INVESTIGATING PATIENT-SPECIFIC RISK FACTORS FOR CHEMOTHERAPY-INDUCED NAUSEA AND VOMITING IN PATIENTS WITH CANCER.

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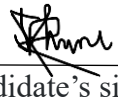
DECLARATION

I, Johara Rahim, student number 2085387, declare that this dissertation is my own work. It is being submitted for the Degree of Master of Pharmacy at the University of Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at any other University.



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PRESENTATIONS ARISING FROM THIS RESEARCH PROJECT

During the course of this degree programme, the following presentations were made based on the research:

- Rahim J.I., Khan R., Orchard A., Kathrada F., Vally M., Demetriou G., 3 September 2024. "Investigating patient-specific risk factors for chemotherapy-induced nausea and vomiting in patients with cancer" presented at the 82nd FIP World Congress of Pharmacy and Pharmaceutical Sciences, Cape Town, South Africa (Poster).
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ABSTRACT

Chemotherapy-induced nausea and vomiting (CINV) is the most common side effect of cancer treatment. Despite adequate antiemesis prophylaxis, this side effect remains poorly controlled and may decrease a patient's quality of life and affect adherence to treatment, leading to poor therapeutic outcomes. Patients experiencing CINV are also susceptible to malnutrition, electrolyte imbalances and dehydration, hence, adequate control of this side effect is imperative. Studies have reported that patient-specific risk factors can contribute to the development of CINV. Tailoring CINV regimens to mitigate patient-specific risk factors could decrease the incidence of nausea and vomiting. Comprehensive treatment regimens could potentially be developed by utilising antiemetic guidelines in conjunction with patient-risk factor assessment allowing for further optimisation of antiemetic treatment regimens in patients that are high risk.

This study was designed to investigate whether evaluating patient-specific risk factors for personalised antiemetic prophylaxis selection could aid in CINV treatment optimisation. A prescription record review and researcher-administered survey were conducted among cancer patients receiving chemotherapy at the outpatient department of a large academic hospital. The questionnaire comprised both open-and close-ended questions designed to investigate the incidence of CINV and the risk factors presenting in this cohort of patients.

A total of 222 patients diagnosed with cancer participated in the study. Among them, 22.5% experienced isolated nausea, 45% reported both nausea and vomiting, and 32.4% remained asymptomatic during the overall phase of treatment. Adherence to antiemetic treatment guidelines was 75.2%, with the highest adherence rates observed in patients who did not develop CINV ($p < 0.001$). This underscores the essential role of appropriate prescribing practices in effectively managing CINV. Significant associations between race and CINV incidence ($p=0.033$) were evident. Patients who received four or more cycles of chemotherapy reported a higher incidence of nausea (44.0%) and nausea accompanied by vomiting (49.0%) during the overall phase. Anticipatory nausea and vomiting was significantly associated with CINV incidence ($p < 0.001$). The use of non-prescription medications, marijuana, and complementary therapies like ginger also influenced CINV prevalence, while alcohol consumption appeared to potentially mitigate these symptoms.

This study underscores the pivotal role of adherence to established antiemetic guidelines in mitigating the burden of CINV, emphasising the need for individualised risk assessment to

optimise antiemetic regimen selection. Incorporating patient-specific risk factors into treatment selection, may potentially enhance the effectiveness of antiemetic therapies and improve overall patient outcomes in the oncology setting.

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5-FU-	5-fluorouracil
5HT-3RA-	Serotonin receptor antagonist
6-MP-	6-mercaptopurine
AIC-	Akaike Information Criterion
ALDH2-	Aldehyde-dehydrogenase-2
ANV-	Anticipatory nausea and vomiting
ASCO-	American Society of Clinical Oncology
AUC-	Area under the curve
BMI-	Body mass index
CI-	Confidence interval
CR-	Complete response
DMEs-	Drug metabolising enzymes
DRA-	Dopamine receptor antagonist
EML-	Essential medicine list
FLIE-	Functional Living Index for Emesis
FPC-	Finite population correction factor
hCG-	Human chorionic gonadotropin
HEC-	High emetogenic chemotherapy
LEC-	Low emetogenic chemotherapy
MASCC/ESMO-	Multinational Association of Supportive Care in Cancer and European Society of Medical Oncology
MEC-	Moderate emetogenic chemotherapy
MinEC-	Minimal emetogenic chemotherapy
NCCN-	National Comprehensive Cancer Network
NDoH-	National Department of Health
NK-1 RA-	Neurokinin-1 receptor antagonist
PTC-	Pharmaceutical and Therapeutics Committee
QoL-	Quality of life
RRR-	Relative Risk Ratio
STGs	Standard treatment guidelines
IV-	Intravenously

CHAPTER 1

1.INTRODUCTION

This introductory chapter provides essential background information on chemotherapy-induced nausea and vomiting (CINV), a significant challenge for patients undergoing cancer treatment. It explores the current landscape of CINV management, including the incidence of CINV, available treatment options, and known patient risk factors. This chapter also includes the research question, aim and objectives of the study.

1.1 Background

Chemotherapy is a fundamental component of most cancer treatment regimens, with the main objective being tumour cell reduction and prevention of metastases (Amjad et al., 2022; Anand et al., 2022; Tilsed et al., 2022). Most chemotherapy treatments target rapidly dividing cells and are non-selective in nature, rendering toxic effects on malignant and normal healthy cells with similar proliferative capacity (Amjad et al., 2022; Anand et al., 2022). This dual impact highlights both the effectiveness and associated adverse effects of chemotherapy (Hanahan and Weinberg, 2011; Behranvand et al., 2022). Side effects can be self-limiting or prolonged, requiring extensive monitoring to uphold the patient's quality of life (QoL) and encourage medicine adherence (Altun and Sekaya, 2018; Nurgali et al., 2018).

Chemotherapeutic agents elicit their effects on cells through various mechanisms of action including, the inhibition of DNA replication, triggering apoptosis, cell growth prevention and interfering with metabolic processes that are essential for cancer cells to survive (Amjad et al., 2022). These mechanisms differ based on the chemotherapeutic agent or combination of chemotherapeutic agents employed, as well as the stage and type of cancer being treated (Amjad et al., 2022). The classification of chemotherapy agents in accordance with mechanism of action is summarised in Table 1.1.

Table 1.1: Classification of chemotherapy agents according to mechanism of action. (Colvin, 2003; Bardal et al., 2011; Lansiaux, 2011; American Cancer Society, 2019; National Cancer Institute, 2022a; Venkatesh and Kasi, 2023; Cancer Research UK, 2024)

Chemotherapeutic drug class	Mechanism of action	Some examples
Alkylating agents	By creating covalent bonds with DNA strands, these agents disrupt DNA replication by causing cross-linking between DNA strands and DNA-protein complexes.	• Busulfan • Carboplatin • Cisplatin • Cyclophosphamide • Ifosfamide, • Oxaliplatin • Dacarbazine
Antimetabolites	These agents inhibit enzymes required for nucleotide synthesis or imitate the structure of nucleotides to inhibit DNA synthesis.	• 5-fluorouracil (5-FU) • 6-mercaptopurine (6-MP) • Capecitabine • Fludarabine • Gemcitabine • Hydroxyurea • Methotrexate
Topoisomerase inhibitors	These agents damage DNA resulting in cellular death due to topoisomerase (enzymes necessary for DNA replication and repair) inhibition. There are two types of topoisomerase inhibitors: topoisomerase I topoisomerase II.	Topoisomerase I inhibitors (also known as camptothecins) include: • Irinotecan • Topotecan Topoisomerase II inhibitors (also known as epipodophyllotoxins) include: • Etoposide • Teniposide

Chemotherapeutic drug class	Mechanism of action	Some examples
Microtubule inhibitors	These agents disrupt the dynamic equilibrium between the α-tubulin and the β-tubulin of the microtubules, leading to mitotic arrest and cell division inhibition. This class of medicines comprises both the taxanes and vinca alkaloids	Taxanes: • Paclitaxel • Docetaxel Vinca alkaloids: • Vincristine • Vinblastine
Anthracyclines	These antibiotics are derived from Streptomyces spp. And exert an anti-tumour effect by intercalating DNA stands, resulting in inhibition of DNA and RNA synthesis. These agents are also capable of inhibiting topoisomerase II, initiating apoptosis through DNA adduct formation and generating free radicals.	• Daunorubicin • Doxorubicin • Bleomycin
Targeted therapies	These drugs target proteins that control cell division and spread of the tumour cells. Targeted therapies include proteasome inhibitors, monoclonal antibodies and tyrosine kinase inhibitors.	Proteasome inhibitors: • Bortezomib Monoclonal antibodies: • Trastuzumab • Rituximab Tyrosine kinase inhibitors: • Erlotinib • Imatinib

Chemotherapy drug class	Mechanism of action	Some examples
Hormonal agents	Hormonal agents are usually employed in the treatment of breast cancer, uterine cancer or prostate cancer in which sex hormones drive tumour cell proliferation. These agents function by preventing the synthesis of the hormone causing the malignancy or by preventing the cancer cells from utilising the hormone that require for proliferation.	Breast cancer hormone therapy: • Tamoxifen • Anastrozole • Fulvestrant • Goserelin • Leuprorelin Prostate cancer hormone therapy: • Bicalutamide • Cyproterone acetate • Flutamide • Goserelin • Leuprorelin • Triptorelin • Buserelin Uterine cancer hormone therapy: • Medroxyprogesterone acetate • Megestrol

Chemotherapeutic agents are usually administered in combination to produce an adequate response and maintain therapeutic efficacy as well as promote cytotoxicity in both resting and multiplying cells to prevent the development of resistance (Mollaei et al., 2021; Amjad et al., 2022). The combination of chemotherapeutic agents is selected based on the type of cancer a patient has been diagnosed with, the location of the tumour and the extent of tumour metastases (American Cancer Society, 2019; Anand et al., 2022).

Chemotherapy is administered in cycles, each consisting of a treatment phase followed by a recovery period, allowing the patient's body to recuperate from its toxic effects (Dickens and Ahmed, 2018; American Cancer Society, 2019). In order to maximise treatment effectiveness, high-dose or dose dense chemotherapy is selected to control the growth of tumours that are more aggressive (Citron, 2008; Bayraktar and Arun, 2012). Moreover, within each cycle, chemotherapy treatments may be administered over several days with patients receiving either

oral medication or infusions over consecutive days to enhance therapeutic efficacy (Roila et al., 2016; Cancer Research UK, 2023).

Chemotherapy is an effective way of treating cancer; however, it can bring forth a myriad of side effects that are challenging to treat including hair loss, fatigue, constipation, diarrhoea, nausea and vomiting (Pearce et al., 2017). The spectrum of side effects experienced differs from patient to patient (American Cancer Society, 2022). This variation may be attributed to the type and dose of chemotherapy regimen administered, the number of cycles the patient must undergo and the patient's general health and capacity to endure such treatment (American Cancer Society, 2022). Additionally, genetic factors and metabolism may also influence the response to chemotherapy, potentially increasing the range of side effects a patient may experience (National Cancer Institute, 2022). Chemotherapy-induced nausea and vomiting (CINV) is one of the most common adverse effects experienced by patients undergoing treatment (Gupta et al., 2021). The incidence of nausea and vomiting related to chemotherapy is reported to occur in approximately 70-80% of patients (Wang, W et al., 2021). Antiemetic prophylaxis is selected based on the emetogenicity of the specified chemotherapeutic regimen (Mosa et al., 2020). With an appropriate prophylactic antiemetic regimen, the incidence of CINV can be reduced to 30-40% (Basch et al., 2011). The risk of nausea and vomiting associated with a treatment regime is stratified into four groups: minimal, low, moderate and high risk (Mosa et al., 2020).

A minimal risk of emesis (MinEC) is a less than 10% risk of CINV without prophylaxis and is associated with antineoplastic drugs including bevacizumab and the vinca alkaloids (Schwartzberg, 2007). Biological agents such as cetuximab and trastuzumab as well as etoposide and taxanes are classified as low emetogenic chemotherapy (LEC) with a 10-30% risk of inducing emesis (Schwartzberg, 2007). Moderate emetogenic chemotherapy (MEC) (30-90%) include regimens that contain oxaliplatin, carboplatin, cyclophosphamide, irinotecan, doxorubicin and epirubicin based regimens (Schwartzberg, 2007). High emetogenic chemotherapy (HEC) regimens include agents such as cisplatin and dacarbazine which have a greater than 90% possibility of inducing CINV (Schwartzberg, 2007). These agents are the backbone of commonly used chemotherapy regimens.

CINV is classified into five categories based on factors such as the time of onset and resistance to treatment (Elhassan et al., 2017). These categories include acute, delayed, anticipatory, breakthrough, and refractory CINV (Elhassan et al., 2017). Acute vomiting occurs within 24

hours of chemotherapy initiation, whereas delayed vomiting may occur 24 hours after treatment and last for up to six days while anticipatory vomiting occurs prior to initiation of cancer treatment (Elhassan et al.,2017). Breakthrough nausea and vomiting occurs within five days of chemotherapy treatment despite the use of adequate prophylaxis agents (Navari, 2015). Refractory nausea and vomiting occur in patients in later cycles, despite appropriate treatment in earlier cycles (Navari, 2015).

Evidence-based guidelines for antiemesis are often utilised by healthcare professionals to guide the selection of treatment based on the emetogenicity of a particular regimen and are imperative in managing the adverse effects of chemotherapy (Jordan et al., 2014). These guidelines recommend the combination of antiemetic agents that should be prescribed based on CINV susceptibility of a chemotherapeutic agent or chemotherapy combination (Aapro et al., 2022). International guidelines widely employed in CINV treatment include, the American Society of Clinical Oncology (ASCO) guideline, the Multinational Association of Supportive Care in Cancer (MASCC) guidelines in collaboration with the European Society for Medical Oncology (ESMO) and the National Comprehensive Cancer Network (NCCN) guidelines.

In South Africa, the National Department of Health (NDoH) provides a framework on palliative care and recommendations on how common side effects related to life-threatening illnesses should be treated, such as nausea and vomiting induced by chemotherapy (NDoH, 2022). In the public sector medication selection is based on the protocol developed by the treatment facility and is guided by the essential medicines list (EML) (NDoH, 2020). Inclusion of medicines in the EML is based on cost-effectiveness, the burden of disease, as well as evidence of safety and efficacy of the treatment. International guidelines such as the MASCC/ESMO and ASCO guidelines are usually employed by the private sector (ICON oncology, 2018). The treatment regimens used in sectors vary, with the private sector not being restricted by the EML and having improved medication access and availability (Mohlala et al., 2010).

Pharmacological and non-pharmacological interventions are utilised to manage CINV. Five pharmacological drug classes are commonly employed in the treatment of CINV and include serotonin-receptor antagonists (5HT-3 RAs), corticosteroids, neurokinin (NK1-RAs) receptor antagonists, cannabinoids and dopamine receptor antagonists (DRA) (Schwartzberg, 2007). Moreover, some cancer patients have turned to alternate and complementary therapies to further improve the management of this devastating side effect (Ayers and Olowe, 2015). CINV may

be alleviated by behavioural therapy including hypnosis, relaxation techniques, yoga and acupuncture as per the recommendation of the NCNN guidelines (Natale, 2018). There is evidence to suggest that complementary medicines as adjunctive therapies could mitigate CINV (Li et al., 2022).

A randomised controlled trial demonstrated that peppermint oil was successful in alleviating CINV, and that aromatherapy could be used in conjunction with conventional treatments to alleviate nausea and vomiting in patients on chemotherapy (Efe and Taşcı, 2021). While the study demonstrated promising results regarding the use of peppermint oil in alleviating CINV, its open-label design introduces a potential for bias, as both patients and researchers were aware of the intervention. Additionally, as this was a pilot study, the small sample size and lack of multicentre involvement limit the generalisability of the findings. Ginger supplementation and modification of the diet are also used as non-pharmacological interventions to alleviate CINV (Gupta et al., 2021). However, given the clinical heterogeneity across studies such as variations in treatment protocols, patient demographics and cancer types, it is challenging to confidently assert the effect of ginger on CINV-related outcomes (Choi et al., 2022). Despite the availability of adequate strategies to eliminate this side effect, a substantial number of patients experiencing CINV still experience refractory CINV (Gupta et al., 2021). Furthermore, chemotherapy induced nausea seems to be a clinical problem that is not optimally treated due to the subjective nature of this side effect and represents an unmet need in addressing CINV. (Smit, Kotze and Du Plessis, 2021).

Nausea and vomiting are symptoms that often occur sequentially; however, nausea has been reported to occur more frequently and sometimes independently of vomiting (Adel, 2017). Additionally, vomiting remains the primary focus of many studies on CINV, with little emphasis on nausea as an independent side effect (Adel, 2017). A Spanish study conducted on 240 patients receiving MEC reported that approximately 20.8% of these patients experienced vomiting, however, 65.8% of participants described feeling either nauseous or significantly nauseous following the administration of chemotherapy, indicating inadequate management of this side effect (Escobar et al., 2015).

A study conducted in Johannesburg (2021), South Africa recruited 95 patients receiving chemotherapy to investigate the incidence, duration and severity of nausea experienced over a seven-month period. All patients received CINV prophylaxis in line with international treatment

guidelines (Smit, Kotze and Du Plessis, 2021). Despite receiving treatment, more than half of the participants reported experiencing nausea in the absence of vomiting during the first two cycles, whilst 45.6% experienced this side effect during the third chemotherapy cycle (Smit, Kotze and Du Plessis, 2021). Moreover, the identified risk factors included female sex, being under 60 years old, and a history of motion or morning sickness, all of which increased the likelihood of nausea among patients (Smit, Kotze and Du Plessis, 2021).

Despite the recommendations made in guidelines, patient-specific risk factors are usually not taken into consideration when prescribing an antiemetic treatment regimen (Mosa et al., 2020). These intrinsic risk factors include experiencing CINV in previous chemotherapy cycles, younger age, patient anticipation of experiencing CINV, a history of morning or motion sickness and a low daily alcohol intake (Adel, 2017). Another factor that could contribute to inadequate antiemesis control is the divide between the perception of a healthcare professional to CINV and the patients' experience of CINV (Grunberg et al., 2004). Furthermore, poor adherence to treatment guidelines and physicians utilising their discretion and experience in treating CINV has given rise to improper management of this debilitating side effect (Clemons, 2018). The incidence of CINV could possibly be reduced by developing strategies to optimise antiemetic guidelines coupled with an evaluation of a patient's personal risk of experiencing nausea and vomiting (Grunberg et al., 2004; Gupta et al., 2021).

Sekine et al. (2013) evaluated potential patient-specific risk factors that could exacerbate CINV such as female sex, patients under 55 years old and occasional alcohol consumption (Sekine et al., 2013). These factors were associated with treatment failure of antiemetic medications and the triggering of nausea during the acute phase of treatment (Sekine et al., 2013). Additionally, it was demonstrated that patients with more than three identified risk factors displayed a higher incidence of CINV and treatment failure in comparison to patients who did not exhibit these risk factors (Sekine et al., 2013).

A clinical trial assessed the efficacy of a CINV risk-prediction model incorporating various patient-related risk factors that could potentially worsen nausea and vomiting experienced during treatment (Dranitsaris et al., 2017). This study demonstrated that utilising a risk prediction algorithm to guide the selection of prophylaxis was more effective in preventing episodes of both acute and delayed phase nausea and vomiting than physician-choice prophylaxis (Dranitsaris et al., 2017). It is worth noting that these predictive models have

limitations, as the development of the algorithms is influenced by factors such as geographical location and a limited sample size. (Dranitsaris et al., 2017). Development of high-sensitivity CINV prediction models could significantly improve nausea and vomiting prophylaxis and lead to the development of highly optimised treatment regimens in the future (Dranitsaris et al., 2017).

1.2 Rationale and Problem Statement

CINV presents with many clinically significant consequences, including malnutrition, metabolic abnormalities, and oesophageal deterioration (Ballatori and Roila, 2003). CINV significantly impacts patients' QoL and can lead to early discontinuation of chemotherapy due to missed follow-up treatments (Krikorian et al., 2018). Successful management of CINV during the first cycle of chemotherapy is crucial, as it can influence the occurrence and severity of CINV in subsequent cycles (Navari et al., 2022). Therefore, optimising antiemetic prophylaxis regimens is essential for improving treatment adherence and patient outcomes.

A significant challenge in CINV management lies in the insufficient consideration of patient-specific risk factors. These factors can profoundly influence both the incidence and severity of CINV, yet they are often inadequately addressed in standard treatment protocols. Failure to account for these individual risks can result in suboptimal prophylaxis and poorer patient outcomes (Mosa et al., 2020). Incorporating a personalised approach that aligns antiemetic regimens with each patient's unique risk profile is imperative for enhancing CINV management.

Additionally, disparities between public and private healthcare sectors exacerbate this issue, as public institutions often have limited access to the full range of recommended antiemetic therapies (De Villers, 2021). These sectoral differences, combined with a lack of individualised care, further contribute to inadequate CINV management in vulnerable populations. Bridging these gaps through equitable access to treatments and a patient-centred approach that integrates risk factors into guideline-based care is essential for improving patient outcomes and ensuring the consistent management of CINV across all settings.

To date, no study has comprehensively examined the influence of patient-specific factors on the incidence of CINV within the South African population. Ultimately, this study will provide valuable insights into the prevalence and nature of CINV within the South African healthcare landscape, offering evidence-based recommendations to optimise CINV management. The

findings will highlight the critical need for integrating patient-specific risk factors into standard treatment protocols, thus ensuring more effective and equitable care for all patients undergoing chemotherapy.

1.3 Research Question

What are the risk factors associated with CINV in patients on recommended CINV prophylaxis treatment regimens?

1.4 Aim

This study aimed to investigate the nature and extent of chemotherapy-induced nausea and vomiting (CINV) and determine whether patient-specific risk factors influence its incidence in patients receiving routine cancer treatment at a tertiary public sector facility in Johannesburg, South Africa.

1.5 Objectives

The following objectives were outlined to achieve the study aim:

- To classify the emetogenic potential of the chemotherapy regimen for each participant by prescription review.
- To evaluate whether the antiemetic regimen prescribed is sufficient and in line with the guidelines of the oncology outpatient unit.
- To investigate the frequency of CINV amongst patients with cancer utilising a survey instrument.
- To determine a patient's personal risk of experiencing CINV through assessment of risk factors using a survey instrument.

CHAPTER 2

2. LITERATURE REVIEW

2.1 Introduction

This chapter reviewed the existing body of research on CINV, examining the emetogenicity of chemotherapy regimens, guideline-recommended antiemetic regimens, treatment of CINV in the South African public sector of health, and a comprehensive review of known patient risk factors.

2.2 The Emetogenicity of Chemotherapy

Cancer is one of the leading causes of premature death worldwide with an estimate of 20 million cases reported in 2022 (World Health Organization, 2024). In 2018, global statistics estimated that of 17 million diagnosed cancer cases, 57.7% required chemotherapy (Jarach, 2019). Chemotherapy remains the cornerstone of cancer pharmacotherapy, targeting integral parts of the cell division process in rapidly dividing cells to prevent metastases (Hellmann et al., 2016; Shields, 2017). Due to the non-selective nature and narrow therapeutic index of chemotherapeutic regimens and resultant toxicity, patients may experience a myriad of side effects with the most common being CINV (Altun and Sonkaya, 2018; Brianna and Lee, 2023). It is estimated that up to 80% of patients receiving chemotherapy will experience treatment induced nausea and vomiting (PDQ Supportive and Palliative Care Editorial Board, 2023).

Nausea and vomiting experienced by patients receiving chemotherapy can significantly impact a patient's ability to tolerate cancer treatment and could lead to delays in administration of chemotherapy and reduction in dosages, which may, in turn, negatively affect therapeutic outcomes (Rao and Fasso, 2012; Gupta et al., 2021; Yeo et al., 2021). Furthermore, CINV can give rise to many other clinically significant problems including mental and physical deterioration of the patient (Rao and Fasso, 2012). Considering the significant impact of CINV on treatment outcomes and patient quality of life, it becomes essential to assess the emetogenicity of chemotherapeutic agents to inform effective management strategies (Rao and Fasso, 2012).

Emetogenicity is described as the potential of a chemotherapeutic agent to induce nausea and vomiting (Rao and Faso, 2012; Majem et al., 2022). Chemotherapeutic agents have been divided into four risk categories as per the ASCO, MASSC/ESMO and NCCN guidelines (Rao and Faso, 2012). The designation of an agent into a specific category is based on the inherent

risk of the agent inciting CINV (Rao and Faso,2012). Emetogenicity, however, is not solely determined by a chemotherapy agent. It is also influenced by the chemotherapy dose, route of administration and patient-specific risk factors (Jin et al., 2021). Table 2.1 outlines various chemotherapeutics and their emetogenic potential.

Table 2.1: Emetogenicity of intravenous anticancer agents (Majem et al., 2022).

Risk category	Chemotherapeutic agent
High (Greater than 90% risk of experiencing CINV)	Anthracycline/cyclophosphamide Cisplatin Carmustine Cyclophosphamide > 1500 mg/m^2 Darcabazine
Moderate (30-90% risk of experiencing CINV)	Azacitidine Bendamustine Cyclophosphamide < 1500 mg/m^2 Daunorubicin Doxorubicin Ifosfamide Irinotecan Oxaliplatin Trabedectin
Low (10-30% risk of experiencing CINV)	Aflibercept Bortezomib Brentuximab Cetuximab Docetaxel Etoposide 5-Fluorouracil Gemcitabine Methotrexate Paclitaxel Topotecan

Risk category	Chemotherapeutic agent
Minimal (< 10% risk of experiencing CINV)	Alemtuzumab Bevacizumab Bleomycin Busulfan Cladribine Fludarabine Pembrolizumab Rituximab Trastuzumab Vinblastine Vincristine Vinorelbine

2.3 The Incidence of Chemotherapy-Induced Nausea and Vomiting

Despite the use of adequate antiemesis prophylaxis to reduce the incidence of CINV, it is estimated that 30%-60% of patients experience either acute (occurring within 24 hours of chemotherapy initiation) or delayed (occurring after 24 hours of chemotherapy initiation) nausea and vomiting (Cohen et al., 2007). A study conducted in ten community oncology clinics on 151 patients reported a 62% occurrence of CINV (Cohen et al., 2007). This study further demonstrated that in a community-based setting, CINV remains a persistent clinical problem and contributes to QoL deterioration by interfering with daily functioning (Cohen et al., 2007). More recent findings by Wang et al. (2021) suggest that the incidence of this distressing side effect may be even higher, affecting approximately 70-80% of patients, indicating that CINV continues to be a widespread and challenging issue even in the presence of prophylactic measures.

Jones et al. (2011) investigated the incidence of CINV in the presence of prophylactic antiemesis therapy on 96 patients receiving either HEC or MEC. Approximately 27.1% of patients reported experiencing nausea and vomiting while receiving guideline-concordant antiemetic prophylaxis (Jones et al., 2011). A European study in which 249 patients were enrolled noted that over a five-day period, 450 emetic episodes (1.8 per patient) were experienced by 243 patients (97.6%) (Glaus et al., 2004). Additionally, most patients reported that CINV had a negative impact on their daily life (Glaus et al., 2004). A study conducted in the United States to assess the prevalence of CINV reported a CINV incidence of 61.2% in 178 patients currently on antiemetic medication (Haiderali et al., 2011). More effective prophylaxis

and mitigation strategies would be required to address CINV as this side effect still remains a prevalent and challenging issue despite the use of prophylactic regimens (Haiderali et al. 2011; D'Souza et al., 2020).

2.4 Incidence of Nausea in Comparison to Vomiting

Nausea and vomiting experienced by patients receiving chemotherapy is often viewed as a single symptom, however, these two symptoms can often occur independently with patients experiencing either nausea or vomiting (Aapro, 2018). Current antiemetics view the vomiting aspect of CINV as the primary endpoint with little emphasis placed on treating nausea (Janelsins et al., 2013; Meissner et al., 2019). Relieving nausea is therefore an unmet need in CINV treatment as it is infrequently reported by patients (Janelsins et al. 2013; Di Maio et al., 2015). The level of nausea experienced by a patient is subjective with no clinical indicator existing to measure its severity (Di Maio et al., 2015). For this reason, treatment of nausea remains sub-optimal and is greatly underestimated by healthcare professionals (Di Maio et al., 2015). Nausea has been reported to occur in 70% of patients receiving HEC and MEC, highlighting the urgent need for improved assessment methods and better management strategies to ensure patient comfort and well-being (Roila et al.,2016).

Torres et al. (2015) aimed to assess whether CINV was optimally controlled by evaluating the experience of breast cancer patients currently receiving an anthracycline-cyclophosphamide-based chemotherapy (Torres et al., 2015). Patients also received adequate antiemetic prophylaxis, however, 71% still reported experiencing nausea (Torres et al., 2015). Nausea was also ranked as the “worst side effect of chemotherapy” over vomiting (Torres et al., 2015). It was concluded that for antiemetic trials to be deemed effective, the absence of both nausea and vomiting should be considered an endpoint to measure a treatment’s success (Torres et al., 2015). This may suggest an ineffectiveness in current antiemetic regimens and indicate a necessity to reevaluate treatment strategies as nausea may have a profound effect on a patient’s daily functioning (Torres et al., 2015).

Further emphasising the significant impact of nausea, a longitudinal secondary analysis conducted on newly diagnosed cancer patients revealed that patients who experienced episodes of nausea both on its own and in combination with vomiting reported a greater impairment in their QoL (Pirri et al., 2013). Approximately 60% of patients experienced chemotherapy-induced nausea (Pirri et al., 2013). Furthermore, in comparison to vomiting, which was only

experienced by 27% of the patients, nausea was illustrated to have a more profound effect on QoL declination (Pirri et al., 2013). Treatment-induced nausea frequently results in a reduced appetite, decreased dietary intake, and challenges in sustaining adequate nutrition, thereby increasing the risk of malnutrition (Pirri et al., 2013). Malnutrition can subsequently weaken a patient's ability to tolerate chemotherapy, impair immune function, and hinder the recovery process, ultimately leading to poorer treatment outcomes (Pirri et al., 2013; Bossi et al., 2022). Therefore, effectively managing nausea, alongside vomiting, is crucial to improving patients' quality of life and potentially enhancing treatment outcomes.

Building on the understanding of nausea's severity, researchers have stratified this side effect into acute, delayed, anticipatory, and refractory categories based on its timing relative to chemotherapy administration (Ryan, 2010; Peppone, 2021). Acute nausea occurs within 24 hours of chemotherapy initiation, whereas delayed nausea is defined as nausea occurring 24 hours after chemotherapy initiation that can last for up to five days (Ryan, 2010). Anticipatory nausea occurs prior to initiation of treatment and may be stimulated by elemental triggers (Roscoe et al., 2011). These triggers are stimuli that are present during chemotherapy administration that a patient, in turn, may associate with the side effects of the treatment, for example, the smell of the treatment room may induce CINV (Roscoe et al., 2011). Patients may also experience refractory nausea in the presence of adequate medication (Peppone, 2021). This classification system highlights the complex nature of chemotherapy-induced nausea, with each type presenting its own management challenges (Peppone, 2021).

Examining the prevalence of delayed nausea in more detail, a study was undertaken with 322 patients receiving either doxorubicin, cisplatin, or carboplatin over two cycles (Hickok et al., 2003). These chemotherapeutic drugs were combined with other agents such as vincristine, cyclophosphamide, etoposide or 5-FU as part of the chemotherapy regimen (Hickok et al., 2003). During the five-day period of the first chemotherapy cycle, 76% of patients developed nausea (Hickok et al., 2003). Approximately 28% of patients experienced acute nausea, while 73% suffered from delayed nausea between the second and fifth day. Similar results were observed in the second cycle, with 68% experiencing delayed nausea. Patients also reported that delayed nausea was more intense and severe than acute nausea (Hickok et al., 2003). Despite receiving antiemetic treatment, the incidence of delayed nausea was higher, indicating that nausea occurring 24 hours after chemotherapy initiation was not adequately controlled (Hickok et al., 2003). Grunberg et al. (2004) concurred with these results and described delayed

nausea as often being underestimated in patients receiving highly and moderately emetogenic chemotherapy as it may present even in the absence of acute nausea. Despite the categorisation of nausea types, its management remains challenging.

Beyond the established classification of acute, delayed, and refractory nausea, the development of anticipatory nausea adds another layer of complexity to chemotherapy-induced nausea management. Approximately 20% of patients report experiencing anticipatory nausea prior to a cycle of chemotherapy (Ryan, 2010). Additionally, by the fourth cycle of chemotherapy, anticipatory nausea presents in 25-30% of patients (Ryan, 2010). There is some evidence to suggest that there is a correlation between the occurrence of anticipatory and delayed nausea (Bovbjerg, 2006). A study conducted on 40 breast cancer patients demonstrated that the presence of conditioned nausea may contribute to the severity of nausea experienced after the commencement of treatment (Bovbjerg, 2006). These findings are corroborated by Molassiotis et al. (2016), who found that anticipatory nausea and vomiting strongly predicted the development of acute and delayed nausea. Chemotherapy-induced nausea remains a significant issue that requires improved control (Ryan, 2010).

The current understanding of CINV, while encompassing various types falls short in effectively controlling nausea. High prevalence across these categories underscores the necessity for more novel therapeutic approaches (Ryan, 2010; Smit, Kotze and Du Plessis, 2021). Furthermore, a potential association between anticipatory, acute and delayed nausea suggests a need for a deeper understanding of the psychological and physiological underpinnings of chemotherapy-induced nausea (Bovbjerg, 2006; Janelsins et al., 2013; Molassiotis et al., 2016). Ultimately, addressing these knowledge gaps and developing more nuanced treatment plans are crucial to ensure patient well-being and optimise treatment outcomes.

2.5 Quality of Life and CINV

CINV can lead to a myriad of other physiological and psychological issues including electrolyte imbalances, malnutrition, increased anxiety levels and physical and mental deterioration (Hesketh, 2008). This places a further strain on a patient receiving chemotherapy, ultimately leading to the development of a negative quality of life (Yeo et al., 2021). Deterioration of QoL as a result of CINV may negatively affect the prognosis of a patient with cancer due to the fear associated with experiencing this side effect leading to treatment withdrawal (Yeo et al., 2021).

Studies have demonstrated that the greatest deterioration of QoL is experienced by patients suffering from both nausea and vomiting during the course of treatment, however, there is evidence that indicates that nausea as an independent side effect impacts QoL more than vomiting (Bloechl-Daum et al., 2006; Farell et al., 2013; Abunahla et al., 2016). Glaus et al. (2004) conducted a study with 249 patients. Patients were asked to fill out the Functional Living Index for Emesis (FLIE) questionnaire to assess the impact that CINV had on QoL (Glaus et al., 2004). It was reported that 51% of patients experienced emesis, while approximately 42-52% of patients experienced nausea over the 10-day period post-chemotherapy (Glaus et al., 2004). Results from the FLIE questionnaire showed that 50% of patients with vomiting and 75% with nausea reported that the side effect negatively impacted their daily activities such as maintaining hobbies, preparing meals, performing minor household tasks and engaging with family and friends (Glaus et al., 2004). Overall, a deterioration in QoL was seen in these patients (Glaus et al., 2004). These findings indicate that nausea independently exerts a substantial negative influence on a patient's daily life and overall well-being, highlighting the critical need for effective management strategies to address both aspects of CINV.

Further elucidating the impact of CINV on QoL, a study conducted in the Netherlands evaluated the duration and timing of CINV on QoL over three chemotherapy cycles in 274 patients (Hilarius et al., 2012). During the first chemotherapy cycle, approximately 39% of patients experienced acute nausea while 68% of patients presented with delayed-phase nausea. Furthermore, it was reported that acute vomiting occurred in 12% of patients and delayed vomiting occurred in 23% of patients (Hilarius et al., 2012). During this cycle, a third of patients indicated that the presence of CINV adversely affected QoL and daily functioning (Hilarius et al., 2012).

Cohen et al. (2007) reinforced this association by demonstrating that patients who experienced both acute and delayed phases of CINV had a more substantial deterioration in QoL compared to those who had no side effects or only experienced symptoms during the delayed phase. Additionally, patients who experienced CINV in earlier treatment cycles were more likely to report a decline in QoL in later cycles (Cohen et al., 2007). Schnell et al. (2003) emphasised that more effective control over CINV may be achieved through the improvement of prevention strategies rather than tailoring treatment. Patient outcomes and QoL can drastically be improved through the implementation of a more personalised approach to CINV to enhance the quality of life of patients undergoing chemotherapy (Schnell et al., 2003). To optimise patient well-being

during cancer treatment, further research is imperative to ameliorate the underlying physiological and psychological mechanisms that contribute to the association between CINV burden and its detrimental effects on patient-reported psychological well-being (Schnell et al., 2003; Yeo et al., 2021). This knowledge can then be leveraged to develop personalised treatment strategies that effectively manage CINV and its associated psychological sequelae (Schnell et al., 2003; Yeo et al., 2021).

2.6 Antiemetics Used for CINV

Multiple international guidelines, including NCCN, ASCO, and MASCC/ESMO, provide evidence-based recommendations for antiemetic agent combinations to mitigate the severity and frequency of CINV (Multinational Association of Supportive Care in Cancer [MASCC]/European Society for Medical Oncology [ESMO], 2016; American Society of Clinical Oncology [ASCO], 2019; National Comprehensive Cancer Network [NCCN], 2023). HEC and MEC regimens are known to induce both acute and delayed CINV phases (Celio, 2022). To effectively manage CINV in these patients, triple-antiemetic regimens that target multiple neurotransmitter pathways are often employed (Celio, 2022). Conversely, for LEC regimens, which primarily induce acute CINV tend to be sufficiently manged with a single antiemetic prophylactic agent (Celio, 2022). The medications outlined in international antiemetic guidelines, with the exception of olanzapine, align with those listed in the WHO EML (World Health Organization, 2023). The specific antiemetic agent combinations recommended for various chemotherapy regimens are detailed in Table 2.2.

Table 2.2: Guideline-recommended antiemetic therapy for CINV (Helsinn, 2019; Hesketh et al., 2020; Herrstedt et al., 2023; Scotté et al., 2023).

Emetogenicity of regimen	ASCO	MASCC/ESMO	NCNN
HEC (Non-anthracycline-based chemotherapy)	**Day 1**: NK-1 RA + 5 HT-3 RA + Dexamethasone + Olanzapine **Day 2-4**: It is recommended that the use of olanzapine and dexamethasone be continued to prevent delayed CINV	**Day 1**: NK-1 RA + 5 HT-3 RA + Dexamethasone+ Olanzapine (given prior to chemotherapy to prevent acute CINV). **Day 2-4**: The use of dexamethasone and olanzapine is recommended to prevent delayed CINV.	**Day 1**: NK-1 RA + 5 HT-3 RA + Dexamethasone+ Olanzapine **Day 2-4**: Olanzapine and dexamethasone are suggested to prevent delayed CINV
HEC (Anthracycline-based chemotherapy + cyclophosphamide)	**Day 1**: NK-1 RA + 5 HT-3 RA + Dexamethasone+ Olanzapine **Day 2-4**: It is recommended that the use of olanzapine should be continued.	**Day 1**: NK-1 RA + 5 HT-3 RA + Dexamethasone + Olanzapine (given prior to chemotherapy to prevent acute CINV). **Day 2-4**: Olanzapine is recommended to prevent delayed CINV.	**Day 1**: NK-1 RA + 5 HT-3 RA + Dexamethasone+ Olanzapine **Day 2-4**: Dexamethasone and olanzapine are recommended to prevent delayed CINV.
MEC (dose-dependent carboplatin)	**Day 1**: NK-1 RA + 5 HT-3 RA + Dexamethasone * Recommended for patients on carboplatin with an area under the curve (AUC) of ≥ 4 mg/mL/min.	**Day 1**: NK-1 RA + 5 HT-3 RA + Dexamethasone given before chemotherapy. * Recommended for patients receiving carboplatin AUC ≥ 5 mg/mL/min.	**Day 1**: NK-1 RA + 5 HT-3 RA + Dexamethasone *Recommended for patients on carboplatin with an AUC of ≥ 4 mg/mL/min. **Day 2-4**: The continued use of dexamethasone is recommended to prevent delayed CINV
MEC (excluding dose-dependent carboplatin)	**Day 1**: 5 HT-3 RA + Dexamethasone	**Day 1**: 5 HT-3 RA + Dexamethasone	**Day 1**: 5 HT3 -RA + Dexamethasone + Olanzapine

Emetogenicity of regimen	ASCO	MASCC/ESMO	NCNN
MEC (cyclophosphamide, doxorubicin, oxaliplatin and other MEC agents that induce delayed CINV)	**Day 1**: 5 HT-3 RA + Dexamethasone **Day 2-3**: Dexamethasone	Day 1: 5 HT-3 RA + Dexamethasone administered before chemotherapy in patients that are receiving oxaliplatin. * Dexamethasone or any other steroid should not be administered after Day 1 in accordance with this guideline. * The MASCC/ESMO guidelines recommends the addition of a NK-1 RA if a patient is female and under 50 years old as female sex and younger age is a CINV risk factor.	
LEC	5 HT-3 RA or a single 8mg dose of Dexamethasone (given prior to chemotherapy administration)	5 HT- 3 RA or Dexamethasone or DRA	5HT-3 RA or Dexamethasone or DRA.
MinEC	No routine antiemetics prescribed.	No routine antiemetics prescribed.	No routine antiemetics prescribed.

