A NOVEL AND DYNAMIC PREDICTION ENGINE FOR PRACTICING PRECISION MEDICINE TO PREVENT CHEMOTHERAPY- INDUCED NAUSEA AND VOMITING

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In Partial Fulfillment
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Doctor of Philosophy

By
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**A NOVEL AND DYNAMIC PREDICTION ENGINE FOR
PRACTICING PRECISION MEDICINE TO PREVENT
CHEMOTHERAPY-INDUCED NAUSEA AND VOMITING**

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DEDICATION

To my loving mother, Meherneka Begum, who is by far the strongest women I have even known, who has been very caring, and who has been very keen for my education regardless of any obstacles.

To the memory of my loving father, Md. Abul Bashar, who is my role model, who raised me as a righteous and hard-working person, and whose last words are always encouraging to me. He inspired me to achieve the goals of my life regardless of any obstacles.

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ORGANIZATION OF THE DISSERTATION

Chapter 1 provides an introduction to the clinical problem of chemotherapy induced nausea and vomiting (CINV). Chapter 2 provides a systematic review on the patient-related risk factors of CINV. Chapter 3 presents the data collection strategy, data overview and characteristics of the data. Chapter 4 presents the results of data mining using various traditional algorithms. There are a total of six datasets (i.e., contexts) and all the datasets were analyzed individually. Chapter 5 presents a new technique for mining context sensitive associative classification rules. Chapter 6 present a novel and dynamic prediction engine that has the capacity to build a highly precise prediction system while preserving the context-sensitiveness in one single system. The prediction performance of the system outperformed many popular prediction methods and all the results of CINV risk prediction published in the literature. Chapter 7 discusses the improvements that was made by this project and concludes the dissertation.

ABSTRACT

Cancer remains the second major cause of death in the United States over the last decade. Chemotherapy is a core component of nearly every cancer treatment plan. Chemotherapy-Induced Nausea and Vomiting (CINV) are the two most dreadful and unpleasant side-effects of chemotherapy for cancer patients. The consequences of CINV include: (1) impaired life quality, (2) poor social life, (3) burden on economy due to loss of workdays, (4) increased healthcare cost, and (5) denial of chemotherapy due to unendurable CINV. There are three clinical guidelines (ASCO, NCCN, and MASCC/ESMO) for the management of CINV. Several patient-specific factors affect the risk of CINV. However, none of the guidelines consider those factors. Not all of patients have the similar emetic risk of CINV. Despite the improvements in CINV management, as many as two-thirds of chemotherapy patients still experience some degree of CINV. As a result, physicians use their personal experiences for CINV treatment, which leads to inconsistent managements of CINV. The overall objective of this study is to improve the prevention of CINV using precise, personalized and evidence-based antiemetic treatment before chemotherapy. Physicians receive feedback about CINV risks of patients from a CINV decision support system based on patient-specific factors. This objective was achieved by accomplishing clinical innovations through the discovery of combined relationships of various patient-specific factors for causing CINV, and informatics innovations through the development of a novel, precise and dynamic prediction engine for practicing precision and personalized medicine in CINV prevention. The approach presented in this dissertation can be applied to any other clinical predictions.

CHAPTER 1 : CHEMOTHERAPY INDUCED NAUSEA AND VOMITING (CINV)

1.1 CANCER

Early diagnosis of cancer and the advancement in its treatments [1–6] have greatly increased the overall five-year relative and absolute survival rates (Figure 1) [5,7–11], but cancer remains the second major cause of mortality after cardiovascular mortality in the United States over the last decade [1,10–12]. The percentage of total mortality for the cardiovascular diseases is only 0.9% higher than that of the cancer in 2010 [12]. The US National Center for Health Statistics estimated that a total of 19 million adults in the US have ever been diagnosed with cancer [13]. Today, more cancer patients are treated than ever before with increasingly complex regimens. In cancer, tumors are formed due to fast, uncontrolled, and limitless growth of cells that can invade adjacent tissues and/or travel to distant sites (metastases) [14,15]. The overall goal of cancer treatments is to remove or destroy those cancerous cells. The main treatment plans for cancer include surgery, radiation therapy, and chemotherapy [16–18]. The goal of surgery is to remove the tumor and some tissues around it. Radiotherapy and/or chemotherapy is used to kill the cancerous

cells. High-frequency rays are used in radiotherapy, and cytotoxic antineoplastic drugs are used in chemotherapy. The drugs used in chemotherapy are also known as chemotherapeutic agents.

Figure 1: Overall 5-Year Relative Survival Rate of Cancer [9]

1.2 CHEMOTHERAPY FOR CANCER TREATMENT

Chemotherapy is a core component of nearly every cancer treatment plan [6]. A large number of cancer patients receive some type of chemotherapy. Hawkins and Grunberg (2009) [17] reported that as many as 1 million Americans receive chemotherapy each year. In cancer, cells are fast-growing, and form a tumor. A chemotherapeutic agent works by entering into the bloodstream and damaging every fast-growing cell as it divides [19]. In addition to destroying tumor cells, a chemotherapeutic agent also damages normal

cells that are fast-growing, including the cells in skin [20,21], bone marrow [22], hair follicles [23,24], and digestive tract [25,26]. As a result, chemotherapy causes many side effects such as nausea, vomiting, hair loss, appetite changes, anemia constipation, and diarrhea among others. [20–28].

1.3 CHEMOTHERAPY INDUCED NAUSEA AND VOMITING

Chemotherapy-induced nausea and vomiting (CINV) are the two most dreadful and unpleasant side-effects of chemotherapy [27–32]. The US National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v4.0 defined nausea as “a disorder characterized by a queasy sensation and/or the urge to vomit” and vomiting as “a disorder characterized by the reflexive act of ejecting the contents of the stomach through the mouth” [33]. The pathophysiology of CINV is a complex process. There are two neurotransmitters involved in vomiting in two different pathways: (1) the serotonin is involved in the peripheral pathway, and (2) a neuropeptide named “substance P” is involved in the central pathway [34,35]. First, the peripheral pathway is associated with the acute phase of CINV that occurs within the first 24 hours of chemotherapy administration. This pathway is primarily located in the gastrointestinal tract, where chemotherapy causes the release of serotonin. CINV occurs when serotonin binds to the 5-hydroxytryptamine (5-HT₃) receptors and sends a signal to the vomiting center in the medulla [34,35]. Second, the central pathway is associated with the delayed phase of CINV that occurs after the first 24 hours of chemotherapy administration and may persist up to one week. This pathway is located in the brain, where chemotherapy triggers the release of substance P that binds to the NK₁ receptor in the vomiting center causing CINV [34,35].

1.4 GUIDELINES FOR CINV MANAGEMENT

There are several antiemetic guidelines for the management of CINV such as the American Society of Clinical Oncology (ASCO) guideline [36,37], the National Comprehensive Cancer Network (NCCN) guideline [38], and the guideline from the Multinational Association of Supportive Care in Cancer (MASCC) in cooperation with the European Society of Medical Oncology (ESMO) [39]. The guideline-recommended standard antiemetic prophylaxis for the management of CINV considers only the emetogenicity of the chemotherapeutic agents. The emetogenicity of chemotherapy is divided into four emetic risk categories: (1) minimal, (2) low, (3) moderate, and (4) high (Table 1). The management of CINV is a complex process since it has two different phases involving different pathophysiology. Furthermore, several patient-related risk factors affect the risk of CINV but none of the guidelines considers those factors [40]. As seen in the emetic risk categories (Table 1), not all patients have the similar emetic risk of CINV. Despite the improvements in CINV management, as many as two-thirds of the patients still experience some degree of CINV; several recent studies reported various percentages of CINV cases with use of antiemetics: 28% [41], 38-52% [42], 56.1% [43], 61.2% [44], and 62% [45]. As a result, physicians use their personal experiences with the treatment of CINV, which leads to inconsistent management of CINV [46].

Table 1: Emetogenicity of Chemotherapy

Degree of Emetogenicity	% of Patients Who Suffer from CINV Without Antiemetics
Minimal	<10%
Low (LEC)	10%-30%
Moderate (MEC)	30%-90%
High (HEC)	>90%

1.5 CONSEQUENCES OF CINV

There are many consequences of CINV that affect both patients and the healthcare system as a whole. **First**, CINV impairs the quality of life in cancer patients due to nutritional deficits, dehydration, and electrolyte imbalance. [44,45,47–49]. **Second**, CINV makes it difficult to socialize with family and friends leading to a poor social life [44,50]. **Third**, CINV creates an economic burden due to loss of workdays [44,51–53]. **Fourth**, CINV increases healthcare costs due to CINV-related outpatient visits, hospitalization, and cost of drugs. [44,49,51–56]. **Fifth**, cancer patients may discontinue chemotherapy due to intolerable CINV leading to poor treatment outcomes, treatment failure, or even death [29,57–59]. In addition to the fact that none of the CINV guidelines considers patient-related risk factors, these problems are the motivation of this study.

1.6 CINV GRADES

The NCI defined three grades for nausea and five grades for vomiting (Table 2). With any chemotherapy, grade 1 (mild) CINV are minimally expected and not considered as clinically significant. However, grade 2 (moderate) to grade 3 (severe) CINV are clinically significant and needs antiemetic prophylaxis (prevention) in-advance before chemotherapy. If CINV is not prevented appropriately, the patient may end having life threatening event (grade 4) leading to death (grade 5).

Table 2: Grading of Nausea and Vomiting [33]

	Nausea	Vomiting
Definition	A disorder characterized by a queasy sensation and/or the urge to vomit.	A disorder characterized by the reflexive act of ejecting the contents of the stomach through the mouth.
Grades		
Grade 1 (Mild)	Loss of appetite without alteration in eating habits	1 - 2 episodes (separated by 5 minutes) in 24 hrs
Grade 2 (Moderate)	Oral intake decreased without significant weight loss, dehydration or malnutrition	3 - 5 episodes (separated by 5 minutes) in 24 hrs
Grade 3 (Severe)	Inadequate oral caloric or fluid intake; tube feeding, TPN, or hospitalization indicated	>=6 episodes (separated by 5 minutes) in 24 hrs; tube feeding, TPN or hospitalization indicated
Grade 4 (Life Threatening)	N/A	Life-threatening consequences; urgent intervention indicated
Grade 5 (Death)	N/A	Death

1.7 CARE OF CINV

If a patient started to have CINV, stopping the consequences become very hard. Thus, using antiemetic treatments before chemotherapy for the prevention of CINV is imperative. The prescription for antiemetics should consider the guideline recommendations as well as the associative effect of various patient-specific risk factors.

1.8 PROBLEM STATEMENT

Despite the improvements in CINV management, as many as two-thirds of the patients still experience some degree of CINV. Several patient-specific factors affect the risk of CINV but none of the guidelines (NCCN, ASCO, MASCC, and ESMO) considers those factors. As a result, physicians cannot fully rely on the guidelines and they use their own experiences using CINV. Consequently, the management of CINV is inconsistent

among physicians since their decisions are subjective to their experiences with the CINV management.

1.9 OVERALL OBJECTIVE, SCOPE AND AIMS

The overall objective of this project is to improve the prevention of CINV using precise, personalized and evidence-based antiemetic treatment before chemotherapy. Physicians receive feedback about CINV risks of patients from a CINV decision support system based on patient-specific factors. The data mining techniques are used to develop a novel and dynamic prediction engine that provides a CINV treatment decision based on the patient-specific factors. This objective will be achieved by accomplishing three specific aims covering data collection, clinical innovations in the discovery of combined relationships of various patient-specific factors for causing CINV, and informatics innovations in the development of a novel dynamic prediction engine for practicing precision and personalized medicine at the point-of-care.

1.9.1 Aim 1

The first aim of the project was to collect potential CINV related risk-factor data by chart review from the MU Ellis Fischel Cancer Center. Two separate datasets for acute and delayed phase of CINV have been collected. Chapter 2 presents the results of a systematic review study on the patient-related risk factors. Chapter 3 presents the details on the data collection plan and the characteristics of data.

1.9.2 Aim 2

The second aim of the project was to apply data mining techniques for predictive analytics. Predicting the risk of CINV before chemotherapy for a chemotherapy patient is important so that physician can make data-driven and evidence-based decision about CINV treatment recommendations. We applied various classification algorithms in this endeavor (Chapter 4).

1.9.3 Aim 3

The third aim of the project was to develop a data mining-based novel and dynamic prediction engine employing the patient-related variables. The prediction engine discovers how the patient-related variables and the emetogenicity of chemotherapy are associated with the risk of CINV (Chapter 5). Unlike pre-computed prediction models using training data, this dynamic prediction engine is revisable in real-time based on the actual treatment outcome (Chapter 6). In addition, this prediction engine provides a decision even though an important variable is unknown at the point-of-care.

1.10 INFORMATICS APPROACH

The final goal is to develop a data mining-based novel and dynamic prediction engine that can precisely perform the prediction job for determining the patients who are at higher risk of causing CINV based on the patients' personal risk factors. The approach involves data mining for generating a classification model and use the model for prediction. We have developed a novel prediction technique using associative classification rules. Using this technique, the system receives a prediction query, retrieves a set of supported

associative classification rules in real-time and dynamically generates a context sensitive prediction result. Figure 2 presents the overall project design.

Figure 2: A Dynamic Approach for Prediction

1.11 SIGNIFICANCE

As described in section 1.5, CINV has significant negative consequences in personal, social, clinical and economic matters. As a result, a good control of this fearful side-effect is very important for minimizing these consequences. CINV guidelines are based on the classification of the chemotherapy drugs into four vague emetic risk groups. Physicians cannot anticipate the exact probability of CINV for a certain patient using this classification scheme. The guidelines do not consider the patient-related risk factors [40]. In fact, the current NCCN guideline (Version 2.2015) for antiemetic therapy stated that “patient factors” and “prior experience with antiemetics” should be considered in addition to the emetic risk of chemotherapy [60].

The main treatment is using antiemetics before chemotherapy for preventing CINV. Over treating all patients is not a viable solution for many reasons: (1) every patients are not at higher risk of CINV, (2) antiemetic medications have their own side-effects, and (3) antiemetic medications are costly. If physicians know which patients are at higher risk of CINV, they can make a precise treatment plan for individual patients. This project solves this important clinical problem by developing a dynamic prediction engine.

1.12 INNOVATION

This project contributes innovation in two categories: (1) clinical innovations, (2) informatics innovations.

1.12.1 Clinical Innovations

To date, the combined relationships of various patient-related factors for causing CINV was unknown. This project discovers these relationships, improves clinical outcomes through data mining and helps physicians for practicing personalized and precision medicine for the management of CINV. The contribution of this project significantly improves overall cancer care and reduces overall cost of care.

1.12.2 Informatics Innovations

The prediction engine proposed in this project is new in comparing to the traditional data mining approaches. The prediction engine consists of several novel features. **First**, this method does not suffer from the issue of losing prediction capacity in a situation when an important variable is unavailable or unknown at the point-of-care. This can still make a prediction based on other important variables. **Second**, the method has higher prediction

power since multiple important rules are used for a prediction query. A new prediction scoring algorithm has been developed for combining multiple rules; this algorithm generates a prediction score for each class of interest that helps with the prediction process. **Third**, the prediction engine keeps all unimportant (rare) rules. **Fourth**, unlike pre-computed prediction models using training data such as decision trees, the prediction engine is dynamic (revisable in real-time). This dynamic process may benefit the unimportant rules to become important as more data is added in real-time. **Fifth**, the approach proposed in this project can be adapted for any other clinical predictions. **Sixth**, the engine can grow from ground-zero by learning in real-time and start providing predictions after minimal growth.

CHAPTER 2 : PATIENT-RELATED RISK FACTORS: A SYSTEMATIC REVIEW

Studies have reported that patient-related factors considerably impact the risk of Chemotherapy-Induced Nausea and Vomiting (CINV). In this chapter, a systematic review of the literature is presented that identifies and summarizes patient-related factors (scattered over various articles) that significantly impact a patient's risk of CINV. Oncologists can use these factors to identify patients at risk for CINV prior to the initiation of a chemotherapy regimen, so that they can focus on more aggressive treatment options for those high risk patients for better treatment outcomes and avoid further complications. The reporting of this systematic review follows the “Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)” guideline [61].

2.1 METHODS

2.1.1 Data Sources

The MEDLINE citation database was searched in March, 2015 for eligible articles using PubMed. The search terms are related to the following terms: antiemetics, chemotherapy-induced nausea and vomiting (CINV) and risk factors. We used a comprehensive search strategy not to miss relevant documents in MEDLINE. Table 3 presents the entire search strategy.

2.1.2 Inclusion and Exclusion Criteria

The inclusion criteria include: (1) studies that reported patient-related risk factors of CINV, (2) any kind of clinical studies such as prospective, retrospective, clinical trial, cross-sectional, cross-over, and case-control studies etc., (3) studies that do not provide any concomitant cancer treatment such as radiotherapy or surgery, and (4) the patient population is adult. We excluded any articles that were not written in English.

2.1.3 Study Selection and Data Extraction

The study selection was performed in two steps. In the first step, we read the titles and abstracts of the citations by the search query in order to screen the articles based on the inclusion/exclusion criteria. In the second step, we read the full-text of the citations selected by the first step. The search criteria did not include any limitation on publication date; the earliest eligible article was published in 1989.

We abstracted information from the eligible full-text articles. Table 4 presents the extracted information that includes the study type, country name, number of patients, type of cancer, emetic risk of the chemotherapy, potential patient-related factors that are included in the data analysis and the factors that were identified as the predictors of CINV.

Table 3: PubMed Search Strategy

Search Topic	Search Strategy
Antiemetics	1. "antiemetics"[All Fields] 2. "antiemetics"[MeSH Terms] 3. "antiemetics"[Pharmacological Action] 4. OR (1,2,3)
CINV	5. "CINV"[All Fields]
Chemotherapy	6. "drug therapy"[MeSH Terms] 7. "drug"[All Fields] AND "therapy"[All Fields] 8. "drug therapy"[All Fields] 9. "chemotherapy"[All Fields] 10. "antineoplastic agents"[MeSH Terms] 11. "antineoplastic"[All Fields] AND "agents"[All Fields] 12. "antineoplastic agents"[All Fields] 13. "antineoplastic"[All Fields] AND "agent"[All Fields] 14. "antineoplastic agent"[All Fields] 15. "antineoplastic agents"[Pharmacological Action] 16. OR (6-15)
Nausea	17. "nausea"[MeSH Terms] 18. "nausea"[All Fields] 19. OR (17, 18)
Vomiting	20. "vomiting"[MeSH Terms] 21. "vomiting"[All Fields] 22. OR (20, 21)
Chemotherapy Induced Nausea and/or Vomiting (CINV)	23. OR (19, 22) 24. AND (16, 23) 25. OR (5, 24)
Risk Factors	26. "risk factors"[MeSH Terms] 27. "risk"[All Fields] AND ("factors"[All Fields] OR "factor"[All Fields]) 28. "risk factors"[All Fields] 29. "risk factor"[All Fields] 30. OR (26-29)
English Language	31. English[Lang]
Final Search Query	32. AND (4, 25, 30, 31)

2.2 RESULTS

Figure 3 presents the trial flow diagram of identifying the eligible articles for this study. A total of 390 articles were identified through the searches conducted in PubMed. We identified additional 11 articles by reviewing the list of references that were not retrieved by the query. The titles and abstracts of those 401 articles were then screened for eligibility. A total of 337 articles were excluded because these articles do not qualify the inclusion criteria described in the methods section. The remaining 64 articles were assessed

in full-text for eligibility and data extraction. We excluded a total of 34 articles after full-text review: (1) 20 articles were excluded because risk factors are cited as the background information of the articles, (2) 3 articles discussed the pharmacogenomics of CINV, (3) 5 articles considered concomitant radiotherapy/surgery, (4) 3 articles presented the risk factors associated with issues other than CINV, (5) 2 articles reported the evaluation of previously developed risk prediction models, and (6) 1 article performed the study on pediatric patients. Finally, we included 30 articles in this study discovering the patient-related risk factors (n=30).

