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Original Research Article

Challenges in chemotherapy-induced nausea and vomiting (CINV) management: A systematic review

Nurul Suhaida Badarudin[1], Noraida Mohamed Shah[1]*, Fuad Ismail[2], Farida Islahudin[1], Nurul Ain Mohd Tahir[1]

[1]Centre of Quality Management of Medicines, Faculty of Pharmacy, Universiti Kebangsaan Malaysia, [2]Department of Radiotherapy & Oncology, Universiti Kebangsaan Malaysia Medical Centre, Kuala Lumpur, Malaysia

For correspondence:* ***Email:* *noraida_mshah@ukm.edu.my*

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Abstract

Purpose: *To systematically evaluate evidence regarding the barriers and challenges associated with chemotherapy-induced nausea and vomiting (CINV).*
Methods: *The databases Pubmed, Ovid, Scopus, Cochrane Library, Wiley Online, and Web of Science were searched using the following keywords: challenges, prevention, CINV, chemotherapy and their corresponding alternative keywords. This review included all studies involving adult cancer patients receiving chemotherapy exclusively, the caretaker, and healthcare professionals handling cancer patients, without geographical restriction. The articles used were in English language and were original primary studies. The data extraction form was developed based on PRISMA guide. The Joanna Briggs Institute (JBI) Critical Appraisal tool was used to assess the quality of the studies.*
Results: *From 1,170 related articles retrieved, 38 were included in this review of which 9 articles were from European countries while 7 were from the United States of America. All articles met the criterion of the JBI critical appraisal. The reviews indicated that the barriers and challenges reported in the management of CINV would include failure to adhere to the antiemetic guideline, misconception about CINV and its prevention, and nausea and delayed CINV.*
Conclusion: *Interventions such as enhancing nausea and delayed vomiting control, raising awareness of antiemetic guidelines among healthcare professionals, and dispelling misconceptions need to be planned and implemented to overcome the barriers and challenges and improve the quality of CINV management.*

Keywords: *Chemotherapy-induced nausea and vomiting (CINV), Nausea, Vomiting, Supportive care, Anti-emetic*

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INTRODUCTION

According to the National Cancer Institute [1], the most common side effects of chemotherapy are nausea and vomiting. Thus, the prevention of chemotherapy-induced nausea and vomiting (CINV) is an important element of supportive care in cancer therapy. Poorly controlled CINV not only causes a substantial increase in the cost of treating CINV complications, but it also causes a delay in subsequent chemotherapy treatment,

at times to the extent of treatment discontinuation, and reduces the quality of the patient's quality of life [2-6].

Globally, the incidence of CINV varies considerably, ranging from 20 to 70 %, depending on factors such as population demographics, geographical locations, prescription protocols, institutional reimbursement for antiemetics, and local drug regulations [7-9]. However, a local study recently conducted established retrospective data where 57 % of highly emetogenic chemotherapy (HEC) patients experienced CINV despite the use of dual antiemetics [10].

Studies related to CINV were primarily focused on the adoption of clinical practice standards despite the fact that CINV management is complex and includes interventions that involve not only medicines but also dietary and psychological components [11]. However, the components of CINV management have not been identified, nor routinely addressed or considered, even though information on this is essential to stakeholders in achieving high-quality cancer care. Thus, this systematic review was conducted to gather information and evidence and evaluate the barriers and challenges in CINV management that could otherwise lead to poorly controlled CINV.

Hence, the primary question of this systematic review was to determine "What are the barriers and challenges to effective CINV management?". Secondly to ascertain "What are the perceptions or perspectives of cancer patients on their CINV management?" and thirdly "What are the views of service providers?" The findings will serve as evidence in the development of guidance on re-strategizing CINV management for cancer patients.

METHODS

Search strategy

This review focused on identifying the barriers and challenges as well as the perception during CINV management. The electronic searches in scientific databases were carried out in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [12]. The following databases were utilized in January 2022: Cochrane Library, Ovid, PUBMED/MEDLINE, SCOPUS, WILEY ONLINE LIBRARY, and WEB OF SCIENCE. Comprehensive strategies were developed, including the use of index and keyword like "Challenges", "Prevention", "CINV" and "Chemotherapy" and the appropriate alternative words. No time limitations were considered for searching and selecting the articles.

Inclusion and exclusion criteria

The inclusion criteria for studies in this review include cancer patients aged 18 years or older who were undergoing chemotherapy exclusively, healthcare professionals handling cancer patients, and caretakers of cancer patients receiving chemotherapy. The studies selected were original primary studies and conducted in the English language. Data on antiemetic effectiveness were excluded.

