Toxicol. Res.
Vol. 28, No. 2, pp. 81-91 (2012)
Open Access http://dx.doi.org/10.5487/TR.2012.28.2.081
pISSN: 1976-8257 eISSN: 2234-2753

Official Journal of Korean Society of Toxicology
Available online at http://www.toxmut.or.kr

Exploring Chemotherapy-Induced Toxicities through Multivariate Projection of Risk Factors: Prediction of Nausea and Vomiting

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(Received January 17, 2012; Revised March 18, 2012; Accepted March 22, 2012)

Many risk factors exist for chemotherapy-induced nausea and vomiting (CINV). This study utilized a multivariate projection technique to identify which risk factors were predictive of CINV in clinical practice. A single-centre, prospective, observational study was conducted from January 2007~July 2010 in Singapore. Patients were on highly (HECs) and moderately emetogenic chemotherapies with/without radiotherapy. Patient demographics and CINV risk factors were documented. Daily recording of CINV events was done using a standardized diary. Principal component (PC) analysis was performed to identify which risk factors could differentiate patients with and without CINV. A total of 710 patients were recruited. Majority were females (67%) and Chinese (84%). Five risk factors were potential CINV predictors: histories of alcohol drinking, chemotherapy-induced nausea, chemotherapy-induced vomiting, fatigue and gender. Period (ex-/current drinkers) and frequency of drinking (social/chronic drinkers) differentiated the CINV endpoints in patients on HECs and anthracycline-based, and XELOX regimens, respectively. Fatigue interference and severity were predictive of CINV in anthracycline-based populations, while the former was predictive in HEC and XELOX populations. PC analysis is a potential technique in analyzing clinical population data, and can provide clinicians with an insight as to what predictors to look out for in the clinical assessment of CINV. We hope that our results will increase the awareness among clinician-scientists regarding the usefulness of this technique in the analysis of clinical data, so that appropriate preventive measures can be taken to improve patients' quality of life.

***Key words*:** Chemotherapy-induced nausea and vomiting, Multivariate projection, Principal component analysis, Principal variables, Risk factors

INTRODUCTION

Patients who are on certain chemotherapies tend to suffer from certain adverse drug reactions, of which chemotherapy-induced nausea and vomiting (CINV) are two of the most distressing (Stieler *et al.*, 2003). The prevalence of CINV ranges from 13~58% for acute nausea and vomiting (NV lasting up to 24 hours after chemotherapy), and 15~75% for delayed nausea and vomiting (NV occurring after 24 hours and lasting up to 5 to 7 days) (Booth *et al.*, 2007; Cohen *et al.*, 2007; Erazo Valle *et al.*, 2006; Grunberg *et al.*, 2004; Liau *et al.*, 2005; Molassiotis *et al.*, 2008). CINV causes extreme discomfort in patients with cancer and can also lead to a decrease in their quality of life, despite preventive therapies with antiemetics (Bloechl-Daum *et al.*, 2006; Roscoe *et al.*, 2010; Schnell, 2003).

CINV is a complicated condition that is affected by many factors, including emetogenicity of chemotherapy regimens (CRegs) and patient-related factors (e.g. young age, female gender, prior CINV experiences, histories of morning and motion sickness, low alcohol use, and presence of anxiety, fatigue and labyrinthitis) (Hesketh, 1999; Lohr, 2008; Molassiotis *et al.*, 2002; National Comprehensive Cancer Network, c2011; Pollera and Giannarelli, 1989; Roscoe *et al.*, 2010; Shih *et al.*, 2009). Some risk factors, such as anxiety and fatigue, are subjective in nature and difficult to quantify. Furthermore, the methodologies of assessing certain risk factors and their evidence as clinical predictors for CINV have been inconsistent. Clinicians need appropriate measures so as to better assess their patients' risks of CINV in daily practice.

Informatics and information technology (IT) have gained increasing acceptance and are becoming extremely popular

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among healthcare professionals. However, the adoption of IT to improve the pharmaceutical care of patients with cancer has been slow. Recently, a multivariate projection technique, known as principal component (PC) analysis, has been employed to investigate the relationships among multiple variables for various medical purposes, such as in the interpretation of repetitive nerve stimulation results (Cengiz and Kuruoğlu, 2006). This technique has also become popular in studies dealing with cancer, such as evaluating various symptom clusters in patients suffering from brain and bone metastases (Chow *et al.*, 2008; Hadi *et al.*, 2008). The principle of PC analysis is to linearly transform an original set of variables into a substantially smaller set of uncorrelated variables that represent most of the information in the original dataset (Dunteman, 1989). Many risk factors that predispose patients to CINV have been identified in the literature, but a large combination of these risk factors have not been studied to identify the ones that play a more important role in patients manifesting this chemotherapy-induced toxicity. PC analysis is well-suited for this purpose, since it reduces the number of variables (CINV risk factors in this case) to only those that explain majority of the variation in the dataset (Asian cancer patients). Therefore, the objective of our study was to utilize this technique to determine which of the treatment-related and patient-related risk factors could be clinically useful for the prediction of CINV in the practice setting.

