

A cross-sectional study on the guideline adherence to antiemetic regimens for chemotherapy-induced nausea and vomiting: A single center retrospective study of 1000 patients.

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Abstract

Background Chemotherapy-induced nausea and vomiting (CINV) is a common symptom in patients who undergoing chemotherapy, it is very important to control CINV to maintain dose intensity and patients' quality of life. To analyze the current situation of CINV for the tumor patients who undergoing chemotherapy, we used a cross-sectional survey to assess CINV status in those patients, and whether the drugs used by doctors in each department met the guidelines, and compared the incidence of acute and delayed CINV overall post-chemotherapy periods. Methods This was a single-center, cross-sectional retrospective study of patients with chemotherapy discharged from different departments of Zhejiang Cancer Hospital in China. Participants reported the occurrence, severity, and impact on daily life of nausea and vomiting from the day of chemotherapy administration up to 5 days, and physicians collected the clinical data from the medical records. Results Data were collected from 875 responses totally. In this study, the overall incidence rate of CINV was 44.34%, acute CINV was 24.57%, and delayed CINV was 39.66%. 19.89% patients had both acute and delayed CINV. The consistency rates of antiemetic with guideline in different departments showed significant gap between the actual usage of drugs and the recommended guidelines ($P=0.001$). In 875 patients, 518 patients received guideline recommended antiemetic regimen, the CINV rates of complete control (CC), defined as the absence of any symptoms, were 61.58%. While the CC rates in other 357 patients were 47.06% ($P<0.001$). Conclusion Overall, clinician adherence to antiemetic guideline recommendations in different departments remained poorly characterized with varying degrees. Future studies should focus on the complete rate as a primary end point rather than complete remission. The standardized management of CINV in patients need to be further strengthened and doctors need to use drugs more regularly to reduce the occurrence of CINV in patients.

Background

Chemotherapy-induced nausea and vomiting (CINV) is ranked the most distressing and persistent side effect by cancer patients undergoing chemotherapy. According to the time of occurrence after chemotherapy receiving, CINV is categorized by acute phase (within the first 24 hours), delayed phase (between 24 and 120 hours), and overall phase (between 0 and 120 hours)¹. Chemotherapeutic agents are stratified on the basis of the risk for inducing acute emesis in the absence of antiemetic prophylaxis into highly emetogenic chemotherapy (HEC), moderately emetogenic chemotherapy (MEC), low emetogenic chemotherapy (LEC), and minimally emetogenic chemotherapy. Without of effective intervention, HEC is associated with nausea and vomiting in approximately 90% probability². In addition to the negative impact on quality of life (QoL), overwhelming evidence show that failure to correctly manage CINV can lead to chemotherapy treatment delays, dose reductions, and increase patient's rejection and healthcare utilization^{3,4}. Data have demonstrated that optimal management of chemotherapy-related symptoms, especially nausea and vomiting, can significantly improve patient-reported outcomes and increase overall survival rate while maintaining treatment intensity^{5,6}.

CINV prophylaxis remains the fundamental strategy, optimum antiemetic prophylactic guidelines have been published by several organizations in accordance with different evidence-based, such as the Multinational Association of Supportive Care in Cancer in collaboration with European Society of Medical Oncology (MASCC/ESMO, 2016)⁷, American Society of Clinical Oncology (ASCO, 2017)⁸, and National Comprehensive Cancer Network (NCCN, 2020)⁹. These updated recommendations should be rapidly implemented in medical practice as they are released. However, guideline adherence remains poorly integrated into routine clinical practice^{10,11}. A variety of barriers against applying guideline recommendations, include physician unawareness, disagreement with the guidance¹². There have been reported that low guideline adoption for patients receiving HEC and MEC both in Europe^{13,14,15} and US^{16,17} recently.

The present study aims to evaluate clinician adherence to prophylactic guidelines for the management of CINV, and offer a more comprehensive status of acute, delayed, and overall CINV by describing the incidence, severity, and impact on QoL at Zhejiang Cancer Hospital in China. By highlighting current gaps in the clinical uptake of these CINV guidance, we hope to enhance individual physician awareness of these recommendations and to inform future efforts to ensure patients receive the highest quality evidence-based cancer care.

