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Title：Chemotherapy-induced nausea and vomiting breast cancer patients from a Chinese multicenter prospective longitudinal observational study

Running title: Chemotherapy-induced nausea and vomiting in Chinese breast cancer patients

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Abstract

Aims: To assess the occurrence of Chemotherapy-induced nausea and vomiting (CINV) after standard antiemetic therapy in the acute (24 h post-chemotherapy) and delayed (2 – 5 days post-chemotherapy) phases, as well as to identify risk factors for CINV in the acute and delayed phases.

Methods: This prospective longitudinal and observational study analyzed the data of 400 breast cancer patients scheduled for chemotherapy over two cycles in two hospitals. The self-report survey was developed to assess the occurrence of CINV and their associated factors. CINV was evaluated with a Multinational Association of Supportive Care in Cancer Antiemetic Tool (MAT) on days 2 and 6 of chemotherapy. The incidence of acute and delayed CINV were presented by frequency and percentage. Generalized equation estimates (GEE) was used to identify risk factors of acute and delayed CINV.

Results: There were 400 evaluable patients with complete Round 1 data, 334 for Round 2 data. Among 400 patients, 29.8% and 23.5% experienced acute and delayed CINV, respectively. Risk factors associated with for acute CINV were pain/insomnia, history of CINV, history of motion sickness (MS), and highly emetogenic chemotherapy regimen, while history of MS, CINV history, number of completed chemotherapy cycle number < 3, and the incidence of acute CINV were risk factors of delayed CINV (all $p < 0.05$).

Conclusions: The findings may help nurses working for Chinese population in identifying patients at risk for CINV and in planning effective program to reduce the occurrence of CINV.

Key-words: CINV, breast cancer, antiemetic guidelines, risk factors

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Introduction

Breast cancer is a global public health problem.[1] In China, the incidence of breast cancer ranks first among women in urban and rural areas, and it is one of the most important malignant tumors endangering the health of residents.[2] Chemotherapy is an important component of the comprehensive treatment of breast cancer, and it will produce a series of adverse reactions[3,4] while bringing benefits to patients' health. Chemotherapy-induced nausea and vomiting (CINV) are the most feared and common side effects experienced by breast cancer patients.[5, 6] According to the time of occurrence, CINV usually can be divided into five types: acute, delayed, anticipatory, breakthrough, or refractory. Clinically, the most common two types are acute and delayed CINV. Acute CINV usually occurs within a few minutes to several hours after administration and commonly resolves within the first 24 hours. Delayed CINV occurs more than 24 hours after chemotherapy and can last 6 to 7 day.[7]

Studies have shown that in the chemotherapy regimens used by breast cancer patients, the incidence of CINV is as high as 60%-90%,[8] especially the late-onset nausea and vomiting, which is the most difficult to control and accurately predict.[9,10] Not only can CINV lead to such problems as electrolyte disorder, malnutrition, but also it can increase the patient's anxiety, depression and other negative emotions, reduce the patients' adherence to treatment, and even lead to interruption of treatment, life-threatening.[11-14] Besides, CINV also causes medical resources burden.[15,16] Therefore, discern its risk factors is crucial for effective management.

In recent years, risk factors of CINV in cancer patients mainly focus on the following aspects:(1)Chemotherapy-related: including the emetic potential of chemotherapy agents, chemotherapy dose and chemotherapy cycle number.[17,18] High emetogenetic chemotherapy (HEC) have more than 90% risk, it is more than 3 times moderate/low chemotherapy.[7] Patients in earlier cycles (cycle no. < 3) are at higher risk of CINV.[19](2)General conditions of patients: age, sex, Body Mass Index(BMI), race, sleep time before chemotherapy. Age<55 and BMI < 27.5 kg/m2 adult breast cancer patients are more likely to have CINV in the acute stage,[20] and Asian women are 2.12 times more likely to be acute CINV than non-Asian women.[21] The risk of acute CINV in women is about 3 times that in men, and the delay period is about 1.5 times.[22] The risk of CINV after less than 7h of sleep before chemotherapy is 1.34 times higher than that after 7h.[23](3) Patients' psychological state: such as anxiety. Patients with anxiety are 2.7 times to experience CINV than those without anxiety.[24] (4)The patient's health history: such as nausea and vomiting, smoking, drinking, motion sickness(MS) and pregnancy reactions. Patients with history of CINV are 3.22 times more likely than those without history of CINV.[25] The risk of CINV in the acute phase of non-smokers is 2.0 times that of smokers, and the risk of CINV in the delayed phase of non-drinkers is 1.90 times that of habitual drinkers.[22] These results can provide reference for clinical selection of antiemetic scheme.

With the exception of the study by Pirri[26] and Molassiotis et al.,[24] there is no clear evidence about the effect of risk factors beyond a single course of chemotherapy. Most of the current studies are single-center, cross-sectional, retrospective studies on breast cancer patients, especially in China. There are population differences between Chinese breast cancer patients and other countries, and the incidence of CINV and risk factors may also be different. Therefore, it is of great significance to further use multi-center, longitudinal, prospective studies to explore the risk factors in the Chinese population. In addition, a previous study has confirmed that the occurrence of CINV in the acute stage will increase the risk of delayed CINV in cancer patients,[27] but whether acute CINV will affect the outcome of delayed CINV in breast cancer remains to be

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explored.

