ORIGINAL RESEARCH

Prospective Validation of a Prediction Tool for Identifying Patients at High Risk for Chemotherapy-Induced Nausea and Vomiting

George Dranitsaris, BPharm, PhD; Nathaniel Bouganim, MD; Carolyn Milano; Lisa Vandermeer, MSc; Susan Dent, MD; Paul Wheatley-Price, MD; Jenny Laporte, RN; Karen-Ann Oxborough, RN; and Mark Clemons, MD

ABSTRACT

Background: Even with modern antiemetic regimens, up to 20% of cancer patients suffer from moderate to severe chemotherapy-induced nausea and vomiting (CINV) (≥ grade 2). We previously developed chemotherapy cycle–based risk predictive models for ≥ grade 2 acute and delayed CINV. In this study, the prospective validation of the prediction models and associated scoring systems is described.

Objective: Our objective was to prospectively validate prediction models designed to identify patients at high risk for moderate to severe CINV.

Methods: Patients receiving chemotherapy were provided with CINV symptom diaries. Prior to each cycle of chemotherapy, the acute and delayed CINV scoring systems were used to stratify patients into low- and high-risk groups. Logistic regression was used to compare the occurrence of ≥ grade 2 CINV between patients considered by the model to be at high vs low risk. The external validity of each system was assessed via an area under the receiver operating characteristic (AUROC) curve analysis.

Results: Outcome data were collected from 97 patients following 401 cycles of chemotherapy. The incidence of ≥ grade 2 acute and delayed CINV was 13.5% and 21.4%, respectively. There was a significant correlation between the risk score and the probability of developing acute and delayed CINV following chemotherapy. Both the acute and delayed scoring systems had good predictive accuracy when applied to the validation sample (acute, AUROC = 0.70, 95% CI, 0.62–0.77; delayed, AUROC = 0.75, 95% CI, 0.69–0.80). Patients who were identified as high risk were 3.1 (P = .006) and 4.2 (P < .001) times more likely to develop ≥ grade 2 acute and delayed CINV than were those identified as low risk.

Conclusion: This study demonstrates that the scoring systems are able to accurately identify patients at high risk for acute and delayed CINV.

Over the past few years in oncology, there has been a rapid rise in publications describing the development of predictive models. As highlighted in a recent editorial, there have been more than 100 predictive models in prostate cancer alone.[1] The intent of such models is to estimate the likelihood of a given patient developing the prognostic or predictive event of interest. Armed with such information, clinicians may be able to act preemptively in order to avoid the event in the first place.

The basic methodology in developing a predictive model involves collecting patient data at the start of an observation period and then documenting which patients have developed the event of interest.[2] Statistical techniques such as multivariable regression analysis and recursive partitioning are then used to identify which patient variables are significantly associated with the event. The final set of coefficients can be used to develop a numerical index or nomogram for identifying patients at high risk through the establishment of thresholds or cut-point scores, via statistical techniques.[3] As a final step, the predictive model must undergo external validation, ideally from an independent sample of patients through a prospective evaluation process.[4] Unfortunately, the majority of predictive models appearing in the oncology literature are not pro-

Author Affiliations: Division of Medical Oncology, The Ottawa Hospital Cancer Centre (Drs Bouganim, Dent, Wheatley-Price and Clemons), and Systemic Therapy Program, Ottawa Regional Cancer Center (Ms Milano, Ms Vandermeer, Ms Laporte, and Ms Oxborough), Ottawa, Ontario, Canada. Dr Dranitsaris is in private practice in Toronto, Ontario.

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Correspondence Author: George Dranitsaris, BPharm, PhD, 283 Danforth Ave, Suite 448, Toronto, Ontario, M4K 1N2, Canada (george.dranitsaris@gmail.com).

