Who Is at Risk for Postdischarge Nausea and Vomiting after Ambulatory Surgery?

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ABSTRACT

Background: About one in four patients suffers from postoperative nausea and vomiting. Fortunately, risk scores have been developed to better manage this outcome in hospitalized patients, but there is currently no risk score for postdischarge nausea and vomiting (PDNV) in ambulatory surgical patients.

Methods: We conducted a prospective multicenter study of 2,170 adults undergoing general anesthesia at ambulatory surgery centers in the United States from 2007 to 2008. PDNV was assessed from discharge until the end of the second postoperative day. Logistic regression analysis was ap-

What We Already Know about This Topic

- Postoperative nausea and vomiting (PONV) can be predicted with a simplified risk score; however, there is no simple model to predict post-discharge nausea and vomiting (PDNV)

What This Article Tells Us That Is New

- Depending on the number of the following factors, *i.e.,* female gender, age <50 yr, a history of nausea or vomiting, and opioid administration or nausea in the postanesthesia care unit, the patient's risk for PDNV can be predicted as 10%, 20%, 30%, 50%, 60%, or 80%

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plied to a development dataset and the area under the receiver operating characteristic curve was calculated in a validation dataset.

Results: The overall incidence of PDNV was 37%. Logistic regression analysis of the development dataset (n = 1,913) identified five independent predictors (odds ratio; 95% CI): female gender (1.54; 1.22 to 1.94), age less than 50 yr (2.17; 1.75 to 2.69), history of nausea and/or vomiting after previous anesthesia (1.50; 1.19 to 1.88), opioid administration in the postanesthesia care unit (1.93; 1.53 to 2.43), and nausea in the postanesthesia care unit (3.14; 2.44–4.04). In the validation dataset (n = 257), zero, one, two, three, four, and five of these factors were associated with a PDNV incidence of 7%, 20%, 28%, 53%, 60%, and 89%, respectively, and an area under the receiver operating characteristic curve of 0.72 (0.69 to 0.73).

Conclusions: PDNV affects a substantial number of patients after ambulatory surgery. We developed and validated a simplified risk score to identify patients who would benefit from long-acting prophylactic antiemetics at discharge from the ambulatory care center.

AMONG the millions of patients undergoing surgery with general anesthesia each year, many suffer from postoperative nausea, vomiting, or both (PONV).[1–3] Severe nausea can be so draining and debilitating that patients have rated it as more serious than postoperative pain.[4] Vomiting increases the risk of pulmonary aspiration of gastric contents and suture dehiscence, and may even lead to esophageal rupture, subcutaneous emphysema, and bilateral pneumothoraces.[5–7] In addition, PONV can delay patient discharge from the postanesthesia care unit (PACU), and it is a leading cause of unexpected hospital admission after ambulatory surgery.[8] As a result, PONV has a considerable economic impact on the U.S. healthcare system.[9] Current consensus guidelines recommend that the use of prophylactic antiemetics be tailored to the patient's risk of developing PONV.[10,11]

The patient's risk of developing PONV can be estimated using a predictive model like our simplified PONV risk score (also known as the Apfel score), which was developed in European inpatients undergoing balanced inhalational anesthesia. According to this score, the risk factors (female gender, history of motion sickness and/or PONV, nonsmoking, and use of postoperative opioids) are each assigned a value of 1, and the incidence of PONV associated with 1, 2, 3, and 4 risk factors is 10%, 21%, 39%, 61%, and 79%, respectively.[12]

Ambulatory surgery procedures are generally less invasive and less extensive than inpatient procedures. Consequently, they entail less exposure to emetogenic inhalational anesthetics and perioperatively administered opioids,[13] which may lead to a lower incidence of nausea and/or vomiting in the PACU. However, nausea and vomiting may also occur after the ambulatory patient has left the hospital. This postdischarge nausea and/or vomiting (PDNV) may be particularly hazardous for ambulatory surgery patients because they no longer have immediate access to fast-onset intravenous antiemetic rescue medication, and they may be unable to tolerate oral medication. In fact, a U.S. study of 154 patients undergoing ambulatory surgery under general anesthesia reported that 35% of patients were significantly distressed by PDNV.[14]

With more than 60% of surgeries in the United States now performed on an ambulatory basis, accounting for millions of procedures with general anesthesia annually, the true incidence and risk factors of PDNV warrant closer scrutiny.[15] We sought to measure the incidence of PONV among ambulatory surgery patients during two distinct periods: in the PACU and outpatient facility before discharge, an outcome we defined as PONV, and after discharge, an outcome we defined as PDNV. It should be noted that both Phases I and II are included in our definition of the PACU period. In addition, we sought to characterize risk factors and/or protective factors, and develop, simplify, and validate a risk score for PDNV that would help clinicians tailor prophylactic regimens to at-risk patients before they are discharged from the hospital.

Materials and Methods

Participants

With the approval of the local institutional review boards of 12 ambulatory surgery centers in the United States (Medical College of Georgia, Augusta, GA; Brigham & Women's Hospital, Boston, MA; University of Virginia, Charlottesville, VA; St. Luke's Episcopal Hospital, Houston, TX; The University of Texas MD Anderson Center, Houston, TX; University of Kansas Medical Center, Kansas City, KS; University of Kentucky, Lexington, KY; Loma Linda University, Loma Linda, CA; University of Louisville, Louisville, KY; University of California – San Francisco (UCSF) Ambulatory Surgery Center, San Francisco, CA; UCSF Medical Center at Mt. Zion, San Francisco, CA; Mayo Clinic Scottsdale, Scottsdale, AZ), 2,493 adult patients scheduled for an elective outpatient surgical procedure during general anesthesia requiring tracheal intubation or a laryngeal mask airway gave their written informed consent to participate in this prospective cohort study from July 16, 2007, to August 28, 2008. Of those patients, 180 were excluded before surgery because they no longer met the eligibility criteria (*e.g.*, because of cancellation of surgery or conversion from planned

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◆ This article is accompanied by an Editorial View. Please see: Lichtor JL, Chung F: Nausea and vomiting treatment after surgery: We still can do better. ANESTHESIOLOGY 2012; 117:454–5.

general anesthesia to sedation); 75 patients were admitted to the center overnight (*e.g.*, because they had obstructive sleep apnea or they lived too far away to go home late in the evening); 16 had medical complications (*e.g.*, they remained intubated and ventilated overnight); and 52 patients could not be reached for postoperative follow-up. This analysis is based on data from the 2,170 patients who completed the study.