Data collection and analysis

Selection of studies

The primary investigator evaluated the abstracts and titles of articles obtained through electronic and manual searches to determine eligibility based on the predefined inclusion or exclusion criteria. When there was a situation where it was difficult to decide based on the title and abstract, the full article was retrieved for further evaluation. Full-text versions of all articles meeting eligibility criteria, as determined by at least one of the reviewers, were acquired for further examination. At this stage, every identified study was evaluated independently for eligibility by the principal researcher. All reviewers were involved in reaching a consensus to resolve any ambiguities regarding eligibility.

Selection of articles

Figure 1 shows the number of articles identified, screened, and finally selected for systematic review. Initially, 1170 were identified through database screening. Thirty were removed due to duplication and a further 1034 were removed after the titles and abstracts were screened. One hundred and six studies were sought for full texts and finally, 38 articles were included in this review.

Included articles

Of the 38 articles selected for systematic review, 9 were from European Countries while 7 were from the United States of America. Twenty-four articles had patients as study subjects, 7 articles involved healthcare professionals (HCPs), and 7 studies had both HCPs and patients as study subjects. Additionally, 3 of the articles selected had qualitative study designs while the rest were mainly quantitative studies using questionnaires.

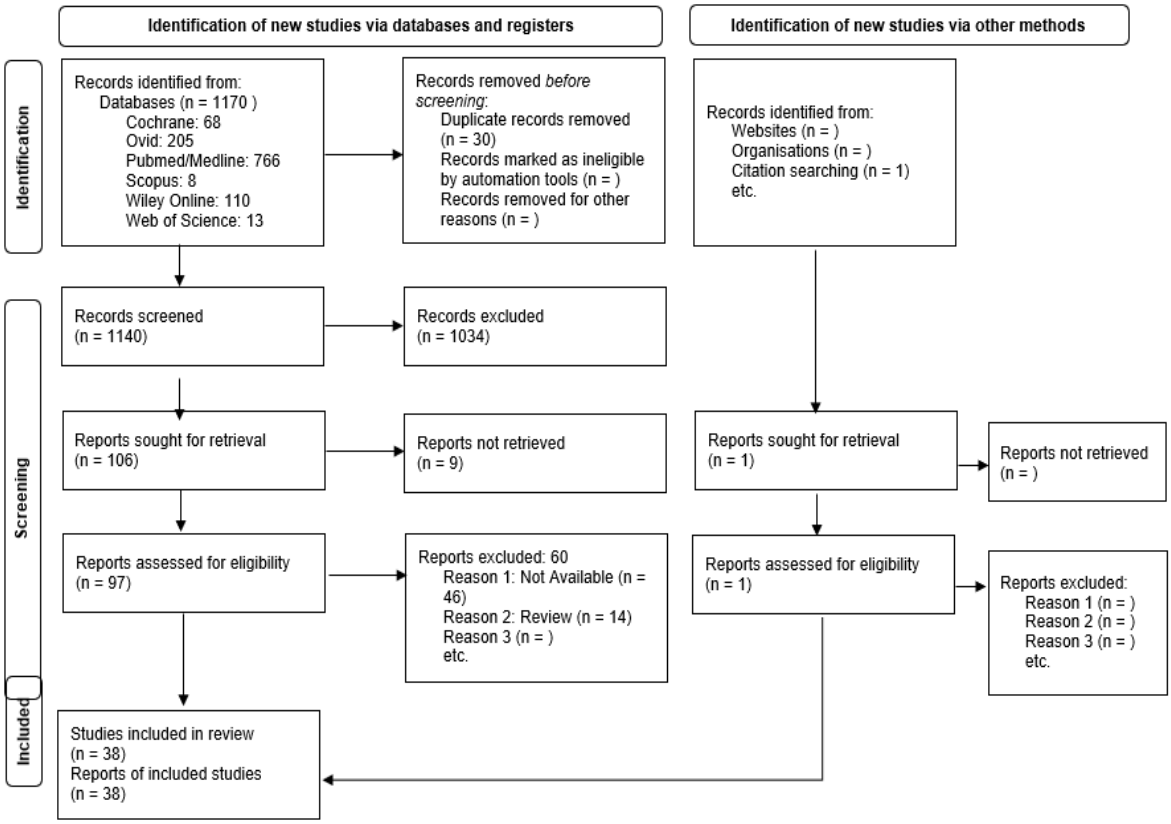

Figure 1: Search flow diagram for systematic review according to PRISMA statement

The sample sizes of these studies ranged from 15 to 17,609. Table 1 summarizes the characteristics of the reviewed articles.

Data extraction and management

The data extraction form was developed based on the PRISMA guide [12]. Any disagreements amongst reviewers about data extraction were discussed and resolved via consensus. Data were entered into an Excel spreadsheet and study details were reported in a Table. Information on the study's methods, such as its design, the total number of individuals, precise timing information, and participant details, were extracted. Geographical location (Country, region, rural/urban area) was also obtained about institutional and community factors. All timing details for barriers and challenges were systematically and comprehensively recorded. Any information relevant to the objectives of this systematic review was also extracted.