Table 4 presents the patient-related risk factors from the 30 studies. Among those 30 studies, 13 studies were multicenter study and 17 studies were single-center study. The study types include retrospective (n=2), prospective (n=17), clinical trial (n=8), cross-sectional (n=1), cross-over (n=1), and case-control (n=1). The studies were performed in various countries around the world: USA (n=6), Canada (n=4), Singapore (n=3), Italy (n=2), Germany (n=1), Japan (n=5), Malaysia (n=1), Netherlands (n=1), Sweden (n=1), Taiwan (n=1), UK (n=1); four studies were performed in multiple countries (n=4). A total of 14,302 patient-records were analyzed by those 30 studies. Nine studies focused on any cancer including both solid and hematological malignancies (n=9), nine studies focused on the solid cancers only (n=9), and twelve studies focused on a specific type of cancer: breast cancer (n=7), colorectal cancer (n=1), gastrointestinal cancer (n=1), lung cancer (n=1), gynecologic cancer (n=1) and ovarian cancer (n=1). Most of the research studied high and moderate emetic risk of the chemotherapies: (1) 9 studies were on the high emetic risk only, (2) 8 studies were on the moderate emetic risk only, (3) 11 studies were on both high

and moderate risk chemotherapies, and (4) two studies were on high, moderate and low risk chemotherapies.

Figure 3: Trial Flow Diagram

Table 4: Patient-Related Risk Factors of CINV

Author (Year)	Study Type	Country	# Patients	Cancer Types	Emetic Risk	Variables Used in the Study	Identified Risk Factors
Kitazaki et al. (2015) [62]	Prospective	Japan	133	Lung	High and moderate	Age, sex, history of CINV, history of motion sickness, alcohol intake	None
Tamura et al. (2015) [63]	Multicenter, prospective, observational	Japan	1910	Any Cancer	High and moderate	Sex, history of motion sickness, history of pregnancy-related nausea/vomiting, history of morning sickness, alcohol intake, age	Young age, female gender, history of motion sickness, history of pregnancy-related nausea/vomiting, history of morning sickness and # of drinks per week < 5
Molassiotis et al. (2014) [64]	Multicenter, prospective, observational	France, Italy, Spain, Belgium, Sweden, UK, Austria, and The Netherlands	991	Solid	High and moderate	Age, sex, cancer type, history of CINV, anxiety, nausea before chemotherapy, Expectancy of CINV	Age < 50, nausea before chemotherapy, history of CINV, anxiety, female gender
Murakami et al. (2014) [65]	Prospective, observational	Japan	92	Any cancer	Moderate	Age, sex, history of previous chemo	Age < 67, female gender
Furukawa et al. (2014) [66]	Prospective	Japan	72	Gynecologic cancer	Moderate	Age, BMI, comorbidity (hypertension), type of cancer, menopause, alcohol intake, smoking history, history of motion sickness, defecations/bowel movement, history of pregnancy-related nausea/vomiting, history of chemo, history of radiotherapy, ascites	Comorbidity (hypertension), history of pregnancy-related nausea/vomiting
Celio et al. (2013) [67]	Multicenter, Retrospective	Austria, Germany, Italy and Spain [68,69]	405	Breast	Moderate	Age	None

Author (Year)	Study Type	Country	# Patients	Cancer Types	Emetic Risk	Variables Used in the Study	Identified Risk Factors
Molassiotis et al. (2013) [70]	Multicenter, prospective, observational	UK	336	Solid	High, moderate and low	Age, expectation of CINV, state anxiety, trait anxiety, symptom distress score, sex, stage of cancer, cancer type, chemotherapy cycle no., alcohol, history of nausea/vomiting (including motion sickness, pregnancy-related or vestibular dysfunction), comorbidities, and amount of sleep prior to treatment in hours	Young age, history of nausea/vomiting, trait anxiety, pain, first cycle of chemotherapy
Sekine et al. (2013) [71]	Prospective	Japan	1,549	Any cancer	High and moderate	Sex, age, performance status, smoking, alcohol	Female gender, age < 55 years, poor performance status, low alcohol intake (non-habitual drinker) and non-smoking habit
Chan et al. (2012) [72]	Prospective	Singapore	156	Gastrointestinal	Moderate	Age, sex, race, alcohol, anxiety, number of prior chemo, prior CINV, history of motion sickness and morning sickness	Prior CINV and moderate to severe anxiety
Fleishman et al. (2012) [73]	Cross-sectional	USA	41	Colorectal	Moderate	Age, Sex, Type of cancer, Stage of cancer, history of motion sickness, history of morning sickness, history of chemotherapy, prior CINV	Female gender and prior CINV
Yap et al. (2012) [74]	Prospective, observational	Singapore	710	Solid	High and moderate	21 symptoms related to anxiety	Fear of dying, fear of the worst, unable to relax, hot/cold sweats, nervousness, faintness, numbness
Higa et al. (2012) [75]	Case-control	USA	25	Solid	Moderate	Substance P, 5-HIAA/creatinine	Pretreatment ratio of substance-p and 5-HIAA/creatinine > 70
Celio et al. (2012) [76]	Multicenter, phase III randomized trial	Italy	324	Solid	Moderate	Age, sex, alcohol	Age < 50
Hilarius et al. (2012) [48]	Multicenter, prospective, observational	Netherlands	277	Any cancer	High and moderate	Age, sex, race, type of cancer, alcohol, pregnancy-related nausea/vomiting, history of motion sickness, performance status	Age < 65, female gender, # of drinks per week < 5
Bourdeanu et al. (2012) [77]	Retrospective	USA	358	Breast	High	Age, race, depression, diabetes, education, GERD, private/public insurance, marital status, medical history, religion, cancer stage, weight and alcohol	Asian race, private insurance, age ≤ 50 and GERD

Author (Year)	Study Type	Country	# Patients	Cancer Types	Emetic Risk	Variables Used in the Study	Identified Risk Factors
Warr et al. (2011) [78]	Multicenter, randomized phase III trial	USA, Germany, Austria, Canada, Hong Kong, Hungary, Spain, UK, Italy, Australia, and Greece [79]	866	Breast	Moderate	Age, alcohol, pregnancy-related nausea/vomiting, history of morning and motion sickness,	Age < 55, # of drinks per week < 5, history of morning sickness
Hassan and Yusoff (2010) [80]	Prospective, observational	Malaysia	158	Breast	High	Age, Sex, Race (Malay, Chinese and Asian Indians)	Race
Hesketh et al. (2010) [81]	Multicenter, randomized phase III trial	Argentina, Brazil, Chile, Colombia, Guatemala, Mexico, Peru, and Venezuela, USA and 14 other countries [82,83]	1,043	Solid	High	Age, sex, alcohol, BMI, history of motion and morning sickness, history of previous chemotherapy, prior CINV	Female gender, age <65, # of drinks per week < 5
Roscoe et al. (2010) [84]	Multicenter, clinical trial	USA	1,696	Any cancer	High and moderate	Cancer type, expectancies for nausea, pregnancy-related nausea/vomiting, history of motion sickness	Breast cancer, young age, expectancies and perceived susceptibility to nausea
Shih et al. (2009) [85]	Prospective, observational	Singapore	91	Breast	High	Age, race, education level, alcohol, history of motion sickness, history of morning sickness, anxiety, prior CINV, frequency of chemotherapy cycle, number of risk factors, chemotherapy cycle no.	Anxiety, prior CINV, history of motion sickness

Author (Year)	Study Type	Country	# Patients	Cancer Types	Emetic Risk	Variables Used in the Study	Identified Risk Factors
Dranitsaris et al. (2009) [86]	Prospective	Canada	200	Any cancer	High and moderate	Age, cancer type, cancer stage, comorbidities, recent surgery within past 3 months, history of motion sickness, history of morning sickness, alcohol, prior CINV, chemotherapy cycle no., meal prior to chemotherapy, number of hours of sleep the night before the chemotherapy, expectation of CINV, anxiety, non-prescription drugs for emesis control before chemotherapy, nausea/vomiting before chemotherapy	Age $\leq$ 40, gynecologic or genitourinary cancer, cancer stage I/II, no existing comorbidity, # of drinks per week $<$ 7, chemotherapy cycle no. $<$ 3, non-prescription drugs for emesis control before chemotherapy
Petrella et al. (2009) [87]	Prospective	Canada	200	Any cancer	High and moderate	Age, cancer type, cancer stage, comorbidities, recent surgery within past 3 months, history of motion sickness, history of morning sickness, alcohol, prior CINV, chemotherapy cycle no., meal prior to chemotherapy, number of hours of sleep the night before the chemotherapy, expectation of CINV, anxiety, non-prescription drugs for emesis control before chemotherapy, nausea/vomiting before chemotherapy	Age $\leq$ 40, prior CINV, nausea/vomiting before chemotherapy, history of morning sickness, non-prescription drugs for emesis control before chemotherapy, chemotherapy cycle no. $<$ 3, lower number of hours slept before the night of chemotherapy
Colagiuri et al. (2008) [88]	Multicenter, clinical trial	USA	691	Any cancer	High	Age, sex, susceptibility to motion sickness, expectancy of CINV	Expectancy of CINV
Booth et al. (2007) [89]	Multicenter, prospective	Canada	143	Breast	Moderate and low	Age, sex, cancer stage, comorbidities, history of motion sickness, history of morning sickness, alcohol, meal prior to chemotherapy, number of hours slept during the preceding night, expectancy of CINV, anxiety, recent surgery	Age $<$ 40, no existing comorbidity, recent surgery, expectancy of CINV, # of drinks per week $<$ 7, no food before chemotherapy, history of morning sickness
Roscoe et al. (2004) [90]	Multicenter, clinical trial	USA	201	Breast	High and moderate	Patient demographics, pregnancy-related nausea/vomiting, history of motion sickness, expectancy of CINV	Expectancy of CINV
Liaw et al. (2003) [91]	Cross-over trial	Taiwan	400	Solid	High	Age, sex, performance status, previous noncisplatin chemotherapy, cancer type	Female gender

Author (Year)	Study Type	Country	# Patients	Cancer Types	Emetic Risk	Variables Used in the Study	Identified Risk Factors
Osoba et al. (1997) [92]	Prospective	Canada	832	Any cancer	High and moderate	Age, sex, history of motion sickness, alcohol, performance status, social functioning, disease site, cancer type, food intake, drowsiness, pre-chemotherapy nausea	Social functioning < 70, pre-chemotherapy nausea, female gender, # of drinks per week < 10
Hursti et al. (1996) [93]	Clinical trial	Sweden	101	Ovarian	High	Age, history of nausea/vomiting (including motion sickness, pregnancy-related, or alcohol-related), neuroticism, autonomic perception, and tumor burden	Tumor burden ≥ 2 cm, age ≥ 55
du Bois et al. (1992) [94]	Multicenter, Prospective	Germany	92	Solid	High	Age, sex, cancer type, number of previous chemotherapy, previous antiemetics, cancer recurrence (new/recurrence)	Female gender, recurrent cancer
Pollera et al. (1989) [95]	Clinical trial	Italy	209	Solid	High	Age, sex, performance status, cancer type	Age ≤ 55 , female gender and poor performance status
GERD: Gastroesophageal Reflux Disease							

Table 5: Patient-Related Factors as the Significant Risk Factors of CINV

Variable Name	# of Studies Including the Variable	# of Studies Finding the Variable as a Significant Risk Factor
Age	26	16
Sex	18	11
Alcohol Intake	17	8
History of CINV or pregnancy-related Nausea/Vomiting	17	8
Anxiety	8	5
Expectancy of CINV	7	3
Chemotherapy Cycle No.	4	3
Comorbidities	6	4
Cancer Type	12	2
History of Morning Sickness	10	3
Performance Status	5	2
Race	5	2
Use of Non-prescription Drugs	2	2
History of Motion Sickness	17	2
Cancer Stage	6	1
Sleeping before Chemotherapy	4	1
Meal before chemotherapy	4	1
Recent surgery	3	1
Smoking History	2	1
Neurotransmitter Measurements (Substance-P, 5-HIAA/creatinine)	1	1
Private/Public Insurance	1	1
Social Functioning	1	1
Nausea/Vomiting before Chemotherapy	3	2
Tumor Burden	1	1
Cancer Recurrence (new/recurrent)	1	1
Symptom Distress Score	1	1

We present the patient-related factors in two categories: the factors that were identified as the risk factors of CINV and the factors that were included in the data analysis and found to be insignificant. In the following, the risk factors are discussed followed by the insignificant factors.

2.2.1 CINV Risk Factors

Table 5 presents a total of 26 patient-related factors that were found to be the significant risk factors of CINV in one or more studies. These 26 risk factors are: age, sex, alcohol intake, history of CINV and/or pregnancy-related nausea/vomiting, anxiety, expectancy of CINV, chemotherapy cycle number, cancer type, history of morning sickness, performance status, race, comorbidities, use of non-prescription drugs, history of motion sickness, cancer stage, sleeping before chemotherapy, meal before chemotherapy, recent surgery, smoking, neurotransmitter measurements (substance-p and 5-hiaa/creatinine), private/public insurance, social functioning, nausea/vomiting before chemotherapy, tumor burden, cancer recurrence (new/recurrent), and symptom distress score.

2.2.1.1 *Age*

Age was analyzed in 26 studies among which 16 studies confirmed that age is a risk factor of CINV (Table 5). Out of those 16 studies, the results of 15 studies are almost consistent; that is, all of those 15 studies confirmed that the younger patients are at higher risk of CINV than the older patients. However, the term “younger age” was not well-defined in those studies; the threshold for determining “younger age” varied from 40 to 67 in twelve studies, and three studies did not determine any age threshold. The thresholds for

determining “younger age” are as follows: age ≤ 40 (n=3), age ≤ 50 (n=3), age ≤ 55 (n=3), age ≤ 65 (n=2), and age < 67 (n=1) (see Table 4). In contrast, one study showed that older patients (age ≥ 55) are at higher risk of CINV [93]. However, in this study, older patients had higher correlation with larger tumor burden (i.e., diameter of the greatest residual tumor ≥ 2 cm). They primarily concluded that the patients with larger tumor burden are at higher risk of CINV. Thus, the effect of older age on CINV may be due to its correlation with larger tumor burden. In general, the younger patients are at higher risk of CINV than the older patients.

2.2.1.2 *Sex*

Gender was analyzed in 18 studies and 11 studies confirmed that female patients are at higher risk of CINV than male patients (see Table 4 and Table 5). One study that initially found female gender at a significantly lower CINV risk in univariate analysis was ultimately found to be insignificant in multivariate analysis and cited the possible explanation as a correlation between gender and other predictive factors (such as age) within the study.

2.2.1.3 *Alcohol Intake*

The impact of alcohol drinking habit on CINV was studied in 17 studies in which 8 studies confirmed that patients with lower alcohol intake are at higher risk of CINV (see Table 4 and Table 5). Most studies (n=7) defined low alcohol intake on the basis of the number of standard drinks per week. For example, Hilarius et al. (2012) [48], Tamura et al. (2015) [63], Warr et al. (2011) [78], and Hesketh et al. (2010) [81] found that patients taking less than 5 standard drinks per week are at higher risk of CINV than patients taking

less than 5 standard drinks per week. Both Dranitsaris et al. (2009) [86] and Booth et al. (2007) [89] reported that patients taking at least one standard drinks per day are at lower risk of CINV. In these two studies, low alcohol intake was defined as the number of drinks per week less than 7. Osoba et al. (1997) [92] defined low alcohol intake as the number of drinks per week less than 10; this study also found low alcohol intake to be a significant risk factors for CINV. In contrast, alcohol intake information has been determined based on patients' alcohol consumption habit only without estimating the number of drinks. For example, Sekine et al. (2013) [71] categorized alcohol consumption habit as the habitual vs. non-habitual drinker; this study reported that non-habitual alcohol drinkers are at higher risk of CINV, but did not provide the definition of habitual drinker.

2.2.1.4 History of CINV and/or pregnancy-related Nausea/Vomiting

A total of 17 studies analyzed the history of CINV and/or pregnancy-related nausea/vomiting. Out of those 17 studies, five studies confirmed that patients experiencing CINV during the prior chemotherapy treatment cycles are at higher risk of CINV during their current cycle. One study confirmed the impact of the history of nausea/vomiting on CINV by combining the history of motion sickness, pregnancy-related nausea/vomiting and vestibular dysfunction into a single variable (i.e., history of nausea/vomiting) [70]; history of CINV was not analyzed in that study. Two studies confirmed that female patients experiencing severe nausea/vomiting during their prior pregnancies are ate higher risk of CINV.

2.2.1.5 Anxiety

Moderate to high anxiety was found to be a risk factor of CINV in 5 studies (out of 8 studies that analyzed that variable); see Table 4 and Table 5. Most of the studies determined the level of anxiety using a Likert scale (e.g., a 4-point Likert scale is graded as none, mild, moderate and high) [96] or a 0-100 mm visual analog scale (VAS) [64]. Yap et al. (2012) [74] studied the impact of 21 anxiety-related symptoms on CINV. They found that 7 symptoms were strongly related to the CINV: fear of dying, fear of the worst, unable to relax, hot/cold sweats, nervousness, faintness, and numbness.

2.2.1.6 Expectancy of CINV

Patients who expect nausea/vomiting after their chemotherapy, regardless of previous experience, are more likely to experience CINV. This attribute has been analyzed in 7 studies out of which 3 studies confirmed the hypothesis.

2.2.1.7 Chemotherapy Cycle Number

This variable has been analyzed in 4 studies in which 2 studies [86,87] demonstrated that patients at earlier cycles (cycle no. < 3) are at higher risk of CINV. A similar result has been reported by Molassiotis et al. (2013) [70] that patients at the first-cycle of chemotherapy are at higher risk of CINV. However, Shih et al. (2009) [85] found no relation of chemotherapy cycle numbers to the risk of CINV.

2.2.1.8 Comorbidities

Two out of 5 studies showed that existing comorbidities (such as diabetes, cardiovascular diseases, gastrointestinal, musculoskeletal, thyroid, and other diseases) reduce the risk of CINV [86,89]. In contrast, Bourdeanu et al. (2012) [77] reported that Gastroesophageal Reflux Disease (GERD) increases the risk of CINV, and Furukawa et al. (2014) [66] reported that hypertension was significantly associated with delayed vomiting of grade 1 or higher.

2.2.1.9 Cancer Type

This variable has been analyzed in 12 studies. Only 2 studies found that some specific cancers increase the risk of CINV: breast cancer patients [84] and genitourinary or gynecologic cancer patients [86] were found to be at higher risk of CINV than other cancer types.

2.2.1.10 History of Morning Sickness

Four studies (out of 10 studies that analyzed this variable) found that patients who experienced morning sickness were at higher risk of CINV [63,78,87,89].