Materials And Methods

study design and setting

This single-center, cross-sectional study was conducted between April 1 and April 30, 2019 at Zhejiang Cancer Hospital. The main inclusion criteria were as follows:

1. Patient's pathological diagnosis is carcinoma;
2. 18 years or older;
3. Undergoing consecutive chemotherapy;
4. Be able to complete the data collection forms;

The exclusion criteria were as follows:

1. Patients with major psychiatric diseases or unstabilized cancer pain;
 1. Long-term recipients of corticosteroids;
 2. Disease-related nausea or vomiting (such as Meniere Syndrome, symptomatic brain metastasis);
 3. Currently participating in clinical trials on prophylactic antiemetic therapy.

Study methods

The main study tools consisted of two parts. Part 1 was patient's medical records, including age, gender, pathological diagnosis, chemotherapy regimen, antiemetic program. Part 2 was patient's feedback recorded by common terminology criteria for adverse events (CTCAE) 4.03 standard using MASCC antiemetic tool (MAT). Participants reported the incidence, frequency and impact on daily life of CINV from the first 24-hour of chemotherapy administration up to 5 days.

After data collection, prescription compatibility between medication prescribed for the management of CINV in our institute and the guideline recommendations was determined for each cancer patient by comparing the type, dose, and route of administration for prescribed medications. And we ranked clinician guideline adherence in different departments. In this study, we defined adherence failure as no antiemetic regimen prescription, non-recommended dose, or non-recommended drugs.

Statistical analysis

We analyzed patient characteristics, chemotherapy regimen courses, and clinician practice patterns using descriptive statistics. Statistical analysis software SPSS 22.0 was used, categorical variables were expressed as a percentage and continuous variables were reported as mean \pm standard deviation (SD). Enumeration data were expressed as number of cases (rate or ratio). χ^2 -Test and Student's t-test were used to assess statistical significance. When $P < 0.05$, the difference had statistical significance.

This study protocol was reviewed and approved by the Research Ethics Committees of participating institutions. All patients signed the written informed consent forms before this study was initiated.

Results

From April 1 to April 30, 2019, a total of 1000 patients were randomly selected from 5468 patients at different departments. After quality inspection, 875 questionnaires were included in statistical analysis after rejecting 25 unqualified questionnaires: 501 from internal medicine department, 184 from surgery department, 172 from radiotherapy department, 18 from interventional department. The average patient age was 56.3 ± 10.5 years within a range of 18–81 years. There were 375 males (42.86%) and 500 females (57.14%). The demographic and clinical characteristics of the patients were pictured in Table 1.

Table 1. Baseline characteristics and demographics of survey respondents.

Baseline characteristics	Patients (N [%])
Department	501 (57.26)
Internal Medicine	184 (21.03)
Surgery	172 (19.66)
Radiotherapy	18 (2.05)
Interventional	56.3 ± 10.5
Age	517 (59.09)
Mean ± SD	358 (40.91)
< 60	
≥ 60	
Gender	
Male	375 (42.86)
Female	500 (57.14)
Diagnosis	154 (17.60)
Lung cancer	189 (21.60)
Breast cancer	73 (8.34)
Gastric cancer	138 (15.77)
Colorectal cancer	78 (8.91)
Ovarian cancer	11 (1.26)
Gallbladder cancer	19 (2.17)
Pancreatic cancer	3 (0.34)
Duodenal cancer	47 (5.37)
Cervical cancer	10 (1.14)
Endometrial cancer	37 (4.23)
Nasopharyngeal cancer	27 (3.09)
Lymphoma	29 (3.31)
Esophageal cancer	

Abbreviation: SD, standard deviation

In this study, 66 antineoplastic drugs were investigated, of which 52 were given intravenously and 14 orally. There were 9, 7, 50 drugs with high, moderate and low emetic risk respectively. The most prescribed prophylactic regimens for the management of CINV in our hospital were neurokinin-1 receptor antagonists (NK-1RA, such as aprepitant), 5-hydroxytryptamine₃ receptor antagonists (5-HT₃RA), promethazine and dexamethasone (DEX) and metoclopramide.

