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Risk factors for postoperative nausea and vomiting after video-assisted thoracic surgery esophagectomy: a prospective cohort study

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Video-assisted thoracic surgery esophagectomy (VATS-E) may increase the risk of postoperative nausea and vomiting (PONV) because it uses a high dosage of anesthesia through a long operative duration. However, no study has examined the risk factors for PONV after VATS-E. Therefore, we investigated the risk factors for PONV to support the appropriate risk management of PONV after VATS-E. This prospective cohort study included 155 patients who underwent VATS-E at the Showa University Hospital between April 1st, 2020 and November 30th, 2022. The primary outcome was the incidence of PONV within 24 h after surgery. Significant independent risk factors associated with the incidence of PONV were selected using multivariate analysis. The association between the number of risk factors for PONV and incidence of PONV was analyzed. One-hundred fifty-three patients were included in the analysis. The patients' median age was 67 years (range, 44–88), and 79.1% were male. PONV occurred in 35 (22.9%) patients. In the multivariate analysis, remifentanil dosage > 89.0 ng/kg/min, albumin ≤ 3.5 g/dL, and eGFR < 60 mL/min/1.73 m^2 were independent significant risk factors for PONV. A significant association was observed between the incidence of and the number of risk factors for PONV (0 factor, 5.8%; 1 factor, 27.3%; ≥ 2 factors, 40.0%; p = 0.001). These three risk factors are useful indicators for selecting patients at high risk of developing PONV after VATS-E. In these patients, avoiding the development of PONV will be possible by performing appropriate risk management.

1. Introduction

Postoperative nausea and vomiting (PONV) is a common complication. The incidence of PONV is 30% (Gan et al. 2020), and many patients experience distress. Particularly, the incidence of PONV within the first 24 h after surgery is as high as 40.6% (Morino et al. 2013).

The Fourth Consensus Guidelines for the Management of PONV recommend identifying the risk factors for PONV and implementing prophylactic management to reduce the incidence of PONV (Gan et al. 2020). In clinical practice, the Apfel score is the most widely used tool for the risk stratification of PONV. The Apfel score is a simple tool comprising four risk factors: female sex, history of motion sickness and/or PONV, nonsmoking status, and postoperative opioid use (Apfel et al. 1999). However, risk factors different from the constituent factors of the Apfel score are reportedly associated with the incidence of PONV (Apfel et al. 2002, 2012; Morino et al. 2013).

Studies have reported that younger age, cholecystectomy, laparoscopic surgery, and gynecologic surgery are risk factors for PONV (Apfel et al. 2012). Additionally, anesthesia duration > 60 min, use of volatile anesthetics, and dosage of remifentanil and fentanyl have been reported as intraoperative risk factors (Apfel et al. 2002, 2012; Morino et al. 2013). Furthermore, some studies have shown that genetic polymorphisms related to the receptor signaling pathway are associated with the incidence of PONV (Nakagawa et al. 2008; Klenke et al. 2020). However, the association between genetic polymorphisms, patient characteristics, intraoperative factors, and the incidence of PONV remains partially explored.

The Apfel score is a comprehensive tool for assessing PONV risk developed for patients with various diseases and those undergoing various surgical procedures. However, in patient populations with specific diseases or surgical procedures, risk factors that differ from the constituent factors of the Apfel score may strongly affect the incidence of PONV. Since many patients with esophageal diseases are male and smokers, they may not be appropriately stratified using the Apfel score. Video-assisted thoracic surgery esophagectomy (VATS-E) may increase the incidence of PONV because it uses a high dosage of anesthesia through a long operative duration (Morino et al. 2013; Yoshida et al. 2018; Matsubara et al. 2020). Additionally, patients who develop PONV are at risk of aspiration, wound dehiscence, and esophageal rupture (Kovac 2000; Atallah et al. 2004). Furthermore, PONV delays early postoperative ambulation and the time of first oral intake (DREAMS Trial Collaborators and West Midlands Research Collaborative, 2017; Abdelaziz et al. 2021). Therefore, it is important to investigate the risk factors associated with PONV in patients undergoing VATS-E.

