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SCIENTIFIC ARTICLE

Development of a multivariable predictive model for postoperative nausea and vomiting after cancer surgery in adults☆

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KEYWORDS
Postoperative nausea and vomiting;
Multivariable model;
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Abstract
Background and objectives: Predicting postoperative nausea and vomiting risk is the cornerstone for deciding prophylaxis. Apfel's score does not define how long a person must be abstinent from smoking to be considered a non-smoker, and the use of intraoperative spinal opioids as a risk factor for predicting postoperative nausea and vomiting is also not addressed. The aim of this study was to quantify predicting postoperative nausea and vomiting risk by an ordinal smoking status and the use of intraoperative opioids (systemic or neuraxial), and to develop a new predictive model.
Methods: Patients scheduled for cancer surgery were prospectively evaluated for predicting postoperative nausea and vomiting in the first 24 h after surgery.
Results: Of 2014 initially included patients, 185 participants were excluded. Smoking status classification was associated with predicting postoperative nausea and vomiting incidence rates of 14.1%, 18.1%, 24.7%, 29.4% and 33.9% for smokers, patients who stopped smoking up to 1 month prior to surgery, one to 6 months prior, more than 6 months prior or patients who never smoked, respectively, which was significant in the multiple comparisons analysis (adjusted $p = 0.015$). The multiple comparisons-adjusted hypothesis tests for association with predicting postoperative nausea and vomiting for sex, age, previous predicting postoperative nausea and vomiting, chemotherapy-induced nausea, and ordinal smoking status had p-values of <0.001. The type of surgery ($p = 0.04$), total fentanyl consumption ($p = 0.04$), both intraoperative and postoperative, were significant predictors. A new model was developed and showed higher discriminative power than Apfel's score (AUC 67.9% vs. 63.7%, $p < 0.001$).

☆ Study conducted at Instituto do Câncer do Estado de São Paulo, São Paulo, SP, Brazil.

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Conclusion: Smoking status showed a significant and linear impact on predicting postoperative nausea and vomiting incidence, and we developed a new model that uses unambiguous smoking and opioid predictors.

PALAVRAS-CHAVE
Náusea e vômito no pós-operatório;
Modelo multivariado;
Câncer;
Tabagismo;
Prognóstico

Desenvolvimento de um modelo preditivo multivariado para náusea e vômito no pós-operatório de cirurgia oncológica em adultos

Resumo
Justificativa e objetivos: A previsão do risco de náusea e vômito no pós-operatório é a base para a decisão da profilaxia. O escore de Apfel não define por quanto tempo uma pessoa deve se abster de fumar para ser considerada não fumante, e o uso de opioide espinhal intraoperatório como fator de risco para náusea e vômito também não é abordado. Nosso objetivo foi quantificar o risco de náusea e vômito no pós-operatório por um estado tabagístico ordinal e o uso de opioides intraoperatórios (sistêmicos ou neuraxiais) e desenvolver um novo modelo preditivo.
Métodos: Pacientes agendados para cirurgia oncológica foram prospectivamente avaliados para náusea e vômito nas primeiras 24 horas após a cirurgia.
Resultados: De 2.014 pacientes inicialmente incluídos, 185 participantes foram excluídos. A classificação de tabagismo foi associada a taxas de incidência de náusea e vômito no pós-operatório de 14,1%, 18,1%, 24,7%, 29,4% e 33,9% para fumantes, pacientes que pararam de fumar até um mês antes da cirurgia, de um a seis meses antes da cirurgia, mais de seis meses antes da cirurgia ou pacientes que nunca fumaram, respectivamente, o que foi significativo na análise de comparações múltiplas ($p = 0,015$ ajustado). Os testes de hipóteses foram ajustadas para múltiplas comparações para associação com náusea e vômito no pós-operatório para sexo, idade, náusea e vômito no pós-operatório anterior, náusea induzida por quimioterapia e estado tabagístico ordinal apresentaram valores de $p < 0,001$. Tipo de cirurgia ($p = 0,04$), consumo total de fentanil ($p = 0,04$) e períodos intraoperatório e pós-operatório foram preditivos significativos. Um novo modelo foi desenvolvido e apresentou um poder discriminativo maior que o escore de Apfel (AUC 67,9% *vs.* 63,7%, $p < 0,001$).
Conclusão: O estado tabagístico mostrou um impacto significativo e linear sobre a incidência de náusea e vômito no pós-operatório e desenvolveu-se um novo modelo que usa preditores não ambíguos de tabagismo e opioides.