Antiemetic 5-HT3 receptor antagonists (RAs) consist of first-generation agents such as granisetron, ondansetron, and dolasetron, as well as the second-generation agent palonosetron. (Schwartzberg, 2007). A study conducted on a paediatric population investigated the efficacy of ondansetron. Despite this serotonin receptor antagonist being successful in decreasing the incidence of CINV experienced, approximately 30% of patients remain refractory to ondansetron (Jacobs et al., 2022). This study concluded that genomic variability is responsible for the response to ondansetron (Jacobs et al., 2022). The limited number of polymorphisms currently investigated necessitates further research to identify a comprehensive set of genetic markers (Singh et al., 2018). This comprehensive understanding will ultimately facilitate the development of personalised treatment strategies that optimise antiemetic efficacy and minimise adverse effects (Singh et al., 2018).

A double-blind randomised trial compared the efficacy of three different antiemetic regimens over seven days: a combination of granisetron and dexamethasone, a metoclopramide and dexamethasone combination, and granisetron as a single agent (Heron et al., 1994). The primary endpoint of this study, defined as a composite outcome, included the absence of nausea, absence of vomiting, and no use of rescue medications (additional antiemetics to alleviate CINV) (Heron et al., 1994). During the acute CINV phase, the combination of granisetron and dexamethasone was the most effective. However, single-agent oral granisetron proved to be far more efficacious than the intravenous combination of dexamethasone and metoclopramide. This aligns with findings of Roila et al. (2005) and Hickok et al. (2005), who reported that first-generation 5-HT-3 RAs are highly effective during the acute phase of CINV, however, these agents exhibited reduced efficacy in managing delayed CINV.

A retrospective records review assessing efficacy of guideline recommended palonosetron evaluated 1587 patient records (Schwartzberg et al., 2019). Overall, 42% of patients receiving MEC and 48% receiving HEC experienced CINV. This indicated that the second generation 5HT3-RA, palonosetron may not sufficiently control CINV (Schwartzberg et al., 2019). It was concluded that to decrease the prevalence of this side effect, alternative emesis prophylactic therapy may need to be employed (Schwartzberg et al., 2019). While Schwartzberg et al. (2019) suggested exploring alternative antiemetic approaches, Sugimori et al. (2017) reported superior efficacy for a combination of aprepitant and palonosetron compared to palonosetron alone in alleviating delayed CINV. Moreover, a study that combined dexamethasone with either palonosetron or granisetron found that during the acute phase, both 5-HT3 RAs displayed

similar efficacy (Saito et al., 2009). However, in the delayed phase, palonosetron was far more efficacious against CINV, with 56.8% of patients achieving complete response (CR)—defined as no emetic episodes and no use of rescue medications—in comparison to 44.5% in the granisetron group (Saito et al., 2009). A more recent study concurred with these findings and further demonstrated that second-generation palonosetron was superior in alleviating delayed phase nausea in comparison to granisetron when combined in a regimen with a corticosteroid and NK-1 RA (Matsumoto et al., 2020).

Although palonosetron is highly efficacious in treating delayed-phase nausea and emesis, costs associated with this drug limit its use (Hsu et al., 2021). An economic analysis found that in a standard triple regimen that included both aprepitant and dexamethasone, the use of granisetron as opposed to palonosetron was more cost-effective in patients receiving a cisplatin-based HEC regimen (Shimizu et al., 2018). This analysis found no statistically significant difference in complete response rates between palonosetron and granisetron ($p=0.0539$), although palonosetron led to less frequent use of rescue medication, suggesting a potential clinical benefit (Shimizu et al., 2018). However, the higher cost of palonosetron did not result in a substantial improvement in overall patient outcomes, making granisetron the more cost-effective option (Shimizu et al., 2018). Similarly, Kashiwa and Matsushita (2019) reported that the cost of a triple antiemetic regimen with palonosetron amounted to 244.33 USD, compared to 122.20 USD with granisetron. While palonosetron was associated with improved efficacy in terms of reducing rescue medication, its higher cost nearly doubled the expense compared to granisetron (Kashiwa and Matsushita, 2019). Although the increased efficacy of palonosetron may justify its higher price in specific cases, the cost-effectiveness analysis indicates that granisetron offers a more viable option in settings where budget constraints are a priority.

Aprepitant is an NK-1 RA used in the treatment of CINV (Aapro, 2018). A randomised double-blind study evaluated the efficacy of aprepitant in patients with different tumour types receiving MEC (Rapoport et al., 2010). Among those receiving anthracycline-based chemotherapy, more patients in the aprepitant group reported no CINV compared to those in the control group across all phases: 68.3% vs. 52.9% in the overall phase, 86.9% vs. 76.0% in the acute phase, and 70.4% vs. 59.8% in the delayed phase (Rapoport et al., 2010). These findings were also consistent for patients receiving non-anthracycline chemotherapy (Rapoport et al., 2010). This study demonstrated that aprepitant was highly efficacious in combatting nausea and vomiting and that the addition of this agent to antiemetic regimens could prove valuable (Rapoport et al., 2010).

Similarly, Wang, DS et al. (2021) evaluated 243 women from four clinical centres in China and found significantly higher CR rates in the aprepitant group compared to the placebo group across all phases. Moreover, aprepitant maintained a comparable safety profile to the placebo, suggesting that incorporation of this antiemetic agent into treatment regimens could reduce the burden of CINV, without increasing the risk of severe adverse events (Wang et al., 2021). However, these studies do not address the broader issue of accessibility, as the high cost and limited availability of aprepitant in developing countries present significant challenges, often leading to the use of more affordable alternatives (Gyawali et al., 2016). Despite its demonstrated clinical efficacy, the widespread adoption of aprepitant is hindered by financial constraints, particularly in resource-limited settings (Gyawali et al., 2016). Qui et al. (2021) conducted a systematic review assessing the cost-effectiveness of aprepitant, finding it to be a cost-effective option for managing CINV. However, the generalisability of these findings is limited by variations in the economic models of the healthcare systems in the included studies, which complicates comparisons and prevents quantitative analysis (Qui et al., 2021).

Corticosteroids are also utilised as antiemetic agents most notably, dexamethasone (Rao and Faso, 2012). This agent can be used as monotherapy in patients receiving low emetogenic chemotherapy, however, dexamethasone is usually employed in combination regimens with a 5HT-3 RA and NK-1 RA (Barbour, 2012). Dexamethasone is recommended for use in acute and delayed CINV with proven efficacy (Aapro et al., 2010). According to international guidelines, it is recommended that a patient on HEC receiving a triple antiemetic regimen be administered with 12 mg of dexamethasone on the first day of chemotherapy and 8 mg on days 2-4 post-chemotherapy (Herrstedt et al., 2016; NCNN, 2019; Hesketh et al., 2020). This is to ensure that both acute and delayed phase CINV is effectively controlled (Herrstedt et al., 2016; NCNN, 2019; Hesketh et al., 2020). However, due to potential adverse effects, the benefits of dexamethasone treatment must be weighed against the potential risks (Aapro et al., 2010). Vardy et al. (2006) investigated the possible side effects of dexamethasone when used as an antiemetic agent. Patients reported suffering from various side effects ranging from moderate to severe intensity including insomnia, agitation, gastroesophageal reflux, and weight gain (Vardy et al., 2006). It was demonstrated that the use of dexamethasone could potentially negatively impact QoL due to the intensity of adverse effects associated with this medicine (Vardy et al., 2006). Despite evidence suggesting that dexamethasone use can negatively impact QoL due to its side effect profile, it remains a cornerstone of CINV prophylaxis in many treatment regimens (Vardy et al., 2006). However, the negative effect on QoL of this treatment

cannot be negated and underscores the necessity for exploring alternative therapeutic agents (Vardy et al., 2006).

Recent research has explored agents like aprepitant that may offer a more favourable efficacy and tolerability profile compared to dexamethasone to further optimise CINV management (Cheng et al., 2022). A single centre open label phase-III randomised trial, conducted in China with 320 colorectal cancer patients aimed to compare whether dexamethasone or aprepitant was more effective at treating CINV when combined with palonosetron (Cheng et al., 2022). This trial demonstrated that aprepitant was more effective than dexamethasone in preventing CINV during the overall and delayed phases (Cheng et al., 2022). In the overall phase, 88.8% of patients in the aprepitant group achieved complete response, compared to 74.2% in the dexamethasone group ($p<0.001$) (Cheng et al., 2022). Similarly, in the delayed phase, aprepitant outperformed dexamethasone with a 90.6% response rate versus 75.5% ($p < 0.0001$) (Cheng et al., 2022). Moreover, both drugs were equally effective in the acute phase, with no significant difference ($p = 0.94$) (Cheng et al., 2022). These results suggest aprepitant provides better long-term protection against CINV, particularly in the delayed phase. However, there was a greater incidence of adverse effects such as dyspepsia, insomnia, sweating, and flushing in the dexamethasone group, positioning aprepitant as the more suitable option (Cheng et al., 2022). A more recent study reported similar findings, demonstrating that an antiemetic regimen that combined fosaprepitant displayed better CR rates than a regimen containing dexamethasone in both the acute and delayed phase in patients receiving HEC (Radhakrishnan et al., 2024). As previously reiterated, despite the proven efficacy of NK-1 RAs, the high costs associated with this drug class remain a concern (Gyawali et al., 2016). A dexamethasone-sparing strategy could be implemented when NK1 RAs are combined with a 5 HT-3 RA (Aapro et al., 2010; Celio et al., 2013; Komatsu et al., 2015). This approach could help reduce the cost burden, maintain effective control of CINV, and minimise dexamethasone-related side effects by limiting its use (Gyawali et al., 2016).

In the ongoing search for effective treatments for CINV, the use of medications from various classes, including olanzapine, an atypical antipsychotic has been explored (Rao and Fasso, 2012). Olanzapine has displayed efficacy in the treatment of acute, delayed, and refractory CINV in patients receiving MEC and HEC (Rao and Fasso, 2012). Navari et al. (2007) conducted a study on 40 chemotherapy naïve patients receiving either HEC or MEC to measure the efficacy of olanzapine when combined with palonosetron and dexamethasone in inducing

CR. Complete response rates during the first chemotherapy cycle were reported to be 100% for acute-phase CINV and 75% for the delayed phase demonstrating the efficacy of this drug in alleviating acute and delayed CINV when combined with palonosetron and dexamethasone (Navari et al., 2007).

Abe et al. (2016) conducted a similar study to evaluate the efficacy of olanzapine in preventing CINV when combined with a triple antiemetic regimen. This study enrolled 40 patients with gynaecological cancers receiving HEC for the first time (Abe et al., 2016). Oral olanzapine was administered prophylactically in conjunction with a triple-antiemetic regimen and the primary endpoint of the study measured whether complete response was achieved (Abe et al.,2016). It was reported that CR was achieved in 92.5 % of patients, while 67.5% did not experience nausea indicating that the addition of this antipsychotic drug to an antiemetic regimen is efficacious in preventing CINV in patients receiving HEC (Abe et al.,2016). The use of this agent, however, remains limited due to overall safety concerns (Rao and Faso, 2012). Adverse effects include hyperglycaemia, hypotension and the potential to induce psychosis in elderly patients with dementia (Coles and Macfarlane, 2021). Despite these concerns, Wang et al. (2018) demonstrated that short-term administration (six days) of olanzapine, in combination with dexamethasone and a 5-HT3 receptor antagonist, was both safe and highly effective against CINV. In their study, which included patients up to 75 years of age, the most severe side effects reported were somnolence and constipation. Although one patient experienced postural hypertension and five had elevated glucose levels, none of these side effects led to the discontinuation of olanzapine (Wang et al., 2018). These findings suggest that, when used short-term, olanzapine remains a viable and effective option for preventing CINV, with manageable side effects.

2.7 Antiemetic Treatments in the South African Public Sector

In South Africa, access to healthcare is inequitable, with only 15% of the population being serviced by the private healthcare sector (Cancer Alliance, 2021). At large, the population mainly receives treatment at public healthcare facilities that display numerous shortcomings characterised by poor infrastructure, long wait times, and inadequate healthcare delivery (Maphumulo and Bhengu, 2019). In the public sector, chemotherapy is usually provided by oncology clinics located in academic hospitals (Cancer Alliance, 2021). The inclusion of specific medications in the EML is guided by clinical evidence of its efficacy and how cost-effective the treatment is compared to other options (NDoH, 2020). Following budget allocation

to individual treatment facilities, a Pharmaceutical and Therapeutics Committee (PTC) within each facility reviews and approves medications for use in cancer treatment, ensuring alignment with the EML (Cancer Alliance, 2021). Table 2.3 exemplifies antiemetic treatment protocols employed at a specific public healthcare facility for CINV management. However, it is crucial to acknowledge that these protocols may deviate from international guidelines due to budgetary constraints and potential limitations in the availability of certain antiemetic agents within the public sector.

Table 2.3: Antiemetic guidelines from an oncology treatment centre in a Johannesburg academic hospital.

Emetogenicity	Incidence	Chemotherapeutic agent	Antiemetic regimen
HEC	Very High (>90%) High (60 - 90%)	Cisplatin Dacarbazine (DTIC) Melphalan (High Dose) Actinomycin D Busulphan (High Dose) Carmustine (BCNU) Cyclophosphamide (High Dose) Doxorubicin + Cyclophosphamide Etoposide (High Dose)	*5HT-3 blocker (ondansetron) + *IV Corticosteroids (dexamethasone) + Oral Corticosteroids + Olanzapine (NK-1 inhibitors pending)

Emetogenicity	Incidence	Chemotherapeutic agent	Antiemetic regimen
MEC	Moderate (30 - 60%)	Doxorubicin Carboplatin Cyclophosphamide (standard dose) Cytarabine Daunorubicin Epirubicin Etoposide Idarubicin Ifosfamide Irinotecan Mitomycin C Mitoxantrone Oxaliplatin	*5HT-3 blocker (ondansetron) + *Corticosteroids (Dexamethasone) +/- Olanzapine (NK-1 inhibitors pending)
LEC	Low (10 - 30%)	Bleomycin Capecitabine 5-Fluorouracil Docetaxel Gemcitabine Melphalan po 6-Mercaptopurine Methotrexate Paclitaxel Chlorambucil	*Dopamine Antagonists (Metoclopramide) +/- *Corticosteroids (Dexamethasone)
MinEC	Minimal (<10%)	Fludarabine Hydroxyurea Vinblastine Vincristine Vinorelbine Rituximab Trastuzumab	No anti-emetics

* Medicines on the current WHO EML list (World Health Organization,2023).

2.8 CINV Management in Clinical Practice

Better treatment outcomes are achieved when antiemetic prescribing guidelines are adhered to (De Laurentiis et al., 2018; Aapro et al., 2022). Variable adherence to guideline-recommended prophylaxis and treatment results in poorly managed CINV (Roeland et al., 2020; Aapro et al., 2022). Aapro et al. (2022) assessed the impact of compliance with guideline-recommended treatment in 1089 patients. It was discovered that only 23% of patients receiving either HEC or MEC were prescribed antiemetics in accordance with a treatment guideline (Aapro et al., 2022). Patients who received guideline-compliant CINV prophylaxis experienced significantly better outcomes (Aapro et al., 2022).

Elhassan et al. (2017) investigated the adherence to ASCO guidelines pertaining to CINV prophylaxis. The findings of this study revealed that a significant portion of prescriptions (90%) did not adhere to established guidelines (Elhassan et al., 2017). Instead, it was reported that the CR rate (no emesis and no rescue medications) over five days was 36% and that excessive utilisation of ondansetron, insufficient use of dexamethasone, and duplicate corticosteroid therapy was observed (Elhassan et al., 2017). Overuse or underuse of medication due to poor adherence to guidelines could be a contributing factor to the prevalence of CINV (Elhassan et al., 2017). These findings highlight the critical role of optimising antiemetic prescribing practices based on established guidelines to improve patient outcomes and potentially reduce the burden of CINV.

Another reason for poor CINV management is that many physicians may potentially underestimate the emetic risk of a specific chemotherapy agent or regimen (Celio, 2022). Di Maio et al. (2015) conducted an analysis of three randomised trials to compare the reporting of six toxicities (nausea, vomiting, anorexia, hair loss, constipation, and diarrhoea) by patients and physicians. The aim was to assess potential discrepancies in the reporting of these toxicities between the two groups (Maio et al., 2015). Side effects reported by clinicians were much lower than those of patients, indicating that certain toxicities may be viewed as subjective and may be underestimated and therefore underreported by healthcare professionals (Di Maio et al., 2015). Furthermore, a quantitative study conducted in Europe with 300 oncologists determined that several reasons could be implicated in not achieving good therapeutic outcomes for CINV. These included physicians underestimating chemotherapy emetogenicity, not prescribing appropriate antiemetics to ensure that patients were effectively managed throughout the CINV risk period and patients not adhering to treatments by skipping doses (Aapro et al., 2018). More

effective CINV management could be achieved through better coordination between the multidisciplinary team and by providing patients with easier and more convenient antiemetic regimens (Aapro et al., 2018).

Selection and administration of antiemetic prophylaxis should be guided by two key factors: the inherent emetogenicity of the specific chemotherapy regimen and its potential to induce delayed CINV (Celio, 2022). Individualised tailoring of antiemetic regimens is crucial to optimise treatment outcomes. This patient-centred approach should incorporate a comprehensive evaluation of individual risk factors and ensure adequate antiemetic coverage throughout the entire emesis risk period (Celio, 2022).

2.9 Non-pharmacological Approach to CINV

In recent years, the adjunctive use of non-pharmacological measures has been highlighted in combatting CINV (Li et al., 2022). Patients perceive these interventions as safer, easier to use and more accessible (Li et al., 2022). These interventions include but are not limited to, acupuncture, aromatherapy, behavioural therapy, and the use of ginger (Li et al., 2022).

Acupuncture forms a part of the practice of traditional Chinese medicine and has been utilised for centuries in the treatment of various illnesses (Huang et al., 2022). Needles are inserted at specific points in the body, which may stimulate the release of certain neurotransmitters and alleviate CINV (Huang et al., 2022). Kong et al. (2022) observed the efficacy of acupuncture when combined with conventional antiemetics in 81 breast cancer patients. It was reported that in patients who were treated with both standard antiemetics and acupuncture, approximately 87.5% experienced no vomiting and 82.5% experienced no nausea (Kong et al., 2022). The inclusion of acupuncture as adjunctive therapy could be beneficial in reducing the incidence of CINV (Kong et al., 2022). Although these results suggest that acupuncture as an adjunctive therapy could help reduce the incidence of CINV, the small sample size limits the generalisability of the findings. Further research, including large-scale clinical trials, is needed to explore the mechanism of acupuncture in CINV and confirm its effectiveness (Huang et al., 2022; Kong et al., 2022).

Aromatherapy uses essential oils to treat many physical and psychological conditions (Brennan et al., 2022). This method has been used as supportive care in patients suffering from CINV (Toniolo et al., 2021). A randomised controlled study divided 60 patients into three treatment groups (Demont et al., 2023). The control group was given canola oil while the other two groups were given ginger essential oil and peppermint essential oil, respectively (Demont et al., 2023). Nausea was reported mostly by patients from the control group. A few cases of vomiting, however, were reported in all three groups (Demont et al., 2023). This suggests that there is some promising evidence that aromatherapy could be used as a form of supportive care for CINV (Demont et al., 2023). However, this study did not account for the varying emetogenicities of the chemotherapy regimens the patients were receiving, which could have influenced the outcomes (Demont et al., 2023). Additionally, the small sample size and lack of control for confounding factors further limit the validity of the findings (Demont et al., 2023). To confirm the potential benefits of aromatherapy for CINV, larger trials with better control of these variables are necessary (Demont et al., 2023).

Ginger is a spice that has been widely used for its affordable and effective antiemetic properties (Lete and Allué, 2016). Many bioactive compounds can be found in ginger that could target areas responsible for causing treatment-induced nausea and vomiting (Kim et al., 2022). Panahi et al. (2012) evaluated the antiemetic efficacy of ginger on acute and delayed CINV. Seventy-eight breast cancer patients were enrolled in this pilot, randomised, open-label clinical trial and allocated to either the control group or the ginger group (Panahi et al., 2012). The use of ginger together with standardised antiemetics proved beneficial in ameliorating nausea in the first six to twenty-four hours post-chemotherapy, however, there was no significant improvement in vomiting (Panahi et al., 2012). These results are consistent with a study conducted by Khadim et al. (2021) where it was demonstrated that ginger was not an effective adjunctive treatment in improving acute and delayed CINV but does retain some anti-nausea properties. While ginger shows potential in reducing nausea in the early post-chemotherapy period, its limited effect on vomiting and delayed CINV suggests that further investigation is needed. Future studies would be required to determine the optimal dosing of ginger and assess its efficacy in combination with other antiemetic regimens (Choi et al., 2022).

Behavioural therapy interventions such as hypnosis and visual imagery have been deemed efficacious strategies for CINV (Mustian et al., 2011). A quasi-experimental study conducted in Iran with 55 breast cancer patients reported a decrease in the incidence and severity of CINV

following a visual imagery intervention held before chemotherapy commencement (Hosseini et al., 2016). However, the quasi-experimental design of this study introduces limitations, particularly the lack of randomisation, which increases the risk of selection bias, making it difficult to determine whether the observed effects were due to the intervention or other factors (Hosseini et al., 2016). Additionally, the small sample size limits the generalisability of the findings (Hosseini et al., 2016). Future studies would benefit from a randomised controlled design with a larger sample size to better assess the efficacy of such interventions in managing CINV (Hosseini et al., 2016). Recent studies conducted on the potential effect of hypnosis on CINV are limited. In a study conducted by Marchioro et al. (2000) involving 16 patients, anticipatory nausea and vomiting completely disappeared in all subjects, and significant control of chemotherapy-induced vomiting was observed in nearly all patients. However, larger, more comprehensive trials are required to deem this intervention effective at alleviating CINV (Marchioro et al., 2000).

Music therapy can improve a patient's mood and method of coping with their feelings surrounding chemotherapy (Pozhan et al., 2023). A recent study conducted in Iran with 60 breast cancer patients explored the use of music therapy as a potential complementary treatment for CINV (Pozhan et al., 2023). Patients were provided with a library of 148 instrumental, relaxation, and religious songs and listened through headphones connected to an MP3 player. Trained nurses supervised five 25-minute sessions, allowing patients to personalise their experience by selecting their preferred music, volume, and timing. It was observed that CINV symptoms were significantly lower in the music therapy group compared to the control group ($p < 0.05$). While these findings suggest that music therapy may be a beneficial adjunct treatment for CINV, further research with larger sample sizes is needed to confirm its generalisability.

The aforementioned studies offer promising preliminary evidence for the use of alternative therapies in CINV management; however, additional large-scale studies are warranted to definitively assess the efficacy and optimal application of a more complementary approach in combatting CINV. Complementary and alternative therapies for CINV management hold the potential to pave the way for the development of synergistic treatment strategies (Li et al., 2022). Integrating effective non-pharmacological approaches with conventional CINV prophylaxis could potentially enhance patient outcomes and improve quality of life for those undergoing chemotherapy (Li et al., 2022).

2.10 Patient-Specific Risk Factors for CINV

Studies have demonstrated that patients may present with intrinsic risk factors that could contribute to the development of CINV regardless of the emetogenicity of a treatment regimen (Tamura et al., 2015; Dranitsaris et al., 2017; Mosa et al., 2020). Despite evidence suggesting that patient-related risk factors may exacerbate CINV incidence, assessment of these factors has not yet been universally incorporated into clinical guidelines. Notably, the NCCN guidelines recommend considering patient risk factors in conjunction with the emetogenicity of a chemotherapy regimen (NCCN, 2015).

Improving antiemetic prophylaxis for CINV management requires a comprehensive approach that considers not only the emetogenic potential of chemotherapy but also individual patient characteristics. Warr (2014) looked at potential prognostic factors that may affect CINV incidence. He theorised that evaluation of patient-specific risk factors could aid in the optimisation of emetic prophylactic regimens. Age, gender, and alcohol consumption were potential factors that contributed to emesis experienced with chemotherapy (Warr, 2014). Other risk factors include, race, smoking status, history of morning and/or motion sickness, type of cancer, cancer stage, cycle number, comorbidities, use of non-prescription medications, hours of sleep and a meal before chemotherapy (Mosa et al., 2020). To further explore the potential impact of these factors, Table 2.4 summarises previous studies that investigated the various risk factors and their potential association with CINV.

Table 2.4: Summary of studies that investigated CINV risk factors (Mosa et al., 2020).

Risk factor investigated	Number of studies investigating risk factor	Number of studies that identified an association
Age	44	27
Female sex	32	18
Race	5	2
Alcohol consumption	32	12
History of morning sickness	15	6
History of motion sickness	25	3
Cycle number	7	2
Comorbidities	7	2
Type of cancer	15	2

Risk factor investigated	Number of studies investigating risk factor	Number of studies that identified an association
Cancer stage	8	1
Use of non-prescription drugs	2	2
Hours of sleep	5	2
Meal before chemotherapy	4	1
Smoking history	4	1
Body mass index	5	1

Morrow (1992) investigated eight characteristics that could affect the development of anticipatory CINV. These characteristics included experiencing nausea and/or vomiting after completion of the first chemotherapy cycle, experiencing moderate, severe, or intolerable nausea after chemotherapy, experiencing moderate, severe or intolerable vomiting post-chemotherapy, being younger than 50 years old, having a history of motion sickness, experiencing an overall weakness after chemotherapy, sweating post chemotherapy and hot flashes after treatment (Morrow, 1992). Patients experiencing four or more of the aforementioned risk factors were more likely to develop anticipatory CINV in subsequent cycles (Morrow, 1992). There was no correlation between the risk factors and the type of cancer the patient was diagnosed with (Morrow, 1992).

Roscoe et al. (2004) summarised patient characteristics that potentially led to the development of nausea and vomiting post-treatment (Roscoe et al., 2004). In patients with cancer receiving the same chemotherapy and dosage, women were more likely than men to experience CINV (Roscoe et al., 2004). Age played a role in CINV development, with patients over 50 years old experiencing less nausea and emesis (Roscoe et al., 2004). Other determinants included increased alcohol intake, a history of motion sickness, and anticipation of developing CINV (Roscoe et al., 2004). A growing body of evidence suggests that various patient-specific factors can significantly influence the risk of developing CINV (Dranitsaris et al., 2017; Uchida et al., 2017; Mosa et al., 2020). By tailoring antiemetic regimens based on a comprehensive evaluation of these individual risk factors, clinicians have the potential to significantly reduce the incidence of CINV, especially in high-risk patients (Mosa et al.,2020).

2.11 Female Sex and CINV

The female sex has been posited as a major CINV risk factor, with women being more likely to develop this adverse effect and less likely to experience relief from antiemetic therapy (Hesketh et al., 2010). The precise mechanism of why being female may contribute to an increased incidence is not well understood. However, a study conducted with a paediatric oncology population found that post-pubertal females had an increased risk of delayed CINV, and postulated, using a female rat model, that systemic oestrogen levels may be the most likely aetiology (Zevy, 2017). Oestrogens play a role in stimulating the serotonergic system, which has been implicated in inducing nausea and vomiting (Zevy, 2017). It has been hypothesised that increasing levels of oestrogen may potentially contribute to the prevalence of CINV in the post-pubertal female oncology population (Zevy, 2017).

An observational study by Baba et al. (2017) investigated CINV in 192 oesophageal cancer patients over seven days. While good control of acute CINV was observed, delayed CINV remained a challenge. This study identified the female sex as a significant risk factor for delayed CINV, underscoring its potential role in guiding the development of individualised treatment regimens (Baba et al., 2017). Similarly, Fujii et al. (2017) corroborated this finding, highlighting female sex as a risk factor for CINV. Furthermore, findings from this study revealed that female patients receiving high-dose cisplatin (≥50 mg/m^2) were more susceptible to treatment-induced nausea compared to males (Fujii et al., 2017).

The female sex has been identified as a significant risk factor for the development of nausea in patients undergoing outpatient chemotherapy (Iihara et al., 2016). This association was demonstrated in a study involving 779 patients treated in an outpatient chemotherapy clinic, where 608 patients received their first chemotherapy cycle. Among them, 106 female patients experienced nausea compared to 52 male patients (Iihara et al., 2016). Multivariate linear regression analysis further confirmed that female patients were nearly twice as likely to develop nausea (OR=1.615, 95% CI: 1.022–2.552; p = 0.004) (Iihara et al., 2016).

Another study conducted on colorectal cancer patients receiving oxaliplatin-based chemotherapy postulated that the use of aprepitant and being female correlated with the incidence of vomiting experienced (Takemoto et al., 2017). This study further demonstrated that male patients achieved CR to antiemetic therapy, reporting no significant cases of nausea and vomiting (Takemoto et al., 2017). Interestingly, it was found that aprepitant use was more

effective in controlling vomiting in the female population (Takemoto et al., 2017). These findings highlight the importance of incorporating sex as a factor when developing personalised CINV management strategies to improve the treatment of this adverse effect.

2.12 Age as a Risk Factor

Several studies have explored the link between age and CINV risk. Younger patients (< 55 years old) appear to be more susceptible to nausea and vomiting during chemotherapy, potentially due to age-related changes in receptor sensitivity (Roscoe et al., 2004). However, the association between age and CINV is not completely clear. This inconsistency may be partly explained by variations in age ranges used across different studies (Sekine et al., 2013). For instance, one study found no significant correlation between age and CINV in a population aged 60-65 years, whereas another study on patients aged 50-55 years demonstrated a link between younger age (< 55) and increased CINV incidence (Italian Group for Antiemetic Research, 1995; Hesketh et al., 1996). Further supporting the potential role of age, a CINV predictive tool developed by Molassiotis et al. (2013) identified younger age as a factor associated with a higher risk of nausea and vomiting.

While younger patients are generally considered more susceptible to CINV a growing body of evidence suggests a more nuanced relationship between age and CINV risk. Kawazoe et al. (2018) highlighted that younger breast cancer patients (<55 years) may be at heightened risk for antiemetic treatment failure, potentially due to age-related physiological differences. However, this association is not always straightforward. Tsuji et al. (2019) also identified age as an independent risk factor, but findings by Hursti et al. (1996) introduce a complexity to the relationship between age and CINV risk. This study reported that while younger patients typically experience more CINV overall, older patients (≥55 years) with larger tumours exhibited a higher incidence of delayed emesis and even acute nausea (Hursti et al., 1996). These findings introduce more nuance and complexity to the simplistic view of age as a sole risk factor, highlighting the importance of investigating the interaction of other factors that may influence this variable.

2.13 Race

The association between race and CINV incidence has been established in only two studies (Hassan and Yusoff, 2010; Bordeanu et al., 2012). Investigation of this risk factor is imperative due to disparities in different racial demographics. Bordeanu et al. (2012) conducted a study on 358 breast cancer patients receiving anthracycline-based chemotherapy and found preliminary evidence that suggested that women of Asian descent experienced more severe CINV in comparison to individuals from other ethnicities or racial backgrounds. Hassan and Yusoff (2010) reported similar findings, stating that the severity of CINV could be influenced by the variation in genetic polymorphisms between different races and ethnicities. These findings, although preliminary, highlight the need for further research to explore the potential role of race as a risk factor for CINV. Understanding these potential racial disparities is crucial for developing equitable antiemetic treatment strategies.

Further complicating CINV management, is the variation of medicine use and access between different racial backgrounds. Check et al. (2016) examined the use of antiemetics post-chemotherapy across different races. This study included 1130 women with breast cancer of which, 1015 patients were white (90%) and 115 (10%) were of African descent. It was reported that black females were 13% less likely to utilise an NK1-RA and receive additional treatment for CINV post-chemotherapy than their white counterparts (Check et al., 2016). Several reasons could elucidate the reasoning behind this discrepancy such as inadequate access to care, underreporting of CINV by black females, or non-investigated factors such as BMI and obesity which could lead to underdosing of chemotherapy and consequentially a smaller chance of experiencing CINV (Griggs et al., 2005). However, given the disproportionately smaller number of black participants, this difference should be interpreted with caution, as the sample size may not provide sufficient statistical power to make definitive comparisons between racial groups.

It is therefore crucial to further explore the relationship between race and CINV to promote the development of well-informed and equitable strategies to alleviate its effects on cancer patients (Hassan and Yusoff, 2010). Remaining informed of the developing patterns and interplay between genetic variations across different races, socioeconomic and socio-cultural factors, and access to healthcare services, clinicians can aim to personalise care to meet the needs of patients from different racial backgrounds (Check et al., 2016).

2.14 The Effect of Alcohol Consumption on CINV

The relationship between alcohol consumption and CINV prevalence is complex. In the presence of suitable antiemetic agents, patients who habitually consume alcohol demonstrated better CINV control (Yap et al., 2012). This inverse correlation may be attributed to the desensitisation of the chemoreceptor trigger zone (Adel, 2017). In contrast, patients who consumed less alcohol were more likely to develop nausea and vomiting (Yap et al., 2012). Hilarius et al. (2012) observed that the relationship between alcohol consumption and CINV demonstrated inconsistency across treatment cycles. During the first treatment cycle, patients with higher weekly alcohol intake experienced significantly lower incidences of acute vomiting compared to those with lower consumption ($p = 0.03$). Similarly, a significant reduction in acute nausea was observed in patients who habitually consumed alcohol by the third treatment cycle ($p = 0.02$). However, beyond these specific instances, no other significant associations between alcohol consumption and CINV were identified, suggesting that the protective effect of alcohol on CINV may not be consistently maintained across different phases of CINV and treatment cycles.

Further evaluation of CINV risk factors by Sekine et al. (2013) in 1549 chemotherapy-naïve patients reinforced the significance of alcohol consumption and its impact on CINV. This study found a significant association between low alcohol intake and CINV treatment failure during the acute phase ($p<0.001$). Additionally, delayed nausea was more frequently observed in patients who did not habitually consume alcohol. This risk factor was particularly notable, as it contributed to failure in achieving complete response to emesis prophylaxis and was linked to a higher incidence of acute nausea (Sekine et al., 2013).

Uchida et al. (2017) reported that lower alcohol intake might be associated with a less effective response to antiemetics such as metoclopramide. This aligns with the findings of a retrospective study that reported that habitual alcohol drinkers were more likely to achieve CR to antiemetic treatment, experiencing no vomiting and requiring no additional medications (Kawazoe et al.,2018). Kawazoe et al. (2018) classified patients with a history of habitual alcohol consumption as low risk for CINV development.

It is worth noting that the lack of a standardised definition for what constitutes 'high' alcohol intake may impact the comparability of results across studies, despite most showing an inverse correlation between alcohol consumption and CINV (Mosa et al., 2020). Nevertheless, several

studies consistently suggest that habitual alcohol use may play a role in reducing CINV risk (Kawazoe et al., 2018; Uchida et al., 2017; Di Mattei et al., 2016; Rha et al., 2016). While there appears to be a potential association between higher alcohol intake and reduced CINV risk, recommending increased alcohol consumption is not a viable option due to its well-documented health risks (Rehm, 2011). Instead, incorporating information on a patient's alcohol habits into their CINV risk assessment could serve as a valuable tool for identifying lower-risk patients and tailoring antiemetic regimens, ultimately enhancing patient comfort and well-being during chemotherapy.

2.15 Previous History of Nausea and Vomiting

It has been reported that patients who are predisposed to experiencing motion and/or morning sickness are more susceptible to CINV (Puri et al., 2018). Motion sickness is caused by an inconsistency between the actual stimuli and the perceived sensory input (Takov and Tadi, 2022). This disturbance leads to the development of nausea and vomiting (Takov and Tadi, 2022). Pregnancy-induced nausea and vomiting, more commonly known as morning sickness, is thought to be caused by fluctuations in hormones, particularly human chorionic gonadotropin (hCG) and oestrogen, which rise significantly during the first trimester (Lee and Saha, 2011).

Molassiotis et al. (2002) evaluated various prognostic factors for post-chemotherapy nausea and vomiting in breast cancer patients, including a history of morning sickness. This study, however, did not establish a significant correlation between this risk factor and the development of CINV (Molassiotis et al., 2002). It is important to note that the study had a small sample size of 71 patients, which may have limited its statistical power to detect such an association, thereby affecting the generalisability of the findings. In contrast, a larger study by Warr et al. (2011) involving 866 patients found that those without a history of morning sickness were less susceptible to experiencing CINV ($p = 0.007$), suggesting that this factor may indeed play a significant role in CINV risk.

The development of risk prediction models may facilitate the assessment and prediction of both acute and delayed CINV (Clemons et al., 2016). Motion sickness and/or morning sickness are included as prognostic factors in these models due to their established association with CINV treatment failure, as demonstrated across various studies (Dranitsaris et al., 2017; Hayashi et al., 2017; Tsuji et al., 2017; Clemons et al., 2016). The predictive accuracy of these models can help identify high-risk patients more likely to experience CINV across both phases (Bougamin

et al., 2012). However, small sample sizes and variations in geographical locations may limit their effectiveness. To address these challenges, Dranitsaris et al. (2017) developed an improved risk prediction model, incorporating a history of morning sickness as one of eight key risk factors strongly associated with CINV. Interestingly, a history of motion sickness was not included in this model.

However, several studies have explored the potential link between a motion sickness history and CINV development. Shih et al. (2009) found that patients with a history of motion sickness had a higher risk of experiencing delayed vomiting. Tsuji et al. (2017) also observed this association, demonstrating that patients with a history of motion sickness were almost four times more likely to experience delayed CINV (OR = 3.89, 95% CI: 1.49–10.19). With regards to the development of acute CINV, Tamura et al. (2015) reported that patients with a history of motion sickness were 2.79 times more likely to develop acute nausea and 2.18 times more likely to develop acute vomiting ($p<0.05$).

Risk prediction models for CINV aim to identify patients at higher risk for developing this unpleasant side effect (Dranitsaris et al., 2017). The inclusion of a history of motion/morning sickness in these risk prediction models indicates that these factors have the propensity to negatively affect CINV outcomes. Moreover, evidence from the existing literature suggests a potential link between these experiences and CINV development, once again highlighting the importance of risk factor assessment for better patient outcomes (Dranitsaris et al., 2017).