Assessment of quality in included studies

The quality of studies was evaluated using The Joanna Briggs Institute (JBI) Critical Appraisal tool [13,14], which encompassed assessing the trustworthiness, relevance, and results of the articles in this study.

Data synthesis

Data were extracted, organized, and duplicates removed using ENDNOTE® Version 20. A summary of basic details of the studies (number and type of participants, study year, study design, and location) was tabulated. The narrative synthesis was used to systematically synthesize findings from multiple studies using various study designs including quantitative and qualitative studies. These findings are presented descriptively.

The barriers and challenges in CINV were categorized into 7 main groups as listed in Table 2. The seven main groups extracted from the thirty-eight (38) articles reviewed were; antiemetic guidelines, misperception, types of CINV, economic, technical, risk factors, and others.

RESULTS

Antiemetic guidelines

Antiemetic guidelines are categorized into 3 sub-groups as follows: non-adherent to guidelines, prescribing trends among oncologists, and lack of familiarity with perceived chemo agents' emetogenicity. Guidelines-inconsistency was reported in 10 studies, prescribing trends were

Table 1: Summary of included articles

First author; year	Location	Study respondents	Number of participants	Method
Aapro; 2018	Europe (Italy, France, Germany, Spain)	oncologist	299 (50 % hospital oncologist; 50 % office-based oncologist)	Online questionnaire
Aapro; 2021	Europe (Italy, France, Germany, Spain)	oncologist	610	Online record form
Aapro; 2022	35 sites in Austria, Bulgaria, Czech Republic, Poland, Romania, and Slovakia	patients	1115	prospective, non-interventional, multicentre study
Abunahlah; 2016	Turkey	patients	100 single center	prospective observational study
Araz; 2018	Turkey	oncologist	137	online questionnaire
Bourdeanu; 2012	US	adult (>18) patient	358	retrospective chart review
Caracuel; 2015	Spain	patients	102	observational perspective
Carnio; 2018	Italy	patients oncologist nurse	188 patients	observational perspective, questionnaire
Chan; 2008	Singapore	oncologist	20	observational perspective, questionnaire
Chan; 2015	Singapore	patients	235	observational perspective
Cohen; 2007	US (10 community oncology clinics)	patients	151	observational prospective
Di Mattei; 2020	Italy	patients	81	observational prospective
Di Maio; 2015	Italy	patients	1090	RCT
Dienlenseger; 2019	16 European countries	nurse	212	online questionnaire
Clark-Snow; 2018	US	nurse	531	questionnaire
Valle; 2006	Mexico (9 oncology centres)	HCP patients	82 patients 19 oncologists and nurse	prospective
Gilmore; 2014	4 oncology practice US	Patients	1295	prospective, cross-sectional, multicentre study
Glaus; 2004	Europe (5 centre)	Patients	248	prospective, cross-sectional, multicentre study
Haiderali; 2011	US (32 oncology centers)	Patients	178	observational prospective
Hernandez; 2015	Canada	Patients	168	Multicentre, randomized, questionnaire
Hilarius; 2012	Amsterdam (9 hospitals)	Patients	225	prospective, multicentre, observational

Note: HCP: healthcare professionals; UK: United Kingdom; US: United States of America; RCT: randomized controlled trial

Table 1: Summary of included articles (*continued*)

First author; year	Location	Study respondents	Number of participants	Method
Hsieh; 2015	Asia Pacific (6 countries)	patients oncologist	648	observational prospective, questionnaire
Ihbe-Heffinger; 2004	German (3 hospitals)	Patients	188	prospective, multicentre, cross-sectional questionnaires
Ilyas; 2020	Saudi Arabia	Patients	98	Cross-sectional, retrospective questionnaires
Krok-Schoen; 2019	US	patients oncologist	22	qualitative, focus group interview
Kus; 2021	Turkey (multicentre)	Patients	238	Face-to-face questionnaires
Lopes-Jimenez; 2006	Spain	Patients	177	multicentre, prospective, observational
Molassiotis; 2008	UK	Patients	102	observational prospective
Molassiotis; 2008	UK	Patients	17	qualitative, face-to-face interview, or over the phone
Navari; 2021	US	Patients	17,609	retrospective, patient record
O'Brien;1993	Canada (2 centres)	Patients	92	questionnaire
Poon; 2013	Singapore	Patients	473	prospective, observational
Salihah; 2016	Malaysia	Patients	15	qualitative, face-to-face interview
Salsman; 2012	US	patients HCP	299 patients 63 oncologist 78 nurse	prospective, questionnaire
So; 2013	Hong Kong	Nurse	103	descriptive cross-sectional questionnaire
Vidall; 2016	UK	Patients HCP	184; 75 physicians, 31 nurses, 78 patients.	multinational, observational questionnaire
Vidall; 2015	UK, France, Italy, Spain, Germany	patients HCP	947; 386 patients 375 oncologists 186 oncology nurses	multinational, observational questionnaire
Badarudin; 2022	Malaysia	Patients	419	retrospective, patient record