Protocol

After informed consent was obtained, relevant preoperative, intraoperative, and postoperative data were collected on standardized forms by trained study personnel. As participants in a cohort study, all patients received standard of care (including use of prophylactic antiemetics perioperatively and postdischarge) according to the patients' local clinical care teams. The patients' experience of nausea and/or vomiting was assessed 30, 60, and 120 min after surgery by trained study personnel. At discharge from the hospital, all patients were instructed to enter their experiences of nausea and/or vomiting into a standardized diary. Information entered into the diary was obtained during a telephone interview on the afternoon or evening of the first and second days following surgery, *i.e.*, at least 24 and 48 h after emergence from anesthesia.

Outcome Measures and Endpoints

Nausea was measured using the clinically standard, 11-point verbal rating scale, for which 0 represents "no nausea" and 10 represents "worst nausea imaginable." Vomiting was quantified as the number of emetic episodes occurring at least 1 min apart during a given time interval. Severe nausea was defined as nausea of 7 or greater on the verbal rating scale, and severe vomiting was defined as three or more emetic episodes during a given time interval. Retching was recorded separately but included with vomiting in the analysis because it involves the same reflex, the only difference being that no gastric content is expelled.

The primary outcome was the proportion of patients with nausea and/or vomiting and/or retching after discharge from the hospital until 48 h after emergence from anesthesia (PDNV). Secondary outcomes were the: (A) proportion of patients with vomiting and/or retching after discharge from the hospital; (B) proportion of patients with nausea after discharge from the hospital; (C) proportion of patients with postoperative nausea and/or vomiting and/or retching in the PACU (PONV); (D) severity of nausea before and after discharge from the hospital; and (E) severity of vomiting before and after discharge from the hospital.

Statistical Analysis

Sample Size Estimation. We expected about 20% of patients to develop PDNV, and the odds ratios (ORs) of risk factors to be in the range of about 2.0.[12,16] To have 80% power at a two-sided P of 0.05 would require 1,486 patients.[17] However, after adjustment for a multiple correlation coefficient of $R^2 = 0.25$ with other covariates, a total of 1,982 patients would be required.[17] We planned to enroll approximately 2,000 patients and, in order to account for some patients not completing the study, we planned to obtain consent from about 20% more patients, for a total of approximately 2,400 patients.

Analysis. After all data were verified and the database was locked, the following steps were taken:

1. Raw incidences and unadjusted ORs according to outcomes and time intervals were calculated.
2. We used data from all but the highest enrolling non-UCSF center as our development cohort. Logistic regression analyses were applied to identify independent predictors for nausea and vomiting for both time intervals, *i.e.*, in the PACU and postdischarge. We investigated a wide range of independent predictors, primarily those that have been shown to be associated with PONV as well as others that have been suspected to influence nausea and/or vomiting: patient-specific variables (female gender, young age, nonsmoking, history of PONV, history of motion sickness, concomitant medications, preexisting diseases); intraoperative variables (use of volatile anesthetics, type and dose of narcotics, supplemental electrolyte infusion, antibiotics, duration of anesthesia, type of surgery, antiemetics including use of glucocorticoids); and postoperative variables (postoperative type and dose of narcotics, incidence of nausea and/or vomiting in the PACU, crystalloid infusion, time and type of first drink and first food intake, time and length of ride home, home activities, and postoperative pain). All narcotic doses were converted to morphine equivalent units.[18]
3. In stepwise forward logistic regression analysis, coefficients of statistically significant independent predictors were calculated and used in the development of a predictive model for PONV in the PACU and for PDNV in ambulatory patients. In our analysis, we used an inclusion threshold of less than 0.05 and an exclusion threshold of more than 0.1, using a forward conditional test for removal. Subsequently, the area under the receiver operating characteristic curve (ROC-AUC) was determined.
4. Next, a simplified risk score was developed by assigning one point to each of the identified independent predictors. We tested the hypothesis that there would be less than a 0.05 absolute difference between the ROC-AUC of the simplified score and that of the coefficient-based prediction model developed in the previous step. It is important to note that the 0.05 absolute difference was chosen as a threshold of clinical relevance, not statistical significance.
5. To validate the simplified score, we determined the ROC-AUC with the data of the highest-enrolling non-UCSF center, and defined a valid score as having an ROC-AUC within 0.05 of that for the development