MATERIALS AND METHODS

Study design and setting. A single-centre, prospective, observational study was conducted between January

Table 1. Chemotherapy regimens and antiemetics received by patients in the study

Type of regimen	Regimen protocol	Regimen details	Antiemetics prescribed[a,b]
Breast cancer regimens	AC	Intravenous Doxorubicin 60 mg/m^2/day, Intravenous Cyclophosphamide 600 mg/m^2/day	Acute antiemetics: Intravenous Granisetron 3 mg, Intravenous Dexamethasone 8 mg Delayed antiemetics: Oral Granisetron 1 mg/day, Oral Dexamethasone 4 mg twice daily
	FAC	Intravenous Doxorubicin 50 mg/m^2/day, Intravenous Cyclophosphamide 500 mg/m^2/day, Intravenous Fluorouracil 500 mg/m^2/day	
	FEC (500/100/500)	Intravenous Epirubicin 100 mg/m^2/day, Intravenous Cyclophosphamide 500 mg/m^2/day, Intravenous Fluorouracil 500 mg/m^2/day	
	FEC (500/75/500)	Intravenous Epirubicin 75 mg/m^2/day, Intravenous Cyclophosphamide 500 mg/m^2/day, Intravenous Fluorouracil 500 mg/m^2/day	
Gastro-intestinal cancers	XELOX	Intravenous Oxaliplatin 130 mg/m^2/day, Oral Capecitabine 2000 mg/m^2/day	Acute antiemetics: Intravenous Ondansetron 8 mg, Intravenous Dexamethasone 8mg Delayed antiemetics: Oral Ondansetron 8 mg/day, Oral Dexamethasone 4 mg twice daily
Head and neck cancers	CDDP 40	Intravenous Cisplatin 40 mg/m^2/day	Acute antiemetics: Intravenous Granisetron 3 mg, Intravenous Dexamethasone 8 mg Delayed antiemetics: Oral Granisetron 1 mg/day, Oral Dexamethasone 4 mg twice daily
	CDDP 100	Intravenous Cisplatin 100 mg/m^2/day	Acute antiemetics: Oral Aprepitant 125 mg, Intravenous Granisetron 3 mg, Intravenous Dexamethasone 8 mg Delayed antiemetics: Oral Aprepitant 80 mg/day (days 2~3), Oral Dexamethasone 4 mg twice daily
	PF (80/1000)	Intravenous Cisplatin 20 mg/m^2/day, Intravenous Fluorouracil 1000 mg/m^2/day, for 4 days	Acute antiemetics: Intravenous Granisetron 3 mg (days 1~4), Intravenous Dexamethasone 8 mg (days 1~4) Delayed antiemetics: Oral Dexamethasone 4 mg twice daily (days 5~9)

[a]Acute antiemetics were given on the day of chemotherapy (day 1), while delayed antiemetics were given on days 2~4, unless stated otherwise.
[b]Oral metoclopramide 20 mg was prescribed up to 4 times daily when needed as rescue therapy.

2007 and July 2010 at the ambulatory treatment unit of the National Cancer Centre, Singapore (NCCS). Inclusion criteria were patients at least 21 years of age with confirmed diagnoses of breast, head and neck, and gastrointestinal cancers. Exclusion criteria were the inability to understand English or Mandarin, and those who refused follow-up for the duration of the study. Patients were on a variety of emetogenic single-day or multiple-day chemotherapy protocols with/without radiotherapy (Table 1) and appropriate antiemetics. This study was approved by the NCCS's institutional review board and written informed consent was obtained from all patients prior to participation in the study.

Procedures and instruments for data collection. Patients were interviewed on their first day of chemotherapy to document their demographics, CINV risk factors (Table 2) and dispensed antiemetics. Patients' anxiety characteristics were evaluated using the Beck Anxiety Inventory (BAI) (Beck *et al.*, 1988), a 21-item instrument for assessing the severity of various anxiety symptoms. This instrument has a high internal consistency of 0.92 and test-retest reliability of 0.75, and was also validated in the local population (Luo *et al.*, 2004).

A standardized self-administered CINV diary was given to patients to record their daily number of vomiting events and intensity of nausea after chemotherapy, and use of antiemetics. Patients on single-day regimens and the multiple-day regimen (PF) completed a 5-day and 9-day diary respectively. Nausea intensity was measured using a 0 to 10 Likert scale in order of increasing intensity. Patients also documented the antiemetics and the periods of the day (morning, afternoon, evening, night) in which they took for delayed and breakthrough CINV. A telephone interview was conducted after diary completion for documentation of their CINV responses. The study design is summarized in Fig. 1.