Note: HCP: healthcare professionals; UK: United Kingdom; US: United States of America; RCT: randomized controlled trial

Table 2: Evidence for barriers to effective CINV management

Category	Barriers/ challenges	First author, year	Findings
Antiemetic Guidelines	Guidelines-inconsistent	Aapro; 2018 [15]	Moderate: 5.0-5.3 (scale 1-7; 7 complete adherence)
		Abunahlah; 2016 [16]	The guideline non-adherent for acute (GAGA) and delayed (GAGD) CINV prevention in the first cycle was 20 and 72%, respectively Guideline non-adherence resulted from over-prescription, under-prescription, and inappropriate dose or inappropriate prescription
		Chan; 2008 [17]	5 % adhered to guidelines for delayed CINV
		Dielenseger; 2019 [18]	HEC: 55 % administered triple agent antiemetic combination.
		Clark-Snow; 2018 [19]	Inconsistencies with guidelines in delayed phase for HEC and MEC settings
		Gilmore; 2014 [20]	Main reason for the lack of adherence was no steroid was prescribed in the delayed phase for HEC
		Ihbe-Heffinger; 2004 [21]	Adherence to ASCO guideline: Acute CINV prophylaxis: 89.2%; Delayed CINV prophylaxis: 49.2%
		Molassiotis; 2008 [22]	Adherence to international guidelines: HEC:41.2%; MEC: 74.5%; LEC: 42.9%; Minimally emetogenic chemotherapy: 66.7%
		Aapro; 2018 [15]	Monotherapy with NK1RA or 5HT3RA (with or without steroids) in HEC
		Navari; 2021 [23]	Non-adherence to antiemesis guidelines due to the omission of NKl RA: Cisplatin course: 34%; AC course: 24%
	Prescribing trends	Aapro; 2021 [24]	low NK1RA used in HEC; 12% were not prescribed with antiemetic
		Aapro; 2022 [6]	Only 23% of patients received CINV prophylaxis that compliant to guidelines Underutilization of NK1RA in HEC, corticosteroids in MEC
		Caracuel; 2015 [11]	Statistically significant adherence to the hospital protocol was observed in patients under 50 years old, who are at a higher risk of emesis (p = 0.015), as well as in patients without prior experience of nausea and vomiting (lower risk, p = 0.010)
		Gilmore; 2014 [20]	Patients receiving cisplatin-based regimens were more prone to receiving CINV prophylaxis that adhered to guidelines, while those treated with dacarbazine were less likely to receive as per guidelines
		Hilarius; 2012 [25]	89 % experienced delayed nausea three days after their first chemotherapy cycle when using a 5HT3 antagonist, while only 56 % of those using either an aprepitant and a corticosteroid combination or a corticosteroid alone reported the same symptom (p = 0.03)
	Lack of familiarity	Aapro; 2021 [24]	Percentage of Oncologists perceived as HEC: 55% cisplatin-based; 51% AC-bases; 24% carboplatin But only the following percentage received guidelines-recommended therapy: 18% cisplatin-based; 24% AC-bases; 7% carboplatin
		Araz; 2019 [26]	Perceived adherence of HEC: Acute: 92% adhere; Delayed: 15% adhere; MEC: Acute: 73% adhere; Delayed: 56% adhere