Introduction

The Society for Ambulatory Anesthesia published Guidelines for the Management of Postoperative Nausea and Vomiting, which aims to predict Postoperative Nausea and Vomiting (PONV) risk and suggests the main strategy to aid in deciding PONV prophylaxis without increasing costs or side effects.[1] Many prediction models have been proposed to date, but Apfel's heuristic is still the most used due to its simplicity and accuracy.[2]

Although commonly used for PONV risk assessment, Apfel's score is imprecise. First, the prediction of postoperative opioid use being true or false is vague, and it is not known how intraoperative opioids, systemic or neuraxial should be considered in calculating the score. Intraoperative opioids, compared to opioid-free anesthesia, probably play an important role in PONV. Neuraxial opioids have a long-lasting effect and might be associated with PONV. Additionally, dichotomising smoking as present or absent is ambiguous: is someone who never smoked at the same risk as someone who stopped smoking one or 6 months before surgery? What length of smoking abstinence in a patient who quit smoking is necessary for the presence of smoking to no longer be considered a PONV protective factor?

In our daily practice, Apfel's heuristic, although seemingly simple, sometimes raises more doubts and data inconsistency than it provides answers because data are collected more than once by more than one professional. In this data modelling study, we intended to select a model without ambiguities that would balance simplicity and accuracy.

Methods

The study was approved by the Ethics Committee of the Faculdade de Medicina da Universidade de São Paulo. Written informed consent was obtained from all subjects. Data

collection was performed prospectively between May 2014 and November 2015 in a tertiary oncological teaching hospital.

Patient selection

All consecutive patients scheduled for surgery in the oncological hospital were assessed for eligibility to participate in the study. Inclusion criteria: patients scheduled to medium or major surgeries, able to communicate in Portuguese and who had an absence of agitation or delirium. Patients who remained under mechanical ventilation after surgery or with incomplete data were excluded.

Data collection

An electronic record system designed for this research was modelled in the electronic patient record system. A specially trained team for research data acquisition composed of nurses and physicians collected data.

Primary outcome

PONV during the first 24 postoperative hours was the primary outcome. Patients were asked about PONV occurrence, and nurses' annotations and medical prescriptions were also checked for PONV or medications used to treat PONV.

Predictors

Smoking status (smoker, has stopped up to one month ago, has stopped between one and six months ago, has stopped for more than six months or has never smoked) was the main predictor of this study. Potential confounding factors, known as PONV predictors, identified in previous studies were also collected, including age, Apfel's score, sex, previous PONV, previous Chemotherapy-Induced Nausea and Vomiting (CINV), prediction of postoperative analgesia based on opioids, surgery, chronic opioid usage, anesthesia technique, neuraxial opioids, intraoperative opioids, ketamine, Post-Anesthesia Care Unit (PACU) tramadol, intraoperative antiemetics and postoperative antiemetics.

Study sample size and missing data

The study sample size was estimated based on our previous study and was not calculated.[3] Only complete cases were used for analysis.

Data analysis and hypothesis testing

Frequentist bivariate association hypothesis testing was performed for every predictor for PONV (dichotomic) using the Chi-squared test or Wilcoxon–Mann–Whitney Test. Multiple comparison analyses (Bonferroni and false discovery rate) were planned and performed, and both unadjusted and adjusted *p*-values are available.

Multivariable modelling and comparison

Multiple logistic regression selection using an exhaustive search for the lowest Akaike Information Criterion (AIC) model was performed. We selected AIC for the model because it balances the cost of prediction and the discriminative power. The Hosmer–Lemeshow test was used for testing each model's statistical significance. Another logistic regression using only Apfel's heuristic as a predictor was modelled for comparison. Models were compared using Delong's method.[4]

Results

The full code and database for data analysis is published in Rpubs (http://rpubs.com/gabrielmng/Leia2017b) and in the Mendeley Database (https://doi.org/10.17632/gsnj8vmgm2.1). There, a detailed table showing the results of the multiple comparison analysis (Bonferroni and False Discovery Rate) is presented.[5]

One hundred eighty-five patients (9.1%) were excluded from the study, and data from 1829 patients were analysed. The study flow chart is shown in Fig. 1, which shows the distribution of the main risk factors is detailed in Table 1. Table 2 shows the distribution of the types of surgeries and their associations with PONV. Table 3 shows the distribution and association of anesthetics and opioids used with PONV in the study population. Table 4 describes the use of intraoperative and postoperative prophylactic antiemetics and their associations with PONV in the study population.

