

# Predictive effect of modified frailty index on postoperative nausea and vomiting in thyroid cancer patients

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## Abstract

Postoperative nausea and vomiting (PONV) are common complications following thyroid cancer surgery, impacting patient well-being, prognosis, and potentially leading to severe complications. Frailty, a critical risk factor for postoperative complications, has not been thoroughly investigated concerning PONV in thyroid cancer patients. This study aimed to explore the correlation between frailty and PONV in thyroid cancer patients. A retrospective analysis was conducted on 908 patients who underwent radical thyroid cancer surgery at Jinan Central Hospital between January 2016 and September 2022. Patients were classified into the PONV group (626 patients) and the non-PONV group (282 patients). General and clinical data were collected for comparison. Independent risk factors for PONV were identified using univariate and multivariate logistic regression analyses. ROC curves evaluated the diagnostic efficiency of various indicators. A predictive model for PONV risk factors was developed, verified using ROC curves, and a scoring system was established. Age, Apfel score, modified frailty index (mFI) score, free fatty acids, uric acid, homocysteine (HCY), and fasting blood glucose were identified as independent risk factors for PONV through multivariable logistic regression analysis. The model achieved an area under the curve of 0.893 (0.871–0.915) in the ROC curve, with a sensitivity of 83.2%, specificity of 79.1%, and a maximum Youden index value of 0.623. mFI exhibited the strongest correlation with PONV post-radical thyroid cancer surgery, with a correlation coefficient of 0.523. The modified frailty index is a significant predictor of postoperative nausea and vomiting in patients undergoing thyroid cancer surgery.

**Abbreviations:** ASA = American Society of Anesthesiologists, BCND = bilateral central neck dissection, DBP = diastolic blood pressure, FBG = fasting blood glucose, FFA = free fatty acids, HCY = homocysteine, HR = heart rate, LSG = laparoscopic sleeve gastrectomy, LT = lobectomy of the thyroid, mFI = modified frailty index, PONV = postoperative nausea and vomiting, ROC = receiver operating characteristic, SBP = systolic blood pressure, TT = total thyroidectomy, UA = uric acid, UCND = unilateral central neck dissection.

**Keywords:** postoperative nausea and vomiting, thyroid cancer, frailty, risk factor

## 1. Introduction

As the predominant malignant neoplasm of the thyroid glands endocrine system, thyroid cancer necessitates surgical intervention as the primary and paramount means for diagnosis and treatment.<sup>[1]</sup> Given the escalating incidence of thyroid cancer

demands,<sup>[2]</sup> it becomes imperative to delineate prognostic indicators and explore strategies aimed at mitigating or preventing associated risks. However, it is well-established that thyroid cancer significantly correlates with heightened occurrences of postoperative complications. One of the prevalent

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The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

The studies involving human participants were reviewed and approved by Ethics Committee of Jinan Central Hospital (ethical number: 2023-075-01). Due to retrospective nature of the study need for informed consent of patients was Waived by Jinan Central Hospital ethics committee. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards, and precautions were taken to anonymize sensitive personal information during data export, there was no invasion of privacy and interference with patient care in this study.

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postoperative complications is postoperative nausea and vomiting (PONV).

Postoperative nausea and vomiting (PONV) constitute frequent undesirable effects stemming from surgery and anesthesia. In select high-risk patients undergoing surgery, the incidence of PONV can escalate to as much as 80%.<sup>[3]</sup> Unresolved PONV may lead to protracted stays in the post-anesthesia care unit and unanticipated hospital admissions, consequently leading to a notable upsurge in overall healthcare expenditures.<sup>[4–6]</sup> Certain surgical procedures have been associated with an elevated incidence of PONV. Studies have shown that laparoscopic procedures, gynecological surgeries, and cholecystectomies heighten the risk of PONV.<sup>[7–12]</sup>

However, our clinical observations, coupled with expert consensus from the Chinese Thyroid Association on postoperative management of differentiated thyroid cancer, indicate a considerable incidence of PONV following differentiated thyroid carcinoma (DTC), ranging from 60% to 76%.<sup>[13]</sup> The incidence of PONV in thyroid surgery can be as high as 80 per cent if no precautions are taken.<sup>[14,15]</sup> Presently, the primary tool employed for predicting a patient's PONV risk is the simplified risk score developed by Apfel et al.<sup>[16]</sup> The Apfel score incorporates predictive factors, such as female gender, a history of motion sickness or PONV, nonsmoker status, and postoperative opioid usage, to estimate PONV risk. Despite the Apfel score's demonstrated accuracy in certain surgical contexts,<sup>[17–19]</sup> our clinical experience reveals instances of PONV post-radical thyroid cancer surgery that do not align well with these established risk factors. Moreover, the Apfel score, being a simplified scale, possesses inherent limitations and lacks universal applicability across diverse surgical scenarios.<sup>[20]</sup> Thus, there is an urgent imperative to investigate novel risk factors for PONV specific to radical thyroid cancer surgery.

An aspect worthy of thorough investigation is frailty, a factor reported to account for a noteworthy proportion, ranging from 13% to 46%, of the surgical demographic, presenting a correlation with adverse postoperative outcomes.<sup>[21]</sup> While frailty is more prevalent among the elderly, it is noteworthy that it can manifest within younger cohorts, particularly in patients contending with chronic ailments like cancer or infectious diseases.<sup>[22]</sup> The Canadian Study of Health and Aging recently introduced a frailty index (FI) to delineate the trajectory of physiological decline, offering predictive value for untoward outcomes across diverse surgical patient cohorts.<sup>[23]</sup>

Over the course of subsequent research, a mFI was derived, simplifying the initial Canadian Study of Health and Aging FI.<sup>[24]</sup> This mFI has demonstrated its efficacy in prognosticating postoperative complications and mortality across a spectrum of surgical patient cohorts,<sup>[25]</sup> and it would seem that some studies have already applied mFI to younger patients.<sup>[26]</sup> Nonetheless, the precise associations between frailty and PONV remain elusive. Consequently, the primary objective of the present study was to scrutinize the link between preoperative frailty and PONV in patients undergoing elective Radical Thyroid Cancer Surgery. Our hypothesis posited an association between frailty and PONV within this specific patient population.