The purpose of this study was to examine the incidence and factors associated with acute and delayed CINV among Chinese breast cancer patients based on two chemotherapy cycle(Not necessarily two consecutive periods, but must receive same chemotherapy regimen).

Subjects and Methods

Study design and patients

A multicenter, longitudinal, prospective, and observational design was used. The patients were recruited from inpatient wards of two hospitals including a cancer hospital and a maternal and child hospital in Hunan province of China. A total of 400 breast cancer patients who scheduled to undergo chemotherapy were recruited between November 2019 and October 2020. Inclusion criteria were: 1) diagnosis of breast cancer by pathology; 2) aged ≥ 18 years old; 3) informed consent; 4) be scheduled to receive chemotherapy. Exclusion criteria were: 1) with cognitive or communication disorders, 2) participating in other related research at the same time, 3) presence of other conditions that might cause nausea or vomiting (e.g., intestinal obstruction,pregnancy). The sample size was estimated according to 5-10 times of the influencing factor entry. According to the results of reviewing relevant literature[28] and group discussion, there are 26 possible risk factors in our research. Allowing for a possible 30 % dropout rate between the two time points for assessing acute and delayed CINV, the final sample size was determined as 338, and 400 cases were finally collected in the study.

Measures and procedure

Definitions

According to the CINV assessment tool of Multinational Association of Supportive Care in Cancer (MASCC), the acute CINV was defined as: cumulative number of vomiting episodes within 24 h ≥1 or nausea level > 3; and the definition of delayed CINV was: cumulative number of vomiting episodes within 2–6 days ≥1 or nausea >3. In other words, acute CINV included chemotherapy induced nausea(chemotherapy induced nausea, CIN) or chemotherapy induced vomiting(chemotherapy induced vomiting, CIV), and the same standard for delayed CINV.

Research Tools

Questionnaire for CINV-related factors of breast cancer patients: The questionnaire included four parts: general information (e.g., age, education, BMI); health history (e.g., degree of CINV in the previous cycle, alcohol consumption, smoking, vomiting of pregnancy, MS, sleep duration before chemotherapy); disease factors (e.g., neoplasm staging, pathological type, and metastatsis); and drug factors (e.g., chemotherapy regimen, chemotherapy cycle number, antiemetic regimen).

MASCC Antiemetic Tool(MAT): The MAT is a CINV self-report scale proposed by MASCC(Multinational Association for Supportive Care in Cancer) in 2007[29] and translated into Chinese by Tan in 2016,[30] which incorporates eight items assessing acute and delayed CINV phase with four each, respectively. Within each phase, including the occurrence, frequency, and severity of nausea and vomiting. Dichotomous items were scored as 0 (No) or 1 (Yes), and continuous variables were scored on scales of 0 to 10. The four items rated in day 2 and day 6 post-chemotherapy were evaluated respectively to create an acute CINV score and a delayed CINV score. This tool has been widely used in clinical practice.[31-32] The MAT is a reliable and valid clinical tool.

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The Cronbach's α coefficiency and content validity of the Chinese version of MAT is 0.71 and 1.00.[33]

Generalized Anxiety Scale (GAD-7): The scale was designed by Spitzer et al in 2006[34] and translated into Chinese by He et al in 2010.[35] It includes seven items assessing the severity of anxiety. Scores can take values from 0-21， patients rate their frequency of symptoms within the last two weeks on a four-point scale ranging from 'not at all'(0-5 point） to 'almost every day'(16-21 point). All patients are classified into two categories in our study, presence anxiety and no anxiety, a score ＞5 is considered anxiety. The Cronbach ′s coefficient and of the the retest reliability of scale is 0.90 and 0.86, respectively.

Data collection and ethical consideration

This study was approved by the Ethics Committee of Hunan Cancer Hospital (No.2019-21). Written informed consent was obtained from all patients. We strictly follow the principle of patient privacy protection.

There is no limit to the chemotherapy cycle number. CINV data were collected face to face on the 2st day after chemotherapy and followed up by telephone on the 6th day after chemotherapy. Data collection was conducted by trained personnel with clinical experience of breast cancer using a standardized questionnaire to ensure the integrity and reliability of data collection. The participants were required for recording diary with or without nausea(intensity of nausea) with or without vomiting (and how many times if applicable), with or without salvage therapy both in the first 24h and between 24h and 6 days after chemotherapy.

Statistical analysis

All statistical analyses were performed using SPSS version 24.0 (IBM Corp., Armonk, NY, USA). Demographic data (age, education, religion, etc.) in the general data of patients were described by frequency and percentage. Measurement data were described by mean±standard deviation. Risk factors for CINV in the collected data sets were analyzed by Generalized Estimated Equation (GEE) using binary logistic regression as correlation function. Using cycle number as various time points, and variables with two-sided p-values < 0.05 were considered statistically significant.