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Table 1

Risk Scoring System for Acute and Delayed Chemotherapy-Induced Nausea and Vomiting (CINV)

ACUTE CINV RISK INDEX	DELAYED CINV RISK INDEX
Start at base score of 10 • If the patient is between 40 and 60 y old, subtract 3 • If the patient is ≥ 60 y old, subtract 4 • If the patient has existing comorbidity (eg, cardiovascular disease, diabetes, gastrointestinal, musculoskeletal, thyroid, other), subtract 2 • If the patient consumes at least one alcoholic drink per day, subtract 1 • If the patient is about to receive cycle 3 or beyond, subtract 1 • If the disease site is gynecological or gastrointestinal, subtract 2 • If the patient is about to receive anthracycline-based chemotherapy, add 1 • If the patient is about to receive platinum-based chemotherapy, add 3 • If the patient has disease stage I or II, add 1 • If the patient is taking nonprescribed treatments for emesis control at home, add 2	Start at base score of 20 • If the patient is ≤ 40 y old, add 8 • If the patient received a 5-HT_3 antiemetic with or without dexamethasone postchemo, add 5 • If the patient had prior nausea/vomiting before starting the current chemo, add 14 • If the patient had morning sickness during a pregnancy (if applicable), add 7 • If the patient is taking nonprescribed antiemetics at home, add 23 • If the patient had one or more vomiting episodes during the first 24 hours postchemo, add 7 • If the patient is about to receive cycle 3 or beyond, subtract 7 • For every hour the patient slept on the night before chemo, subtract 1

spectively validated on a sample of patients who were not part of the initial model-development cohort.[1]

Even if a predictive model has undergone both internal and external validation, it may not be ready for adoption because it has not been established that its application will do more good than harm to patients.[1] The final objective of any predictive model is to accurately identify patients at high risk and, with this information, to adapt clinical decisions that hopefully will result in improved patient outcomes. Ultimately, this can be demonstrated only through a randomized, controlled trial in which patients are allocated into a usual-practice control group or receive prediction model–guided care with preestablished medical interventions for those deemed to be at high risk. Therefore, the true success of any predictive index would be apparent if patients receiving model-guided care had improved clinical outcomes compared with the usual-care group. Given the overall complexity and cost of model development and validation, it is not surprising that relatively few have been adopted into clinical practice.

In 2009, our group developed and externally validated 2 predictive indexes for acute and delayed, moderate to severe (ie, ≥ grade 2; see Table 1) chemotherapy-induced nausea and vomiting (CINV).[5,6] Major predictors for acute and delayed CINV were consistent with the literature and included (1) age younger than 40 years, (2) platinum- or anthracycline-based chemotherapy, (3) low alcohol consumption, (4) emesis in earlier cycles of chemotherapy, (5) previous history of morning sickness, and (6) prior emetic episodes within the same or from previous chemotherapy regimens (Table 1).[5,6] The initial studies suggested that the acute and delayed CINV indexes were able to correctly classify approximately 68% of patients into low- and high-risk groups, which were based on a final set of cut-point scores.[5,6]

As part of the external validation process, 2 planned prospective studies were undertaken in a sample of patients from 2 cancer centers that were not part of the original model-development study. In the first of these studies, involving 94 patients who received 181 cycles of chemotherapy, up to 74% of patients were correctly classified into high- and low-risk groups, depending on where the cut-point score was set.[7]

In this article, we report the findings of the second external validation study, which enrolled 97 patients who received a total of 401 cycles of chemotherapy. The primary objective of the current study was to prospectively validate the prediction scoring systems for acute and delayed CINV in an independent sample of patients receiving outpatient chemotherapy. The final objective of this initiative will be to determine if optimal emesis control can be achieved using validated predictive models.

METHODS

Patients

Patients with a range of malignancies who were scheduled to receive outpatient chemotherapy at the Ottawa Hospital Cancer Centre and the Irving Greenburg Family Cancer Centre, also in Ottawa, were approached about the study. Once written informed consent was received, the initial data collection consisted of patient demographics, disease-related information, and potential predictive factors for CINV such as a history of motion sickness, a history of morning sickness during a previous pregnancy (if applicable), and daily alcohol consumption.