## 2. Methods

### 2.1. Study population

We leveraged the hospital's medical big data system to compile data on 908 consecutive patients admitted to Jinan Central Hospital between January 2016 and September 2022, all patients underwent radical thyroid cancer with central neck lymph node dissection because of a malignant thyroid cancer. These patients were segregated into 2 groups: the PONV group (626 cases) and the non-PONV group (282 cases), based on the presence or absence of PONV. Comprehensive general data encompassing age, systolic and diastolic blood pressure, heart

rate, and clinical data involving coagulation routine, blood routine, liver and kidney function, blood glucose, blood electrolytes, and blood lipids were meticulously collected for both groups.

### 2.2. Inclusion criteria

- (1) Patients falling within ASA (American Society of Anesthesiologists) classifications I to III, aged 18 years or older, irrespective of gender.
- (2) Absence of preoperative radiotherapy treatment.
- (3) Underwent radical thyroid cancer surgery, and patients who have not developed distant metastases. (M0 stage).
- (4) Availability of complete clinical case data.
- (5) Pathological type papillary thyroid carcinoma.

### 2.3. Exclusion criteria

- (1) Presence of comorbid psychiatric disorders.
- (2) Incomplete clinical history information, with 1 or more missing mFI items.
- (3) Medical history information entailing patient privacy concerns.
- (4) Occurrence of intraoperative adverse events.

### 2.4. Clustering criteria

Drawing from postoperative follow-up results provided by the Department of Anesthesiology's postoperative follow-up team and augmented by details on antiemetic drug usage within 24 hours post-surgery from the hospital's medical big data system and medical records, patients were categorized into either the PONV group or the non-PONV group based on the presence or absence of postoperative nausea and vomiting.

- (1) PONV group: Patients experiencing nausea and vomiting within 24 hours post-surgery.
- (2) Non-PONV group: Patients not reporting nausea and vomiting post-surgery.

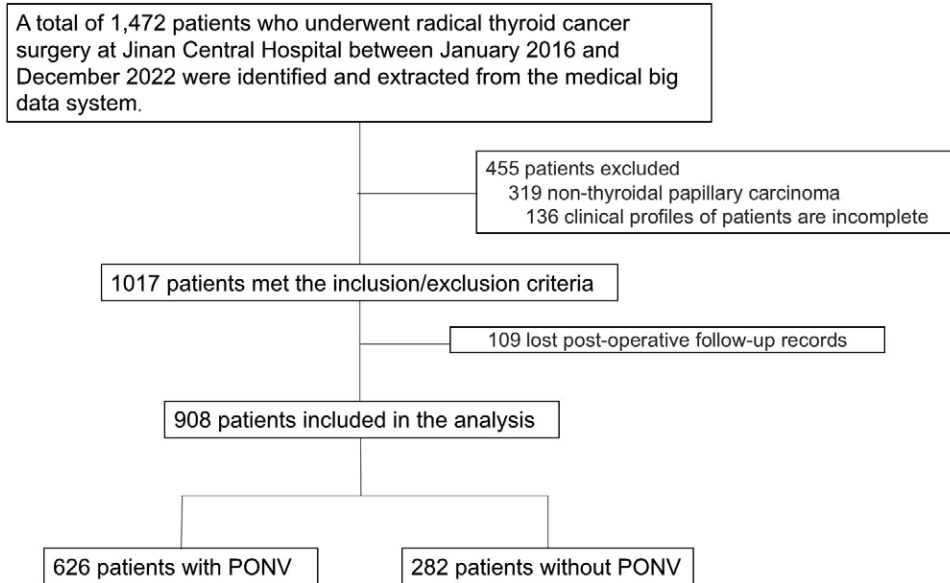
### 2.5. Collection of general information

Patient age, height, weight, smoking history, alcohol consumption history, operative and anesthetic data such as preoperative comorbidities and medications, type of surgery, duration of operation and anesthesia, and past medical history pertinent to radical thyroid cancer surgery were extracted from the medical history section of the hospital's medical big data system.

In this retrospective study, we selected the same standardized anesthesia protocol for radical thyroid cancer cases. Each participant underwent their surgical procedures under a uniform general anesthesia regimen, integrating inhalation agents. The anesthesia protocol remained consistent across all cases, encompassing the following sequence: induced anesthesia involving rocuronium, propofol, etomidate, and isoflurane; and maintained anesthesia featuring isoflurane inhalation, propofol, and remifentanyl. The oxygen to air (O<sub>2</sub>/air) ratio is 1:1, which equates to a 50% oxygen concentration.

### 2.6. Frailty assessment

For frailty assessment, we opted to employ the mFI using the hospital's medical big data system. The mFI was analyzed using a total score method, wherein each mFI item carries a weight of 1 point, yielding a cumulative mFI score reflecting the extent of the patient's frailty and number of defects. The mFI allows frailty to be calculated as the sum of the points, by which patients were



**Figure 1.** Patient flow chart. PONV = postoperative nausea and vomiting.

categorized into non-frail (mFI = 0), pre-frail (mFI = 1–2), and frail (mFI ≥ 3). The mFI comprises a total of 11 entries:

- (1) History of diabetes mellitus.
- (2) Preoperative independent functioning status (nonindependent).
- (3) Chronic obstructive pulmonary disease or pneumonia.
- (4) History of congestive heart failure.
- (5) History of myocardial infarction within 6 months.
- (6) History of percutaneous coronary intervention/stent implantation/angina.
- (7) History of hypertension requiring medication.
- (8) History of peripheral vascular disease/ischemic resting pain.
- (9) Impaired sensory function.
- (10) History of transient ischemic attacks or cerebrovascular accidents.
- (11) History of cerebrovascular accident combined with neurological impairments.

## 2.7. Apfel score assessment

Likewise, we conducted Apfel scoring based on the information sourced from the medical history system and personal medical records provided by the postoperative follow-up team. The Apfel score comprises factors such as female gender, a history of motion sickness or PONV, nonsmoking status, and postoperative opioid usage. Each criterion carries a weight of 1 point, and the cumulative score is tallied, reflecting an escalating risk of PONV with higher scores.