2.2.1.11 Performance Status (PS)

The performance status was estimated by the “Eastern Cooperative Oncology Group (ECOG) Performance Status” [97] scale. ECOG performance status is graded at six individual levels (0-5): (1) 0 indicates fully active, (2) 1 indicates ambulatory and able to carry out light works, (3) 2 indicates ambulatory but unable to carry out any works, (4) 3

indicates capable of only limited self-care, (5) 4 indicates completely disabled, and (6) 5 indicates dead. This variable has been analyzed in 5 studies in which 2 studies reported that poor performance status (i.e. the value of PS is greater than 1 indicating that the patient is not fully active) is a risk factor of CINV [71,95].

2.2.1.12 Race

The impact of race on CINV has been analyzed in 5 studies in which two studies demonstrated that patients from certain races are at higher risk of CINV. Bourdeanu et al. (2012) [77] demonstrated that Asian female breast cancer patients are at higher risk of CINV than Caucasian, African American, and Hispanic patients. Hassan and Yusoff (2010) [80] studied the three races in Malaysia (Malay, Chinese, and Asian Indians) and demonstrated that the Chinese patients were at higher risk of CINV in comparison to the other two ethnicities.

2.2.1.13 Use of Non-prescription Drugs

Two studies demonstrated that the use of non-prescription drugs at home before chemotherapy for nausea/vomiting control significantly increased the risk of CINV [86,87]. Both of the studies analyzed the same dataset separately for the acute and delayed phase of CINV. The names of the non-prescription drugs were not reported in those studies.

2.2.1.14 History of Motion Sickness

Two out of 17 studies demonstrated that the history of motion sickness is a risk factor of CINV [85]. Motion sickness is defined as sickness that is caused due to motion while traveling by car, train, airplanes or boats.

2.2.1.15 Cancer Stage

There are five stages in cancer: stage 0, I, II, III, and IV. The variable “cancer stage” has been analyzed in six studies but only one study reported that patients with early stages of cancer (stage I and II) are at higher risk of CINV during the acute phase [86]; the reasoning behind this fact was not discussed in this study. In contrast, cancer stage was reported to be not significant for developing CINV during the delayed phase using the same dataset [87].

2.2.1.16 Sleeping before Chemotherapy

Petrella et al. (2009) [87] reported that with the increase of the number of hours of sleep in the night before the chemotherapy, the probabilities of CINV during delayed phase decreased. In contrast, this variable had no significant impact on developing CINV during acute phase using the same dataset [96]. There are two other studies that analyzed the variable, but found no impact on developing CINV (see Table 4).

2.2.1.17 Meal before Chemotherapy

Booth et al. (2007) [89] reported that having no food before chemotherapy increased the probability of CINV. As such, this study suggested that the importance of eating a small amount of food prior to treatment should be emphasized during pre-chemotherapy education so that the risk of developing CINV could be reduced. Three other studies analyzed this attribute, but found no impact on CINV (see Table 4).

2.2.1.18 Recent Surgery

Booth et al. (2007) [89] reported that having surgery within the past three months of chemotherapy increased the probability of CINV. Two other studies analyzed this attribute as well, but found no impact on CINV (see Table 4).

2.2.1.19 Smoking History

Two studies conducted in Japan by Sekine et al. (2013) [71] and Furukawa et al. (2014) [66] analyzed the impact of smoking on CINV. Among those studies, only the study by Sekine et al. (2013) [71] reported that non-smokers are at higher risk of CINV than smokers.

2.2.1.20 Neurotransmitter Measurements

Substance-P and 5-HIAA/creatinine are two neurotransmitter measurements that are measured from blood and urine sample respectively. Higa et al. (2012) [98] studied the correlation of these neurotransmitters with the development of CINV due to moderately emetogenic chemotherapy (MEC). This study reported that the ratio of substance-P to 5-HIAA/creatinine greater than 70 is significantly associated with the development of CINV during delayed phase due to MEC.

2.2.1.21 Private/Public Insurance

Bourdeanu et al. (2012) [77] performed a study in USA on breast cancer patients and demonstrated that patients having private health insurances are at higher risk of CINV than the ones having public health insurances such as state or federally funded insurances.

2.2.1.22 Social Functioning

Social functioning is a variable within the health-related quality-of-life (HQL) indicator. Osoba et al. (1997) [92] reported that a social functioning score less than 70 is a significant predictor of CINV. The social functioning score is measured by the European Organization for Research and Treatment (EORTC) Core Quality of Life Questionnaire (QLQ-C30) [99]. The score ranges from 0 to 100, and a higher score indicates that the level of functioning is higher.

2.2.1.23 Nausea/Vomiting Before Chemotherapy

Petrella et al. (2009) [87] demonstrated that nausea/vomiting before chemotherapy is a significant predictor of CINV during the delayed phase, but not in the acute phase [86]. Molassiotis et al. (2014) [64] also supported that nausea prior to chemotherapy was a predictor of CINV, but this finding was significant for both the delayed and the acute phases.

2.2.1.24 Tumor Burden

Tumor burden/load is indicative of the amount of cancer in the body. Hursti et al. (1996) [93] categorized the tumor burden into two groups: (1) minimal tumor burden was defined as the diameter of the greatest residual tumor being less than 2 centimeters, and (2) large tumor burden was defined as the diameter of the greatest residual tumor being greater or equal to 2 centimeters. This study reported that the ovarian cancer patients with larger tumor burdens are at higher risk of CINV.

2.2.1.25 Cancer Recurrence (new/recurrent)

du Bois et al. (1992) [94] demonstrated that recurrent cancer patients are at higher risk of CINV than new cancer patients. This variable is related to the history of chemotherapy since patients with recurrent cancer likely went through more chemotherapy in the past.

2.2.1.26 Symptom Distress Score

Molassiotis et al. (2013) [70] used Symptom Distress Score [100] to measure the symptoms present before chemotherapy. This scale measures the symptom distress for a total of 13 items such as nausea, appetite, insomnia, pain, fatigue, bowel pattern, concentration, appearance, outlook, breathing, cough, frequency of nausea, and frequency of pain. Molassiotis et al. (2013) [70] reported that out of these 13 items, only pain was linked with the development of CINV.

2.2.2 Non-significant Factors

Table 6 presents a total of 16 patient-related factors that were not found to be significantly related to the prediction of CINV in any study. These factors are history of previous chemo (n=6), depression, (n=1), education (n=2), marital status (n=1), religion (n=1), weight (n=1), BMI (n=2), frequency of chemotherapy cycle (n=1), number of risk factors (n=1), drowsiness (n=1), neuroticism (n=1), autonomic perception (n=1), menopause (n=1), defecations (bowel movement) (n=1), history of radiotherapy (n=1), and ascites (n=1).

Table 6: Insignificant Patient-Related Factors

Attribute Name	# of Studies
History of Previous Chemo	6
Depression	1
Education	2
Marital Status	1
Religion	1
Weight	1
BMI	2
Frequency of chemotherapy cycle	1
Number of risk factors	1
Drowsiness	1
Neuroticism	1
Autonomic perception	1
Menopause	1
Defecations (bowel movement)	1
History of radiotherapy	1
Ascites	1

2.3 DISCUSSIONS

A significant amount of research has been performed to identify the patient-related risk factors of CINV. We have identified 30 studies through a systematic literature search strategy. These studies included a total of 42 patient-related variables in which 26 factors were found to have significant impact on the risk of CINV. Three factors are demographic-related: younger patients, female gender, and Asian race. A total of sixteen factors are innate to patient's physiology or influenced by physiology, and may alter the pathophysiology of CINV (i.e., intrinsic); these factors include history of CINV or pregnancy-related nausea/vomiting, anxiety, expectancy of CINV, absence of

comorbidities, cancer type (i.e., breast, genitourinary or gynecologic cancer), history of morning sickness, poor performance status, history of motion sickness, early stage of cancer, lower number of hours of sleep before chemotherapy, recent surgery within the past three months, a higher ratio of neurotransmitter measurements, nausea/vomiting before chemotherapy, larger tumor burden, recurrent cancer, and higher symptom distress score. Seven factors may influence the pathophysiology of CINV that are external in nature (i.e., extrinsic); these factors include low alcohol intake, patients at earlier cycles (≤ 3) of chemotherapy, use of non-prescription drugs at home for emesis control before chemotherapy, no food intake before chemotherapy, non-smoking habit, having private insurance, and low social functioning.

None of the studies considered all 42 variables simultaneously. The average number of variables included per study was 7.06 with a minimum of 1 and a maximum of 16 (median = 6 and standard deviation = 4.18). The average number of significant risk factors that were reported per study was 2.7 with a minimum of 0 and a maximum of 7 (median = 2 and standard deviation = 1.99). The maximum number of patient-related risk factors that were reported by a single study was 7 (n=3) followed by 5 (n=3) and 4 (n=2). Dranitsaris et al. (2009) [86], Petrella et al. (2009) [87] and Booth et al. (2007) [89] reported 7 risk factors. Tamura et al. (2015) [63], Molassiotis et al. (2014) [64], and Molassiotis et al. (2013) [70] reported 5 risk factors. Sekine et al. (2013) [71] and Osoba et al. (1997) [92] reported 4 risk factors.

2.4 SIGNIFICANCE OF THIS SYSTEMATIC REVIEW

The significance of this study is threefold. **First**, the current CINV guidelines that are basically based on antiemetics for the risk of CINV can be augmented using the findings from this review (i.e., a comprehensive list of significant patient-related factors) so that oncologists can consider these factors when they predict CINV. **Second**, the findings of the study can be used to discover associations among those patient-related factors. While it is important to identify individual patient-related factors, the more important research may be to discover how those individual factors are associated one another in terms of the risk of CINV. **Third**, this review may lay the foundation for the construction of CINV prediction models. Currently, CINV prediction models based on antiemetics and patient-related factors are unsatisfactory [70,86,87,96,101]. This indicates that associations among patient-related factors are not fully identified, and/or there are some important, yet hidden, patient-related factors.

2.5 LIMITATIONS

We have identified four limitations of this systematic review study. **First**, only two studies included the low emetogenic chemotherapy (LEC) in conjunction with the high and moderate emetogenic chemotherapy. None of the studies independently analyzed patient related risk factors for LEC. Thus, the literature does not confirm whether patient-related factors have an impact on CINV due to LEC. **Second**, the number of subjects in the studies are not large enough; half of the studies employed less than 243 subjects. The average number of subjects per study was 476.7 with a minimum of 25 and a maximum of 1,910 (standard deviation=504.7). **Third**, the methods for determining the significance level of

risk factors were not consistent across different studies. **Fourth**, the cut-off/threshold for numerical variables were not similar across different studies. For example, five different age cut-offs were used for determining younger patients who are at risk for developing CINV.

2.6 CONCLUSION

This systematic review study has identified and summarized patient-related factors that significantly impact a patient's risk of CINV. The identification of patients at risk for CINV based on key risk factors prior to the initiation of a chemotherapy regimen is imperative. Oncologists may be able to selectively focus on more aggressive treatments on those high risk patients. Although there are 30 significant risk factors (see Table 5), most studies used only two to three significant factors as well as many non-significant factors, as discussed in the discussion section. Therefore, future studies are needed that include as many significant risk-factors as possible to see how, in combinations, they may affect the risk of CINV.

CHAPTER 3 : CLINICAL DATA

3.1 DATA SOURCES

This was a single-center retrospective study. The data were collected by retrospective record review from the electronic medical records used at the University of Missouri Ellis Fischel Cancer Center. The study was approved by the MU Health Sciences IRB (project number 1208541).

3.2 INCLUSION AND EXCLUSION CRITERIA

The patients who received chemotherapy and standard antiemetic prophylaxis (based on national antiemetic guidelines) at the oncology outpatient service during the period of June 1, 2010 to July 31, 2012 were included in the study. The patients, who were treated with concurrent radiotherapy or surgical procedure, were excluded from the study. Also, the patients with missing information were excluded from the study.

3.3 DATA COLLECTION PLAN

The first aim of this project was to collect data. There are two phases of CINV: acute phase and delayed phase. We planned to collect two independent datasets for each phases of CINV. The rationale behind collecting two independent datasets was that the pathophysiology of CINV for acute phase is different than the delayed phase. The

pathophysiology of CINV is a complex process (see section 1.3). Since the acute and delayed CINV follows two different pathophysiology, we plan to discover the patient-related risk factors for causing CINV during both phases independently. As such, two independent datasets were needed.

In each dataset, there are three groups of data based on the emetogenicity of chemotherapy regimens. The degree of emetogenicity of chemotherapy regimens is divided into four emetic risk categories: minimal, low, moderate, and high (see section 1.4). The minimal risk category of chemotherapy for causing CINV is not clinically important since only less than 10% of patients suffers from CINV. Thus, we collected data in three groups corresponding to three clinically important categories: low, moderate and high.

3.4 CLASS BALANCING

The dataset may suffer from class-imbalance problem for a group of data. For example, less than 30% patients suffer from CINV due to low emetogenic chemotherapy (LEC). With the use of standard antiemetic treatment, this percentage will be further reduced. As such, the dataset will have far less number of CINV cases than no-CINV cases. Another example is the high emetogenic chemotherapy (HEC) group where the number of CINV cases are very higher than the no-CINV cases. Our major classes of interest includes both CINV and no-CINV cases. As a result, class balancing in each group of data (LEC, MEC and HEC) was deemed necessary. This was achieved by making the size of dataset in each class for each group approximately equal.

3.5 VARIABLE SELECTION

In order to identify the potential patient-related variables for causing CINV, we have completed a systematic review study by following the “Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)” guideline [61]. Chapter 2 presents the results of the study. We searched MEDLINE to identify the articles that demonstrated patient-related risk factors of CINV through clinical studies. A total of 30 articles were selected for this study. A total of 26 patient-related risk-factors were documented. In this project, we included 13 independent variables and 1 dependent variable (CINV outcome) based on the recommendations from the chemotherapy experts in the MU Elis Fischel Cancer Center; see Table 7 for data descriptions. The rationale behind choosing those 13 variables is two-fold. First, the experts consider some of those variables as clinically significant for causing CINV based on their experience. Second, those variables are easy to collect during a clinical encounter. This is important because the prediction model should be readily usable at the point-of-care before chemotherapy.

Table 7: Patient-Related Variables

Variable Name	Description and Data Domain
Age	Age of the patient
Sex	Male or Female
Race	Asian, Hispanic, White, African American
Body Mass Index (BMI)	Calculated based on the height and weight of the patient
Type of cancer	Solid Cancers: <ul style="list-style-type: none"> – Breast cancer – Lung cancer – Colorectal and anal cancer – Genitourinary cancer – Other solid cancers Hematological Cancers: <ul style="list-style-type: none"> – Leukemia both acute and chronic – Myeloma – Lymphoma both acute and chronic – Other heme malignancies
Stage of Cancer	The severity of a person's cancer based on the extent of the original (primary) tumor and whether or not cancer has spread in the body. There are five stages: 0, I, II, III, and IV.
Number of Comorbidities	Up to four comorbidities are considered: <ul style="list-style-type: none"> – Cardiovascular diseases: heart diseases/coronary artery diseases, high blood pressure, high cholesterol, atrial fibrillation, or any cardiac arrhythmia – Respiratory system diseases: asthma, COPD, or chronic bronchitis, etc. – Chronic pain syndrome – Other diseases: moderate to severe Gastroesophageal reflux disease (GERD), crohn's disease, any chronic gallbladder, any chronic pancreatic problem, chronic diarrhea/constipation, or any moderate to severe psychiatric illnesses.
Alcohol Consumption	This attribute describes the alcohol drinking habit of the patient. The patients having two or less standard drinks per week are considered as low alcohol drinking habit; otherwise, the patients are considered as high alcohol drinking habit.
Current smoker	This attribute describes the smoking habit of the patient. This is mainly characterized by the nicotine dependence that can occur with cigarette smoking, smokeless tobacco use and/or Cigar or pipe use. A current smoker is defined as the person had any nicotine dependence in last 30 days.
Anxiety	This attribute describes whether the patient had anxiety during treatment. This has been determined from the psychosocial evaluation report by a social worker or a physician.
Dehydration	This attribute describes whether the patient had dehydration or not before the chemotherapy
Number of prior chemotherapy regimens	This attribute describes the number of different chemotherapy regimens that has been used for a patient previously. A chemotherapy regimen consists of multiple cycles of same chemotherapy.
History of previous CINV	This attribute describes whether the patient had at least grade 2 to 4 CINV in their last cycle of chemotherapy.
Symptoms (Sx)/CINV Outcome	This attribute describes the use of antiemetic outcome. The use of antiemetics is based on the national guidelines. The patients suffering from grade 2 or more severe CINV with the use of guideline-based antiemetics are considered as CINV positive; otherwise, the patients are considered as CINV negative.

3.6 ELECTRONIC DATA CAPTURE

The MU-iCATS's Research Informatics Core was used as a central location for data processing and management. The MU-iCATS has implemented an electronic data capture system called Research Electronic Data Capture (REDCap) [102,103], which was developed by Vanderbilt University. Figure 4 presents the REDCap data collection instrument for this project. The REDCap data collection instrument consists of both numerical coding and text labels in the data entry forms for 14 variables including the class variable. This resolved the issue of data coding error. For text entry of numerical data, validation rules were applied. Both datasets were verified by an oncologist for clinical correctness.

Record ID	3054
Age * must provide value	<input type="text"/> <small>Age of the patient during chemotherapy</small>
Sex * must provide value	☐ Male ☐ Female <small>reset</small>
Race * must provide value	☐ Asian ☐ Hispanic ☐ White ☐ African American <small>reset</small>
Body Mass Index (BMI) * must provide value	<input type="text"/> <small>BMI during chemotherapy</small>
Type of Cancer * must provide value	☐ Breast Cancer ☐ Lung Cancer ☐ Colorectal and Anal Cancer ☐ Genitourinary Cancer ☐ Other Solid Cancers ☐ Leukemia both Acute and Chronic ☐ Myeloma ☐ Lymphoma both Acute and Chronic ☐ Other Heme Malignancies <small>reset</small>
Stage of Cancer * must provide value	☐ Stage 0 ☐ Stage I ☐ Stage II ☐ Stage III ☐ Stage IV <small>reset</small>
Number of Comorbidities * must provide value	☐ 1 ☐ 2 ☐ 3 ☐ 4 <small>reset</small>
Alcohol Consumption * must provide value	☐ The patient have LOW (two or less drinks per week) or NO alcohol consumption habit ☐ The patient consumes more than two drinks per week <small>reset</small>
Is the Patient a Current Smoker? * must provide value	☐ The Patient is NOT a current smoker ☐ The patient is a current smoker <small>reset</small>
Anxiety * must provide value	☐ The Patient had NO Anxiety during Chemotherapy ☐ The Patient had Anxiety during Chemotherapy <small>reset</small>
Dehydration * must provide value	☐ The Patient had NO Dehydration before Chemotherapy ☐ The Patient had Dehydration before Chemotherapy <small>reset</small>
Number of Prior Chemotherapy Regimen * must provide value	<input type="text"/> <small>Number of different chemotherapy regimen that has been used for a patient previously. A chemotherapy regimen consists of multiple cycles of same chemotherapy</small>
Emetogenicity of Chemotherapy * must provide value	☐ Low Emetogenic Chemotherapy (LEC) ☐ Moderate Emetogenic Chemotherapy (MEC) ☐ High Emetogenic Chemotherapy (HEC) <small>reset</small>
History of Previous CINV * must provide value	☐ The Patient had NO CINV (Grade 2 to 4) during the Last Cycle of Chemotherapy ☐ The patient had CINV (Grade 2 to 4) During the Last Cycle of Chemotherapy <small>reset</small>
Symptoms (Sx)/CINV Outcome * must provide value	☐ The Patient had less than Grade 2 CINV ☐ The Patient had at least Grade 2 or more Severe CINV <small>reset</small>

Figure 4: REDCap Data Collection Instrument

3.7 DATA SUMMARY

A total of 6,124 records were collected based on the inclusion and exclusion criteria described in section 3.2; the acute phase dataset contains 3,053 records and the delayed phase dataset contains 3,071 records. Table 8 and Table 9 presents the breakdown of both datasets in terms of three chemotherapy categories and two treatment outcomes. Table 10 and Table 11 presents the overview of both acute and delayed phase dataset, consecutively.