Most classical PONV risk factors were confirmed in our sample (sex, age, previous postoperative PONV, postoperative opioid use and non-smoking). We confirmed that CINV is associated with an increase in PONV incidence (from 22.6% to 41.9%, $p = 0.00001$). The detailed history of smoking was also related to the occurrence of nausea and vomiting (Table 1 and Fig. 2). Surgeries were not strongly associated with PONV, except orthopaedic surgeries. Neuraxial opioid usage, intraoperative fentanyl dose, and PACU tramadol usage and dose were significantly associated with PONV. Dexamethasone (intraoperative and postoperative), dimenhydrinate (intraoperative) and metoclopramide (intraoperative) were the only antiemetics with a statistically significant association with PONV, but they were not confirmed after the multiple comparison analysis.

The new multivariable model selected smoking history, sex, age, previous CINV, previous PONV, neuraxial opioid usage and total intraoperative fentanyl dose as PONV predictors (Tables 5 and 6). Both the new model and Apfel's heuristics were significant ($p < 0.001$) by the Hosmer–Lemeshow Goodness of Fit test. Table 5 shows the logistic regression of the new model. The area under the Receiver Operating Characteristic (ROC) Curve (AUC) of the new model was 67.9%, and Apfel's AUC was 63.7%, with a significant difference in the discrimination power ($p < 0.001$) (Fig. 3). We show a table with sensitivities and specificities for important point estimates in the ROC curve in Table 7.

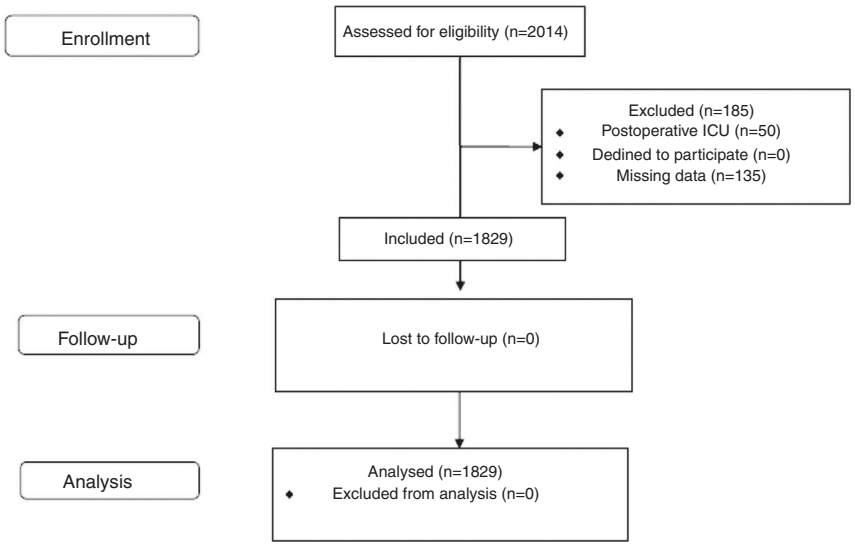

Figure 1 Study flow diagram.

Table 1 Distributions of the main risk factors. Data are presented in absolute number or as the mean (standard deviation).

Predictor	No PONV	PONV	PONV (%)	*p*-Value
Sex				<0.0001
Female	707	404	36.3%	
Male	559	159	22.1%	
Apfel score				<0.0001
0	52	8	13.3%	
1	219	57	20.6%	
2	534	168	23.9%	
3	379	217	36.4%	
1	82	113	57.9%	
Age (years)	58.5 (13.3)	55.5 (14.8)		0.0001
Previous PONV or motion sickness				<0.0001
No	1053	196	47.9%	
Yes	213	367	25.8%	
Postoperative opioids				0.03
No	367	135	26.9%	
Yes	899	428	32.2%	
Non-smoking				<0.0001
No	344	104	23.2%	
Yes	922	459	33.2%	
Chronic opioid user				0.78
No	1077	485	31%	
Yes	164	70	29.9%	
History of previous CINV				<0.0001
No previous chemotherapy	804	336	29.4%	
CINV	213	154	41.9%	
No CINV	249	73	22.6%	
When stopped smoking				<0.0001
Currently smoking	73	12	14.1%	
1 month of cessation	27	6	18.1%	
1–6 months of cessation	76	25	24.7%	
>6 months of cessation	412	172	29.4%	
Never smoked	678	348	33.9%	

Table 2 Surgery types and PONV incidence by surgery in our sample.