2.16 Anticipatory Nausea and Vomiting

Anticipatory nausea and vomiting (ANV) is described as a variant of CINV and is triggered by psychological factors in patients who have previously received chemotherapy (Roscoe et al., 2011; Kamen et al., 2014; Molassiotis et al., 2016). In patients experiencing ANV, nausea and vomiting are elicited by specific sensory stimuli associated with the treatment room where chemotherapy is administered (Rodriguez, 2013). ANV is unique in the sense that it is not induced by the administration of cytotoxic chemotherapy, but rather by psychological processes (Rodriguez, 2013). This subset of CINV is distressing and can lead to treatment abscondment (Rodriguez, 2013).

Due to the psychological nature of ANV, the employment of behavioural interventions remains a first-line treatment option (Kamen et al., 2014). The use of psychotropic drugs such as short-acting benzodiazepines like lorazepam may also prove beneficial, however, behavioural treatments have been deemed more effective (Kamen et al., 2014). Systematic desensitisation is an evidence-based approach utilised in ANV patients to break the association between the conditioned response (i.e., developing nausea and vomiting) and a specific stimulus, such as the sight or smell of the treatment room (Dubord 2011; Kamen et al., 2014). Other non-pharmacological therapies such as hypnosis, acupuncture and exercise have also been used in the treatment of ANV (Mustian et al., 2011).

ANV and its effect on CINV are well documented in the literature. Roscoe et al. (2004) investigated whether patient expectations of nausea and vomiting prior to chemotherapy contributed to the development of CINV in 194 breast cancer patients receiving HEC. The findings of this study indicated that patients who anticipated nausea and vomiting were five times more likely to experience CINV (Roscoe et al., 2004). A prospective cohort study involving 121 female patients further supported these findings, demonstrating that those who anticipated nausea experienced it more severely than those who did not (Meissner et al., 2019). These results suggest that ANV is triggered not only by specific stimuli related to the treatment environment but also by the anxiety surrounding the expectation of CINV (Meissner et al., 2019). Moreover, a meta-analysis by Colagiuri and Zachariae (2008) found a positive correlation between patients who strongly anticipated nausea and the frequency of experiencing this side effect. Notably, the association between nausea expectation was more significant in patients who had undergone multiple chemotherapy cycles compared to those receiving their first infusion. This observation can be explained by the fact that patients with prior chemotherapy experience are more conditioned to expect post-chemotherapy nausea, having already developed an awareness of the side effect (Colagiuri and Zachariae, 2008).

ANV can significantly impact a patient's well-being (Rodriguez, 2013). Current antiemetic medications are primarily designed to target the physical mechanisms of nausea and vomiting and may not effectively address ANV due to its psychological nature (Kamen et al., 2014). Addressing the psychological factors that cause ANV as well as implementing effective strategies to manage this distressing symptom could lead to a more positive treatment experience (Kamen et al., 2014).

2.17 Type of Cancer

The prevalence of CINV may be greater in patients who are diagnosed with certain cancers. For example, patients diagnosed with colon cancer, certain lymphomas or testicular cancer may be more susceptible to developing treatment-induced nausea and vomiting (Hesketh et al., 2017). However, this may be due to the aggressive and often highly emetogenic regimens used to treat these cancers and does not demonstrate a direct correlation between cancer type and experiencing CINV (Hesketh et al., 2017).

Roscoe et al. (2010) found that patients with breast cancer had an elevated risk of developing nausea and vomiting. The study examined various risk factors that exacerbated CINV and found that breast cancer patients receiving doxorubicin were more likely to experience the side effect in comparison to patients with other cancers receiving the same treatment (Roscoe et al., 2010). It is worth noting that patients diagnosed with breast cancer are mostly female, with female sex being a major CINV risk factor (Mosa et al., 2020). Therefore, it cannot be definitively concluded that breast cancer would elevate the risk of CINV. Given the limited research on the effect that cancer type has on CINV, it is evident that more comprehensive studies are needed. Future research should focus on large-scale, multicentre trials that include diverse cancer types to delineate specific patterns and susceptibilities.

2.18 Cancer Stage

Cancer staging is the process of describing the size of a primary tumour and the degree of metastases in the body to determine patient prognosis and selection of the most appropriate treatment (Patel and West, 2020). Cancer stage is denoted in numerals and ranges from 0, I, II, III and IV (Mosa et al., 2020). Stage 0 is indicative of a cancer that is localised and has not invaded surrounding tissue, while a higher cancer stage denotes a tumour that has metastasised (Rosen and Sapra, 2023). A single study found that patients diagnosed with either stage I or stage II cancer were more likely to develop acute CINV, however, the rationale for this collinearity was not described in the study (Dranitsaris et al., 2009). Utilising the same data set, Petrella et al. (2009) found that cancer stage was an insignificant variable in predicting the occurrence of delayed CINV.

2.19 Chemotherapy Cycle Number

Experiencing CINV in previous cycles is an established risk factor for experiencing this side effect in future cycles (Molasiotis et al., 2014). A prospective cohort study conducted by Petrella et al. (2009) established that the cycle number had a potential effect on the likelihood of developing CINV. This risk factor was included in the development of a CINV predictive tool to aid in identifying patients who are at high risk, allowing greater optimisation of antiemetic prophylaxis regimens and improved therapeutic outcomes (Petrella et al., 2009). Moreover, patients in earlier chemotherapy cycles (< 3) are at greater risk of developing CINV (Petrella et al., 2009). Similarly, Molassiotis et al. (2013) found that patients were at the highest risk of developing treatment-induced nausea and vomiting during their first chemotherapy cycle. This variable was also investigated by Dranitsaris et al. (2017) who found that experiencing CINV in the first two chemotherapy cycles was a risk factor that led to the development of nausea and vomiting in later cycles. However, studies conducted by Hayashi et al. (2017) and Di Mattei (2016) failed to establish a correlation between cycle number and CINV, only noting that a history of CINV in previous treatments could elevate the risk of developing this side effect.

Recent evidence has shown that the duration of CINV during the first chemotherapy cycle may predict its recurrence in subsequent cycles (Navari et al., 2023). Patients who experienced nausea and vomiting for more than two days after their first chemotherapy infusion were more likely to develop CINV in future cycles (Navari et al., 2023). This secondary analysis included 402 breast cancer patients receiving anthracycline-cyclophosphamide-based chemotherapy. During the first chemotherapy cycle, 24.6% of patients experienced CINV prophylaxis failure (Navari et al., 2023), and approximately 49.8% of these patients went on to experience CINV in cycles 2–4 (Navari et al., 2023). Furthermore, patients who experienced nausea and vomiting for more than three days were even more likely to develop CINV in subsequent cycles (Navari et al., 2023). It was concluded that patients experiencing prolonged CINV during the first cycle should be closely monitored to prevent this side effect in later infusions (Navari et al., 2023).

2.20 Body-mass Index (BMI)

There is conflicting evidence in the literature regarding the role that BMI plays in the development of CINV (Gilmore et al., 2014; Binder and Saunders, 2018; Kawazoe et al., 2018; Hayashi et al., 2019; Yeo et al., 2022). A retrospective observational study conducted in 103 breast cancer patients receiving anthracycline-based chemotherapy together with a triple antiemetic regimen comprising aprepitant, palonosetron and dexamethasone sought to identify

a high-risk CINV population (Kawazoe et al., 2018). The findings of this study revealed that patients with a BMI greater than 27.5 kg/m² were more likely to experience antiemetic treatment failure overall and during the acute phase, signifying that this population is at a higher risk of developing nausea and vomiting related to their chemotherapy (Kawazoe et al., 2018). Hayashi et al. (2019) performed a CINV risk analysis in patients receiving a combination of 5-fluorouracil, epirubicin and cyclophosphamide and also concluded that BMI was a significant contributing factor to CINV (Hayashi et al., 2019).

On the contrary, a prospective observational study conducted on 1295 patients receiving HEC or MEC found that patients that were either overweight or obese had a 21% and 23% less chance of developing treatment-related nausea and vomiting respectively (Gilmore et al., 2014). However, an association between BMI and CINV was not definitively established in a study conducted in 5570 female patients (Binder and Saunders, 2018). A recent study by Yeo et al. (2022) found that there was some evidence to suggest that obesity may be a protective factor against the development of nausea, however, additional investigation would be required to definitively confirm this.

2.21 Comorbidities

Comorbidity in patients with cancer is described as the presence of another medical condition in conjunction with cancer (Ofori-Asenso et al., 2019). It has been estimated that two out of every three adults aged 65 years and older present with at least one comorbidity (Herrstedt et al., 2022). The most common additional medical conditions in patients with cancer include cardiovascular disease, hypertension, pulmonary disease, diabetes mellitus and musculoskeletal disease (Koo et al., 2020). Additionally, anticancer agents and supportive care therapy may render negative effects on other medical conditions, potentially exacerbating these conditions or interfering with their management (Herrstedt et al., 2022).

A study conducted by Booth et al. (2007) showed that patients with existing medical conditions such as cardiovascular disease, gastrointestinal disease, thyroid disease and diabetes had a decreased risk of experiencing CINV. Dranitsaris et al. (2009) reported similar results. Another study conducted in Asian women with breast cancer found that gastroesophageal reflux disease (GERD) is a clinically important predictor of CINV and may exacerbate it (Bordeanu et al., 2012). Assessment of comorbid conditions in patients with cancer is imperative as these

conditions could potentially influence both the likelihood of CINV occurrence and the effectiveness of supportive care therapy (Herrstedt et al., 2022).

2.22 Smoking History

Esra et al. (2011) hypothesised that patients with a history of smoking experienced a lower incidence of CINV, suggesting that smoking might function as a behavioural therapy by providing distraction, thereby reducing nausea and vomiting. This study, which included 121 patients receiving a cisplatin-containing regimen, found that the incidence of nausea and vomiting was significantly higher in non-smokers compared to smokers ($p < 0.001$). However, smoking cannot be recommended as a non-pharmacological intervention against CINV due to the substantial health risks associated with it (Varghese and Muntode Gharde, 2023). Nevertheless, these findings suggest that distraction and stress relief mechanisms may play a role in mitigating the incidence of CINV (Esra et al., 2011).

Sekine et al. (2013) also explored smoking as a CINV risk factor and found that non-smokers experienced a higher incidence of CINV treatment failure during the acute phase. Similarly, a Brazilian study involving 152 patients receiving either HEC or MEC evaluated risk factors associated with antineoplastic CINV during the first chemotherapy cycle (Simino et al., 2020). This prospective cohort study identified an inverse relationship between former smoking status and achieving a complete response during delayed-phase CINV, indicating that being a former smoker may be a risk factor for CINV (Simino et al., 2020).

Cannabis displays excellent antiemetic properties, making it a suitable alternative treatment for CINV (Wilkie et al., 2016). The effects of the synthetic derivative of cannabis, nabilone and dronabinol have been well-researched and are regarded as efficacious antiemetic agents (Wilkie et al., 2016). There is, however, limited data on the antiemetic efficacy of smoked cannabis or its derivatives in comparison to other first-line antiemetic treatments. For this reason, the use of marijuana has not been recommended by any CINV guidelines (Todaro, 2012). Smoking has been implicated in aggravating the symptoms of cancer treatment, leading to a decrease in quality of life in comparison to non-smokers and for this reason, smoking cessation should be emphasised in patients with cancer (Peppone et al., 2011).

2.23 Diet and CINV

Non-pharmacological interventions such as the implementation of dietary modifications are not considered a first-line alternative in the management of CINV, however, clinical guidelines such as the NCCN suggest that a change in diet during chemotherapy may prove beneficial in the prevention of treatment-induced nausea and emesis (Lyman et al., 2018; NCCN 2018). Several eating habit strategies have been suggested to alleviate potential gastrointestinal symptoms associated with CINV such as eating small, frequent meals, consuming food in a cool environment, avoiding foods with unpleasant odours and eating dry and bland foods such as crackers, toast and oats (Lima et al., 2012). A prospective observational study also demonstrated that not eating before receiving chemotherapy may elevate a patient's risk of experiencing CINV (Booth et al., 2007). This study proposed that it was imperative to educate patients on the importance of eating a small meal prior to receiving treatment (Booth et al., 2007).

Mardas et al. (2017) aimed to establish whether diet influenced the gastrointestinal side effects of chemotherapy. This study enrolled 56 patients undergoing chemotherapy, of which 44 completed all questionnaires (Mardas et al., 2017). Overall, 80% of patients experienced nausea showing that there was a significant association between gastrointestinal side effects and dietary intake (Mardas et al., 2017). Patients reported that consumption of oily foods led to the development of severe nausea and vomiting and foods such as eggs, candies and dairy products caused moderate nausea (Mardas et al., 2017). Limiting the intake of specific foods whilst undergoing chemotherapy should be considered in clinical practice to reduce the incidence of CINV (Mardas et al., 2017).

Triple-regimen antiemetics may be ineffective against CINV in patients receiving cisplatin-based chemotherapy (Hori et al., 2018). As a result, patients with cancer reported consuming less food in the days following their chemotherapy treatments (Hori et al., 2018). Implementing nutritional counselling to ameliorate CINV may be beneficial in patients with cancer to better their nutritional status (Hori et al., 2018). Gala et al. (2022) also acknowledged the importance of CINV nutritional education in patients with cancer. The Mediterranean diet, which includes eating fruits, vegetables, and whole grains, may be beneficial in managing this side effect (Gala et al., 2022). Healthcare professionals should emphasise that patients follow diets ensuring adequate energy and protein intake to improve CINV control (Gala et al., 2022). By focusing on such balanced diets, patients may better manage their symptoms and enhance their overall well-being.

2.24 Sleep Quality

Poor sleep quality can lead to gastrointestinal diseases such as inflammatory bowel disease (IBD), irritable bowel syndrome (IBS), peptic ulcer disease (PUD) and GERD (Khanijow et al., 2015). A link between sleep disturbances and gastrointestinal symptoms has been established, however, the effect that poor sleep quality has on CINV is largely unresearched (Jung et al., 2016). A prospective observational study conducted in Ulsan, South Korea aimed to investigate the effects of poor sleep quality on CINV (Jung et al., 2016). One hundred and ninety-eight early-stage breast cancer patients were recruited to participate in this study (Jung et al., 2016). The Pittsburgh Sleep Quality Index, the Insomnia Severity Index, the Epworth Sleepiness Scale, and the Hospital Anxiety and Depression Scale were utilised to assess patient characteristics and sleep quality prior to enrolment into this study (Jung et al., 2016). Nausea was reported to occur in approximately 35.4% of patients, while vomiting occurred in more than a quarter of the study population (Jung et al., 2016). It was concluded that an association between poor sleep quality and CINV existed and that issues regarding sleep should be considered in CINV management in the future (Jung et al., 2016).

Petrella et al. (2009) reported that patients who received less sleep prior to receiving chemotherapy had a higher likelihood of experiencing delayed CINV. Similarly, Dranitsaris et al. (2017) illustrated that less than seven hours of sleep prior to treatment could act as a predictive factor for CINV, especially during the delayed phase. Interestingly, there was no association found between acute CINV and sleep quality (Dranitsaris et al., 2013). Individuals presenting with a late chronotype, a sleep-wake schedule characterised by staying up late and being most alert during the evening, have an elevated risk of experiencing CINV (Lee et al., 2017). This risk factor may also need to be taken into consideration by clinicians to effectively manage CINV (Lee et al., 2017). More research is needed to comprehensively understand the effect of sleep on CINV. Preliminary studies suggest that poor sleep quality may exacerbate CINV, but comprehensive data is lacking. Future studies should aim to explore the mechanisms behind this interaction and develop interventions that address both sleep quality and CINV simultaneously in patients with cancer.

2.25 Rationale for Investigating CINV Risk Factors

The literature has demonstrated that several risk factors could significantly contribute to the frequency and severity of CINV experienced by a patient. Unmanaged CINV could lead to other physiological complications such as malnutrition, dehydration and electrolyte imbalances

(Soefje, 2018). Moreover, patients who experience uncontrolled CINV may develop negative associations to chemotherapy (Krikorian, 2018). This could have adverse implications for treatment compliance as a patient may delay their chemotherapy or discontinue it completely if side effects become too debilitating (Krikorian, 2018). Additionally, adherence to treatments for comorbid conditions may also be compromised, as the burden of managing severe side effects can affect a patient's ability to follow through with their overall treatment plan (Drzayich et al., 2018). Understanding patient-specific risk factors that exacerbate the incidence of CINV is crucial in developing efficacious strategies to mitigate this adverse effect (Navari et al., 2013). Notable progress has been achieved in controlling CINV, with various pharmacological and non-pharmacological strategies employed to ameliorate this side effect (Moradian and Howell, 2015). Nevertheless, CINV still afflicts a significant portion of patients (40%) receiving chemotherapy, emphasising the necessity for additional research to understand the complex interactions and mechanisms in which patient-related risk factors affect CINV to develop tailored antiemetic regimens that meet individual patient's needs (Gupta et al.,2021; Dranitsaris et al., 2017).

This study seeks to address the clinical and therapeutic challenges posed by CINV, a side effect with significant implications for patient compliance and overall treatment outcomes. By investigating the emetogenic potential of prescribed chemotherapy regimens, adherence to antiemetic guidelines, and the prevalence and risk factors associated with CINV, this research aims to develop insights that can inform tailored interventions to ameliorate CINV, thereby optimising patient care and enhancing treatment efficacy in a tertiary public sector facility in Johannesburg, South Africa.

CHAPTER 3

3. METHODOLOGY

3.1 Introduction

A descriptive cross-sectional quantitative study was conducted, incorporating patient record reviews and a researcher-administered survey. This approach aimed to investigate the extent of CINV and the risk factors contributing to it in patients with cancer. Patient interviews were utilised to gather comprehensive data on patient experiences, adherence to antiemetic regimens, and associated outcomes, complementing the information obtained from patient records regarding chemotherapy and CINV regimens. This chapter outlines the methodology of this study.

3.2 Study Site

The study was conducted at an oncology outpatient clinic at a tertiary academic hospital located in Johannesburg, South Africa, which operates in the public health sector.

3.3 Study Period

The clinic operates from Monday to Friday, and data collection was conducted over a 16-week period between November 2023 and February 2024. The researcher visited the clinic two to three times per week during this period to collect data.

3.4 Study Population and Sample Size

3.4.1 Inclusion criteria

- English-speaking patients with cancer. The study was conducted without the availability of translation services, necessitating the inclusion of only English-speaking participants. This criterion ensured clear communication between patients and the researcher, allowing for accurate data collection and the consistent administration of questionnaires and interviews.
- Patients over the age of 18 years.
- Patients receiving chemotherapy at Charlotte Maxeke Johannesburg Academic Hospital (CMJAH). This criterion ensured a standardised treatment setting, as all patients received care at the same hospital. This consistency helped control variations in treatment protocols, care quality, and support services that could influence the study outcome.
- Patients with solid tumours. The study aimed to investigate CINV in a specific subgroup of cancer patients. Patients with solid tumours may have different chemotherapy regimens and responses compared to those with haematological malignancies, which could impact the

incidence and severity of CINV. This focus allowed for more targeted data collection and analysis

- Patients on routine intravenous chemotherapy as CINV is more common in patients on intravenous chemotherapy.

3.4.2 Exclusion criteria

- Pregnant women. Pregnancy itself can be associated with nausea and vomiting. This could confound the study results, making it difficult to distinguish between nausea and vomiting caused by pregnancy and that caused by chemotherapy
- Patients receiving radiotherapy/surgery within two weeks of treatment. Patients who have undergone radiation or surgery within the last two weeks were excluded due to the possibility of these patients' experiencing nausea and vomiting related to their surgery or radiation.

3.4.3 Sample size

The oncology outpatient clinic receives 2000 patients a month. Using the Stata 18 software, a sample size was determined from this population. To ensure a conservative sample size, it was essential to identify the proportion of patients not experiencing CINV. According to the literature, 70–80% of chemotherapy patients are likely to experience nausea and vomiting (Wang, W et al., 2021). Therefore, an estimate of 20–25% was selected to represent patients without CINV. Based on a 20% estimate for patients not experiencing CINV, with an 8% margin of error and a 95% confidence interval (CI), the resulting sample size was 222 patients. Fig 3.1 depicts the imputed sample size model.

```
Estimated sample size for a one-sample proportion test
Score z test
H0: p = p0  versus  Ha: p != p0

Study parameters:

        alpha =    0.0500
        power =    0.8000
        delta =    0.0780
           p0 =    0.2000
           pa =    0.2780
         diff =    0.0780

Estimated sample size:

            N =       222
```

Figure 3.1: Stata input for generating the sample size

3.5 Ethical Considerations

To conduct this study, approval was obtained from the Wits Human Ethics Research Committee (Medical) (Appendix A). No identifiable information was captured during the study or survey, and patient confidentiality was strictly maintained throughout the research. Each potential participant received a participant information sheet detailing relevant information about the study, including its purpose, procedures, risks, and benefits. This information was presented in layman's terms to ensure comprehension, and the researcher/data collectors were available to answer any questions. A distress protocol was set in place should any patients experience any discomfort during the interview process (Appendix B). Written consent was obtained from each participant prior to the commencement of the study, emphasising the right to withdraw at any time without any negative consequences. Permission to conduct the study was granted by the head of the oncology department (Appendix C) and the CEO of Charlotte Maxeke Johannesburg Academic Hospital (Appendix D). The University of the Witwatersrand Protocol Assessment Committee approved the protocol to conduct the study (Appendix E).

3.6 Data Collection

3.6.1 Development of the survey instrument

The researcher-administered survey used in this study was developed based on established tools, including the MASCC Antiemesis Tool (MAT), the Helsinn online CINV risk assessment tool, and the Morrow Assessment of Nausea and Emesis (MANE) tool (Morrow et al., 1998; Borjeson et al., 2021; Helsinn, 2023). These frameworks ensured comprehensive coverage of relevant data on CINV and associated risk factors. The survey underwent face validation by supervisors and interns to refine its content, address omissions, and ensure its relevance. This process ensured the tool’s accuracy before data collection began.

The electronic survey captured using REDCap© comprised 43 questions and was divided into four sections. REDCap© is a secure, web-based platform designed to facilitate data collection and management for research studies. Section A focused on demographic data, such as age, sex, and race. Section B concentrated on prescription reviews, where information regarding chemotherapy regimens, antiemetic prophylaxis, and protocol adherence was extracted directly from patient prescriptions. Sections C and D formed the patient interview component. Section C investigated the occurrence and severity of CINV, while Section D explored potential risk factors for CINV, such as sleep patterns, history of motion sickness, alcohol consumption, and use of complementary therapies.

Of the 43 questions, 28 were close ended, predominantly in multiple-choice or yes/no formats, while 8 were open-ended to allow for more detailed responses. The remaining questions in Section B were derived directly from patient prescriptions. Open-ended responses were recorded verbatim by the researcher or data collectors, ensuring the integrity of qualitative data.

3.6.2 Process of Data Collection

Patients awaiting consultation were provided with an overview of the study. Participant information sheets (Appendix F) were distributed to those interested, and informed consent was obtained using a standardised form (Appendix G). Administration of the survey occurred concurrently with chemotherapy administration to align with workflow logistics. Since prescriptions were issued only during oncologist consultations, this process ensured that both patient input and prescription details were accessible simultaneously.

Surveys were conducted by the researcher and trained data collectors, all of whom held a Bachelor of Pharmacy degree. Training sessions ensured a standardised approach to administering the survey and managing informed consent. Each interview took 10–15 minutes, and patient confidentiality was maintained by excluding identifiable information. Patient files were marked with coloured stickers to prevent duplication and were removed once the study concluded.

A moderate number of patients were proficient in English, which ensured that the language barrier did not significantly impact the data collection process. For patients who experienced discomfort during chemotherapy, the interview was paused and resumed later if the patient felt more comfortable. However, if the patient was unable to continue the interview, the incomplete survey responses were excluded from the study to maintain the integrity and reliability of the dataset. This approach was in line with the distress protocol warranted by ethical research and minimised the risk of data inconsistencies while prioritising patient well-being.

3.7 Reliability and Validity

To ensure validity, the survey was developed using established, validated tools to ensure it comprehensively addressed CINV and its associated risk factors. The face validation process involved feedback from ten volunteers, including supervisors and interns, who assessed the content for relevance and completeness. Their feedback was used to refine the survey and

address omissions. Additionally, REDCap© was utilised to minimise data entry errors, as its secure web-based design includes built-in error-checking mechanisms to improve data integrity.

Reliability was ensured through several measures. A standardised survey was used to maintain consistency in data collection across all participants. Data collectors received comprehensive training on administering the survey, obtaining informed consent, and recording responses. The pilot testing of the survey ensured consistent interpretation of questions. Furthermore, open-ended responses were documented verbatim to maintain the richness of qualitative data. The use of coloured stickers on patient files prevented duplicate data collection, further enhancing reliability.

3.8 Data Management

No identifiable information was collected from this study. Patient confidentiality was strictly maintained. All data obtained from the study was securely stored in a digital format, protected by password encryption. The data will be retained for a period of six years with access to the data strictly limited to authorised personnel, including the researcher and supervisors, to maintain confidentiality.

3.9 Data Sorting

The data collected from the survey on REDCAP© was exported into Microsoft Excel® and analysed using the Stata 18 software. Responses to open-ended questions, such as those concerning concurrent comorbidities, prescription and non-prescription medications, and complementary or alternative therapies, were organised into broader, contextually relevant categories. This categorisation allowed for a clearer understanding and analysis of the data.

3.10 Statistical Analysis

The data analysis process involved several steps to ensure thorough and accurate results. All variables in this study were categorical. Descriptive statistics and frequency distributions were generated to summarise the fundamental characteristics of the dataset. This analysis included the use of graphs and tables to visually present the data. These descriptive statistics provided an initial overview of the data distribution, helping to understand the underlying patterns and trends within the dataset. Inferential statistics were then employed to draw conclusions, make predictions and identify causal relationships between variables within the data.

Fisher's exact test and Pearson chi-square tests were employed to evaluate the associations between covariates and the primary outcome, offering insights into potential correlations or dependencies within the dataset. The primary outcome was defined as the incidence of CINV during the overall phase, encompassing both acute and delayed CINV. This outcome was categorised into three distinct groups: "Only Nausea," "Nausea with Vomiting," and "No Nausea and Vomiting." Additionally, outcomes for acute nausea, acute vomiting, delayed nausea, and delayed vomiting were examined in relation to risk factors to identify which factors exacerbated the incidence during different phases of CINV. Anomalies and outliers in the data were identified through this comprehensive analysis, aiding in identifying areas that require further investigation and highlighting potential study limitations. A bivariate analysis was conducted on significant risk factors to further quantify the degree of association between these variables and the outcomes. Variables found to be significant in the bivariate analysis were then included in a multivariate logistic regression model. The model with the smallest Akaike Information Criterion (AIC) value, was selected. A two-tailed test of significance was assumed, and a p-value of less than 0.05 was considered the threshold for statistical significance.

CHAPTER 4

4. RESULTS

4.1 Introduction

This chapter presents a comprehensive analysis of the factors influencing CINV among the study participants. Risk factors for overall, acute and delayed CINV were evaluated, with outcomes categorised as only nausea, nausea and vomiting, and no nausea and vomiting. Statistical analyses, including Fisher's exact and chi-square tests, were employed to estimate the associations between these covariates and CINV outcomes. Additionally, to further elucidate the impact of selected risk factors, a bivariate and multivariate analysis was conducted.

4.2 Demographic Information

A total of 222 patients were interviewed and, their prescriptions were subsequently reviewed. Most patients (70.7%) were between the ages of 39-64, with smaller proportions aged 18-38 and ≥ 65. In terms of sex, females made up a notable 71.2% of the sample, compared to 28.8% of males. Racially, the largest group was Black/African patients, comprising 57.2% of the total, followed by White/European patients at 26.6%., with the remaining races contributing 16.2%. Table 4.1 represents a descriptive analysis of patients receiving chemotherapy based on age, sex and race.

Table 4.1: Demographic information of patients receiving chemotherapy.

Demographics	Total	Total
	N	%
Age		
18-38	32	14.4
39-64	157	70.7
≥65	33	14.9
Total	222	100
Sex		
Female	158	71.2
Male	64	28.8
Total	222	100
Race		
Black/African	127	57.2
White/European	59	26.6
Other (Indian/Coloured)	36	16.2
Total	222	100

4.3 Cancer and Chemotherapy Regimen Characteristics

Patients were treated for various cancers in different stages of disease. Less common cancers were grouped under the category "*Other*" and included adenocarcinoma, thoracic cancer, leiomyosarcoma, melanoma, myeloma, neck cancer, synovial sarcoma, bladder cancer, bone cancer, lung cancer, Kaposi sarcoma, cervical cancer, ovarian cancer, and prostate cancer. Fifteen patients were diagnosed with stage I cancer, 19 with stage II, 47 with stage III and 68 with stage IV. Approximately one-third of patients (32.9%) were either uncertain of their cancer stage or waiting for their cancer to be staged. Additionally, various chemotherapy regimens with different levels of emetogenicity were administered, with 37 patients (16.7%) receiving HEC, 104 patients (46.8%) receiving MEC, and 81 patients (36.5%) receiving LEC/MinEC. Patients underwent a variable number of chemotherapy cycles. The characteristics of the patients receiving intravenous chemotherapy are summarised in Table 4.2.

Table 4.2: Type of cancer, stage and chemotherapy regimen of patients receiving intravenous chemotherapy.

Cancer and chemotherapy variables	Total	Total
	N	%
Cancer diagnosis		
Breast cancer	120	54.1
GIT cancers	41	18.5
Other	36	16.2
Lymphoma	25	11.3
Total	222	100
Cancer Stage		
1	15	6.8
2	19	8.6
3	47	21.2
4	68	30.6
Uncertain	73	32.9
Total	222	100
Chemotherapy regimen		
Carboplatin containing regimens	55	24.8
Cyclophosphamide containing regimens	36	16.2
Docetaxel-containing regimens	31	14
Gemcitabine	10	4.5
Other	19	8.6
Oxaliplatin	35	15.8
Paclitaxel	26	11.7
Trastuzumab	10	4.5
Total	222	100

	Total	Total
	N	%
Emetogenicity		
High emetogenicity	37	16.7
Low/Min emetogenicity	81	36.5
Moderate emetogenicity	104	46.8
Total	222	100
Cycle number		
1	19	8.6
2	49	22.1
3	55	24.8
≥4	99	44.6
Total	222	100

4.4 The Incidence and Severity of CINV.

Patients were questioned about their experiences with acute and delayed vomiting, including the frequency of episodes, as well as the occurrence and severity of acute and delayed nausea. The analysis revealed that 27.5% of patients experienced acute vomiting within the first 24 hours post-chemotherapy. Among those who experienced acute vomiting, most had 1-2 episodes, a smaller proportion had 3-4 episodes, and a few had 5-6 episodes. Acute nausea was experienced by 44.6% of patients, with the severity distributed as mild (19.4%), moderate (17.1%), and severe (8.1%). Delayed vomiting was reported by 34.2% of patients, with the majority experiencing 1-2 episodes, some experiencing 3-4 episodes, and a minority experiencing 5-6 episodes. Delayed nausea was experienced by 45.9% of patients, with its severity rated as mild (21.2%), moderate (18%), and severe (6.8%). Incidences of acute and delayed CINV were combined to form a category that demonstrated the overall incidence of CINV in this study population. The impact of CINV on this cohort is further summarised in Table 4.3.

4.4.1 The incidence of nausea vs vomiting

In this study, 99 patients (44.6%) experienced acute nausea and 102 (45.9%) experienced delayed phase nausea. Nausea of variable severity was observed in the study population. Upon further examination of these findings, during the overall phase, 22.5% of patients experienced isolated nausea, whereas 45% experienced both nausea and vomiting. This indicates that most cases of nausea reported during either phase (acute and delayed) culminated with episodes of vomiting (Table 4.3).

Table 4.3: CINV prevalence and severity.

	Total	**Total**
	N	**%**
Acute vomiting i.e. vomiting in the first 24 hours post-chemotherapy experienced:		
Patient did not experience acute vomiting	161	72.5
Patient experienced acute vomiting.	61	27.5
Total	222	100
Frequency of acute vomiting:		
1-2	37	16.7
3-4	20	9
5-6	4	1.8
Patient did not experience acute vomiting	161	72.5
Total	222	100
Acute nausea i.e. nausea experienced in the first 24 hours post-chemotherapy experienced:		
Patient did not experience acute nausea	123	55.4
Patient experienced acute nausea	99	44.6
Total	222	100
Severity of acute nausea:		
Mild	43	19.4
Moderate	38	17.1
Patient did not experience acute nausea	123	55.4
Severe	18	8.1
Total	222	100
Delayed vomiting i.e. vomiting in the days following chemotherapy experienced:		
Patient did not experience delayed vomiting	146	65.8
Patient did experience delayed vomiting	76	34.2
Total	222	100
Frequency of delayed vomiting:		
1-2	49	22.1

	Total	Total
	N	%
3-4	23	10.4
5-6	4	1.8
Patient did not experience delayed vomiting	146	65.8
Total	222	100
Delayed nausea i.e. nausea that occurred in the days following chemotherapy experienced:		
Patient did not experience delayed nausea	120	54.1
Patient did experience delayed nausea	102	45.9
Total	222	100
Severity of delayed nausea:		
Mild	47	21.2
Moderate	40	18
Severe	15	6.8
Patient did not experience delayed nausea	120	54.1
Total	222	100
The overall incidence of CINV.		
Patient only experienced nausea	50	22.5
Patient experienced both nausea and vomiting	100	45
Patient did not experience nausea or vomiting	72	32.4
Total	222	100

4.5 CINV Treatment and Adherence to Treatment Protocol

Patients were prescribed prophylaxis based on the expected emetogenicity of the chemotherapy regimen they were receiving. Four groups were assessed:

a) Triple antiemetic therapy: Dexamethasone IV, 5HT-3 RA (ondansetron) IV stat with 5-HT-3 RA (oral)/Metoclopramide as an additional antiemetic.
b) Monotherapy: Dexamethasone IV (LEC patients)
c) No Antiemetics: Only for patients receiving MinEC
d) Combination therapy: 5HT-3 RA IV and Dexamethasone IV.

Within the treatment groups, the findings showed varied effectiveness (Table 4.4). The triple antiemetic group included patients experiencing isolated nausea (four patients), while 15.3% of patients did not experience CINV. Similarly, in the group receiving only dexamethasone, 6.9% of patients did not experience any nausea or vomiting. Furthermore, the group receiving combination therapy with a 5-HT3 receptor antagonist and dexamethasone reported the highest overall CINV incidence. Notably, even in the "*No Antiemetics*" group, which consisted of patients undergoing minimally emetogenic chemotherapy, a noteworthy proportion of patients (12%) still experienced nausea without vomiting. However, it is important to note that these observations were not statistically significant (p=0.239). These findings are detailed in Table 4.4.

Table 4.4: CINV prophylaxis prescribed to patients.

***Prescribed antiemetic regimens**								
	Only nausea		**Nausea and vomiting**		**No nausea and vomiting**		**Total**	
	N	**%**	**N**	**%**	**N**	**%**	**N**	**%**
Dexamethasone IV 5HT-3 RA (ondansetron) IV stat (Ondansetron/Metoclopramide given as additional antiemetic)	4	8	12	12	11	15.3	27	12.2
Dexamethasone IV	6	12	15	15	5	6.9	26	11.7
No antiemetics	6	12	3	3	4	5.6	13	5.9
5HT-3 RA (ondansetron) IV Dexamethasone IV	34	68	70	70	52	72.2	156	70.3
Total	50	100	100	100	72	100	222	100

** p=0.239 (Fischer's exact test)*

Antiemetic regimens administered to patients were evaluated for adherence to established treatment protocols. Patients experiencing both nausea and vomiting (36%) were more likely to have been prescribed antiemetic regimens that deviate from the protocol compared to those with just nausea (34%) or no symptoms at all (2.8%). Conversely, adherence rates were highest among those with no CINV (97.2%). A significant association was found between the likelihood

of experiencing CINV and adherence to clinical guidelines (p=0.001). These findings are illustrated in Figure 4.1.

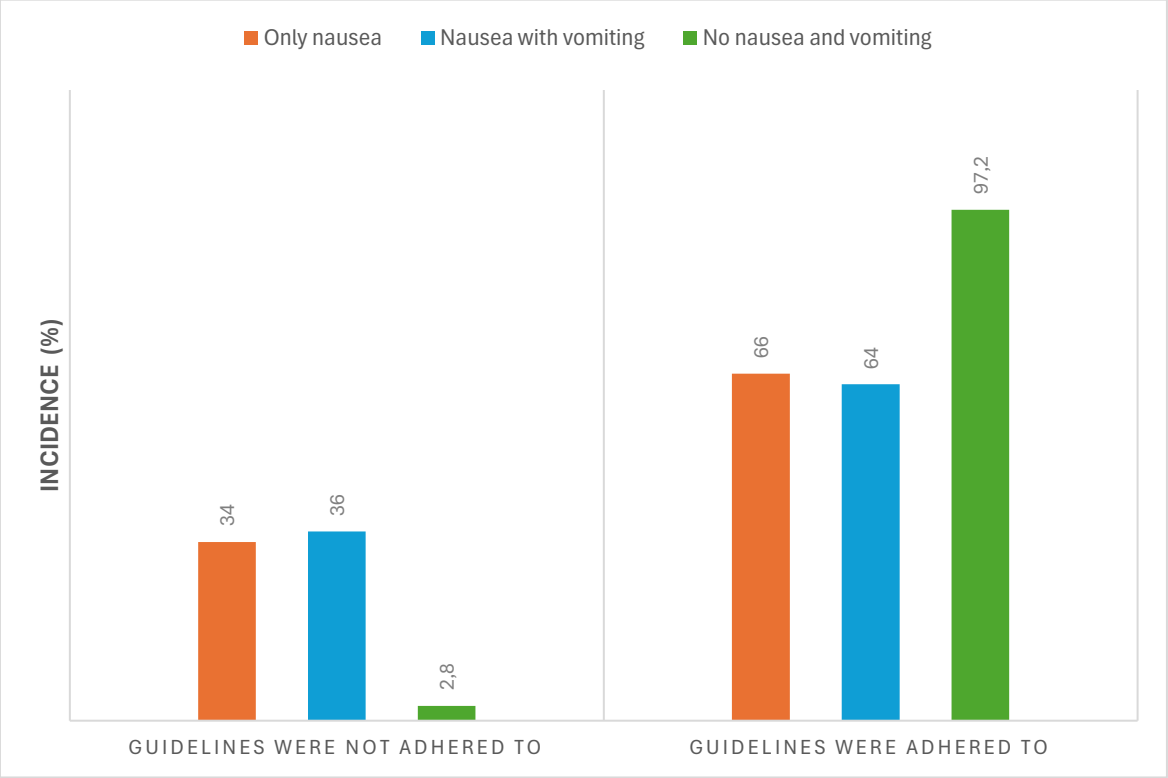

Figure 4.1: The effect of guideline adherence/non-adherence on overall CINV incidence. *

**Association between the likelihood of experiencing CINV and adherence to clinical guidelines (p=0.001).*

Deviations from the protocol were also evaluated. In the HEC group where olanzapine and corticosteroids were not included, 16% of patients experienced nausea alone, while a similar proportion (15%) experiencing both nausea and vomiting. Notably, none of the patients in this group reported complete absence of symptoms. This pattern continued, although with less pronounced severity, in the LEC/MinEC group requiring additional antiemetics. Here, 18% and 16% of patients experienced nausea alone and nausea with vomiting, respectively. A small percentage (2.8%) of patients within this group reported no symptoms. The most concerning observation was in the MEC group requiring additional antiemetics. All five patients (100%) in this category experienced nausea and vomiting, suggesting limitations in controlling CINV with the initial regimen for MEC. These findings were statistically significant (p=0.001). Table 4.5 gives a more comprehensive breakdown of these findings.

Table 4.5: Non-compliance to guidelines and CINV prevalence.