Results

Baseline patient characteristics

A total of 420(90%) eligible patients approached signed informed consent forms. Of these, 20(5.0%) were later excluded from the analysis because of not receiving intended chemotherapy (n = 1), death of patient (n = 1), not completing diary (n = 16), or not completing dataset (n = 2).(Figure 1). Complete data were available for 400 patients and were included in the current analyses, with some attrition for Round 2(n = 334). The Round 1 result of general information showed that the age of patients ranged from 25 to 77, with a mean age of 50.38±9.24 years. Education approached 80% having only completed junior high school, BMI mainly focused on 18.5-27.9. The content of health history indicated that 95.7% patients had no history of alcohol consumption and 98.2% had no history of smoking; About disease factors, 89.5% of pathological type was invasive non-specific carcinoma, 52% patients had metastasis. In treatment factors, patients in earlier chemotherapy cycles (cycle no. < 3) accounted for 52%. National

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Comprehensive Cancer Network (NCCN Guidelines Version 2.2020 Antiemesis)/2016 MASCC and ESMO update guideline[7,36] has classified commonly used chemotherapy agents into high(emetic risk > 90%, including AC(anthracycline cyclophosphamid) combination defined as any chemotherapy regimen that contains an anthracycline and cyclophosphamid,cisplatin, epirubicin > 90 mg/m2, doxorubicin ≥ 60 mg/m2), moderate(30% – 90%, including cyclophosphamid ≤ 1500 mg/m2, doxorubicin < 60 mg/m2, epirubicin ≤ 90 mg/m), low or slight(< 30%, including navelbine, TAX(taxol), xeloda, gemcitabine, docetaxel.) risk categories based primarily on clinical trial evidence(low and slight emetics were classified as low in our study), with moderate and high emetics accounting for 73.7%. Additional information is summarized in **Table 1.**

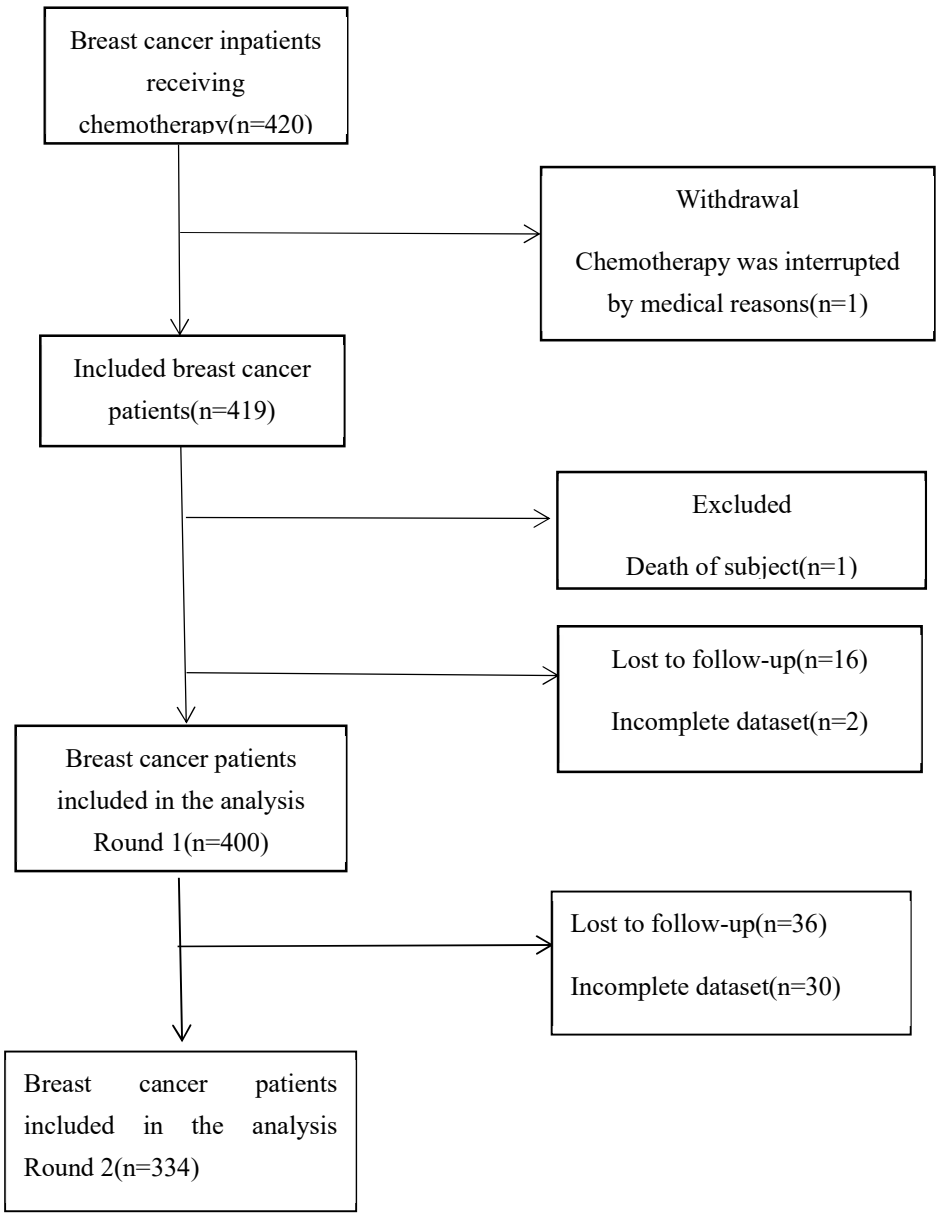

Figure1 Patients' flowchart

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Table 1 Patient characteristics（The Round 1)