Definitions of CINV responses. A patient was considered to have acute vomiting or nausea respectively if at least one vomiting episode or nausea scores greater than or equal to 1 (on a scale of 0~10) was reported on day 1 of single-day chemotherapies and days 1~4 of multi-day chemotherapies. These parameters were similarly defined for delayed vomiting or nausea if these occurred any day after the first day of chemotherapy (days 2~5 for single-day regimens, days 5~9 for multi-day regimens). A vomiting episode was defined as a single vomit or retch, or any number of continuous vomits or retches, separated from each other for at least 1 minute. A number of other parameters, referred to as clinical or CINV endpoints, were also employed (Arpornwirat *et al.*, 2009; Gralla *et al.*, 2005; Herrstedt *et al.*, 2009; Hesketh *et al.*, 2009; Jordan *et al.*, 2009; Mueller *et al.*, 2009; Yeo *et al.*, 2009): (a) complete response (CR: no vomiting and no rescue antiemetics), (b) complete protection (CP: no vomiting, no significant nausea (scores 0~2) and no rescue antiemetics), and (c) complete control (CC: no vomiting, no nausea (score 0), and no rescue antiemetics).

Antiemetic treatment. Antiemetic management was regulated by a guideline established by the NCCS Pharmacy and Therapeutics Committee whereby standardized prophylactic antiemetic regimens comprising of a neurokinin-1 antagonist, serotonin antagonist and dexamethasone were given to patients for prevention of acute and delayed CINV (Table 1). At the NCCS, aprepitant-based antiemetic

Table 2. List of risk factors analyzed in the study population

Risk factors	Parameters analyzed
Age	Less than 50 years old/equal to or greater than 50 years old
Anxiety	Scores of anxiety symptoms based on the Beck Anxiety Inventory
Concurrent radiotherapy	Presence/absence
Earache/ringing in the ears	Presence/absence before the initiation of chemotherapy
Emetogenicity of chemotherapy	Low/moderate/high
Fatigue/tiredness	a) Fatigue interference: Degree in which fatigue interferes with the patient's ability to engage in daily activities (since time of cancer diagnosis or the last 6 months, whichever is shorter) b) Fatigue severity: Degree of fatigue severity that the patient is experiencing at the time of survey administration Both parameters were analyzed based on a Likert scale of 0 to 10
Gender	Female/male
History of alcohol use	a) Non-drinker (or drank negligible amounts of alcohol throughout lifetime)/drinker b) Period of drinking: Ex-drinker/current drinker c) Frequency of drinking: Social drinker (< 1 drink/day)/chronic drinker (≥ 1 drink/day)
Histories of chemotherapy-induced nausea and vomiting (where applicable)	a) Nausea: None/mild/moderate/severe b) Vomiting: None/mild/moderate/severe
History of morning sickness (where applicable)	Presence/absence
History of motion sickness	Presence/absence