***Reason for non-compliance to guidelines:**								
	Only nausea		**Nausea and vomiting**		**No nausea and vomiting**		**Total**	
	N	**%**	**N**	**%**	**N**	**%**	**N**	**%**
Regimen was according to guidelines	33	66	64	64	70	97.2	167	75.2
HEC regimen: Olanzapine and oral corticosteroid not added.	8	16	15	15	0	0	23	10.4
LEC regimen: Additional antiemetics added to regimen	9	18	16	16	2	2.8	27	12.2
MEC regimen: Additional antiemetics added to regimen	0	0	5	5	0	0	5	2.3
Total	50	100	100	100	72	100	222	100

**p=0.001 (Fischer's exact test)*

4.5.1 Guideline compliance and acute vomiting prevalence.

Of the 61 patients who experienced acute vomiting, 68.9% of antiemetic regimens were guideline compliant. Upon examination of the group of patients that did not report acute vomiting, 77.6% of patients received antiemetic regimens that adhered to the treatment protocol, however, there was no significant association between adherence to clinical guidelines and the incidence of CINV in these groups ($p > 0.05$). Further analysis of non-compliance reasons revealed that among patients who experienced acute vomiting, 11.5% of those on a HEC regimen were not prescribed olanzapine and an oral corticosteroid, contrary to the treatment protocol. Additionally, 16.4% of patients on LEC/MinEC and 3.3% on MEC reported experiencing acute vomiting, despite the employment of additional antiemetics. This difference, however, was also not statistically significant ($p > 0.05$). Table 4.6 details these findings.

Table 4.6: Guideline compliance vs acute vomiting prevalence.

***Compliance with guidelines:**						
	No acute vomiting		**With acute vomiting**		**Total**	
	N	**%**	**N**	**%**	**N**	**%**
The patient did not receive guideline-compliant antiemetics	36	22.4	19	31.1	55	24.8
The patient received guideline-compliant antiemetics	125	77.6	42	68.9	167	75.2
Total	161	100	61	100	222	100
†Reasons for non-compliance:						
Regimen was according to the guideline.	125	77.6	42	68.9	167	75.2
HEC regimen: Olanzapine and oral corticosteroid not added.	16	9.9	7	11.5	23	10.4
LEC/MinEC regimen: Additional antiemetics added because the patient still had CINV	17	10.6	10	16.4	27	12.2
MEC regimen: Additional antiemetics because patient had CINV	3	1.9	2	3.3	5	2.3
Total	161	100	61	100	222	100

**p=0.176 (Chi-square test)*

† p=0.535 (Chi-square test)

4.5.2 Guideline compliance and acute nausea prevalence

Upon examining the group of patients who did not experience acute nausea and those who did, 80.5% and 68.7% received guideline-concordant therapy, respectively. This difference was statistically significant ($p < 0.05$). Reasons for non-compliance to antiemetic guidelines, revealed that 13.1% of patients receiving HEC reported experiencing acute nausea, however, additional antiemetics such as olanzapine and an oral corticosteroid were not prescribed.

Furthermore, 14.1% of patients receiving LEC/MinEC and 4.0% of patients receiving MEC reported acute nausea despite additional antiemetics added to the regimen. The incidence of acute nausea in patients undergoing chemotherapy, comparing those whose antiemetic regimens followed the treatment facility's guidelines against those who did not is summarised in Table 4.7.

Table 4.7: Guideline compliance vs acute nausea prevalence.

***Compliance to guidelines:**						
	No acute nausea		**With acute nausea**		**Total**	
	N	**%**	**N**	**%**	**N**	**%**
Patient did not receive guideline-compliant antiemetics.	24	19.5	31	31.3	55	24.8
Patient did receive guideline-compliant antiemetics.	99	80.5	68	68.7	167	75.2
Total	123	100.0	99	100.0	222	100.0
†Reasons for non-compliance:						
Regimen was according to guideline.	99	80.5	68	68.7	167	75.2
HEC regimen: Olanzapine and oral corticosteroid not added.	10	8.1	13	13.1	23	10.4
LEC/MinEC regimen: Additional antiemetics added because patient still had CINV	13	10.6	14	14.1	27	12.2
MEC regimen: Additional antiemetics added because patient has CINV	1	0.8	4	4.0	5	2.3
Total	123	100.0	99	100.0	222	100.0

**p=0.043 (Chi-square test)*

† *p=0.142 (Chi-square test)*

4.5.3 Guideline-compliance and delayed vomiting prevalence

Table 4.8 presents the incidence of delayed vomiting in chemotherapy patients, analysed in relation to adherence to the treatment facility's antiemetic regimen guidelines. Among the 146

patients who did not experience delayed vomiting, 121 (82.9%) were on regimens that adhered to guideline recommendations. In contrast, among the 76 patients who experienced delayed vomiting, 46 (60.5%) were on guideline-compliant regimens. Although a higher percentage of patients on guideline-compliant regimens did not experience delayed vomiting compared to those who did, the difference in adherence to clinical guidelines between these groups was not statistically significant ($p > 0.05$). Further analysis of non-compliance reasons revealed distinct patterns. Among the 76 patients who experienced delayed vomiting, 18.4% were on HEC regimens that lacked the addition of olanzapine and an oral corticosteroid. Additionally, within the delayed vomiting cohort, 17.1% of patients were on LEC/MinEC regimens and 3.9% on MEC regimens where additional antiemetics were prescribed.

Table 4.8: Guideline compliance vs delayed vomiting prevalence.

***Compliance to guidelines:**						
	No delayed vomiting		**With delayed vomiting**		**Total**	
	N	**%**	**N**	**%**	**N**	**%**
The patient did not receive guideline-compliant antiemetics.	25	17.1	30	39.5	55	24.8
The patient did receive guideline-compliant antiemetics.	121	82.9	46	60.5	167	75.2
Total	146	100.0	76	100.0	222	100.0
†Reasons for non-compliance:						
The regimen was according to the guideline.	121	82.9	46	60.5	167	75.2
HEC regimen: Olanzapine and oral corticosteroid not added.	9	6.2	14	18.4	23	10.4
LEC/MinEC regimen: Additional antiemetics added because patient still had CINV	14	9.6	13	17.1	27	12.2
MEC regimen: Additional antiemetics added because patient has CINV	2	1.4	3	3.9	5	2.3
Total	146	100.0	76	100.0	222	100.0

** p=0.001 (Chi-square test) † p=0.002 (Chi-square test)*

4.5.4 Guideline-compliance and delayed nausea prevalence

Of the 120 patients who did not report experiencing delayed nausea, 106 (88.3%) patients received guideline-concordant antiemetic therapy. In contrast within the delayed nausea group, 59.8% of patients received antiemetics in line with the treatment protocol. The difference between these two groups, in terms of the incidence of delayed nausea and guideline adherence, was statistically significant (p=0.001). The reasons for non-compliance were further analysed. Within the delayed nausea group, 17.6% of patients receiving HEC experienced this side effect, however, neither olanzapine nor an oral corticosteroid was added to address this. Moreover, among the 102 patients who experienced delayed nausea, 18.6% were receiving LEC/MinEC regimens, and 3.9% were on MEC regimens with additional antiemetics prescribed, nevertheless, this side effect persisted. These findings are shown in Table 4.9.

Table 4.9: Guideline-compliance vs delayed nausea prevalence.

***Compliance to guidelines:**						
	No delayed nausea		**With delayed nausea**		**Total**	
	N	**%**	**N**	**%**	**N**	**%**
Patient did not receive guideline-compliant antiemetics.	14	11.7	41	40.2	55	24.8
Patient did receive guideline-compliant antiemetics.	106	88.3	61	59.8	167	75.2
Total	120	100.0	102	100.0	222	100.0
†Reasons for non-compliance:	P=0.001					
Regimen was according to guideline.	106	88.3	61	59.8	167	75.2
HEC regimen: Olanzapine and an oral corticosteroid not added.	5	4.2	18	17.6	23	10.4
LEC regimen: Additional antiemetics added because patient still had CINV	8	6.7	19	18.6	27	12.2

Compliance to guidelines						
	No delayed nausea		With delayed nausea		Total	
	N	%	N	%	N	%
MEC regimen: Additional antiemetics because patient still had CINV	1	0.8	4	3.9	5	2.3
Total	120	100.0	102	100.0	222	100.0

**p=0.001 (Chi-square test)*

†p=0.001 (Chi-square test)

4.6 CINV Risk Factors

This section presents the findings of the investigation into risk factors associated with CINV. Fischer's exact and chi-square tests were conducted to assess the statistical significance of any associations between various factors and CINV development. Results for risk factors evaluated during the overall phase are depicted in Appendix I. Risk factors that could potentially exacerbate acute and delayed CINV were also evaluated.

4.6.1 Age

The analysis of age-related differences in CINV revealed notable patterns. Participants aged 39-64 exhibited the highest incidence of nausea alone while nausea accompanied by vomiting accounted for 74% of cases, whereas those who were ≥ 65 years demonstrated a more balanced distribution across the various CINV categories. These observations, however, were not statistically significant (p=0.054) (Appendix I).

Acute vomiting was not significantly affected by age, however, the highest number of reported cases was observed in the 39-64 age group at 70.5%, compared to other age groups, though this difference was not statistically significant (p=0.818). The prevalence of acute nausea was found to have a statistically significant relationship with age (p=0.038). Patients aged 39 to 64 experienced acute nausea at a higher rate, with 75.8% affected. In terms of delayed nausea, there was no significant age-related impact, with 13.7% of patients aged 18-38, 76.5% aged 39-64, and 9.8% aged 65 and older experiencing delayed nausea (p=0.123). Similarly, the incidence of delayed vomiting following chemotherapy was not significantly influenced by age, with 17.1% of patients aged 18-38, 56.3% aged 39-64, and 9.2% aged 65 and older reporting delayed vomiting (p=0.201). Figure 4.2 illustrates these findings.

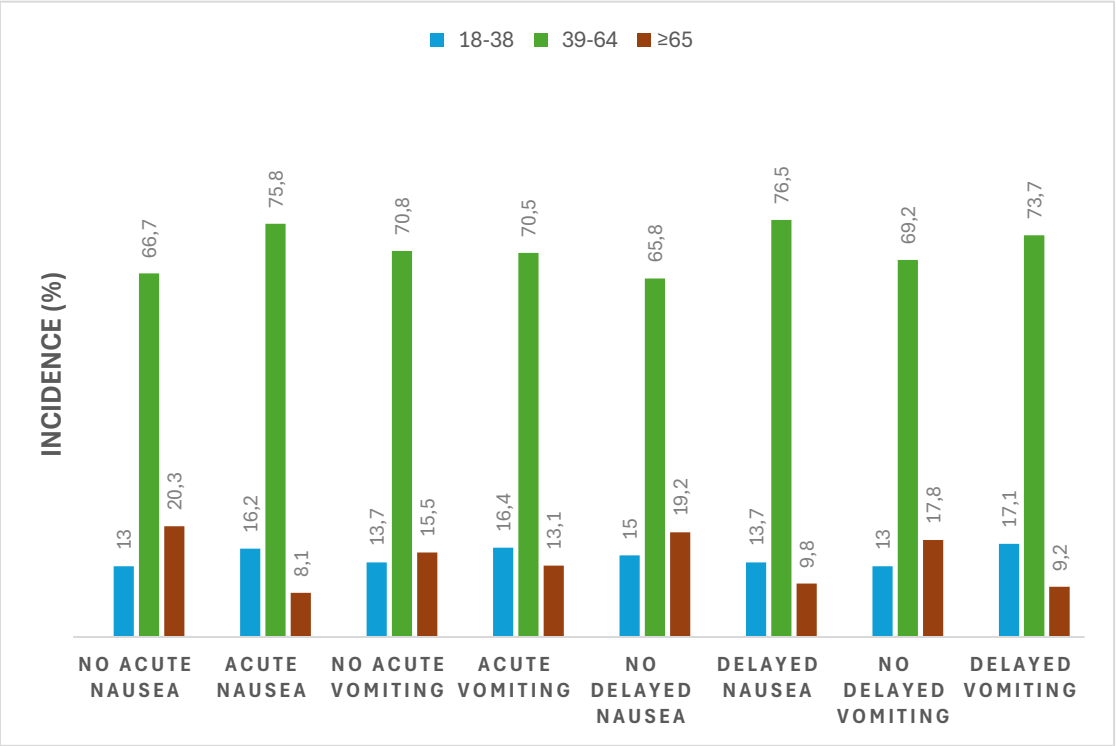

Figure 4.2: Age-related effects on acute and delayed CINV incidence. *†‡ §

**The prevalence of acute nausea was found to have a statistically significant relationship with age (p=0.038).*

† Acute vomiting was not significantly affected by age (p=0.818).

‡ Delayed nausea had no significant age-related impact (p=0.123).

§ Delayed vomiting following chemotherapy was not significantly influenced by age (p=0.201)

4.6.2 Sex

The comparison of CINV incidence between sexes revealed that females experienced isolated nausea more frequently (82%) compared to males (18%). However, this difference was not statistically significant (p=0.126) indicating insufficient evidence to confirm a sex-based disparity in CINV presentation within this cohort (Appendix I). Sex had no influence, statistically speaking, on the occurrence of acute nausea (p=0.891) or acute vomiting (p=0.423), despite a higher number of reported cases for both symptoms among females (70.7% for nausea and 67.2% for vomiting) during the first 24 hours post-chemotherapy. Similarly, no significant differences were observed in delayed nausea (p=0.190) or delayed vomiting (p=0.335) between sexes, with 75.5% of females reporting delayed nausea compared to 24.5% of males, and 67.1% of females experiencing delayed vomiting compared to 32.9% of males. The effect of sex on acute and delayed CINV is illustrated in Figure 4.3.

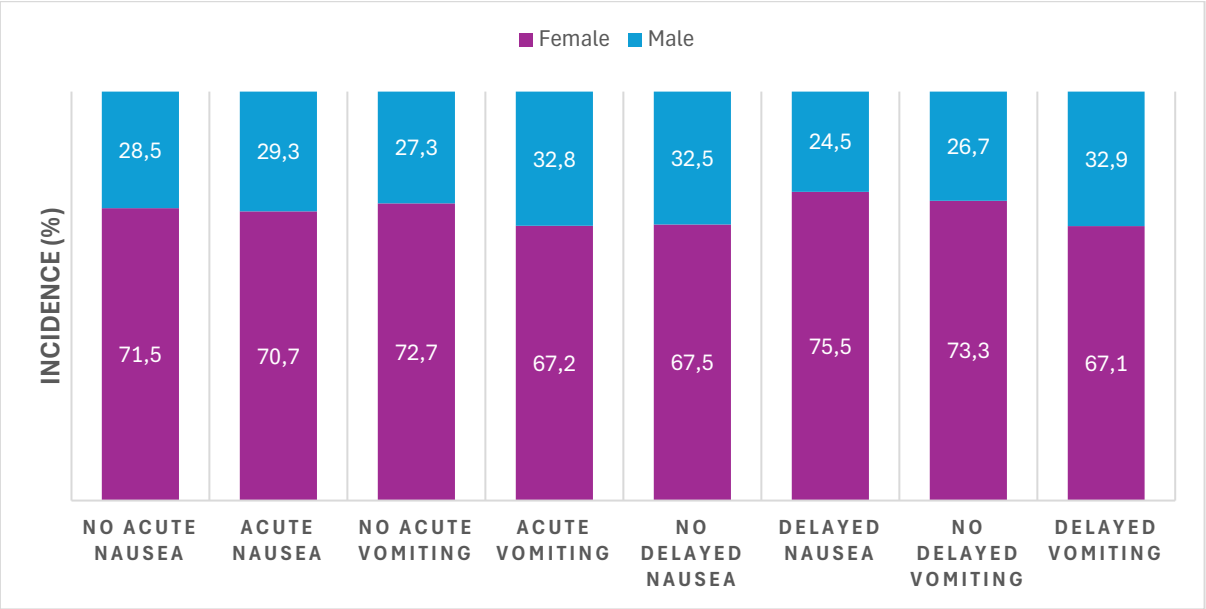

Figure 4.3: The effect of sex on the incidence of acute and delayed CINV. *†‡ §

**Sex had no influence, statistically speaking, on the occurrence of acute nausea (p=0.891).*

† Sex did not influence the occurrence of acute vomiting (p=0.423).

‡ No significant differences were observed in delayed nausea prevalence (p=0.190).

§ There was no statistically significant association between sex and delayed vomiting (p=0.335).

4.6.3 Race

Racial analysis indicated that Black patients experienced a higher incidence of CINV compared to other racial groups, with 48% experiencing only nausea and 51% experiencing both nausea and vomiting. In contrast, White participants had a lower proportion experiencing only nausea, with a comparable number experiencing both nausea and vomiting. Patients from other racial backgrounds (Indian and Coloured) reported having fewer episodes of isolated nausea and nausea with vomiting. However, Black patients also experienced higher rates of being asymptomatic (72,2%) during the overall phase. The statistically significant p-value of 0.033 indicates a notable disparity in the incidence of CINV among different racial groups (Appendix I).

A cursory analysis of the data suggested that Black patients had a higher incidence of acute nausea (50.5%) compared to other racial groups, however, statistical analysis indicated that this difference was not significant (p = 0.061). Similarly, trends indicated that both Black and White patients experienced higher rates of acute vomiting (49.2% and 32.8%, respectively), though this association was also not statistically significant (p=0.311). However, a statistically significant difference was observed in delayed nausea incidence among Black (48%), White (33.3%), and Other (Indian/Coloured) patients (18.6%) (p=0.035). No significant differences

were found in delayed vomiting incidence across racial groups (p=0.467). These trends are depicted in Figure 4.4.

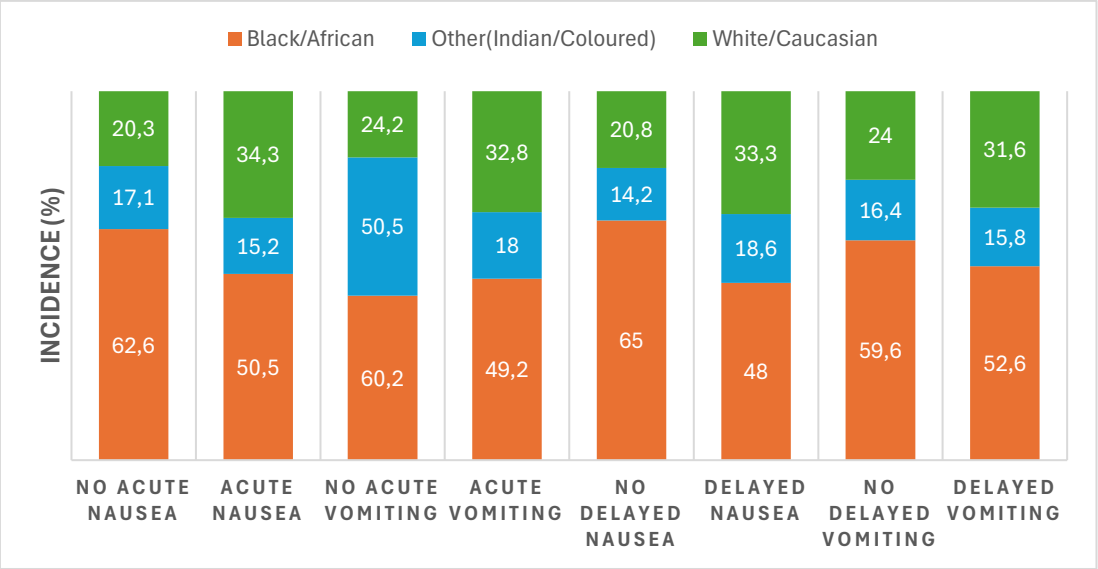

Figure 4.4: The effect of race on the incidence of acute and delayed CINV. *†‡ §

** There was no association between race and the incidence of acute nausea (p=0.061).*

† The prevalence of acute vomiting was not affected by race (p=0.311).

‡ A significant association was established between race and the incidence of delayed nausea (p=0.035).

§ No significant differences were found in delayed vomiting incidence across racial groups (p=0.467).

4.6.4 Cancer diagnosis

CINV incidence across various cancer diagnoses revealed that breast cancer patients had the highest incidence of isolated nausea (64%) and nausea with vomiting (51%). There was no significant difference in CINV incidence based on cancer diagnosis (p = 0.545) (Appendix I). Furthermore, cancer diagnosis showed a trend towards significance concerning the incidence of acute nausea (p=0.057), with breast cancer patients experiencing higher rates (50.5%). Similarly, the trend towards significance was observed in the incidence of acute vomiting, with breast cancer patients also exhibiting a higher incidence (47.5%) compared to other cancer types, although this finding was not statistically significant (p=0.076). While cancer diagnosis did not significantly affect delayed nausea rates, a higher incidence was observed in breast cancer patients (52.9%) (p=0.291). Additionally, the analysis revealed that cancer diagnosis did not significantly influence delayed vomiting rates, however, higher incidences were noted among participants with breast cancer (46.1%) and GIT cancers (23.7%) (p=0.321). Figure 4.5 illustrates these findings.

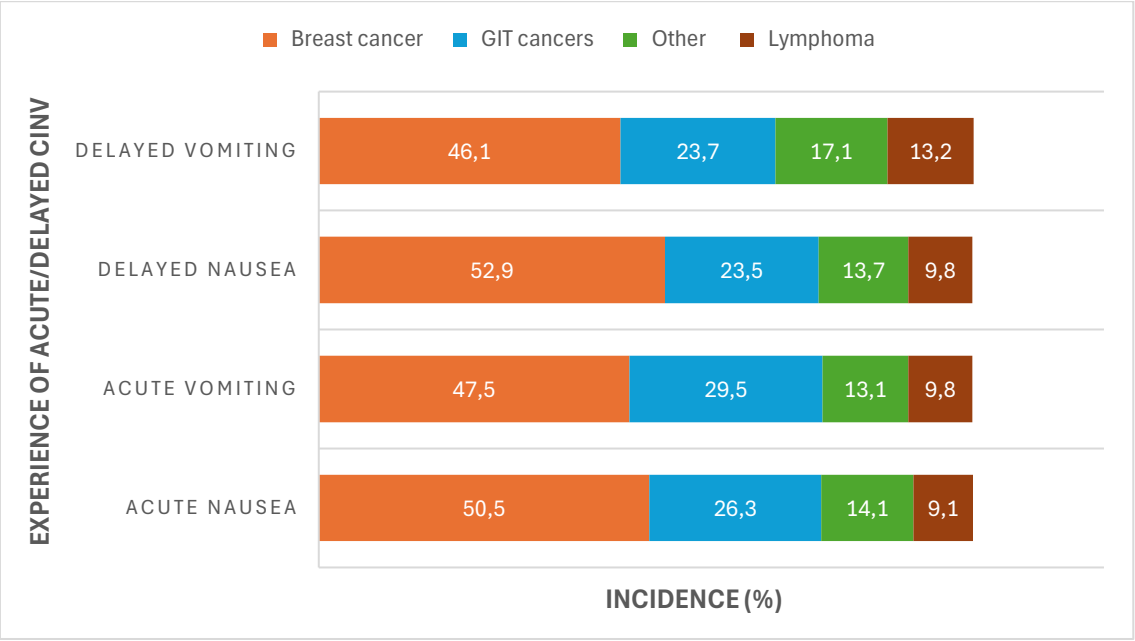

Figure 4.5: The effect of cancer type on acute and delayed CINV incidence. *†‡ §

**Cancer diagnosis showed a trend towards significance concerning the incidence of acute nausea (p=0.057), with higher rates observed in breast cancer patients.*

† A trend towards significance was also noted for the incidence of vomiting, with breast cancer patients exhibiting a higher incidence (p=0.076).

‡ Cancer diagnosis did not significantly affect delayed nausea rates, although breast cancer patients had higher rates (p=0.291).

§ Cancer diagnosis did not significantly influence delayed vomiting rates, but higher incidences were noted in breast and GIT cancers (p=0.321).

4.6.5 Cancer stage

The distribution of CINV across various cancer stages demonstrated that stage 4 patients had the highest incidence of both nausea and vomiting, accounting for 32% of cases. Although there was no statistically significant difference across cancer stages, there was a noticeable trend suggesting that higher cancer stages may be associated with more severe CINV symptoms. However, it is important to highlight that a substantial proportion of patients (32.9%) were unaware of their cancer stage. As a result, no definitive association between cancer stage and CINV incidence could be established from this study (Appendix I). Due to the large proportion of patients unsure of their cancer stage, the potential effects of cancer stage on acute and delayed CINV could also not be accurately assessed.

4.6.6 Emetogenicity

The effect of emetogenic potential on CINV revealed that participants receiving MEC had the highest incidence of only nausea (40%) and both nausea and vomiting (50%). HEC was associated with lower incidences of only nausea (16%) and both nausea and vomiting (16%), compared to MEC and LEC or MinEC. These differences were not statistically significant (p = 0.765) (Appendix I).

Table 4.10 illustrates the effect of the emetogenic potential of chemotherapy regimens on the incidence of both acute and delayed CINV. For acute nausea, the emetogenicity of the chemotherapy regimen was not a significant factor (p=0.247). Similarly, the incidence of acute vomiting was not significantly impacted by the emetogenic potential of the regimen (p=0.153). Regarding delayed nausea, the emetogenicity of the chemotherapy regimen also did not show a significant effect (p=0.815). Although higher rates of delayed vomiting were observed among patients receiving MEC regimens (44.7%), this difference was also not statistically significant (p=0.849).

Table 4.10: The effect of emetogenicity on the incidence of acute/delayed CINV

Emetogenic potential	**No acute nausea**	**Acute nausea**	**No acute vomiting**	**Acute vomiting**	**No delayed nausea**	**Delayed nausea**	**No delayed vomiting**	**Delayed vomiting**
	N (%)	**N (%)**	**N (%)**	**N (%)**	**N (%)**	**N (%)**	**N (%)**	**N (%)**
High emetogenicity	24 (19.5)	13 (13.1)	29 (18)	8 (13.1)	19 (15.8)	18 (17.6)	23 (15.8)	14 (18.4)
Low/Min emetogenicity	47 (38.2)	34 (34.3)	63 (39.1)	18 (29.5)	46 (38.3)	35 (34.3)	53 (36.3)	28 (36.8)
Moderate emetogenicity	52 (42.3)	52 (52.5)	69 (42.9)	35 (57.4)	55 (45.8)	49 (48.0)	70 (47.9)	34 (44.7)
Total (n=222)	123 (100.0)	99 (100.0)	161 (100.0)	61 (100.0)	120 (100.0)	102 (100.0)	146 (100.0)	76 (100.0)
P-Value (Chi-square test)	p=0.247		p=0.153		p = 0.815		p=0.849	

4.6.7 Cycle number

The distribution of CINV across different chemotherapy cycles showed that patients in their fourth cycle experienced the highest incidence of both nausea and vomiting (49%) as well as isolated nausea (44%). This association was statistically significant (p=0.001) (Appendix I). A significant correlation was observed between the number of chemotherapy cycles completed and the incidence of acute nausea, with a particularly high incidence in the fourth cycle, where 46.5% of patients experienced symptoms (p=0.003). Similarly, the incidence of acute vomiting increased with the number of cycles, with a statistically significant association (p=0.004).

Regarding delayed CINV, patients who completed four or more chemotherapy cycles had the highest incidence of delayed nausea (49.0%) (p=0.001) and delayed vomiting (51.3%) (p=0.001). The trends of acute and delayed CINV in relation to the number of chemotherapy cycles are illustrated in Figure 4.6.

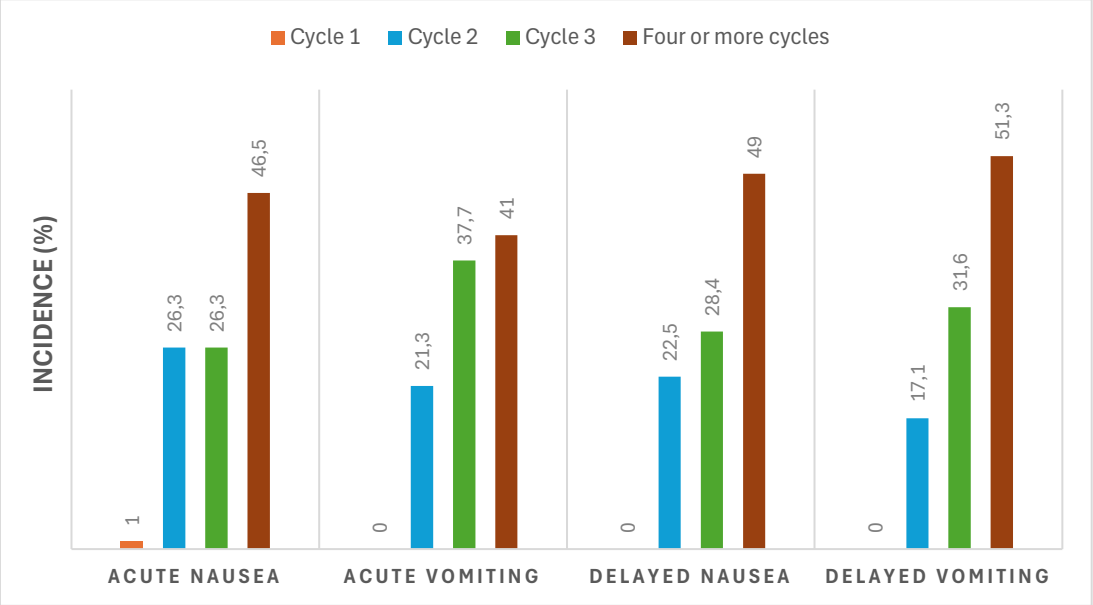

Figure 4.6: The effect of cycle number on acute and delayed CINV incidence. *†‡ §

**A significant correlation was observed between the number of chemotherapy cycles completed and the incidence of acute nausea, with the highest incidence occurring in the fourth cycle (46.5%) (p=0.003).*

† The incidence of acute vomiting increased with the number of cycles, showing a statistically significant association (p=0.004).

‡ Patients who completed four or more chemotherapy cycles had the highest incidence of delayed nausea (49.0%) (p=0.001).

§ A statistically significant association was also noted for delayed vomiting, with the highest incidence observed in patients completing four or more chemotherapy cycles (51.3%) (p=0.001).

4.6.8 Hours of sleep

The analysis of the relationship between sleep duration and CINV showed that patients who slept for 8-10 hours had the highest incidence of nausea alone (44%) and nausea with vomiting (46%). Patients with 4-7 hours of sleep exhibited slightly lower incidences of nausea alone (42%) and both nausea and vomiting (41%). Those with the shortest sleep duration, 1-3 hours, had the lowest incidence of isolated nausea (14%) and nausea with vomiting (13%). However, these variations were not statistically significant (p=0.959). The impact of CINV on patients' sleep was minimal, with the vast majority (92.3%) reporting no disturbances. However, a small proportion (7.7%) did experience difficulties with sleep due to CINV (Appendix I). Sleep duration did not have a significant impact on the incidence of acute nausea (p=0.420). Similarly, no statistically significant association was found between the number of hours slept and the incidence of acute vomiting (p=0.278). Regarding delayed nausea, sleep duration did not significantly influence its incidence, with comparable rates observed among patients sleeping

4-7 hours (41.2%), and 8-10 hours (41.2%) (p=0.217). The incidence of delayed vomiting was not significantly affected by sleep duration, with rates reported as 13.2% for those sleeping 1-3 hours, 36.8% for 4-7 hours, and 50% for 8-10 hours, demonstrating no significant difference (p = 0.739). Figure 4.7 illustrates the effect of sleep duration on the incidence of both acute and delayed CINV.

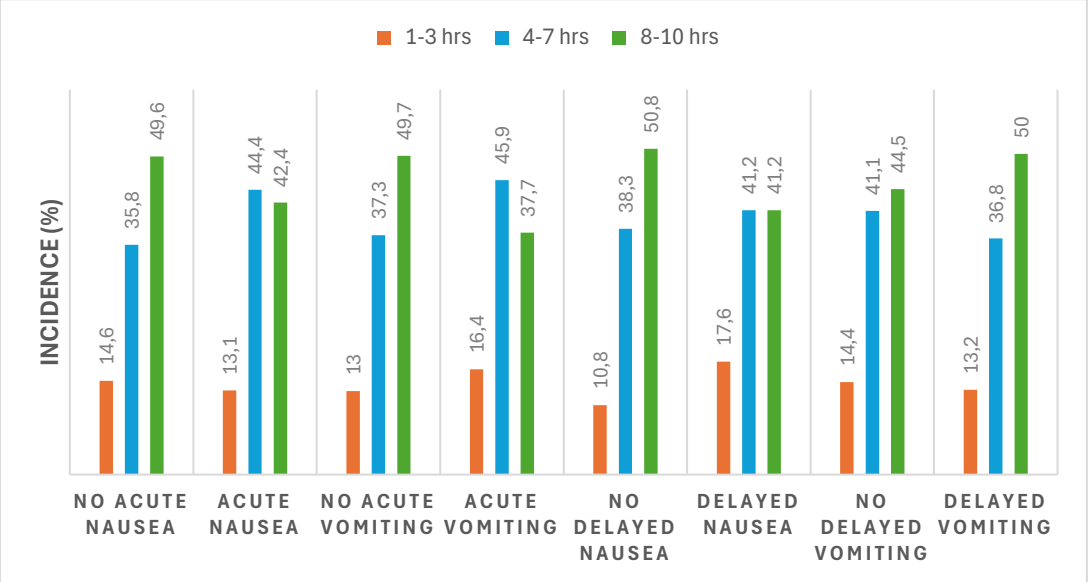

Figure 4.7: The effect of sleep duration on the incidence of acute and delayed CINV. *†‡ §

**Sleep duration did not significantly impact the incidence of acute nausea (p=0.420).*

† No statistically significant association was observed between sleep duration and acute vomiting (p=0.278).

‡ Sleep duration did not significantly influence the incidence of delayed nausea (p=0.217).

§ No significant difference in delayed vomiting rates was observed across different sleep durations (p=0.739).

4.6.9 Anticipatory nausea and vomiting

Anticipatory nausea and vomiting were reportedly not experienced by 55% of participants, while 18% reported experiencing it often, and 27% experiencing it sometimes. A statistically significant difference in the incidence of overall CINV was observed based on the presence of ANV (p=0.001). This finding indicates a significant association between experiencing anticipatory nausea and vomiting prior to chemotherapy and the incidence of CINV (Appendix I).

ANV was significantly associated with acute nausea, with a strong correlation between ANV and higher rates of acute nausea (p=0.001). Similarly, ANV was significantly linked to acute vomiting, with those experiencing ANV more likely to report acute vomiting (p=0.010). Regarding delayed nausea, there was a strong association with ANV, where participants who experienced ANV often or sometimes had a higher overall rate of CINV (28.4% and 31.4%,

respectively) compared to those who did not (40.2%) (p=0.001). Likewise, ANV was strongly associated with delayed vomiting, with a higher overall rate observed among patients who anticipated CINV often or sometimes (28.9% and 31.6%, respectively) compared to those who did not (39.5%) (p=0.001). Figure 4.8 illustrates the relationship between ANV and the incidence of both acute and delayed CINV.

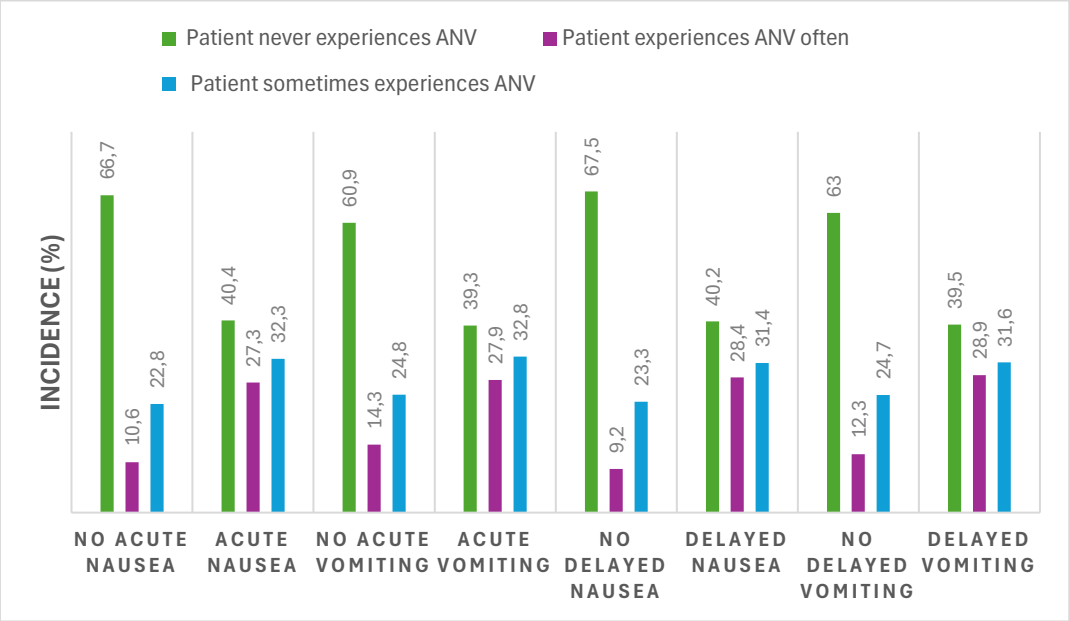

Figure 4.8: The effect of ANV on acute and delayed CINV incidence. *†‡ §

**A significant association was observed between ANV and acute nausea (p=0.001).*

† ANV was significantly linked to acute vomiting (p=0.010).

‡ A strong association was found between ANV and delayed nausea (p=0.001).

§ ANV was significantly associated with delayed vomiting (p=0.001).

4.6.10 History of motion sickness

A significantly higher proportion of patients without a history of motion sickness reported no nausea and vomiting (97.2%). In contrast, only 2.8% of patients with a history of motion sickness did not experience nausea and vomiting. A statistically significant difference was observed (p=0.001) (Appendix I).

For acute nausea, only 12.2% of patients with a history of motion sickness did not experience nausea, while a significant 39.4% reported experiencing acute nausea, representing a more than threefold increase in incidence compared to those without motion sickness (60.6%). This difference was statistically significant (p=0.001). Among patients with a history of motion sickness, 45.9% experienced acute vomiting, while 16.1% did not. In contrast, for those without such a history, 54.1% experienced acute vomiting and 83.9% did not (p=0.001). This pattern continued for delayed CINV, where an increase in incidence was observed in patients who were

more prone to experiencing motion sickness, indicating that patients with such a history were less likely to have avoided experiencing no delayed nausea (p=0.003) and no delayed vomiting (p=0.001). These findings are illustrated in Figure 4.9.

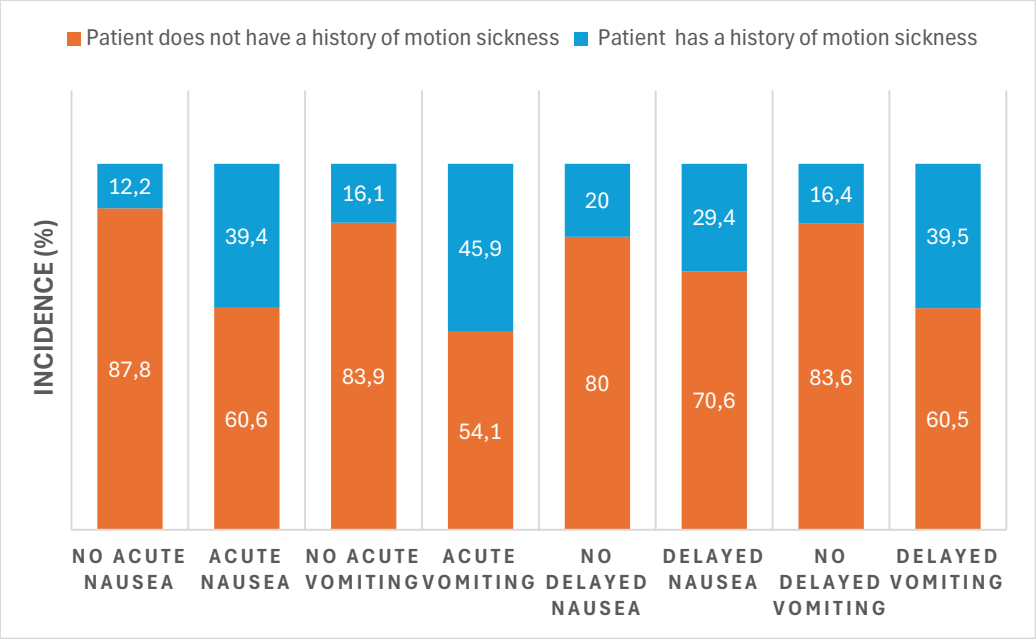

Figure 4.9: The effect of a history of motion sickness acute and delayed CINV. *†‡ §

**A significant association was observed between a history of motion sickness and acute nausea, with a more than threefold increase in incidence compared to those without motion sickness (p=0.001).*

† Patients with a history of motion sickness were significantly more likely to experience acute vomiting (p=0.001).