Table 8: Acute Phase Data Summary

CINV Treatment Group	# of records	CINV=Yes	CINV=No
High Emetogenic Chemo (HEC)	1,026	504 (49.12%)	522 (50.88%)
Moderate Emetogenic Chemo (MEC)	1,012	506 (50%)	506 (50%)
Low Emetogenic Chemo (LEC)	1,015	506 (50.15%)	509 (49.85%)
Grand Total	3,053	1,519 (49.75%)	1,534 (50.25%)

Table 9: Delayed Phase Data Summary

CINV Treatment Group	# of records	CINV=Yes	CINV=No
High Emetogenic Chemo (HEC)	1,166	586 (50.26%)	580 (49.74%)
Moderate Emetogenic Chemo (MEC)	891	447 (50.17%)	444 (49.83%)
Low Emetogenic Chemo (LEC)	1,014	519 (51.18%)	495 (48.82%)
Grand Total	3,071	1,552 (50.54%)	1,519 (49.46%)

Table 10: Acute Phase Data Overview

		Acute Phase			
		LEC N (%)	MEC N (%)	HEC N (%)	Total N (%)
Age	Min	21 (NA)	25 (NA)	25 (NA)	21 (NA)
	Median	51 (NA)	54 (NA)	58 (NA)	53 (NA)
	Mean	51.34 (NA)	55.55 (NA)	56.04 (NA)	54.32 (NA)
	Max	78 (NA)	78 (NA)	78 (NA)	78 (NA)
	Std. Dev	12.86 (NA)	12.68 (NA)	12.73 (NA)	12.92 (NA)
	21-40 years	228 (22.46%)	110 (10.87%)	111 (10.82%)	449 (14.71%)

	41-60 years	507 (49.95%)	515 (50.89%)	496 (48.34%)	1,518 (49.72%)
	61-80 years	280 (27.59%)	387 (38.24%)	419 (40.84%)	1,086 (35.57%)
BMI					
	Min	19 (NA)	19 (NA)	19 (NA)	19 (NA)
	Max	29 (NA)	30 (NA)	29 (NA)	29 (NA)
	Mean	30.03 (NA)	30.25 (NA)	29.93 (NA)	30.07 (NA)
	Median	39 (NA)	39 (NA)	39 (NA)	39 (NA)
	Std. Dev	4.77 (NA)	4.77 (NA)	4.86 (NA)	4.80 (NA)
	Underweight (Below 18.5)	0 (00.00%)	0 (00.00%)	0 (00.00%)	0 (00.00%)
	Normal (18.5 – Below 25)	88 (08.67%)	75 (07.41%)	101 (09.84%)	264 (08.65%)
	Overweight (25.0 – Below 30)	427 (42.07%)	422 (41.70%)	431 (42.01%)	1,280 (41.93%)
	Obese (30.0 and Above)	500 (49.26%)	515 (50.89%)	494 (48.15%)	1,509 (49.43%)
Number of Comorbidity					
	1	253 (24.93%)	300 (29.64%)	399 (38.89%)	952 (31.18%)
	2	464 (45.71%)	469 (46.34%)	402 (39.18%)	1,335 (43.73%)
	3	95 (09.36%)	90 (08.89%)	113 (11.01%)	298 (09.76%)
	4	203 (20.00%)	153 (15.12%)	112 (10.92%)	468 (15.33%)
Gender					
	Female	611 (60.20%)	502 (49.60%)	539 (52.53%)	1,652 (54.11%)
	Male	404 (39.80%)	510 (50.40%)	487 (47.47%)	1,401 (45.89%)
Race					
	Asian	69 (06.80%)	77 (07.61%)	58 (05.65%)	204 (06.68%)
	African American	178 (17.54%)	190 (18.77%)	164 (15.98%)	532 (17.43%)
	Hispanic	71 (07.00%)	73 (07.21%)	68 (06.63%)	212 (06.94%)
	White	697 (68.67%)	672 (66.40%)	736 (71.73%)	2,105 (68.95%)
Stage of Cancer					
	Stage I	151 (14.88%)	224 (22.13%)	111 (10.82%)	486 (15.92%)
	Stage II	111 (10.94%)	160 (15.81%)	79 (07.70%)	350 (11.46%)
	Stage III	467 (46.01%)	385 (38.04%)	507 (49.42%)	1,359 (44.51%)
	Stage IV	286 (28.18%)	243 (24.01%)	329 (32.07%)	858 (28.10%)
Alcohol Consumption					
	Low	567 (55.86%)	540 (53.36%)	290 (28.27%)	1,397 (45.76%)
	High	448 (44.14%)	472 (46.64%)	736 (71.73%)	1,656 (54.24%)
Smoking Status					
	Not a Current Smoker	501 (49.36%)	396 (39.13%)	481 (46.88%)	1,378 (45.14%)
	Current Smoker	514 (50.64%)	616 (60.87%)	545 (53.12%)	1,675 (54.86%)
Dehydration					
	No	507 (49.95%)	518 (51.19%)	568 (55.36%)	1,593 (52.18%)
	Yes	508 (50.05%)	494 (48.81%)	458 (44.64%)	1,460 (47.82%)
Anxiety					
	No	462 (45.52%)	520 (51.38%)	469 (45.71%)	1,451 (47.53%)
	Yes	553 (54.48%)	492 (48.62%)	557 (54.29%)	1,602 (52.47%)
Number of Previous Chemotherapy					
	0	406 (40.00%)	386 (38.14%)	263 (25.63%)	1,055 (34.56%)
	1	259 (25.52%)	329 (32.51%)	470 (45.81%)	1,058 (34.65%)
	2	178 (17.54%)	229 (22.63%)	201 (19.59%)	608 (19.91%)
	3	113 (11.13%)	68 (06.72%)	92 (08.97%)	273 (08.94%)
	4	59 (05.81%)	0 (00.00%)	0 (00.00%)	59 (01.93%)
Prior CINV					
	No	516 (50.84%)	432 (42.69%)	569 (55.46%)	1,517 (49.69%)

	Yes	499 (49.16%)	580 (57.31%)	457 (44.54%)	1,536 (50.31%)
Type of Cancer					
	Breast	72 (07.09%)	85 (08.40%)	74 (07.21%)	231 (07.57%)
	Lung	140 (13.79%)	144 (14.23%)	150 (14.62%)	434 (14.22%)
	Colorectal & anal	89 (08.77%)	82 (08.10%)	86 (08.38%)	257 (08.42%)
	Genitourinary	119 (11.72%)	131 (12.94%)	113 (11.01%)	363 (11.89%)
	Other solid cancer	84 (08.28%)	65 (06.42%)	78 (07.60%)	227 (07.44%)
	Leukemia both acute and chronic	152 (14.98%)	162 (16.01%)	151 (14.72%)	465 (15.23%)
	Myeloma	120 (11.82%)	99 (09.78%)	113 (11.01%)	332 (10.87%)
	Lymphoma both acute and chronic	134 (13.20%)	140 (13.83%)	148 (14.42%)	422 (13.82%)
	Other heme malignancies	105 (10.34%)	104 (10.28%)	113 (11.01%)	322 (10.55%)
CINV Outcome					
	No CINV	506 (49.85%)	506 (50.00%)	522 (50.88%)	1,534 (50.25%)
	CINV	509 (50.15%)	506 (50.00%)	504 (49.12%)	1,519 (49.75%)

Table 11: Delayed Phase Data Overview

		Delayed Phase			
		LEC N (%)	MEC N (%)	HEC N (%)	Total N (%)
Age					
	Min	21 (NA)	25 (NA)	25 (NA)	21 (NA)
	Max	52 (NA)	54 (NA)	57 (NA)	54 (NA)
	Mean	53.11 (NA)	55.09 (NA)	55.88 (NA)	54.73 (NA)
	Median	78 (NA)	78 (NA)	78 (NA)	78 (NA)
	Std. Dev	12.95 (NA)	12.78 (NA)	12.83 (NA)	12.91 (NA)
	21-40 years	173 (17.06%)	111 (12.46%)	137 (11.75%)	421 (13.71%)
	41-60 years	514 (50.69%)	449 (50.39%)	552 (47.34%)	1,515 (49.33%)
	61-80 years	327 (32.25%)	331 (37.15%)	477 (40.91%)	1,135 (36.96%)
BMI					
	Min	19 (NA)	19 (NA)	19 (NA)	19 (NA)
	Max	29 (NA)	30 (NA)	29 (NA)	29 (NA)
	Mean	30.08 (NA)	30.27 (NA)	29.88 (NA)	30.06 (NA)
	Median	39 (NA)	39 (NA)	39 (NA)	39 (NA)
	Std. Dev	4.77 (NA)	4.84 (NA)	4.83 (NA)	4.82 (NA)
	Underweight (Below 18.5)	0 (00.00%)	0 (00.00%)	0 (00.00%)	0 (00.00%)
	Normal (18.5 – Below 25)	84 (08.28%)	77 (08.64%)	117 (10.03%)	278 (09.05%)
	Overweight (25.0 – Below 30)	427 (42.11%)	358 (40.18%)	485 (41.60%)	1,270 (41.35%)
	Obese (30.0 and Above)	503 (49.61%)	456 (51.18%)	564 (48.37%)	1,523 (49.59%)
Number of Comorbidity					
	1	266 (26.23%)	256 (28.73%)	414 (35.51%)	936 (30.48%)
	2	467 (46.06%)	417 (46.80%)	478 (40.99%)	1,362 (44.35%)
	3	102 (10.06%)	81 (09.09%)	128 (10.98%)	311 (10.13%)
	4	179 (17.65%)	137 (15.38%)	146 (12.52%)	462 (15.04%)
Gender					
	Female	564 (55.62%)	465 (52.19%)	601 (51.54%)	1,630 (53.08%)

	Male	450 (44.38%)	426 (47.81%)	565 (48.46%)	1,441 (46.92%)
Race					
	Asian	61 (06.02%)	54 (06.06%)	62 (05.32%)	177 (05.76%)
	African American	179 (17.65%)	175 (19.64%)	189 (16.21%)	543 (17.68%)
	Hispanic	62 (06.11%)	74 (08.31%)	74 (06.35%)	210 (06.84%)
	White	712 (70.22%)	588 (65.99%)	841 (72.13%)	2,141 (69.72%)
Stage of Cancer					
	Stage I	172 (16.96%)	187 (20.99%)	110 (09.43%)	469 (15.27%)
	Stage II	112 (11.05%)	112 (12.57%)	83 (07.12%)	307 (10.00%)
	Stage III	447 (44.08%)	378 (42.42%)	601 (51.54%)	1,426 (46.43%)
	Stage IV	283 (27.91%)	214 (24.02%)	372 (31.90%)	869 (28.30%)
Alcohol Consumption					
	Low	526 (51.87%)	479 (53.76%)	551 (47.26%)	1,556 (50.67%)
	High	488 (48.13%)	412 (46.24%)	615 (52.74%)	1,515 (49.33%)
Smoking Status					
	Not a Current Smoker	444 (43.79%)	411 (46.13%)	549 (47.08%)	1,404 (45.72%)
	Current Smoker	570 (56.21%)	480 (53.87%)	617 (52.92%)	1,667 (54.28%)
Dehydration					
	No	642 (63.31%)	524 (58.81%)	629 (53.95%)	1,795 (58.45%)
	Yes	372 (36.69%)	367 (41.19%)	537 (46.05%)	1,276 (41.55%)
Anxiety					
	No	463 (45.66%)	465 (52.19%)	605 (51.89%)	1,533 (49.92%)
	Yes	551 (54.34%)	426 (47.81%)	561 (48.11%)	1,538 (50.08%)
Number of Previous Chemotherapy					
	0	484 (47.73%)	315 (35.35%)	313 (26.84%)	1,112 (36.21%)
	1	191 (18.84%)	322 (36.14%)	512 (43.91%)	1,025 (33.38%)
	2	172 (16.96%)	202 (22.67%)	231 (19.81%)	605 (19.70%)
	3	108 (10.65%)	52 (05.84%)	110 (09.43%)	270 (08.79%)
	4	59 (05.82%)	0 (00.00%)	0 (00.00%)	59 (01.92%)
Prior CINV					
	No	620 (61.14%)	531 (59.60%)	713 (61.15%)	1,864 (60.70%)
	Yes	394 (38.86%)	360 (40.40%)	453 (38.85%)	1,207 (39.30%)
Type of Cancer					
	Breast	71 (07.00%)	69 (07.74%)	88 (07.55%)	228 (07.42%)
	Lung	132 (13.02%)	132 (14.81%)	171 (14.67%)	435 (14.16%)
	Colorectal & anal	87 (08.58%)	70 (07.86%)	97 (08.32%)	254 (08.27%)
	Genitourinary	118 (11.64%)	109 (12.23%)	134 (11.49%)	361 (11.76%)
	Other solid cancer	84 (08.28%)	63 (07.07%)	96 (08.23%)	243 (07.91%)
	Leukemia both acute and chronic	154 (15.19%)	132 (14.81%)	165 (14.15%)	451 (14.69%)
	Myeloma	122 (12.03%)	94 (10.55%)	127 (10.89%)	343 (11.17%)
	Lymphoma both acute and chronic	142 (14.00%)	123 (13.80%)	163 (13.98%)	428 (13.94%)
	Other heme malignancies	104 (10.26%)	99 (11.11%)	125 (10.72%)	328 (10.68%)
CINV Outcome					
	No CINV	495 (48.82%)	444 (49.83%)	580 (49.74%)	1,519 (49.46%)
	CINV	519 (51.18%)	447 (50.17%)	586 (50.26%)	1,552 (50.54%)

3.8 DATA CHARACTERISTICS

This section describes the characteristics of each data domains in terms of their predictive nature (i.e., the probability of CINV) for three treatment categories and two phases of CINV.

3.8.1 Age vs. CINV Outcome

In our systematic review, we have found that younger patients were at higher risk of CINV. However, age cutoff was not well-defined; the threshold for determining younger age varied from 40 to 67. Figure 5 presents the probability of CINV against age. The probability of CINV varied only for low emetogenic chemotherapy (LEC) in acute and delayed phase; younger patients had higher chance of CINV which is consistent with the literature. From the graph, we observe that patients less than 40 years old were at higher risk of CINV for LEC. For moderate and high emetogenic chemotherapies, the probability of CINV was about 50% for any ages for both acute and delayed phases.

Figure 5: Age vs. Probability of CINV

3.8.2 BMI vs. CINV Outcome

In the literature, the BMI was found to be non-significant for CINV prediction. However, in our dataset, we observed that BMI has some impacts on the probability of CINV for LEC in both acute and delayed phase (Figure 6). In acute phase, the patients with lower BMI were at lower risk of CINV for low and moderate chemotherapies. In contrast, in delayed phase, patients with lower BMI were at higher risk of CINV for high emetogenic chemotherapies. However, in delayed phase, patients with higher BMI were at higher risk of CINV.

Figure 6: BMI vs. Probability of CINV

3.8.3 Number of Comorbidities vs. CINV Outcome

Figure 7 presents that the probability of CINV increases with the increase of number of comorbidities. For high emetogenic chemotherapies, the probability of CINV is about 73.21% for acute phase and 86.3% for delayed phase. For other cases, the probability is around 50%.

Figure 7: Number of Comorbidities vs. Probability of CINV

3.8.4 Gender vs. CINV Outcome

The probability of CINV for both males and females were around 50% (Figure 8). Overall this is not a good predictor but may have some impact in a sub population.

Figure 8: Gender vs. Probability of CINV

3.8.5 Race vs. CINV Outcome

In the dataset, the Hispanic population showed lower risk of CINV (around 40% are at risk of CINV) than other population for both moderate and high emetogenic chemotherapies (Figure 9). Thus, race seems to have some predictive power for Hispanic population. Around 50% of the White, African American and Asian population were at risk of CINV; thus, race does not seem to be a predictive factor for White, African American and Asian population.

Figure 9: Race vs. Probability of CINV

3.8.6 Stage of Cancer vs. CINV Outcome

For high emetogenic chemotherapies, the patients are at similar risk of CINV with around 50% probability for any stages of cancer (Figure 10). However, stage 3 and 4 patients were at higher risk of CINV than stage 1 and 2 patients for low and moderate emetogenic chemotherapies in both phases.

Figure 10: Stage of Cancer vs. Probability of CINV

3.8.7 Alcohol Consumption vs. CINV Outcome

The patients who drink lower amount of alcohol are at higher risk of CINV than the patients who drink higher amount of alcohol; similar pattern is observed for any type of chemotherapies (Figure 11). This is consistent with the findings in the literature.

Figure 11: Alcohol Consumption vs. Probability of CINV

3.8.8 Smoking vs. CINV Outcome

The current smokers are at higher risk of CINV than the non-smokers. For smokers, the probability of CINV is higher at the acute phase than delayed phase (Figure 12).

Figure 12: Current Smoker vs. Probability of CINV

3.8.9 Dehydration vs. CINV Outcome

The patients with dehydration symptom are at higher risk of CINV than the patients without having dehydration. In the CINV dataset, the probability of CINV varied from 73% to 83% depending on the context (Figure 13).

Figure 13: Dehydration vs. Probability of CINV

3.8.10 Anxiety vs. CINV Outcome

The patients having anxiety are at higher risk of CINV than the patients with no anxiety (Figure 14); the probability of CINV is higher at acute phase than delayed phase.

Figure 14: Anxiety vs. Probability of CINV

3.8.11 Number of Previous Chemotherapy vs. CINV Outcome

With the increase of number of previous chemotherapies, the probability of CINV has also increased. The patients who received more than 2 chemotherapy regimens were at very high risk of CINV (Figure 15).

Figure 15: Number of Previous Chemotherapy vs. Probability of CINV

3.8.12 Prior CINV vs. CINV Outcome

The patients, who had CINV either in acute or delayed phase during the last cycle of chemotherapy, were at higher risk of chemotherapy (Figure 16). The probability of CINV ranges from 72% to 86% percent in the acute phase and 57% to 82% in the delayed phase depending on the type of chemotherapy.

Figure 16: Prior CINV vs. Probability of CINV

3.8.13 Type of Cancer vs. CINV Outcome

The probability of CINV for various type of cancers varied based on the type of chemotherapy. In acute phase, leukemia and myeloma patients had higher probability of CINV for low emetogenic chemotherapies, colorectal cancer patients had higher probability of CINV for moderate emetogenic chemotherapies, and lung cancer and lymphoma patients had higher probability of CINV for high emetogenic chemotherapies. For delayed phase, lung cancer patients had higher probability of CINV for low emetogenic chemotherapies, colorectal cancer patients had higher probability of CINV for moderate

emetogenic chemotherapies, and breast and lung cancer patients had higher probability of CINV for high emetogenic chemotherapies (Figure 17).