However, no study has examined the risk factors for PONV after VATS-E. If the risk factors for PONV after VATS-E could be identified, appropriate risk management for PONV may be possible in patients at high risk of PONV. Therefore, we investigated the risk factors for PONV to support the appropriate risk management of PONV after VATS-E.

Table 1: Patient characteristics (n = 153)

Variables	N (%) or Median (min–max)
Age	67 (44–88)
Male	121 (79.1)
BMI	21.0 (14.5–28.7)
ASA physical status	
1	27 (17.6)
2	117 (76.5)
3	9 (5.9)
Alcohol use (times/week)	3 (0–7)
Apfel related item	
Apfel score	
0	1 (0.7)
1	40 (26.1)
2	83 (54.2)
3	24 (15.7)
4	0 (0.0)
Unknown	5 (3.3)
Apfel score component	
History of motion sickness / PONV	2 (1.3)
Smoking at the time of diagnosis	51 (33.3)
Use of postoperative opioids	146 (98.6)
Disease	
Esophageal cancer	142 (92.8)
Other	11 (7.2)
History of surgery	86 (56.2)
Hemodynamics	
Systolic blood pressure (mmHg)	119 (88–167)
Diastolic blood pressure (mmHg)	74 (41–111)
Heart rate (bpm)	75 (45–115)
Blood test data	
WBC ($\times 10^3/\mu L$)	4.3 (1.7–10.5)
Hb (g/dL)	11.8 (8.4–16.1)
PLT ($\times 10^4/\mu L$)	24.4 (8.1–54.1)
ALT (U/L)	15 (5–77)
D-dimer (μg/mL)	0.92 (0.40–8.45)
Alb (g/dL)	3.9 (2.4–4.7)
eGFR ($mL/min/1.73m^2$)	78.5 (24.2–134.5)
Na (mEq/L)	141 (129–147)
K (mEq/L)	4.3 (2.9–5.2)
CRP (mg/dL)	0.08 (0.02–7.66)
HbA1c (%)	5.9 (4.3–7.8)
Perioperative medication	
Antiemetic for prevention	75 (49.0)
Anesthesia techniques	
INHA	149 (97.4)
TIVA	4 (2.6)
Intraoperative	
Propofol (mg/kg)	1.5 (0–47.7)
Fentanyl (μg/kg)	5.7 (1.4–15.8)
Remifentanil (ng/kg/min)	89.5 (0–280.1)
Intravenous anesthesia	
Remimazolam	15 (9.8)
Midazolam	8 (5.2)
Peripheral nerve block	13 (8.5)
Postoperative analgesia	
PCEA	140 (91.5)
IV-PCA	13 (8.5)

BMI body mass index, *ASA* american society of anesthesiologists, *bpm* beats per minute, *WBC* white blood cell, *Hb* hemoglobin, *PLT* platelet, *ALT* alanine aminotransferase, *Alb* albumin, *eGFR* estimated glomerular filtration rate, *Na* serum sodium level, *K* serum potassium level, *CRP* c-reactive protein, *HbA1c* hemoglobin A1c, *INHA* inhalational anesthesia, *TIVA* total intravenous anesthesia, *PCEA* patient-controlled epidural analgesia, *IV-PCA* intravenous patient-controlled analgesia