Just prior to each cycle of chemotherapy, additional information was collected, including (1) the scheduled antiemetic prophylaxis, (2) the anticancer agent(s) prescribed, (3) the patient's expectation of becoming nauseous following chemotherapy, (4) food intake the morning of chemotherapy, and (5) the number of hours of sleep the night before chemotherapy. Also at this time, anxiety levels were measured via a 4-point Likert scale (graded as none, mild, moderate, and high). For the patients in this study, no predefined antiemetic prescriptions were built into the chemotherapy regimen; rather, antiemetics were prescribed by the medical oncologist,

and no adjustment was made based on the calculated acute or delayed CINV risk score. Permission to conduct the study was received by the local institutional ethics review board.

Classification of Patients

Prior to each cycle of chemotherapy, the acute and delayed scoring systems were applied to estimate risk scores for each patient for that cycle of chemotherapy (Table 1). From the original model-development studies, patients with acute and delayed scores that were ≥ 7 and > 16, respectively, were categorized as being at high risk for a CINV event.[5,6] These were the risk-score cut points identified in the original model-development studies. With these cut points, the risk model sensitivity (ie, true-positive rate), specificity (ie, true-negative rate), and correct classification rate were maximized.[5,6]

Collection of Outcomes Data

Patients were provided with a diary for daily self-reporting of events. Data collection included the number of vomiting episodes; the occurrence, intensity, and duration of nausea in the first 24 hours and from days 2 through 5 following chemotherapy; and the use of nonprescribed drugs at home for emesis control. The National Cancer Institute's Common Terminology Criteria for Adverse Events (NCI CTCAE) V4.0 was used to capture the grade of both acute and delayed nausea and vomiting (grades 0–4). To obtain additional information about the patient's perceived severity of emetic events, each episode of nausea and vomiting was rated using a 4-point Likert scale (none vs mild vs moderate vs severe). Patients were contacted by telephone the day after chemotherapy and on day 5 to ensure that the diary was completed accurately. After they completed each chemotherapy cycle, patients were asked to rate their overall control of vomiting and nausea using a 4-point Likert scale (1 = terrible to 4 = excellent).

Statistical Analysis and Validation of the Scoring Systems

Demographic data and disease characteristics were presented descriptively. The primary end points in the current study were the incidence of moderate to severe (ie, $\geq$ NCI CTCAE grade 2) acute and delayed CINV. The end points were defined as a composite measure consisting of NCI CTCAE grade 2 to 4 nausea and vomiting or moderate to severe vomiting and nausea as described in the 4-point Likert scale.

To measure the association between the calculated risk score and the probability of acute and delayed CINV, 4 univariate logistic regression analyses with an adjustment for clustering on each chemotherapy cycle number were undertaken. In the initial model-development phase of the study, the scoring system was designed to reflect clustering within a patient receiving consecutive cycles of chemotherapy. Patient score and risk category (high vs low) were the lone independent variables in the logistic regression models. The intent of this analysis was to determine the probability of acute and delayed CINV by patient score and the odds ratio (OR) for an acute and delayed event by risk category (high vs low). The probability of acute and delayed CINV for each patient was determined by the following:

$$1/\left[1 + \text{exponential}^{(\text{constant} + \text{risk score} \times \text{model coefficient})}\right]$$

The constant and model coefficient for the variable risk score were obtained from the univariate logistic regression analyses. The goodness of fit of the univariate models was then assessed with the Hosmer-Lemeshow test.[8]