Variable	Category	Number	Percentage (%)
Age (years)			
	<40	51	12.8
	40–60	297	74.3
	≥60	72	13.0
Marital status			
	Married	382	95.5
	Other	18	4.5
Education			
	Primary school and below	152	38.0
	Junior high school	164	41.0
	High school or technical secondary school	40	10.0
	Junior college and above	44	11.0
BMI			
	<18.5	13	3.3
	18.5–23.9	219	54.7
	24–27.9	136	34.0
	≥28	32	8.0
Work status			
	Yes	35	8.8
	No	365	91.2
Alcohol consumption			
	Yes	17	4.3
	No	383	95.7
Smoking			
	Yes	7	1.8
	No	393	98.2
CINV history			
	Yes	152	38.0
	No	248	62.0
PS			
	≤1	326	81.6
	≥2	74	18.4
Sleep <7 hours before chemotherapy			
	Yes	189	47.3
	No	211	52.8
History of MS			
	Yes	191	52.3
	No	209	47.7
History of vomiting during pregnancy			
	Yes	179	44.8
	No	221	55.2
Pain/insomnia			
	Yes	226	56.5
	No	174	43.5
Constipation			
	Yes	124	31.0
	No	276	69.0
Over-the-counter home medicines			
	Yes	19	4.8
	No	381	95.2
Pre-chemotherapy anxiety			
	Yes	109	27.3
	No	291	72.7
Diabetes			
	Yes	25	6.3
	No	375	93.7
Hypertension			

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	Yes	52	13.0
	No	348	87.0
Chronic renal insufficiency			
	Yes	2	0.5
	No	398	99.5
Coronary heart disease			
	Yes	10	2.5
	No	390	97.5
Metastasis			
	Yes	208	52.0
	No	192	48.0
Pathological pattern			
	Invasive non-specific carcinoma	358	89.5
	Other	42	10.5
Disease stage			
	1	61	15.2
	2	190	47.5
	3	111	27.8
	4	38	9.5
Chemotherapy regimen			
	Low	105	26.3
	Moderate	80	20.0
	High	215	53.7
Chemotherapy cycle number			
	< 3 cycles	211	52.8
	≥ 3 cycles	189	47.2
Antiemetic regimen			
	Single	127	31.8
	Double	154	38.5
	Triple	119	29.7

Note. Chemotherapy regimens: Low: navelbine, TAX (taxol), xeloda, gemcitabine, docetaxel; Moderate : cyclophosphamide+doxorubicin; High: cis-platinum, pharmorubicin.

Antiemetic:Single (dexamethason); Double(5-HT3-receptor antagonists + Dexamethasone); Triple(5-HT3-receptor antagonists +Dexamethasone +NK1-receptor antagonist).

Abbreviations: BMI, body mass index; CINV, chemotherapy-induced nausea and vomiting; MS, motion sickness; PS, performance status.

Occurrence of CINV

Although antiemetic pre-treatment and post-treatment were provided in accordance with the guidelines, due to individual variations or differences in tolerance, a considerable number of patients still developed CINV. The proportions were different among cycles in several CINV outcomes. In Round 1, chemotherapy induced nausea(CIN) and CINV in delayed phase was the case for 19.8% and 23.0%, with statistically significant (but not necessarily clinically important) decline over the subsequent cycles. The prevalence of delayed CINV was relatively low. Delayed CINV occurred in 92 (23.0%) patients and 37 (11.0%), in Round 1and Round 2, respectively. Nausea and vomiting in the acute phase were slight higher than those in the delayed phase, and the incidence of nausea was higher than that of vomiting at all phases. **Table 2** shows the prevalence of CINV patients in two Round.

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Table 2 Proportions of CINV: Outcomes by Chemotherapy Phase and Round

Variable	Round 1 (N =400), n (%)	Round 2 (N = 333), n (%)	P value
Acute phase			
CIN	88（22.0）	62（18.6）	0.250
CIV	46（11.5）	49（14.7）	0.203
CINV	107（26.8）	86（25.8）	0.759
Delayed phase			
CIN	79（19.8）	28（8.4）	**＜0.001**
CIV	33（8.3）	20（6.0）	0.238
CINV	92（23.0）	37（11.1）	**＜0.001**

Abbreviations: CIN, chemotherapy-induced nausea; CIV, chemotherapy-induced vomiting; CINV, chemotherapy-induced nausea and vomiting.

Analyses of factors predictive for acute CINV control

The assignment of the independent variables are shown in **Table 3**. With the patient's identification number as the main variable, the number of current chemotherapy cycles as the in vivo variable, and the occurrence of CINV as the dependent variable, we conducted GEE model analysis including data for all collected factors. As shown in **Table 4**, the GEE model analysis revealed that pain/insomnia(OR = 2.0, 95% CI: 1.3 – 2.9, p = 0.001), history of CINV (OR = 3.4, 95% CI: 2.3 – 5.1, p < 0.001), history of MS (OR = 1.5, 95% CI: 1.0 – 2.3, p =0.034), and high emetic chemotherapy regimen (OR = 3.6, 95% CI: 2.2 - 6.0, p < 0.001) were significantly associated with an increased odds for an occurrence of CINV in acute phases.