2. Investigation and results

2.1. Patient characteristics

The characteristics of the 153 patients are shown in Table 1. The median age was 67 years (range, 44–88), and 121 patients (79.1%) were male. In total, 117 patients (76.5%) had an ASA physical status of 2, 83 patients (54.2%) had an Apfel score of 2, and 142 patients (92.8%) had esophageal cancer. The proportions of patients receiving prophylactic antiemetic medications were as follows: dexamethasone, 72 patients (47.1%); ondansetron, four patients (2.6%); and metoclopramide, one patient (0.7%). The median dosages of intravenous anesthetic medications were as follows: propofol, 80 mg (range, 0–2600); fentanyl, 300 μg (range, 100–1100); and remifentanil, 2210 μg (range, 0–11839). The median operative duration was 409 min (range, 189–793), The median anesthesia duration was 496 min (range, 239–888), and the median intraoperative blood loss was 142 mL (range, 0–2360). All SNPs in this study were in Hardy–Weinberg equilibrium ($p > 0.05$).

2.2. Outcome

The incidence of PONV and the time from the end of surgery to the onset of PONV are shown in Table 2. PONV occurred in 35 patients (22.9%): among them, 26 patients (17.0%) had nausea and nine patients (5.9%) had vomiting. PONV occurred in seven patients (20.0%) 0–2 h after surgery and in 22 patients (62.9%) 13–24 h after surgery. Eleven patients (42.3%) in the nausea group and four patients (44.4%) in the vomiting group received antiemetic medication.

Table 2: Incidence of PONV within 24 h after VATS-E

Outcomes	N
Symptom	
Nausea	26
Vomiting	9
Onset of PONV*	
0–2 h	7
3–6 h	3
7–12 h	3
13–24 h	22

PONV postoperative nausea and vomiting, *VATS-E* video-assisted thoracic surgery esophagectomy
*: The time from the end of surgery to the onset of PONV

2.3. Univariate analysis

The results of the univariate analysis are shown in Tables 3 and 4. The proportions of patients with Alb ≤ 3.5 g/dL (40.0% vs. 21.2%, p = 0.025), eGFR < 60 mL/min/1.73 m^2 (25.7% vs. 11.0%, p = 0.030), ondansetron use (11.4% vs. 0.0%, p = 0.002), and remifentanil dosage > 89.0 ng/kg/min (68.6% vs. 44.9%, p = 0.014) were significantly higher in the PONV group than in the non-PONV group. The frequencies of the *ABCB1* 2677 G > T/A genotypes GG, GT, GA, TT, TA, and AA were 20.2%, 30.1%, 17.0%, 15.7%, 14.4%, and 2.6%, respectively, and were significantly associated with the incidence of PONV (p = 0.040).

2.4. Multivariate analysis

The ORs and 95% confidence intervals for each factor are shown in Table 5. Remifentanil dosage > 89.0 ng/kg/min (OR = 2.785, p = 0.018), Alb ≤ 3.5 g/dL (OR = 2.498, p = 0.035), and eGFR < 60 mL/min/1.73 m^2 (OR = 3.477, p = 0.018) were independent significant risk factors for the incidence of PONV.

2.5. Association between risk factors for PONV and the incidence of PONV

The relationship between the risk factors and the incidence of PONV is shown in Fig. 1. The proportion of patients with PONV was increased according to the number of risk factors extracted in the multivariate analysis (0 factor, 5.8%; 1 factor, 27.3%; and ≥ 2 factors, 40.0%, p = 0.001).

3. Discussion

In this study, eGFR < 60 mL/min/1.73 m^2, remifentanil dosage > 89.0 ng/kg/min, and Alb ≤ 3.5 g/dL were independent risk factors for PONV after VATS-E. It was clarified that risk factors different from constituent factors of Apfel score affected the incidence of PONV after VATS-E. To the best of our knowledge, this is the first study to identify the risk factors for PONV after VATS-E. Moreover, it was also shown that the incidence of PONV increases as the number of these risk factors increases. Therefore, these risk factors are useful as indicators for selecting patients at high risk of developing PONV after VATS-E. In patients with a high risk of developing PONV, avoiding the development of PONV will be possible by performing appropriate risk management of PONV.