## 2.8. Statistical analysis

Data analysis was performed using SPSS 25.0 (Armonk, NY: IBM Corp) and R (4.2.1). Missing data ≥ 10% were deleted and < 10 % were interpolated using multiple interpolation. The linear relationship between each continuous variable and the outcome variable was assessed using Pearson correlation coefficients, while Spearman correlation was applied for non-parametric data. Continuous variables analyzed using t-tests or Mann–Whitney U-tests; Categorical variables assessed through chi-square tests or Fisher exact tests. ROC curves were employed to assess the diagnostic effects of relevant indicators

individually. Multiple regression was utilized to identify risk factors. A visualized logistic Nomograms model was established.  $P < .05$  were considered to indicate statistical significance.

## 3. Results

### 3.1. Comparison of general information

A total of 908 patients were enrolled in this study, comprising 626 patients in the PONV group and 282 patients in the non-PONV group (Fig. 1). A *t*-test was employed to compare demographic characteristics between the 2 groups of patients undergoing radical thyroid cancer surgery. The results demonstrated no statistically significant differences in age ( $56 [56.05 \pm 12.50]$  vs  $53 [53.12 \pm 12.64]$ ,  $P = .938$ ), heart rate ( $78 [78.44 \pm 7.04]$  vs  $78 [78.16 \pm 6.53]$ ,  $P = .260$ ), systolic blood pressure ( $126 [126.59 \pm 15.04]$  vs  $125 [125.87 \pm 13.82]$ ,  $P = .120$ ), diastolic blood pressure ( $80 [80.88 \pm 8.17]$  vs  $81 [81.03 \pm 8.88]$ ,  $P = .873$ ), smokers ( $33 [5.30\%]$  vs  $14 [5.00\%]$ ,  $P = .540$ ), Duration of anesthesia ( $124 [123.85 \pm 39.69]$  vs  $127 [127.13 \pm 40.60]$ ,  $P = .092$ ), Duration of operation ( $109 [109.48 \pm 39.51]$  vs  $113 [112.71 \pm 40.38]$ ,  $P = .087$ ), between the PONV and non-PONV groups. There were 114 (18.20%) male patients in the PONV group, significantly fewer than the 66 (23.40%) in the non-PONV group ( $P < .05$ ). Refer to Table 1 for details.

### 3.2. LASSO regression for identification of inclusion factors

LASSO regression: Clinical data of the patients were analyzed using LASSO regression to determine the optimal  $\lambda$  values. In this study, we selected  $\lambda_{\min}$  as the optimal  $\lambda$  value, as it corresponds to the model with the lowest cross-validation error, indicating the best fit. The LASSO regression mainly included patients' baseline information (age, gender, systolic blood pressure, diastolic blood pressure, heart rate, history of smoking, history of alcohol consumption), laboratory indices (liver function, renal function, blood lipids, coagulation routine, blood routine, blood glucose and other indices), surgery-related indices (anesthesia time, surgery time, extent of resection, ASA), Apfel, mFI, tumor stage. The optimal  $\lambda$  value identified in our research was 0.0429. We utilized 10-fold cross-validation to evaluate the robustness of the

**Table 1****Comparison of baseline data between the 2 groups of patients.**

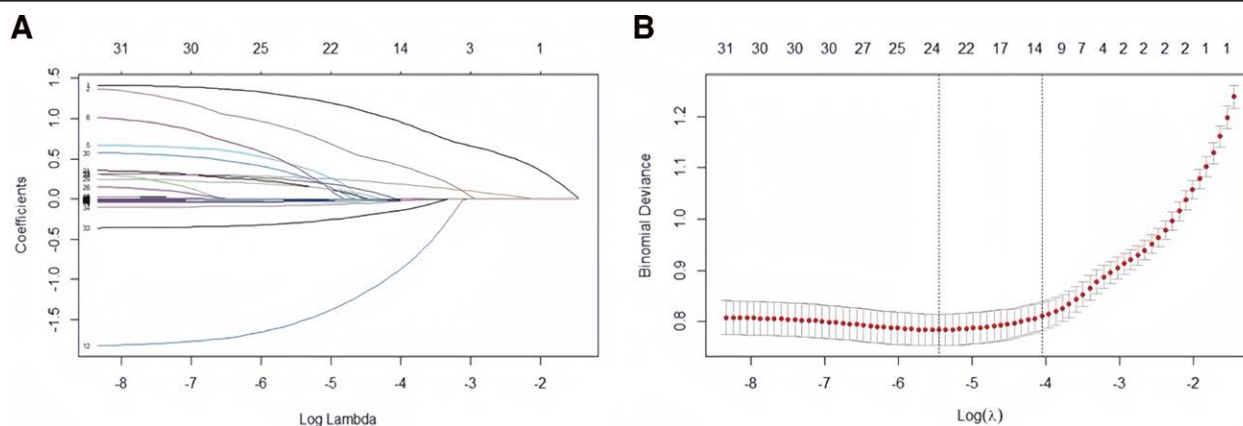
		P group (n = 626)	NP group (n = 282)	P-value
Sex-male (%)		114 (18.20%)	66 (23.40%)	.043*
Age-yrs		56.05 ± 12.50	53.12 ± 12.64	.938
SBP-mm Hg		126.59 ± 15.04	125.87 ± 13.82	.12
DBP-mm Hg		80.88 ± 8.17	81.03 ± 8.88	.873
HR-beats/min		78.44 ± 7.04	78.16 ± 6.53	.26
Smoking-n (%)		33 (5.30%)	14 (5.00%)	.54
Drinking-n (%)		31 (5.00%)	16 (5.70%)	.379
Duration of anesthesia (min)		123.85 ± 39.69	127.13 ± 40.60	.092
Duration of operation (min)		109.48 ± 39.51	112.71 ± 40.38	.087
mFI-n (%)	<.001**			
	0	75 (12.00%)	159 (56.40%)	
	1	133 (21.20%)	79 (28.00%)	
	2	115 (18.40)	27 (9.60%)	
	3	241 (38.50%)	14 (5.00%)	
	4	37 (5.90%)	3 (1.10%)	
	5	20 (3.20%)	0 (0.00%)	
	6	5 (0.80%)	0 (0.00%)	
Apfel-n (%)	<.001**			
	0	27 (4.31%)	13 (4.61%)	
	1	98 (15.65%)	60 (21.28%)	
	2	470 (75.09%)	209 (74.11%)	
	3	31 (4.95%)	0 (0.00%)	
ASA	.41			
	1	44 (7.03%)	29 (10.28%)	
	2	564 (90.10%)	241 (85.46%)	
	3	18 (2.87%)	12 (4.26%)	
	4	0 (0.00%)	0 (0.00%)	
Extent of resection-n (%)				
LT + UCND		187 (29.87%)	100 (35.46%)	.094
TT + UCND		169 (27.00%)	71 (25.18%)	.565
TT + BCND		270 (43.13%)	111 (39.36%)	.287
T stage-n (%)	.744			
	1	420 (67.09%)	192 (68.09%)	
	2	21 (3.35%)	8 (2.84%)	
	3	166 (26.52%)	76 (26.95%)	
	4	19 (3.04%)	6 (2.12%)	
N stage-n (%)	.609			
	0	376 (60.06%)	164 (58.16%)	
	1a	250 (39.94%)	118 (41.84%)	