‡ A history of motion sickness was significantly associated with delayed nausea (p=0.003).

§ A significant association was found between a history of motion sickness and delayed vomiting (p=0.001).

4.6.11 History of morning sickness

Approximately, 43.2% of females reported experiencing morning sickness during pregnancy. Among these patients, those with a history of morning sickness reported a higher incidence of nausea (44%) and nausea with vomiting (45%), although a p-value of 0.691 suggests there was no significant difference in CINV incidence based on morning sickness experiences during pregnancy (Appendix I).

Patients with a history of morning sickness during a previous pregnancy reported a higher incidence of acute nausea (44.4%), however, this result was not statistically significant (p=0.895). Similarly, while a higher incidence of acute vomiting was observed in these patients (44.3%), this observation was also not significant (p=0.419). Regarding delayed nausea, morning sickness during a previous pregnancy did not significantly impact the incidence (p=0.255). Additionally, there was no significant effect on delayed vomiting rates (p=0.844).

These results are shown in Table 4.11. The category "N/A for this patient" refers to patients who were either male or females who had never experienced pregnancy.

Table 4.11: The effect of a history of morning sickness on acute/delayed CINV.

Variable	No acute nausea	Acute nausea	No acute vomiting	Acute vomiting	No delayed nausea	Delayed nausea	No delayed vomiting	Delayed vomiting
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
N/A for this patient	47 (38.2)	38 (38.4)	59 (36.6)	26 (42.6)	51 (42.5)	34 (33.3)	54 (37)	31 (40.8)
No history of morning sickness	24 (19.5)	17(17.2)	33(20.5)	8 (13,1)	23 (19,2)	18(17,6)	28 (19,2)	13 (17,1)
History of morning sickness	52 (42.3)	44 (44.4)	69 (42.9)	27 (44,3)	46 (38,3)	50 (49)	64 (43,8)	32 (42,1)
Total (n=222)	123 (100)	99 (100)	161 (100)	61 (100)	120 (100)	102 (100)	146 (100)	76 (100)
P-Value (Chi-square test)	p= 0.895		p=0.419		p= 0.255		p=0.844	

4.6.12 Alcohol consumption

An analysis of alcohol consumption patterns among patients revealed that 63.5% abstained from alcohol, while 36.5% reported drinking alcohol. The incidence of nausea with vomiting was higher among non-drinkers (71%) compared to drinkers (29%), with the prevalence of isolated nausea being consistent across both groups. There was a statistically significant difference in the incidence of CINV between these groups (p=0.041). Further examination of alcohol consumption frequency demonstrated that individuals who consumed alcohol 1-3 times per month exhibited a higher incidence of CINV (both isolated nausea and nausea with emesis) compared to those who consumed alcohol more frequently (1-6 times per week) or rarely. Overall, non-drinkers showed the highest incidence of CINV. The difference in CINV incidence

based on the frequency of alcohol consumption was statistically significant (p=0.020) (Appendix I).

The frequency of alcohol consumption was not a significant factor for acute nausea (p=0.059). However, it significantly influenced the occurrence of acute vomiting, with a higher prevalence observed among non-drinkers (67.2%) and rare drinkers (13.1%), and this difference was statistically significant (p=0.011). In contrast, the frequency of alcohol consumption did not significantly impact the incidence of delayed nausea (p=0.158) or delayed vomiting (p=0.507). Figure 4.10 illustrates the relationship between the frequency of alcohol consumption and its impact on both acute and delayed CINV.

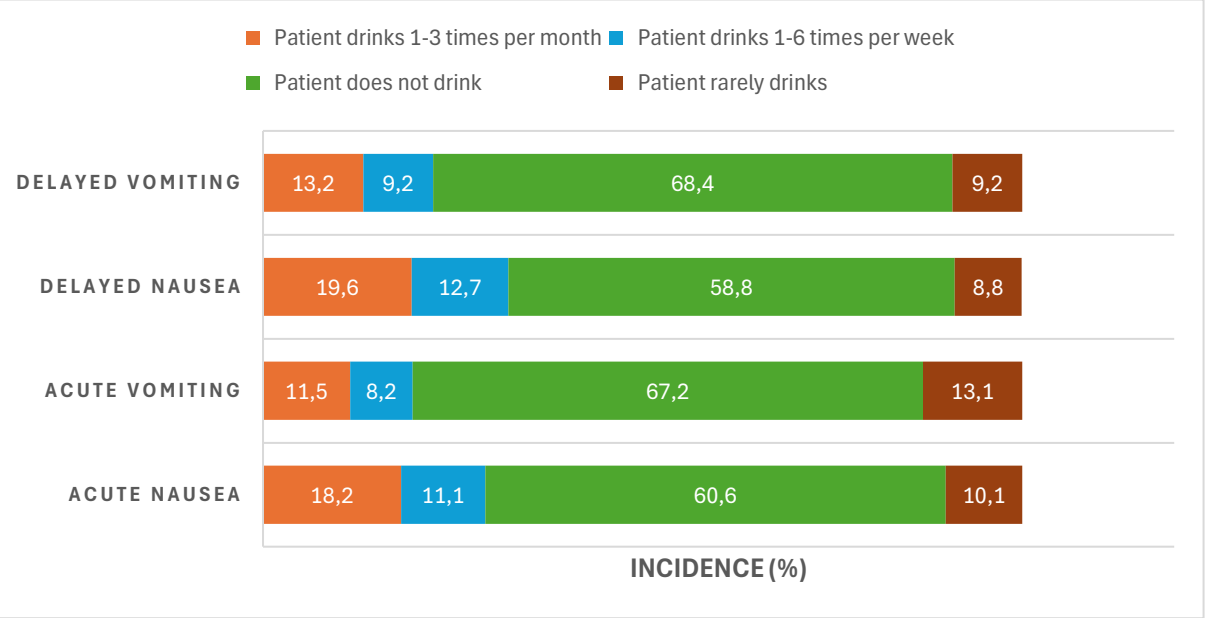

Figure 4.10: The effect of alcohol consumption on the incidence of acute and delayed CINV.

*†‡ §

** The frequency of alcohol consumption was not significantly associated with acute nausea (p=0.059).*

† A significant association was observed between alcohol consumption frequency and acute vomiting, with higher prevalence among non-drinkers and rare drinkers (p=0.011).

‡ Alcohol consumption frequency did not significantly impact delayed nausea (p=0.158).

§ No significant association was found between alcohol consumption frequency and delayed vomiting (p=0.507).

4.6.13 Comorbidities and the use of prescription/nonprescription medication

In this study, 50.9% of patients reported no chronic conditions, while 49.1% had one other chronic condition. Among these, hypertension (19.8%) and HIV (13.5%) were the most prevalent. Less common conditions included chronic pain (3.6%), diabetes (6.8%), GERD

(3.2%), and mental health disorders such as anxiety, depression, and insomnia (2.3%). There was no statistically significant difference in the incidence of overall CINV based on the presence of specific chronic conditions (p=0.165) (Appendix I).

The presence of a concurrent chronic condition was not a significant factor for acute nausea (p=0.227). However, a higher incidence of acute vomiting was observed in patients with concurrent hypertension (13.1%) or HIV (16.2%), and this finding was statistically significant (p=0.039). Additionally, the presence of chronic conditions did not significantly impact the rates of delayed nausea (p=0.464) or delayed vomiting (p=0.642). These findings are shown in Figure 4.11.

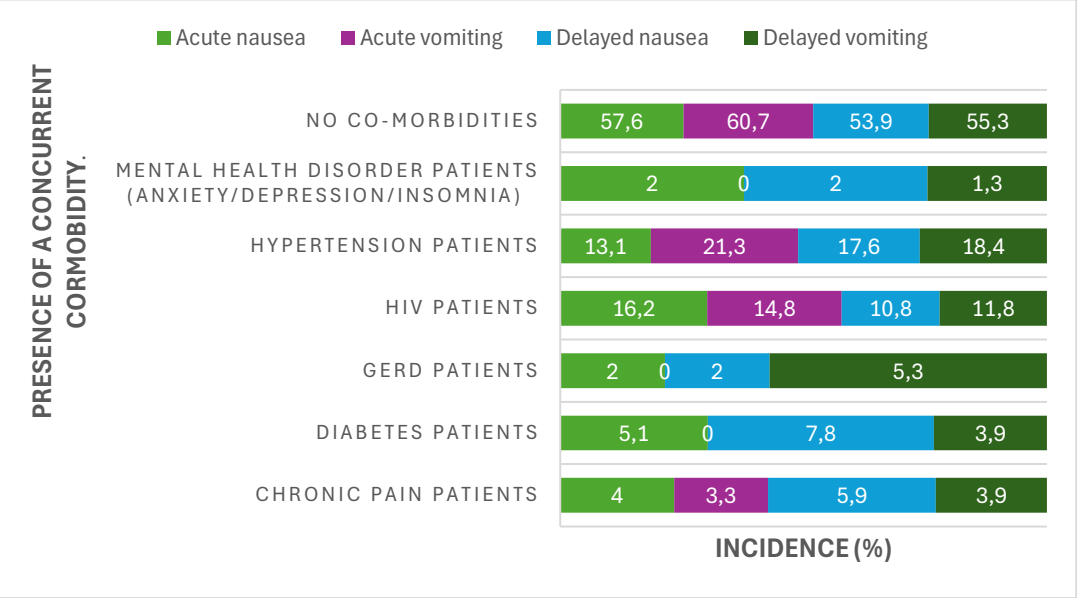

Figure 4.11: The impact of concurrent chronic conditions on the incidence of acute and delayed CINV. *†‡ §

The presence of a concurrent chronic condition was not significantly associated with acute nausea (p=0.227).

† A significant association was observed between specific chronic conditions and acute vomiting (p=0.039).

‡ Chronic conditions did not significantly impact delayed nausea rates (p=0.464).

§ No significant association was found between chronic conditions and delayed vomiting rates (p=0.642).

Approximately 50.9% of patients were not using any prescription medications, while 49.1% were on prescription medications. The analysis revealed a statistically significant difference in the incidence of CINV based on medication use (p= 0.047). Among those taking medication, the reported medications included antidepressants (2.3%), antiretroviral drugs (ARVs) (13.5%), diabetes medications (6.8%), GERD medications (3.2%), antihypertensive medications

(19.8%), and opioids (3.6%). No statistically significant difference was found between CINV incidence based on the specific type of medication used (Appendix I).

The use of prescription medications for another chronic condition did not significantly impact the incidence of acute nausea (p = 0.215), however, it did have a statistically significant impact on acute vomiting (p = 0.039). Prescription medication use did not significantly affect the rates of delayed nausea (p=0.464) or delayed vomiting (p=0.676). Table 4.12 demonstrates the impact of different prescription medications on acute and delayed CINV.

Table 4.12: The effect of prescription medications on acute and delayed CINV.

Types of prescription medications	**No acute nausea**	**Acute nausea**	**No acute vomiting**	**Acute vomiting**	**No delayed nausea**	**Delayed nausea**	**No delayed vomiting**	**Delayed vomiting**
	N (%)	**N (%)**	**N (%)**	**N (%)**	**N (%)**	**N (%)**	**N (%)**	**N (%)**
Antidepressants (Fluoxetine/citalopram/ diazepam/amitriptyline)	3 (2.4)	2 (2.0)	5 (3.1)	0 (0.0)	3 (2.5)	2 (2.0)	4 (2.7)	1 (1.3)
ARVs	14 (11.4)	16 (16.2)	21 (13.0)	9 (14.8)	19 (15.8)	11 (10.8)	21 (14.4)	9 (11.8)
Diabetes medications (Metformin)	10 (8.1)	5 (5.1)	15 (9.3)	0 (0.0)	7 (5.8)	8 (7.8)	12 (8.2)	3 (3.9)
GERD treatment (cimetidine/PPI)	5 (4.1)	2 (2.0)	7 (4.3)	0 (0.0)	5 (4.2)	2 (2.0)	3 (2.1)	4 (5.3)
Hypertension medication	31 (25.2)	13 (13.1)	31 (19.3)	13 (21.3)	26 (21.7)	18 (17.6)	30 (20.5)	14 (18.4)
Opioids (Tramadol/Morphine)	4 (3.3)	4 (4.0)	6 (3.7)	2 (3.3)	2 (1.7)	6 (5.9)	5 (3.4)	3 (3.9)
No comorbidities	56 (45.5)	57 (57.6)	76 (47.2)	60.7	58 (48.3)	55 (53.9)	71 (48.6)	42 (55.3)
Total (n=222)	123 (100.0)	99 (100.0)	161 (100)	61 (100.0)	120 (100.0)	102 (100.0)	146 (100.0)	76 (100.0)
P-value (Fischer's exact test)	p=0.215		p = 0.039		p= 0.464		p=0.676	

Overall, 55.4% of patients reported not using any non-prescription medications, while 44.6% reported using them. There was no significant difference in the incidence of CINV based on the use of non-prescription medications (p=0.597). Among those using non-prescription medications, 33.8% were taking analgesics or antipyretics (such as paracetamol, aspirin, or ibuprofen), 2.7% were taking antihistamines, and 8.1% were using vitamins (B, C, D, magnesium). There was no significant difference in overall CINV incidence based on the type of non-prescription medication used (p=0.455) (Appendix I).

The use of non-prescription medications did not significantly impact the prevalence of acute vomiting (p=0.578). However, a significant association was observed between non-prescription medication use and acute nausea (p=0.048), with patients currently using analgesics reporting a higher incidence (32.3%) in comparison to other medications. Additionally, the use of non-prescription medications did not significantly affect the rates of delayed nausea (p=0.753) or delayed vomiting (p=0.860). The findings on the effect of non-prescription medication use on acute and delayed CINV are demonstrated in Table 4.13.

Table 4.13: The effect of non-prescription medication on acute and delayed CINV.

Types of non-prescription medications	**No acute nausea**	**Acute nausea**	**No acute vomiting**	**Acute vomiting**	**No delayed nausea**	**Delayed nausea**	**No delayed vomiting**	**Delayed vomiting**
	N (%)	**N (%)**	**N (%)**	**N (%)**	**N (%)**	**N (%)**	**N (%)**	**N (%)**
Analgesics/Antipyretics (paracetamol/aspirin/ ibuprofen)	43 (35.0)	32 (32.3)	58 (36.0)	17 (27.9)	41 (34.2)	34 (33.3)	49 (33.6)	26 (34.2)
Antihistamines	0 (0.0)	6 (6.1)	4 (2.5)	2 (3.3)	2 (1.7)	4 (3.9)	3 (2.1)	3 (3.9)
Vitamins (b,c,d,magnesium)	10 (8.1)	8 (8.1)	14 (8.7)	4 (6.6)	9 (7.5)	9 (8.8)	12 (8.2)	6 (7.9)
Patient did not take non-prescription medications	70 (56.9)	53 (53.5)	85 (52.8)	38 (62.3)	68 (56.7)	55 (53.9)	82 (56.2)	41 (53.9)
Total (n=222)	123 (100.0)	99 (100.0)	161 (100.0)	61 (100.0)	120 (100.0)	102 (100.0)	146 (100.0)	76 (100.0)
P-value (chi-square test)	p=0.048		p = 0.578		p= 0.753		p=0.860	

4.6.14 Eating habits

Approximately 81.1% of patients reported consuming a meal before chemotherapy, while 18.9% did not. The incidence of CINV was similar between those who had eaten and those who had not, indicating no significant difference (p=0.964). Among those who consumed a meal, 27.5% ate a heavy meal (high in fats, carbohydrates, proteins, and processed sugars), while 53.6% consumed a light meal (lower in proteins, carbohydrates, fats, and processed sugars). There was no significant difference in overall CINV incidence based on the type of meal consumed (p=0.734) (Appendix I). The type of meal eaten was neither a contributing factor to acute nausea (p=0.085) nor acute vomiting (p=0.096). Similarly, there was no association between the meal eaten and delayed nausea (p=0.196) or delayed vomiting (p=0.515). Figure 4.12 illustrates the impact of the type of meal consumed on the incidence of acute and delayed CINV.

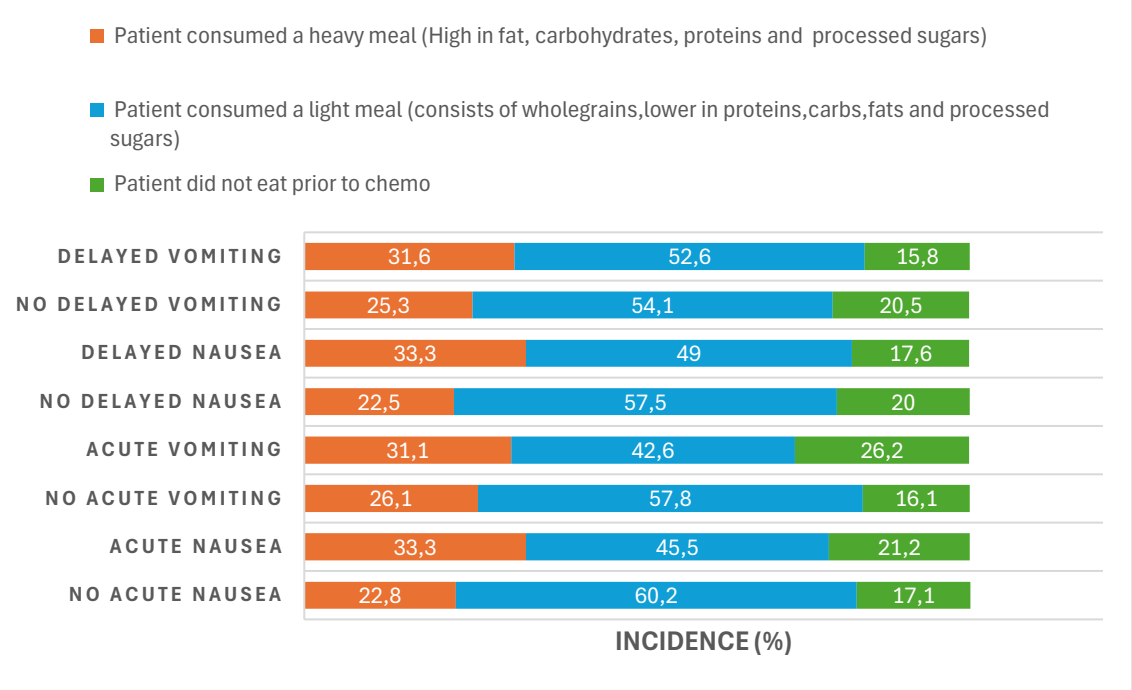

Figure 4.12: The effect of type of meal consumed on acute and delayed CINV incidence. *†‡ §

**The type of meal consumed was not significantly associated with acute nausea (p=0.085).*

† No significant association was found between the type of meal and acute vomiting (p=0.096).

‡ The type of meal did not significantly impact delayed nausea (p=0.196).

§ No significant relationship was observed between the type of meal and delayed vomiting (p=0.515).

4.6.15 Smoking history and marijuana use

The relationship between smoking and CINV was analysed among patients, with 68% reporting that they had never smoked, 17.6% identifying as former smokers, and 14.4% as current smokers. The analysis indicated no significant difference in CINV incidence based on smoking

status (p=0.136). Among current smokers, 6.3% smoked 1-9 cigarettes per day, and 8.1% smoked 10-20 cigarettes per day. No statistically significant difference in CINV incidence based on the number of cigarettes smoked was observed (p=0.231). Among former smokers, 11.3% had smoked 1-9 cigarettes per day, and 6.3% had smoked 10-20 cigarettes per day. However, the relationship between the number of cigarettes smoked by former smokers and the incidence of CINV was not statistically significant (p=0.199). Marijuana use was reported by 5.9% of participants, with 78.8% never having used marijuana and 15.3% being former users. A statistically significant difference in CINV incidence was observed based on marijuana use (p=0.014). Former and current marijuana users were more likely to experience isolated nausea or nausea with vomiting and were less likely to be asymptomatic compared to those who never used marijuana (Appendix I).

Smoking status was not significantly associated with acute nausea (p=0.083). While it did not have a statistically significant effect on the incidence of acute vomiting (p=0.073), non-smokers experienced a higher proportion of cases, accounting for 57.4%. Additionally, non-smokers exhibited the highest number of cases of delayed nausea, although this association was not statistically significant (p=0.637). Former smokers, on the other hand, had the lowest incidence of delayed vomiting (18.4%), however, this observation was not statistically significant (p=0.104). These findings are depicted in Figure 4.13.

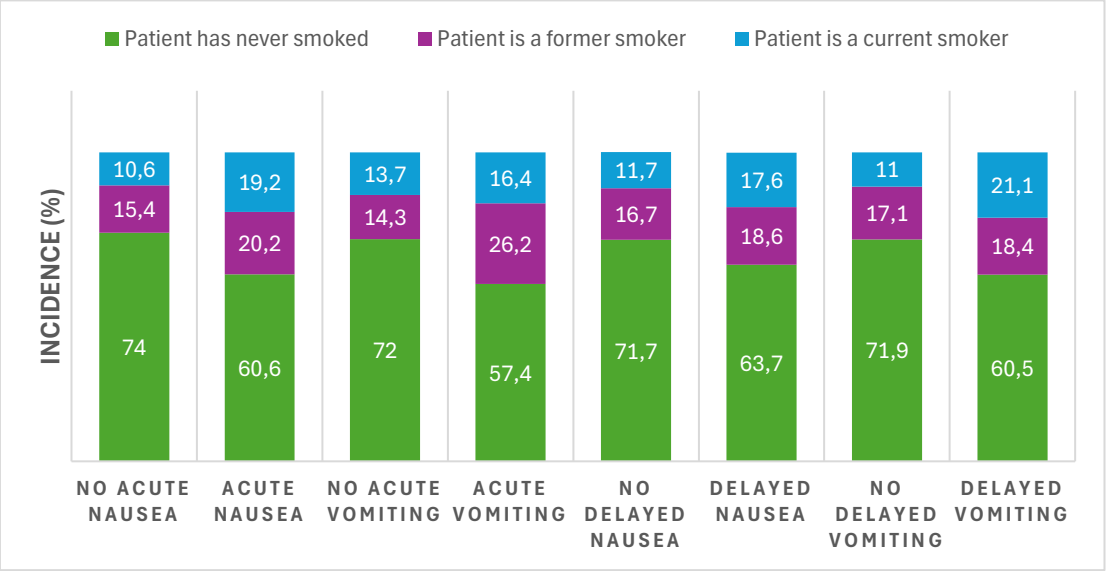

Figure 4.13: The effect of smoking status on the incidence of acute and delayed CINV. *†‡ §

**Smoking status was not significantly associated with acute nausea (p=0.083).*

† No statistically significant association was found between smoking status and acute vomiting, though non-smokers reported a higher proportion of cases (p=0.073).

‡ Smoking status did not significantly impact delayed nausea (p=0.637).

§ Former smokers had the lowest incidence of delayed vomiting, but this finding was not statistically significant (p=0.104).

In contrast, marijuana use demonstrated a statistically significant association with acute nausea (p=0.006). While marijuana use did not significantly impact the incidence of acute vomiting (p=0.053) or delayed vomiting (p=0.123), former users demonstrated a 7.9% increase in delayed nausea rates, and current users showed a 7.3% increase. This difference was statistically significant (p=0.012). The effects of marijuana use on acute and delayed CINV are presented in Figure 4.14.

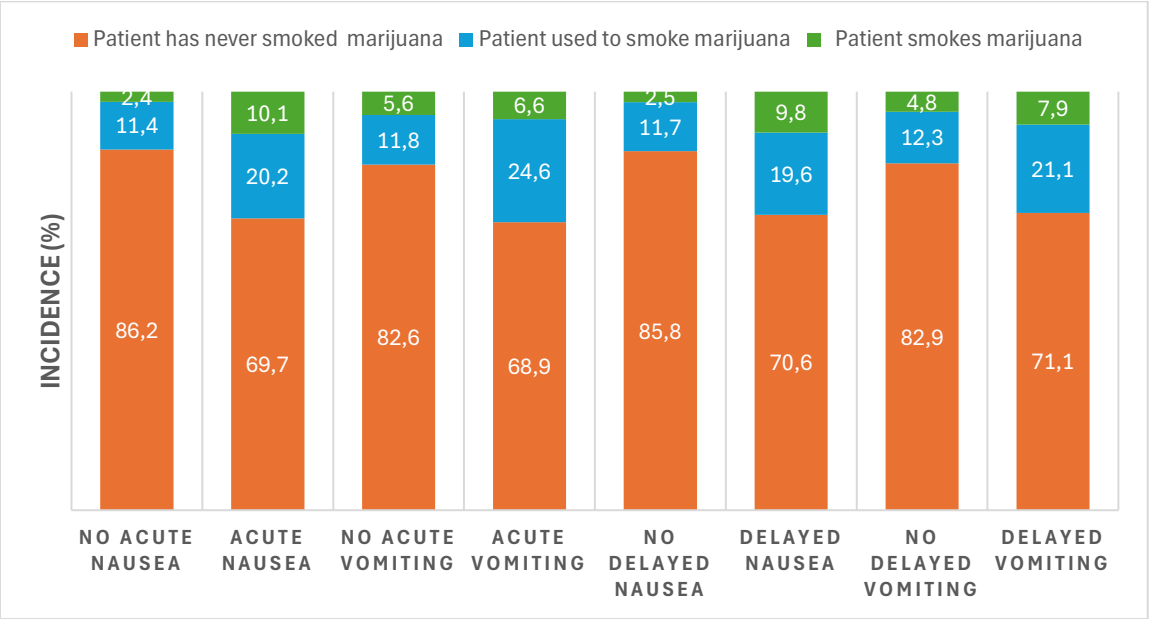

Figure 4.14: The effect of marijuana use on the incidence of acute and delayed CINV. *†‡ §

**Marijuana use was significantly associated with acute nausea (p=0.006).*

† Marijuana use did not significantly impact acute vomiting (p=0.053).

‡ A statistically significant association was found between marijuana use and delayed nausea, with higher rates among former and current users (p=0.012).

§ Marijuana use was not significantly associated with delayed vomiting (p=0.123).

The data presented in Table 4.14 indicates that the number of cigarettes smoked was not significantly associated with acute nausea (p=0.170), acute vomiting (p=0.140), delayed nausea (p=0.495), or delayed vomiting (p=0.209). Patients who reported smoking 10-20 cigarettes a day experienced higher rates of acute nausea (11.1%), delayed nausea (10.8%), and delayed vomiting (11.8%) in comparison to patients who smoked 1-9 cigarettes per day. The prevalence of acute vomiting was the same across these two groups. Despite these variations, none of the observations were statistically significant.

Table 4.14: The effect of number of cigarettes smoked on the incidence of acute and delayed CINV.

Number of cigarettes smoked	No acute nausea	Acute nausea	No acute vomiting	Acute vomiting	No delayed nausea	Delayed nausea	No delayed vomiting	Delayed vomiting
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
1-9 cigarettes	6 (4.9)	8 (8.1)	9 (5.6)	5 (8,2)	7 (5.8)	7 (6.9)	7 (4.8)	7 (9.2)
10-20 cigarettes	7 (5.7)	11 (11.1)	13 (8.1)	5 (8.2)	7 (5.8)	11 (10.8)	9 (6.2)	9 (11.8)
Patient is a former smoker	19 (15.4)	20 (20.2)	23 (14.3)	16 (26.2)	20 (16.7)	19 (18.6)	25 (17.1)	14 (18.4)
Patient has never smoked	91 (74.0)	60 (60.6)	116 (72.0)	35 (57.4)	86 (71.7)	65 (63.7)	105 (71.9)	46 (60.5)
Total (n=222)	123 (100.0)	99 (100.0)	161 (100.0)	61 (100.0)	120 (100.0)	102 (100.0)	146 (100.0)	76 (100.0)
P-value (Chi-square test)	p =0.170		p=0.140		p=0.495		p=0.209	

4.6.16 Complementary/alternative treatments for CINV

The use of non-pharmacological interventions for managing CINV was analysed, categorising lemon water, peppermint tea, and moringa as "complementary treatments," while aromatherapy, meditation, acupuncture, and music therapy were grouped under "alternative therapies." Ginger use was examined as a separate category.

In this study, 5.0% of patients reported using alternative therapies, 8.6% used complementary treatments, and the majority, 86.5%, did not use any complementary or alternative therapies. A statistically significant difference in CINV incidence was observed based on the use of complementary and alternative therapies (p=0.011). Additionally, 15.3% of participants used ginger to alleviate CINV, while 84.7% did not. The analysis revealed a statistically significant difference in CINV incidence associated with ginger use (p=0.018), suggesting that ginger may influence the CINV experience among patients (Appendix I).

The use of complementary and alternative therapies was significantly associated with higher rates of acute nausea (p=0.029) and acute vomiting (p=0.011). In the ginger use group, a 16.1% increase in acute nausea was observed (p=0.001), however, use of ginger did not significantly impact acute vomiting (p=0.267). While the use of complementary and alternative therapies

showed a trend towards significance for delayed vomiting rates (p=0.073), ginger use was significantly associated with delayed vomiting (p=0.035). Notably, a higher percentage of patients who used ginger to alleviate delayed vomiting (22.4%) continued to experience this symptom compared to those who found relief with ginger (11.6%). Furthermore, complementary and alternative therapy use did not exhibit a statistically significant association with delayed nausea rates (p=0.053), however, the use of ginger demonstrated a significant association (p=0.002). Figures 4.15 and 4.16 illustrate the impact of complementary/alternative treatments and ginger on acute and delayed CINV, respectively.

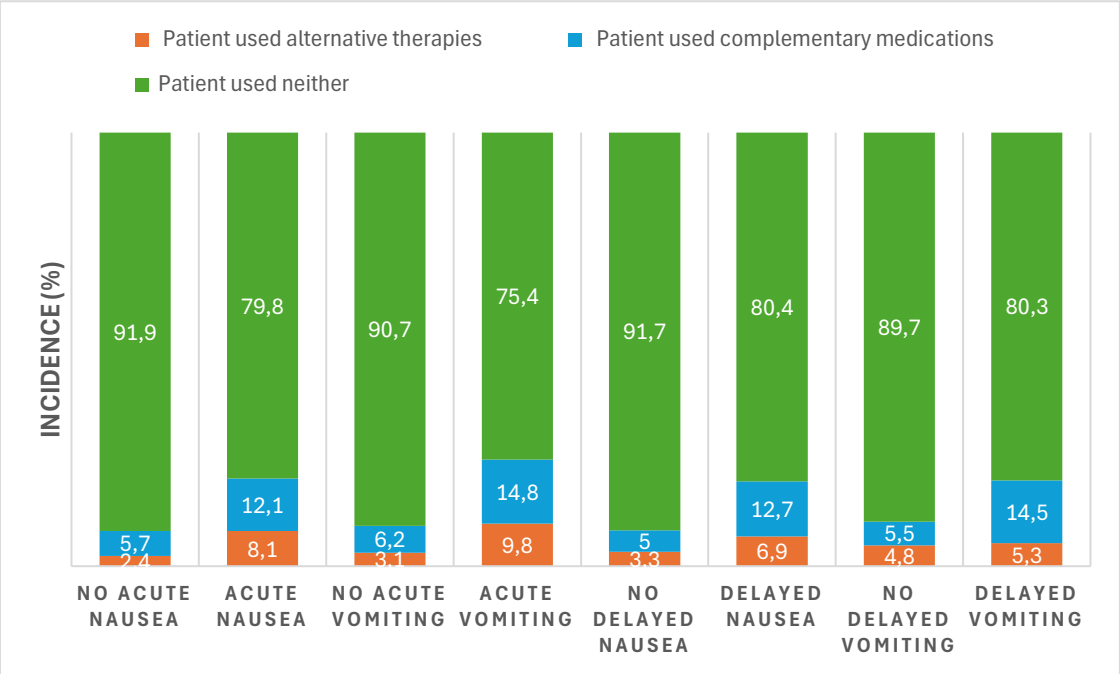

Figure 4.15: The impact of complementary/alternative treatments on acute and delayed CINV.

*†‡ §

**Complementary and alternative therapy use was significantly associated with higher rates of acute nausea (p=0.029).*

† A significant association was observed between complementary therapy use and acute vomiting (p=0.011).

‡ Complementary therapy use showed a trend towards significance for delayed vomiting (p=0.073).

§ Complementary therapy use was not significantly associated with delayed nausea (p=0.053).

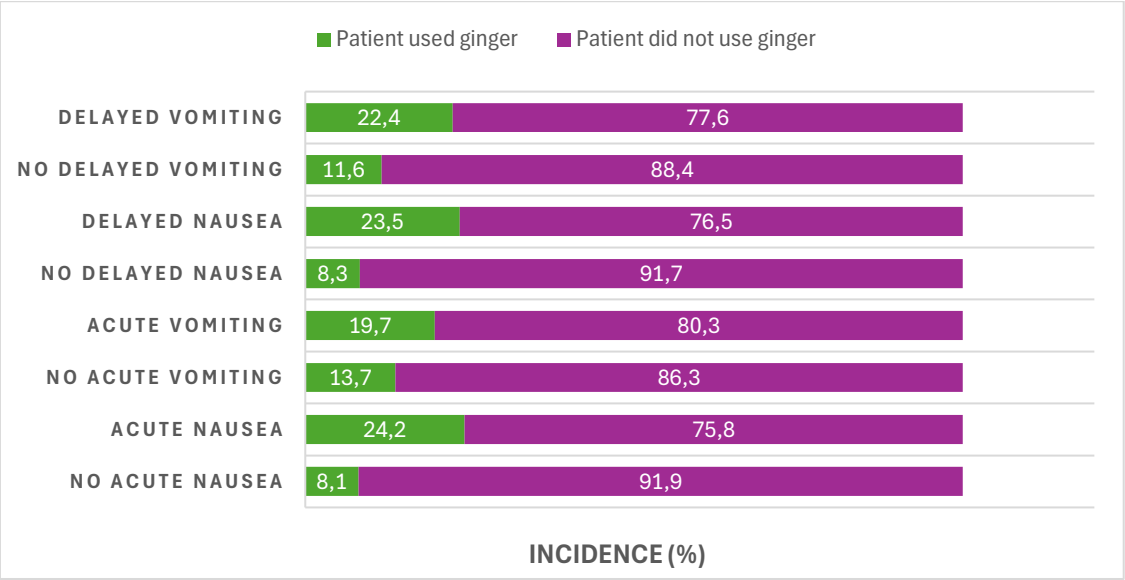

Figure 4.16: The impact of ginger use on the incidence of acute and delayed CINV. *†‡ §

**Ginger use was significantly associated with higher rates of acute nausea (p=0.001).*

† Ginger use did not significantly impact the incidence of acute vomiting (p=0.267).

‡ A significant association was observed between ginger use and delayed vomiting (p=0.035).

§ Ginger use was significantly associated with delayed nausea (p=0.002).

4.6.17 BMI

Prior to chemotherapy administration, nurses collected anthropometric data such as height and weight. Patients were asked to provide their height and weight to facilitate the calculation of BMI, as this information was not documented on the prescription. However, two patients were unable to recall their height, resulting in the analysis being restricted to 220 patients for this specific variable. BMI categories were defined using standard criteria: underweight (<18.5), healthy weight (18.5–24.9), overweight (25–29.9), and obese (≥ 30) (Weir and Jan, 2023). The study found no statistically significant differences in CINV incidence across BMI categories (p= 0.229). However, an interesting trend emerged: patients with a healthy weight and those who were obese experienced comparable proportions of nausea (40% and 36%, respectively). Similarly, rates of nausea accompanied by vomiting were nearly identical between healthy weight and overweight patients (36% and 39%, respectively). Underweight patients reported a remarkably lower prevalence of CINV compared to other groups (nausea: 4%; nausea with vomiting: 3%) (Appendix I).

BMI was not significantly associated with acute nausea (p=0.523), although a higher prevalence was observed among patients with a healthy BMI (41.4%). Similarly, BMI did not significantly impact acute vomiting rates (p=0.125), however, there was a slight trend suggesting a higher incidence among overweight (37.7%) and healthy weight (44.3%) patients. Regarding delayed CINV, BMI did not significantly affect delayed vomiting rates, with similar rates reported

across all BMI categories, except the underweight category (p=0.669). While higher incidences of delayed nausea were reported among patients with a healthy BMI (39.2%) and those who were overweight (30.4%), these observations were not statistically significant (p=0.856). Table 4.15 demonstrates the effect of BMI on acute and delayed CINV.

Table 4.15: The effect of BMI on the incidence of acute and delayed CINV.

BMI Category	No acute nausea	Acute nausea	No acute vomiting	Acute vomiting	No delayed nausea	Delayed nausea	No delayed vomiting	Delayed vomiting
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
18.5-24.9 (Healthy weight)	44 (36.4)	41 (41.4)	58 (36.5)	27 (44.3)	45 (38.1)	40 (39.2)	57 (39.6)	28 (36.8)
25-29.9 (Overweight)	43 (35.5)	30 (30.3)	50 (31.4)	23 (37.7)	42 (35.6)	31 (30.4)	44 (30,6)	29 (38.2)
< 18.5 (Underweight)	6 (5)	2 (2)	8 (5)	0 (0)	4 (3,4)	4 (3.9)	5 (3,5)	3 (3.9)
≥30 (Obese)	28 (23.1)	26 (26.3)	43 (27)	11 (18)	27 (22.9)	27 (26.5)	38 (26,4)	16 (21.1)
Total (n=220)	121 (100)	99 (100)	159 (100)	61 (100)	118 (100)	102 (100)	144 (100)	76 (100)
P-value (Fischer's exact test)	p=0.523		p= 0.125		p=0.856		p=0.669	

4.7 Bivariate Analysis of Risk Factors that Affect the Incidence of CINV During the Overall Phase

Significant factors identified through Fischer's exact test and chi-square tests were further analysed using a bivariate approach to assess how strongly each risk factor was associated with CINV. The factors assessed included race, adherence to antiemetic treatment protocols, anticipatory nausea and vomiting, history of motion sickness, alcohol consumption and frequency, presence of concurrent chronic conditions, use of prescription medications, marijuana use, and the use of ginger to alleviate CINV. The baseline outcome for the analysis was patients who experienced no nausea and vomiting.

Among Black patients, it was observed that the majority did not experience symptoms (72.2%). The analysis revealed that White patients were significantly more likely to experience these symptoms, being 3.4 times more likely to experience isolated nausea (p = 0.013) and 3.0 times

more likely to have nausea with vomiting (p = 0.007), compared to Black patients. Non-adherence to the antiemetic treatment protocol emerged as another critical risk factor, with a significantly higher risk of both nausea (cRRR = 0.05, p = 0.001) and nausea with vomiting (cRRR = 0.05, p = 0.001). Patients who often or sometimes anticipated CINV were found to have a markedly higher risk of experiencing these symptoms compared to those who rarely anticipated it. Conversely, factors such as concurrent comorbidities, alcohol consumption, and use of prescription medications did not show significant associations with CINV outcomes.