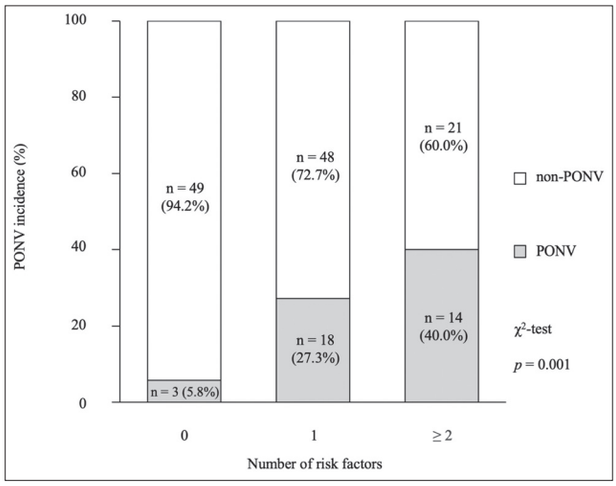

Fig. 1: Association between risk factors for postoperative nausea and vomiting (PONV) and the incidence of PONV.

Table 3: Univariate analysis of risk factors for PONV after VATS-E

Variables	Cutoff value	PONV (n=35) N (%)	Non-PONV (n=118) N (%)	p-Value
Age	< 65	15 (42.9)	45 (38.1)	0.615
	≥ 65	20 (57.1)	73 (61.9)	
Sex	Male	25 (71.4)	96 (81.4)	0.205
	Female	10 (28.6)	22 (18.6)	
BMI (kg/m^2)	< 22	24 (68.6)	71 (60.2)	0.368
	≥ 22	11 (31.4)	47 (39.8)	
ASA physical status	1	7 (20.0)	20 (16.9)	0.678
	2/3	28 (80.0)	98 (83.1)	
Alcohol use (times/week)	≤ 3	18 (51.4)	60 (50.8)	0.952
	> 3	17 (48.6)	58 (49.2)	
Apfel related item				
Apfel score	0/1/2	27 (77.1)	97 (85.8)	0.223
	3/4	8 (22.9)	16 (14.2)	
Apfel score component				
History of motion sickness and/or PONV	Yes	1 (2.9)	1 (0.8)	0.406
Smoking at the time of diagnosis	No	24 (68.6)	78 (66.1)	0.785
Postoperative opioid use	Yes	34 (97.1)	112 (99.1)	0.418
Disease	Esophageal cancer	31 (88.6)	111 (94.1)	0.275
	Other	4 (11.4)	7 (5.9)	
History of surgery	Yes	21 (60.0)	65 (55.1)	0.607
Hemodynamics				
Systolic blood pressure (mmHg)	< 130	27 (77.1)	79 (67.5)	0.277
	≥ 130	8 (22.9)	38 (32.5)	