As part of the validation process, the predictive accuracy of each risk-scoring system was determined by measuring the specificity, sensitivity, and area under the receiver operating characteristic (AUROC) curve.[9,10] These parameters were estimated with an adjustment for clustering within a patient receiving multiple cycles of chemotherapy. *Discrimination* refers to the ability of a diagnostic test or predictive index to accurately identify patients at low or high risk for the event under investigation and is often presented as the AUROC.[10] In addition to establishing the above characteristics using the original cut points for differentiating between low and high risk for CINV (ie, a score of ≥ 7 and > 16 for acute and delayed CINV, respectively), 2 further thresholds were tested. For the acute CINV risk index, cut-point scores of ≥ 9 and ≥ 11 were evaluated. For the delayed CINV risk index, cut-point scores of > 12 and > 20 were tested. Therefore, evaluating 3 cut-point scores for each risk index allowed the identification of optimal risk score thresholds. All of the statistical analyses were performed using Stata, V11.0 (StataCorp, College Station, Texas).

RESULTS

From November 2010 to March 2011, 175 patients were approached for the study. Of these, 97 completed and returned their diaries, 8 declined to take part, 6 were ineligible, 30 did not return their diaries, 14 felt too unwell to complete their diaries, and 20 died. Over the evaluation period, 97 patients received a total of 401 cycles of chemotherapy. The median age of patients was 60 years, and 73% were women (Table 2). Approximately 52% of patients had breast cancer, but the other major solid tumor malignancies were also represented (Table 2).

The majority of patients (76%) had stage III or IV disease, 45% had other concomitant medical conditions (eg, diabetes, cardiovascular disease), and approximately 80% were chemotherapy-naive. In addition, 32% of patients reported that they consumed at least 1 alcoholic beverage on a daily basis (Table 2).

Over the 401 cycles of treatment, the chemotherapy was platinum- or anthracycline-based in 27% and 12% of patients, respectively. Prior to each cycle, approximately 79% of patients received a 5-hydroxytryptamine$_3$ (5-HT$_3$) antiemetic (eg, ondansetron) as part of their primary prophylaxis. A 5-HT$_3$ antiemetic was used postchemotherapy in approximately 68% of cycles. Dexamethasone was used as part of prechemotherapy primary prophylaxis in approximately 77% of cycles and postchemotherapy in 43% of cycles. Aprepitant, a neurokinin 1 (NK$_1$) receptor antagonist, was used in

Table 2

Patients and Treatment Characteristics in the Validation Sample

CHARACTERISTIC	VALIDATION SAMPLE (N = 97)
Median age, y (range)	60 (28–100)
Female gender	73.1%
Type of cancer	
Breast	52.5%
Gastrointestinal	2.1%
Genitourinary	4.3%
Lung	16.8%
Other	24.3%
Stage I/II vs III/IV	23.7% vs 76.3%
Concomitant medical conditions[a]	45.4%
Chemotherapy-naive	80.4%
Emesis with previous chemotherapy	12.4%
History of motion sickness	23.7%
History of morning sickness during pregnancy	27.8%
Daily alcohol intake	31.9%
Number of cycles delivered	401
Type of chemotherapy	n = 401
Platinum-based	27.2%
Anthracycline-based	12.2%
Taxane	31.7%
Other	28.9%
Prechemotherapy antiemetics	n = 401
None	3.7%
Ondansetron/granisetron alone	3.0%
Dexamethasone ± prochlorperazine	15.0%
Dexamethasone + ondansetron	62.6%
Ondansetron + aprepitant	8.8%
Prochlorperazine alone	0.5%
Prochlorperazine + ondansetron	4.0%
Other[b]	2.4%
Postchemotherapy antiemetics	n = 401
None	4.2%
Ondansetron alone	11.2%
Dexamethasone ± prochlorperazine	8.5%
Dexamethasone + ondansetron	14.7%
Ondansetron + aprepitant	3.7%
Prochlorperazine alone	9.2%
Prochlorperazine + ondansetron	12.7%
Dexamethasone + ondansetron + prochlorperazine	20.4%
Other[b]	15.4%

[a] Cardiovascular disease, diabetes, gastrointestinal, musculoskeletal, thyroid, other.
[b] The majority of these regimens included ondansetron and aprepitant with other drugs.