Table 2: Evidence for barriers to effective CINV management *(continued)*

Category	Barriers/ challenges	First author, year	Findings
Misperception	Fearful of side effects of antiemetics	Chan; 2008 [17]	Corticosteroid: gastric irritation, insomnia, weight, worsening hypertension, and diabetes. Metoclopramide: restlessness and increased risk of Parkinsonian symptoms
		Haiderali; 2011 [27]	Patients used dexamethasone less often during the delayed phase compared to the acute phase because of previous side effects experienced by patients
		Salsman; 2012 [28]	Patient: "I was concerned about the side effects of medicines that might be given to me to treat my nausea or vomiting" HCP: "I am concerned about the side effects of medicines that might be prescribed to treat my patients' nausea or vomiting."
		Vidall; 2016 [29]	The primary barriers to prescribing prophylactic antiemetics included concerns regarding the antiemetics side effect profile and tolerability. Twenty-seven percent of physicians and 19% of nurses identified this as a contributing factor.
	Underestimation of emetogenic potential	Aapro; 2018 [15]	Percentage of Oncologist perceived MEC for following agents: 11%: Cisplatin > 50 mg/m^2 83%: Cisplatin < 50 mg/m^2 21%: Cyclophosphamide > 1500 mg/m^2 33%: anthracycline-cyclophosphamide
	Underestimation of CINV incidence	Hsieh; 2015 [9]	Over half of the physicians underestimated nausea rates across all phases (52–72%), while the mean predicted rates for emesis exceeded the mean observed rates after HEC and MEC in all phases
		Lopez-Jimenez; 2006 [30]	Physicians and nurses underestimated the incidence vs observed incidence: delayed nausea: 65 vs 87% (p = 0.02) delayed emesis: 44 vs 78% (p = 0.02)
		Vidall; 2015 [31]	HCP overestimate the incidence of CINV than patients recalled following their last chemotherapy and despite patients recalling an improvement of symptoms but underestimated its impact on patients' daily lives.
		Di Maio; 2015 [32]	HCP underestimates the risk of CINV (poor to moderate)
	Perception gap between HCP and patients	Carnio; 2018 [33]	The agreement between HCP and patients is mainly moderate, slightly increasing over time, and becoming substantial for some items
		Vidall; 2015 [31]	Nausea severity and impact experienced by the patient were greater than perceived by the HCP
		Salsman; 2012 [28]	Patients prioritized other aspects of treatment over managing nausea and vomiting (p < 0.0001). Patients preferred healthcare providers to focus on curing their illness rather than controlling nausea and vomiting (p < 0.0001). Providers' awareness of effective treatments for nausea or vomiting was significantly greater (p < 0.0001), while patients expressed a strong desire to limit medication use (p < 0.0001)
		Vidall; 2016 [29]	Healthcare professionals reported that around two-thirds of patients were fully adhering to their prescribed antiemetic regimen at home (59% of physicians and 66% of nurses). However, only 42 % of patients indicated that they followed their regimen consistently.

Table 2: Evidence for barriers to effective CINV management *(continued)*

Category	Barriers/ challenges	First author, year	Findings
Misperception *continued*	Uncertainty of CINV control with antiemetic	Ilyas; 2020 [34]	When it came to managing their CINV symptoms, 57.5% of patients stated antiemetics worked exceptionally well, while 22.9% said they worked moderately to well.
	CINV severity perception	Kus; 2021 [36]	Negative illness perception was positively correlated with CINV grades ($p < 0.001$)
		Salihah; 2016 [37]	"Nausea is debilitating, it could be to feel nauseous without vomiting."
Type of CINV	Delayed CINV	Cohen; 2007 [3]	A major issue that is frequently overlooked and untreated is delayed emesis, which occurs in part because the patient has these symptoms after leaving the clinic.
		Di Mattei; 2020 [38]	Recall bias when reported delayed CINV due to extended length of recall period (3 weeks)
		Dielenseger; 2019 [18]	The delayed phase presents challenges in the control of CINV (64%)
		Clark-Snow; 2018 [19]	Second most challenges/unmet needs were identified as controlling CINV during the delayed phase.
		Valle; 2006 [39]	Incidences of delayed nausea (42% predicted vs 75% observed) and delayed emesis (32% predicted vs 63% observed) after HEC were underestimated by healthcare providers
		Glaus; 2004 [40]	High incidence of delayed emesis was due to the use of cyclophosphamide, a known inducer of late emesis and patient was not optimally treated
		Ilyas; 2020 [34]	The degree of delayed nausea and the patients' assessment of how much superior anti-emetics assisted them in managing CINV symptoms were significantly negative correlated ($p = 0.009$; $r = -0.327$).
	CINV in Cycle 1	Cohen; 2007 [3]	78% of patients with CINV at cycle 1 also developed CINV at cycle 2, and 68% of patients with CINV at cycle 1 also had CINV at cycle 3.
		Hernandez; 2015 [8]	Nausea: In the first cycle, 31% of patients reported having the worst nausea, and 16% reported having the same nausea in the following cycles. Vomiting: 4% had the same level of vomiting during each period, while 11% had their worst episode during the first cycle.
		Molassiotis; 2008 [22]	Acute nausea in cycle 1 was linked to acute nausea in cycles 2 and 3 ($r = 0.60–0.70$ $p < 0.001$) and delayed symptoms in cycles 2 and 3 ($r = 0.38–0.61$, $p < 0.001$). Acute vomiting in cycle 1 was also linked to acute vomiting in all future cycles ($r = 0.36–0.47$, $p < 0.05$).