Diastolic blood pressure (mmHg)	< 80	27 (77.1)	77 (65.8)	0.206
	≥ 80	8 (22.9)	40 (34.2)	
Heart rate (bpm)	< 60	7 (20.0)	11 (9.3)	0.130
	≥ 60	28 (80.0)	107 (90.7)	
Blood test data				
WBC ($\times 10^3/\mu L$)	< 3.3	9 (25.7)	22 (18.6)	0.361
	≥ 3.3	26 (74.3)	96 (81.4)	
Hb (g/dL)	< lower limit	25 (71.4)	95 (80.5)	0.251
	≥ lower limit	10 (28.6)	23 (19.5)	
PLT ($\times 10^4/\mu L$)	< 15.8	2 (5.7)	13 (11.0)	0.522
	≥ 15.8	33 (94.3)	105 (89.0)	
ALT (U/L)	≤ upper limit	33 (94.3)	107 (90.7)	0.733
	> upper limit	2 (5.7)	11 (9.3)	
D-dimer (μg/mL)	≤ 1.00	20 (57.1)	66 (55.9)	0.899
	> 1.00	15 (42.9)	52 (44.1)	
Alb (g/dL)	≤ 3.5	14 (40.0)	25 (21.2)	0.025**
	> 3.5	21 (60.0)	93 (78.8)	
eGFR ($mL/min/1.73m^2$)	< 60	9 (25.7)	13 (11.0)	0.030**
	≥ 60	26 (74.3)	105 (89.0)	
Na (mEq/L)	≤ 145	33 (94.3)	118 (100.0)	0.051*
	> 145	2 (5.7)	0 (0.0)	
K (mEq/L)	≤ 4.8	33 (94.3)	110 (93.2)	1.000
	> 4.8	2 (5.7)	8 (6.8)	
CRP (mg/dL)	≤ 0.14	27 (77.1)	76 (64.4)	0.158
	> 0.14	8 (22.9)	42 (35.6)	
HbA1c (%)	≤ 6.0	22 (64.7)	72 (63.7)	0.916
	> 6.0	12 (35.3)	41 (36.3)	
Perioperative medication				
Antiemetic for prevention				
Ondansetron	Yes	4 (11.4)	0 (0.0)	0.002**
Metoclopramide	Yes	1 (2.9)	0 (0.0)	0.229
Dexamethasone	Yes	14 (40.0)	58 (49.2)	0.341
Intraoperative				
Propofol (mg/kg)	< 1.4	18 (51.4)	44 (37.3)	0.135
	≥ 1.4	17 (48.6)	74 (62.7)	
Fentanyl (μg/kg)	≤ 3.0	2 (5.7)	7 (5.9)	1.000
	> 3.0	33 (94.3)	111 (94.1)	
Remifentanil (ng/kg/min)	≤ 89.0	11 (31.4)	65 (55.1)	0.014**
	> 89.0	24 (68.6)	53 (44.9)	
Remimazolam	Yes	4 (11.4)	11 (9.3)	0.748
Midazolam	Yes	3 (8.6)	5 (4.2)	0.384
Peripheral nerve block	Yes	4 (11.4)	9 (7.6)	0.496
Postoperative analgesia	PCEA	31 (88.6)	109 (92.4)	0.496
	IV-PCA	4 (11.4)	9 (7.6)	
Operative duration (min)	≤ 391	12 (34.3)	52 (44.1)	0.303
	> 391	23 (65.7)	66 (55.9)	
Anesthesia duration (min)	≤ 468	12 (34.3)	50 (42.4)	0.392
	> 468	23 (65.7)	68 (57.6)	
Blood loss (mL)	< 213	21 (60.0)	83 (70.3)	0.250
	≥ 213	14 (40.0)	35 (29.7)	

(Lower limit of Hb. Male:13.7 Female:11.6), (Upper limit of ALT. Male:42 Female:23)
PONV postoperative nausea and vomiting, *VATS-E* video-assisted thoracic surgery esophagectomy, *BMI* body mass index, *ASA* american society of anesthesiologists, *BPM* beats per minute, *WBC* white blood cell, *Hb* hemoglobin, *PLT* platelet, *ALT* alanine aminotransferase, *Alb* albumin, *eGFR* estimated glomerular filtration rate, *Na* serum sodium level, *K* serum potassium level, *CRP* c-reactive protein, *HbA1c* hemoglobin A1c, *PCEA* patient-controlled epidural analgesia, *IV-PCA* intravenous patient- controlled analgesia, **: < 0.05 *: < 0.1

Table 4: Association between genetic polymorphisms related to the receptor signaling pathway in PONV and the incidence of PONV