Figure 17: Type of Cancer vs. Probability of CINV

CHAPTER 4 : DATA MINING

Data mining or knowledge discovery in databases (KDD) is a process of extracting previously unknown and potentially useful information or patterns from data. In general, data mining algorithms are categorized into two groups: descriptive or unsupervised learning and predictive or supervised learning. In supervised learning, the class labels of the observations or tuples are known whereas in unsupervised learning, the class labels of the tuples are unknown. Data mining techniques were found to be very useful in predictive analytics on medical data [104]. In this study, we needed to develop a prediction model, which falls into the category of supervised learning or classification.

4.1 CLASSIFICATION METHODS

Classification is a supervised learning method for building classification models based on a dataset (called training data) and the values in classifying attribute (called class label). The classification model is used to predict class label which is categorical. Classification is a two-step process in which the model is constructed in the first step and the accuracy of the model is determined using a dataset (called test dataset) in the second step. The accuracy of the classification model is the percentage of test dataset tuples that are correctly classified by the model. In order to overcome the over fitting problem, the test dataset must be independent of the training dataset. In general, the classification model

consists of IF-THEN rules or mathematical formula. In the following sections, some classification techniques are described.

4.1.1 Decision Tree

The decision tree is a flow-chart-like tree structure in which the test on an attribute is presented by an internal or non-leaf node, the outcomes of the tests are presented by the branches, and the class labels correspond to the leaf nodes. The decision tree is constructed in a top-down, recursive, and divide-and-conquer manner. All attributes are assumed to be categorical; otherwise, continuous-valued attributes are discretized to form categories (e.g. age is a continuous-valued attribute which can be categorized into two groups: young and old). The key step in the decision tree construction process is the selection of attribute that best partitions the tuples into distinct classes. The attribute is selected based on the attribute selection measures such as information gain, gain ratio, or gini index, etc. At the beginning of the tree construction, all the training tuples are at the root node. The training tuples are recursively partitioned based on the selected attributes. The partitioning stops if the class label of all tuples in a given node is same, or no attributes left for partitioning, or no tuples left for partitioning.

In classification, the classification model corresponds to the decision tree from which the classification rules can easily be generated. In order to determine the unknown class label of a new observation, a path from root node to leaf node of the decision tree is traversed to test the attributes of the tuple against the corresponding non-leaf node and the class label of the tuple is determined by the leaf node.

The decision tree algorithms mainly differ based on the attribute selection measures and the tree pruning mechanisms. Iterative Dichotomiser 3 (ID3) was introduced by Ross

Quinlan in 1979 [105], where information gain is used as the attribute selection measure. The information gain of an attribute is defined as the difference between the information required to classify a training tuple before and after the partitioning by the attribute. The attribute with the highest information gain is selected as the splitting criterion, which constructs a simple tree and minimizes the number of tests needed to classify a given tuple. The main drawback of the information gain measure is its biasness towards the attribute that corresponds to tests with many outcomes (i.e. branches).

In order to overcome the drawback of ID3, a successor of ID3 known as C4.5 was introduced by Quinlan [106]. C4.5 uses the *gain ratio* (an extension to information gain) as the attribute selection measure, which is defined as the ratio between the information gain and the split information value of the attribute. The split information value of an attribute is defined as the potential information generated by splitting the training dataset into a number of partitions, which corresponds to the outcomes of the test on the attribute. The attribute for splitting criterion is selected with the highest gain ratio. The main drawback of the gain ratio is that it becomes unstable when the split information value becomes zero. This scenario is handled by applying a constraint, which states that the information gain for a splitting criterion must be larger than all other splitting criteria. An improved version of C4.5 was developed by Quinlan, known as C5.0/See5 [107]. The C5.0 is a commercial data mining tool which is faster than C4.5 with lower error rate and smaller tree size, and memory requirement for large dataset is also less.

The Classification and Regression Trees (CART) [108] were invented by Brieman et al. in parallel to the ID3 around the same time, which is a generation of binary decision tree. The Gini index is used as the attribute selection measure in CART. The Gini index

measures the impurity of the training dataset D , which is defined as: $Gini(D) = 1 - \sum_{i=1}^m p_i^2$, where p_i is the probability that a tuple in D belongs to class C_i . The Gini split for splitting D into D_1 and D_2 of size n_1 and n_2 respectively, based on attribute A , is defined as: $Gini_A(D) = \frac{n_1}{n} Gini(D_1) + \frac{n_2}{n} Gini(D_2)$. The reduction in impurity is measured by the difference between $Gini(D)$ and $Gini_A(D)$. The attribute with the maximum reduction in impurity (or minimum Gini index) is selected as the splitting criteria.

After tree construction, the branches, that reflect anomalies in the training data due to noise or outliers, are identified and removed (known as tree pruning step) to overcome the over-fitting of the data and to improve the classification accuracy. Two approaches are adopted for tree pruning: pre-pruning and post-pruning. In pre-pruning, the tree construction is halted early depending on the predefined threshold for splitting criterion of a node and the node becomes a leaf. The post-pruning approach is more common, in which sub-trees are removed from the constructed tree at a node and the node becomes a leaf. In CART, the pruning algorithm is known as “cost complexity” (a post-pruning approach), which is a function of number of leaves and error rate. The tree with smallest size and minimum cost complexity is chosen. In C4.5, the pruning algorithm is known as “pessimistic pruning”, which is similar to cost complexity. The main difference between these two algorithms is that, the cost complexity algorithm uses the pruning dataset (independent of training dataset) and the pessimistic pruning algorithm uses the training dataset for error rate estimation. Another algorithm for tree pruning is based on the Minimum Description Length (MDL) principle. A hybrid approach combining pre-pruning and post-pruning can also be applied.

4.1.2 Naïve Bayesian Classification

The Naïve Bayesian classification is the simplification of Bayesian classification [109]. The Bayesian classifier predicts the probability of class membership of a given tuple and is based on the Bayes' theorem. The Bayes' theorem requires initial knowledge of many probabilities, that is, computational cost is significant. The Naïve Bayesian classifier simplifies the computation involved by applying an assumption called class conditional independence; that is, values of different attributes in a given class are independent of each other. However, in many cases class conditional assumption is unrealistic, particularly in medical data, where many attributes containing patient symptoms and health conditions are strongly related (for example, blood pressure and body mass index). As such, this assumption is a main drawback of Naïve Bayesian classifier. In general, the performance of Naïve Bayesian classifier is better than decision trees and also demonstrates high speed and accuracy on large datasets. As a result, the Naïve Bayesian classifier is widely used in medical data mining regardless of violations of attribute independence assumption.

4.1.3 Neural Network

The neural network is a backpropagation learning algorithm, which is a set of weighted connection between input/output units. During construction of the classification model, the weights of the connections are adjusted to correctly predict the class label of the input tuple [110]. The main drawbacks of the neural network are longer training time and poor interpretability. However, the computation time of the neural network can be reduced by parallel computation as it is inherently parallel in nature. The advantages of neural network include high tolerance of noisy data, ability to classify patterns, and suitability for

continuous-valued inputs and outputs. It is also useful for classifying a dataset without or little prior knowledge of relationships between attributes and classes. This classification technique is widely used in pathology and laboratory medicine.

4.2 DATA MINING TOOLS

There are several tools available for data mining. We used two most widely used tools called WEKA[111] and R [112].

4.3 MODEL VALIDATION

Three performance measures were compared for benchmarking: accuracy, sensitivity, and specificity. 10-fold cross validation were used for model validations. The dataset is divided into 10 parts. In each iteration, 9 parts were used for model construction and one part was used for model validation.

4.4 DATA MINING RESULTS

In this section, the data mining results for six individual datasets are presented. We primarily mined the datasets using the decision tree algorithm in WEKA (called J48) [106] and compared the prediction results with four other algorithms: (1) Naïve Bayes [113], (2) Logistic Regression classifier[114], (3) Neural Network (Voted Perceptron) [115], and (4) Support Vector Machine (using sequential minimal optimization) [116]. The rationale behind using decision tree as the primary model was two-fold. First, the model is easy to explain to the clinicians, and (2) the model usually provides better prediction performance.

4.4.1 Decision Tree (Dataset: Acute, LEC)

Figure 18 presents the decision tree model for predicting CINV in the acute phase for low emetogenic chemotherapies. The model predicts 94.8% of the records correctly with 96.3% correct predictions for the positive outcome of CINV (i.e., sensitivity) and 93.3% correct predictions for the negative outcome of CINV (i.e., specificity). The performance of the model was compared with Neural Network, Logistic Regression, Support Vector Machine, and Naïve Bayes (Figure 19). Overall, the best performance was given by Naïve Bayes; the accuracy is 96.6%, the sensitivity is 96.3%, and the specificity is 96.8%).

Figure 18: Decision Tree – Acute, LEC

Figure 19: Prediction Result on Acute Phase and Low Emetogenic Chemotherapy Dataset

4.4.2 Decision Tree (Dataset: Delayed, LEC)

Figure 20 presents the decision tree model for predicting CINV in the delayed phase for low emetogenic chemotherapies. The model predicts 88.5% of the records correctly with 88.2% correct predictions for the positive outcome of CINV and 88.7% correct predictions for the negative outcome of CINV. The performance of the model was compared with Neural Network, Logistic Regression, Support Vector Machine, and Naïve Bayes (Figure 21). Overall, the best performance is given by Support Vector Machine; the accuracy is 89.5%, the sensitivity is 87.8%, and the specificity is 91.3%.

Figure 20: Decision Tree – Delayed, LEC

Figure 21: Prediction Result on Delayed Phase and Low Emetogenic Chemotherapy Dataset

4.4.3 Decision Tree (Dataset: Acute, MEC)

Figure 22 presents the decision tree model for predicting CINV in the acute phase for moderate emetogenic chemotherapies. The model predicts 90.2% of the records correctly with 90.3% correct predictions for the positive outcome of CINV and 90.1% correct predictions for the negative outcome of CINV. The performance of the model was compared with Neural Network, Logistic Regression, Support Vector Machine, and Naïve Bayes (Figure 23Figure 19). Overall, the best performance is given by Naïve Bayes; the accuracy is 90.8%, the sensitivity is 89.3%, and the specificity is 92.3%.

Figure 22: Decision Tree – Acute, MEC

Figure 23: Prediction Result on Acute Phase and Moderate Emetogenic Chemotherapy Dataset

4.4.4 Decision Tree (Dataset: Delayed, MEC)

Figure 24 presents the decision tree model for predicting CINV in the delayed phase for moderate emetogenic chemotherapies. The model predicts 79.3% of the records correctly with 76.3% correct predictions for the positive outcome of CINV and 82.4% correct predictions for the negative outcome of CINV. The performance of the model was compared with Neural Network, Logistic Regression, Support Vector Machine, and Naïve Bayes (Figure 25Figure 19). Overall, the best performance is given by Naïve Bayes; the accuracy is 81.5%, the sensitivity is 81.7%, and the specificity is 81.3%.

Figure 24: Decision Tree – Delayed, MEC

Figure 25: Prediction Result on Delayed Phase and Moderate Emetogenic Chemotherapy Dataset

4.4.5 Decision Tree (Dataset: Acute, HEC)

Figure 26 presents the decision tree model for predicting CINV in the acute phase for high emetogenic chemotherapies. The model predicts 88.7% of the records correctly with 90.3% correct predictions for the positive outcome of CINV and 87.2% correct predictions for the negative outcome of CINV. The performance of the model was compared with Neural Network, Logistic Regression, Support Vector Machine, and Naïve Bayes (Figure 27Figure 19). Overall, the best performance is given by the Decision Tree model. The second best performance is given by Naïve Bayes; the accuracy is 88.6%, the sensitivity is 88.5%, and the specificity is 88.7%.

Figure 26: Decision Tree – Acute, HEC

Figure 27: Prediction Result on Acute Phase and High Emetogenic Chemotherapy Dataset

4.4.6 Decision Tree (Dataset: Delayed, HEC)

Figure 28 presents the decision tree model for predicting CINV in the delayed phase for high emetogenic chemotherapies. The model predicts 81.0% of the records correctly with 85.2% correct predictions for the positive outcome of CINV and 76.7% correct predictions for the negative outcome of CINV. The performance of the model was compared with Neural Network, Logistic Regression, Support Vector Machine, and Naïve Bayes (Figure 29Figure 19). Overall, the best performance is given by the Decision Tree model. The second best performance is given by the Logistic Regression classifier; the accuracy is 74.5%, the sensitivity is 73.4%, and the specificity is 75.7%.

Figure 28: Decision Tree – Delayed, HEC

Figure 29: Prediction Result on Delayed Phase and High Emetogenic Chemotherapy Dataset

CHAPTER 5 : MINING CONTEXT SENSITIVE ASSOCIATIVE CLASSIFICATION RULES

We further explored the association rule-based classification approach for dynamic prediction. Several association-rule based classification algorithms have been proposed [117]: (1) classification based association (CBA) [118], (2) Classification based on multiple association rules (CMAR) [119], (3) association rule-based classifier with all categories (ARC-AC) [120], (4) classification based on predictive association rules (CPAR) [121], (5) classification based on Atomic Association Rules (CAAR) [122], (6) associative classifier based on positive and negative rules [123], (7) Live and Let Live (L^3) [124], (8) multi-class and multi-label associative classification approach (MMAC) ,[125] (9) multi-class classification based on association rule approach (MCAR) [126], (10) class based associative classification (CACA) [127], (11) associative classification based on closed frequent itemsets (ACCF) [128], (12) ACN: associative classifier with negative rules (ACN) [129], (13) associative classification based on compactness of rules (ACCR) [130], (14) adaptive associative classification (ADA) [131], and (15) modified multi-class classification based on association rule (MMCAR) [132].

In this chapter, the concept of associative classification with context sensitivity is introduced. The next chapter (Chapter 6) covers the development of a dynamic prediction engine using associative classification rules; we have developed a new classification algorithm using multiple rules. The concept of mining associative classification rules with

context sensitivity is derived from the concept of association rule mining. As such, in this chapter, the techniques for mining association rules are discussed first followed by the techniques for mining context sensitive associative classification rules.

5.1 ASSOCIATION RULE MINING

A very popular method for mining associations among a set of items is the Association Rule Mining (also known as the frequent itemset mining) [133]. Association rule mining (ARM) is a method of identifying associations among a set of items or objects in a database. ARM is also known as frequent itemset mining. The outcome of ARM is association rules - statements of the form $X \rightarrow Y$. Here, X is the left hand side (LHS) or antecedent and Y is the right hand side (RHS) or consequent. ARM technique was originally designed to work with a market basket dataset, in which the dataset consists of a set of grocery transactions and a transaction contains a set of items [133,134]. Figure 30 presents an example of a frequent itemset and an association rule derived from this frequent itemset. ARM requires two user input parameters (i.e., *support* indicating the measure of usefulness, and *confidence* indicating the measure of certainty) to filter out uninteresting association rules; see section 5.1.3 for more details.

Figure 30: Association Rule Example

ARM was successfully applied in medical informatics research to discover associations among drugs and diseases [135]. It was also found to be useful in text mining [136] and web usage mining [137].

5.1.1 Apriori

A novel association mining algorithm is Apriori [134,138]. The Apriori algorithm works by generating candidate itemsets and calculating their support counts. In order to calculate the support count of each candidate itemset, a full database scan is required. Thus, the computational performance of the algorithm could be extremely poor especially there are a lot of itemsets. The Apriori algorithm uses prior knowledge of frequent itemsets to eliminate infrequent candidate itemsets. This is known as Apriori property, which states that the subsets of a frequent itemset is also frequent. This property is used for pruning

infrequent itemsets after candidate generation in every iteration before DB scans. Thus, the pruning step reduces the number of database scans, which leads to considerable performance improvement.

5.1.2 FP-Growth

The main performance bottleneck of the Apriori algorithm is the costly generation of a large number of candidate itemsets. An alternative method to the Apriori algorithm is FP-Growth [139], which does not generate candidate itemsets. In FP-Growth, a compact but complete frequent pattern tree (FP-tree) structure is constructed by scanning the database only twice. In the first scan, frequent 1-itemsets are generated. In the second scan, a FP-tree is constructed. Finally, the FP-tree is mined for generating the frequent itemsets.

5.1.3 Association Rule Quality Measures

The quality of an association rule is indicated based on several measurements. These are discussed in the following.

5.1.3.1 *Support*

The support of an association rule is the percentage of transactions that contain the itemset in the DB (Equation 1). This indicates the usefulness of the rule. This is used to filter out uninteresting association rules. If we consider the transaction database in Table 12, there are total 9 transactions. For the association rule {Bread, Butter} $\rightarrow$ {Sugar}, the itemset {Bread, Butter, Sugar} appears 2 times in the database. Thus, the support of the association rule is 22.22% (2/9).

Support

$$= \frac{\text{Number of transactions that contain an itemset}}{\text{Total Number of transactions (N)}}$$

Equation 1: Association Rule – Support

Table 12: Example Transactions for Illustrating Support, Confidence and Lift

ID	Transactions
1	Bread, Butter, Sugar
2	Butter, Egg
3	Butter, Milk
4	Bread, Butter, Egg
5	Bread, Milk
6	Butter, Milk
7	Bread, Milk
8	Bread, Butter, Milk, Sugar
9	Bread, Butter, Milk

5.1.3.2 Confidence

The confidence of an association rule is the conditional probability that the consequent (the right-hand side) will appear given the occurrence of the antecedent (the left-hand side) (Equation 2). In other words, it shows how frequently the consequent occurs in transactions containing antecedent. This indicates the certainty of the rule. This measure is also used to filter out uninteresting association rules. If we consider the transaction database in Table 12, for the association rule {Bread, Butter} → {Sugar}, the itemset {Bread, Butter, Sugar} is found 2 times and the itemset {Bread, Butter} is found 4 times. Thus, the confidence of the association rule is 50% ($\frac{\text{support}(\{\text{Bread, Butter, Sugar}\})}{\text{support}(\{\text{Bread, Butter}\})} = \frac{2/9}{4/9} = 2/4 = 50\%$).

$$\text{Confidence} = \frac{\text{Support}(X \cup Y)}{\text{Support}(X)}$$

Equation 2: Association Rule - Confidence

5.1.3.3 Lift

The lift of an association rule is the ratio of the support measure of the rule with the multiplication of the support measure of the left hand side or antecedent and the support measure of the right hand side or consequent (Equation 3). This indicates the associativity of the rule. If we consider the transaction database in Table 12, for the association rule {Bread, Butter} → {Sugar}, the support of {Bread, Butter, Sugar} is 2/9, the support of {Bread, Butter} is 4/9 and the support of {Sugar} is 2/9. Thus, the lift of the association

$$\text{rule is } \left(\frac{\text{support}(\{Bread, Butter, Sugar\})}{\text{support}(\{Bread, Butter\}) * \text{support}(\{Sugar\})} = \frac{2/9}{4/9 * 2/9} = 2.25 \right).$$

$$\text{Lift} = \frac{\text{Support}(X \cup Y)}{\text{Support}(X) * \text{Support}(Y)}$$

Equation 3: Association Rule - Lift

The support measure of an itemset can be explained by the concept of probability. Support (X U Y) represents the probability that items in X and items in Y co-occur together, support (X) represents the probability that items in X co-occur together and support (Y) represents the probability that items in Y co-occur together. If RHS is independent of LHS, the multiplication of their individual probability will be equal to the probability of the itemset. Thus, the lift value becomes 1 representing the independence of LHS and RHS. If

it is less than 1, they are negatively correlated. If it is greater than 1, they are positively correlated. This can be illustrated by using the transaction database in Table 13, where there are more occurrences of the item sugar. For the association rule $\{Bread, Butter\} \rightarrow \{Sugar\}$, the support of $\{Bread, Butter, Sugar\}$ is 4/9, the support of $\{Bread, Butter\}$ is 4/9 and the support of $\{Sugar\}$ is 9/9. Thus, the lift of the association rule is 1 ($\frac{support(\{Bread, Butter, Sugar\})}{support(\{Bread, Butter\}) * support(\{Sugar\})} = \frac{4/9}{4/9 * 9/9} = 1$). In this example, the LHS occurs regardless of RHS.

