n = 7) included, representing only a small fraction (1.8%) of the initially screened literature. Although strict inclusion and exclusion criteria were applied to ensure study quality, this may restrict the generalizability of the findings and increase the risk of publication bias. Additionally, the literature search was limited to published English-language articles, excluding grey literature sources such as clinical trial registries and dissertations, as well as non-English publications, which may have resulted in the omission of relevant studies. Future updates should aim to incorporate a broader range of sources to enhance comprehensiveness.

Conclusions

In summary, Apr demonstrates excellent efficacy in preventing CINV in CRC patients undergoing MHEC regimens such as FOLFOX, mFOLFOX6, FOLFIRI, CAPOX and SOX, while exhibiting a favourable safety profile. Nevertheless, future multicentre, large-scale, high-quality randomized controlled trials are needed to further validate the antiemetic effects of Apr and to inform the development of optimal antiemetic strategies for CRC chemotherapy patients.

Acknowledgement

Not applicable.

Funding

Not applicable.

Availability of data and materials

The data generated in the present study are included in the figures and/or tables of this article.

Ethics approval and consent to participate

Not applicable.

AI use disclosure

Not applicable.

Conflict of interest

The authors declare no conflict of interest.

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