Table 1. Patient Characteristics, Anesthesia, and Surgery

Patient Characteristics	Total Population (No. 2,170): Overall	Development Dataset (No. 1,913): Evaluation	Validation Dataset (No. 257): Validation
Age (years)	49.5 ± 15.4 (2,169)	50.2 ± 15.4 (1,913)	44.8 ± 14.6 (256)
Females	64.7 (1,404/2,170)	65.9 (1,260/1,913)	56.0 (144/257)
Ethnicity			
Caucasian	73.5 (1,595/2,170)	73.6 (1,408/1,913)	72.8 (187/257)
African-American	9.6 (209/2,170)	9.7 (185/1,913)	9.3 (24/257)
Latino	5.1 (111/2,170)	5.5 (106/1,913)	1.9 (5/257)
Asian	3.2 (69/2,170)	3.6 (69/1,913)	0.0 (0/257)
Other	8.6 (186/2,170)	7.6 (145/1,913)	16.0 (41/257)
BMI (kg/m^2)	28.3 ± 6.9 (2,157)	28.3 ± 6.8 (1,913)	28.5 ± 7.2 (256)
Nonsmoker	84.8 (1,840/2,170)	85.3 (1,631/1,913)	81.3 (209/257)
History of PONV	29.3 (636/2,170)	29.5 (565/1,913)	27.6 (71/257)
History of motion sickness	25.3 (550/2,170)	25.1 (481/1,913)	26.8 (69/257)
History of migraine	23.4 (508/2,169)	22.2 (425/1,912)	32.3 (83/257)
with nausea	15.6 (338/2,169)	14.6 (279/1,912)	23.0 (59/257)
ASA status	2.0 ± 0.63 (2,169)	2.0 ± 0.62 (1,912)	1.8 ± 0.63 (257)
Drinks per week	2.5 ± 5.0 (2045)	2.5 ± 5.1 (1,796)	2.2 ± 3.6 (249)
Anesthesia			
Inhalational Agents			
Sevoflurane	66.4 (1,386/2,088)	60.8 (1,164/1,842)	86.4 (222/246)
Desflurane	32.3 (674/2,088)	34.1 (652/1,842)	8.6 (22/246)
Isoflurane	1.3 (28/2,088)	1.4 (26/1,842)	0.8 (2/246)
Opioid Analgesics	95.4 (2071/2,170)	95.9 (1,835/1,913)	91.8 (236/257)
Morphine equivalences (mg)	15.1 ± 10.9 (2,071)	16.3 ± 10.8 (1,835)	14.3 ± 8.8 (236)
Fentanyl (mcg)	141 ± 96 (1,981)	146.4 ± 95 (1,789)	103.5 ± 92 (192)
Prophylactic Antiemetics			
Serotonin antagonists	77.4 (1,680/2,170)	77.7 (1,487/1,913)	75.9 (195/257)
Dexamethasone	48.0 (1,041/2,170)	45.6 (872/1,913)	65.8 (169/257)
Dopamine antagonists	12.9 (280/2,170)	13.4 (256/1,913)	8.6 (22/257)
Histamine antagonists	2.5 (55/2,170)	2.7 (51/1,913)	1.6 (4/257)
Surgery	**Overall**	**Development**	**Validation**
Procedure			
Breast surgery	10.3 (223/2,170)	10.7 (204/1,913)	7.4 (19/257)
Cholecystectomy	4.4 (96/2,170)	5.0 (96/1,913)	0.0 (0/257)
Hernia	4.2 (90/2,170)	4.7 (89/1,913)	0.4 (1/257)
Gynecologic	11.0 (238/2,170)	12.1 (231/1,913)	2.7 (7/257)
Dilatation & curettage	8.4 (183/2,170)	9.1 (174/1,913)	3.5 (9/257)
Cystoscopy	6.0 (131/2,170)	6.8 (131/1,913)	0.0 (0/257)
Prostate	3.6 (78/2,170)	4.1 (78/1,913)	0.0 (0/257)
ENT	8.6 (186/2,170)	8.7 (167/1,913)	7.4 (19/257)
Orthopedic	6.1 (132/2,170)	5.5 (106/1,913)	10.1 (26/257)
Knee arthroscopy	10.7 (231/2,170)	8.1 (154/1,913)	30.0 (77/257)
Upper extremity	6.5 (141/2,170)	5.0 (96/1,913)	17.5 (45/257)
General	20.3 (441/2,170)	20.2 (387/1,913)	21.0 (54/257)
Surgical Approach			
Arthroscopy	14.1 (305/2,170)	10.5 (200/1,913)	40.9 (105/257)
Endoscopy	20.8 (451/2,170)	22.7 (434/1,913)	6.6 (17/257)
Laparoscopy	13.2 (287/2,170)	14.8 (284/1,913)	1.2 (3/257)
Conventional	51.9 (1,127/2,170)	52.0 (995/1,913)	51.4 (132/257)
OR time (hours)	1.67 ± 0.86 (2,169)	1.66 (1,912)	1.79 (257)
Duration of surgery (hours)	1.10 ± 0.76 (2,168)	1.03 (1,911)	1.26 (257)
Postanesthesia Care Unit			
Opioids	63.3 (1,374/2,170)	62.7 (1,200/1,913)	67.7 (174/257)
Morphine equivalence (mg)	9.4 ± 11.4 (1,374)	9.25 ± 11.4 (1,200)	10.14 ± 11.1 (174)
Fentanyl (mcg)	35.2 ± 53.4 (901)	32.7 ± 52.0 (739)	54.4 ± 59.6 (162)
Antiemetics			
Serotonin antagonists	9.4 (203/2,170)	9.4 (179/1,913)	9.3 (24/257)
Dexamethasone	0.6 (12/2,170)	0.6 (11/1,913)	0.4 (1/257)
Dopamine antagonists	3.3 (71/2,170)	3.6 (69/1,913)	0.8 (2/257)
Histamine antagonists	9.3 (202/2,170)	9.1 (175/1,913)	10.5 (27/257)

(*continued*)

Table 1. Continued

Surgery	Overall	Development	Validation
Prophylactic Antiemetics	4.3 (93/2,170)	4.6 (88/1,913)	1.9 (5/257)
Rescue Antiemetics	13.5 (293/2,170)	13.4 (256/1,913)	14.4 (37/257)
Length of PACU stay (h:min) (95% CI)			
No PONV	2:20 [2:17–2:23]	2:23 [2:19–2:26]	2:03 [1:56–2:09]
Nausea only	2:56 [2:48–3:03]	3:00 [2:52–3:09]	2:24 [2:12–2:37]
Vomiting	3:18 [3:02–3:34]	3:31 [3:15–3:46]	2:46 [1:03–4:29]
PONV	3:02 [2:55–3:09]	3:06 [2:59–3:14]	2:26 [2:14–2:38]

Values are percentages or means with standard deviations unless specified otherwise.

ASA = American Society of Anesthesiologists; BMI = body mass index; ENT = ears, nose, and throat; OR = operating room; PACU = postanesthesia care unit; PONV = postoperative nausea and/or vomiting.

dataset. Furthermore, we plotted corresponding incidences for any nausea, moderate, severe nausea, and for any vomiting and severe vomiting.

6. In addition, to explore whether the use of a new simplified PDNV risk score could significantly improve the clinician's ability to predict PDNV compared with established PONV risk scores, we determined the ROC-AUC of the highest-enrolling non-UCSF center for both the simplified PDNV score and the simplified PONV score. We defined an absolute difference of 0.05 as a clinically relevant improvement in prediction.

Analyses were conducted using SPSS version 19 (SPSS Inc., Chicago, IL) and STATA Intercooled version 10 (StataCorp LP, College Station, TX).