Table 3

Factors Predictive for Acute and Delayed Nausea and Associated Outcomes Data

CHARACTERISTIC	VALIDATION SAMPLE (N = 401 CYCLES)
A meal prior to chemotherapy	95.5%
Median number hours of sleep night before chemotherapy (range)	6 (0–10)
Taking nonprescribed drugs at home for emesis control	11.2%
Patient expectation of nausea/vomiting just to each treatment cycle	6.5%
Patient anxiety just prior to each treatment cycle	
None	64.1%
Mild	14.0%
Moderate	22.0%
Patient assessment of overall vomiting control after each cycle	
Excellent	87.7%
Satisfactory	8.7%
Poor	2.5%
Terrible	1.0%
Missing	0.5%
Patient assessment of overall nausea control after each cycle	
Excellent	61.3%
Satisfactory	27.4%
Poor	9.2%
Terrible	1.5%
Missing	0.5%
≥ Grade 2 CINV within the first 24 h	13.5%
≥ Grade 2 CINV from days 2 to 5	21.4%
Mean duration of acute nausea, h (range)	1.5 (0–24)
Mean duration of delayed nausea, h (range)	3.7 (0–96)
Calculated acute CINV risk score, median (range)[a]	6 (0–13)
Patient cycles determined to be at high risk for acute CINV (score ≥ 7)	44.9%
Calculated delayed CINV risk score, median (range)[b]	13 (0–65)
Patient cycles determined to be at high risk for delayed CINV (score > 16)	39.1%

[a] Based on the original publications,[5,6] an acute score ≥ 7 was considered to be high risk for acute chemotherapy-induced nausea and vomiting (CINV).
[b] A delayed score > 16 was considered to be high risk for delayed CINV.

only 11% of cycles before and after chemotherapy (Table 2). Prior to the next cycle of chemotherapy, 15 patients (11.2% of cycles) stated that they had used a nonprescribed treatment at home for nausea and vomiting control. These drugs included dimenhydrinate, bismuth subsalicylate (Pepto-Bismol; Procter & Gamble, Cincinnati, Ohio), and antacids.

Potential risk factors and CINV outcomes data are presented in Table 3. Patients reported that they slept a median of 6 hours the night before chemotherapy, and 95.5% stated that they had a meal prior to receiving chemotherapy treatment. Prior to each cycle, only 6.5% of patients over 401

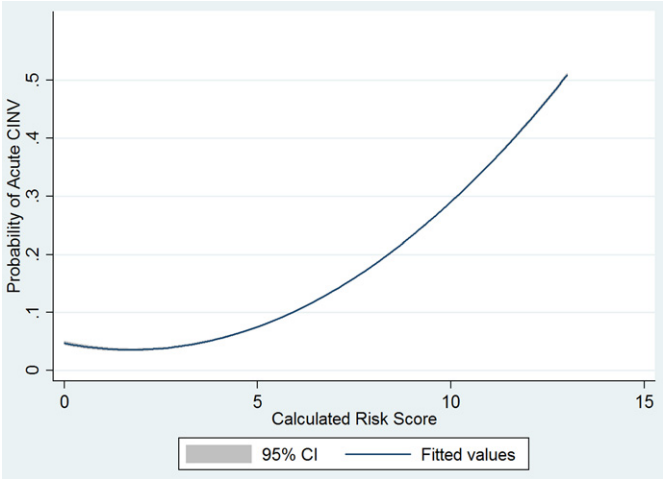

Figure 1 Association between the probability of acute chemotherapy-induced nausea and vomiting (CINV) and the calculated score.

cycles expected to have nausea and vomiting, and their anxiety was moderate in only 22% of cases (Table 3). Of these, none of the patients stated that they had a high anxiety level before the start of treatment.