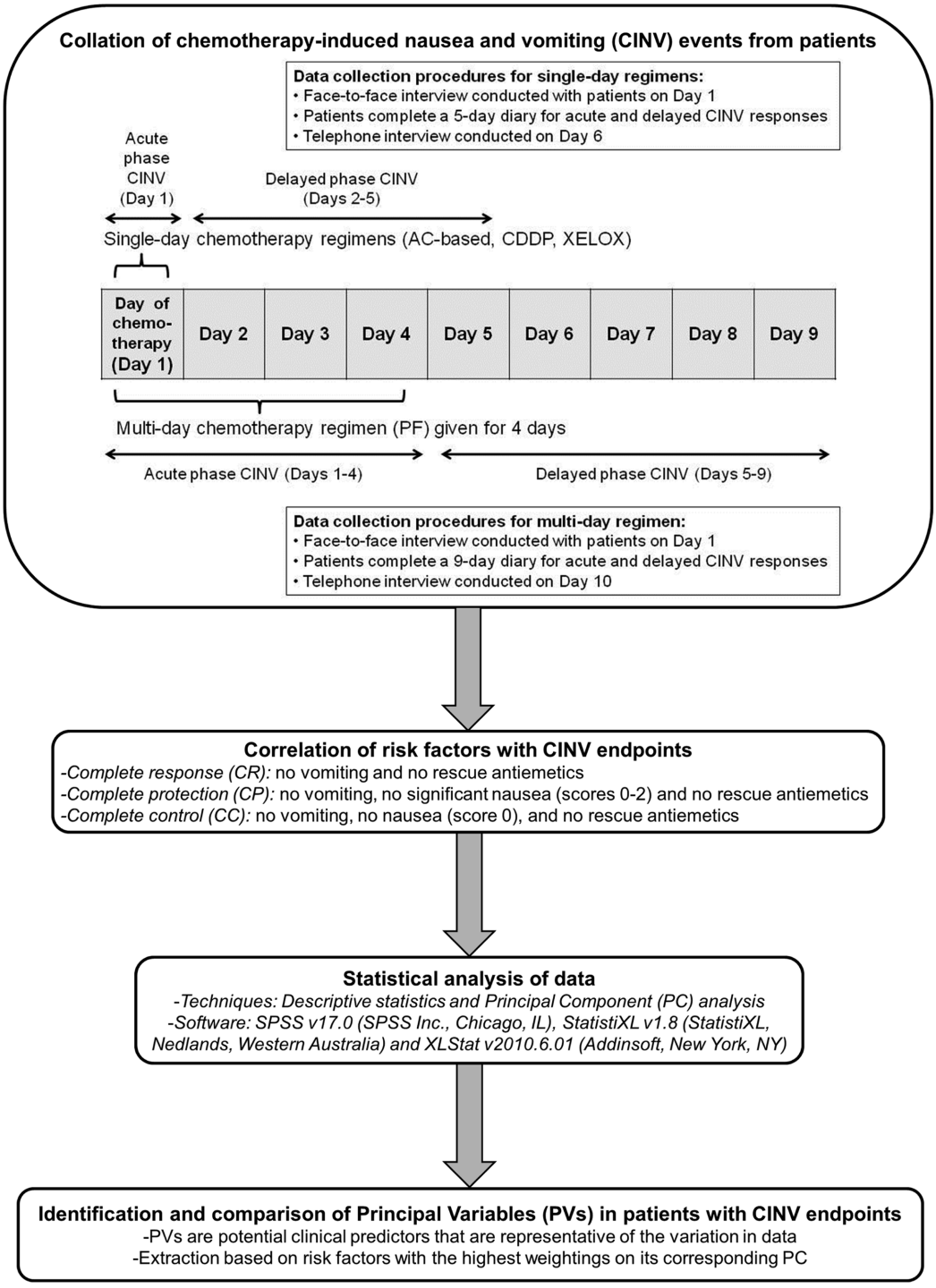

Fig. 1. Summary of the study design.

regimens would only be recommended as first-line prophylaxis for high-dose cisplatin-based CRegs. However, the aprepitant-based antiemetic regimen could also be prescribed based on risk factor assessments by oncology clinicians (e.g., poor control of CINV in the previous chemotherapy cycle). A four-day supply (30 tablets) of the dopamine antagonist, metoclopramide, was also given to patients as rescue therapy for breakthrough emesis, to be taken when needed.

Data analyses. Descriptive statistics were used to summarize patient demographics and CINV characteristics. PC analysis was performed to analyze the various risk factors.

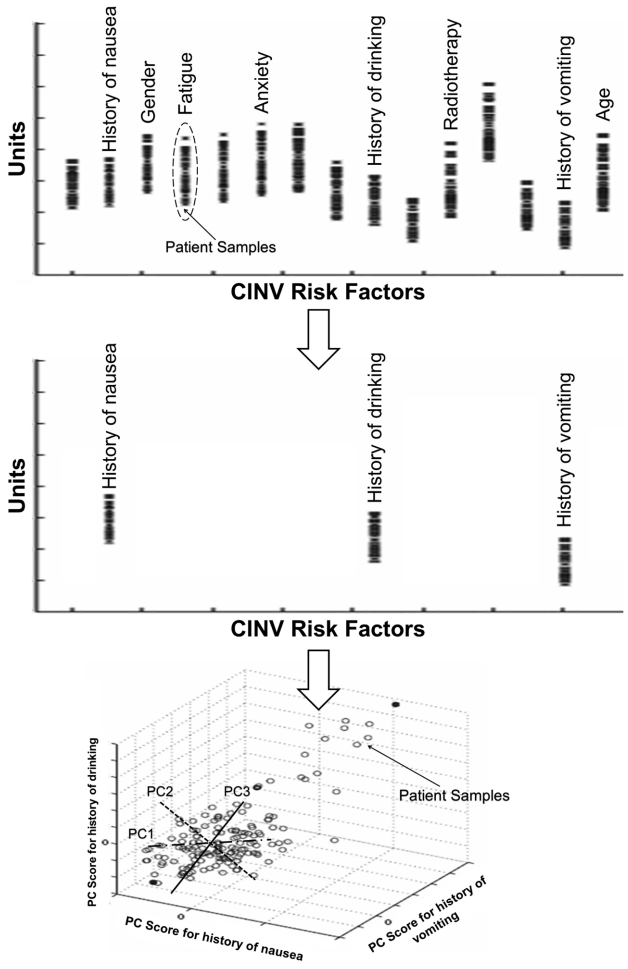

Fig. 2. Illustration of how PC analysis was applied in this study.

For illustrative purposes and easy understanding by clinicians who may otherwise not be familiar with this multivariate projection technique, the following describes the concept of how PC analysis can be applied to clinical patient populations (Fig. 2). In this study, every CINV risk factor (also known as a variable) can be plotted for the patient samples. For 'n' variables, the patients can be plotted in 'n-dimensional' space. PC analysis reduces the data into a subset of variables that can represent most of the variation in the total dataset (i.e. the overall risk of experiencing CINV). To simplify this concept, let's use 3 variables (e.g. histories of alcohol drinking, chemotherapy-induced nausea, and vomiting) to represent the overall CINV risks of the patients. As shown in Fig. 2, each patient can be plotted in 3-dimensional space based on the PC scores of the variables. The plotted data is centered so that it varies around zero. A hypothetical line of best fit (known as a PC) can be drawn in the 3-dimensional space to explain the variation in the whole set of data. PC1 (dotted and dashed line) gives the direction of maximum variance, while PC2 (dashed line) is at right angles to PC1 and oriented to the direction which gives the maximum remaining variability. In turn, PC3 (solid line) is at right angles to both PCs 1 and 2. This reiterative process goes on for the remaining PCs until the rest of the variability in the data is explained. It is important to note that all the PCs have a common origin of centered data, and since the PCs are perpendicular to each other, the variables are uncorrelated. In this study, the eigenvectors (or weightage) of the variables (i.e. risk factors) were used to interpret the PC data based on decomposition of the correlation matrix. The number of PCs selected was based on a combination of Jolliffe's eigenvalue cut-off, Catell's scree plot and an 80% variance cut-off.