Analysis of compliance with CINV guideline

Adherence to different regimens for the prophylaxis of CINV in our hospital was compliant in 61.68%, 61.41%, 52.91%, and 27.78% at internal medicine department, surgery department, radiotherapy department, and interventional department, respectively (Table 2).

Table 2. Prevalence of Guideline-Consistent CINV Prophylaxis for Chemotherapy, and the Main Cause of Inconsistency (n = 875)

Emetogenic potential group	Guideline consistency N (%)	N of patients with guideline inconsistency	
Type of drugs			
i.v. high	60 (21.28)	222	
lack of NK-1RA		187	
metoclopramide, DEX and 5-HT3RA		25	
promethazine, DEX and 5-HT3RA		33	
low DEX dose in the acute period		82	
i.v. moderate	96 (44.65)	119	
lack of DEX		96	
both different 5-HT3RA		23	
DEX and metoclopramide		5	
extra DEX dose in the acute period		4	
i.v. low	231 (95.45)	11	P = 0.01
no antiemetic treatment	36 (100)	8	
i.v. minimal	2 (28.57)	0	
oral high/moderate	93 (100)	5	
no antiemetic treatment	309 (61.68)	4	
DEX and promethazine	113 (61.41)	1	
oral low	91 (52.91)	0	
type of departments	5 (27.78)		
internal medicine			
surgery			
radiotherapy			
interventional			

As depicted in Table 2, in the highly emetogenic risk group, the most two essential reasons for lack of adherence to the guideline recommendations were lack of NK-1RA like aprepitant prescription, and low dose of DEX. Across moderate emetogenic potential group, omission of DEX and extra 5-HT3RA prescription were the principal cause of nonadherence.

CINV incidence and Rate of complete control

With respect to the primary outcome, the incidence rate of acute phase CINV was 24.57%, delayed phase CINV was 39.54%, and the overall CINV was 44.23%. 19.89% patients had both acute and delayed CINV (Fig.1). During the overall period, the incidence of CINV was higher in the delayed phase than in the acute phase; nausea was more frequent across the overall observation period (43.66% VS 18.86%). However, vomiting was more severe and had a greater impact on life than nausea (Fig.2).

Rate of complete control (CC) was defined absence of nausea and vomiting. The CC rates of emetogenic regimens in overall phases was increased by 14.52% (61.58% VS 47.06%, $P < 0.001$) when compliance antiemetic regimens were compared with non-compliance regimens (Table 3). Compliance with the antiemetic guideline could better prevent occurrence of CINV beyond the overall risk period.

Table 3. Relationship between CINV complete control rate and antiemetic regimens recommended by the guideline

	Patients [N (%)]	Rate of CC (%)	
i.v. HEC	60 (21.28)	60.00	
Guideline consistency	222 (78.72)	46.85	
Guideline inconsistency			
i.v. MEC			
Guideline consistency	96 (44.65)	57.29	
Guideline inconsistency	119 (55.35)	48.74	$P < 0.001$
i.v. LEC	231 (95.45)	62.34	
Guideline consistency	11 (4.55)	45.45	
Guideline inconsistency	2 (28.57)	100.00	
oral HEC and MEC	5 (71.43)	20.00	
Guideline consistency	518 (59.20)	61.85	
Guideline inconsistency	357 (40.80)	47.06	
The overall			
Guideline consistency			
Guideline inconsistency			

Discussion

Patients with carcinomas generally experience numerous unpleasant symptoms during the course of disease, many previous clinical studies have indicated that the standardized combined usage of antiemetic drugs can protect more than 70% patients from CINV suffering. Multiple analyses for CINV-related hospital admissions have revealed that costs exceed 10000 dollars per event during the first 5 days after chemotherapy^{18,19}. CINV directly affects patient cancer care and healthcare utilization, and leading international cancer experts recognize that the development and update of effective antiemetic strategy represents an advance in oncology. Due to complexities in real conditions such as medical insurances policies, patient compliance, and clinical professionalism in real practice, however, we found that CINV remains a significant challenge in oncology^{5,10,11,20}. Our findings align with prior work suggesting that specific situations of CINV were far more complicated than clinical study results.