The data are presented as mean ± SD for continuous variables and n for categorical variables.

Abbreviations: ASA, American Society of Anesthesiologists; BCND, bilateral central neck dissection; DBP, diastolic blood pressure; HR, heart rate; LT, lobectomy of the thyroid; mFI, modified frailty index; PONV, postoperative nausea and vomiting; SBP, systolic blood pressure; TT, total thyroidectomy; UCND unilateral central neck dissection.

\*  $P < .05$ .

\*\*  $P < .01$ .



**Figure 2.** LASSO regression. (A) The result of LASSO regression. (B) The result of cross-validation. LASSO = least absolute shrinkage and selection operator.

model, resulting in 14 independent variables (mFI, Apfel, age, SBP, free fatty acids [FFA], ALT, uric acid [UA], HCY, fasting blood glucose [FBG], FIB) for further analysis (Fig. 2).

Multivariable Regression: The independent variables identified through LASSO regression were included in multivariable logistic regression analysis. The results displayed that age, Apfel



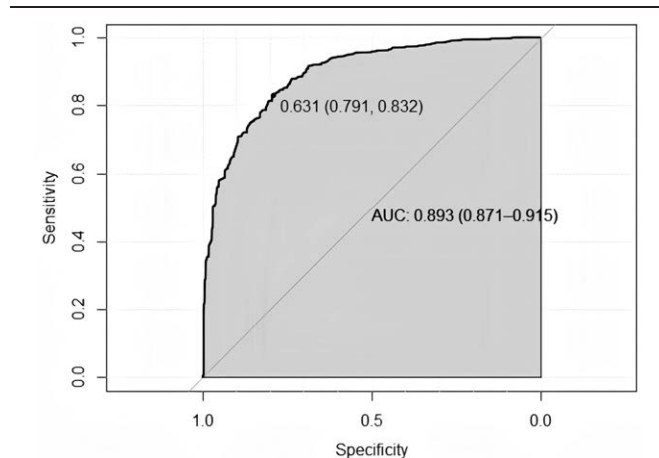
**Table 2**  
Multivariable analysis of PONV in radical thyroid cancer surgery.

	B	P	Exp (B)	95% CI
mFI	1.34	<.001*	3.83	3.03 to 4.84
Apfel	0.85	<.001*	2.33	1.55 to 3.50
Age	-0.05	<.001*	0.96	0.94 to 0.97
FFA	-1.82	<.001*	0.16	0.07 to 0.37
UA	<-0.01	.003**	0.99	0.99 to 1.00
HCY	0.29	<.001*	1.33	1.24 to 1.43
FBG	-0.35	.002**	0.7	0.57 to 0.88

Abbreviations: FBG = fasting blood glucose; FFA = free fatty acids; HCY = homocysteine; mFI = modified frailty index; UA = uric acid.

\* $P < .001$ .

\*\* $P < .01$ .



**Figure 3.** The ROC curve. The AUC of the predictive model was 0.893 (95% CI: 0.871–0.915) with sensitivity and specificity of 87.4% and 92.8%. AUC = area under curve, ROC = receiver operator characteristic curve.

score, mFI score, FFA, UA, HCY, and FBG were significantly different (Table 2).

### 3.3. Line diagrams and validation

Based on the multivariable logistic regression results, a prediction model for PONV with 7 independent risk factors was established using the equation  $Y = 0.21 + 0.85 \times \text{Apfel} + (-0.05) \times \text{age} + (-1.82) \times \text{FFA} + (-0.004) \times \text{UA} + 0.29 \times \text{HCY} + (-0.35) \times \text{FBG}$ . The model's prediction probability underwent ROC curve analysis, yielding an area under the curve of 0.893 (0.871–0.915), a sensitivity of 83.2%, specificity of 79.1%, and a maximum Youden index of 0.623 (Fig. 3).

A column-line graph visualized the logistic model, replacing the 7 independent risk factors. HCY emerged as the primary predictor of PONV after radical thyroid cancer surgery, with the highest predictive effect (maximum of 100 points), followed by mFI (maximum of 43 points). Variables such as Apfel, age, FFA, UA, and FBG exhibited lesser predictive effects (Fig. 4).

The patients were classified into 3 groups based on their mFI scores (non-frail [mFI = 0], pre-frail [mFI = 1–2], and frail [mFI ≥ 3]), and the correlation between this classification and PONV was analyzed. (Table 3). The findings revealed statistically significant discrepancies in the incidence of PONV among patients with disparate degrees of frailty. The prevalence of PONV demonstrated a notable increase with the progression of frailty.

The calibration analysis curve demonstrated high accuracy of the model with a mean absolute error of 0.015 (Fig. 5).

Clinical decision analysis curves illustrated a positive benefit of the model within the threshold probability range of 0.01 to 0.99 (Fig. 6).