Table 2: Evidence for barriers to effective CINV management *(continued)*

Category	Barriers/ challenges	First author, year	Findings
Type of CINV *continued*	Chemotherapy -induced nausea (CIN) vs hemotherapy-induced vomiting (CIV)	Glaus; 2004 [40]	Mean FLIE score for all nausea domains was below 6, whereas most of those for the vomiting domain were above 6. All mean scores were lower than 6, suggesting that nausea following chemotherapy had a negative impact on patients' daily life
		Haiderali; 2011 [27]	Vomiting was far less common than nausea, indicating that nausea is the primary issue that CINV patients deal with.
		Haiderali; 2011 [27]	Compared to patients who suffered vomiting ($ 71.07 per patient), those who suffered severe nausea had a greater mean expense ($ 802.40) related to health care utilization.
		Hernandez; 2015 [8]	Based on patients who experienced CINV, 44% chose nausea and worse compared to 2% who reported vomiting.
		Krok-Schoen; 2019 [41]	According to both patients and doctors, the most common and severe adverse effect of chemotherapy was nausea.
		Molassiotis; 2008 [22]	> 50% patients undergoing HEC and MEC, nausea—both acute and delayed—is a serious concern.
		Molassiotis; 2008 [35]	Patients expressed that they felt worse from nausea than from vomiting because they normally felt better after vomiting. Once nausea established, patients reported that nausea was difficult to control.
		O'Brien; 1993 [42]	the risk of nausea relative to emesis increased over time
Economic	Lack of reimbursement	Aapro; 2022 [6]	Underutilization of NKR1A may be to lack of reimbursement in some participating countries in Europe.
		Dielenseger; 2019 [18]	27 and 25% of respondents, respectively, identified the cost of the product and medications not included in the formulary as the primary obstacles.
		Badarudin; 2022 [10]	Limited use of NK1RA was due to its high cost, therefore doctors only prescribe it based on their judgement and the institutional medication budget reimbursement.
	High cost related to CINV	Ihbe-Heffinger; 2004 [21]	Patient receiving cisplatin-containing regimen, had previous episodes of emesis, and presence of delayed CINV were characteristics linked to high expenditures attributable to CINV.
		O'Brien; 1993 [42]	The average total additional cost per patient with nausea or emesis was estimated to be $ 184.
Technical	Communicatio n barrier between HCP and patients	Krok-Schoen; 2019 [41]	Specific questions on CINV should be asked instead of general pain. The patient found it less difficult to communicate with the nurses than the physician. The doctor spoke quickly and short, hence, patient found it easier to communicate with the nurses. The language was one of the reasons for it. Because they are typically introverted, Hispanic women might not talk freely about their symptoms.
		Salsman; 2012 [28]	Patients sought to appear strong by refusing to inform the physician of their nausea or vomiting, HCP: "If my patients' nausea or vomiting is bothersome enough, they will let me know"
	CINV management and support	Vidall; 2016 [29]	44% of patients, 33% of doctors, and 58% of nurses reported the hospital clinical care team's support system as lack or nonexistent in the days after chemotherapy or radiation treatment. Compared to 13 % of doctors and 6% of nurses, 23% of patients said there was no procedure in place that allowed them to express their CINV/RINV problems.

Table 2: Evidence for barriers to effective CINV management *(continued)*

Category	Barriers/ challenges	First author, year	Findings
Risk factors	HCP	Araz; 2019 [26]	Older participants, academicians, and oncologists with more than five years of experience in an oncology department were more likely to follow the delayed phase antiemetic guidelines.
	Cancer-receiving chemotherapy patients	Bourdeanu; 2012 [43]	Asian descent remained a statistically significant independent predictor for clinically important CINV (OR = 2.12, 95% CI 1.18–3.81)
			private vs public insurance, younger age (< 50), GERD as predictors of clinically important CINV.
		Carnio; 2018 [33]	Anxiety represents a strong predictor of CINV
		Chan; 2008 [17]	Oncologist identified anxiety (28%), gender (25%), and age (17%) as at higher risk of developing CINV
		Chan; 2015 [44]	Chemotherapy-induced vomiting was found to be 2.4 times more common in patients with a poor performance status (ECOG ≥1) compared to those with a good performance status (OR = 2.4, 95% CI: 1.1-5.8, p = 0.046).
		Di Mattei; 2020 [38]	Patient has medium to high expectations of nausea as risk factor for the development of nausea
		Kus; 2021 [36]	The Generalized Anxiety Disorder-7 scale: Higher anxiety levels were positively correlated with more severe emesis (r = 0.329; p < 0.001).
		Lopez-Jimenez; 2006 [30]	Younger patient and history with emesis were significant variables for CINV in multivariate analysis
		Poon; 2013 [45]	Patients who scored low on fatigue interference (≤ 3) had a higher probability of experiencing complete protection against CINV, which includes no vomiting, nausea, or breakthrough antiemetics (adjusted odds ratio = 1.57, 95% CI (1.45, 3.08), p = 0.027).
Others	Complexity of antiemetic regimen	Aapro; 2018 [15]	The complexity could be a factor in the inadequate antiemetic regimen's administration.
		Aapro; 2022 [6]	Triple prophylaxis agents' administration can be challenging, necessitating the administration of antiemetic with various dosages, timings, and formulations.
		Krok-Schoen; 2019 [41]	Patients were not interested in adding another drug to their already complex regimen while clinicians responded to nausea with a additional prescription.
		Salsman; 2012 [28]	In general, patients preferred and made an effort to take less medications.
			Additionally, HCPs strive to limit number of medications due to concerns that treating patients' nausea or vomiting may interfere with their other medications.
		Vidall; 2016 [29]	Patients' reluctance to add more pills to their regimens was one of the key causes of their partial adherence.
	Physician's preference	Dielenseger; 2019 [18]	The main barrier was thought to be physician preference (39%)
		Clark-Snow; 2018 [19]	The biggest perceived barrier to CINV control was physician preference.