The analysis also highlighted that former marijuana users were 3.3 times more likely to experience only nausea and 3.61 times more likely to experience nausea with vomiting. Current marijuana smokers faced an even higher risk, being 9.17 times more likely to experience only nausea and 6.33 times more likely to experience nausea with vomiting than non-users. Interestingly, not using ginger was linked to a lower risk of experiencing both isolated nausea and nausea accompanied by vomiting. These findings are presented in Table 4.16.

Table 4.16: Bivariate analysis of risk factors associated with the incidence of CINV (overall phase).

	Only nausea			Nausea and vomiting		
Variable	**cRRR**	**95%CI**	**P-Value**	**cRRR**	**95%CI**	**P-value**
Race						
Black	***REF**	**REF**	**REF**	**REF**	**REF**	**REF**
Indian/Coloured	2.4	0.87-6.7	0.092	1.9	0.79-4.71	0.151
White	3.4	1.27-7.9	0.013	3.0	1.35-6.51	0.007
Adherence to antiemetic guidelines						
Regimen adhered to guidelines.	**REF**	**REF**	**REF**	**REF**	**REF**	**REF**
The regimen did not adhere to guidelines.	0.05	0.012-0.25	0.000	0.05	0.012-0.22	0.000
Experiencing anticipatory nausea and vomiting (ANV)						
The patient rarely experienced ANV.	**REF**	**REF**	**REF**	**REF**	**REF**	**REF**
Patient often experienced ANV.	5.19	1.49-18.12	0.010	8.36	2.71-25.80	0.000
Patient sometimes experienced ANV.	2.07	0.86-4.99	0.102	2.94	1.39-6.20	0.005
History of motion sickness						
The patient did not have a history of motion sickness.	**REF**	**REF**	**REF**	**REF**	**REF**	**REF**
The patient did have a history of motion sickness.	11.05	2.35-51.98	0.002	23.33	5.41-100.61	0.000
Consumption of alcohol						
The patient does not consume alcohol.	**REF**	**REF**	**REF**	**REF**	**REF**	**REF**
The patient consumes alcohol.	1.67	0.80-3.46	0.171	0.68	0.36-1.30	0.242

	Only nausea			Nausea and vomiting		
Variable	**cRRR**	**95%CI**	**P-Value**	**cRRR**	**95%CI**	**P-value**
Frequency of alcohol of alcohol consumption						
1-3 times per month	**REF**	**REF**	**REF**	**REF**	**REF**	**REF**
1-6 times per week	0.51	0.16-1.60	0.245	0.64	0.20-2.10	0.464
The patient does not drink.	0.44	0.17-1.10	0.080	1.58	0.63-3.94	0.329
The patient rarely drinks.	0.79	0.09-6.5	0.823	4.5	0.79-25.77	0.091
Presence of a concurrent comorbidity						
The patient does not have another comorbidity.	**REF**	**REF**	**REF**	**REF**	**REF**	**REF**
The patient has another comorbidity.	1.54	0.74-3.22	0.247	0.66	0.36-1.21	0.178
Prescription medications use						
The patient does not use other prescription medications.	**REF**	**REF**	**REF**	**REF**	**REF**	**REF**
The patient does use other prescription medications.	1.54	0.74-3.21	0.247	0.66	0.36-1.21	0.178
Marijuana use						
The patient has never smoked marijuana.	**REF**	**REF**	**REF**	**REF**	**REF**	**REF**
The patient used to smoke marijuana.	3.3	1.03-10.59	0.045	3.61	1.28-10.18	0.015
The patient does smoke marijuana.	9.17	1.03-81.50	0.047	6.33	0.76-52.81	0.088
Ginger use to alleviate CINV						
Patient uses ginger	**REF**	**REF**	**REF**	**REF**	**REF**	**REF**
The patient does not use ginger.	0.27	0.078-0.93	0.037	0.22	0.07-0.68	0.008

***REF-** *Reference Category, against which the relative risk ratios (RRR) of other categories are compared*

4.8 Multivariate Analysis of Risk Factors that Affect the Incidence of CINV During the Overall Phase

A multivariate analysis was conducted to identify risk factors influencing CINV. Significant factors were identified through bivariate analysis. These factors were subsequently included in the multivariate model. To ensure model stability and optimal fit, the AIC was employed, with the model yielding the lowest AIC value being selected as the final model. It is important to note that not all significant factors from the bivariate analysis were included in the final multivariate model, as the selection process aimed to achieve a more efficient model with the best possible fit by minimising the AIC.

White patients were three times more likely to experience isolated nausea compared to Black patients (95% CI: 1.02–8.84; p = 0.045). In contrast, the "*Other (Indian/Coloured)*" category did not demonstrate a significant association (p = 0.495). For nausea with vomiting, neither the *"Other (Indian/Coloured)"* category (Relative risk ratio [RRR]=1.09; 95% CI: 0.33–3.61; p = 0.887) nor the White group (RRR=1.93; 95% CI: 0.71–5.26; p = 0.198) differed significantly from Black patients. This suggests race may influence experiencing isolated nausea, particularly among White patients, but not both symptoms.

Adherence to antiemetic guidelines was a significant protective factor against both nausea alone and combined nausea and vomiting. Patients whose regimens adhered to the guidelines were significantly less likely to experience nausea alone (RRR =0.03, 95% CI: 0.006-0.141, $p < 0.001$) and combined nausea and vomiting (RRR = 0.02, 95% CI: 0.004-0.100, $p < 0.001$), compared to those whose regimens did not adhere to the guidelines. ANV was also a significant factor. Patients who often experienced ANV were 5.08 times more likely to experience nausea alone ($p = 0.029$) and 6.53 times more likely to experience combined nausea and vomiting ($p = 0.006$). Patients who sometimes experienced ANV had a marginal association with combined nausea and vomiting (RRR = 3.47, 95% CI: 1.37-8.82, $p = 0.009$), though the association was not statistically significant for nausea alone ($p = 0.085$).

A history of motion sickness was another significant predictor. Patients with a history of motion sickness had a substantially increased risk of experiencing isolated nausea (RRR = 8.02, 95% CI: 1.52-42.41, $p = 0.014$) and nausea with vomiting (RRR = 12.81, 95% CI: 2.70-60.79, $p < 0.001$) compared to those without such a history. Former marijuana smokers were more than three times more likely to experience nausea compared to non-smokers (95% CI: 0.87–13.88; $p = 0.078$). Current marijuana smokers demonstrated an even greater risk (RRR: 8.47; 95% CI: 0.70–101.95; $p = 0.092$). Both former and current marijuana smokers exhibited a higher risk of nausea and vomiting compared to non-smokers. Former smokers were over three times more likely to experience these symptoms (95% CI: 0.93–12.36; $p = 0.065$), while current smokers had nearly twelve times the risk (RRR= 11.80; 95% CI: 0.99–140.33; $p = 0.051$). However, none of these findings reached statistical significance. Patients who used ginger to alleviate CINV were more likely to experience isolated nausea, though this was not statistically significant ($p = 0.085$). In contrast, the likelihood of experiencing combined nausea and vomiting was significantly higher in the ginger use group (RRR= 4.49; 95% CI: 1.21–16.70; $p = 0.025$) compared to patients who did not use ginger. Findings are summarised in Table 4.17.

Table 4.17: Multivariate analysis of risk factors that affect the incidence of CINV during the overall phase.

	Only nausea			Nausea and vomiting		
Variable	**RRR**	**95% CI**	**P-Value**	**RRR**	**95% CI**	**P-value**
Race						
Black	***REF**	**REF**	**REF**	**REF**	**REF**	**REF**
Other (Indian/Coloured)	1.55	0.44-5.48	0.495	1.09	0.33-3.61	0.887
White	3.01	1.02-8.84	0.045	1.93	0.71-5.26	0.198
Adherence to antiemetic guidelines						
The regimen did not adhere to the guideline.	**REF**	**REF**	**REF**	**REF**	**REF**	**REF**
The regimen adhered to the guideline.	0.03	0.006-0.141	0.000	0.02	0.004-0.100	0.000
Experiencing anticipatory nausea and vomiting (ANV)						
The patient rarely experienced ANV.	**REF**	**REF**	**REF**	**REF**	**REF**	**REF**
The patient experienced ANV often.	5.08	1.18-21.90	0.029	6.53	1.71-24.96	0.006
Patient sometimes experienced ANV.	2.44	0.88-6.71	0.085	3.47	1.37-8.82	0.009
History of motion sickness						
The patient does not have a history of motion sickness.	**REF**	**REF**	**REF**	**REF**	**REF**	**REF**
The patient does have a history of motion sickness	8.02	1.52-42.41	0.014	12.81	2.70-60.79	0.001
Marijuana use						
The patient does not smoke marijuana.	**REF**	**REF**	**REF**	**REF**	**REF**	**REF**
The patient used to smoke marijuana	3.47	0.87-13.88	0.078	3.39	0.93-12.36	0.065
The patient smokes marijuana	8.47	0.70-101.95	0.092	11.80	0.99-140.33	0.051
Ginger use to alleviate CINV						
The patient does not use ginger.	**REF**	**REF**	**REF**	**REF**	**REF**	**REF**
The patient uses ginger	3.47	0.84-14.35	0.085	4.49	1.21-16.70	0.025

***REF**: *Reference Category, against which the relative risk ratios (RRR) of other categories are compared.*

4.8 Chapter Summary

In summary, the study examined the incidence and risk factors associated with CINV across various demographic and clinical parameters. The analysis revealed that factors such as age, sex, cancer diagnosis, and chemotherapy regimen showed varied impacts on the incidence of CINV. Notably, race, the number of chemotherapy cycles, anticipatory nausea and vomiting, and the use of complementary therapies, including ginger were significant factors influencing CINV prevalence. The findings also highlighted the importance of considering patients' history of motion sickness, use of certain prescription and non-prescription medications while on chemotherapy and lifestyle factors like smoking, marijuana use and alcohol consumption in managing CINV. Adherence to antiemetic treatment protocols was also a critical factor in the management of this side effect. The study found that while most patients received appropriate antiemetic prophylaxis, there were instances of suboptimal adherence to recommended protocols. The next chapter will delve deeper into the implications of these findings, comparing them with existing literature, and discuss potential strategies for improving CINV management based on the study results.

CHAPTER 5

5. DISCUSSION

5.1 Introduction

The incidence of CINV experienced by patients with cancer and patient characteristics associated with an increased risk of CINV was investigated at a tertiary academic hospital in Johannesburg, South Africa. This chapter discusses the study findings on the prevalence of CINV in this cohort, the utilisation and efficacy of antiemetic regimens prescribed and the association of various risk factors on treatment-induced nausea and vomiting.

A large proportion of cancer patients undergoing chemotherapy remain afflicted with CINV, presenting a significant challenge for clinicians and a substantial burden on patients experiencing this adverse effect (Mosa et al., 2020). The prevalence of CINV exhibits variability across patient populations (Hesketh et al., 2017). This heterogeneity is primarily driven by the emetogenic potential of the administered chemotherapy regimen (Mosa et al.,2020). Moreover, the use of different antiemetic prophylaxis regimens and the presence of patient-related risk factors can also influence CINV incidence (Mosa et al., 2020; Aapro et al., 2022). While Dranistsaris et al. (2017) have made strides in developing a predictive algorithm for identifying high-risk CINV patients, research on patient-specific risk factors in the South African context remains limited. Notably, Smit, Kotze and Du Plessis (2021) investigated the prevalence of nausea (independent of vomiting) in this population, however, a comprehensive analysis of patient characteristics and their association with CINV is currently lacking.

5.2 Demographic Information

Our study sample exhibited a predominance of females (71.2%) compared to males (28.8%). The observed sex distribution aligns with national demographic trends, where females represent the majority of the population (Stats SA, 2022). Furthermore, national cancer incidence data from Stats SA (2018) indicates that females account for a higher proportion of diagnosed cancer cases (51.3%). This pre-existing disparity in cancer diagnoses between sexes may explain the observed gender imbalance in our sample population.

The racial composition of our study participants (57.2% Black, 26.6% White, 10.8% Coloured, and 5.4% Indian) partially reflects national demographic data (Stats SA, 2022). While Black Africans represent the majority population in South Africa, the current sample demonstrates a discrepancy in the representation of the Coloured and Indian populations compared to national

figures. The underrepresentation of Coloured and Indian populations in the study cohort might be elucidated by potential variations in cancer epidemiology across racial groups (National Cancer Registry, 2019). Furthermore, these observed discrepancies could also be influenced by socioeconomic disparities that impact access to early detection strategies, awareness of cancer signs and symptoms, and available treatment options (National Cancer Registry, 2019).

The age distribution of patients demonstrated that the 39–64-year-old group represented the largest proportion of the sample (Figure 4.2). This strategic grouping aligns with established epidemiological data demonstrating a significantly lower incidence of cancer in younger adults (aged 18-38 years). The National Cancer Registry data from South Africa corroborates this trend, with a reported median age of diagnosis at 59 years for females and 64 years for males (National Cancer Registry, 2019). Similarly, Roscoe et al. (2000) stratified patients into age groups to investigate differences in the incidence and management of CINV, recognising that physiological responses and treatment tolerability vary across age demographics, emphasising the importance of such groupings in clinical research.

5.3 The Incidence and Severity of CINV

This study demonstrated a high prevalence of CINV among patients receiving intravenous chemotherapy on antiemetic prophylaxis, with 27.5% of the cohort experiencing acute vomiting and 44.6% experiencing acute nausea. These percentages are higher than those reported by Aapro (2018), who found that in the presence of antiemetic prophylaxis, acute nausea occurs in up to 35% of patients and acute vomiting in 13%. The observed prevalence of delayed CINV in this study (34.2% for vomiting and 45.9% for nausea) (Table 4.3) aligns with findings reported by Grunberg et al. (2004) and Escobar et al. (2015) who demonstrated that 20-50% of patients still experience delayed phase CINV despite the employment of adequate antiemetic prophylaxis. Baburaj et al. (2017) reported comparable findings, with a significant proportion of patients experiencing acute nausea (54%) and acute vomiting (36.5%) despite the use of guideline-recommended antiemetic prophylaxis. However, their study observed a lower prevalence of delayed CINV (nausea: 15.5%, vomiting: 14.5%) compared to the current investigation (Table 4.3). This difference could be attributed to the difference in antiemetic agents used as NK-1 RAs are not utilised in the South African public sector for the treatment of CINV.

Bouganim et al. (2012) found that 17.7% of patients experienced grade 2 CINV, characterised by more than mild nausea and more than a single episode of vomiting, during the acute phase, with 18.2% affected during the delayed phase. Bouganim et al. (2012) also identified moderate-to-severe nausea as the dominant symptom among patients experiencing CINV. In line with these findings, our study revealed that a notable number of patients endured multiple episodes of acute vomiting, and a significant portion suffered from moderate-to-severe nausea (Table 4.3). Similarly, delayed phase CINV posed substantial challenges, with a considerable percentage of patients reporting frequent vomiting episodes and moderate-to-severe nausea.

5.4 Influence of Chemotherapy Regimen Emetogenicity on CINV Prevalence

Patients received chemotherapy regimens with varied emetogenicities. Our study did not reveal a statistically significant association between emetogenicity and CINV prevalence (p=0.765). LEC and MinEC are considered distinct categories when assessing CINV risk. However, due to the limited number of patients receiving MinEC in our study, we were unable to analyse them as a separate group. Despite this, the lack of association between emetogenicity and CINV outcomes may not solely be attributed to the distinction between LEC and MinEC, as broader factors such as limited sample size and the heterogeneity in patient populations and antiemetic regimens are likely to have played a more significant role in obscuring potential differences in CINV risk. Dranitsaris et al. (2017) have similarly argued that, in real-world settings, patient variability and differences in antiemetic prophylaxis make it challenging to statistically differentiate the effects of emetogenicity on the prevalence and severity of CINV. Pirri et al. (2013) and Fraunholz et al. (2011) implicated the type of chemotherapy as a CINV risk factor. However, these studies did not account for the heterogeneity in antiemetic regimens based on chemotherapy type which can also influence CINV incidence. These differences in prophylactic treatment could have significantly impacted CINV outcomes, making it difficult to isolate the effect of chemotherapy type alone. Future research should focus on larger patient cohorts where patient-related factors are controlled to avoid confounding results. This approach would allow for a clearer understanding of whether emetogenicity alone affects CINV risk.

D'Souza et al. (2020) identified a gap in knowledge regarding the comprehensive characterisation of CINV incidence. This review highlighted that existing observational studies often focus solely on patients receiving HEC regimens. These studies reported CINV incidence rates ranging from 15% to 70% but may not be generalisable to a broader population due to the exclusion of patients receiving moderately or low emetogenic chemotherapy. D'Souza et al.

(2020) also determined that 25% of patients receiving MEC exhibited an elevated susceptibility to developing CINV, which aligns with the findings of the current study where patients on MEC experienced the highest rates of isolated nausea (40%) and nausea with vomiting (50%) during the overall phase, however, this observation was not statistically significant (p=0.765). Nevertheless, it is worth noting that the risk model employed by D'Souza et al. (2020) incorporated patient factors other than emetogenicity and it cannot be definitively concluded that emetogenicity solely affects the outcome of CINV, further highlighting the complexity of this adverse effect.

5.5 Antiemetic Prophylaxis Regimens and Adherence to Treatment Protocols

Several international guidelines have been established to guide clinicians in the selection of the most appropriate antiemetic regimen based on the emetogenic potential of the chemotherapy regimen and evidence-based recommendations (Escobar et al., 2015). In the South African public sector, availability, cost-effectiveness and the public healthcare budget dictate medications that are included in treatment protocols and may not always align with international guidelines and recommendations (NDoH, 2020). The national EML, however, utilises the WHO EML list as a guidance document and tailors treatment lists according to local need (World Health Organization, 2023). In contrast, the private sector offers more medication options, which are largely determined by medical aid formularies (Perumal-Pillay and Suleman, 2020). Antiemetic regimens employed at the tertiary academic hospital where the current study was conducted are reflected in Table 2.3. A key difference between the treatment protocol where the study was conducted, and international guidelines is the use of NK-1 RA's which are not utilised in the public sector due to the higher costs associated with this antiemetic agent.

The evaluation of antiemetic prescribing practices demonstrated a high rate of concordance, reducing the risk of CINV in these patients (p=0.001). Both bivariate and multivariate analyses underscored the critical importance of adherence to antiemetic guidelines in managing CINV. The bivariate analysis revealed that non-adherence to the antiemetic treatment protocol significantly increased the risk of both isolated nausea and combined nausea and vomiting (p<0.001). Similarly, the multivariate analysis further confirmed that patients whose regimens adhered to the guideline had a markedly lower risk of experiencing these symptoms (p<0.001). These findings collectively highlight the protective effect of guideline adherence and emphasise the need for strict compliance with antiemetic protocols to effectively reduce the incidence of CINV. Gilmore et al. (2014) evaluated 1295 chemotherapy-naive patients and found that those

receiving guideline-concordant antiemetic care had significantly better outcomes in preventing CINV compared to those receiving guideline-inconsistent care, which is consistent with the findings of our study (Figure 4.1). Over the 5 days following chemotherapy, the incidence of CINV-free outcomes was higher in the guideline-compliant group compared to the guideline-inconsistent group (53.4% vs. 43.8%; $p < 0.001$) (Gilmore et al., 2014). After adjusting for confounding variables, patients receiving treatments that adhered to guidelines therapy were 1.31 more likely to not experience any CINV (95% CI: 1.07–1.69; $p = 0.037$), demonstrating a significant protective effect of guideline adherence (Gilmore et al., 2014). Aapro et al. (2022) demonstrated similar findings, further underscoring the critical role of following antiemetic guidelines in reducing CINV.

The discretion observed in patients not receiving antiemetics according to treatment guidelines in the current study may reflect clinical decisions to incorporate rescue antiemetics, such as oral 5HT3 receptor antagonists or metoclopramide, for those receiving MEC or LEC/MinEC. Although additional antiemetics were prescribed, they may not have been administered optimally, as these ongoing symptoms of breakthrough CINV persisted without adequate relief. These observations suggest a potential lack of efficacy of the additional antiemetic regimens employed in these patients for managing CINV. However, improper use or non-compliance with prescribed oral antiemetics by patients may also be a contributing factor to the occurrence of CINV (Aapro et al., 2018).

In accordance with international guidelines, the addition of either an oral 5HT-3 RA or metoclopramide for patients on LEC still experiencing CINV concurs with the treatment facility's choice of rescue antiemetics suggesting that there may be an interplay of other factors causing CINV in these patients (Helsinn, 2019). However, for patients on MEC, the NCCN recommends the use of an NK-1 RA in patients who experience antiemetic treatment failure (Helsinn, 2019). The current study highlights potential limitations in the efficacy of the existing antiemetic regimens used at the study site, particularly for patients receiving MEC or HEC requiring additional therapy. The data concurs with research by Elhassan et al. (2017) and Navari and Schwartzberg (2018), who suggest that the incorporation of NK-1 RAs into antiemetic protocols for patients receiving either HEC or MEC could significantly improve CINV control. The findings from this study, coupled with the existing evidence, suggest that the implementation of NK-1 RAs as part of the treatment protocols at the research site warrants further investigation and consideration.

For HEC, only a single patient received the correct antiemetic regimen. Notably, the majority of the patients who received HEC still experienced nausea and vomiting yet did not receive guideline-concordant rescue therapy with medications like olanzapine and oral corticosteroids (Table 4.5). There was a statistically significant association between non-adherence to the antiemetic protocol of the treatment facility and CINV incidence ($p = 0.001$). Non-adherence to established clinical guidelines is a significant problem, as highlighted by Hilarius et al. (2012). This issue can be further compounded by clinician overestimation of CINV control, particularly in patients receiving HEC, as suggested by Jordan et al. (2015). Fernandez-Ortega et al. (2012) reinforces this concern, demonstrating that low adherence rates to treatment guidelines are associated with poor patient outcomes. These findings as well as the findings of our study emphasises the importance of implementing strategies to improve adherence to established guidelines to improve therapeutic outcomes.

5.6 Nausea as an Independent Side Effect

Smit, Kotze and Du Plessis (2021) investigated the incidence of nausea in the absence of vomiting in a South African context. It was found that a significant proportion of patients continued to experience nausea throughout the entire CINV risk period (Smit, Kotze and Du Plessis, 2021). Our data revealed that during the overall phase, 22.5% of patients experienced nausea and 45% experienced nausea with vomiting. This differs from the findings of Smit, Kotze and Du Plessis (2021) where it was reported that 61.8% of patients experienced nausea without vomiting while only 24.2% experienced both symptoms. This pattern persisted across all three cycles (Smit, Kotze and Du Plessis, 2021). The findings of our study regarding CINV prevalence may differ from those reported by Smit, Kotze and Du Plessis (2021) due to a methodological discrepancy (Table 4.3). The prior study was conducted at a private oncology centre and might have employed different antiemetic classes and dosages compared to the public hospital setting of the current study. Due to differences in prophylaxis, the study by Smit, Kotze and Du Plessis (2021) may have managed vomiting more effectively which could explain why the current study observed a high prevalence of nausea that progressed to vomiting.

The current study finds that the incidence of delayed nausea (45.9%) is concerning. A critical gap exists in the current body of research regarding the independent evaluation of nausea as a CINV endpoint. An earlier study done by Grunberg et al. (2004) reported the incidence of delayed nausea to be 60%. Substantial advancements have been achieved in the optimisation of

antiemetic regimens and refinement of CINV management guidelines since then, however, a more recent study conducted by Chow et al. (2023) corroborates that treatment of delayed nausea is a significant problem and is always experienced at a higher incidence than acute nausea. A potential reason for this is the underestimation of the incidence of delayed CINV by clinicians and the impression that patients who do not experience acute CINV are less likely to experience delayed nausea and vomiting (Rapoport, 2017).

Analysis of our data revealed that 48.0% of patients receiving MEC experienced delayed nausea (Table 4.10). Of note, 34.3% of patients receiving either LEC or MinEC also reported suffering from delayed nausea. Molassiotis et al. (2008) observed that a change in antiemetic therapy was more likely to occur if a patient experienced acute CINV, but no changes were made to antiemetic prophylaxis in patients with delayed CINV. Furthermore, delayed nausea was experienced the most in patients receiving HEC or MEC, respectively (Molassiotis et al. (2008). This differs from the findings of our study where delayed nausea was mostly experienced by patients on either MEC or LEC/MinEC (Table 4.10). Antiemetic prophylaxis regimens for patients receiving LEC remain a topic of limited research, with effective treatment strategies yet to be definitively established (Hayashi et al., 2017). The potential influence of patient-specific characteristics on the incidence of delayed CINV in patients receiving LEC warrants further investigation (Hayashi et al., 2017). Although not fatal, nausea associated with chemotherapy can substantially reduce quality of life and hinder patients' ability to engage in normal activities (Aapro et al., 2012). This side effect compromises patient recovery from chemotherapy (Bashashati and McCallum,2014). Therefore, treatment of nausea is imperative.

International guidelines unanimously agree on the addition of olanzapine to combat delayed nausea (Helsinn, 2019). The benefits of this agent for nausea control have also been reported in studies conducted by Abe et al. (2016) and Chiu et al. (2016). The utilisation of olanzapine at the tertiary institution where the current study was conducted was limited. Taking into account the growing body of evidence supporting its efficacy in controlling delayed nausea, particularly when combined with standard antiemetic regimens, increased usage of this agent could prove advantageous in decreasing the prevalence of delayed nausea.

5.7 Age as a Risk Factor

This study did not establish a causal relationship between age and CINV incidence ($p=0.054$) (Appendix I). Younger age is a well-established CINV risk factor (Roscoe et al.,2010). Earlier

studies such as those conducted by Booth et al. (2007) and Dranitsaris et al. (2009) reported an association between younger age (younger than 40 years) and an increased risk of experiencing CINV. Bordeanu et al. (2012) found that in patients younger than 50, CINV remains a significant problem, emphasising younger age as a strong CINV predictor. The aforementioned studies were all carried out in a larger cohort than the current study. The present study may not have been sufficiently powered to detect a true association. Furthermore, only 32 patients within the 18-38 age group were enrolled in this study in comparison to a much larger proportion (n=157) of patients in the 39-64 age group. With such a disproportionate age distribution and the small number of younger patients, the true effects of younger age as a risk factor cannot be accurately determined.

Roscoe et al. (2010) stated that in the case of nausea, younger age is a major predictor, while Mizuno et al. (2016) further demonstrated that younger age affects nausea more specifically during the delayed phase. Our study found that while the younger age group (18-38) did experience delayed nausea, this was not statistically significant (p=0.123). These results are parallel to the findings of Hayashi et al. (2017) who failed to posit age as a risk factor for delayed nausea. Similarly, Tsuji et al. (2017) also reported no significant association between age and delayed nausea.

Our data, however, revealed a significant association between age and the incidence of acute nausea (p=0.038) (Figure 4.2). Patients aged 39-64 years were most affected, with a notable prevalence, while younger patients (18-38 years) and those over 65 years were less frequently impacted. Although this trend was also observed for both acute and delayed vomiting, no statistically significant association with age was identified for these outcomes (p=0.818 and p=0.201, respectively).

Previous research suggests that older patients may be less susceptible to CINV compared to younger populations (Mizuno et al., 2016; Hesketh et al., 2019). The findings of the current study partially support this notion, demonstrating a lower prevalence of acute nausea in the over-65 age group compared to younger patients. However, the definition of "elderly" in previous studies (60 years) differed from our age threshold (≥ 65 years). It is important to acknowledge that knowledge regarding CINV risk in patients over 65 years remains limited. Data from randomized controlled trials (RCTs) might not fully generalise to this population (Herrstedt et al., 2022). RCT participants are often younger and have fewer comorbidities

compared to the broader population of older adults undergoing chemotherapy (Herrstedt et al., 2022). These findings underscore the need for further research to elucidate the risk factors for CINV in elderly patients, given that cancer is being increasingly diagnosed in this population (Estapé, 2018).

A potential limitation to consider is the variability in the operational definition of "younger age" across studies in the literature. The age threshold considered substantially varies, ranging between 40-67 years old, with Celio et al. (2012) reporting that an age < 50 years is a risk factor for CINV, while Hesketh et al. (2010) demonstrated that patients younger than 65 were more likely to experience treatment-induced nausea and vomiting. Murakami et al. (2014) employed the broadest age range, reporting that patients younger than 67 had a greater likelihood of CINV. This heterogeneity could potentially hinder the identification of consistent age-related effects on CINV, begging the use of standardised reference ages for research on age as a potential risk factor for CINV.

5.8 The Association Between Sex and CINV

Female sex has been identified as a potential risk factor for CINV, with studies indicating a trend towards lower response rates in this population (Sekine et al., 2013; Molassiotis et al., 2014; Iihara et al., 2016). Our data revealed that females experienced nausea and vomiting more frequently than males, and also reported experiencing isolated nausea more often. Despite these observations, no significant difference in CINV risk between male and female patients was established ($p=0.126$).

While the present investigation did not identify a relationship between sex and CINV, previous evidence suggests a potential role for this factor in CINV susceptibility. For instance, Hilarius et al. (2012) reported that across several cycles, CINV prevalence was always higher in female patients. Similarly, the findings of our study demonstrated a higher incidence of CINV in both the acute and delayed phases in female participants ($p > 0.05$). Another study by Uchida et al. (2017) found that it was imperative to consider the sex of a patient when prescribing initial prophylaxis due to female gender being identified as an independent risk factor of failure to antiemetic prophylaxis. The disproportionate distribution of sex in this study might have contributed to a lack of sufficient statistical power to detect a potential difference in CINV risk between males and females.

Our findings, (Appendix I) however, regarding the lack of association between sex and CINV are not entirely inconsistent with some previous research. A study that enrolled 1198 patients identified eight risk factors that predicted the incidence and severity of CINV. Interestingly, female gender was not considered a significant predictive factor (Dranitsaris et al., 2017). Similarly, another investigation by Hayashi et al. (2017) found no correlation between sex and CINV ($p=0.12$). This finding is further substantiated by Kitazaki et al. (2015) who conducted a study on patients with lung cancer receiving either HEC or MEC and found that female gender had no effect on CR rates to antiemetic therapy.

Other studies, however, have demonstrated that female patients are at a higher risk of experiencing CINV (Hu et al., 2016; Mizuno et al., 2016; Takemoto et al., 2017; Tsuji et al., 2019). In a cohort with an unequal sex distribution where multiple risk factors were evaluated, exploration of potential reasons for the discrepancy between our findings and existing literature could provide valuable insights. Future research could benefit from a comprehensive examination between sex and other risk factors to identify patient subgroups in which being female may heighten susceptibility to CINV.

5.9 Race as a Risk Factor

Data regarding the association between race and CINV is limited, with only two studies reporting a correlation (Hassan and Yusoff, 2010; Bordeanu et al., 2012). Consistent with the limited research available, our study supports a potential association between race and CINV incidence ($p=0.033$). Black patients experienced the greatest incidence of nausea as an independent symptom and combined nausea and vomiting followed by White patients and other races (Indian/Coloured). However, a bivariate and multivariate analysis revealed that while Black patients have a higher absolute incidence of CINV, the relative risk comparison suggests that, compared to Black patients where more patients of this racial group reported higher rates of no symptoms, White patients have a disproportionately higher likelihood of experiencing these symptoms, particularly isolated nausea ($p< 0.05$).

The observed association between race and CINV aligns with some previous studies. Bordeanu et al. (2012) found that in comparison to other racial backgrounds, Asian females were more predisposed to experiencing CINV. An earlier study conducted by Hasan and Yusoff (2010) in a Malaysian population found that Chinese patients exhibited a higher risk of CINV compared to Malays and Asian Indians. Although a bivariate analysis conducted by the present study

suggested that patients who identified as either Indian or Coloured might have a higher likelihood of experiencing CINV, this conclusion cannot be definitively drawn due to the large confidence intervals and the grouping of Indian and Coloured patients together under the category of "*Other*." Furthermore, our study population did not include East Asian participants due to their limited representation within the tertiary academic hospital during the study period. While our findings suggest a potential association between race and CINV, the limited representation of East Asians restricts our ability to generalise these findings to this specific demographic. However, research by Hassan and Yusoff (2010) emphasises the potential value of personalised antiemetic regimens based on genetic and pharmacogenomic factors, highlighting the need for future studies to incorporate more diverse populations to explore this variable.

Pharmacogenomics is a rapidly evolving field investigating the influence of genetic variation on individual drug response (Goodman and Brett, 2021). This field holds promise for the development of personalised medicine by tailoring therapeutic regimens based on a patient's unique genetic makeup (Goodman and Brett, 2021). Racial variability in drug response can be largely attributed to differences in the prevalence of polymorphisms within genes which encode drug-metabolising enzymes (DMEs) and drug transporters (Tamargo et al., 2022). This has been demonstrated with drugs such as warfarin, clopidogrel, and statins, where genetic variations influence drug pharmacokinetics, ultimately affecting treatment efficacy and safety profiles (Tamargo et al., 2022). Specific gene polymorphisms could increase the risk of a patient experiencing CINV (Eliasen et al., 2020). Moreover, the presence or absence of certain enzymes in drug metabolism across different racial groups can lead to variable metabolism and response to antiemetic treatments (Jin et al., 2021).

Findings of the present study suggest race may be a factor influencing CINV prevalence, however, further investigation with larger and more diverse cohorts is crucial to validate these findings and explore potential biological mechanisms underlying these disparities in CINV susceptibility across racial groups. Investigating the influence of polymorphisms on antiemetic response across diverse populations is essential to optimise personalised CINV treatment regimens.

5.10 Cancer Diagnosis and Stage

There was no association between cancer type and CINV incidence (p=0.545), however, descriptive data indicated that patients with breast cancer reported the highest prevalence of both isolated nausea and nausea accompanied by vomiting (Appendix I). This was followed by patients with gastrointestinal cancers, other malignancies, and lymphoma. Roscoe et al. (2010) reported that women with breast cancer were more prone to experiencing treatment induced vomiting. This partially aligns with the findings of the current study, where patients with breast cancer experienced a higher incidence of both acute and delayed nausea and vomiting compared to those with other types of cancer. However, no significant association was established between cancer type and the occurrence of these symptoms (Figure 4.5).

A potential limitation of the study by Roscoe et al. (2010) is the inherent sex bias within the breast cancer population, as the vast majority of breast cancer patients are female. Since prior evidence suggests a higher baseline risk of CINV in females compared to males, this sex disparity within the breast cancer group could potentially confound the observed association between cancer type and CINV (Uchida et al., 2017). Dranitsaris et al. (2009) reported an increased risk of acute CINV in patients with genitourinary or gynaecological cancers. However, our study was unable to confirm this association, due to a limited number of patients diagnosed with these specific cancer types in our cohort. While only these two studies have reported potential links between specific cancers and CINV risk, limitations in our study design and the lack of definitive confirmation in the literature warrant further exploration into this patient risk factor.

Dranitsaris et al. (2009) reported a potential association between earlier cancer stages (I or II) and an increased risk of acute CINV. However, Petrella et al. (2009), investigating the same cohort, did not observe a similar association for delayed CINV. In our study, limitations in data collection prevented establishing a definitive link between cancer stage and CINV prevalence. A significant portion of our participants lacked information regarding their cancer stage, hindering our ability to assess this relationship effectively. Incomplete staging workup at the time of data collection for a significant portion (32.9%) of the participants limited our ability to definitively assess the association between cancer stage and CINV prevalence.

Another factor could be limited patient recall or difficulties comprehending their diagnoses due to language barriers during the informed consent process. Language barriers between patients

and healthcare providers can significantly impede the provision of optimal healthcare services (Al Shamsi et al., 2020). Additionally, cultural norms in some populations may emphasise deference to healthcare providers, potentially discouraging patients from asking clarifying questions even if they have limited understanding of the information presented (Schlemmer and Marsh, 2006). This dynamic can inadvertently restrict patient autonomy in healthcare decision-making (Schlemmer and Marsh, 2006). Language barriers between patients and healthcare providers can elevate the risk of adverse effects to treatments due to compromised communication (Cohen et al.,2005). To provide a more equitable and culturally competent standard of care, healthcare professionals should strive to develop a deeper understanding of their patients' ethnic backgrounds (Naidoo, 2014).

5.11 Chemotherapy Cycle Number

This study observed a trend of increased CINV incidence during the overall phase with higher numbers of chemotherapy cycles (Appendix I). Patients who had received four or more cycles reported a higher frequency of nausea, both alone and accompanied by vomiting. A statistically significant association was identified ($p=0.001$). There is, however, a discrepancy between the findings of the current study and the current body of literature.

Molassiotis et al. (2013) reported a trend of decreasing CINV risk with subsequent chemotherapy cycles, with the highest risk observed during the first cycle. However, generalisability of their findings may be limited due to the homogenous patient population, consisting solely of individuals of European descent. In contrast, the current study included a predominantly African/Black patient population. Ethnic variations in drug metabolism are well-documented, potentially influencing CINV presentation (Singh et al., 2018; Eliasen et al., 2020). This difference in ethnicity might explain the observed discrepancy between our findings and those of Molassiotis et al. (2013). Dranitsaris et al. (2017) corroborates the observations of Molassiotis et al. (2013) regarding a potential decline in CINV risk across chemotherapy cycles. However, similar to the previous study, this research also did not account for potential inter-individual variability due to pharmacogenomic factors.

While some studies have not observed a link between cycle number and CINV incidence, it is important to consider methodological differences. Hayashi et al. (2017) did not report a potential causal relationship between cycle number and CINV incidence, however, this study only included patients receiving LEC, whereas our study considered a broader range of

emetogenicities (Appendix I). LEC carries a lower risk of inducing CINV (10-30%), potentially masking any cycle-related trends compared to regimens with higher emetogenic potential. Di Mattei et al. (2016) also did not observe an association between cycle number and CINV. However, this study included a small sample size (n=94) and an only female population, potentially reducing its statistical power to detect risk factors like the influence of cycle number on CINV incidence.

Our findings partially align with those of Kim et al (2015) that demonstrated that CINV experienced in earlier cycles was a strong predictor of CINV in future cycles. Preliminary evidence from the current study suggests an upwards trend of CINV as the patient experiences more cycles.

5.12 Sleep and CINV

Our study investigated the potential association between sleep duration the night before chemotherapy and the incidence of CINV. Although patients who reported sleeping 8-10 hours or 4-7 hours the prior night exhibited a higher frequency of isolated nausea, nausea with vomiting, acute CINV, and delayed CINV compared to those with less sleep, these observations did not translate into statistically significant associations (Appendix I). Notably, a small percentage of patients reported CINV-related sleep disturbances, with 12% attributing this to nausea alone and 11% to vomiting. This observation may reflect the impact of ANV experienced before chemotherapy or the typical nausea and vomiting that commonly occurs as a result of chemotherapy administration.

Research on the effects of sleep and CINV are limited. The findings of the current study differ from those of Dranitsaris et al. (2017) that demonstrated that less hours of sleep could elevate the risk of delayed CINV, making this variable a strong predictor of CINV development. These findings are parallel to those of Jung et al. (2016) where poor sleep quality and insomnia negatively affected CINV outcomes. It is important to acknowledge that the findings of Jung et al. (2016) may have limited generalisability due to focus on a specific population - breast cancer patients receiving a pre-defined chemotherapy regimen. In contrast, the current investigation encompasses a broader range of cancer types (excluding haematological malignancies) and incorporates a wider variety of chemotherapy regimens.

The current study, however, relied on self-reported sleep duration, which might not fully capture the complex nature of sleep and its potential influence on CINV. Jung et al. (2016) employed

validated tools like the Pittsburgh Sleep Quality Index, the Epworth Sleepiness Scale, and the Insomnia Severity Index to assess various aspects of sleep quality beyond just duration. Incorporating similar validated sleep assessment tools in future studies could provide more nuanced insights into the relationship between sleep and CINV.