Results

The average age of outpatients studied was 49.5 yr; 64.7% were women, 84.8% were nonsmokers, and 29.3% had a history of PONV (table 1). The four largest surgical groups were general surgery (20.3%), gynecological surgery (11.0%), knee arthroscopy (10.7%), and breast surgery (10.3%), together accounting for more than 50% of all surgeries conducted. Although none of the centers used propofol-based total intravenous anesthesia, some patients received propofol doses of 100–400 mg (n = 752) and more than 400 mg (n = 130) as an additional infusion or as boluses. Among all patients, 66.4% received sevoflurane and 77.4% received a prophylactic serotonin antagonist; all but two patients who received a prophylactic serotonin antagonist received ondansetron. Furthermore, 749 patients (34.5%) and 262 (12.1%) received two and three intraoperative antiemetics, respectively.

1. In the PACU, 19.9% of patients had nausea, 3.9% had vomiting, and 20.7% had nausea and/or vomiting (fig. 1, table 2). After discharge, 36.6% had nausea, 11.9% had vomiting, 37.1% had nausea and/or vomiting, 13.3% had severe nausea, and 5.0% had severe vomiting (fig. 1).
2. In the development dataset (n = 1,913), stepwise forward logistic regression analysis showed that female gender, age less than 50 yr, history of PONV, duration of surgery more than 1 h, 125 or more mcg fentanyl, ondansetron, arthroscopy, laparoscopy, and opioids administered in the PACU were statistically significant independent pre-

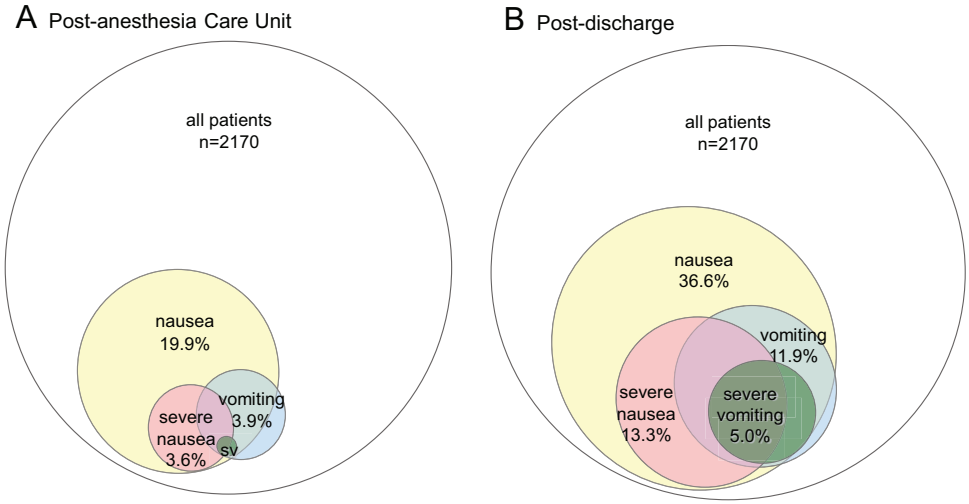

Fig. 1. Percentage of patients who experienced nausea and/or vomiting (*A*) in the postanesthesia care unit and (*B*) postdischarge. The incidence of severe vomiting (SV) in the postansesthesia care unit was 0.2%.

Table 2. Percentage of Patients in Each Time Interval Who Experienced Nausea and/or Vomiting

Postanesthesia Care Unit	Day Postsurgery	Postoperative Day 1	Postoperative Day 2	Nausea	Vomiting	Nausea and/or Vomiting
PACU				19.9	3.9	20.7
	DPS			28.8	8.5	28.8
		POD1		18.3	3.9	18.4
			POD2	12.4	2.1	12.5
Day of Surgery				38.0	10.8	38.7
Postoperative period until POD1				42.1	13.1	42.8
Postoperative period until POD2				44.1	14.2	44.8
	Postdischarge until POD1			34.1	10.8	34.4
	Postdischarge until POD2			36.6	11.9	37.1

DPS = day postsurgery; PACU = postanesthesia care unit; POD1 = postoperative day 1; POD2 = postoperative day 2.

dictors for nausea and/or vomiting in the PACU (table 3, fig. 2). After discharge, *i.e.*, for PDNV, statistically significant independent predictors were female gender, age less than 50 yr, history of PONV, opioids in the PACU, and nausea in the PACU, but not nonsmoking status or ondansetron (table 4). Risk factors (*e.g.*, history of motion sickness or migraine, American Society of Anesthesiologists physical status, drinking status, adjuvant peripheral nerve block) that were not statistically significant are not listed in tables 3 and 4.

3. During the stepwise forward logistic regression analysis, five factors were shown to predict the patient's risk of PDNV. According to this analysis, the patient's risk for PDNV could be estimated by $p = 1/(1+e^{-z})$, in which P is the probability that PDNV will occur and z = 0.43 (if female) + 0.77 (if age less than 50 yrs) +

Table 3. Incidences with Bivariate and Multivariate Odds Ratios for Factors that Potentially Influence PONV in the PACU in the Development Dataset (Patients, No. 1,913)