Following the completion of each chemotherapy cycle, patients were asked to rate their overall control of vomiting and nausea using a 4-point Likert scale. Following the completion of 401 cycles of systemic therapy, 87.7% considered the control of vomiting to have been excellent, compared with only 61.3% in the case of nausea (Table 3). Vomiting and nausea control were reported to have been poor or terrible in only 3.5% and 10.7% of patients cycles, respectively. When the composite end point of moderate to severe nausea and vomiting (≥ grade 2) was determined, an acute- and delayed-CINV event occurred in 13.5% and 21.4% of cycles, respectively. The findings suggested that nausea was the most problematic symptom, with each moderate to severe event in the acute and delayed setting lasting a mean of 1.5 to 3.7 hours, respectively (Table 3).

External Validation: Acute CINV Risk Index

As part of the external validation process, the acute- and delayed-risk scores were calculated for each patient prior to each cycle of chemotherapy (Tables 1 and 3). Approximately 45% of patient cycles were considered to be high risk for acute CINV according to the original cut point of ≥ 7.[5] Patients who were considered to be at high risk for acute CINV had a median score of 8 compared with a median of 6 in patients considered to be at low risk ($P < .001$). Figure 1 illustrates the association between the probability of acute CINV and the calculated risk score in the cohort of patients who had received 401 chemotherapy cycles. Supporting the original model-development studies, patients with higher scores had an increased likelihood of suffering from an acute CINV event (Figure 1). For each additional unit, there was a 37% relative increase in the risk of acute CINV (OR = 1.37, $P < .001$).

The intent of the AUROC analysis was to identify a threshold where the sensitivity and specificity of a predictive tool are maximized. Using a cut-point score ≥ 7, the associated sensitivity and specificity were 68.5% and 58.8%, respectively, with 60.1% of patient treatment cycles being correctly classified as high or low risk (Table 4). The univariate logistic regression analysis that used this cut point revealed that patients who were considered to be at high risk were 3.1 times more likely to suffer from an acute CINV event compared with patients considered to be low risk by the index (OR = 3.1, $P = .006$). Raising the cut point to ≥ 9 reduced the sensitivity but improved both the specificity to 86.7% (ie, 97 additional true negatives would be picked up) and the proportion of patients correctly classified to 80.3% (Table 4). However, the drawback of raising the cut point to ≥ 9 would be that 16 true positives would be missed.

The interpretation is that raising the cut point to ≥ 9 would increase the number of true negatives (ie, people who are deemed to be at low risk by the index who do not have a CINV event) at the expense of missing some true positives, 16 patients in this case. Raising the cut-point score to ≥ 11 did not have an appreciable impact on the predictive power of the acute CINV risk model and would result in more true positives being missed (Table 4). Therefore, the oncologist would need to decide between using ≥ 7 or ≥ 9 as the threshold for classifying patients as "high risk," while being aware of the drawbacks in terms of over- and undertreating patients (ie, false positives vs false negatives).

External Validation: Delayed CINV Risk Index

Approximately 39% of patient cycles were considered to be high risk for delayed CINV according to the original cut-point score of > 16. The association between the probability of delayed CINV and the calculated risk score is illustrated in Figure 2. The findings of the univariate logistic regression analysis with patient risk score as the lone predictor variable generated a relative odds of 8% (OR = 1.08, $P < .001$) for each additional unit determined by the delayed CINV index (Figure 2). Prior to each cycle of chemotherapy, patients were also classified as being at high or low risk for delayed CINV using various cut-point scores (Table 4). In the original publication describing the delayed CINV model development, the AUROC analysis suggested a risk score of > 16 as the optimal cut point for differentiating between high and low risk for delayed CINV. With such a cut point, the associated sensitivity and specificity were 66.3% and 68.2%, respectively, with 67.8% of patient treatment cycles being correctly classified (Table 4). Logistic regression analysis revealed that patients with risk scores > 16 (ie, who were at high risk according to the original classification) were 4.2 times more likely to have a delayed CINV event compared with patients who had scores ≤ 16 (OR = 4.2, $P < .001$).