Table 13: Example of Transactions for Illustrating Independence (Lift=1)

Transaction ID	Transactions
1	Bread, Butter, Sugar
2	Butter, Egg, Sugar
3	Butter, Milk, Sugar
4	Bread, Butter, Egg, Sugar
5	Bread, Milk, Sugar
6	Butter, Milk, Sugar
7	Bread, Milk, Sugar
8	Bread, Butter, Milk, Sugar
9	Bread, Butter, Milk, Sugar

5.2 ASSOCIATION RULE MINING TOOLS

There are several tools available for association rule mining. However, a single tool does not support all the things needed for experiments. We used two programs: the “arules” package [140] in the R software [141] for generating frequent itemsets, and the FP-growth algorithm [142,143] in WEKA (version 3.6.8) [111] for generating association rules. The reason for using two programs is that the arules package cannot produce association rules

containing more than one item in the consequent (also known as many-to-many association rules) [144] and WEKA does not produce frequent itemsets. The *arules* package in R takes the market basket format as input or any data frame with discrete values in each column can be converted to transactions. In WEKA, the sparse ARFF [145] format is needed for the input of WEKA FP-Growth algorithm, where each attribute value pair is represented as variable.

5.3 EXAMPLES OF ASSOCIATION RULE MINING

5.3.1 Mining Healthcare Data

In healthcare research, ARM has unearthed important associations among drugs and diseases [135]. For example, Chen et al. (2003) [146] used ARM to discover co-prescription patterns in the National Health Insurance Research Database (NHIRD) managed by Taiwan National health Insurance. An example association rule that was discovered by the study is $\{Muscle\ relaxants, centrally\ acting\ drugs\} \rightarrow \{antacid\}$ (*support*=3.8%, *confidence*=77.5%), which indicates that 77.5% of patients who take muscle relaxants and centrally acting drugs take antacid and the portion of the transactions in the database that meet the association rule is 3.8%. The analysis by Tai & Chiu (2009) [43] on NHIRD database revealed important association of diseases with Attention Deficit/Hyperactivity Disorder (ADHD) that is a highly common chronic behavior condition in childhood.

5.3.2 Mining Association of PubMed Search Tags

The author (ASMM) applied association rule mining technique on a large day-long PubMed log dataset [147] in order to discover hidden associations among search tags [148,149]. The dataset contains nearly 3 million search queries [150]. We discovered association rules both at the query level [148] and at the session level [149]. In Mosa and Yoo (2014) [149], we applied ARM technique for identifying the associations or co-occurrences of search tags in the search sessions. In this study, a search session is considered as a transaction and a set of search tags in the session is considered as an itemset. The output of ARM is a set of association rules of the form $X \rightarrow Y(\text{support, confidence})$; that is, if a user uses a set of search tags in X (the antecedent) also uses a set of search tags in Y (the consequent). In this study, we used the FP-Growth association mining algorithm.

We performed ARM in two steps. In the first step, we generated frequent itemsets with 0.02 (i.e., 2%) of the minimum support. The minimum support was set to 0.02 because the dataset is very sparse. The total number of frequent itemsets was 131. We analyzed these 131 frequent itemsets to identify the maximal itemsets using the “is.maximal” function of the arules package resulting 12 maximal itemsets. A maximal itemset is a frequent itemset that have no superset among the frequent itemsets [151]. For example, if $A=\{a, b, c, d\}$, $B=\{a, b, c\}$, and $C=\{b, c, d\}$ are three frequent itemsets, where $B \subset A$ and $C \subset A$, then A is the maximal itemset. We know from the apriori principal that any subset of a frequent itemset is also frequent. So, we choose only the maximal itemsets because their subsets are redundant for our particular goal. We presented a total of 8 maximal frequent itemsets (out of 12) in Table 14 and Table 15. The remaining four maximal frequent itemsets are not presented because two itemsets are of size one and the

other two itemsets do not have any strong association rules. In the second step, we generated the association rules ($X \rightarrow Y$) with 0.5 (i.e., 50%) of the minimum confidence. The association rules were generated using all the frequent itemsets. The total number of association rules was 515. Out of the 515 association rules, only the rules consisting of maximal frequent itemsets were extracted.

Among the 8 maximal frequent itemsets, three of them consist of purely informational tags (maximal frequent itemset no. 1, 2, and 3 in Table 14). Search tags are categorized into informational or navigational based on their underlying intent. Refer to our recent article Mosa and Yoo (2013) [148] for the complete list of informational and navigational search tags. Itemset no. 1 have six search tags in which two of them are topical search fields (i.e., [MESH TERMS] and [MESH MAJOR TOPIC] tags), one of them is for searching a word or number in various text fields (i.e., [TEXT WORD] tag), and the remaining three tags represent filtering of search results based on: the language of the article (i.e., [LANGUAGE] tag) and/or the publication type of the article (i.e., [PUBLICATION TYPE] tag) and/or the subject, citation status or journal category of the article (i.e., [SUBSET] tag). We found a total of 48 association rules consisting of these six search tags (itemset no. 1) satisfying the minimum confidence of 50% but we present only 12 association rules (R01 to R12 in Table 14) having more than 90% of confidence. Thus, all these search tags in itemset no. 1 and its subsets are very strongly associated with one another and commonly used within the same search sessions.

Table 14. Association Rules Consisting of Informational Tags only

Rule ID	Association Rule	Conf.
	Itemset No. 1 (Supp. = 0.032): [LANGUAGE], [MESH MAJOR TOPIC], [MESH TERMS], [PUBLICATION TYPE], [SUBSET], [TEXT WORD]	
R01	[MESH TERMS], [PUBLICATION TYPE], [MESH MAJOR TOPIC], [TEXT WORD], [SUBSET] ==> [LANGUAGE]	0.99
R02	[LANGUAGE], [PUBLICATION TYPE], [MESH MAJOR TOPIC], [TEXT WORD], [SUBSET] ==> [MESH TERMS]	0.98
R03	[MESH TERMS], [LANGUAGE], [PUBLICATION TYPE], [MESH MAJOR TOPIC], [TEXT WORD] ==> [SUBSET]	0.97
R04	[PUBLICATION TYPE], [MESH MAJOR TOPIC], [TEXT WORD], [SUBSET] ==> [MESH TERMS], [LANGUAGE]	0.97
R05	[MESH TERMS], [PUBLICATION TYPE], [MESH MAJOR TOPIC], [TEXT WORD] ==> [LANGUAGE], [SUBSET]	0.96
R06	[MESH TERMS], [LANGUAGE], [MESH MAJOR TOPIC], [TEXT WORD], [SUBSET] ==> [PUBLICATION TYPE]	0.95
R07	[LANGUAGE], [PUBLICATION TYPE], [MESH MAJOR TOPIC], [TEXT WORD] ==> [MESH TERMS], [SUBSET]	0.94
R08	[MESH TERMS], [MESH MAJOR TOPIC], [TEXT WORD], [SUBSET] ==> [LANGUAGE], [PUBLICATION TYPE]	0.94
R09	[LANGUAGE], [MESH MAJOR TOPIC], [TEXT WORD], [SUBSET] ==> [MESH TERMS], [PUBLICATION TYPE]	0.93
R10	[PUBLICATION TYPE], [MESH MAJOR TOPIC], [TEXT WORD] ==> [MESH TERMS], [LANGUAGE], [SUBSET]	0.92
R11	[MESH MAJOR TOPIC], [TEXT WORD], [SUBSET] ==> [MESH TERMS], [LANGUAGE], [PUBLICATION TYPE]	0.91
R12	[MESH TERMS], [LANGUAGE], [MESH MAJOR TOPIC], [TEXT WORD] ==> [PUBLICATION TYPE], [SUBSET]	0.90
	Itemset No. 2 (Supp. = 0.038): [TITLE ABSTRACT], [PUBLICATION TYPE]	
R13	[TITLE ABSTRACT] ==> [PUBLICATION TYPE]	0.60
	Itemset No. 3 (Supp. = 0.020): [SUBHEADING], [MESH TERMS]	
R14	[SUBHEADING] ==> [MESH TERMS]	0.89

We found five maximal frequent itemsets (out of eight) that contains purely navigational/bibliographic search tags (maximal itemset no. 4, 5, 6, 7 and 8 in Table 15). The intent of navigational or bibliographic searches is to identify specific documents. Maximal frequent itemset no. 6, 7 and 8 have five items in each itemset, in which three of them are common (i.e., [PUBLICATION DATE], [PAGINATION], [VOLUME]). The search tag [ISSUE] is common in itemset no 6 and 7, the tag [JOURNAL] is common in itemset no. 7 and 8, and the tag [AUTHOR] is common in itemset no. 6 and 8. Thus, itemset no 6, 7 and 8 are subset of {[PUBLICATION DATE], [PAGINATION], [VOLUME], [ISSUE], [JOURNAL], [AUTHOR]}. We discovered 7, 7 and 8 association rules for itemset no. 6, 7 and 8, respectively (Table 15). The confidence of these rules ranges from 53% to 97%. So these six search fields are strongly correlated. A search query having these six search fields will retrieve only a single article.

Table 15. Association Rules Consisting of Navigational Tags Only

Rule ID	Association Rule	Conf.
	Itemset No. 4 (Supp. = 0.021): [FIRST AUTHOR NAME], [PUBLICATION DATE]	
R01	[FIRST AUTHOR NAME] ==> [PUBLICATION DATE]	0.77
	Itemset No. 5 (Supp. = 0.035): [ENTREZ DATE], [PUBLICATION DATE]	
R02	[ENTREZ DATE] ==> [PUBLICATION DATE]	0.063
	Itemset No. 6 (Support=0.021): [PUBLICATION DATE], [PAGINATION], [AUTHOR], [ISSUE], [VOLUME]	
R03	[PUBLICATION DATE], [PAGINATION], [AUTHOR], [ISSUE] ==> [VOLUME]	0.97
R04	[PUBLICATION DATE], [VOLUME], [AUTHOR], [ISSUE] ==> [PAGINATION]	0.89
R05	[PAGINATION], [VOLUME], [AUTHOR], [ISSUE] ==> [PUBLICATION DATE]	0.87
R06	[PUBLICATION DATE], [AUTHOR], [ISSUE] ==> [PAGINATION], [VOLUME]	0.87
R07	[PAGINATION], [AUTHOR], [ISSUE] ==> [PUBLICATION DATE], [VOLUME]	0.85
R08	[VOLUME], [AUTHOR], [ISSUE] ==> [PUBLICATION DATE], [PAGINATION]	0.77
R09	[AUTHOR], [ISSUE] ==> [PUBLICATION DATE], [PAGINATION], [VOLUME]	0.74
	Itemset No. 7 (Supp. = 0.037): [PUBLICATION DATE], [JOURNAL], [PAGINATION], [ISSUE], [VOLUME]	
R10	[PUBLICATION DATE], [JOURNAL], [PAGINATION], [ISSUE] ==> [VOLUME]	0.98
R11	[PUBLICATION DATE], [JOURNAL], [VOLUME], [ISSUE] ==> [PAGINATION]	0.89
R12	[PUBLICATION DATE], [JOURNAL], [ISSUE] ==> [PAGINATION], [VOLUME]	0.86
R13	[JOURNAL], [PAGINATION], [VOLUME], [ISSUE] ==> [PUBLICATION DATE]	0.81
R14	[JOURNAL], [PAGINATION], [ISSUE] ==> [PUBLICATION DATE], [VOLUME]	0.79
R15	[JOURNAL], [VOLUME], [ISSUE] ==> [PUBLICATION DATE], [PAGINATION]	0.71
R16	[JOURNAL], [ISSUE] ==> [PUBLICATION DATE], [PAGINATION], [VOLUME]	0.68
	Itemset No. 8 (Support=0.038): [PUBLICATION DATE], [JOURNAL], [PAGINATION], [AUTHOR], [VOLUME]	
R17	[PUBLICATION DATE], [JOURNAL], [PAGINATION], [AUTHOR] ==> [VOLUME]	0.85
R18	[PUBLICATION DATE], [JOURNAL], [VOLUME], [AUTHOR] ==> [PAGINATION]	0.85
R19	[JOURNAL], [PAGINATION], [VOLUME], [AUTHOR] ==> [PUBLICATION DATE]	0.82
R20	[JOURNAL], [VOLUME], [AUTHOR] ==> [PUBLICATION DATE], [PAGINATION]	0.69
R21	[PUBLICATION DATE], [PAGINATION], [VOLUME], [AUTHOR] ==> [JOURNAL]	0.65
R22	[PUBLICATION DATE], [VOLUME], [AUTHOR] ==> [JOURNAL], [PAGINATION]	0.55
R23	[PAGINATION], [VOLUME], [AUTHOR] ==> [PUBLICATION DATE], [JOURNAL]	0.53
R24	[PUBLICATION DATE], [PAGINATION], [AUTHOR] ==> [JOURNAL], [VOLUME]	0.53

The association rules in Table 14 and Table 15 are useful because advance features such as search tags are used by experienced users [147]. The rules can be used to develop an intelligent PubMed search interface. For example, PubMed can automatically

recommend the use of certain tags based on the other tags used in the query. This intelligent interface will help the users to build a query using proper search tags and reduce the frequency of query refinement.

5.4 ASSOCIATION RULE VISUALIZATION

We also extended an association rule visualization software for 3D visualization of association rules with multiple items in the consequent. The association rules presented in Table 14 are visualized in Figure 31 using the “Association Rule Viewer” (ARV) software [152] that implements the novel 3D visualization technique described in Wong et al. (1999) [136]. We also visualized the association rules presented in Table 15 in Figure 32. The association rules are visualized in a checkerboard-like 2D matrix where one association rule is presented in one column; a green cell represents that the corresponding item belongs to the antecedent set (X) and a red cell represents that the corresponding item belongs to the consequent set (Y). The support and confidence measures are visualized as two bar charts along the Z-axis. For example, R12 in Figure 31 visualizes the rule: {[MESH TERMS], [LANGUAGE], [MESH MAJOR TOPIC], [TEXT WORD] ==> [PUBLICATION TYPE], [SUBSET]} (support: 3.2% and confidence: 90%). The ARV software can visualize only many-to-one association rules so we modified the source code of the software for visualizing many-to-many association rules.

Figure 31. Visualization of association rules consisting of informational tags only

Figure 32. Visualization of association rules consisting of navigational/bibliographic tags only

5.5 DATA REPRESENTATION AND ALGORITHM

In the association mining experiment on PubMed log (presented in [148,153]), we exploited, the most widely-used association mining algorithm, Apriori in WEKA with the minimum support = 0.02 and the minimum confidence = 0.5. This experiment was conducted on a computer with two Intel Xeon CPUs (at 3.00 GHz) and 24.0 GB RAM. The Apriori algorithm was run for more than five full days consuming more than 20GB system memory, but we were unable to get a result using the algorithm. To tackle this problem, we converted the ARFF input file into a sparse ARFF [51] in which only positive (here, “Y”) values are stored. The sparse format significantly reduced the file size from 6.32 MB to 1.55 MB. Then, we used the FP-Growth algorithm because it was proven to be more efficient than Apriori (while Apriori generates a lot of candidate itemsets, FP-Growth does not) and because, more importantly, it generates and store only positive rules containing “Y” values. We got a result (a set of association rules) within 5 seconds (we used the same support and confidence values). We would like to stress that selecting a right data format and algorithm could be critical to successful data mining.

5.6 ASSOCIATION RULE MINING STEPS

The association rules are mined in two steps (Figure 33); First, all frequent patterns are generated based on a user-defined support parameter. Second, association rules are identified from the frequent patterns based on a user-defined confidence parameter. With the decrease of support count, the number of association rule generated could be increased exponentially depending on confidence; Figure 34 presents the number of association rule generated using our CINV dataset (containing all 6,124 records from both the acute and

the delayed phase datasets). The processing time of the FP-Growth algorithm is much lower than that of the Apriori algorithm (Figure 35).

Our main goal was to use association rules for classification. We developed a novel algorithm for mining association rules that will be used for classification. The concept of associative classification and the novel technique for direct mining of associative classification rules are discussed in the following sections.

Figure 33: Association Rule Mining Steps

Figure 34: Number of Association Rule Growth Chart

Figure 35: Processing Time for Generating Association Rules

5.7 ASSOCIATIVE CLASSIFICATION RULES

Associative classification rules are a subset of association rules where the RHS or consequent of the rule contains only the class/dependent variable along with its label (Figure 36). In order to predict CINV based on patient-related risk factors, we would like to mine all the rules where a set of the risk factors are presented in the LHS of the rule and the occurrence of CINV is presented in the RHS of the rule.; for example: {Dehydration=Yes, Anxiety=Yes} → {CINV=Yes}.

Figure 36: Associative Classification Rule

5.8 CONTEXT SENSITIVE MINING

For the problem of CINV prediction, there are three treatment groups and two independent phases of CINV (see Chapter 3 for the data collection plan). As a result, there are six groups of data (Figure 37): (1) low emetogenic chemotherapy – acute phase, (2) low emetogenic chemotherapy – delayed phase, (3) moderate emetogenic chemotherapy – acute phase, (4) moderate emetogenic chemotherapy – delayed phase, (5) high emetogenic chemotherapy – acute phase, (6) high emetogenic chemotherapy – delayed phase. In Chapter 4, we presented the data mining results on six contexts independently so that data in one context is not used for prediction in another context. In this section, we are introducing the concept of context sensitivity in the prediction process named as context sensitive prediction. For context sensitive prediction using association rules, we introduce

a term context sensitive associative classification rules, which is described in the next paragraph.

Figure 37: Example of Contexts from the CINV Dataset

Figure 38 presents an example of a context sensitive associative classification rule. Here, context elements are appended to the items in the LHS. For example, in the association rule **(CINV Phase=Acute, Emetogenicity=HEC)** **(Dehydration=Yes, Anxiety=Yes)** $\rightarrow$ **CINV=Yes**, **(CINV Phase=Acute, Emetogenicity=HEC)** presents contexts, **(Dehydration-Yes, Anxiety=Yes)** presents risk factors (i.e., items) and **CINV=Yes** presents the class.