This study showed that during 2019, adherence to the guideline recommendations for the prevention of CINV associated with chemotherapy regimens was suboptimal in actual practice in the Zhejiang Cancer Hospital. Noticeable is the reported consistently low medication rate of NK-1RAs in the HEC setting. Even though NK-1RAs were suggested in guidelines for CINV management following HEC regimens and some MEC regimens²¹. In addition, low dose of DEX across HEC and MEC settings, in combination with DEX-based regimens are largely not qualified per guidelines. A propensity score-matched analysis about the efficacy of one-day versus multiple-day DEX for CINV indicated that the antiemetic regimen of one-day DEX strategy leads to poorly controlled nausea in the delayed phase²². In this study, the occurrence of acute and delayed CINV exceeded 35% during real-world clinical practice, even if preventive antiemetic therapies were used. Our research showed that the guideline compliance rate was 59.20% for preventive antiemetic treatment and merely 21.28% in the i.v. HEC group. Similar prospective observational studies in aboard have also been reported: adherence to guidelines was analyzed in a study enrolling 1198 patients at various centers across Europe between 2008 and 2015 showed a 14.3% adherence rate in the HEC setting during the acute period²³. Notable is the high proportion of HEC treatments and for which poor associated antiemetic prophylaxis was used. This alarming result may be explained by clinicians' marked underestimation of the emetic potential of chemotherapy and by their lack of understanding of antiemetic guidelines. Relevant surveys in Europe and US of oncologists²⁴ and oncology nurses²⁵ consistently reported low compliance with antiemetic guidelines. Considering about that NK-1RAs are not included for medical insurance reimbursement yet in China as well as their expensive price, so these drugs are difficult to access. This actual situation may also lead to significant utilization in NK-1RAs.

Our outcomes also reported that the incidence rate of CINV was high in delayed phase. This finding may be explained that we used CC as the study endpoint. Most clinical trials focused on single outcomes and set the complete remission (CR, nausea that does not affect quality of life with no vomiting and no salvage therapy) as the primary endpoint, which had been pointed out by some scholars that the efficacy could likely be overestimated²⁶. While CC can be more objectively and comprehensively reflect the picture of CINV. In this large cross-sectional study, the overall CC rate in guideline-consistency patients was only 61.85%, which means that the painful of patients throughout the chemotherapy cycle is more severe than expected. During overall period, although the incidence rate of nausea was higher, the adverse effects of

vomiting on patients had exceeded nausea because persistent vomiting were more discomfort and had more negative impact on QoL.

Strengths of this study included that the large, population-based design focused on status in real practice world. However, the main limitation of this study is the patients from a single institution, thus resulting in conclusions based on limited representation.

Future research should identify the key barrier for implementation of guideline recommended prophylaxis.

Conclusion

Substantial gaps exist in oncologists' adherence to CINV prophylaxis guidelines in the Zhejiang Cancer Hospital. In the real practice, the CC rate of CINV still remains poorly characterized, therefore efforts to improve adherence to the guideline recommendations for the prevent of CINV and make sure evaluate the absence of any symptoms as a primary endpoint. Better communication and awareness of antiemetic guidelines must be taken to reduce the burden of CINV.

Declarations

Ethics approval and consent to participate

The present study was authorized by the Ethics Committee of Zhejiang Cancer Hospital. All procedures performed in studies were in accordance with the ethical standards. All participations provided written informed consent.

Consent for publication

Not applicable.

Availability of data and material

All data generated or analyzed during this study are included in this published article.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

JY provided the direction and guidance throughout the preparation of this manuscript. CL, LC, QX and MS wrote the whole manuscript. JL and QW critically revised the manuscript. All authors have read and approved the final manuscript.