Table 3 CINV risk factor scale

Variable	Score
	No = 0, Yes = 1
Sleep < 7 hours before chemotherapy	
Pain/ insomnia	No = 0, Yes = 1
Diabetes	No = 0, Yes = 1
History of MS	No = 0, Yes = 1
History of CINV	No = 0, Yes = 1
Pre-chemotherapy anxiety	No = 0, Yes = 1
Chemotherapy cycle number	< 3 cycles = 1, ≥3 cycles = 2
Chemotherapy regimen	low = 1, moderate = 2, high = 3
Acute CINV occurred	No = 0, Yes = 1

Abbreviations: BMI, body mass index; MS, motion sickness; CINV, chemotherapy-induced nausea and vomiting

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Table 4 GEE model to identify factors associated with acute CINV

Variable	B	SE	Wald	Exp(B) (95% CI)	P value
Pain/insomnia					
No	Ref				
Yes	0.671	0.196	11.700	2.0(1.3-2.9)	**0.001**
Diabetes					
No	Ref				
Yes	0.672	0.378	3.152	2.0(0.9-4.1)	0.076
Pre-chemotherapy anxiety					
No	Ref				
Yes	0.405	0.213	3.618	1.5(1.0-2.3)	0.057
History of CINV					
No	Ref				
Yes	1.222	0.210	33.992	3.4(2.3-5.1)	**< 0.001**
History of MS					
No	Ref				
Yes	0.422	0.199	4.516	1.5(1.0-2.3)	**0.034**
Chemotherapy regimens					
Low	Ref				
Moderate	0.708	0.300	5.569	2.0(1.1-3.7)	**0.018**
High	1.279	0.258	24.610	3.6(2.2-6.0)	**< 0.001**

Note: Values in the GEE model indicate $P < 0.10$ as the criterion for selection and show the table. Significant P-values in the GEE analysis model (< 0.05) are also indicated in bold.

P-value derived from unadjusted generalized equation estimation models, using cycle number as various time points; patients who were lost to follow-up in later cycle(s) were assumed missing at random.

Abbreviations: CI, confidence interval; CINV, chemotherapy-induced nausea and vomiting; OR, odds ratio; GEE, generalized equation estimates

Factors predictive for delayed CINV control

In the delayed phase, the GEE model analysis revealed that history of CINV(OR = 1.7 ; 95% CI, 1.1 – 2.7, p = 0.012), history of MS(OR = 1.6; 95%CI,1.0-2.5), and acute CINV occurred (OR = 2.8; 95% CI, 1.9 – 4.2, p < 0.001) were associated with an increased odds of delayed CINV. In contrast, number of chemotherapy cycle completed was significantly associated with a reduced risk for CINV in delayed phase (OR = 0.5; 95% CI, 0.3 – 0.8, p = 0.003). The risk of CINV was higher in the first two chemotherapy cycle numbers than in subsequent rounds of chemotherapy (**Table 5**).

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Table 5 Generalized equation estimates (GEE) to identify risk factors for delayed CINV

Variable	B	SE	Wald	Exp(B) (95% CI)	P value
Sleep <7 hours before chemotherapy					
No	Ref				
Yes	0.359	0.214	2.830	1.4(0.9-2.2)	0.093
Acute CINV occurred					
No	Ref				
Yes	1.029	0.207	24.621	2.8(1.9-4.2)	**< 0.001**
History of CINV					
No	Ref				
Yes	0.549	0.220	6.242	1.7(1.1-2.7)	**0.012**
History of MS					
No	Ref				
Yes	0.483	0.223	4.689	1.6(1.0-2.5)	**0.030**
Chemotherapy cycle number					
<3	Ref				
≥3	-0.685	0.231	8.832	0.5(0.3-0.8)	**0.003**

Note: Values in the GEE model indicate P < 0.10 as the criterion for selection and show the table. Significant P-values in the GEE analysis model (< 0.05) are also indicated in bold.

P-value derived from unadjusted generalized equation estimation models, using cycle number as various time points; patients who were lost to follow-up in later cycle(s) were assumed missing at random.

Abbreviations: CI, confidence interval; CINV, chemotherapy-induced nausea and vomiting; OR, odds ratio; GEE, generalized equation estimate

Discussion

This study aims to understand the occurrence of CINV in Chinese mainland and identify modifiable factors associated with CINV among breast cancer patients. The findings highlights a considerable proportion of participants suffered CINV, and the association of CINV with treatment and patient-related factors. This study identified pain/insomnia, history of CINV, history of MS, highly emetogenic chemotherapy regimens are associated with increased acute CINV, and history of MS, history of CINV, chemotherapy cycle number, the incidence of acute CINV are associated with rising of delayed CINV. As far as we know, previous studies of breast cancer CINV in China tend to be retrospective studies, and multi-center, longitudinal, prospective studies is a lightspot in this study.

The incidence of nausea and vomiting following chemotherapy administration is difficult to fully control. As depicted in **table 2**, the incidence of nausea was significantly higher than that of vomiting, both in the acute phase and in the delayed phase, which was consistent with previous studies.[37] Nausea is more difficult to control than vomiting in chemotherapy. Nausea subjectivity is stronger, and the mechanisms are more complex. It is worth noting that in our study, CINV in the acute stage is even slightly higher than that in the delayed stage. It may be related to adequate antiemetic prophylaxis. Moreover, the discharged patient received dietary guidance and psychological comfort from nurses. This may be also helpful to control CINV in the delayed phase.