Figure 38: Context Sensitive Associative Classification Rule

The quality measure (support, confidence and lift) of context sensitive associative classification rules can be computed either in global context or in local context. In global context, measures are calculated based on the entire dataset. In local context, the measures are calculated based on a subset of the dataset that fits within the context. The context sensitivity should be considered when a dataset is highly imbalanced in class. The CINV prediction problem is a good example; see Chapter 3 for class imbalance issue. In this study, our dataset was made class-balanced for better comparison between classes. In order to investigate the impact of the quality measures in a class imbalanced situation, we created an imbalanced dataset from the balanced dataset. Table 16 presents the quality measures from the imbalanced dataset for both global and local contexts. For low emetogenic chemotherapy, we observed that some rules show weak associativity (lift <1) within local context whereas the same rules show strong associativity within global context (lift > 1). As such, we considered context sensitive measures for context sensitive mining; see Equation 4 for context sensitive support, Equation 5 for context sensitive confidence and Equation 6 for context sensitive lift.

Table 16: Examples of Context Sensitive Associative Classification Rules from a Class Imbalanced Data

Association Rules	Measures are calculated based on the entire dataset			Measures are calculated based on a subset for each context		
	Support	Confidence	Lift	Support	Confidence	Lift
(CINV Phase=Acute, Emetogenicity=HEC) (Anxiety=Yes) → CINV=Yes	0.09	0.95	1.54	0.70	0.95	1.14
(CINV Phase=Delayed, Emetogenicity=HEC) (Anxiety=Yes) → CINV=Yes	0.06	0.77	1.24	0.43	0.77	1.06
(CINV Phase=Acute, Emetogenicity=MEC) (Anxiety=Yes) → CINV=Yes	0.18	0.94	1.52	0.62	0.94	1.25
(CINV Phase=Delayed, Emetogenicity=MEC) (Anxiety=Yes) → CINV=Yes	0.12	0.81	1.31	0.42	0.81	1.30
(CINV Phase=Acute, Emetogenicity=LEC) (Anxiety=Yes) → CINV=No	0.02	0.72	1.89 ^a	0.21	0.72	0.80 ^b
(CINV Phase=Delayed, Emetogenicity=LEC) (Anxiety=Yes) → CINV=No	0.03	0.86	2.26 ^a	0.41	0.86	0.98 ^c
^a Strong association with respect to the entire dataset ^b Weak association with respect to the context ^c Independent association with respect to the context						

Support	=	$\frac{\text{Number of transactions that contain an itemset}}{\text{Total Number of transactions (N)}}$
Context Sensitive Support (CSS)	=	$\frac{\text{Number of transactions containing an itemset within a context}}{\text{Total number of transaction within this context}}$

Equation 4: Context Sensitive Support

Confidence	$= \frac{\text{Support} (\text{CONTEXTS} \cup \text{ITEMS} \cup \text{CLASS})}{\text{Support} (\text{CONTEXTS} \cup \text{ITEMS})}$
Context Sensitive Confidence	$= \frac{\text{CS Support} (\text{CONTEXTS} \cup \text{ITEMS} \cup \text{CLASS})}{\text{CS Support} (\text{CONTEXTS} \cup \text{ITEMS})}$

Equation 5: Context Sensitive Confidence

Lift	$= \frac{\text{Support} (\text{CONTEXTS} \cup \text{ITEMS} \cup \text{CLASS})}{\text{Support} (\text{CONTEXTS} \cup \text{ITEMS}) * \text{Support} (\text{CLASS})}$
Context Sensitive Lift	$= \frac{\text{CS Support} (\text{CONTEXTS} \cup \text{ITEMS} \cup \text{CLASS})}{\text{CS Support} (\text{CONTEXTS} \cup \text{ITEMS}) * \text{CS Support} (\text{CONTEXTS} \cup \text{CLASS})}$

Equation 6: Context Sensitive Lift

5.9 MINING CONTEXT SENSITIVE ASSOCIATIVE CLASSIFICATION RULES USING REGULAR ALGORITHMS

Figure 39 presents a four-step process for mining the context sensitive associative classification rules using a traditional association algorithm and tools. Step 1 and step 2 are similar to the traditional association rule mining steps. Step 3 is for selecting rules for context sensitivity and step 4 is for selecting classification rules having class labels in the RHS only. The number of context sensitive association classification rules are very low in comparison to the number of all association rules. Figure 40 shows the comparison between the number of association rules and the number of context sensitive association

classification rules for different support parameters; the entire CINV dataset (using all of the 6,124 records) was used.

In order to simplify the steps shown in Figure 39, we developed a novel associative classification algorithm based on the concept of a frequent pattern tree, which is able to mine the context sensitive associative classification rules in one single step. The details of the algorithm is provided in next two sections. First, we construct a context sensitive frequent associative classification tree (CS-FACT) that preserves the entire dataset in a compact frequent pattern tree. Second, the CS-FACT tree is mined to produce context sensitive associative classification rules in one single step without generating the candidate itemsets (like Apriori) or generating the all frequent patterns (like Apriori or FP-Growth).

Figure 39: Steps for Mining Context Sensitive Associative Classification Rule using Regular Algorithms

Figure 40: Number of Context Sensitive Associative Classification Rules

5.10 CONTEXT SENSITIVE FREQUENT ASSOCIATIVE CLASSIFICATION TREE (CS-FACT)

The entire database is converted to a compressed tree structure preserving the association information of the itemsets with respect to contexts and classes. We name the tree as “context sensitive frequent associative classification tree” (CS-FACT). The tree is mined in a divide-and-conquer manner using a bottom-up approach. A conditional database is generated from the tree for each prefix pattern and a conditional CS-FACT tree is generated for each conditional sub-database. This helps the algorithm to mine the tree in a recursive manner in order to grow the prefix patterns and reduce the size of sub-databases in each recursion. Due to the bottom-up mining approach, the tree is generated such a way so that the items are inserted at the upper nodes, and the contexts are inserted at the lower

nodes followed by inserting the classes at the leaf nodes. This ordering mechanism is the key for direct mining of context sensitive associative classification rules as the algorithm can explore the sub-databases related to classes and contexts as prefix-patterns. This reduces the exploration of unnecessary areas of the database significantly. Algorithm 1 presents the construction process of a CS-FACT tree. The algorithm for mining the CS-FACT tree is described in the next section.

Figure 41(a) presents an example transaction database in order to illustrate the Algorithm 1. First, the transaction database is scanned in order to generate a header table; the header table contains the list of contexts, items and classes, and their support counts. The header table is sorted in support count descending order of items followed by contexts and classes, consecutively. Figure 41(b) presents the ordering of the items in the header table and Figure 41(c) presents the ordering of the transactions as the order of items in the header table. In this example database, I stands for an item, CT stands for a context and C stands for a class.

Second, the root node of a CS-FACT tree is created. The database is scanned for the second time in order to insert the transactions in the tree. A branch is created for each transaction. A transaction is sorted according to the order of the items in the header table. For example, the first transaction $\{CT2;I1;I2;C1\}$ is sorted as $\{I2;I1;CT2;C1\}$ (Figure 41(c)) and a branch is created where I2 is linked to root, I1 is linked to I2, CT2 is linked to I1, and C1 is linked to CT2 (Figure 42(a)). The count of each node is set to 1. The second transaction $\{I2;CT1;C1\}$ would result in a branch where I2 is linked to root, CT1 is linked to I2 and C1 is linked to CT1. This branch will share the I2 node as a common prefix with the first branch. Therefore, the count of I2 node is incremented to 2 (Figure 42 (b)). The

count of the common prefix nodes are incremented by 1 every time a branch is generated. Figure 42(a), Figure 42 (b), Figure 43, Figure 44, Figure 45, Figure 46, Figure 47, Figure 48, and Figure 49 presents the steps of inserting the transactions 1 through 9 in a CS-FACT tree. The insertion path is indicated with red arrows.

Algorithm 1: Construction of Context Sensitive Frequent Associative Classification Tree

Input:

- D, a transaction database
- List of **contexts**
- List of **classes**

procedure CS_FACT(D, **contexts, **classes**)**

- (1) Scan the transaction database D and create a set **headerTable**, containing the list of **contexts**, **items** and **classes**, and their support count.
- (2) Order **headerTable** in support count descending order of **items** followed by **contexts** and **classes**, consecutively.
- (3) Create the root node of a CS-FACT tree named **csFactTree** and label the node as root.
- (4) For each transaction T in D do the following:
 - a. Order the **items**, **contexts** and **classes** in T according to the order of **headerTable**.
 - b. Set currentNode to root.
 - c. For each element in T do the following
 - i. Call **insertElementToCSFACT(element, 1, currentNode)**; this procedure returns a childNode.
 - ii. set currentNode to childNode
- (5) Return the **csFactTree**.

procedure insertElementToCSFACT(element, countOfElement, currentNode)

- (1) If currentNode has a childNode such that childNode.elementName = element.name, then do the following:
 - a. increment childNode.count by countOfElement.
 - b. Return childNode
- (2) Else create a new node called childNode and do the following:
 - a. Set childNode.element-name to element.name
 - b. Set childNode.count to countOfElement
 - c. Set childNode.parent to currentNode
 - d. Link childNode to the nodeLinks where childNode.element-name=nodeLinks.element-name
 - e. Return childNode

(a) Transactions	(b) Sorted Item List (headerTable)		
Transaction #1: CT2;l1;l2;C1	Item	count	Index
Transaction #2: CT1;l2;C1	l2	7	0
Transaction #3: CT1;l2;l3;C1	l1	6	1
Transaction #4: CT2;l1;l2;C1	l3	6	2
Transaction #5: CT1;l1;l3;C2	l6	1	3
Transaction #6: CT2;l2;l3;C2	CT2	3	4
Transaction #7: CT1;l1;l3;C2	CT1	6	5
Transaction #8: CT1;l1;l2;l3;C2	C1	6	6
Transaction #9: CT1;l1;l2;l3;l6;C2	C2	7	7
(c) Sorted Transactions			
Transaction #1: l2;l1;CT2;C1			
Transaction #2: l2;CT1;C1			
Transaction #3: l2;l3;CT1;C1			
Transaction #4: l2;l1;CT2;C1			
Transaction #5: l1;l3;CT1;C2			
Transaction #6: l2;l3;CT2;C2			
Transaction #7: l1;l3;CT1;C2			
Transaction #8: l2;l1;l3;CT1;C2			
Transaction #9: l2;l1;l3;l6;CT1;C2			

Figure 41: Example of Transactions for Generating Context Sensitive Associative Classification Tree – (a) Transaction, (b) Sorted item list, (c) Sorted Transactions

Figure 42: Construction of CS-FACT - (a) Insert Transaction #1 and (b) Insert Transaction #2

Figure 43: Construction of CS-FACT - Insert Transaction #3

Figure 44: Construction of CS-FACT - Insert Transaction #4

Figure 45: Construction of CS-FACT - Insert Transaction #5

Figure 46: Construction of CS-FACT - Insert Transaction #6

Figure 47: Construction of CS-FACT - Insert Transaction #7

Figure 48: Construction of CS-FACT - Insert Transaction #8s

Figure 49: Construction of CS-FACT - Insert Transaction #9

5.11 MINING CONTEXT SENSITIVE ASSOCIATIVE CLASSIFICATION RULE USING CS-FACT

Algorithm 2 presents the detailed process for mining a CS-FACT tree for producing context sensitive associative classification rules. In the first iteration, the algorithm starts with a class as a prefix-pattern, and generates a conditional sub-database and CS-FACT tree for this class. The sub-database is also called as conditional pattern base. For generating a conditional pattern base for this class, all the node-links of the class are listed first. For each node-link of this class, a path from the parent of the class-node to the root of the tree is generated; the items in this path form a transaction, which becomes a part of the conditional pattern base for this class. The count of all the items in this transaction is set to the support count of the class-node. For example, the conditional pattern base for the class C1 is {CT2;I1;I2:2}, {CT1;I2:1}, and {CT1;I2;I3:1} (Figure 50); here, the prefix-pattern is {C1}. This conditional pattern based is used for generating a conditional CS-FACT tree (Algorithm 1). Figure 51 presents the conditional frequent pattern tree generated from the conditional pattern base for the class C1. This tree represents the conditional pattern base for transactions containing C1 and does not contain any class.

In the second iteration, a new prefix pattern is generated for each context by appending the context to a class prefix-pattern, and a conditional pattern base and a CS-FACT tree is generated for this prefix-pattern. At this point, the prefix-pattern contains classes and contexts, and the conditional CS-FACT trees contains only the items. For example, a prefix-pattern is generated for C1 by appending the context CT2 as {CT2, C1:2}; see the procedure generatePrefixPattern in Algorithm 2. Then, a conditional CS-FACT tree is generated for this prefix-pattern (see Figure 52 and Figure 53).

In the subsequent iterations, a prefix-pattern is grown by appending the items from the conditional CS-FACT tree; see the procedure `mine_CS_ACR` in Algorithm 2. This is a recursive procedure. A conditional CS-FACT tree is further mined if the corresponding prefix-pattern contains a class item and a context item. This step is very useful because unnecessary rules are not generated. Every time a prefix-pattern is generated, the pattern is tested for eligibility (the prefix pattern contains a class item and a context item); a context sensitive associative classification rule is generated immediately for an eligible prefix-pattern. Figure 54 presents all the context sensitive associative classification rules generated from the transaction database in Figure 41(a).

Algorithm 2 generates the support count for the entire rule only but not for the antecedent (LHS) or consequent (RHS); thus calculations of confidence and lift are not possible. At the same time, we do not want to scan the entire database to generate support count for those itemsets because the database scan is an expensive process. We developed another algorithm to generate support count for any itemset from a CS-FACT tree; thus additional database scan is not required. Algorithm 3 illustrates the detailed steps. First, the itemset is ordered according to the order of the items in the header table. For the last element in the ordered itemset, all the node-links are listed from the CS-FACT tree. Second, for a node in the node-links, a path from the node to the root is generated. A pattern is generated for this path if the path contains all the items in the itemset. The support count of the pattern is set to the least support count of the elements in the itemset. Finally, the support count of the itemset is calculated by taking the summation of the support count of all the patterns. Figure 55 presents the steps for generating the support count for the itemset $\{I1, I3\}$. Following this method, we also pre-compute all the support count for each

contexts and the support count for each context and class combinations; these are used for calculating the context sensitive measures as explained in section 5.8.

Algorithm 2: Mining Context Sensitive Associative Classification Rule using CS-FACT

<p>Input:</p> <ul style="list-style-type: none"> • csFactTree, a CS-FACT tree • List of classes • headerTable, containing the list of contexts, items and classes, and their support count; ordered as support count descending order of items followed by contexts and classes, consecutively. • minConfidence, the minimum confidence for each rule
<p>procedure mine_ACR (csFactTree, classes)</p> <ol style="list-style-type: none"> (1) For each classItem in classes do the following: <ol style="list-style-type: none"> a. Call generatePrefixPattern(null, classItem); this procedure returns a prefixPattern b. Call conditionalPatternBase(classItem, csFactTree); this procedure returns a conditionalPatternBase c. Call CS_FACT(conditionalPatternBase, contexts, classes); this procedure returns a conditionalFrequentPatternTree d. Call mine_CS_ACR (conditionalFrequentPatternTree, prefixPattern)
<p>procedure mine_CS_ACR (conditionalFrequentPatternTree, prefixPattern)</p> <ol style="list-style-type: none"> (1) For each element in the headerTable of conditionalFrequentPatternTree do the following: <ol style="list-style-type: none"> a. Call generatePrefixPattern(prefixPattern, element); this procedure returns a newPrefixPattern b. If the newPrefixPattern does not contain a class and/or a context then do nothing c. Else do the following: <ol style="list-style-type: none"> i. Generate a contextSensitiveAssociativeClassificationRule from the conditionalFrequentPatternTree <ol style="list-style-type: none"> 1. If contextSensitiveAssociativeClassificationRule.confidence $\geq$ minConfidence then keep the rule ii. Call conditionalPatternBase(element, conditionalFrequentPatternTree); this procedure returns a conditionalPatternBase iii. Call CS_FACT(conditionalPatternBase, contexts, classes); this procedure returns a newConditionalFrequentPatternTree iv. If newConditionalFrequentPatternTree is not empty then call this procedure recursively as mine_CS_ACR(newConditionalFrequentPatternTree, newPrefixPattern)
<p>procedure generatePrefixPattern (prefixPattern, element)</p> <ol style="list-style-type: none"> (1) Append element to the prefixPattern (2) Set support count of prefixPatter to element.count (3) Return prefixPattern
<p>procedure conditionalPatternBase(element, csFACTree)</p> <ol style="list-style-type: none"> (1) Find all nodeLinks of the element from the csFactTree (2) Create an empty conditionalPatternBase (3) For each node in nodeLinks do the following: <ol style="list-style-type: none"> a. Generate a set of items named pathToRootItemset containing all the elements in the path from node.parent to root b. Set support count for pathToRootItemset as node.support_count. c. Add pathToRootItemset to conditionalPatternBase (4) Return conditionalPatternBase

Conditional pattern-base
for a class {C1:4}

- {CT2;i1;i2:2}
- {CT1;i2:1}
- {CT1;i2;i3:1}

Figure 50: Generate a conditional pattern-base

Figure 51: Conditional Frequent Pattern Tree for a Class

Figure 52: Prefix Pattern and Association Rule

Figure 53: Conditional Frequent Pattern Tree for a Prefix Pattern

$[[\{CT2\}:3; \{I1\}:2] \rightarrow C1]:2$
$[[\{CT2\}:3; \{I2\}:3] \rightarrow C1]:2$
$[[\{CT2\}:3; \{I2; I1\}:2] \rightarrow C1]:2$
$[[\{CT1\}:6; \{I1\}:4] \rightarrow C2]:4$
$[[\{CT1\}:6; \{I3\}:5] \rightarrow C2]:4$
$[[\{CT1\}:6; \{I1; I3\}:4] \rightarrow C2]:4$
$[[\{CT1\}:6; \{I2; I1\}:2] \rightarrow C2]:2$
$[[\{CT1\}:6; \{I2; I3\}:3] \rightarrow C2]:2$
$[[\{CT1\}:6; \{I2; I1; I3\}:2] \rightarrow C2]:2$

Figure 54: Context Sensitive Associative Classification Rules

Algorithm 3: Mining Support Count for an Itemset using a CS-FACT Tree

Input:

- **csFactTree**, a CS-FACT tree
- an itemset
- **headerTable**, containing the list of **contexts**, **items** and **classes**, and their support count; ordered as support count descending order of **items** followed by **contexts** and **classes**, consecutively.

procedure generateSupportCount (csFactTree, itemset)

- (1) Order the **items**, **contexts** and **classes** in the **itemset** according to the order of **headerTable**.
- (2) For the **lastElement** in the ordered **itemset** find all the **nodeLinks**
- (3) Create a **patternList**
- (4) For each **node** in **nodeLinks** do the following:
 - a. Generate a set of items named **pathToRootItemset** containing all the elements in the path from node to root
 - b. If **pathToRootItemset** contains all the elements in the itemset then do the following:
 - i. Generate a **pattern** from **pathToRootItemset** containing all the elements in the itemset.
 - ii. Set support count of **pattern** to the least support count of the elements in the pattern
 - iii. Add **pattern** to the **patternList**
- (5) Calculate **supportCount** for the **itemset** as the summation of the patterns in the **patternList**
- (6) Return **supportCount**

Figure 55: Mining Support Count for Antecedent

As discussed in the section 5.9 that mining context sensitive association classification rules using regular association rule mining algorithms is a multi-step process. On the other hand, our algorithm generates the rules in one single step (Figure 56). The CS-FACT does not require the generation of intermediate candidate itemsets (like in the Apriori algorithm) or generating the all possible frequent itemsets (like in the Apriori or FP-Growth algorithm). Thus, our method requires very lower processing time than other algorithms (Figure 57).