	Variables	Incidence (%)	Unadjusted OR (95% CI)	Adjusted OR (95% CI)	*P* Value
Patient characteristics	Gender, female/male	25.2/12.1	2.45 (1.88–3.20)	2.19 (1.63–2.95)	<0.001
	Age, younger than 50/50 yr or older	27.2/14.4	2.22 (1.77–2.80)	1.79 (1.39–2.30)	<0.001
	History of PONV, yes/no	27.4/18.0	1.73 (1.37–2.18)	1.43 (1.11–1.84)	0.006
	Non-smoking, yes/no	21.2/18.1	1.22 (0.88–1.69)	—	
Intraoperative variables	Surgery, 1 h or more/Less than 1 h	27.0/16.4	1.89 (1.51–2.37)	1.83 (1.41–2.38)	<0.001
	Fentanyl, 125 mcg or more/Less than 125 mcg	25.0/15.7	1.79 (1.42–2.26)	1.48 (1.13–1.92)	0.004
	Ondansetron, yes/no	20.8/20.7	1.01 (0.77–1.31)	0.70 (0.52–0.94)	0.017
	Glucocorticoids, yes/no	23.2/18.6	1.32 (1.06–1.65)	—	
Surgery	Breast	16.7	0.82 (0.52–1.28)	—	
	Cholecystectomy	40.6	2.80 (1.74–4.52)	—	
	Cystoscopy	9.2	0.41 (0.22–0.79)	—	
	Dilatation & Curettage	19.5	0.99 (0.63–1.56)	—	
	ENT	22.2	1.17 (0.75–1.81)	—	
	Other gynecologic	26.8	1.50 (1.02–2.20)	—	
	Hernia	19.1	0.97 (0.54–1.73)	—	
	Knee arthroscopy	26.0	1.44 (0.93–2.23)	—	
	Other orthopedic	17.0	0.84 (0.48–1.47)	—	
	Prostate	7.7	0.34 (0.14–0.81)	—	
	Upper extremity	22.9	1.22 (0.71–2.08)	—	
	General surgery	19.6	1.00 (Reference)	—	
Approach	Arthroscopic	26.0	1.72 (1.20–2.45)	1.97 (1.33–2.91)	0.001
	Endoscopic	15.7	0.91 (0.67–1.24)	1.13 (0.81–1.58)	0.47
	Laparoscopic	38.0	3.00 (2.24–4.01)	2.39 (1.72–3.34)	<0.001
	Conventional	17.0	1.00 (Reference)	—	
Postoperative	Opioids in PACU (yes/no)	25.4/12.9	2.30 (1.78–2.97)	1.51 (1.14–2.01)	0.005

Adjusted odds ratios for variables that were not statistically significant, and thus not included in the model, are indicated by a dash. 5-HT_3 = 5-hydroxytryptamine type 3; ENT = ears, nose, and throat; OR = odds ratio; PACU = postanesthesia care unit; PONV = postoperative nausea and/or vomiting.

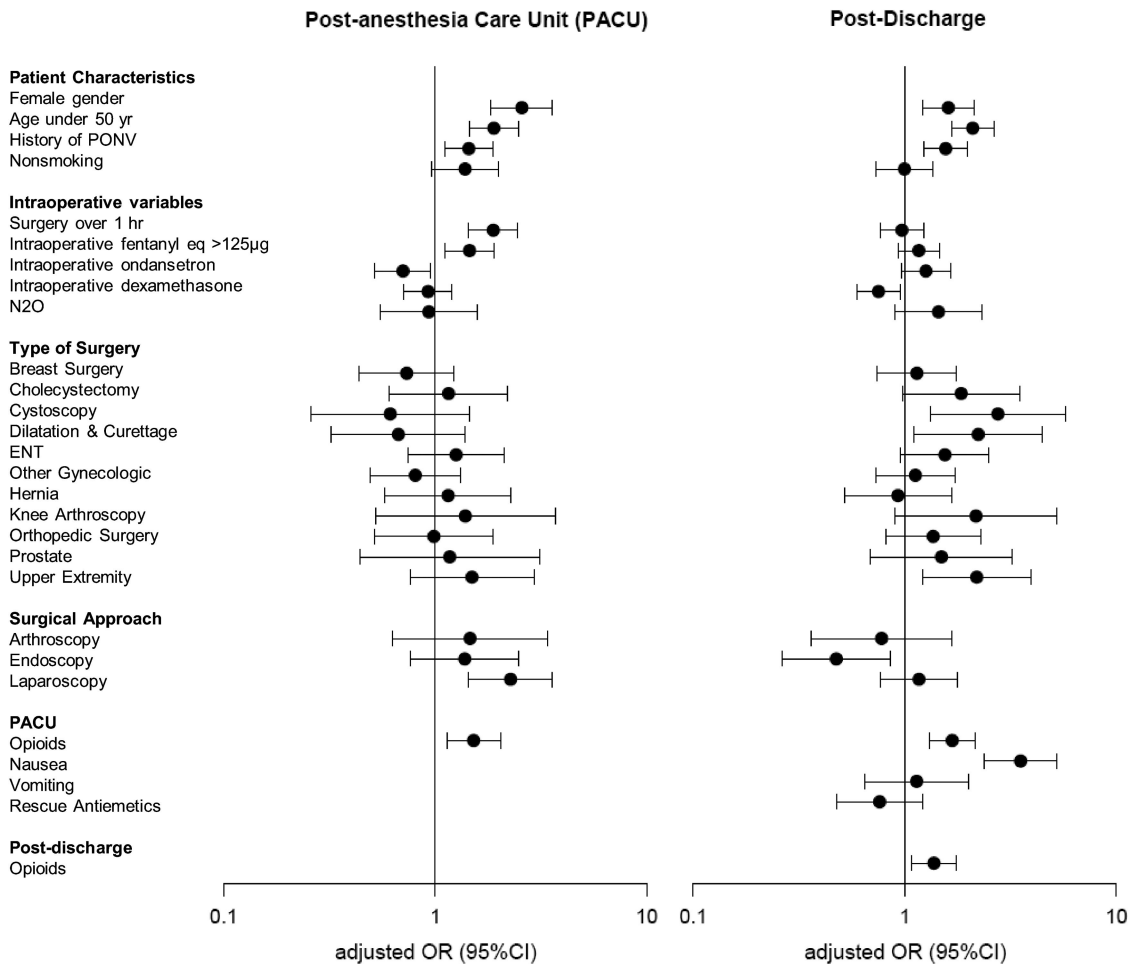

Fig. 2. Adjusted odds ratios (OR) from multiple logistic regression analysis for nausea and/or vomiting in the postanesthesia care unit (PACU) and postdischarge in the evaluation dataset. ENT = ears, nose, and throat; N_2O = nitrous oxide; PONV = postoperative nausea and vomiting.

0.41 (if history of PONV) + 0.66 (if opioids were needed in the PACU) + 1.14 (if nauseated in the PACU) − 2.42. The prediction model based on these coefficients had an ROC-AUC (95% CI) of 0.737 (0.715 to 0.759; fig. 3).