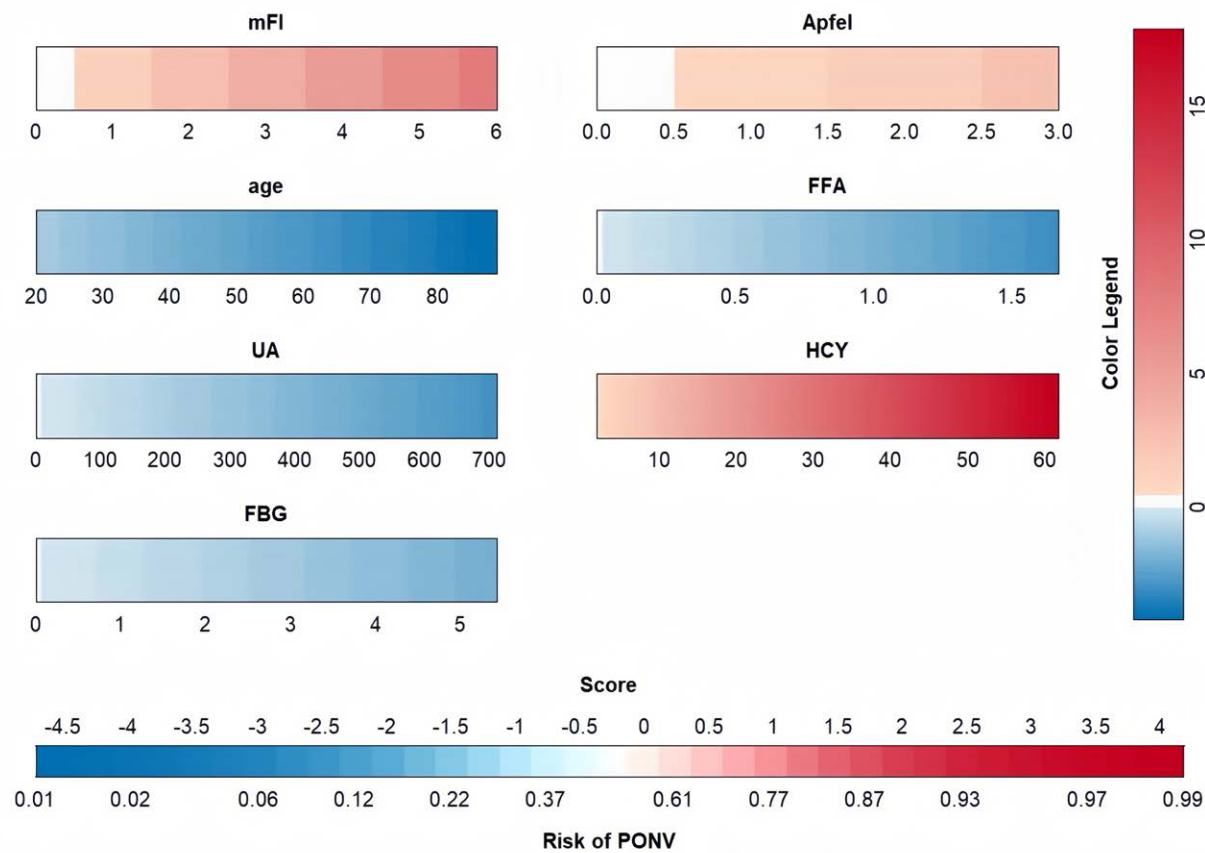
## 4. Discussion

In this retrospective analysis, we discerned a heightened risk of PONV among frail patients undergoing elective radical thyroidectomy for thyroid cancer. Remarkably, the predictive accuracy of PONV associated with frailty surpassed that of the Apfel scoring system.

The incidence of PONV in our study stood at 68.9%, akin to the incidence reported for PONV in DTC by the Chinese Thyroid Association.<sup>[13]</sup> Interestingly, our findings regarding the occurrence of postoperative nausea and vomiting were in concordance with the aforementioned association's observations. Earlier studies have underscored the heightened occurrence of PONV in laparoscopic abdominal surgery, gynecological procedures and Thyroid surgery.<sup>[27,28]</sup> But we should pay more attention to thyroid surgery PONV, not only due to its elevated prevalence but also due to potential complications such as wound fracture and hemorrhage, warranting thorough vigilance.<sup>[4–6]</sup>

The precise mechanism triggering postoperative PONV following thyroid surgery remains elusive. It has been shown that excessive intraoperative neck tilt, postoperative pain, neck edema, psychological factors, side effects of anesthetic drugs, intraoperative stimulation of the vagus nerve<sup>[15,29]</sup> and increased intracranial pressure and cerebral ischemia<sup>[30]</sup> during surgery can lead to the development of PONV. In this experiment, both mFI scores and Apfel scores demonstrated correlation with PONV, notably, our experiment revealed that the mFI score outperformed the Apfel score in predicting PONV. This variance may be attributed to the infrequent postoperative use of opioid analgesics following radical thyroid cancer surgery, rendering the Apfel score suboptimal for this particular surgical context, given the diverse factors that may precipitate PONV, underscoring the limitations of any brief predictive risk score.<sup>[19]</sup>

Presently, acknowledged risk factors for PONV include Apfel score-related variables (female sex, history of PONV or motion sickness, nonsmoking status, postoperative opioid use), younger age, general anesthesia, use of inhalational anesthetics, duration of anesthesia and surgery, and type of surgery.<sup>[31]</sup> Our study corroborates the correlation between the Apfel score and age, aligning with prior research. However, notably, the mFI showed a stronger correlation, introducing novel factors not previously recognized as PONV risk determinants. Our experiment demonstrated that the FI served as a robust predictor of PONV occurrence post-radical thyroid cancer surgery. As detailed in the background, frailty is not exclusive to the elderly population but is also prevalent among younger individuals, particularly



**Figure 4.** Nomogram plot. FBG = fasting blood glucose, FFA = free fatty acids, HCY = homocysteine, mFI = modified frailty index, UA = uric acid.