Figure 56: Steps for Mining Context Sensitive Associative Classification Rule using CS-FACT

Figure 57: Processing Time for Generating Context Sensitive Associative Classification Rules using CS-FACT

CHAPTER 6 : THE PREDICTION ENGINE

6.1 A DYNAMIC APPROACH

We have developed the prediction engine based on a dynamic approach (see Figure 58). The training phase consists of generating context sensitive associative classification rules and pruning the unnecessary rules. The dynamic prediction phase involves extracting all qualified associative classification rules for a prediction query within a context in real-time and generating a dynamic prediction recommendation based on those rules.

Figure 58: Training and Prediction Steps

6.2 SYSTEM ARCHITECTURE

Figure 59 presents the system architecture for the prediction engine and Figure 60 presents the flow diagram of the system. A prediction process first starts with a prediction query, which is then processed by the prediction engine and passed to the rule-extractor module. The rule-extractor module passes all the qualified rules to the multi-rule predictor module, which generates a prediction recommendation. The training step is driven by the CS-FACT tree, which is a compact tree structure preserving enough information for mining necessary rules. The tree can be updated in real-time by adding a set of transactions to the tree, and the association rule database can be updated accordingly from the tree. As a result, a prediction result is always based on the up-to-date knowledge. The system components are described in the following sections.

Figure 59: System Architecture

Query Formation:

(Contexts) AND (Risk Factors) => (Prediction Variable)

Example:

(CINV Phase=Acute, Emetogenicity=High) AND (Dehydration=Yes, Anxiety=Yes) => (CINV=??)

Figure 61: Prediction Query

6.2.2 Prediction Query Processor

The prediction query processor is designed to process a prediction query and extract the components of the query. A prediction query has three components: contexts, risk factors and class/dependent variable (Figure 62).

Figure 62: Prediction Query Processor

6.2.3 Rule Extractor

Algorithm 4 shows the rule extractor process. This is a two-step process (see Figure 63). In summary, for each rule in the rule database, if the contexts of the rule matches the contexts of the query (the first step) and the items of the rule is a subset of the risk factors in the prediction query (the second step), then the rule is marked as qualified. All qualified rules are used in the process of the dynamic prediction. Figure 64 illustrates a rule extraction example. In this example, there are five rules in the database and three rules are qualified for the prediction query.

Step 1: Match for Contexts

Step 2: Match for items

• Hash Mapping is used for faster matching

Figure 63: Rule Extractor Steps

Algorithm 4: Rule Extractor

Input:

- **predictionQuery**, a prediction query containing **contexts** and **riskFactors**
- **csACR**, all context sensitive associationve classification rules

procedure ruleExtractor (predictionQuery, csACR)

(1) Create a **ruleSet**

(2) For each **rule** in **csACR** do the following

- a. If contexts of the **rule** matches contexts of the **predictionQuery** and **items** of the rule is a subset of the **riskFactors** in the prediction query then add the rule to the **ruleset**

(3) Return **ruleSet**

Figure 64: Rule Extractor Example

6.2.4 Multi-Rule Dynamic Predictor

The multi-rule predictor uses all qualified rules for making a prediction recommendation. If all qualified rules recommend the same class, then the class is returned as prediction. In the example in Figure 65, all the qualified rules refer to CINV=Yes; thus, the prediction outcome is CINV=Yes. Otherwise, a prediction score is calculated for each class based on the qualified rules per class.

Figure 65: Multi-Rule Predictor Example

6.3 PREDICTION SCORE

After extracting all the qualified rules for a prediction query, there could be two scenarios: (1) all the qualified rules recommend the same class, and (2) multiple classes are recommended by the qualified rules. For the first scenario, the prediction result is straightforward as only a single class is recommend. However, for the second scenario, the system needs to know which class has the highest impact so that a prediction result can be generated. The impact of a recommended class is estimated by computing a prediction score for the class. The prediction score is estimated by taking the sum of quality measures of all qualified rules within a group (Equation 7). We considered three major association rule measures (support, confidence and lift) as well as their combinations in a weighted manner yielding additional four measures: support*confidence, support*lift,

lift*confidence, and support*lift*confidence. For all calculation, context sensitive measures were used.

$$\text{Prediction Score} = \frac{\sum_{i=1}^{\text{\# of Rules in the group}} \text{Quality Measure of Rule}_i}{\text{\# of Rules in the group}}$$

Equation 7: Prediction Score

6.4 TRAINING STEP

There are two steps in the training process. In the first step, context sensitive associative classification rules are discovered from the training dataset using Algorithm 2. These rules are stored in a rule database. In the second step, unnecessary rules are pruned. We considered two types of pruning: (a) pruning complementary rules, and (b) pruning weak rules.

In the rule database, many associative classification rules are conflicting or complementary. For example, for binary classification, if one rule is discovered with 80% of confidence, there is another rule with the same antecedent but different class label with 20% of confidence; such as, (Dehydration=Yes AND Anxiety=Yes) => (CINV=Yes) [Conf: 80%] and (Dehydration=Yes AND Anxiety=Yes) => (CINV=No) [Conf:20%]. This situation is conflicting or complementary. We used a confidence threshold (> 50%) to prune those rule. This is done at the rule generation step without requiring any extra processing step.

As described in Section 5.1.3.3, a value of 1 for lift represents that the antecedent (LHS) is independent (LHS) of the consequent (RHS). Also, a value of less than 1 for lift

represents a weaker association. Thus, any rules with the value of lift less than or equal to 1 are pruned. This is also done immediately after the rule generation. Context sensitive lift can prune more rules than the lift measure within the global context. Figure 66 presents the reduction of the number of rules on a class-imbalanced dataset.

Figure 66: Reduction of Number of Rules on an Imbalanced Dataset

6.5 DYNAMIC PREDICTION STEPS

6.5.1 Extracting Rules

The rule extractor component is used for extracting the rules that are qualified for the prediction query (see section 6.2.3). Those queries are then passed to the multi-rule predictor for making a dynamic prediction recommendation.

6.5.2 Dynamic Prediction

For making a dynamic recommendation based on multiple qualified rules, we experimented two different approaches: (1) all rule approach, and (2) rule ranking approach.

6.5.2.1 All Rule Approach

In this approach, all the qualified rules are used in the prediction process (Figure 67). If all the rules recommend the same class, then the class is returned as prediction. Otherwise, the rules are grouped based on class (here, there are only two groups) and then a prediction score is computed from the rules in each group. The class with the highest prediction score is recommended as the prediction outcome.

Figure 67: Multi-Rule Dynamic Predictor –All Rule Approach

6.5.2.2 Rule Ranking Approach

In the rule ranking approach, top n rules are used in the prediction process instead of using all qualified rules (Figure 68). First, the rules are ranked based on association rule measures (discussed below). Second, top n rules are then used for prediction similar to the all rule approach.

In order to develop a rule ranking mechanism, we compared four association rule measures. These measures are: (1) context sensitive support, (2) context sensitive confidence, (3) context sensitive lift, and (4) rule length. Here, support refers to the prevalence of the rule in the database, confidence refers to the accuracy of the rule and lift indicates the correlation between the antecedent and the consequent of the rule. Figure 71 presents the rule ranking mechanism by comparing confidence at the first level, support at the second level, lift at the third level, and rule length at the fourth level. This rule ranking approach has been adopted in various associative classification algorithms [118,128] in which only confidence, support and rule length are compared. In our approach, we used the lift measure in addition to those measures.

Figure 68: Multi-Rule Dynamic Predictor –Rule Ranking Approach

Rule Ranking

Figure 69: Rule Ranking

6.6 SYSTEM VALIDATION AND RESULTS

Three performance measures were compared for benchmarking: accuracy, sensitivity, and specificity. 10-fold cross validation was used to compute the three measures.

6.6.1 Benchmarking All Rule Approach

We experimented the all rule approach for various support and confidence thresholds. We used five measures for computing prediction scores: (1) each rule has similar impact (i.e., 1 is added to the score for each rule), (2) confidence, (3) support * confidence, and (4) lift* confidence, and (5) support * lift * confidence. We observed that lower support and higher confidence provide higher accuracy, sensitivity, and specificity (Figure 71). The highest accuracy, sensitivity and specificity are observed at support=0.003, and confidence =0.9 when the lift*confidence measure was used. The accuracy, sensitivity, and specificity were 87.6%, 87.0%, and 88.2% respectively.

Figure 70: Benchmarking – All Rule Approach

6.6.2 Benchmarking Rule Ranking Approach

We also benchmarked the rule ranking approach for top 1 to top 101 rules with 2 intervals (i.e., all the odd numbers between 1 to 101). The best result was observed when top 9 rules and the ranking mechanism of the “confidence-support-lift-rule length” (see Figure 71) were used. The accuracy, sensitivity, and specificity were 87.85%, 87.54%, and 88.2% respectively.

Both the all-rule approach and the rule-ranking approach outperformed most-frequently used classifiers in this field (Figure 71): (1) Neural Network, (2) Logistic regression, (3) Support Vector Machine, (4) Naïve Bayes and, and (5) Decision Tree. We used those classification algorithms in Weka [111] for this comparison. In addition, the rule ranking approach outperformed the all-rule approach. In the all-rule approach, the best performance was observed for lower support but higher confidence threshold. Determining the threshold for support and confidence is a trial-and-error approach. Instead, the rule ranking approach is preferable.

Figure 71: Comparison of Prediction Engine with Other Algorithms

6.6.3 Prediction Using Any Number of Variables

Traditional classification/prediction approaches require the same variables used in a classification model when an object or instance is predicted. If a variable used in a classification model is missing for some reason when an object is predicted, traditional approaches cannot predict the object without the variable (or they must build a new classification model from training data without the variable). For example, the “prior CINV” variable is not available for the first cycle of chemotherapy (Figure 72). Other

examples could be dehydration and anxiety status that are often unreported at the point-of-care. The prediction engine does not suffer from this issue that is common in a clinical setting as the system preserves the complete knowledge as rules from the training data and processes the prediction query in real-time. Although the top risk factor (e.g., dehydration in Figure 70) is missing, the system is able to predict a case without the top risk factor based on other variables. As a result, the system produces very high prediction performance in those situations.

Figure 72: Loss of prediction capacity – Unavailable or Unreported Variable Situation

Filling a missing variable in a prediction query could be a solution to this issue. However, this is not feasible at the point-of-care because the predicted value of the missing variable could significantly affect the prediction. In order to compare the prediction performance of a traditional approach (i.e., the decision tree algorithm in Weka) with the prediction engine, we modified a prediction query so that the missing variable had one of the possible values of the variable for the traditional approach as a “fixed” model because without filling out the missing value it does not work. However, the original query was

input into the prediction engine. We performed total seven comparison experiments: (1) Figure 73 shows a comparison of the prediction performance without dehydration, (2) Figure 74 is for a case without anxiety, (3) Figure 75 is without prior_cinv (4) Figure 76 is without both dehydration and anxiety, (5) Figure 77 is without dehydration and prior_cinv, (6) Figure 78 is without anxiety and prior_cinv, and (7) Figure 79 is without dehydration, anxiety and prior_cinv. In all the cases, the traditional approach showed either higher sensitivity and far lower specificity or higher specificity and far lower sensitivity compared with the prediction engine. It is impossible to know what predicted value of the missing variable would result in high sensitivity or high specificity. Thus, this “guessing” approach does not work in a clinical setting. Unlike the traditional approach, the prediction engine showed balanced performance.

Figure 73: Comparison of Prediction with Incomplete Query (dehydration is missing in the query)

Figure 74: Comparison of Prediction with Incomplete Query (anxiety is missing in the query)

Figure 75: Comparison of Prediction with Incomplete Query (prior_cinv is missing in the query)

Figure 76: Comparison of Prediction with Incomplete Query (dehydration & anxiety is missing in the query)

Figure 77: Comparison of Prediction with Incomplete Query (dehydration & prior_cinv is missing in the query)

Figure 78: Comparison of Prediction with Incomplete Query (anxiety & prior_cinv is missing in the query)

Figure 79: Comparison of Prediction with Incomplete Query (dehydration, anxiety & prior_cinv is missing in the query)

CHAPTER 7 : DISCUSSION

Careful examination of appropriate patient-specific risk-factors prior to selecting pre-medications for CINV is imperative in cancer care [60,154]. This has short term and long term effect in cancer care [57,84,92,99]. Better control of CINV may lead to improved tolerability of the therapy, less anxiety, higher patient's satisfaction, and avoidance of immediate discontinuation of the therapy. In the short term, better CINV control would allow for avoidance of hospitalization, less side effect of the regimen, better food and fluid intake, maintenance of baseline weight, maintenance of performance status, adherence to the interval and duration of the complete therapy, and significantly less physiological and psycho-social stress both to cancer patients and caregivers. Moreover, all these characteristics may translate to both improved progression-free survival (PFS) and overall survival (OS) [57,84,91,92,99]. There are several medical and economical long-term effects. In the long term, it may contribute to better recovery for the patients, early rehabilitation in personal, social and professional life, and a positive consideration for further chemotherapy in the future for recurrent or secondary malignancies leading to better treatment outcome. Its economic effects are enormous as they may reduce both the direct and indirect health care costs as well as reduce lost workdays [84,91,92,99].

To date, the comprehensive relationships of various patient-related factors for causing CINV were unknown. This project discovered important relationships through data mining that helps physicians for practicing personalized and precision medicine for the

management of CINV leading to improved clinical outcomes. This project could significantly improve overall cancer care and reduce overall cancer treatment cost. We have developed a highly accurate prediction system that is dynamic and updateable in real-time. Six datasets (three chemotherapy groups and two phases of CINV in each chemotherapy group) were analyzed individually so that the prediction models were built based on the evidence from the corresponding dataset. A novel context-sensitive prediction system (named as “prediction engine”) was introduced. The system does not suffer from the issue of losing prediction capacity in a situation when a set of important variables is unavailable or unknown at the point-of-care. The system has higher prediction power since multiple important rules are used for a single prediction. A new prediction scoring algorithm was designed to compute a prediction score from multiple rules. The prediction engine keeps all unimportant (rare) rules. The support value may increase for the rare rules with the addition of more data to the system in real-time. The dynamic nature of the system may benefit the unimportant or rare rules to become important as more data is added in real-time. The approach proposed in this project can be adapted for any other clinical predictions.

7.1 CINV PREDICTION IN THE LITERATURE

We also performed a systematic literature review in order to find related studies for CINV prediction. We followed the same search strategy as the systematic review described in Chapter 2. We found a total of 5 articles discussing three different risk prediction models of CINV.

The first model [86] was built for the acute phase of CINV using a dataset containing 864 cycles of chemotherapy received from 200 patients and the model validation was done using a test dataset containing 695 cycles of chemotherapy received from 146 patients. This was a single center prospective study performed in Canada. The patients received either high or moderate emetogenic chemotherapy. The prescriptions for antiemetics medications were based on the ASCO guidelines. The authors of the study performed three validation studies: the first one is as part of the original study [86] and the other two prospective studies [96,101] for validating the models independently from the training data (see Table 17).

Table 17: Performance of Risk Scoring Algorithm for Acute CINV

Study (Year)	Optimal Risk Score Cutoff	Accuracy	Sensitivity	Specificity
Dranitsaris et al. (2009) [86]	≥ 7 to < 9	67.4%	78.6%	64.8%
Bouganim et al. (2012) [101]	≥ 7	55.8%	71.9%	52.3%
	≥ 9	74.6%	53.1%	79.2%
Dranitsaris et al. (2013) [96]	≥ 7	60.1%	68.5%	58.8%
	≥ 9	80.3%	86.7%	31.3%

The second model [87] was built for the delayed phase of CINV using the same dataset as Dranitsaris et al. (2009) [86]. The data analysis method is same as the original study (dealing with the acute phase) while the risk scoring algorithm for the delayed phase is different than the one in the original study. The details of the algorithm are presented in Petrella et al. (2009) [87]. They performed three validation studies: the first one in the original study [87] and the other two prospective studies [96,101] for validating the models independently from the training data (see Table 18).

Table 18: Performance of Risk Scoring Algorithm for Delayed CINV

Author (Year)	Optimal Risk Score Cutoff	Accuracy	Sensitivity	Specificity
Petrella et al. (2009) [87]	$> 16 \text{ to } \leq 20$	67.9%	72%	64.4%
Bouganim et al. (2012) [101]	> 16	54.7%	75.8%	50.0%
	> 20	73.5%	57.6%	77.0%
Dranitsaris et al. (2013) [96]	> 16	58.6%	77.9%	53.3%
	> 20	67.8%	66.3%	68.2%

The third model was developed by Molassiotis et al. (2013) [70] using a training dataset containing 791 cycles of chemotherapy received from 286 patients. The model validation was performed using a test dataset from 50 chemotherapy patients (the number of cycles in the test dataset is not disclosed in the article). This was a multicenter prospective study performed in the United Kingdom. The patients received high, moderate or low emetogenic chemotherapy. The prescriptions for antiemetics medications were based on the MASCC guidelines. This study developed three different logistic regression models: one for the acute phase of CINV, another for the delayed phase of CINV, and the other for overall CINV (both the acute and delayed phases). The details of the models are presented in Molassiotis et al. (2013) [70]. The results of the model validation are presented in Table 19.

Table 19: Performance of three CINV logistic regression models by Molassiotis et al. (2013) [70]

CINV Phase	Accuracy	Sensitivity	Specificity
Acute	Not reported	76.1%	48.9%
Delayed	Not reported	80.4%	47.2%
Overall (Acute and Delayed)	Not reported	79.0%	50.0%

Figure 80 compares the prediction performance of the prediction engine with the prediction performance published in the literature (shown in Table 17, Table 18, and Table 19). Only one study attempted to produce a combined model for both acute and delayed phases of CINV. Rest of the studies developed and reported their models individually. The prediction performance of the proposed prediction engine was reported for both the acute and delayed phases together (see context-sensitive prediction in Chapter 6). The prediction engine produced a high performance in comparison to the prediction results from the literature. Only one study [96] reported 86.7% of a sensitivity, which is comparable to the proposed approach. However, the high sensitivity was archived at the cost of the very low specificity (31.3%). Overall, we believe that the prediction engine outperforms all the models reported in the literature for CINV prediction.

Figure 80: CINV Prediction from the Literature vs. the Prediction Engine

7.2 LIMITATIONS

The project has a few limitations. First, the data was collected by retrospective record review. A prospective validation is needed to confirm the usefulness of the model in real clinical setting. Second, studies showed that female patients with pregnancy-related nausea and vomiting have a higher risk of CINV. However, this information was missing in our dataset. With this information, the prediction results could be considerably enhanced. Third, the data has a lower representation of Asians and Hispanics. A multi-center and/or

multi-national study including various populations is needed to overcome this shortcoming.

7.3 CONCLUSION

The prediction engine presented in this dissertation has the capacity to build a highly precise prediction system while preserving the context-sensitiveness in one single system. The prediction performance of the system outperformed many popular prediction methods and all the results of CINV risk prediction published in the literature. We used the patient-specific risk factors for making personalized treatment recommendations for CINV. This project solved a real clinical problem that will shorten the gap between clinical practices and evidence-based guidelines for CINV management leading to the practice of personalized and precise treatment recommendation, better life quality of patient and reduced healthcare cost.

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VITA

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