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To actively prevent and treat CINV in patients with breast cancer, it is necessary to evaluate the therapeutic and individual factors that influence its development in patients. Several factors influencing acute CINV were identified, including pain/insomnia, history of CINV, history of MS, and chemotherapy regimen. In this study, pain/insomnia is a risk factor of CINV (odds ratio: 2.0, 95% confidence interval 1.3 – 2.9, p = 0.001). Pain/insomnia are associated with CINV, as previously reported.[38] Pain/insomnia will aggravate the physical burden of patients, make their physical strength decline, reduce the ability to deal with adverse reactions, and thus more prone to CINV. This suggests that more attention should be paid to the management of CINV for patients with symptoms such as pain and insomnia before chemotherapy. Factors significantly influencing acute CINV are previous history of nausea and vomiting, people with a history of CINV is 3.4 times more likely to experience acute CINV than those without such a history. This finding is similar to previous studies,[39–42] which reports that nausea and vomiting are usually caused by conditioned stimuli. Patients with a prior history of CINV are at higher risk of nausea and vomiting when exposed to the same stimuli. MS is defined as disorder of orientation and balance caused by exposure to passive motor stimulation.[43] It mainly manifests as vestibular and autonomic nervous reaction symptoms, such as dizziness, headache, upper abdominal discomfort, nausea, and vomiting, and primarily involves the vestibular cortex and hippocampus. We found that the risk of developing delayed CINV is 1.0 ‑ 2.3 times higher in MS history patients relative to those with no history of this condition, consistent with previous research.[44] The nausea and vomiting reflex arc may be more responsive in subjects with MS, and this is aggravated by chemotherapy. But the factor did not been found in the previous analysis based on one round of data. The final factor associated with acute CINV is the chemotherapy regimen. High-risk emetic drugs commonly used in breast cancer chemotherapy include platinum, cyclophosphamide, and anthracycline, and CINV control is less than ideal in patients administered these substances.[45] The emetic potential of drugs has long been recognized as an important factor influencing CINV. The risk of acute CINV is 3.6 times higher in chemotherapy regimens with high than low emetogenic chemotherapy in our study. The risk of acute CINV is still high, although prophylactic treatment is strictly in accordance with the guidelines during chemotherapy. The treatment of this group of patients needs further improvement.

We have found some new evidence on risk factors for delayed CINV. Delayed CINV has four influencing factors: history of MS, history of CINV, chemotherapy cycle number, and acute CINV. The occurrence of acute CINV is a significant factor influencing delayed CINV, which is a new information. Although patients with acute CINV received higher doses of antiemetics, they still experienced delayed CINV, suggesting that individual factors determine who is more susceptible to CINV or who does not respond to antiemetics, especially those with a history of CINV or MS. The results are helpful for nurses to identify the high-risk group of delayed CINV and carry out symptom assessment and treatment education in time.. The number of chemotherapy cycle numbers was closely related to CINV occurrence, we found higher risk following the initial cycle compared with later ones. The risk after three or more cycles of chemotherapy is only 0.5 times that following the first two cycles, consistent with an earlier report.[19] It may be that patients who have experienced chemotherapy gradually acclimate to the process and can better withstand the adverse reactions.

Japan Society of Clinical Oncology (2015) Guidelines point out that fully integrating individual patient characteristics is more effective in reducing CINV than considering only the emetic potential of a drug[46] however, how risk factors in breast

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cancer patients can be comprehensively and accurately assessed remains problematic. This study provides new evidence of the relative importance and contribution of specific personal and clinical characteristics to CINV development in breast cancer patients, besides it had been proved history of CINV and chemotherapy regimens are associated factors among breast cancer patients reported by previous studies.[7,39] The subjects in the present study are all female, excluding any influence of sex. Age is not an independently associated factor in this study, however, it opposes the widely accepted clinical view that young patients are more prone to CINV.[47] This may due to the strong correlation between age and other variables, since when all variables were assessed in multivariate analysis, age are not significant predictors of CINV. Therefore, although young people still have a higher proportion of CINV than old people, there is no significant statistically difference.

Strengths and limitations

The strengths of this study were that it was a prospective evaluation of CINV during the period of its occurrence, which avoided inaccuracies associated with retrospective investigations. In addition, data from the same subject in two chemotherapy cycles, which is a longitudinal study, with more continuity. Although this was a multicenter study, its scope was limited to one province in China, which may not be representative of all patients and could have introduced bias. Additional investigations are needed to determine whether our findings can be generalized to other ethnic groups.

Implication

Personal factors should be taken into consideration by the multidisciplinary treating team in breast cancer especially those having history of CINV and pain/insomnia symptoms before chemotherapy should be paid attention. If the patients occurs acute CINV, medical staff need give higher attention in the delay phase. The next step would be to more concretely incorporate these factors in both the antiemetic trials and the routine management of patients, identifying those patients that are at higher risk for CINV and supporting them more aggressively.

Conclusion

The results of this study highlight that a significant proportion of participants suffered from
CINV, although the incidence of CINV was lower than in previous studies. This study is the first time to prove that in patients with breast cancer chemotherapy, patients with pain / insomnia and chemotherapy cycles less than 3 are at high risk, while patients with acute CINV increase the risk of delayed CINV. The results may be helpful for Chinese nurses to identify high-risk patients with CINV and develop effective symptom management programs, and can likely be extrapolated to other Asian populations, highlighting the need for additional research in this area.

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References

[1]Barrios CH, Reinert T, Werutsky G. Global Breast Cancer Research: Moving Forward. Am Soc Clin Oncol Educ Book. 2018;38:441-450

[2]Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2018;68(6):394-424.

[3]Gibbons A, Groarke A. Coping with chemotherapy for breast cancer: Asking women what works. Eur J Oncol Nurs. 2018;35:85-91.