Table 3				
The correlation of PONV with different frailty status.				
	non-frail (n = 234)	pre-frail (n = 354)	Frail (n = 320)	P-value
PONV-n (%)	75 (32.05%)	248 (70.06%)	303 (94.69%)	<.001

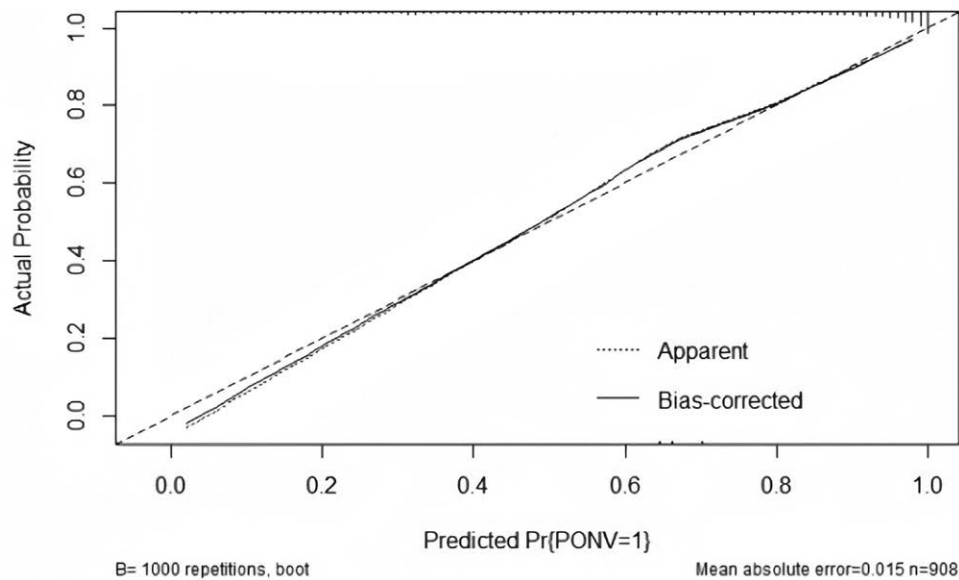
Abbreviation: PONV = postoperative nausea and vomiting.

those grappling with cancer.<sup>[22]</sup> Frail individuals, burdened by compromised cardiovascular and cerebral vascular systems, may experience intraoperative cerebral ischemic episodes, stimulating the centers for nausea and vomiting. Moreover, the diminished multisystemic function in frail patients may contribute to postoperative nausea and vomiting.<sup>[32]</sup> Additionally, frailty patients may experience reduced glomerular filtration rates and hepatic impairment, potentially leading to drug accumulation and prolonged half-life of drugs metabolized renally and hepatically, particularly opioids and other agents prone to inducing PONV. This presents a promising avenue for further exploration into PONV risk factors. Consequently, the etiology of PONV remains intricate, influenced by multifarious factors necessitating comprehensive investigation and understanding.

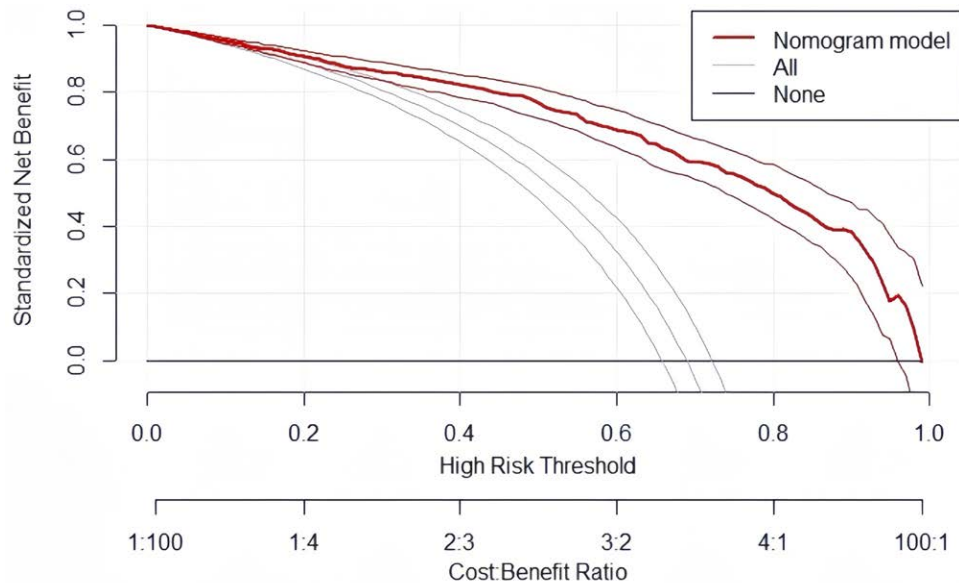
Multivariate analyses in our study showed independent risk factors of PONV including age, Apfel score, mFI, FFA, UA, HCY, and FBG. Among these factors, mFI exhibited the most robust correlation with postoperative PONV after radical thyroid cancer surgery. Concurrently, Apfel score, HCY, and age demonstrated substantial correlations and predictive potential.

It is noteworthy that, in addition to the well-established correlates of Apfel and age, our study unveiled HCY as a significant factor. Given its association with hypertension, cardiovascular diseases, and diabetes mellitus,<sup>[33]</sup> coupled with its strong

correlation with mFI observed in our study, implying elevated HCY levels in patients with high mFI scores, HCY could emerge as a PONV predictor. Further validation of this predictive role warrants exploration. On the other hand, our findings indicated a negative correlation between FFA, UA, and FBG and PONV, it has been demonstrated in previous studies that preoperative hypoglycemia in patients undergoing thyroid surgery is associated with an increased risk of developing PONV,<sup>[34]</sup> this finding is in accordance with our observations. This could be due to improved glucose metabolism, increased gastric emptying due to the low osmolarity of ingested fluids,<sup>[35]</sup> normalization of digestive tract function and alleviation of the psychological stress response. FFA have been linked to the development of diabetes and metabolic syndrome, and have emerged as a major link between obesity, the development of the metabolic syndrome, and atherosclerotic vascular disease. Furthermore, FFA serves as a signaling molecule, regulating pivotal biological functions through its active participation in an array of energy metabolic pathways,<sup>[36]</sup> however, the role of this mechanism in the occurrence of PONV remains uncertain, and further investigation is required to elucidate the underlying mechanism. UA is 1 of the most abundant antioxidants in humans and is postulated to play a role in maintaining blood pressure, neuroprotection, anti-aging and anti-cancer, among other functions. It is imperative



**Figure 5.** Calibration plot. The predictive models had good calibration with a mean error of 0.015.



**Figure 6.** Clinical decision analysis curve. The DCA curve showed that using the model to predict the development of PONV more benefit when the probability of PONV between 0.01 and 0.99. DCA = decision curve analysis, PONV = postoperative nausea and vomiting.

that UA levels remain within the normal range in order to maintain optimal physiological health, lower UA levels may weaken the physiological defense.<sup>[37]</sup> The findings of our study indicate that low preoperative UA levels are associated with an increased risk of PONV. We hypothesize that this may be linked to the antioxidant properties of UA. Recent studies have shown that changes in inflammatory mediators, electrolytes and other substances in the blood or cerebrospinal fluid stimulate the vomiting center and chemoreceptor trigger zone<sup>[38]</sup> and that changes in blood levels of FFA and UA may also be involved in this process, but the exact mechanisms need to be further investigated.