Note: HCP: healthcare professionals; HEC: highly emetogenic chemotherapy; MEC: moderately emetogenic chemotherapy; LEC: low emetogenic chemotherapy; FLIE: Functional Living Index-Emesis; ASCO: American Society of Clinical Oncology; AC: Combination of Anthracycline and Cyclophosphamide; 5HT3RA: 5HT3 Receptor Antagonist; NK1RA: Neurokinin-1 Receptor Antagonist; RINV: radiotherapy-induced nausea and vomiting

Table 2: Evidence for barriers to effective CINV management (continued)

Category	Barriers/ challenges	First author, year	Findings
Others *(continued)*	Patients' lack of knowledge	Krok-Schoen; 2019 [41]	Patients' anxiety and fear were exacerbated by the fact that they frequently had no idea what chemotherapy was like or the possible adverse effects.
		Salsman; 2012 [28]	Experiencing vomiting or nausea indicated that the medication was effective.
		Vidall; 2016 [29]	The primary causes of patients' partial adherence to their regimens were low severity of symptoms and a lack of a "preventive mindset," which is the unwillingness to take medication if feeling well. The most common justifications offered by patients for not reporting CINV symptoms were 50% recognized CINV as an inevitable side effect of cancer treatment and 42% believed that the symptoms were not severe enough to be reported
	Lack proactive assessment	So; 2013 [46]	While 34.0% of nurses only conducted CINV assessments when patients stated that CINV was an issue, 48.1% of nurses said that CINV assessments at work were mostly directed by the clinician's knowledge and experience, through observation and direct questioning of patients about their feelings. For the CINV risk assessment, 22.3% of participants felt they were not as prepared.
	Lack of time and high workload	So; 2013 [46]	Main reported barriers were time constraints and a demanding workload.

Note: HCP: healthcare professionals; HEC: highly emetogenic chemotherapy; MEC: moderately emetogenic chemotherapy; LEC: low emetogenic chemotherapy; FLIE: Functional Living Index-Emesis; ASCO: American Society of Clinical Oncology; AC: Combination of Anthracycline and Cyclophosphamide; 5HT3RA: 5HT3 Receptor Antagonist; NK1RA: Neurokinin-1 Receptor Antagonist; RINV: radiotherapy-induced nausea and vomiting

reported in 5 studies, while the lack of familiarity with perceived chemo agents' emetogenicity was reported in 2 studies.

Misperception

Misperception are further sub-categorized into 6 sub-groups which are: fearful of the side effects of antiemetics, underestimation of emetogenic potential, underestimation of CINV incidence, CINV perception gap between HCPs' and patients' experiences, uncertainty on CINV control with antiemetic, and CINV severity perception. A total of 15 studies were categorized under this group. The most reported misperceptions were: being fearful of the side effects of antiemetics, underestimation of CINV incidence, and the CINV perception gap between HCPs and cancer patients. It was revealed that both patients and HCPs were concerned about the adverse effects of antiemetics. HCPs tended to underestimate the emetogenic potential of chemo-agents and CINV incidences during the chemotherapy course.

Type of CINV

Types of CINV can be further sub-categorized into 3 sub-groups: delayed CINV as reported by 7 studies, CINV that occurred in Cycle 1, reported by 3 studies, and lastly, nausea following chemotherapy as a more significant issue compared to chemotherapy-induced vomiting, reported in 8 studies.

Economic

Lack of reimbursement for controlling CINV, especially with the use of Neurokinin-1 Receptor Antagonist (NKR1A) was reported as the barrier in CINV management in 3 studies and high cost imputable to CINV was regarded as a challenge in effective CINV control, reported in 2 studies.

Technical

Technical barriers were reported in 3 studies. They involved communication barriers between HCPs and patients, and inadequate CINV management and support system by hospital management.