A subset of the variables, known as principal variables (PVs), was used to represent the variation in the dataset. These PVs were represented by the risk factors that had the highest weightings on its corresponding PC, and were identified for patients with and without the clinical endpoints (CR, CP and CC). From this subset, those PVs that could distinguish patients with and without CINV were determined. PVs exhibited by the former group of patients (i.e. those who did not achieve the clinical endpoints), but not by the latter group, were identified as potential clinical CINV predictors. The percentage contributions of these clinical predictors to their PCs were compiled together with their direction cosines, which were reflective of the correlations between their PCs and symptom axes. A value closer to 1 would mean a greater correlation between the PC and that particular predictor. The software programmes StatistiXL v1.8 (StatistiXL, Nedlands, Western Australia) and XLStat v2010.6.01 (Addinsoft, New York, NY) were used for PC analysis and SPSS v17.0 (SPSS Inc., Chicago, IL) was used to calculate the descriptive statistics.

RESULTS

Demographics and CINV characteristics of patients. A total of 1027 patients were approached, of which 233 patients (23%) rejected participation in the study and 84 patients (8%) were either lost to follow up or handed in incomplete CINV diaries. The resultant number of recruited patients was 710 (69%). Among these, 139 (20%) were on highly-emetogenic chemotherapies (HECs), 361 (51%) were on anthracycline-based (AC-based) regimens and 210 (30%) were on XELOX regimens.

Mean age of the patients was 52.9 ± 10.3 years, with majority (63%) being over 50 years of age (Table 3). More than half (67%) were females. This was due to the percentage skew of females on AC-based regimens (99.7%). In contrast, females explained only 21% and 42% of the patients on HECs and XELOX regimens respectively. Most patients were Chinese (84%), married (80%) and of a secondary school education (42%).

Generally, most patients suffered from delayed CINV; with triple the proportion suffering from delayed nausea

Table 3. Demographics and CINV characteristics of patients

Patient demographics	Number of patients in all regimens (%)[a], n = 710	Number of patients in HEC regimens (%)[a], n = 139	Number of patients in AC-based regimens (%)[a], n = 361	Number of patients in XELOX regimens (%)[a], n = 210
Age (years)				
< 30	8 (1)	4 (3)	2 (1)	2 (1)
30~39	61 (9)	19 (14)	41 (11)	1 (1)
40~49	195 (28)	46 (33)	130 (36)	19 (9)
50~59	266 (38)	46 (33)	138 (38)	82 (39)
≥ 60	180 (25)	24 (17)	50 (14)	106 (51)
Race				
Chinese	593 (84)	114 (82)	293 (81)	186 (89)
Malay	72 (10)	15 (11)	43 (12)	14 (7)
Indian	23 (3)	3 (2)	14 (4)	6 (3)
Others	22 (3)	7 (5)	11 (3)	4 (2)
Gender				
Male	233 (33)	110 (79)	1 (0.3)	122 (58)
Female	477 (67)	29 (21)	360 (99.7)	88 (42)
Marital status				
Single	94 (13)	17 (12)	56 (16)	21 (10)
Married	571 (80)	121 (87)	278 (77)	172 (82)
Divorced	13 (2)	0 (0)	7 (2)	6 (3)
Widowed	19 (3)	1 (1)	7 (2)	11 (5)
Highest education level				
No education	34 (5)	0 (0)	19 (5)	15 (7)
Primary	185 (26)	30 (22)	91 (25)	64 (31)
Secondary	295 (42)	60 (43)	151 (42)	84 (40)
Pre-university	118 (17)	26 (19)	61 (17)	31 (15)
Graduate	56 (8)	16 (12)	30 (8)	10 (5)
Postgraduate	22 (3)	7 (5)	9 (3)	6 (3)
CINV characteristics	**Number of patients in all regimens (%)[b]**	**Number of patients in HEC regimens (%)[b]**	**Number of patients in AC-based regimens (%)[b]**	**Number of patients in XELOX regimens (%)[b]**
Chemotherapy-induced nausea				
Acute	387 (55)	75 (54)	240 (67)	72 (34)
Delayed	472 (67)	90 (65)	278 (77)	104 (50)
Chemotherapy-induced vomiting				
Acute	103 (15)	16 (12)	77 (21)	10 (5)
Delayed	156 (22)	35 (25)	89 (25)	32 (15)
Complete response (CR)				
Acute	537 (76)	110 (79)	243 (67)	184 (88)
Delayed	450 (63)	77 (55)	213 (59)	160 (76)
Overall	409 (58)	70 (50)	182 (50)	157 (75)
Complete protection (CP)				
Acute	428 (60)	89 (64)	173 (48)	166 (79)
Delayed	325 (46)	58 (42)	129 (36)	138 (66)
Overall	297 (42)	51 (37)	113 (31)	133 (63)
Complete control (CC)				
Acute	308 (43)	62 (45)	112 (31)	134 (64)
Delayed	219 (31)	43 (31)	75 (21)	101 (48)
Overall	194 (27)	35 (25)	62 (17)	97 (46)

[a]Percentages may not add to 100% due to missing data and rounding of figures.
[b]Percentages may be over 100% due to patients suffering from multiple effects.