[4]Jodar M, Jacquin JP, Vallée J. Perception des effets indésirables de la chimiothérapie et de l'hormonothérapie par les femmes prises en charge pour un cancer du sein [Perception of adverse reactions of chemotherapy and hormone therapy by women treated for breast cancer]. Therapie. 2016;71(3):263-273.

[5] Schnell F . Chemotherapy-induced nausea and vomiting: the importance of acute antiemetic control. Oncologist. 2003; 8(2):187.

[6]Haniadka R, Popouri S, Palatty PL, Arora R, Baliga MS. Medicinal plants as antiemetics in the treatment of cancer: a review. Integr Cancer Ther. 2012;11(1):18-28.

[7]David S , Michael J. Berger , Sally Barbour , et al. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®): Antiemesis, ［EB/OL］. Antiemesis(Version 2 . 2020). ［2020 — 04 — 23］http://guide.medlive.cn/

[8]Chan VT, Yeo W. Antiemetic therapy options for chemotherapy-induced nausea and vomiting in breast cancer patients. Breast Cancer (Dove Med Press). 2011;3:151-160.

[9]Naito Y, Kai Y, Ishikawa T, et al. Chemotherapy-induced nausea and vomiting in patients with breast cancer: a prospective cohort study. Breast Cancer. 2020;27(1):122-128.

[10]Gilmore J, D'Amato S, Griffith N, Schwartzberg L. Recent advances in antiemetics: new formulations of 5HT3-receptor antagonists. Cancer Manag Res. 2018;10:1827-1857.

[11]Soefje SA. Strategies to improve CINV outcomes in managed care. Am J Manag Care. 2018;24(18 Suppl):S398-S404.

[12]Wang SY, Yang ZJ, Zhang Z, Zhang H. Aprepitant in the prevention of vomiting induced by moderately and highly emetogenic chemotherapy. Asian Pac J Cancer Prev. 2014;15(23):10045-10051.

[13]Grunberg SM, Slusher B, Rugo HS. Emerging treatments in chemotherapy-induced nausea and vomiting. Clin Adv Hematol Oncol. 2013;11(2 Suppl 1):1-18. .

[14]Carnio S, Galetta D, Scotti V, et al. Chemotherapy-induced nausea and vomiting (CINV) in patients with advanced lung cancer during the first-line treatment: assessment by physicians, nurses, and patients from an Italian multicenter survey. Support Care Cancer. 2018;26(6):1841-1849.

[15]Burke TA, Wisniewski T, Ernst FR. Resource utilization and costs associated with chemotherapy-induced nausea and vomiting (CINV) following highly or moderately emetogenic chemotherapy administered in the US outpatient hospital setting. Support

Care Cancer. 2011;19(1):131-140.
[16]Lachaine J, Yelle L, Kaizer L, Dufour A, Hopkins S, Deuson R. Chemotherapy-induced emesis: quality of life and economic impact in the context of current practice in Canada. Support Cancer Ther. 2005;2(3):181-187.
[17]Tsuji D, Suzuki K, Kawasaki Y, et al. Risk factors associated with chemotherapy-induced nausea and vomiting in the triplet antiemetic regimen including palonosetron or granisetron for cisplatin-based chemotherapy: analysis of a randomized, double-blind controlled trial. Support Care Cancer. 2019;27(3):1139-1147. .
[18]Kim HK, Hsieh R, Chan A, et al. Impact of CINV in earlier cycles on CINV and chemotherapy regimen modification in subsequent cycles in Asia Pacific clinical practice. Support Care Cancer. 2015;23(1):293-300.
[19]Dranitsaris, G., Joy, A., Young, S., Clemons, M., Callaghan, W., and Petrella, T. Identifying patients at high risk for nausea and vomiting afterchemotherapy: the development of a practical prediction tool. I. Acutenausea and vomiting. Support Oncol.2009;7: W1 – W8.
[20]Kawazoe H, Murakami A, Yamashita M, et al. Patient-related Risk Factors for Nausea and Vomiting with Standard Antiemetics in Patients with Breast Cancer Receiving Anthracycline-based Chemotherapy: A Retrospective Observational Study. Clin Ther. 2018;40(12):2170-2179.
[21]Bourdeanu L. Assessment of the severity of chemotherapy-induced nausea and vomiting in Asian women vs. non-Asian women with breast cancer[J]. Dissertations & Theses - Gradworks, 2010.
[22]Sekine I, Segawa Y, Kubota K, Saeki T. Risk factors of chemotherapy-induced nausea and vomiting: index for personalized antiemetic prophylaxis. Cancer Sci. 2013;104(6):711-717. [23]Dranitsaris G, Molassiotis A, Clemons M, et al. The development of a prediction tool to identify cancer patients at high risk for chemotherapy-induced nausea and vomiting. Ann Oncol. 2017;28(6):1260-1267.
[24]Molassiotis A, Aapro M, Dicato M, et al. Evaluation of risk factors predicting chemotherapy-related nausea and vomiting: results from a European prospective observational study. J Pain Symptom Manage. 2014;47(5):839-848.e4.
[25]Hayashi T, Shimokawa M, Matsuo K, et al. Risk factors for delayed chemotherapy-induced nausea and vomiting with low-emetic-risk chemotherapy: a prospective, observational, multicenter study. Cancer Manag Res. 2018;10:4249-4255.
[26]Pirri C, Katris P, Trotter J, et al. Risk factors at pretreatment predicting treatment-induced nausea and vomiting in Australian cancer patients: a prospective, longitudinal, observational study. Support Care Cancer 2011;19:1549e1563.
[27]Liau CT, Chu NM, Liu HE, Deuson R, Lien J, Chen JS. Incidence of chemotherapy-induced nausea and vomiting in Taiwan: physicians' and nurses' estimation vs. patients' reported outcomes. Support Care Cancer. 2005;13(5):277-286.
[28]Mosa ASM, Hossain AM, Lavoie BJ, Yoo I. Patient-Related Risk Factors for Chemotherapy-Induced Nausea and Vomiting: A Systematic Review. Front Pharmacol. 2020;11:329.
[29]Molassiotis A, Coventry PA, Stricker CT, et al. Validation and psychometric assessment of a short clinical scale to measure chemotherapy-induced nausea and vomiting: the MASCC antiemesis tool. J Pain Symptom Manage. 2007;34(2):148-159.
[30] Tan JY, Suen LK, Molassiotis A. Psychometric assessment of the Chinese version of the MASCC Antiemesis Tool (MAT) for measuring chemotherapy-induced nausea and vomiting. Support Care Cancer. 2016;24(9):37
[31]Li X, Qin Y, Liu W, Zhou XY, Li YN, Wang LY. Efficacy of Ginger in Ameliorating Acute and Delayed Chemotherapy-Induced Nausea and Vomiting Among Patients With