Risk factors

Patient-related risk factors were reported to affect the effective control of CINV in 8 studies. These are mainly younger patients, with poor performance status, high anxiety levels, and a history of CINV in those previously treated with chemotherapy.

Others

HCP attitudes, such as physician's preference of antiemetic choice, the lack of proactive assessment, inadequate time and high workload were reported as barriers to effective CINV control. Besides that, the complexity of the antiemetic regimen and patients' lack of knowledge on CINV were also described as barriers in the included studies.

DISCUSSION

This systematic review has revealed a host of barriers and challenges to CINV management that were categorized into the seven main groups discussed earlier. The highest number of barriers and challenges reported falls under the 'type of CINV' group. Nausea induced by chemotherapy was the most commonly reported barrier in managing CINV compared to others. Nausea involves the sensation of an urge to vomit which may be short or prolonged, and it can be psychological or physiological in origin. It is frequently difficult for people affected to describe. However, it is usually very inconveniencing and uncomfortable feeling in the chest, upper abdomen, or back of the throat [47,48]. Delayed CINV was second to follow under this group. Delayed emesis is a significant problem and is often underestimated, underreported, and not treated. The neuropharmacological mechanism of delayed CINV is not well understood, and the prevention of delayed CINV has largely been based on empiric results [49].

Next, stakeholders' misperception was among the most critical barriers to managing CINV. Being fearful of the side effects of antiemetics like corticosteroids was reported by both HCPs and patients. It is a well-understood concern, however, antiemetics are actually very well-tolerated [50]. In fact, the effects from the short-term use of these agents wears off within a week [51]. This systematic review revealed that differences in perception between HCPs and patients were prominently reported. Although a good relationship between HCPs and patients is a vital starting point in improving CINV outcomes and patients' perception on their quality of life [52], poor patient-clinician communication may result in misunderstandings and misconceptions of overall chemotherapy goals including controlling CINV [53].

Economic issues are noteworthy barriers to be addressed especially in low to middle-income countries. Repurposing an old drug such as olanzapine for CINV prophylaxis is one of the solutions and a cost-effective alternative in these

countries [54-56]. Insurers may also adopt innovative coverage designs to encourage the appropriate use of antiemetics such as including cost-sharing coverage of antiemetics among patients starting chemotherapy regimens with a high risk of CINV [57].

CINV related to patient risk factors may be challenging to address as it is uniquely specific to patients. A significant percentage of patients who receive chemotherapy continue to experience nausea and vomiting despite receiving antiemetic treatment as per standard guidelines [8,58,59]. Implementing the CINV risk assessment tool together with chemotherapy emetogenicity risk assessment steered by the guidelines may proactively optimize the control of CINV. Anxiety, among others, was repeatedly reported as the patient-related factor that significantly contributed to CINV. Olanzapine is worthwhile to be instituted as an antiemetic and anxiolytic in this regard [60].

The complexity of the antiemetic regimen was also another important barrier in CINV management. Consolidating cancer patients' drug therapy is always needed regardless of antiemetic or other symptomatic treatment following chemotherapy [61]. Issues pertaining to HCP attitudes and clinic/hospital management in the prevention of CINV were another challenge to CINV management. HCPs were not providing adequate antiemetic control, despite guidelines being available. Oncologist preferences in prescribing antiemetics, lack of manpower in hospital settings and time-consuming tasks in managing CINV, and lack of proactive action in assessing CINV were among the barriers reported in this review [18,19,46].

Limitations of this study

This review identified multifaceted barriers and challenges in controlling CINV that can be used in future interventions to optimize CINV outcomes. Its limitation was mainly due to its general outcome of summarizing barriers and challenges of CINV management without focusing on certain types of barriers and challenges. This led to various study designs being included and this caused inconsistency that includes outcomes of clinical or statistical heterogeneity.

CONCLUSION

Addressing the barriers and challenges of CINV management is critical for high-quality of cancer care. Barriers and challenges particularly nausea and delayed CINV, failure to adhere to the antiemetic guideline, as well as misconceptions on CINV and its prevention are among the barriers and challenges in the management of CINV. The results of this study could be used by health service providers, in planning and implementing interventions to improve CINV management.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Conflict of Interest

No conflict of interest associated with this work.

Contribution of Authors

We declare that this work was done by the authors named in this article and all liabilities pertaining to claims relating to the content of this article will be borne by the authors. Badarudin NS and Mohamed Shah N carried out the data collection and data analysis and worked on the write-up of the article. Ismail F, Islahudin F, and Mohd Tahir NA assisted in the research design of the research and assisted in the discussion of the write-up. All authors read and approved the manuscript for publication, and met the criteria for authorship as established by the International Committee of Medical Journal Editors (ICJME).

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