(67%) than vomiting (22%). A decreasing trend was observed in patient proportions that achieved the endpoints of CR (58%), CP (42%) and CC (27%). This trend occurred for both the acute and delayed responses, as well as among the various categories of CRegs. Patients on XELOX achieved the highest CINV endpoints (CR, CP and CC), which was

Table 4. Risk factors identified as principal variables for the prediction of clinical CINV endpoints

Clinical CINV endpoints	Risk factors identified as principal variables			
	Overall patient population (n = 710)	Patients on HEC regimens (n = 139)	Patients on AC-based regimens (n = 361)	Patients on XELOX regimens (n = 210)
Overall complete response (CR)	• Fatigue interference (PC4)	• Ex-/current drinkers (PC1) • History of chemotherapy-induced vomiting (PC1) • Gender (PC4)	--	• Social/chronic drinkers (PC1) • History of chemotherapy-induced nausea (PC2) • Fatigue interference (PC3)
Overall complete protection (CP)	--	• Ex-/current drinkers (PC1)	• Fatigue severity (PC4)	• Fatigue interference (PC3)
Overall complete control (CC)	--	• Ex-/current drinkers (PC1) • Fatigue interference (PC3) • Fatigue severity (PC4)	• Fatigue severity (PC4)	--

CR: No vomiting and no rescue antiemetics
CP: No vomiting, no significant nausea and no rescue antiemetics
CC: No vomiting, no nausea and no rescue antiemetics

Table 5. Clinical predictors of CINV identified in the study population ($n_{all} = 710$, $n_{HEC} = 139$, $n_{AC\text{-}based} = 361$, $n_{XELOX} = 210$)

Risk factor	Variation in patients with regards to complete response (CR) (% variation, eigenvector)			Variation in patients with regards to complete protection (CP) (% variation, eigenvector)			Variation in patients with regards to complete control (CC) (% variation, eigenvector)		
	Acute	Delayed	Overall	Acute	Delayed	Overall	Acute	Delayed	Overall
Ex-/current drinkers									
All	--	--	--	--	--	--	--	--	--
HEC	--	20.8% of PC1, 0.421/ -0.421	20.6% of PC1, -0.405/ 0.405	--	22.9% of PC1, 0.411/ -0.411	23.0% of PC1, 0.399/ -0.399	--	25.0% of PC1, -0.423/ 0.423*	26.0% of PC1, -0.411/ 0.411*
AC-based	--	--	--	11.8% of PC3, 0.538/ -0.538	--	--	12.3% of PC3, 0.592/ -0.592	--	--
XELOX	13.7% of PC2, 0.543/ -0.543	--	--	--	--	--	--	--	--
Social/chronic drinkers									
All	9.6% of PC4, -0.408/ 0.408	--	--	--	--	--	--	--	--
HEC	--	--	--	--	--	--	--	--	--
AC-based	17.3% of PC1, 0.535/ -0.535*	--	--	--	--	--	--	--	--
XELOX	--	17.4% of PC1, 0.458/ -0.458	17.6% of PC1, 0.459/ -0.459	18.0% of PC1, -0.426/ 0.426	--	--	--	--	--
Non-drinkers									
All	--	--	--	--	6.2% of PC6, 0.534	6.1% of PC6, 0.588	--	--	--
HEC	--	--	--	--	--	--	--	--	--
AC-based	--	--	--	--	--	--	--	--	--
XELOX	--	--	--	--	--	--	--	--	--