5.13 Anticipatory Nausea and Vomiting

Patients experiencing only nausea and both nausea and vomiting reported a higher rate of ANV compared to those experiencing neither according to the results of the current study. Moreover, patients that did not experience any nausea and vomiting are much more likely to not have experienced ANV at all. There was a statistically significant association between the prevalence of ANV and CINV incidence ($p=0.001$). The findings of the present study also demonstrated a significant association between acute and delayed CINV incidence and experiencing ANV. Patients who did not experience ANV during any of these phases were less likely to have CINV, as further confirmed by a bivariate analysis ($p<0.05$). Similarly, a multivariate analysis revealed that experiencing ANV was a strong predictor of CINV ($p<0.05$).

ANV is characterised by the fear and expectation of experiencing treatment-induced nausea and vomiting, which subsequently triggers CINV (Roscoe et al., 2011). Due to the underlying psychological mechanisms driving ANV, this symptom is challenging to manage effectively with conventional antiemetic regimens (Roscoe et al., 2011). The combined use of benzodiazepines and behavioural therapy has proven effective in managing ANV (Roscoe et al., 2011). However, this approach is not included in the treatment protocol at the site where the current study was conducted, highlighting an unmet need in the management of CINV. The relationship between ANV and CINV is emphasised in the literature, establishing ANV as a major risk factor (Dranitsaris et al., 2017).

Many studies primarily focus on the effect that CINV expectation has on nausea as an independent symptom. This may be due to nausea not being as effectively controlled as vomiting and a more subjective observation (Smit, Kotze and Du Plessis, 2021), warranting more investigations into mechanisms that could affect it. Hickok et al. (2001) reported that anticipatory nausea developed in 40% of patients who expected the symptom, a finding that is consistent with the results of the current study. A Korean study reported similar results, stating that nausea expectation needs to be taken into account prior to administering chemotherapy to improve control of this symptom (Rha et al., 2016).

A study conducted on a South African cohort, failed to report a statistically significant association between ANV and nausea (Smit, Kotze and Du Plessis, 2021). The current investigation shares similarities in design with the study by Smit, Kotze and Du Plessis (2021), encompassing patients with diverse cancer diagnoses receiving a variety of chemotherapy regimens. However, the prior study was limited by a relatively small sample size (n=95). This limitation might have reduced its statistical power to definitively identify ANV as a risk factor for CINV. Expectation of CINV has been incorporated into risk prediction models, underscoring the importance of considering this factor when evaluating a patient's inherent risk of experiencing CINV (Dranitsaris et al., 2017). By incorporating routine assessment of ANV alongside the inclusion and implementation of evidence-based interventions for its management in treatment protocols especially in the South African public sector, healthcare professionals can potentially create a more comprehensive approach to CINV prevention.

5.14 History of Motion Sickness

Data from this study indicates a significant association between a history of motion sickness and the incidence of CINV during the overall phase ($p = 0.001$) (Appendix I). A bivariate analysis demonstrated that individuals with a history of motion sickness were 11.05 times more likely to experience isolated nausea and 23.03 times more likely to experience both nausea and vomiting compared to those without such a history. This predisposition also emerged as a significant predictor of CINV in a multivariate analysis ($p<0.05$). A history of motion sickness also increased the risk of a patient experiencing acute vomiting and delayed CINV. This finding suggests that a predisposition to motion sickness may be an imperative risk factor to take into consideration when prescribing antiemetic prophylaxis.

These results concur with those of Shih et al. (2009), reporting that a history of motion sickness may be a clinical indicator for CINV, particularly delayed vomiting (Figure 4.9). Tsuji et al. (2017) further states that motion sickness susceptibility is a significant independent risk factor for delayed CINV. Tamura et al. (2015) demonstrated that this risk factor was strongly associated with the development of acute nausea. A more recent study by Yeo et al. (2024) acknowledged that presence of this predisposition was associated with antiemetic treatment failure. These findings underscore the robust correlation between motion sickness history and the occurrence of both acute and delayed CINV symptoms.

It is noteworthy that the four studies establishing a causal relationship between this prognostic factor and CINV were conducted predominantly within Asian populations. Prior research indicates that patients of Asian descent have a higher propensity for experiencing CINV due to interethnic variability in drug metabolism (Hassan and Yusoff, 2010; Bordeanu et al., 2012). Conversely, the present investigation, which focused on a predominantly African cohort, also identified a history of motion sickness as a significant risk factor for CINV. This finding suggests that intrinsic characteristics, such as race, may not significantly influence this clinical predictor, thereby broadening the generalisability of a motion sickness history as a risk factor for CINV. Consideration of this susceptibility may potentially guide future preventative strategies and patient management approaches to CINV in clinical settings.

5.15 History of Morning Sickness

Female patients who had been pregnant before were asked if they experienced morning sickness during their pregnancy. There was no significant association between a history of morning sickness and overall CINV ($p = 0.691$). This observation remained true for both acute and delayed phases of CINV. The literature, however, has highlighted the impact of a previous history of morning sickness on CINV.

Pregnancy-induced vomiting leads to a lower likelihood of CR to antiemetic prophylaxis (Yeo et al., 2024). This statement is reiterated in a study conducted by Dranitsaris et al. (2017). Moreover, the findings of Mizuno et al. (2016) reported that morning sickness history was a significant risk factor for the development of delayed vomiting. Morning sickness experienced during a previous pregnancy seems to be a significant risk factor that dictates response to antiemetic therapy and CINV outcome (Dranitsaris et al., 2017). Inclusion of this prognostic factor together with seven other major patient factors into risk predictive models, highlights its significant contribution to CINV prevalence (Dranitsaris et al., 2017).

A potential reason for the discrepancy between the findings of the present study and previous studies is the total number of females patients enrolled. While our study included 158 females, only 96 reported experiencing morning sickness during pregnancy. In contrast, the studies conducted by Yeo et al. (2024) and Dranitsaris et al. (2017) had 123 and 449 females with this risk factor, respectively. Moreover, the study by Mizuno et al. (2016) only included a female cohort making detection of this risk factor easier due to an increased sample size of relevant participants. Tanioka et al. (2013) did not report an association between morning sickness and

CINV, however, similar to our study, the total female population was 94 and may have not been sufficiently powered to detect a discernible difference. Future studies comprising of a larger female population would be required to further investigate the potential mechanism that causes a collinearity between this risk factor and CINV.

5.16 Alcohol Consumption

Data from the current study suggests a potential association between alcohol consumption and CINV incidence (Appendix I). The findings demonstrate that among patients who do not drink alcohol, a higher percentage experienced both nausea and vomiting compared to those who do consume alcohol. Nausea did not seem to be impacted by whether a patient consumed alcohol or not during the overall phase. However, the frequency of alcohol consumption also appears to play a role, with those consuming alcohol 1-3 times per month or 1-6 times per week reporting lower rates of isolated nausea and nausea with emesis compared to non-drinkers and rare drinkers. These differences were statistically significant for overall drinking ($p=0.041$) and frequency of drinking ($p=0.020$), suggesting that an inverse relationship may exist between alcohol consumption and CINV incidence. Additionally, findings also suggest a statistically significant association between alcohol frequency and experiencing acute vomiting ($p=0.011$). A bivariate analysis revealed that non-drinkers and less frequent drinkers were likely to experience symptoms of CINV, however, this finding was not statistically significant ($p>0.05$).

During the overall phase, an increased CR rate to antiemetic therapy was observed in patients that consume alcohol more often than those who do not (Kawazoe et al., 2018). This counterintuitive association has also been reported by Uchida et al. (2017), demonstrating that patients that did not consume alcohol were at a significant risk of experiencing CINV. The exact mechanism of this inverse correlation is not known, however, Uomori et al. (2017) proposes that a difference in the aldehyde-dehydrogenase-2 (ALDH2) enzyme that is primarily involved in the metabolism of alcohol may be the reason. A decreased CINV risk for habitual alcohol drinkers was only reported in patients that had a variant of the ALDH2 enzyme (Uomori et al., 2017). Recommending patients to drink more is not advisable due to the numerous health risks posed by habitual alcohol consumption, however, Uomori et al. (2017) emphasises the importance of considering genetic polymorphisms to further improve CINV management. It is worth noting that the ALDH2 variant is particularly prevalent in East Asian populations and this polymorphism may not fully influence the link between high alcohol consumption and

decreased CINV risk as this study was conducted in a cohort that did not include patients from this demographic.

Evidence may infer a potential protective effect of alcohol against CINV, although it is important to highlight limitations associated with this risk factor. Firstly, our study only considered the frequency of alcohol consumption among patients and did not account for the quantity of alcohol consumed. This omission may affect the accuracy of the findings, as the amount of alcohol intake could also have a significant impact on the relationship between alcohol consumption and CINV. Secondly, the defined amount of what constitutes low alcohol consumption per week varies between studies. Rha et al. (2016) defines low alcohol consumption as fewer than four drinks per week, while Dranitsaris et al. (2009) sets the threshold at fewer than seven. This variation suggests inherent biases due to differing methods of measuring alcohol intake (Mosa et al., 2020). Future research may require a more standardised approach in measuring both the frequency and quantity of alcohol consumed to explore the underlying mechanisms of this association and limit confounding factors that may affect it.

5.17 Concurrent Comorbidities and the Use of Prescription/Non-Prescription Medication

Our study revealed a statistically significant association ($p=0.047$) between the presence of other chronic conditions and the incidence of CINV during the overall phase (Appendix I). However, a bivariate analysis suggests that a concurrent comorbidity is not significantly associated with CINV outcomes. When examining specific chronic conditions, certain comorbidities appear more frequently among patients with CINV. For example, conditions like hypertension and HIV display a higher CINV prevalence. This trend indicates that patients with these particular health issues might be at an increased risk of developing CINV. However, these differences were not statistically significant ($p=0.165$). Patients with concurrent hypertension or HIV exhibited a higher incidence of acute vomiting, a finding that was statistically significant ($p=0.039$) The incidence of acute nausea and delayed nausea and vomiting did not yield a significant association with this risk factor.

No significant difference was found in the distribution of types of prescription medication among the different CINV groups. This lack of variation suggests that while the overall use of prescription medications is associated with CINV, no specific class of medication appears to be the primary driver of this association ($p = 0.165$). However, prescription medication use was

significantly associated with acute vomiting ($p = 0.039$) but showed no effect on outcomes for acute nausea or delayed CINV ($p > 0.05$). Bivariate analysis further indicated that the use of prescription medications did not significantly influence the prevalence of CINV.

There was no association between the use of non-prescription medications and CINV, in both the acute and delayed phase ($p=0.597$). Specific drug classes such as analgesics/antipyretics, antihistamines, and vitamins appear to be unlikely contributors to CINV ($p=0.455$). However, a significant association was found between non-prescription medication use and acute nausea ($p=0.048$), with patients currently using analgesics reporting a higher incidence (32.3%). Reported studies indicate that analgesics generally cause nausea (Singh et al.,2016; Ames, 2022). It is important to consider that this association may not be solely attributable to chemotherapy, as the analgesics used could also contribute to inducing nausea (Singh et al.,2016; Ames, 2022).

Research investigating the role of comorbidities and concurrent medications use and its effect on CINV is limited. Booth et al. (2007) suggested that the absence of comorbid conditions could potentially increase the risk of CINV, although the exact mechanism was not elucidated. Conversely, the present study suggests that patients with other chronic conditions may be more prone to experiencing CINV. Furukawa et al. (2014) suggested that antihypertensive use might serve as a protective factor against delayed vomiting, however, this contrasts with the findings of the current study, which observed a greater proportion of patients on antihypertensives experiencing delayed vomiting ($p>0.05$). Furthermore, patients on antihypertensives reported more cases of acute vomiting, with this association reaching statistical significance ($p < 0.05$). Additionally, Bordeanu et al. (2012) reported that GERD might increase CINV susceptibility, a finding that also differs with the results of our study. Only two studies have evaluated the use of non-prescription medication and its effect on CINV, both utilising the same data set. Dranitsaris et al. (2009) reported that patients using non-prescription medications are more likely to experience acute CINV, while Petrella et al. (2009) found similar results for delayed CINV. Although the specific names of the non-prescription medications were not provided, it was noted that all non-prescription medications used were specifically intended to treat emesis caused by chemotherapy.

The differences in findings of the aforementioned studies and our study may be attributed to variations in patient demographics. All three studies that reported a relationship between

chronic conditions and CINV were conducted in all-female populations being treated for breast or gynaecological cancers. In contrast, the present study included patients of both sexes with various types of cancers. Additionally, treatment protocols for chronic conditions vary by country. For example, Furukawa et al. (2014) observed less CINV in patients on antihypertensives, however, the specific medications used were not disclosed. To the best of our knowledge, this is the first analysis to examine the effect of non-prescription medication use for self-limiting illnesses as a potential risk factor for CINV and identify a potential link between analgesic use and increased acute nausea incidence in chemotherapy patients, highlighting an important area for further investigation and consideration in clinical practice. More studies employing a broader patient demographic and detailed medicine reporting to explore the underlying mechanisms by which chronic conditions and their treatments influence CINV.

5.18 Eating Habits

Patients were asked about the meal they ate prior to receiving chemotherapy. A key observation was that a substantial majority of patients consumed a meal before chemotherapy administration, with no significant difference in the incidence of CINV (overall phase) between those who did and did not eat ($p=0.964$). This suggests that eating prior to chemotherapy does not have a strong impact on the occurrence of CINV symptoms. Furthermore, there was no significant difference in the incidence of CINV between those who consumed light meals and those who ate heavier, high-fat, high-carbohydrate meals ($p=0.734$). Additionally, no association was found between eating habits and the different phases of CINV. This infers that the type of meal consumed may not play a decisive role in the occurrence of CINV symptoms.

There is limited research on the impact of CINV on nutritional intake, despite its potential to cause malnutrition and reduce quality of life (Marx et al., 2016). To prevent further physical deterioration of a patient due to poor nutritional status, it is crucial to further optimise CINV preventative strategies. The significance of specific eating habits in cancer patients is well-documented for the prevention of unpleasant gastrointestinal symptoms associated with chemotherapy (Calixto-Lima et al., 2012). Booth et al. (2007) emphasised the importance of consuming a small meal prior to chemotherapy, as omitting this could increase the risk of experiencing CINV, particularly during the acute phase, although the present study did not corroborate this finding. Certain foods, including oils, dairy products, foods high in sugar, apples, bananas, and processed meat, have been reported to promote nausea in patients (Mardas

et al., 2022). The "heavy meals" category in the current investigation included meals containing processed meat, oils, and dairy products. Despite this, the study did not observe the same association between these foods and an increased incidence of CINV. This discrepancy suggests that the relationship between specific dietary habits and CINV may be more complex and influenced by additional factors not accounted for in the current study.

While diet and nutrition are typically not the primary treatment for CINV, clinical practice guidelines indicate that dietary interventions can complement antiemetic therapies and enhance their effectiveness (Lyman et al 2018; NCCN 2018). Mardas et al. (2022) identified specific foods that exacerbated gastrointestinal symptoms. In addition to this, energy intake, micronutrients and macronutrients consumption was also taken into consideration with food records being evaluated by a dietician (Mardas et al., 2022). This highlights a potential limitation of the current study, which did not account for these confounding factors. Instead, the food consumed by patients was categorised into broad, predefined groups, potentially introducing bias into the analysis. Future studies should incorporate detailed dietary assessments and consider the impact of specific nutrients and food types on CINV to provide more comprehensive and accurate recommendations.

5.19 Smoking Status and Marijuana Use

An analysis was conducted to explore the relationship between smoking status and the risk of CINV. There was no association between smoking status (current, former, or never smoked) and the likelihood of experiencing nausea, nausea with vomiting, or no symptoms ($p = 0.136$). Additionally, the number of cigarettes smoked by current ($p = 0.231$) and former smokers ($p = 0.199$) did not significantly impact CINV risk (Appendix I). Similarly, no significant associations were found between smoking status and the likelihood of experiencing acute or delayed symptoms. While there was a slight trend towards increased CINV incidence among smokers, non-smokers overall exhibited the highest rates of CINV. The number of cigarettes smoked did not influence the incidence of acute or delayed CINV.

Four studies have been conducted in Japanese populations to determine whether smoking was a potential CINV risk or protective factor (Sekine et al., 2013; Furukawa et al., 2014; Kawazoe et al., 2018; Nawa-Nishikagi et al., 2018). Only Sekine et al. (2013) found that non-smokers had a greater chance of experiencing acute CINV. While evidence from the present study (Figure 4.13) indicates that there was no significant association between smoking status and

acute CINV, non-smokers tended to experience acute nausea (60.6%) and acute vomiting (57.4%) more frequently than smokers or former smokers, aligning with the findings of Sekine et al. (2013). However, according to the findings of Nawa-Nishikagi et al. (2018), Kawazoe et al. (2018) and Furukawa et al., (2014) smoking status was considered an insignificant factor. Notably, the study by Sekine et al. (2013) had a much larger sample size and included patients of both sexes, various cancer types and chemotherapy regimens. In contrast, the other three studies had smaller sample sizes and more homogeneous populations, including only females and female-specific cancer types, reducing generalisability of the findings. Advising patients on the health risks of smoking is imperative regardless of whether this habit may reduce the risk of CINV or not. A larger and more diverse study population is required to determine whether smoking plays a role in the development of CINV or not, enabling clinicians to make more informed decisions regarding patient care.

Patients were also asked about marijuana use. Interestingly, non-smokers of marijuana experienced more instances of being asymptomatic compared to users and former users. Non-smokers exhibited a higher percentage of no symptoms during the overall. This observation was statistically significant ($p=0.014$). A bivariate analysis revealed that former and current marijuana smokers were 3.3 and 9.3 times more likely to experience isolated nausea, respectively ($p<0.05$). An elevated risk for nausea and vomiting was also observed in this group. Furthermore, a multivariate analysis demonstrated a greater prevalence of CINV in this group ($p>0.05$). Upon examining the incidence of acute and delayed CINV, patients that did not smoke marijuana reported less acute nausea, acute vomiting, delayed nausea and delayed vomiting denoting a strong association between non marijuana smokers and experiencing these symptoms.

The oral synthetic cannabis derivatives, nabilone and dronabinol, have been extensively studied and are considered effective antiemetic agents (Wilkie et al., 2016). However, there is a lack of research on the antiemetic efficacy of smoked cannabis/marijuana (Todaro, 2012). Cotter (2009) reported that smoked marijuana displayed similar antiemetic efficacy to oral cannabinoids. However, medicinal use of marijuana is controversial, limiting trials to further investigate its potential use against CINV (Todaro 2012; Wilkie et al.,2016). This substance also exhibits an unpredictable pharmacokinetic profile, potentially diminishing the efficacy of chemotherapy (Bodine and Kemp, 2023). Additionally, marijuana use is associated with various adverse effects including dizziness, drowsiness, dry mouth, confusion, and nausea (Briscoe and

Casarett, 2018). The present study reported a higher occurrence of acute and delayed nausea and overall CINV in patients that used marijuana. Furthermore, marijuana smoke contains carcinogenic compounds making it unsuitable for recommendation to cancer patients even if future studies could definitively prove antiemetic benefits (Kramer,2015). These concerns highlight the importance of encouraging cessation of marijuana use in patients undergoing chemotherapy.

5.20 Use of Complementary/Alternative Therapies

The data on the use of complementary and alternative therapies for treating CINV reveals significant trends and disparities among different patient groups ($p=0.011$) (Appendix I). Patients experiencing isolated nausea demonstrated limited use of both alternative therapies (8%) and complementary medications (8%), with the majority abstaining from these treatments. Among those experiencing both nausea and vomiting, the use of complementary medications decreases slightly (7%), while the use of alternative therapies remains modest (14%). Conversely, in the group without symptoms, the use of any complementary or alternative therapies is almost negligible, with nearly all patients refraining from these therapeutic options. This pattern underscores a general reluctance or lack of need to adopt complementary and alternative therapies. It was observed that acute and delayed CINV symptoms were slightly higher in patients that used complementary/alternative therapies patients with a significant difference in acute nausea, acute vomiting and delayed nausea (Figure 4.15).

With regards to the use of ginger in alleviating CINV during the overall phase, the data indicates that while ginger is used by some patients to alleviate CINV, the majority do not opt for this treatment, regardless of their symptoms. The use of ginger was higher among patients who experience both nausea and vomiting compared to those with nausea only or no symptoms. This trend suggests that patients with more severe symptoms might be more inclined to try alternative remedies such as ginger. There was a difference in ginger use across the groups, illustrating the relationship between the severity of CINV symptoms and the likelihood of using ginger as a complementary treatment ($p=0.018$). However, the data did not reveal reduced CINV symptoms within this cohort. In fact, a steady increase in both acute and delayed CINV was observed in the ginger-using group. A bivariate analysis revealed that non-ginger users were 73% less likely to experience nausea and 78% less likely to experience both nausea and vomiting during the overall phase in comparison to ginger users ($p<0.05$). Moreover, a multivariate analysis revealed that the use of ginger as a remedy for CINV was found to be a

significant predictor of nausea with vomiting ($p<0.05$). Patients who used ginger were 3.47 times more likely to experience nausea alone and nearly five times more likely to experience both nausea and vomiting compared to those who did not use ginger. This suggests that patients who turn to ginger may already be at a higher risk for CINV or that ginger use may not be as effective in preventing these symptoms as commonly believed.

Nonpharmacological interventions are frequently utilised alongside conventional antiemetics to manage CINV (Li et al., 2022). This approach reflects a growing interest in integrative medicine and the potential benefits of complementary and alternative therapies (Li et al., 2022). The current study categorised the use of aromatherapy, meditation, acupuncture, and music therapy as alternative therapies (Appendix I). Aromatherapy can help alleviate both acute and delayed CINV (Wang et al.2020). Essential oils with peppermint are particularly effective due to their strong antiemetic properties (Wang et al.,2020). The present study found that only three patients made use of this intervention, therefore no conclusive observations could be made. Meditation is also effective at treating CINV, inducing a state of relaxion making this technique particularly useful for ANV (Kothari et al.,2019). The same observation cannot be reported by the present study as only a single patient employed this technique. Findings by Tai (2020) deemed acupuncture as effective in decreasing the severity of CINV experienced, particularly as an adjunct with an antiemetic regimen. However, the current investigation, only noted a single patient utilise this approach, limiting the ability to observe significant effects due to the extremely limited population. Jing et al. (2017) suggests that nursing staff play soothing music in the chemotherapy room given the evidence that this approach can act as a distraction technique, improve a patient's mood and inadvertently reduce CINV. However, due to a limited number of patients using this technique (n=5), no observations could be made to confirm these findings.

There is a substantial body of evidence demonstrating the scientific validity of these alternative therapies (Yan et al., 2023; Sun et al., 2020; Wei et al., 2020). A limitation of the current study was grouping these therapies under a single umbrella term due to the limited number of patients using these interventions. Future studies need to include larger sample sizes to further standardise these approaches, thereby facilitating the incorporation of these interventions into standard clinical practice.

The present study categorised moringa, peppermint tea, and lemon water as complementary therapies used by patients to manage CINV. While moringa has gained attention as a potential therapeutic agent, evidence supporting its efficacy in managing CINV is limited. Wijaya et al. (2023) reported nausea as a side effect of moringa use. Further research is needed to explore its safety and effectiveness in the context of CINV management. Peppermint tea and lemon water have not been explored for their potential role in CINV alleviation, however, these agents do contain aromatic properties (Li et al., 2022). Beloni and Toniolo (2021) propose that the use of these compounds as inhalants is superior to oral preparations in reducing CINV. The classification of these complementary treatments into a single category and the relatively small number of patients utilising them hindered a more in-depth analysis of their individual effects on CINV. Future studies with larger more diverse populations focused on specific complementary therapies are necessary to establish their efficacy and safety in managing CINV.

Ginger has emerged as a potential complementary treatment for CINV. Choi et al. (2022) reported a potential benefit of ginger supplementation in reducing the risk of acute vomiting. Similarly, Kim et al. (2022) observed a reduction in CINV among ginger users. However, Crichton et al. (2019) cautioned against widespread ginger recommendation due to methodological limitations in existing studies. The findings of the present study reiterate these concerns as a trend of increased CINV prevalence was reported in the group using ginger. Moreover, managing the heterogeneity in clinical factors across studies, such as cancer types, antiemetic regimens and patient groups, is crucial to ameliorate understanding of the true impact of ginger on CINV (Choi et al., 2022). To fully elucidate the role of ginger in CINV management, future research with larger sample sizes where clinical variations are controlled is imperative. Such studies should investigate the optimal use of ginger to provide definitive evidence-based recommendations.

5.21 BMI

The impact of BMI on the incidence of CINV was explored, stratifying patients into four groups: healthy weight, overweight, underweight, and obese. The data suggests that patients with a healthy weight and those classified as overweight exhibited the highest incidence of both nausea with vomiting (Appendix I). Additionally, patients with a healthy weight and those who were obese reported higher rates of isolated nausea. Underweight patients reported fewer cases of CINV, suggesting a potential variation in CINV occurrence based on BMI, however, the differences observed were not statistically significant ($p=0.229$). The absence of acute vomiting

cases in the underweight category and the varied incidences in other groups suggest that BMI may influence the likelihood of experiencing acute vomiting during chemotherapy. However, the overall difference across categories was not statistically significant ($p= 0.125$). Furthermore, across all three symptoms—delayed nausea, acute nausea, and delayed vomiting—healthy weight and overweight patients reported experiencing more CINV compared to underweight and obese patients. However, none of these differences were statistically significant.

The association between BMI and the development of CINV presents with inconsistent findings in existing literature. A recent study by Yeo et al. (2024) suggested that obesity may serve as a protective factor against CINV, with similar findings reported by Kawazoe et al. (2018). The results of the current study also indicate that obese patients experienced less nausea with vomiting in comparison to patients who were overweight or at a healthy weight ($p>0.05$). According to Gilmore et al. (2014), overweight and obese patients have a 23% lower chance of experiencing CINV. However, a study by Binder and Saunders (2018) involving 5570 female patients found no association between CINV and obesity. The present study acknowledges a limitation in the BMI assessment method, as height and weight were self-reported by patients, with the possibility of under- and overestimation. Additionally, two patients were unable to recall these values. Yeo et al. (2024) also emphasises the limitations of BMI as a sole indicator of the physical status of an individual and proposes that a more comprehensive evaluation of body composition, encompassing factors beyond BMI, might provide valuable insights into the potential association between obesity and CINV.

5.22 Chapter Summary

The outcome of this study indicates that CINV remains prevalent among patients, despite existing treatment protocols. The adherence to these protocols is not consistently observed, which could contribute to the continued incidence of CINV. While isolated nausea is a concern, the combination of nausea with vomiting poses a more significant issue. A comprehensive assessment of risk factors is crucial in understanding and managing CINV. Several risk factors have shown a strong association with CINV in this cohort. There is an evident gap in the systematic evaluation of these risk factors, contributing to suboptimal management of CINV. The inclusion of an educational program emphasising the importance of risk factor assessment, along with regular reviews by the oncology care team, could substantially impact the management and reduction of this distressing side effect. Improving adherence to established protocols would further enhance the effectiveness of these interventions.

CHAPTER 6

6. CONCLUSION

6.1 Introduction

This chapter highlights the key findings, study conclusions, limitations, and recommendations for clinical practice and future research. The study underscores the complex nature of CINV and the various factors influencing its incidence. While CINV remains a common and challenging side effect of chemotherapy, this study has demonstrated that a comprehensive understanding of patient demographics, clinical factors, and adherence to antiemetic treatment protocols can significantly impact the effectiveness of CINV management.

6.2 Dissemination of Findings

Dissemination of findings from this study was carried out across multiple platforms to ensure a broad reach among relevant stakeholders. Results were shared with clinical pharmacy students, providing them with valuable insights into the management of CINV and patient care. Additionally, a presentation on the risk factors pertaining to CINV was delivered to master's students to contribute to their academic understanding. The findings were also presented to prescribers in the ward to directly influence clinical decision-making. At an international level, the study was disseminated at the Fédération Internationale Pharmaceutique (FIP), allowing for engagement with a global audience (Appendix J). Furthermore, a sub-analysis of the results will be presented at the 6th European Congress of Oncology Pharmacy (ECOP6) (Appendix K).

6.3 Study Limitations

A key limitation of this study is the large confidence intervals observed in both the bivariate and multivariate analyses. These wide intervals suggest a degree of uncertainty around the estimated risk factors, which may reduce the precision of the findings. Consequently, the identified risk factors should be interpreted with caution, and further research is needed to confirm these associations with larger cohorts at more treatment sites. Additionally, the data collection was conducted manually by the researcher and trained data collectors. Patients were interviewed about their experiences with CINV and were asked about potential risk factors. It is important to note that some patients may not have provided truthful responses, particularly regarding sensitive topics such as alcohol consumption, smoking status, marijuana use, and certain concurrent conditions like an HIV diagnosis. This potential for reporting and recall bias

may have significant implications, potentially leading to misrepresentation of the true prevalence and impact of these factors on CINV.

Due to logistical constraints, patient interviews were conducted while patients were receiving their chemotherapy. This setting was selected because it was the only opportunity for the researcher to review prescriptions and interview patients simultaneously. As a result, a stadiometer and scale could not be used to obtain precise height and weight measurements. Instead, the researcher relied on the patients' self-reported data and that of previous measurements taken by nurses, hence the possibility of inaccurate information being recorded. This can lead to misclassification of BMI categories, thereby affecting the study's findings related to BMI as a risk factor for CINV. Furthermore, two patients were unable to recall their height and weight, limiting the assessment of BMI as a risk factor to 220 patients.

Other limitations of the study with regard to the risk factors that were assessed, included a disproportionate distribution of sex among patients, which may have implications for the accurate assessment of the impact of female sex on the incidence and severity of CINV. The study population also had a limited number of participants in the 18-38 age group, restricting the evaluation of the effect of younger age on exacerbating CINV symptoms.

Another significant limitation was the incomplete data on cancer stage, as many patients were unaware of their cancer stage. This lack of information prevented a comprehensive analysis of the impact of cancer stage on CINV risk. While sleep duration was recorded, there was no assessment of sleep quality, which could have provided a more nuanced understanding of its relationship with CINV. The categorisation of food intake into broad groups limited the ability to identify specific foods that may increase the prevalence of CINV. This broad categorisation potentially masked the effects of dietary components. Patients using complementary and alternative medications were few, which limited the evaluation of the effectiveness of these interventions in alleviating CINV. Lastly, certain risk factors could not be analysed using a bivariate and multivariate model due to the number of observed cases in specific categories being few, hindering the testing of the strength of an association if any.

6.4 Future Recommendations

Future multi-site studies with larger sample sizes are recommended to definitively confirm these preliminary findings. A more extensive dataset would provide greater statistical power,

allowing for more precise estimates of risk factors and reducing the uncertainty observed in the confidence intervals of the current study. This approach would help to establish a clearer understanding of the risk factors for CINV.

Given the observed limitations in the efficacy of current antiemetic regimens, particularly for patients receiving MEC and HEC, there is a need to consider the inclusion of NK-1 RAs in the treatment protocols. This aligns with international guidelines and evidence suggesting improved CINV control with NK-1 RAs, especially for patients who have experienced antiemetic treatment failure. As noted in the treatment facility's protocol, the use of NK-1 RAs is pending approval, highlighting the necessity for expedited integration of these agents once they are approved for use. This will ensure that patients have access to the most effective antiemetic regimens, improving overall management of CINV.

Training programs should be implemented to educate healthcare providers about the importance of adherence to established antiemetic protocols. This training should address common misconceptions about CINV control and emphasise the need for a more proactive approach in managing breakthrough symptoms. Specifically, the use of olanzapine should be highlighted, especially in cases of delayed CINV, as it has shown effectiveness in controlling symptoms not adequately managed by standard regimens. Additionally, patients should be provided with comprehensive education about the potential side effects of chemotherapy, the importance of reporting symptoms of CINV, and the available options for managing these symptoms. This education can help improve patient engagement and adherence to prescribed antiemetic regimens, ensuring better overall management of CINV. Healthcare professionals should also strive to understand the ethnic and cultural backgrounds of patients. This approach could improve patient engagement, adherence to prescribed antiemetic regimens, and overall management of CINV, by ensuring that care strategies are tailored to the diverse cultural and personal contexts of the patient population.

A comprehensive investigation of the interplay between sex and other risk factors on CINV susceptibility could be crucial for identifying patient subgroups where female sex may increase vulnerability to CINV. Investigating the influence of genetic polymorphisms on antiemetic response across diverse populations is recommended, to optimise personalised CINV treatment regimens. Pharmacological and non-pharmacological interventions aimed at alleviating ANV should be explored for inclusion into CINV treatment protocols. The findings of this study raise

awareness of future considerations for protocol development for the management of CINV in patients with cancer.

6.5 Conclusion

The challenge of CINV remains a significant concern in cancer treatment, with various factors influencing the effectiveness of supportive oncology care and antiemetic regimens. This study has reviewed the use of antiemetic therapies at a tertiary academic hospital, highlighting the discrepancies between international guidelines and local practices due to constraints such as availability, cost-effectiveness, and public healthcare budget limitations. This study underscores the importance of concordance with specified treatment protocols, improved use of olanzapine for delayed CINV and the incorporation of NK-1 RAs for improved CINV management.

This study emphasises the importance of taking into account patient-specific risk factors in the management of CINV. It adds to the growing body of evidence highlighting the need for individualised patient assessments to optimise treatment outcomes. There is a critical need for a more nuanced understanding of patients' ethnic backgrounds and other individual factors to effectively tailor antiemetic regimens. Recognising that genetic differences can significantly influence susceptibility to CINV and the response to treatment, it is imperative to incorporate these considerations into clinical practice. This includes a comprehensive assessment of factors such as a history of motion sickness and ANV, which may predispose patients to more severe CINV, and the use of non-prescription medications and non-pharmacologic interventions, which could interact with prescribed antiemetics. The use of substances like marijuana, which some patients may use to self-manage symptoms, also requires careful consideration due to its potential effects on CINV. Similarly, alcohol consumption habits need to be assessed as they may affect liver function and drug metabolism, even though this risk factor may serve as a protective factor against CINV. Incorporating these individual factors into patient histories allows for the identification of high-risk individuals and enables healthcare providers to develop more personalised and effective antiemetic strategies. This tailored approach is essential for enhancing CINV management and improving patient outcomes, highlighting the necessity for a more patient-centred approach in clinical settings.

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Appendix A: Ethics Clearance Certificate

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

R14/49 Miss Johara Irshaad Rahim

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

CLEARANCE CERTIFICATE NO. M230543 M230922-A-0003

NAME: (Principal Investigator)	Miss Johara Irshaad Rahim
DEPARTMENT:	Pharmacy and Pharmacology Charlotte Maxeke Johannesburg Academic Hospital Radiology The Oncology Outpatient Unit
PROJECT TITLE:	Investigating patient-specific risk factors for chemotherapy induced nausea and vomiting in patients with cancer
DATE CONSIDERED:	26-May-2023
DECISION:	Approved unconditionally
CONDITIONS:	N/A
NOTE:	Application Number: MED23-03-136
SUPERVISORS:	Mrs R. Khan, Dr A. Orchard, Mr M. Vally, Mrs F. Kathrada and Prof G. Demetriou
APPROVED BY:	Prof P. Ruff, Chairperson, HREC (Medical)
DATE OF APPROVAL:	22-Sep-2023 **EXPIRY DATE:** 21-Sep-2028

This clearance certificate is valid for 5 years from data of approval. Extension may be applied for.

DECLARATION OF INVESTIGATOR(S)

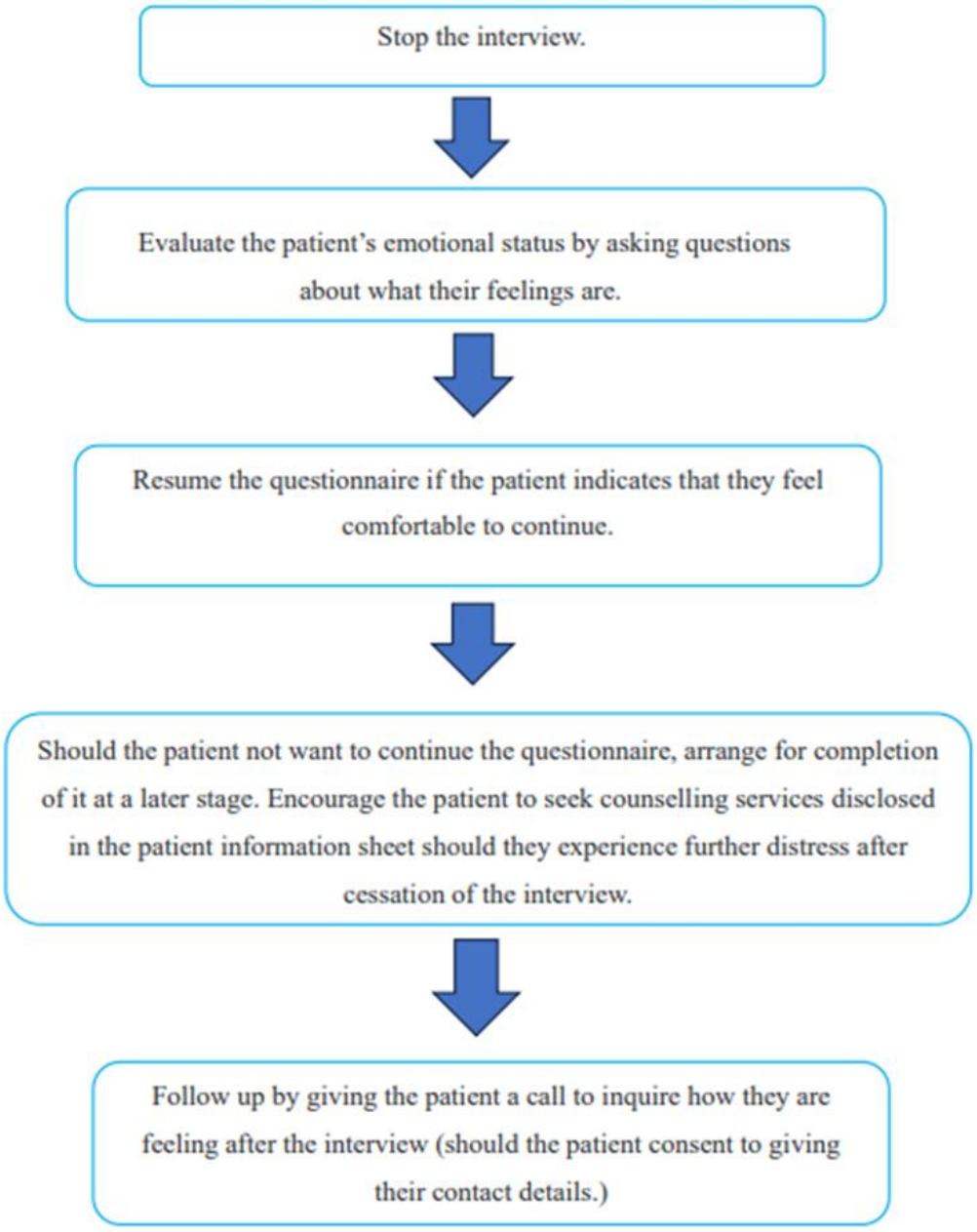
I/we fully understand the conditions under which I am/we are authorized to carry out the abovementioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated, from the research protocol as approved, I/we undertake to resubmit the application to the Committee. **I agree to submit a yearly progress report** in the month date of convened meeting each year until study is closed. Failure to submit annual report will result in ethics clearance certificate suspension. The date for annual re-certification will be one year after the date of convened meeting where the study was initially reviewed. Unreported changes to the application may invalidate the clearance given by the HREC (Medical). Email a signed copy of ethics clearance certificate to HREC-Medical.ResearchOffice@wits.ac.za

Signature of Principal Investigator

2023/09/22
Date

Appendix B: Distress protocol

Should a patient display any signs of distress when asked about sensitive topics during the researcher-administered questionnaire the following steps will be taken:



Appendix C: HOD approval letter

Department of Medicine

CM Johannesburg Acedemic Hospital

P Bag X39
JOHANNESBURG
2000
Tel : + 27 11 488 3495
Fax: + 27 11 488 4515

13/03/23

Dear M Bogoshi and CMHAH Research Committee:

RE:MS JOHARA RAHIM

This is to certify that Ms Johara Rahim has been given permission to conduct research in the Division of Medical Oncology at Charlotte Maxeke Academic Hospital.