4. A simplified risk score in which each factor counted as one point led to an ROC-AUC of 0.706 (0.681 to 0.730; fig. 3). The absolute difference between 0.737 and 0.706 was less than the predefined clinically relevant absolute difference of 0.05. Furthermore, the ROC-AUC of the simplified PONV score – which was previously developed for inpatients in Europe – was only 0.630 (0.603 to 0.656). According to this simplified PDNV score, when zero, one, two, three, four, or five of these five risk factors was present, the associated PDNV incidences were 10.9%, 18.3%, 30.5%, 48.7%, 58.5%, or 79.7%, respectively. In addition, when patients were grouped according to their predicted risk into six groups based on the five predictors, the calibration plot of the predicted and actual incidences of PDNV resulted in a calibration line having a slope of 0.942 and an intercept of 0.006 (fig. 4A).
5. In the validation cohort (n = 257), when patients were grouped according to their predicted risk into six groups, the calibration plot of the predicted and actual incidences of PDNV resulted in a calibration line having a slope of 1.075 and an intercept of negative 0.044 (fig. 4B). The ROC-AUC of the simplified risk score was 0.721 (0.657 to 0.785; fig. 5) in the validation cohort. Figure 6 displays the incidences for any nausea, moderate, severe nausea, and for any vomiting and severe vomiting. Note that the ROC-AUC of the smaller validation dataset was higher than the ROC-AUC of the development dataset, and that the incidences differ somewhat from the PDNV incidences of the development dataset listed in point 4, which reflects typical random variation.
6. The ROC-AUC of the simplified PONV score in the validation cohort was 0.674 (0.607 to 0.741; fig. 5). With a sample size of 257, the validation cohort was too small to detect whether there was a statistically significant difference between the ROC-AUCs of the simplified PDNV score and the simplified PONV score. However, there was an absolute difference of 0.047 between the ROC-

Table 4. Incidences with Unadjusted and Adjusted Odds Ratios with 95% CIs for Variables that Potentially Influence PDNV in the Development Dataset

	Variables	Incidence (%)	Unadjusted OR (95% CI)	Adjusted OR (95% CI)	*P* Value
Patient characteristics	Gender, female/male	42.6/26.0	2.11 (1.72–2.60)	1.54 (1.22–1.94)	<0.001
	Age, younger than 50/50 yr or older	46.9/27.1	2.38 (1.97–2.88)	2.17 (1.75–2.69)	<0.001
	History of PONV, yes/no	46.7/32.9	1.79 (1.47–2.19)	1.50 (1.19–1.88)	<0.001
	Non-smoking, yes/no	36.6/39.0	0.90 (0.70–1.17)	—	
Intraoperative variables	Surgery, 1 h or more/Less than 1 h	38.6/35.8	1.13 (0.93–1.36)	—	
	Fentanyl, 125 mcg or more/ Less than 125 mcg	41.2/31.8	1.51 (1.25–1.82)	—	
	Ondansetron, yes/no	38.2/32.6	1.28 (1.02–1.60)	—	
	Glucocorticoids, yes/no	37.8/36.2	1.07 (0.89–1.29)	—	
Surgery	Breast	35.9	0.57 (0.36–0.91)	—	
	Cholecystectomy	65.6	1.31 (0.78–2.18)	—	
	Cystoscopy	27.5	0.81 (0.46–1.43)	—	
	Dilatation & Curettage	37.9	0.75 (0.46–1.23)	—	
	ENT	34.7	2.56 (1.43–4.60)	—	
	Other gynecologic	42.9	0.51 (0.29–0.89)	—	
	Hernia	31.5	0.82 (0.49–1.36)	—	
	Knee arthroscopy	49.4	0.71 (0.43–1.19)	—	
	Other orthopedic	37.7	1.01 (0.62–1.63	—	
	Prostate	14.1	0.22 (0.10–0.47)	—	
	Upper extremity	42.7	0.62 (0.34–1.13)	—	
	General surgery	30.0	1.00 (Reference)	—	
Approach	Arthroscopic	47.5	0.48 (0.37–0.63)	—	
	Endoscopic	28.3	0.83 (0.58–1.19)	—	
	Laparoscopic	52.1	0.36 (0.27–0.50)	—	
	Conventional	34.3	1.00 (Reference)	—	
Postoperative	Opioids in PACU (yes/no)	44.4/24.4	2.48 (2.02–3.04)	1.93 (1.53–2.43)	<0.001
	Nausea in PACU (yes/no)	62.5/30.5	3.79 (3.00–4.79)	3.14 (2.44–4.04)	<0.001
	Vomiting in PACU (yes/no)	63.8/35.8	3.16 (1.98–5.03)	—	
	Rescue in PACU (yes/no)	62.1/33.1	3.32 (2.53–4.36)	—	
	Opioids post discharge (y/n)	42.9/27.0	2.04 (1.67–2.49)	—	

Adjusted odds ratios for variables that were not statistically significant, and thus not included in the model, are indicated by a dash. 5-HT_3 = 5-hydroxytryptamine type 3; ENT = ears, nose, and throat; OR = odds ratio; PACU = postanesthesia care unit; PDNV = postdischarge nausea and/or vomiting PONV = postoperative nausea and/or vomiting.

AUCs of the two risk scores, which was very close to our 0.05 threshold for clinical relevance.

Discussion

In this large, multicenter cohort study, 37.1% of patients had PDNV, 13.3% had severe nausea, 11.9% had vomiting, and 5% had severe vomiting. These incidences were significantly higher than expected, especially given the patient and surgery profile of ambulatory procedures, as well as the relatively low incidence of PONV in the PACU (fig. 1, table 2). Considering that about one third of the approximately 35 million ambulatory surgeries performed in the United States annually use general anesthesia,[15] these findings translate into approximately 4.3 million patients experiencing PDNV every year.

The high incidence shown in our study is almost identical to the 35% incidence reported in a study of 154 ambulatory surgery patients conducted in the United States more than a decade ago.[14] Although the incidence of PDNV in a Canadian study was only 9.1%,[19] several factors may have contributed to this relatively low incidence. For example, PONV is triggered primarily by inhalational anesthetics and opioids used for general anesthesia,[13] and it is well-known that using a peripheral regional nerve block instead of general anesthesia significantly reduces the likelihood of PONV.[20] Although all patients enrolled in our study underwent general anesthesia, about half of the patients in the Canadian study received a regional nerve block or monitored anesthesia care. Furthermore, in the Canadian study, many patients who did receive general anesthesia underwent very brief procedures like dilation and curettage, and therefore received only intravenous propofol for maintenance instead of inhalational anesthetics.