Table 5. Continued

Risk factor	Variation in patients with regards to complete response (CR) (% variation, eigenvector)			Variation in patients with regards to complete protection (CP) (% variation, eigenvector)			Variation in patients with regards to complete control (CC) (% variation, eigenvector)		
	Acute	Delayed	Overall	Acute	Delayed	Overall	Acute	Delayed	Overall
Fatigue interference									
All	11.7% of PC3, 0.440	10.7% of PC4, 0.389	10.2% of PC4, 0.484	10.3% of PC4, 0.495	9.3% of PC4, 0.379	--	9.7% of PC4, 0.438	--	--
HEC	--	--	--	10.3% of PC5, 0.512	10.3% of PC4, 0.508	--	--	12.5% of PC3, 0.481	11.8% of PC3, 0.477
AC-based	5.8% of PC8, -0.449	--	--	--	--	--	13.4% of PC2, 0.438	--	--
XELOX	--	--	13.9% of PC3, 0.454	--	12.2% of PC3, 0.447	13.4% of PC3, 0.486	14.9% of PC2, 0.472	--	--
Fatigue severity									
All	--	--	--	--	--	--	--	--	--
HEC	--	5.7% of PC7, 0.547	--	--	--	--	5.4% of PC8, -0.400	5.9% of PC8, -0.297	10.3% of PC4, 0.456
AC-based	--	--	--	--	--	9.2% of PC4, 0.367	--	9.8% of PC4, 0.451	9.8% of PC4, 0.411
XELOX	--	--	--	12.9% of PC3, 0.436	--	--	--	--	--
Gender									
All	17.7% of PC1, 0.476	17.3% of PC1, 0.482	--	17.6% of PC1, 0.449	--	--	16.2% of PC1, 0.499	--	--
HEC	--	--	10.7% of PC4, 0.461	11.1% of PC4, 0.551	--	--	11.4% of PC4, 0.548	9.8% of PC5, 0.455	--
AC-based	--	--	--	--	--	--	--	--	--
XELOX	--	11.9% of PC4, 0.477	--	--	--	--	--	11.3% of PC3, 0.409	--
History of chemotherapy-induced nausea									
All	--	--	--	--	--	7.4% of PC5, 0.434	7.2% of PC5, 0.479	--	--
HEC	--	--	--	--	4.3% of PC9, 0.427	4.6% of PC9, 0.549	--	4.9% of PC9, 0.483	5.0% of PC9, 0.442
AC-based	--	--	--	12.7% of PC3, 0.444	13.2% of PC3, 0.456	--	--	12.9% of PC2, 0.430	--
XELOX	--	16.5% of PC2, 0.427	17.0% of PC2, 0.433	8.3% of PC5, 0.547	--	--	--	--	--
History of chemotherapy-induced vomiting									
All	--	--	--	--	--	--	--	--	4.5% of PC10, -0.386
HEC	--	21.6% of PC1, 0.453	20.5% of PC1, 0.465	--	20.8% of PC1, 0.449	--	--	19.2% of PC1, 0.461	--
AC-based	--	--	--	--	4.9% of PC10, 0.436	--	12.8% of PC3, 0.442	4.7% of PC10, 0.445	--
XELOX	--	--	--	7.9% of PC6, 0.598	--	--	--	--	--

All: All regimens inclusive of HEC, AC-based and XELOX regimens.
HEC: Highly-emetogenic regimens (CDDP40, CDDP100 and PF regimens).
AC-based: AC-based regimens (AC, FAC and FEC regimens).
XELOX: XELOX regimen.
*Direction cosine is greater than 0.71, therefore the risk factor is closely related to its principal component.

consistent with the low proportions who suffered from acute and delayed NV.

Identification of CINV predictors through multivariate projection of risk factors. Five risk factors played essential roles in distinguishing the clinical endpoints for patients on moderately-emetogenic chemotherapies (MECs) and HECs - histories of alcohol drinking, chemotherapy-induced nausea, chemotherapy-induced vomiting, fatigue and gender (Table 4). The former 3 risk factors distinguished the clinical endpoints in patients on HECs and XELOX.

Generally, patients who drank less alcohol were more prone to suffering from CINV. Non-drinkers was a clinical predictor of patients who did not achieve delayed and overall CP (6.1~6.2% of PC6) when the whole patient population was taken into account (Table 5). However, the period of drinking (ex-/current drinkers) was more important than the frequency of drinking (social/chronic drinkers) when differentiating the endpoints of patients on CRegs of higher emetogenicity, such as the HECs (20.6~26.0% of PC1) and AC-based regimens (11.8~12.3% of PC3). In contrast, the frequency of drinking (social/chronic drinkers) played a more essential role for differentiating the endpoints of patients on CRegs that were less emetogenic (17.4~18.0% of PC1 for XELOX).

Histories of chemotherapy-induced nausea and chemotherapy-induced vomiting played more obvious roles in distinguishing the endpoints in patients on AC-based and XELOX regimens, and HECs, respectively. History of vomiting better distinguished patients without CR for more highly emetogenic CRegs (20.5~21.6% of PC1), while history of nausea explained higher variation proportions in AC-based (12.7% of PC3 - 12.9% of PC2) and XELOX patients (8.3% of PC5 - 17.0% of PC2).

Generally, fatigue interference was a better predictor of CINV than fatigue severity in the overall patient population. Fatigue interference could distinguish patients without overall CR across all the CRegs. In fact, its role was of a higher priority (PC3) compared to fatigue severity (PC4) when analyzed in the separate CReg categories (Table 4). Patients on HECs (10.3% of PC5 - 12.5% of PC3) and XELOX (12.2% of PC3 - 14.9% of PC2) who suffered from CINV tended to be more easily distinguished based on fatigue interference. On the other hand, both factors managed to distinguish CC in the AC-based population (9.8% of PC4 - 13.4% of PC2) (Table 5).