Surgery	Proportion %	No PONV	PONV	PONV (%)	*p*-Value
Gastrointestinal	29.4%	375	161	30%	0.5579
Breast	15.4%	191	90	32%	reference
Urologic	12.5%	155	74	32.3%	0.9452
Gynaecological	12.3%	145	80	35.5%	0.4040
Orthopaedic	7.5%	110	28	20.2%	0.0128
Thoracic	6.7%	85	37	30.3%	0.7357
Exploratory laparotomy	5.2%	71	25	26%	0.2723
Head and neck	1.7%	26	5	16.1%	0.0758
Other	9.3%	57	35	38%	0.2894

Table 3 Possible anesthesia-related predictors. Data are presented in absolute number or as the mean (standard deviation).

Anesthetic variable	No PONV	PONV	PONV %	*p*-Value
Neuraxial opioid				0.024
No	522	200	27.7%	
Yes	744	363	32.7%	
Remifentanil				0.35
No	1028	468	31.2%	
Yes	238	95	28.5%	
Continuous sufentanil				0.12
No	1257	554	30.5%	
Yes	9	9	50%	
Fentanyl total dose (mcg)	179 (252)	219 (294)		0.0058
Sufentanil total dose (mcg)	23.8 (52)	18 (29)		0.12
Intraoperative ketamine				0.063
No	1164	532	31.3%	
Yes	102	31	23.3%	
Ketamine dose (μg)	0.053	1.4 (7.6)		0.053
Intraoperative morphine				0.48
No	1060	479	31.1%	
Yes	205	83	28.8%	

Discussion

We were able to generate a new multiple logistic regression model to predict PONV. Some investigators may argue that it is important to develop simple heuristics, but we feel that simpler heuristics might be a step back in our attempt to mitigate PONV. This study quantified a significant and linear impact of smoking status on PONV incidence and developed a new model using unambiguous smoking and opioid predictors that may help researchers to better stratify patients for PONV and guide their decisions on prophylactic treatment.

This is a prognostic study based on prospective observations. It includes many expected limitations of this type of study, such as no cause and effect conclusions from the associations found and confounding data by indication.

Low model complexity is essential for point-of-care anesthesia. Although we know that educational interventions increase adherence, we do not know how long adherence lasts.[6] There is evidence that adherence to current PONV guidelines is low both in our institution and elsewhere.[3,7] Even when a standard operating procedure was proposed, anesthesiologists continued using the same strategy for patients in most anesthesia occasions.[7] Technological solutions, such as support decision systems, might help increase adherence to more complex protocols, and there is already evidence of this fact.[8]

Although we built a model with statistical significance that presents a higher AUC, our model is much more complex than Apfel's model and less easily applied in daily practice. If this model is not implemented in an electronic health system or through a smartphone app, it will be less useful than the existing algorithms. Our model has not been used in an independent validation sample, and Apfel's model has been validated in several previous studies.

As stated previously, the simplified Apfel's model has two ambiguous variables: the use of opioids during the postoperative period and non-smoking status. Apfel et al. [2] defined the use of opioids in the postoperative period; however, the clinical effects of spinal anesthesia, epidural opioids or

Table 4 Prophylactic antiemetic association with PONV. Data are presented in number (proportion) or as the mean (standard deviation).