Enhanced recovery after surgery (ERAS) involves a multidisciplinary approach to optimize perioperative management, aiming for swift and improved patient recovery post-surgery.<sup>[39]</sup> In the context of radical thyroid cancer surgery, PONV during the postoperative period, particularly in patients with significant neck fibrillation, significantly heightens the risk of postoperative hemorrhage, potentially delaying recovery and

escalating hospitalization costs.<sup>[4–6]</sup> Thus, effective PONV management is pivotal for expeditious recuperation after this surgery. Identifying high-risk PONV individuals remains a crucial challenge. Our study effectively combines the mFI with postoperative PONV assessment following radical thyroid cancer surgery, demonstrating the mFI's superior predictability compared to the Apfel score. This presents a novel foundation for identifying high-risk PONV patients in clinical practice.

In our study, focusing on patients undergoing elective or limited radical thyroid cancer surgery, the preoperative phase emerged as an opportune moment for assessing frailty and Apfel scoring. Employing both scoring criteria optimally enhances the accuracy of identifying those at a higher risk of PONV. While recognized risk factors for PONV, such as age, gender, smoking history, PONV history, or motion sickness, may not be amenable to short-term preoperative improvement, frail patients can benefit from preoperative exercise through a recently proposed prehabilitation concept, mitigating the risk of PONV.<sup>[40]</sup> However,

the strategies for preventing postoperative PONV extend beyond this approach. Ongoing prospective studies investigating a triple antiemetic regimen (fosaprepitant, ondansetron, and dexamethasone) for thyroid surgery hold promise. In summary, a holistic approach encompassing preoperative enhancement of patient frailty and pharmacological PONV prophylaxis is pivotal to curbing PONV incidence and attaining ERAS goals.

Our study boasts significant strengths, including a substantial sample size of patients undergoing radical thyroid cancer surgery, a proficient anesthesiology department postoperative follow-up team, and a thorough exploration of the association between frailty scores and postoperative PONV following radical thyroid cancer surgery. However, certain limitations should be acknowledged. Firstly, this was a single-center retrospective study, potentially impacting results due to some missing clinical data. Despite efforts to mitigate this by excluding patients with substantial missing data and utilizing multiple interpolation methods for completion, some impact on the results might persist. Secondly, the study's participant pool was limited to adult patients undergoing radical thyroid cancer surgery, limiting the direct generalizability of results to the broader surgical population. Thirdly, despite adjusting for potential confounders, there could be unaccounted variables like lesion location and tumor size, emphasizing the influence of these unmeasured confounders. Lastly, the mFI does not specifically measure certain frailty phenotypes like weakness and reduced physical activity. Nonetheless, the mFI remains a widely adopted tool for frailty assessment in surgical patients due to its feasibility of assessment using routinely available medical record data. Furthermore, the mFI has demonstrated predictive capacity for regression and postoperative complications across various surgical procedures.<sup>[25]</sup>

## 5. Conclusion

Our retrospective study affirms a direct correlation between frailty and PONV among patients undergoing radical thyroid cancer surgery. Our findings underscore the significance of preoperative frailty assessment (mFI) in enhancing the accuracy of PONV risk screening post-radical thyroid cancer surgery. It is hoped that these risk factors will be validated in subsequent large-scale cohort studies and generalized to a greater number of different types of surgery and surgical populations. It would also be beneficial for further large-scale cohort studies to be conducted in order to identify other risk factors and to develop a more accurate prediction model for PONV.