The incidence and severity of PDNV after ambulatory surgery with general anesthesia appears to have been greatly underestimated, most likely because PONV in the PACU is less frequent and rarely severe for outpatients compared to inpatients. In our study, only 3.6% of outpatients had severe nausea and 0.2% had severe vomiting in the PACU, com-

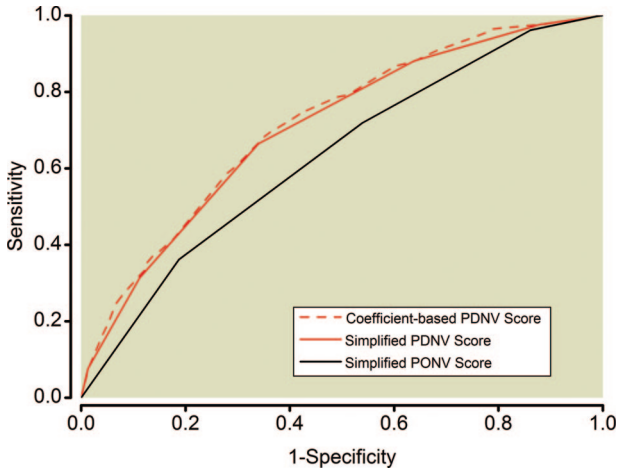

Fig. 3. Receiver operating characteristic curves of the coefficient-based postdischarge nausea and/or vomiting (PDNV) prediction model, simplified PDNV risk score, and simplified postoperative nausea and vomiting (PONV) risk score[12] in the development dataset.

pared with 13.3% who had severe nausea and 5.0% who had severe vomiting postdischarge (fig. 1). Indeed, despite the high incidence of PDNV, only 4.4% of patients in our study received antiemetic prophylaxis acting long enough to prevent PDNV before they were discharged from the ambulatory care center – regardless of their risk for PDNV.

Risk Factors and Independent Predictors

Risk Factors for Nausea and/or Vomiting in the PACU. The risk factors for PONV in the PACU identified in this cohort study are consistent with those previously reported for inpatients.[12,16,21,22] Patient-specific independent predictors were female gender, age less than 50 yr, and history of PONV. Anesthesia- and surgery-specific factors were higher doses of intraoperative and postoperative opioids, duration of surgery more than 1 h, and a laparoscopic surgical approach. Although cholecystectomies were associated with the highest incidence of PONV in the PACU (table 2), the multivariable analysis suggests that this was because of the predominantly laparoscopic approach, so that type of surgery no longer reached statistical significance (table 3, fig. 2).

Risk Factors for Postdischarge Nausea and/or Vomiting. Although the patient-specific risk factors of female gender, age less than 50 yr, and history of PONV were predictors for both PONV in the PACU and PDNV, nonsmoking status was not an independent predictor for PDNV. The lower incidence of PONV in the PACU in smokers is probably not because of an acute antiemetic effect of nicotine. In fact, the use of the nicotine patch has been shown to increase, not prevent, nausea[23]; its use has never been associated with a reduced incidence of PONV.[24] Instead, smokers may have adapted to nicotine-induced and γ-aminobutyric acid-mediated increases of intrasynaptic dopamine release, and are thus likely to have relatively lower dopamine levels immediately after surgery. Similar

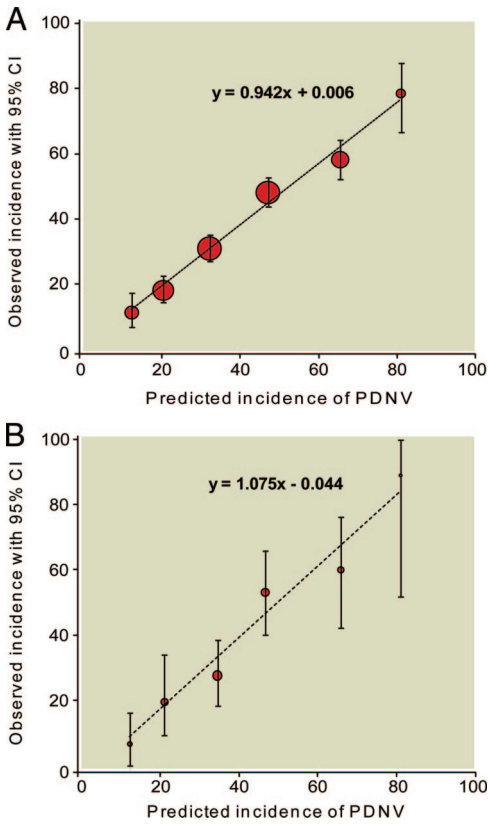

Fig. 4. Calibration plot of the predicted and actual incidences of postdischarge nausea and vomiting (PDNV) with 95% CI in (*A*) the development dataset and (*B*) the validation dataset. The predicted risk is based on the analysis of 1,913 patients in the development dataset, and applied to the incidences of 257 patients in the evaluation dataset. The circle area of the data points is proportional to the sample size of each risk classification group.

to the antiemetic effect of dopamine receptor antagonists like metoclopramide,[25] reduced dopaminergic stimulation may have protective effects that disappear after patients are discharged and resume smoking.

Another difference between risk factors for PONV in the PACU and PDNV is that surgical approach was not statistically significant for PDNV. Considering that this statistical significance observed for PONV in the PACU came primarily from the increased incidence after laparoscopy, it is possible that increased arterial carbon dioxide and HCO_3 levels associated with laparoscopy may equilibrate in the PACU, so that this emetogenic effect is no longer relevant after patients are discharged.

The main difference between risk factors for PONV and PDNV was that patients who experienced nausea in the PACU had a 3-fold increased risk for PDNV.