Prophylactic antiemetics	No PONV	PONV	*p*-Value
Number of antiemetics used	1.39 (0.7)	1.38 (0.7)	0.40
Intraoperative ondansetron			0.22
No	262	102	
Yes	1004	461	
Intraoperative ondansetron dose (mg)	6 (3.2)	6.3 (3.1)	0.13
Intraoperative dexamethasone			0.002
No	527	278	
Yes	739	285	
Intraoperative dexamethasone dose (mg)	3.9 (3.8)	3.3 (3.7)	0.002
Intraoperative dimenhydrinate			0.015
No	1261	554	
Yes	5	9	
Intraoperative dimenhydrinate dose (mg)	0.13 (2.3)	0.55 (4.4)	0.0064
Intraoperative metoclopramide			0.0013
No	1246	539	
Yes	20	24	
Intraoperative metoclopramide dose	0.15 (1.2)	0.4(2)	0.0005
Intraoperative droperidol			0.041
No	1260	555	
Yes	6	8	
Intraoperative droperidol dose (mg)	0.02 (0.36)	0.06 (0.59)	0.03

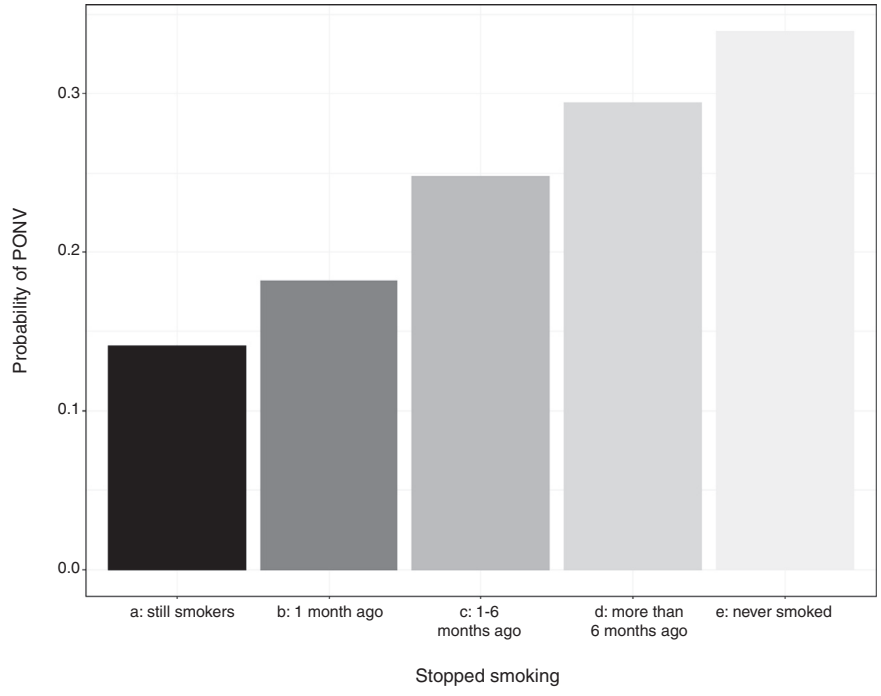

Figure 2 PONV probability by smoking status.

Table 5 New model selected from multiple logistic regression for predicting PONV.

Predictor	Coefficient	*p*-Value
Intercept	−1.79	<0.001
When stopped smoking?		<0.001
Never stopped	0	
1 month ago	0.48	
1–6 months ago	0.80	
>6 months ago	1.08	
Never smoked	1.14	
Male sex	−0.57	<0.001
Age (years)	−0.01	0.002
Previous PONV	0.77	<0.001
Previous CINV		0.001
No	0	
Yes	0.57	
No previous chemotherapy	0.27	
Neuraxial opioid used	0.30	0.005
Fentanyl total intraoperative dose (mcg)	0.0005	0.002

Table 6 Postoperative drug association with PONV. Data are presented in absolute number or as the mean (standard deviation).

Postoperative drug	No PONV	PONV	*p*-Value
Postoperative ondansetron			0.28
No	841	359	
Yes	423	203	
Postoperative dexamethasone			0.038
No	1171	537	
Yes	91	26	
Postoperative dimenhydrinate			0.28
No	1254	562	
Yes	8	1	
Postoperative droperidol			0.075
No	1168	514	
Yes	2	4	
Postoperative metoclopramide			0.38
No	1109	503	
Yes	153	60	
PACU Tramadol			0.02
No	1217	527	
Yes	49	36	
Tramadol dose PACU (mg)	3.1 (16)	5.4 (21)	0.017

systemic opioids can last up to 24 h, which would change the odds of PONV in a similar manner to the effect of postoperative opioid use on PONV. The non-smoking status applied as a dichotomous variable may be misleading since the effect on PONV varies, as we showed in this study, where the ordinal smoking status was nearly linearly associated with PONV (Fig. 2).