Lastly, female gender was a more useful CINV predictor for CRegs that incorporated heterogeneous populations, as exemplified by the mixed male to female ratios in the HEC and XELOX populations. This risk factor predicted patients who did not achieve the clinical endpoints particularly in acute phase CINV (16.2~17.7% of PC1) (Table 5). It separated patients who did not achieve acute CR, CP and CC from those who did, especially those on HECs (9.8% of PC5 - 11.4% of PC4) and XELOX (11.9% of PC4 - 11.3% of PC3). All these risk factors could potentially be used in combination as clinical predictors of CINV in the supportive care of cancer patients.

DISCUSSION

This study utilized a multivariate projection technique to identify a combination of risk factors that are useful in clinical prediction of CINV. From our knowledge, this is the first study that uses a computational technique to analyze such a large combination of risk factors. The 5 clinical predictors identified here strengthen the evidence for CINV prediction in Asian cancer patients. Females were previously reported to be more likely to suffer from post-chemotherapy NV (Abbrederis *et al.*, 2009; Osoba *et al.*, 1997), and this was also identified as a useful predictor in our study, particularly in "gender neutral" CRegs that are not dominated by a particular gender. In fact, more males seemed to achieve better overall CR and CP than females. However, our study went a step further to show that gender can also be used to predict patients who might not achieve CC.

Fatigue has been reported as a predisposing factor to post-chemotherapy nausea (Osoba *et al.*, 1997), and also contributes to the duration and frequency of acute vomiting (Molassiotis *et al.*, 2002). In this study, fatigue interference was a better clinical predictor in patients on HECs and XELOX, since it exhibited a higher priority role than severity in the PC analysis results. Although clinicians using fatigue as a CINV predictor could base their assessments on both interference and severity for AC-based populations, fatigue interference might be more useful as a predictor for patients on the other CRegs instead.

Histories of CINV accounted for relatively high percentage variances among all the clinical predictors. History of vomiting was more predictive of patients who did not achieve overall CR in HECs, and this result was consistent with literature suggesting that chemotherapy-induced vomiting may cause emesis in subsequent chemotherapies (Lohr, 2008; Navari and Province, 2006). On the other hand, distinguishing the endpoints through history of nausea was supported by trials reporting that higher nausea severity was experienced by non-chemo-naïve patients, and that nausea control was adversely affected by prior CINV experience in breast cancer patients (Abali and Celik, 2007; Gralla *et al.*, 2003). However, our study also extrapolated this result to XELOX patients, thus adding to the already sparse literature on this CReg.

The PV approach used in this study has several advantages over overall interpretation of the PCs (Al-Kandari and Jolliffe, 2001). Some variables, such as anxiety and fatigue, are difficult to measure due to their subjectivity, hence may not accurately reflect the PC when an overall interpretation

is made. Moreover, if there are many non-trivial loadings on multiple variables, the PCs can be difficult to interpret, in contrast to the variables themselves, which are usually readily interpretable. In addition, eigenvectors (weightages) were used instead of loadings (correlations) for interpretation of the PVs. Since the eigenvectors are proportional to loadings in PC analysis, either vector can be used for data interpretation (Dunteman, 1989). However, the purpose of this study was to identify a subgroup of risk factors that would be useful CINV predictors in the practice setting. Thus, it was only logical that PVs, which represent the PCs, were interpreted in relation to their weightages.

The main limitations of this study were its small sample size, particularly of patients with head and neck cancers, and the predominance of males and females in the head and neck (79.1% males), and breast cancer (99.7% females) populations. However, the gender ratios were representative of the respective cancer populations in Singapore (de Kok *et al.*, 2008; Lim, 2008; National Registry of Diseases Office, 2009). Certain biases (recall and information bias) could also have occurred due to the subjectivity of some interview questions, such as those regarding fatigue and anxiety. Furthermore, even though this research studied a variety of CINV risk factors, there were others reported in literature that were not being considered here because evidences of these factors as CINV predictors have been scarce (Booth *et al.*, 2007; Dranitsaris *et al.*, 2009; Molassiotis *et al.*, 2002; Osoba *et al.*, 1997). Future work on the prediction of CINV based on PC analysis and similar techniques could target these factors, and should include larger sample sizes to achieve approximate subject to variable ratios of 5 : 1 to 10 : 1. These sample sizes can be achieved by involving a range of other cancer types and CRegs that are moderately or highly emetogenic.

In summary, this study has utilized PC analysis, a multivariate projection technique, to distinguish the clinical endpoints of CR, CP and CC in patients with cancer having certain risk factors. Five risk factors (histories of alcohol drinking, chemotherapy-induced nausea, chemotherapy-induced vomiting, fatigue, gender) have been identified as potential clinical predictors of CINV that may be useful to practitioners in cancer supportive care. This study not only illustrates the usefulness of PC analysis as a potential technique in analyzing clinical population data for CINV, but also provides clinicians with an insight as to which clinical predictors to look out for in Asian patients, so that appropriate management can be taken to relieve the distress in patients undergoing emetogenic chemotherapy, and ultimately, improve their quality of life.

ACKNOWLEDGEMENT

Assoc. Prof. Alexandre Chan has received speaker honorarium, research and educational grants from Merck Sharp & Dohme. The other authors have no conflict of interest directly relevant to the study.

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