This research will be towards the degree of Master of Pharmacy (MPharm) through the department of Pharmacy and Pharmacology, Division of Clinical Pharmacy at the University of Witwatersrand on the topic of "Investigating patient-specific risk factors for chemotherapy induced nausea and vomiting in patients with cancer."

Yours Sincerely

Prof Georgia Demetriou
Academic Head of Medical Oncology
University of the Witwatersrand
Acting Head Division of Medical Oncology
Department of Medicine CMJAH
Intern/Comm Service curator CMJAH

Appendix D: CMJAH CEO approval letter

GAUTENG PROVINCE
HEALTH
REPUBLIC OF SOUTH AFRICA

CHARLOTTE MAXEKE JOHANNESBURG
ACADEMIC HOSPITAL

Enquiries: *Ms N. Mzila*
Email: Nolwazi.Mzila@gauteng.gov.za
Tel: *011 488 3365*
Ref: *1/7/2*
Date: 28 September 2023

GP_202304_007

DEAR MS. JOHARA RAHIM

RE: PROVISIONAL APPROVAL OF STUDY

TITLE: Investigating patient-specific risk factors for chemotherapy induced nausea and vomiting in patients with cancer.

Permission is granted for you to conduct the above-mentioned study as described in your request provided:

1. Charlotte Maxeke Johannesburg Academic Hospital will not in any way incur or inherit costs as a result of the said study.
2. Your study shall not disrupt services at the study sites.
3. Strict confidentiality shall always be observed.
4. Informed consent shall be solicited from patients participating in your study.

Please liaise with the HOD and Unit Manager or Sister in charge to agree on the dates and time that would suit all parties.

Kindly forward this office with the results of your study on completion of the research.

Supported / ~~Not Supported~~

Signed at:2023-10-02 11:31:17 +02:00
Reason:Witnessing Jayshina Punwasi

Dr J. Punwasi
Clinical Director

Approved / ~~Not Approved~~

Ms G. Bogoshi
Chief Executive Officer: CMJAH

Appendix E: Research protocol approval letter

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

Private Bag 3 Wits, 2050
Fax: 027117172119
Tel: 02711 7172076

Reference: Mrs Sandra Benn
E-mail: sandra.benn@wits.ac.za

26 June 2023
Person No: 2085387
PAG

Miss JI Rahim
P.o. Box 984
Piet Retief
2380
South Africa

Dear Miss Johara Rahim

Master of Pharmacy: Approval of Title

We have pleasure in advising that your proposal entitled *Investigating patient-specific risk factors for chemotherapy induced nausea and vomiting in patients with cancer* has been approved. Please note that any amendments to this title have to be endorsed by the Faculty's higher degrees committee and formally approved.

Yours sincerely

Mrs Sandra Benn
Faculty Registrar
Faculty of Health Sciences

Appendix F: Participant Information Sheet

Department of Pharmacy and Pharmacology

Faculty of Health Sciences I 7 York Road Parktown, 2193 I Johannesburg I South Africa I Tel: +27 11 717 2552

PARTICIPANT INFORMATION SHEET

Investigating patient-specific risk factors for chemotherapy induced nausea and vomiting in patients with cancer.

Principle Investigator: Johara Rahim (MPharm candidate, University of Witwatersrand)
Supervisors: Mrs Razeeya Khan, Dr Ané Orchard, Muhammed Vally, Prof. Georgia Demetriou

Dear Sir/Madam

My name is Johara Rahim. I am a Master of Pharmacy student currently registered at the University of Witwatersrand. I am humbly inviting you to participate in my research study. Before you decide to participate it is important for you to understand why the research is being done and what it will involve. Please take your time to read this information sheet and feel free to ask questions if there is anything you are uncertain about. Your participation is entirely voluntary. There will be no penalty should you choose not to take part in this study. You are free to withdraw from this study at any stage, and there will be no penalties should you decide to stop taking part at any point of the study.

The research study.

Chemotherapy-induced nausea and vomiting is one of the most common side effects of chemotherapy, affecting the majority of patients that are on treatment. Recent research has shown that there are risk factors such as younger age, female sex, alcohol consumption and history of motion/morning sickness that may contribute to the development of nausea and vomiting in patients. This study will investigate these risk factors for chemotherapy induced nausea and vomiting in patients with cancer. Your participation will involve the completion of

a survey. The survey is made up of 3 sections. The first section will collect information on your age, sex and race. Two sections will entail questions about how often you experience nausea and vomiting whilst on treatment and the various risk factors such as age and gender. To evaluate the treatment regimen that you are currently on, your prescription will be reviewed. The researcher will complete the survey for you by asking you the questions. Completion of the survey will take around 10-15 minutes.

Who will be included in this study?

Patients who can speak English with cancer.

Patients over the age of 18 years.

Patients with solid tumours.

Patients on routine intravenous chemotherapy

Confidentiality

Please note that all information will remain confidential. Your names will not be recorded in this study and no identifying information will be collected. Raw data will be available to only the researcher and the supervisors.

Risks

Patients may experience some mild discomfort during the interview as some questions may make you feel sensitive. If you do feel emotional while you are answering questions, please let me know. You will be referred to the Gauteng Centre of Excellence for Palliative care for additional support.

Benefits

You will not receive any direct benefits from participating in this study, and there are no disadvantages or penalties for not participating.

Outputs

The findings of the study or a summary of the findings may be requested after the study is completed. The study is expected to be completed in December 2023. We look forward to your participation and to sharing the results of the survey with you.

Ethics Clearance:

This study has been approved by the Human Research Ethics Committee (Medical) of the University of the Witwatersrand, Johannesburg.The role of this Committee is to safeguard the rights and dignity of all human subjects who agree to participate in a research project and the integrity of the research. If you have any concern over the way the study is being conducted, please contact the Chairperson of this Committee who is Professor Paul Ruff, who may be contacted via any one member of the secretariat. The telephone numbers for the Committee secretariat are 011 717 2700/1234/2656/1252 and the e-mail addresses are Zanele.Ndlovu@wits.ac.za, Rhulani.Mukansi@wits.ac.za, Mapula.Ramaila@wits.ac.za and Iain.Burns@wits.ac.za.

For further information regarding this study, you may contact:

1) Johara Rahim (Principal Investigator), email: 2085387@students.wits.ac.za
2) Mrs Razeeya Khan (Primary Supervisor), email: Razeeya.Khan@wits.ac.za
3) Dr Ané Orchard (Co-Supervisor), email: Ane.Orchard@wits.ac.za
4) Muhammed Vally (Co-Supervisor), email: Muhammed.Vally@wits.ac.za
5) Prof. Georgia Demetriou, email: georgia.demetriou@wits.ac.za Thank you for taking the time to consider participation.

Kind regards

Johara Rahim

MPharm candidate, Department of Pharmacy and Pharmacology, University of Witwatersrand.

Appendix G: Patient consent form

Department of Pharmacy and Pharmacology

Faculty of Health Sciences I 7 York Road Parktown, 2193 I Johannesburg I South Africa I Tel: +27 11 717 2552

Consent Form

Investigating patient-specific risk factors for chemotherapy induced nausea andvomiting in patients with cancer.

Principle Investigator: Johara Rahim (MPharm candidate, University of Witwatersrand)
Supervisors: Mrs. Razeeya Khan, Dr Ané Orchard, Muhammed Vally, Prof. Georgia Demetriou

I hereby confirm that I have accurately read and understood the information sheet provided by the researcher, and I understand the following:

- I understand that participation is voluntary, and that I will not be penalised for non-participation
- I understand that I may withdraw from the study at any time and that withdrawal at any stage does not incur any harm or penalty
- I understand that the researcher will use my responses for furthering research, education and training
- I understand that I have the right to not answer any questions I do not feel comfortable answering.
- I understand that this study requires that a questionnaire be completed and my prescription to be reviewed
- I understand that my privacy will be respected, and that my personal identifiable details willnot be made available.

I hereby agree that I have understood the requirements of this project and I am willing to participate in the survey.

Signature: _____ Date: _____

Appendix H: Survey Instrument

Investigating patient-specific risk factors for chemotherapy induced nausea and vomiting (CINV) in patients with cancer.

A. Demographic Information

(Information will be obtained from patient)

	Question	Response
1	Age	18-38 39-64 ≥65
2	Sex	Male Female Other Prefer not to say
3	Race	Black/African White/European Mixed Ethnicity/Coloured South Asian/Indian East Asian Other, specify

B. Patient Chemotherapy regimen

(Information will be obtained from prescription review)

	Question	Response
I	Cancer diagnosis:	
II	Cancer Stage:	
1	Current chemotherapy regimen.	
2	Emetogenicity of chemotherapy regimen:	High emetogenicity (HEC) Moderate emetogenicity (MEC) Low emetogenicity (LEC) Minimal emetogenicity (MinEC)
3	Cycle Number	□ 1 □ 2 □ 3 □ ≥4
4	What CINV prophylaxis is the patient currentlyreceiving and what is the dosage prescribed?	
5	Is the antiemetic prophylaxis regimen prescribed inline with the oncology unit's guidelines?	Yes No
6	If not, why?	

C. The incidence of CINV

(Information will be obtained from the patient)

	Question	Response
7	Have you experienced any vomiting in the past 24hours?	Yes No
8	If you have experienced vomiting, how many times did ɒccur?	1-2 3-4 5-6
9	Have you experienced any nausea in the absence of vomiting within the past 24 hours?	Yes No
10	If you have experienced nausea within the first 24hours of treatment, please rate how severe it was: *(Aims*	Mild Moderate Severe
11	Have you experienced any vomiting after 24 hours ormore of receiving treatment?	Yes No
12	If so, how many times did it occur?	1-2 3-4 5-6
13	Have you experienced any nausea in the absence of vomiting after 24 hours or more of receiving treatment? *(Aims to fulfil objective 3.3)*	Yes No
14	If you have experienced nausea after 24 hours ofreceiving treatment, please rate how severe it was: *(Aims to fulfil objective 3.3)*	Mild Moderate Severe

D. Risk Factors associated with CINV.

(Information will be obtained from the patient)

	Question	Response
15	How many hours of sleep do you usually get?	1-3 hrs 4-7 hrs 8-10 hrs
16	Has CINV affected your ability to sleep?	No Yes
17	Prior to beginning chemotherapy, did you anticipate experiencing nausea and vomiting?	Often Sometimes Not at all
18	Do you have a history of motion sickness or experiencenausea and vomiting whilst travelling in a car, taxi, busetc.?	Yes No
19	Do you have a history of morning sickness? (*Applicable if patient is female and has been pregnant before*)	Yes No N/A
20	Do you drink alcohol?	No Yes
21	How often do you consume alcohol?	1-3 times per month 1-6 times per week Rarely Patient does not drink
22	Do you suffer from any other co-morbidities/chronic conditions?	Yes No
23	If yes, please specify:	
24	Are you currently taking any prescription medications?	No Yes

25	If yes, please specify:	
26	Are you currently taking any non-prescription medications?	No Yes
27	If yes please specify:	
28	Did you eat a meal prior to coming in to receivetreatment today?	Yes No
29	What food did you eat?	
30	Are you a smoker?	Yes, I am No, I have never No, but I used to.
31	If you are a smoker, how many cigarettes do you smoke per day?	1-9 cigarettes 10-20 cigarettes
32	If you are a former smoker, how many cigarettes did you smoke?	1-9 cigarettes 10-20 cigarettes
33	Do you smoke marijuana? *(Aims to fulfil objective 3.4)*	No, I have never No, but I used to Yes, I do
34	What other complementary/alternative therapies are you using to treat CINV?	Peppermint tea Music therapy Meditation Acupuncture Aromatherapy Other, please specify:
35	Have you ever used ginger to alleviate CINV?	No Yes
36	What is your height?	
37	What is your weight?	
38	BMI:	

Appendix I: Table of CINV incidence during the overall phase based on patient-related risk factors.

	CINV Incidence (Overall Phase)							
	Only nausea		Nausea and vomiting		No nausea and vomiting		Total	
	N	%	N	%	N	%	N	%
Age range of study participant								P = 0.054
18-38	7	14	17	17	8	11.1	32	14.4
39-64	37	74	74	74	46	63.9	157	70.7
≥65	6	12	9	9	18	25	33	14.9
Total	50	100	100	100	72	100	222	100
Sex								P = 0.126
Female	41	82	70	70	47	65.3	158	71.2
Male	9	18	30	30	25	34.7	64	28.8
Total	50	100	100	100	72	100	222	100
Race								P=0.033
Black	24	48	51	51	52	72.2	127	57.2
Other (Indian/Coloured)	10	20	17	17	9	12.5	36	16.2
White	16	32	32	32	11	15.3	59	26.6
Total	50	100	100	100	72	100	222	100
Cancer Diagnosis								P=0.545
Breast cancer	32	64	51	51	37	51.4	120	54.1
GIT cancers	7	14	23	23	11	15.3	41	18.5
Other	6	12	15	15	15	20.8	36	16.2

	CINV Incidence (Overall Phase)							
	Only Nausea		Nausea with vomiting		No nausea and vomiting		Total	
	N	%	N	%	N	%	N	%
Lymphoma	5	10	11	11	9	12.5	25	11.3
Total	50	100	100	100	72	100	222	100
Cancer stage								
1	2	4	5	5	8	11.1	15	6.8
2	7	14	9	9	3	4.2	19	8.6
3	13	26	22	22	12	16.7	47	21.2
4	16	32	29	29	23	31.9	68	30.6
Uncertain	12	24	35	35	26	36.1	73	32.9
Total	50	100	100	100	72	100	222	100
Emetogenicity								P=0.765
High emetogenicity	8	16	16	16	13	18.1	37	16.7
Low/Min emetogenicity	22	44	34	34	25	34.7	81	36.5
Moderate emetogenicity	20	40	50	50	34	47.2	104	46.8
Total	50	100	100	100	72	100	222	100
Cycle Number								P=0.001*
1	1	2	0	0	18	25	19	8.6
2	12	24	20	20	17	23.6	49	22.1
3	15	30	31	31	9	12.5	55	24.8
4	22	44	49	49	28	38.9	99	44.6
Total	50	100	100	100	72	100	222	100

*Fischer's exact test

	CINV Incidence (Overall Phase)							
	Only nausea		Nausea with vomiting		No nausea and vomiting		Total	
	N	%	N	%	N	%	N	%
Hours of sleep prior to receiving chemotherapy.								P=0.959
1-3 hrs	7	14	13	13	11	15.3	31	14
4-7 hrs	21	42	41	41	26	36.1	88	39.6
8-10 hrs	22	44	46	46	35	48.6	103	46.4
Total	50	100	100	100	72	100	222	100
Effect of CINV on ability to sleep.								
CINV did not affect ability to sleep.	44	88	89	89	72	100	205	92.3
CINV did affect ability to sleep.	6	12	11	11	0	0	17	7.7
Total	50	100	100	100	72	100	222	100
Experience of anticipatory nausea and vomiting (ANV) prior to chemotherapy.								P=0.001*
Patient never experienced ANV	26	52	42	42	54	75	122	55
Patient experienced ANV often.	10	20	26	26	4	5.6	40	18
Patient sometimes experienced ANV.	14	28	32	32	14	19.4	60	27
Total	50	100	100	100	72	100	222	100
History of motion sickness.								P=0.001*
Patient did not have a history of motion sickness.	38	76	60	60	70	97.2	168	75.7
Patient did have a history of motion sickness.	12	24	40	40	2	2.8	54	24.3
Total	50	100	100	100	72	100	222	100

*Fischer's exact test

	CINV Incidence (Overall Phase)							
	Only nausea		Nausea with vomiting		No nausea and vomiting		Total	
	N	%	N	%	N	%	N	%
History of morning sickness								P=0.691
Patient was male/never been pregnant	16	32	38	38	31	43.1	85	38.3
Patient did not have a history of morning sickness	12	24	17	17	12	16.7	41	18.5
Patient has a history of morning sickness	22	44	45	45	29	40.3	96	43.2
Total	50	100	100	100	72	100	222	100
Consumption of alcohol								P=0.041
Patient does not drink	25	50	71	71	45	62.5	141	63.5
Patient does drink	25	50	29	29	27	37.5	81	36.5
Total	50	100	100	100	72	100	222	100
Frequency of alcohol consumption								P=0.020*
1-3 times per month	14	28	11	11	11	15.3	36	16.2
1-6 times per week	9	18	9	9	14	19.4	32	14.4
Patient does not drink	25	50	71	71	45	62.5	141	63.5
Patient rarely drinks	2	4	9	9	2	2.8	13	5.9
Total	50	100	100	100	72	100	222	100
Concurrent comorbidities								P=0.047
Patient does not have another comorbidity	19	38	59	59	35	48.6	113	50.9
Patient does have another comorbidity	31	62	41	41	37	51.4	109	49.1
Total	50	100	100	100	72	100	222	100

*Fischer's exact test

	CINV Incidence (Overall Phase)							
	Only nausea		**Nausea with vomiting**		**No nausea and vomiting**		**Total**	
	N	**%**	**N**	**%**	**N**	**%**	**N**	**%**
Types of comorbidities present								P=0.165*
Chronic pain	4	8	3	3	1	1.4	8	3.6
Diabetes	6	12	3	3	6	8.3	15	6.8
GERD	0	0	4	4	3	4.2	7	3.2
HIV	8	16	11	11	11	15.3	30	13.5
Hypertension	11	22	19	19	14	19.4	44	19.8
Mental health disorders (Anxiety/depression/insomnia)	2	4	1	1	2	2.8	5	2.3
no co-morbidities	19	38	59	59	35	48.6	113	50.9
Total	50	100	100	100	72	100	222	100
Prescription medication use								P=0.047
Patient does not use other prescription medications	19	38	59	59	35	48.6	113	50.9
Patient does use other prescription medications	31	62	41	41	37	51.4	109	49.1
Total	50	100	100	100	72	100	222	100
Types of prescription medications used								P=0.165*
Antidepressants (Fluoxetine/citalopram/diazepam/amitryptiline)	2	4	1	1	2	2.8	5	2.3
ARVs	8	16	11	11	11	15.3	30	13.5
Diabetes medications (Metformin)	6	12	3	3	6	8.3	15	6.8
GERD treatment (cimetidine/PPI)	0	0	4	4	3	4.2	7	3.2
Hypertension medication	11	22	19	19	14	19.4	44	19.8
Opiods (Tramadol/Morphine)	4	8	3	3	1	1.4	8	3.6
no co-morbidities	19	38	59	59	35	48.6	113	50.9

*Fischer's exact test

	CINV Incidence (Overall Phase)							
	Only nausea		**Nausea with vomiting**		**No nausea and vomiting**		**Total**	
	N	**%**	**N**	**%**	**N**	**%**	**N**	**%**
Total	50	100	100	100	72	100	222	100
Use of non-prescription medications								P=0.597
Patient does not use non-prescription medications	27	54	59	59	37	51.4	123	55.4
Patient does use other prescription medications	23	46	41	41	35	48.6	99	44.6
Total	50	100	100	100	72	100	222	100
Types of non-prescription medications used.								P=0.455*
Analgesics/Antipyretics (paracetamol/aspirin/ibuprofen)	16	32	31	31	28	38.9	75	33.8
Antihistamines	3	6	3	3	0	0	6	2.7
Vitamins (b,c,d,magnesium)	4	8	7	7	7	9.7	18	8.1
Patient did not take non-prescription medications	27	54	59	59	37	51.4	123	55.4
Total	50	100	100	100	72	100	222	100
Meal eaten prior to chemotherapy								P=0.964
Patient did not eat a meal	10	20	19	19	13	18.1	42	18.9
Patient did eat a meal	40	80	81	81	59	81.9	180	81.1
Total	50	100	100	100	72	100	222	100
Type of meal eaten								P=0.734
Heavy meal (High in fat, carbohydrates, proteins and processed sugars)	14	28	31	31	16	22.2	61	27.5

*Fischer's exact test

	CINV Incidence (Overall Phase)							
	Only nausea		**Nausea with vomiting**		**No nausea and vomiting**		**Total**	
	N	**%**	**N**	**%**	**N**	**%**	**N**	**%**
Light meal (consists of wholegrains, lower in proteins, carbohydrates,fats and processed sugars)	26	52	50	50	43	59.7	119	53.6
Patient did not eat prior to chemo	10	20	19	19	13	18.1	42	18.9
Total	50	100	100	100	72	100	222	100
Smoking status								P=0.136
Patient has never smoked	32	64	62	62	57	79.2	151	68
Patient is a former smoker	9	18	20	20	10	13.9	39	17.6
Patient is a current smoker	9	18	18	18	5	6.9	32	14.4
Total	50	100	100	100	72	100	222	100
Number of cigarettes smoked as a current smoker								P=0.231*
1-9 cigarettes	3	6	8	8	3	4.2	14	6.3
10-20 cigarettes	6	12	10	10	2	2.8	18	8.1
Patient is a former smoker	9	18	20	20	10	13.9	39	17.6
Patient has never smoked	32	64	62	62	57	79.2	151	68
Total	50	100	100	100	72	100	222	100
Number of cigarettes smoked as a former smoker								P=0.199*
1-9 cigarettes	6	12	14	14	5	6.9	25	11.3
10-20 cigarettes	3	6	6	6	5	6.9	14	6.3

*Fischer's exact test

	CINV Incidence (Overall Phase)							
	Only nausea		**Nausea with vomiting**		**No nausea and vomiting**		**Total**	
	N	**%**	**N**	**%**	**N**	**%**	**N**	**%**
Patient has never smoked	32	64	62	62	57	79.2	151	68
Patient is a current smoker	9	18	18	18	5	6.9	32	14.4
Total	50	100	100	100	72	100	222	100
Marijuana use								P=0.014*
Patient has never smoked marijuana	36	72	73	73	66	91.7	175	78.8
Patient used to smoke marijuana	9	18	20	20	5	6.9	34	15.3
Patient smokes marijuana	5	10	7	7	1	1.4	13	5.9
Total	50	100	100	100	72	100	222	100
Use of complementary/alternative therapies to treat CINV								P=0.011*
Patient used alternative therapies	4	8	7	7	0	0	11	5
Patient used complementary medications	4	8	14	14	1	1.4	19	8.6
Patient used neither	42	84	79	79	71	98.6	192	86.5
Total	50	100	100	100	72	100	222	100
Ginger use to alleviate CINV experienced?								P=0.018
Patient uses ginger	9	18	21	21	4	5.6	34	15.3
Patient does not use ginger	41	82	79	79	68	94.4	188	84.7
Total	50	100	100	100	72	100	222	100

*Fischer's exact test

	CINV Incidence (Overall Phase)							
	Only nausea		Nausea with vomiting		No nausea and vomiting		Total	
	N	%	N	%	N	%	N	%
BMI								P=0.229*
18.5-24.9 (Healthy weight)	20	40	36	36	29	41.4	85	38.6
25-29.9 (Overweight)	10	20	39	39	24	34.3	73	33.2
<18.5 (underweight)	2	4	3	3	3	4.3	8	3.6
> 30 (Obese)	18	36	22	22	14	20	54	24.5
Total	50	100	100	100	70	100	220	100

* Fischer's exact test

Appendix J: FIP poster presentation

Investigating patient-specific risk factors for chemotherapy induced nausea and vomiting in patients with cancer

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Introduction

Chemotherapy-induced nausea and vomiting (CINV) is the most common side effect of cancer treatment. Despite the use of adequate antiemetic prophylaxis, CINV remains poorly controlled, significantly reducing a patient's quality of life and potentially impacting adherence to cancer treatment, which can lead to suboptimal therapeutic outcomes. Research has shown that patient-specific risk factors contribute to the development of CINV. The identification and management of patient-specific risk factors remain underexplored in various contexts. To date, no study has comprehensively examined the influence of patient-specific factors on the incidence of CINV within the South African population. By integrating antiemetic guidelines with patient-specific risk assessments, comprehensive treatment regimens could be developed to further optimise antiemetic strategies for high-risk patients. This research is not only essential for improving patient care in South Africa but could also provide insights applicable to other underrepresented populations globally.

Aim

This study aimed to investigate the nature and extent of CINV in patients receiving routine treatment for cancer in a tertiary public sector facility in Johannesburg, South Africa.

Methodology

Researcher presented the study to patients in a group setting and distributed participant information sheets. Informed consent was obtained from interested patients.

Concurrent interviews and prescription reviews were conducted during chemotherapy administration.

Data was collected using a validated questionnaire covering demographics, chemotherapy regimens, CINV occurrence, and risk factors.

Collected data was analysed to identify the extent of CINV and associated risk factors.

References

Aapro M. (2018). CINV: still troubling patients after all these years, *Support Care Cancer*, 26 (1), p.5–9.
Abunahlah, N., et al. (2016). Impact of adherence to antiemetic guidelines on the incidence of chemotherapy-induced nausea and vomiting and quality of life. *Int. J Clin. Pharm.*, 38, pp.1464-1476.

Results and discussion

- Our study found a significant prevalence of CINV among the cohort, with 45% experiencing both nausea and vomiting, 22.5% experiencing only nausea, and 32.4% having no symptoms (Figure 1).

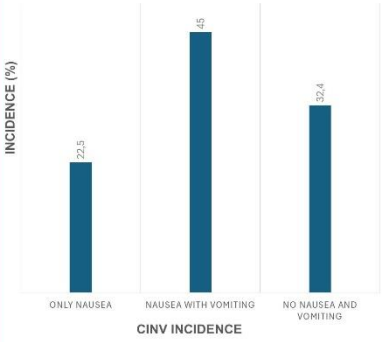

Figure 1: Prevalence of CINV in the study cohort.

- Adherence to antiemetic guidelines significantly reduced CINV incidence, as demonstrated in Figure 2, where guideline adherence correlated with lower rates of both nausea and vomiting.

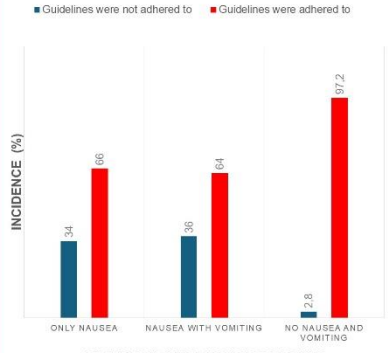

Figure 2: Adherence to antiemetic guidelines vs CINV incidence.

- Significant risk factors were tested in a multivariate logistic regression model to quantify their association with CINV, with the most stable model selected based on the Akaike Information Criterion (AIC) (Table 1).

Acknowledgements

A special thanks to the biostatisticians, Dr. Clarence Yah and Prof. Elena Liebhaber, for their invaluable assistance with the statistical analysis and interpretation.

Results and discussion (cont.)

Table 1: Multivariate analysis of significant risk factors.

	Only nausea			Nausea and vomiting		
Variable	RRR	95%CI	P-Value	RRR	95%CI	P-value
Race						
Black	REF	REF	REF	REF	REF	REF
Other (Indian/Coloured)	1.55	0.44-5.48	0.495	1.09	0.33-3.61	0.887
White	3.01	1.02-8.84	0.045	1.93	0.71-5.26	0.198
Adherence to antiemetic guidelines						
Regimen did not adhere to guideline.	REF	REF	REF	REF	REF	REF
Regimen adhered to guideline.	0.03	0.006-0.141	0.000	0.02	0.004-0.100	0.000
Experiencing anticipatory nausea and vomiting (ANV)						
Patient rarely experienced ANV.	REF	REF	REF	REF	REF	REF
Patient experienced ANV often.	5.08	1.18-21.90	0.029	6.53	1.71-24.96	0.006
Patient sometimes experienced ANV.	2.44	0.88-6.71	0.085	3.47	1.37-8.82	0.009
History of motion sickness						
Patient does not have a history of motion sickness.	REF	REF	REF	REF	REF	REF
Patient does have a history of motion sickness	8.02	1.52-42.41	0.014	12.81	2.70-60.79	0.001
Marijuana use						
Patient does not smoke marijuana	REF	REF	REF	REF	REF	REF
Patients used to smoke marijuana	3.47	0.87-13.88	0.078	3.39	0.93-12.36	0.065
Patient smokes marijuana	8.47	0.70-101.95	0.092	11.80	0.99-140.33	0.051
Ginger use to alleviate CINV						
Patient does not use ginger	REF	REF	REF	REF	REF	REF
Patient does use ginger	5.02	1.35-18.68	0.016	5.87	1.69-20.34	0.005

REF*-Reference Category, against which the relative risk ratios (RRR) of other categories are compared.

- Several significant risk factors for CINV were identified. Non-adherence to antiemetic guidelines was strongly associated with higher CINV incidence. In line with existing literature, ANV and motion sickness were confirmed as significant risk factors for CINV. The association between marijuana use and increased CINV risk highlights a gap in current literature, warranting further research. Additionally, the unexpected finding that ginger use correlated with higher CINV incidence suggests the need for more nuanced investigations into its effectiveness. These findings highlight the complexity of managing CINV.

Conclusion

The challenge of CINV is a significant concern in cancer treatment, with various factors influencing the effectiveness of antiemetic regimens. The present study underscores the importance of concordance with specified treatment protocols, improved use of olanzapine for delayed CINV and the incorporation of NK-1 RAs for improved CINV management, adding the growing body of evidence for the need for individualised patient assessments to optimise treatment outcomes. This includes a comprehensive assessment of factors such as a history of motion sickness, ANV and use of complementary treatments which may predispose patients to CINV. Identification of high-risk individuals enables healthcare providers to develop personalised and effective antiemetic strategies to enhance CINV management and improve patient outcomes.

Appendix K: ECOP poster presentation

ECOP 6 European Conference of Oncology Pharmacy

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Investigating the extent of comorbidity in a cohort of patients with cancer in a resource limited setting

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*Department of Medical Oncology, University of the Witwatersrand, South Africa

Introduction

Comorbidity in patients with cancer is common, and more so as the aging population increases (Sarfati, Koczwara, and Jackson 2016). Non-communicable diseases and cancer are public health priorities globally and in South Africa, which also has a high patient burden of Human Immunodeficiency Virus infections (HIV) and tuberculosis comorbidity (Peltzer 2018). The economic burden of managing multimorbidity impacts on the distribution of health resources (Tran et al. 2022). In resource limited settings, navigating the public healthcare system for patients with cancer multimorbidity is challenging (Mendenhall et al. 2019). This study investigated the extent of comorbidity in outpatients with cancer at a large public sector academic hospital in South Africa.

Methodology

Ethics Approval obtained from Wits HREC

Sub-analysis of a descriptive cross-sectional cohort study

Concurrent interviews and prescription review conducted ion patients >18yrs with solid tumours receiving chemotherapy

Data collected using an electronic validated REDCap researcher administered questionnaire

Data analysed using descriptive statistics to identify the extent of comorbidity

Results and Discussion

Data from 222 patient records were analysed, of which 158 (71.17%) were female patients, higher than the recorded average % of female patients with cancer in the country (51.3%). Most patients were of Black ethnicity (57.21%), less than the general population.

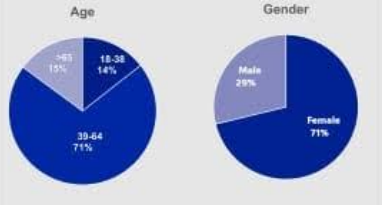

Fig 1: Age and gender distribution of cohort

Results and Discussion (cont)

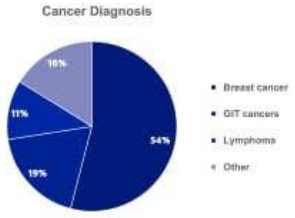

Fig 2: Common cancers in outpatient cohort

The most common cancer diagnosis was breast cancer (54.05 %), followed by GIT cancers, which are in the top 5 cancers affecting the South African population.

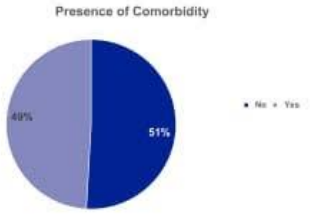

Fig 3: Comorbidity distribution of cohort

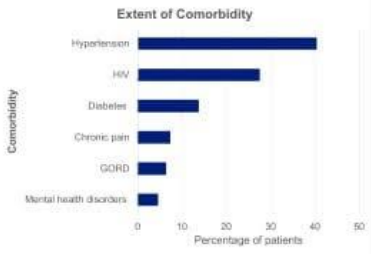

Fig 4: Common comorbidity in cohort

Comorbidity was present in 49.1% of patients, with hypertension, HIV and diabetes being the most common comorbid conditions respectively. Mental health comorbid conditions included anxiety, depression and insomnia

Use of prescription medicines other than chemotherapy was noted in 51.4% of patients, interestingly no additional anti-emetics agents were prescribed. The most common prescription medicines used are described in Fig 4. Fluoxetine and citalopram were common in those using antidepressant medicines, metformin, cimetidine/PPIs, tramadol and morphine were also commonly reported.

Results and Discussion (cont)

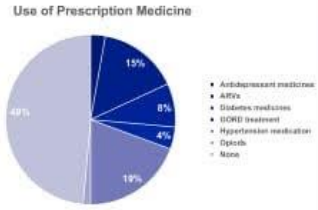

Fig 5: Prescription Medicines used by cohort

Cardiovascular risk factors of smoking (14.41%), and increased BMI (57.57%) were present in this cohort.

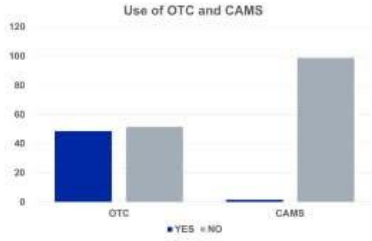

Fig 6: Comorbidity distribution of cohort

Overall, 55.4% of patients reported not using any non-prescription medications. Commonly, analgesics or antipyretics (paracetamol, aspirin, or ibuprofen) were used. This out-of-pocket expense needs to be addressed.

Conclusion

These findings describe the extent of comorbidity, medicine use and risk factors for cardiovascular disease in this population. Given the co-occurrence of disease, the patient to be reviewed at more than one clinic, with a resulting increase in disease, financial, and resource burden for the patient. Clinicians should consider simultaneous management of common comorbidity in patients with cancer to provide a seamless traverse of patients with life-threatening disease through the public health care system in South Africa.

References and Acknowledgements

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The authors acknowledge the assistance of the biostatisticians, Dr Clarence Yah and Prof. Elena Libhaber

Appendix L: Plagiarism declaration

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PLAGIARISM DECLARATION TO BE SIGNED BY ALL HIGHER DEGREE STUDENTS

SENATE PLAGIARISM POLICY: APPENDIX ONE

I Johara Rahim (Student number: 2085387) am a student registered for the degree of Master of Pharmacy in the academic year 2024.

I hereby declare the following:

- I am aware that plagiarism (the use of someone else's work without their permission and/or without acknowledging the original source) is wrong.
- I confirm that the work submitted for assessment for the above degree is my own unaided work except where I have explicitly indicated otherwise.
- I have followed the required conventions in referencing the thoughts and ideas of others.
- I understand that the University of the Witwatersrand may take disciplinary action against me if there is a belief that this is not my own unaided work or that I have failed to acknowledge the source of the ideas or words in my writing.
- I have included as an appendix a report from "Turnitin" (or other approved plagiarism detection) software indicating the level of plagiarism in my research document.

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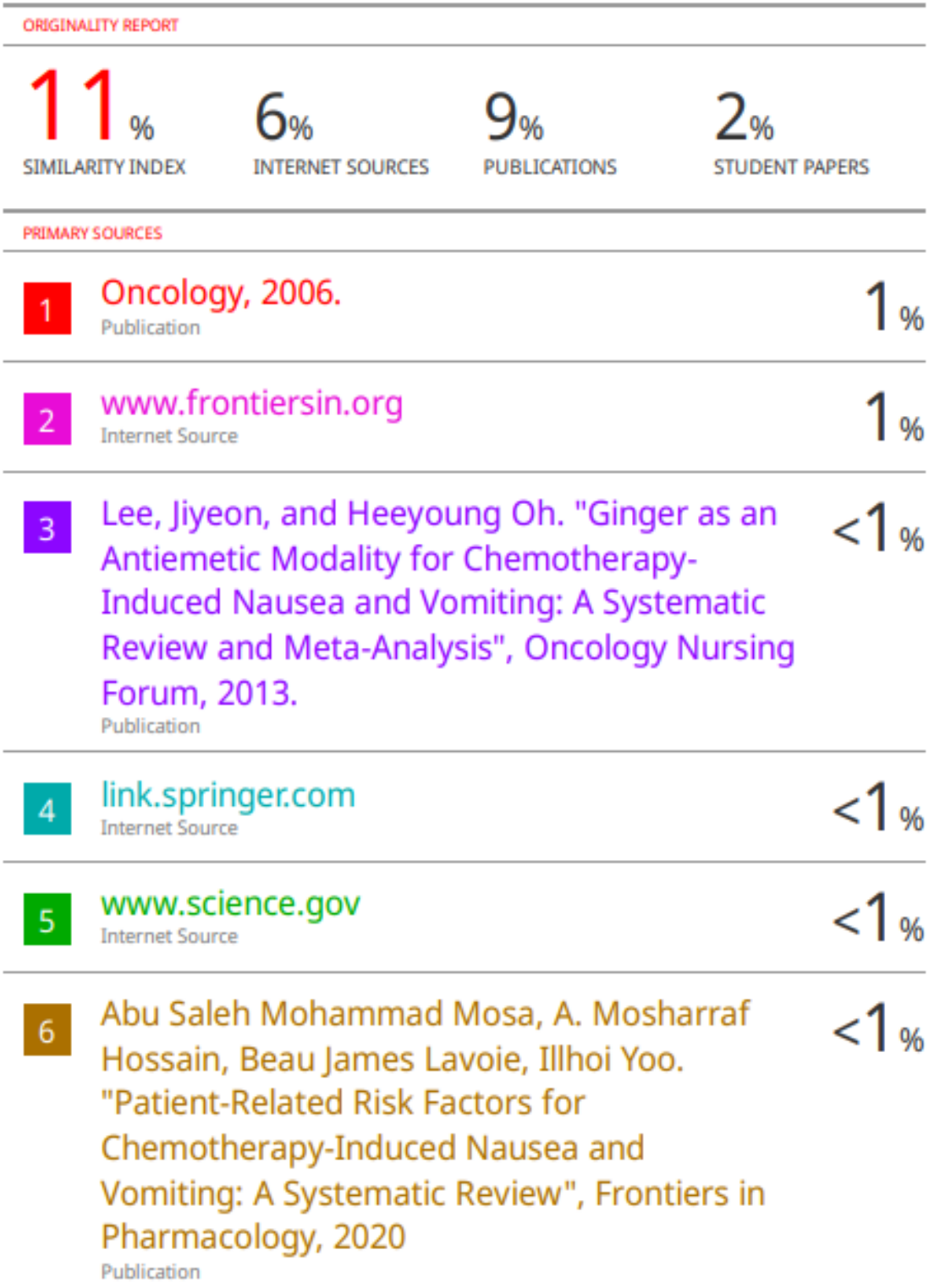
Appendix M: Turnitin report



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4	link.springer.com Internet Source	<1%
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6	Abu Saleh Mohammad Mosa, A. Mosharraf Hossain, Beau James Lavoie, Illhoi Yoo. "Patient-Related Risk Factors for Chemotherapy-Induced Nausea and Vomiting: A Systematic Review", Frontiers in Pharmacology, 2020 Publication	<1%