Lung Cancer Receiving Cisplatin-Based Regimens: A Randomized Controlled Trial. Integr Cancer Ther. 2018;17(3):747-754.
[32]Yao Y, Ji C, He Y, Pan Y. Relationship between Helicobacter pylori infection and vomiting induced by gastrointestinal cancer chemotherapy. Intern Med J. 2017;47(7):792-797.
[33]Brearley SG, Clements CV, Molassiotis A. A review of patient self-report tools for chemotherapy-induced nausea and vomiting. Support Care Cancer. 2008;16:1213-1229.
[34]Spitzer RL, Kroenke K, Williams JB, Löwe B. A brief measure for assessing generalized anxiety disorder: the GAD-7. Arch Intern Med. 2006;166(10):1092-1097.
[35]He XY, Li CB, Qian J, Cui HS, Wu WY. A study on the reliability and validity of generalized Anxiety Scale in general hospitals. Shanghai Psychiatry.2010;(04):200-203.
[36]Molassiotis A, Aapro M, Herrstedt J, Gralla R, Roila F. MASCC/ESMO Antiemetic Guidelines: Introduction to the 2016 guideline update. Support Care Cancer. 2017;25(1):267-269.
[37] Hsieh R K , Chan A , Kim H K , et al. Baseline patient characteristics, incidence of CINV, and physician perception of CINV incidence following moderately and highly emetogenic chemotherapy in Asia Pacific countries. Supportive Care in Cancer. 2015; 23(1):263-272.
[38]Molassiotis A, Stamataki Z, Kontopantelis E. Development and preliminary validation of a risk prediction model for chemotherapy-related nausea and vomiting. Support Care Cancer 2013;21:2759 – 67.
[39]Molassiotis A, Aapro M, Dicato M, Gascon P, Novoa SA, Isambert N, et al. Evaluation of risk factors predicting chemotherapy-related nausea and vomiting: Results from a European prospective observational study. J Pain Symptom Manage 2014;47:839-48.
[40]Molassiotis A, Lee PH, Burke TA, Dicato M, Gascon P, Roila F, et al. Anticipatory nausea, risk factors, and its impact on chemotherapy-induced nausea and vomiting: Results from the Pan European Emesis Registry Study. J Pain Symptom Manage. 2016;51:987-93.
[41] Chan A, Tan SH, Low XH, Yap KY. Antiemetic effectiveness and nausea and vomiting incidence during capecitabine and oxaliplatin chemotherapy. Nurs Res. 2012;61(6):405-412.
[42] Rha SY, Park Y, Song SK, Lee CE, Lee J. Controlling chemotherapy-induced nausea requires further improvement: symptom experience and risk factors among Korean patients. Support Care Cancer 2016;24:3379-89.
[43]Golding JF. Motion sickness. Handb Clin Neurol. 2016;137:371-390.
[44]Tsuji, Y., Baba, H., Takeda, K., Kobayashi, M., Oki, E., Gotoh, M., et al.Chemotherapy-induced nausea and vomiting (CINV) in 190 colorectal cancer patients: a prospective registration study by the CINV study groupof Japan.Expert Opin. Pharmacother.2017;18:753 – 758.
[45]Bouganim N, Dranitsaris G, Hopkins S, Vandermeer L, Godbout L, Dent S, et al. Prospective validation of risk prediction indexes for acute and delayed chemotherapy-induced nausea and vomiting. Curr Oncol 2012;19:e414 – 21.
[46]Aogi K, Takeuchi H, Saeki T, et al. Optimizing antiemetic treatment for chemotherapy-induced nausea and vomiting in Japan: Update summary of the 2015 Japan Society of Clinical Oncology Clinical Practice Guidelines for Antiemesis. Int J Clin Oncol. 2021;26(1):1-17.
[47]Iihara H, Fujii H, Yoshimi C, et al. Control of chemotherapy-induced nausea in patients receiving outpatient cancer chemotherapy. Int J Clin Oncol. 2016;21(2):409-418.