Antiemetics. Contrary to previous thoughts,[26] ondansetron is equally efficacious against nausea as it is against vomiting, with an OR of 0.68[27,28] similar to the 0.70 OR in this multicenter study. However, intraoperatively administered ondansetron did not reduce the risk of PDNV (fig. 2), most likely because of its short plasma half-life of about 3 h. In fact,

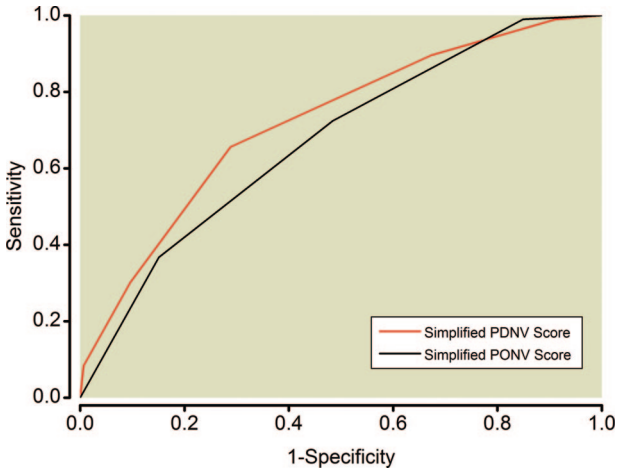

Fig. 5. Receiver operating characteristic curves of the established simplified postoperative nausea and vomiting (PONV) risk score and the new simplified postdischarge nausea and vomiting (PDNV) risk score in the validation dataset.

patients who received ondansetron had a somewhat higher risk for PDNV, which almost looks like a rebound effect (fig. 2). Almost half of all patients received intraoperative dexamethasone (table 1). Glucocorticoids did not appear to reduce PONV in the PACU but significantly reduced PDNV (fig. 2).

Several studies have reported that propofol has an antiemetic effect at subhypnotic doses.[29–31] However, Scuderi *et al.* were unable to demonstrate such effects at similar concentrations,[32] and Hvarfner *et al.* suggest that the antiemetic effect of propofol is detectable only with concurrent sedation,[33] in which case the effect is similar to that of lorazepam. Furthermore, given the short half-life of propofol, and the similarity between total intravenous anesthesia and inhalational anesthesia in the late postoperative period,[13] total intravenous anesthesia does not appear to be a substitute for an effective antiemetic for PDNV.

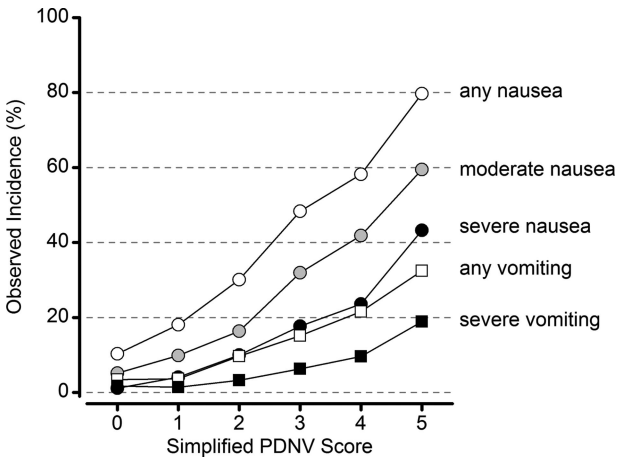

Fig. 6. Relationship between the simplified postdischarge nausea and vomiting (PDNV) risk score and the incidence of PDNV in the validation dataset.

Prediction Model for PDNV

The five statistically significant independent risk factors for PDNV were female gender, age less than 50 yr, history of PONV, opioids administered in the PACU, and nausea in the PACU. We used the coefficients of these factors to create a prediction model for PDNV with an acceptable discriminating power of an ROC-AUC curve of 0.74. However, for practical purposes, simplifying the calculation to one point for every risk factor present permits a risk prediction with an ROC-AUC curve of 0.72, which we consider clinically similar to that of the more complex calculation. To make the prediction model even simpler to remember, the incidence of PDNV was approximately 10%, 20%, 30%, 50%, 60%, or 80% when zero, one, two, three, four, or five of the independent risk factors were present, respectively. It is interesting that – even though the risk factors for nausea and for vomiting apparently were not identical – those factors also give a rough estimate of patients' risk for vomiting or severe nausea after being discharged home, which is about one third of their risk for PDNV in general. Moreover, the risk for severe vomiting after discharge can be estimated to be about half the risk for severe nausea or vomiting in general. Thus, the risk for severe vomiting is about one sixth of the risk for PDNV in general.

Because the size of the validation cohort was only 257 patients, future studies conducted by independent investigators at other centers will be needed to confirm the value of our newly developed PDNV score. However, considering that this simplified score was based on data from 12 centers across the United States, and that the ROC-AUC of the validation cohort was quite similar to that of the development cohort, it is fair to assume that this score will have a reasonable degree of external validity in other centers. Furthermore, because the absolute difference between the ROC-AUCs of the simplified PONV and PDNV scores was about 0.05, we believe that the use of a new risk score specific to outpatients is warranted, even though the validation cohort was not actually sufficiently powered to detect a statistically significant difference between the two simplified scores. However, a difference would not be surprising given that our simplified PONV score was developed in European inpatients for PONV through 24 h, whereas our PDNV score was developed in U.S. outpatients for PDNV through 48 h. Because of differences in length of the procedure, exposure to anesthetics, patient mobility and access to cigarettes, some of the predictors – likely the triggers – are different for PONV and PDNV.

Based on the results from the validation cohort, the use of our simplified PDNV risk score is useful to identify at-risk patients who are likely to benefit from long-acting prophylactic antiemetics like dexamethasone, aprepitant, palonosetron, and transdermal scopolamine, either alone or in combination. However, the efficacy of these agents for PDNV needs to be confirmed in future studies.

Conclusions

PDNV is a common and sometimes severe adverse outcome for ambulatory patients. By identifying the five most important independent predictors – female gender, age less than 50 yr, history of PONV, opioids administered in the PACU, and nausea in the PACU – we developed a new risk score for estimating the individual patient's risk of PDNV. The incidence of PDNV is approximately 10%, 20%, 30%, 50%, 60%, or 80% when zero, one, two, three, four, or five of these predictors are present, respectively. Clinicians whose patients undergo general anesthesia for ambulatory surgery might find this information useful when making decisions about the need for prophylactic antiemetics before patients are discharged from the hospital.

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