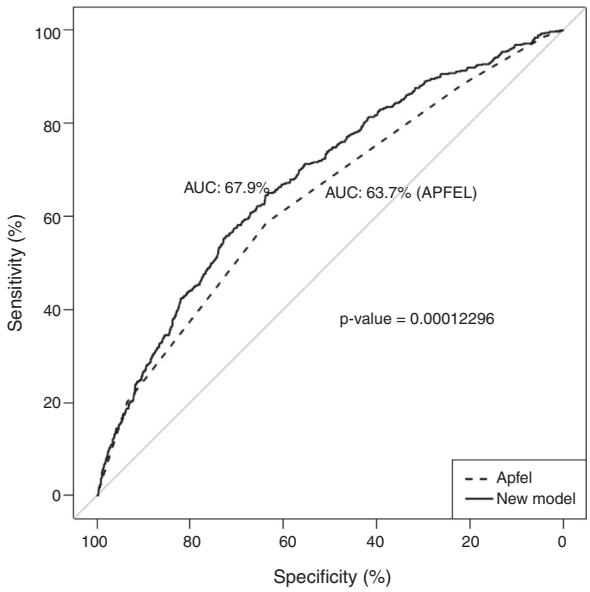

Figure 3 Receiver Operating Characteristic (ROC) curves for the new model and for Apfel's model.

In our hospital, we have strived to apply Apfel's score over the past few years, but these ambiguities have often resulted in conflicting classifications in our administrative database, such as a patient being classified as having three risk factors when evaluated by one nurse and two risk factors when evaluated by another, depending on how the smoking status was addressed. Smoking and opioid-related variables in Apfel's model cause this confusion because they are subjective variables.

Our results point to an increased incidence of PONV related to intraoperative intravenous opioids, neuraxial opioids and postoperative opioids. We know that even when fentanyl 2 $\mu g \cdot kg^{-1}$ is used for anesthesia induction; it increases the odds of PONV when compared to remifentanil.[9] We also know that spinal and epidural opioids increase PONV.[10] In our study, neuraxial opioids increased the odds of PONV by 18.3%. Therefore, although our model asks for more data, our model may be easier to understand than Apfel's opioid-related risk factor, which is incomplete. The other result we obtained is that the ordinal smoking status was nearly linearly associated with PONV (Fig. 2). To our knowledge, this association has never been published.

Again, previous CINV was reaffirmed as a PONV predictor in cancer patients, and we had already shown CINV to be a significant predictor for this population.[7] Thus, CINV was again included in the selected model. Although we used multiple regression models, other modelling techniques can be more informative, such as Bayesian Networks that deal with collinearity, which is common in multifactorial complications such as PONV, using hierarchical non-linear relationships to generate cause and effect hypotheses.[11] However, Bayesian Networks are not suitable to address both categorical and numerical variables, which is the case for our model; therefore, a Bayesian Network was not used.

Table 7 95% Confidence Intervals (95% CI) of the coordinates of ROC curve of the new model computed with 2000 stratified bootstrap replicates. Data are median proportion (95% CI) or real number (95% CI). The best threshold method was the closest point to the top-left.

Parameter	Best threshold	Median sensitivity	Median specificity
Specificity	67.1 (55.9–74.7)	75.2 (72.4–78.8)	0.5 (0.5–0.5)
Sensitivity	61.6 (53.1–72.1)	0.5 (0.5–0.5)	0.74 (0.69–0.78)
Accuracy	65.7 (60.8–69.2)	67.4 (65.2–69.9)	0.57 (0.55–0.58)
Negative predictive value	79.8 (77.4–82.4)	1.67 (1.60–1.75)	1.12 (1.11–1.12)
Positive predictive value	45.8 (41.9–50.7)	0.22 (0.22–0.22)	0.32 (0.30–0.34)
Threshold	0.31 (0.27–0.33)	0.347	0.26

Conclusion

In this study, we developed a new model to predict PONV with higher discriminative power than Apfel's model, and ours does not depend on ambiguous factors used in Apfel model's such as the patient's smoking status or the prediction of postoperative opioid usage.

Conflicts of interest

The authors declare no conflicts of interest.

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