If the cut-point score were increased to > 20, the sensitivity would be reduced to 41.7% but the specificity would increase to

Table 4

Detailed Analysis of Risk Scoring System for Acute and Delayed Chemotherapy-Induced Nausea and Vomiting (CINV)

SCORE CUT POINT	CINV INCIDENCE	SENSITIVITY[b]	SPECIFICITY[c]	CORRECTLY CLASSIFIED	ODDS RATIO[d] (95% Confidence Interval)
Acute CINV[a]					
≥ 7	20.6%	68.5%	58.8%	60.1%	3.1 (1.4–6.9)
≥ 9	31.3%	31.3%	86.7%	80.3%	4.1 (1.6–10.6)
≥ 11	35.3%	11.1%	96.8%	85.3%	3.8 (1.4–10.6)
Delayed CINV[a]					
> 12	31.3%	77.9%	53.3%	58.6%	4.0 (2.1–7.7)
> 16	36.3%	66.3%	68.2%	67.8%	4.2 (2.2–8.1)
> 20	41.8%	41.7%	85.6%	74.3%	4.2 (2.0–8.9)

[a] From the original publication, patients with a risk score ≥ 7 were considered to be at high risk for an acute CINV event. Patients with a risk score > 16 were considered to be at high risk for a delayed CINV event.

[b] The proportion of patients who had a CINV event and were classified as high risk.

[c] The proportion of patients who did not have a CINV event and were classified as low risk.

[d] Risk of a moderate to severe CINV event in patients determined to be at high vs low risk by the respective scoring systems.

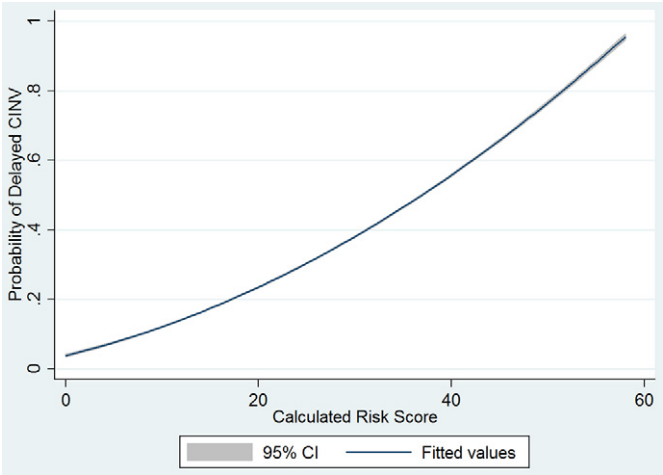

Figure 2 Association between the probability of delayed chemotherapy-induced nausea and vomiting (CINV) and the calculated score.

85.6% (ie, 40 additional true negatives would be picked up) and the proportion of patients correctly classified would rise to 74.3% (Table 4). However, as in the former case, raising the risk score cut-off to > 20 would mean that 14 true positives would be missed. Lowering the risk score cutoff to > 12 would have the opposite effect. Ten additional true positives would be identified by the index, but 47 patients would be incorrectly classified as being at high risk (ie, false positives). In addition, a threshold of > 12 would result in only 58.6% of patients being correctly classified as high or low risk.

Area under the ROC Curve

For the final validation of the acute- and delayed-risk prediction tools, the calculated risk scores and the probabilities for acute and delayed CINV events were used in an AUROC analysis. The findings suggested that the AUROC curve for the acute- and delayed-risk indexes was acceptable at 0.70 (95% CI, 0.62–0.77) and 0.75 (95% CI, 0.69–0.80), respectively, which supports the external validity of each prediction index.