## Author contributions

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## References

- [1] Pacini F, Castagna MG, Brilli L, Pentheroudakis G; ESMO Guidelines Working Group. Thyroid cancer: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. *Ann Oncol*. 2012;23:vii110–9.
- [2] Chen AY, Jemal A, Ward EM. Increasing incidence of differentiated thyroid cancer in the United States, 1988–2005. *Cancer*. 2009;115:3801–7.
- [3] Gan TJ, Meyer TA, Apfel CC, et al. Consensus guidelines for the management of postoperative nausea and vomiting. *Anesth Analg*. 2014;118:85–113.
- [4] Fortier J, Chung F, Su J. Unanticipated admission after ambulatory surgery: a prospective study. *Canadian J Anaesth*. 1998;45:612–9.
- [5] Gold BS, Kitz DS, Lecky JH, Neuhaus JM. Unanticipated admission to the hospital following ambulatory surgery. *JAMA*. 1989;262:3008–10.
- [6] Hill RP, Lubarsky DA, Phillips-Bute B, et al. Cost-effectiveness of prophylactic antiemetic therapy with ondansetron, droperidol, or placebo. *Anesthesiology*. 2000;92:958–67.
- [7] Sinclair DR, Chung F, Mezei G. Can postoperative nausea and vomiting be predicted? *Anesthesiology*. 1999;91:109–18.
- [8] Apfel CC, Kranke P, Katz MH, et al. Volatile anaesthetics may be the main cause of early but not delayed postoperative vomiting: a randomized controlled trial of factorial design. *Br J Anaesth*. 2002;88:659–68.
- [9] Apfel CC, Kranke P, Eberhart LH. Comparison of surgical site and patient's history with a simplified risk score for the prediction of postoperative nausea and vomiting. *Anaesthesia*. 2004;59:1078–82.
- [10] Cohen MM, Duncan PG, DeBoer DP, Tweed WA. The postoperative interview: assessing risk factors for nausea and vomiting. *Anesth Analg*. 1994;78:7–16.
- [11] Stadler M, Bardiau F, Seidel L, Albert A, Boogaerts JG. Difference in risk factors for postoperative nausea and vomiting. *Anesthesiology*. 2003;98:46–52.
- [12] Wallenborn J, Gelbrich G, Bulst D, et al. Prevention of postoperative nausea and vomiting by metoclopramide combined with dexamethasone: randomised double blind multicentre trial. *BMJ*. 2006;333:324–9.
- [13] Chinese Thyroid Association, Chinese Collage of Surgeons, Chinese Medical Doctor Association, Chinese Research Hospital Association Thyroid Disease Committee. Expert consensus on postoperative management of differentiated thyroid cancer (2020 edition). *Chin J Pract Surg*. 2020;40:1021–8.
- [14] Zou Z, Jiang Y, Xiao M, Zhou R. The impact of prophylactic dexamethasone on nausea and vomiting after thyroidectomy: a systematic review and meta-analysis. *PLoS One*. 2014;9:e109582.
- [15] Sonner JM, Hynson JM, Clark O, Katz JA. Nausea and vomiting following thyroid and parathyroid surgery. *J Clin Anesth*. 1997;9:398–402.
- [16] Apfel CC, Läärä E, Koivuranta M, Greim CA, Roewer N. A simplified risk score for predicting postoperative nausea and vomiting: conclusions from cross-validations between two centers. *Anesthesiology*. 1999;91:693–700.
- [17] Tran VN, Fitzpatrick BJ, Das S. Antiemetics and Apfel scores in orthopedic surgery. *Hosp Pharm*. 2023;58:511–8.
- [18] Pierre S, Benais H, Pouymayou J. Apfel's simplified score may favourably predict the risk of postoperative nausea and vomiting. *Canadian J Anaesth*. 2002;49:237–42.
- [19] Weibach C, Rahe-meyer N, Raymonds K, Weissig A, Scheinichen D, Piepenbrock S. Postoperative nausea and vomiting (PONV): usefulness of the Apfel-score for identification of high risk patients for PONV. *Acta Anaesthesiol Belg*. 2006;57:361–3.
- [20] Laskin DM, Carrico CK, Wood J. Predicting postoperative nausea and vomiting in patients undergoing oral and maxillofacial surgery. *Int J Oral Maxillofac Surg*. 2020;49:22–7.
- [21] Zhu LY, Ji MH, Zhang YF, Xia JY, Yang JJ. Frailty and short-term outcomes in elderly patients following elective noncardiac surgeries: a prospective cohort study. *J Clin Anesth*. 2020;64:109820.
- [22] Handforth C, Clegg A, Young C, et al. The prevalence and outcomes of frailty in older cancer patients: a systematic review. *Ann Oncol*. 2015;26:1091–101.
- [23] Searle SD, Mitnitski A, Gahbauer EA, Gill TM, Rockwood K. A standard procedure for creating a frailty index. *BMC Geriatr*. 2008;8:24.
- [24] Rockwood K, Andrew M, Mitnitski A. A comparison of two approaches to measuring frailty in elderly people. *J Gerontol A Biol Sci Med Sci*. 2007;62:738–43.
- [25] Wachal B, Johnson M, Burchell A, et al. Association of modified frailty index score with perioperative risk for patients undergoing total laryngectomy. *JAMA Otolaryngol Head Neck Surg*. 2017;143:818–23.
- [26] Ali B, Choi EE, Barlas V, Petersen TR, Morrell NT, McKee RG. Modified frailty index (mFI) predicts 30-day complications after microsurgical breast reconstruction. *J Plast Surg Hand Surg*. 2022;56:229–35.
- [27] Matthews C. A review of nausea and vomiting in the anaesthetic and post anaesthetic environment. *J Perioper Pract*. 2017;27:224–7.
- [28] Macario A, Weinger M, Carney S, Kim A. Which clinical anesthesia outcomes are important to avoid? The perspective of patients. *Anesth Analg*. 1999;89:652–8.
- [29] Fukuda H, Koga T. Stimulation of glossopharyngeal and laryngeal nerve afferents induces expulsion only when it is applied during retching in paralyzed decerebrate dogs. *Neurosci Lett*. 1995;193:117–20.



- [30] Ominaga K, Toshiyuki N. The twenty-degree reverse: trendelenburg position decreases the incidence and severity of postoperative nausea and vomiting after thyroid surgery. *Anesth Analg*. 2006;103:1260–3.
- [31] Kienbaum P, Schaefer MS, Weibel S, et al. Update on PONV: what is new in prophylaxis and treatment of postoperative nausea and vomiting? Summary of recent consensus recommendations and Cochrane reviews on prophylaxis and treatment of postoperative nausea and vomiting. *Anaesthesist*. 2022;71:123–8.
- [32] Cappe M, Laterre PF, Dechamps M. Preoperative frailty screening, assessment and management. *Curr Opin Anaesthesiol*. 2023;36:83–8.
- [33] Kumar A, Palfrey HA, Pathak R, Kadowitz PJ, Gettys TW, Murthy SN. The metabolism and significance of homocysteine in nutrition and health. *Nutr Metab*. 2017;14:78.
- [34] Rajan S, Rahman AA, Kumar L. Preoperative oral carbohydrate loading: effects on intraoperative blood glucose levels, post-operative nausea and vomiting, and intensive care unit stay. *J Anaesthesiol Clin Pharmacol*. 2021;37:622–7.
- [35] Yilmaz N, Cekmen N, Bilgin F, Erten E, Ozhan MO, Coşar A. Preoperative carbohydrate nutrition reduces postoperative nausea and vomiting compared to preoperative fasting. *J Res Med Sci*. 2013;18:827–32.
- [36] Boden G. Obesity and free fatty acids. *Endocrinol Metab Clin North Am*. 2008;37:635–46, viii.
- [37] Wen S, Arakawa H, Tamai I. Uric acid in health and disease: from physiological functions to pathogenic mechanisms. *Pharmacol Ther*. 2024;256:108615.
- [38] Stoops S, Kovac A. New insights into the pathophysiology and risk factors for PONV. *Best Pract Res Clin Anaesthesiol*. 2020;34:667–79.
- [39] Williamsson C, Karlsson N, Stureson C, Lindell G, Andersson R, Tingstedt B. Impact of a fast-track surgery programme for pancreaticoduodenectomy. *Br J Surg*. 2015;102:1133–41.
- [40] Milder DA, Pillinger NL, Kam PCA. The role of prehabilitation in frail surgical patients: a systematic review. *Acta Anaesthesiol Scand*. 2018;62:1356–66.