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Abbreviations

CINV	chemotherapy-induced nausea and vomiting
QoL	quality of life
CC	complete control
HEC	emetogenic chemotherapy
MEC	moderately emetogenic chemotherapy
LEC	low emetogenic chemotherapy
MASCC	Multinational Association of Supportive Care in Cancer
ESMO	European Society of Medical Oncology
ASCO	American Society of Clinical Oncology
NCCN	National Comprehensive Cancer Network
CTCAE	common terminology criteria for adverse events
MAT	Multinational Association of Supportive Care in Cancer antiemetic tool
SD	standard deviation
NK-1RA	neurokinin-1 receptor antagonists
5-HT3RA	5-hydroxytryptamine ₃ receptor antagonists
DEX	dexamethasone
CR	complete remission

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Figures

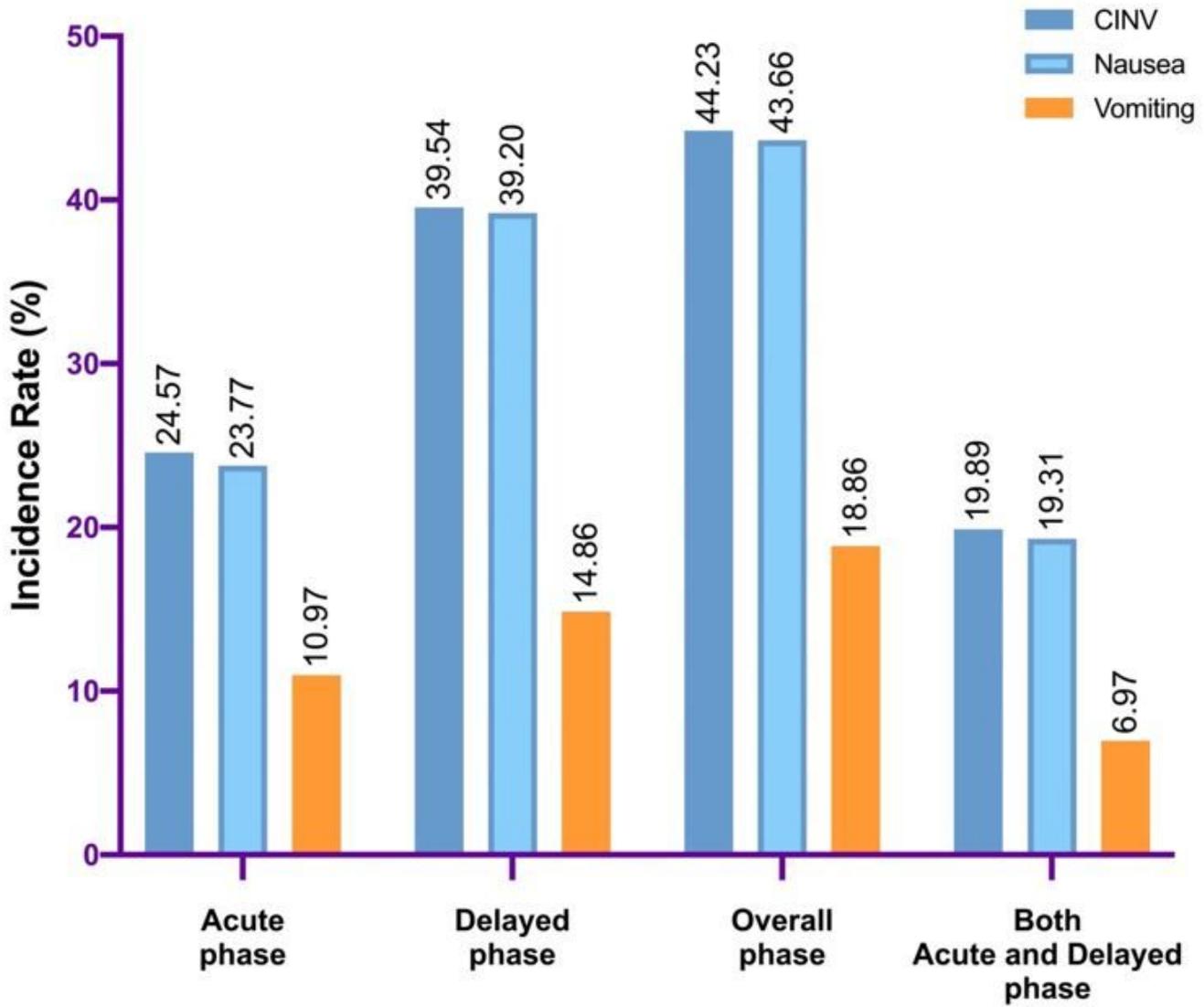


Figure 1

Incidence of CINV, nausea and vomiting in various phase

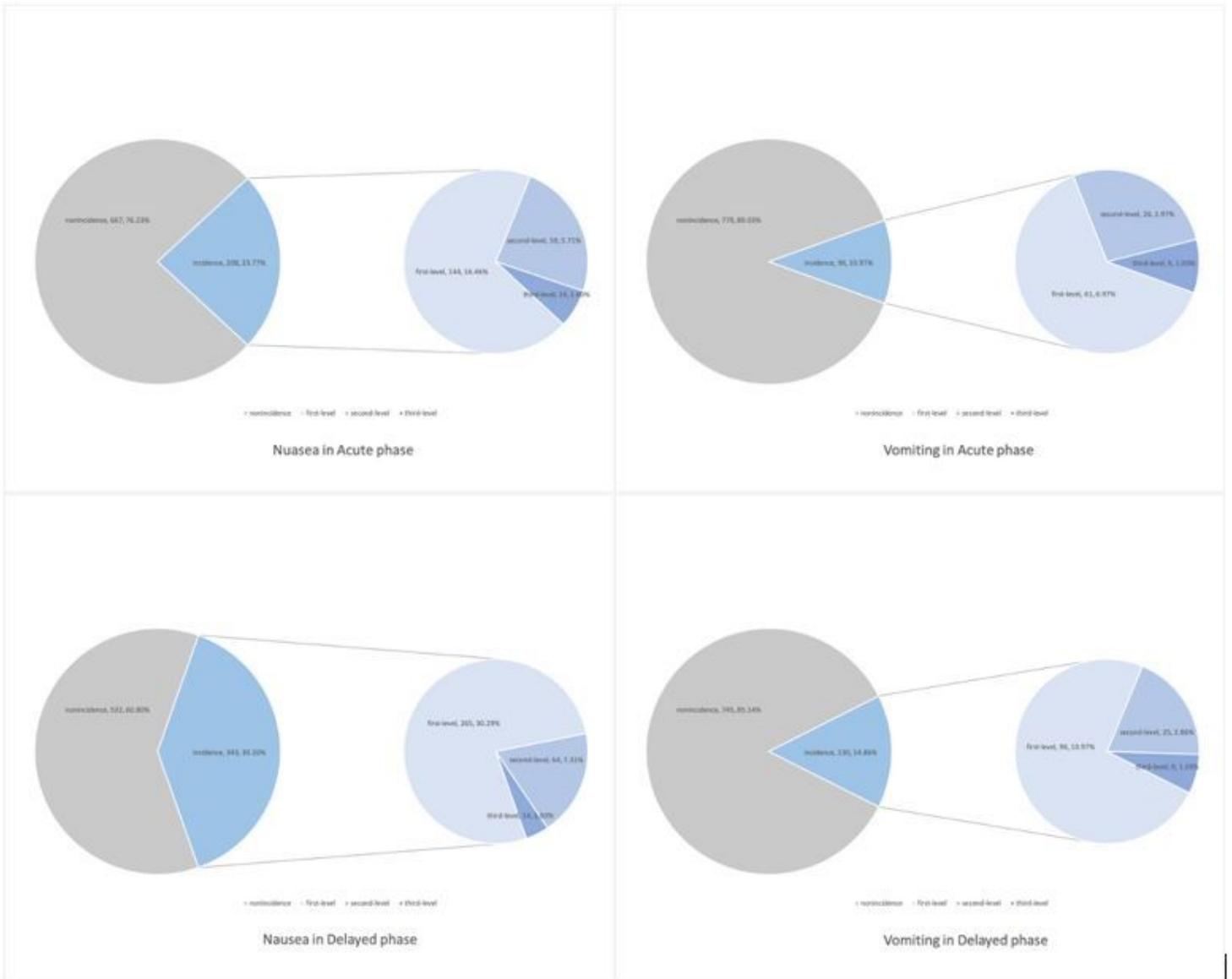


Figure 2

The impact of nausea and vomiting in daily life