DISCUSSION

Despite important advances in their prevention, nausea and vomiting remain among the most unpleasant and feared side effects of cancer chemotherapy.[11] Poorly controlled CINV can result in treatment delays, dose reductions, the need for additional antiemetic prophylaxis, increased health-care-resource use (eg, hydration), and/or the premature discontinuation of chemotherapy. In addition, antiemetics themselves are not without clinically significant toxicity, such as steroid-induced psychosis and constipation from 5-HT_3 receptor antagonists. Clinical care could be improved and dose intensity could be maintained if episodes of significant CINV could be accurately predicted, with steps taken in advance to prevent their occurrence. Such steps might include the use of more appropriate antiemetic medication as well as forewarning the patient and initiating a more intensive early monitoring scheme and action plan for early intervention.

To provide the necessary tools for identifying patients at high risk for acute and delayed CINV, we previously developed scoring systems and prospectively validated them.[5–7] As part of the validation process, we evaluated their overall performance in a new sample of 97 patients from 2 cancer centers that were not involved in the original model-development studies. The results suggested that the risk scores were significantly correlated with the probability of acute and delayed CINV and able to correctly classify up to 80% of patients into high- and low-risk groups if the cut-point scores were raised. Based on the original recommended cut-point scores, patients who were identified as being at high risk for acute and delayed CINV were approximately 3 to 4 times more likely to have a moderate to severe event than were patients considered to be at low risk. Therefore, the former

group of patients would be candidates for more intensive and targeted antiemetic therapy.

One of the drawbacks of the majority of predictive tools reported in the oncology literature is that there is a lack of data demonstrating that their use improves overall patient outcomes. With the completion of the current study, the acute- and delayed-CINV risk indexes have now been prospectively validated in 2 independent patient samples.[7]

The final step in the current initiative is to demonstrate that risk model–guided antiemetic therapy improves overall nausea and vomiting control. Our group has procured funding from the Canadian Breast Cancer Foundation for a randomized, controlled trial in which eligible patients will be randomized into an experimental or a usual-care group. Prior to the start of chemotherapy, an emesis risk score will be calculated for both acute and delayed emesis for patients in the experimental group. Patients who are considered to be at high risk for acute and delayed CINV will receive standardized antiemetic therapy that is based on international treatment guidelines.[12,13] Patients who are deemed to be at low risk by the models will not have their initial antiemetic changed.

To illustrate the planned interventions in high-risk patients, aprepitant will be used prior to the start of chemotherapy and continued for 3 days. In addition, the prechemotherapy dose of dexamethasone will be increased to 20 mg intravenously and continued as 8 mg orally twice daily for 3 days. Lastly, all patients who are considered to be at high risk for acute and delayed CINV will receive ondansetron prior to chemotherapy and for at least 24 hours afterward. We hypothesize that risk model–guided interventions during the randomized trial will improve nausea and vomiting control relative to the usual-care control group.

There are a number of limitations in the current study that need to be acknowledged. There is evidence in the clinical trial literature that acute emesis is primarily mediated through serotonin receptor stimulation, whereas delayed CINV is due to multiple neurotransmitter involvement, with the opiate and neurokinin receptors playing a dominant role. Therefore, the weighting of each pathway will make an important contribution to validating any CINV prediction tool, especially in the delayed phase. As a result, the selected cut point for delayed CINV may not prevent symptom development, even with the addition of a neurokinin receptor antagonist.

In addition, the sample size was small and patient data were obtained from only 2 institutions. Approximately 52% of our sample consisted of breast cancer patients, and fewer than 5% of patients had either gastrointestinal or genitourinary malignancies. The predictive accuracy of the acute and delayed index was adequate, with AUROC curves of 0.70 and 0.75, respectively; but there is room for improvement. We also considered only cancer patients receiving outpatient chemotherapy. As a result, the indexes may not be applicable to hospitalized patients.

Despite these limitations, the indexes are easy to apply and can discriminate between high- and low-risk patients, and the threshold can be varied depending on a patient's and/or clinician's risk tolerance. However, their ultimate clinical utility will be demonstrated only through the planned randomized trial.

Conflict of Interest Disclosures: The authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest and none were reported.

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