Polymorphism	Genotype	N (%)	PONV (n=35) N (%)	Non-PONV (n=118) N (%)	*p*-Value
LAMB3 rs2076222	CC	85 (55.6)	22 (62.8)	63 (53.4)	0.582
	CA	61 (39.8)	12 (34.3)	49 (41.5)	
	AA	7 (4.6)	1 (2.9)	6 (5.1)	
TRPC3 rs1465040	CC	80 (52.3)	16 (45.7)	64 (54.2)	0.252
	CT	64 (41.8)	15 (42.9)	49 (41.6)	
	TT	9 (5.9)	4 (11.4)	5 (4.2)	
OPRM1 rs1799971	AA	52 (34.0)	8 (22.9)	44 (37.3)	0.188
	AG	72 (47.0)	21 (60.0)	51 (43.2)	
	GG	29 (19.0)	6 (17.1)	23 (19.5)	
KCNJ6 rs2070995	CC	70 (45.8)	18 (51.4)	52 (44.1)	0.665
	CT	70 (45.8)	15 (42.9)	55 (46.6)	
	TT	13 (8.4)	2 (5.7)	11 (9.3)	
KCNJ6 rs2835859	TT	136 (88.8)	30 (85.7)	106 (89.9)	0.637
	TC	16 (10.5)	5 (14.3)	11 (9.3)	
	CC	1 (0.7)	0 (0.0)	1 (0.8)	
CHRM3 rs2165870	GG	76 (49.6)	17 (48.6)	59 (50.0)	0.932
	GA	70 (45.8)	16 (45.7)	54 (45.8)	
	AA	7 (4.6)	2 (5.7)	5 (4.2)	
TACR1 rs3771836	TT	88 (57.5)	22 (62.9)	66 (55.9)	0.513
	TG	59 (38.6)	11 (31.4)	48 (40.7)	
	GG	6 (3.9)	2 (5.7)	4 (3.4)	
TACR1 rs3755468	TT	28 (18.3)	9 (25.7)	19 (16.1)	0.411
	TC	83 (54.2)	18 (51.4)	65 (55.1)	
	CC	42 (27.5)	8 (22.9)	34 (28.8)	
DRD3 rs6280	TT	69 (45.1)	16 (45.7)	53 (44.9)	0.489
	TC	67 (43.8)	17 (48.6)	50 (42.4)	
	CC	17 (11.1)	2 (5.7)	15 (12.7)	
DRD2 rs1800497	GG	67 (43.8)	16 (45.7)	51 (43.2)	0.792
	GA	72 (47.0)	15 (42.9)	57 (48.3)	
	AA	14 (9.2)	4 (11.4)	10 (8.5)	
ABCB1 rs1045642	CC	59 (38.6)	10 (28.6)	49 (41.5)	0.221
	CT	68 (44.4)	20 (57.1)	48 (40.7)	
	TT	26 (17.0)	5 (14.3)	21 (17.8)	
ABCB1 rs2032582	GG	31 (20.3)	3 (8.6)	28 (23.7)	0.029**
	GT/GA	72 (47.0)	23 (65.7)	49 (41.6)	
	TT/TA/AA	50 (32.7)	9 (25.7)	41 (34.7)	
5HT3A rs1176713	AA	80 (52.3)	16 (45.7)	64 (54.2)	0.356
	AG	63 (41.2)	15 (42.9)	48 (40.7)	
	GG	10 (6.5)	4 (11.4)	6 (5.1)	

PONV postoperative nausea and vomiting, *LAMB3* laminin subunit beta 3, *TRPC3* transient receptor potential canonical 3, *OPRM1* opioid receptor mu 1, *KCNJ6* potassium inwardly rectifying channel subfamily J member 6, *CHRM3* cholinergic receptor muscarinic 3, TACR1 tachykinin receptor 1, *DRD3* dopamine receptor D3, *DRD2* dopamine receptor D2, *ABCB1* ATP(Adenosine tri-phosphate) binding cassette subfamily B member 1, *5HT3A* 5-hydroxytryptamine receptor 3A, **: <0.05

Table 5: Multivariate analysis of risk factors for PONV after VATS-E

Variables		β	OR	95%CI	*p*-Value
Remifentanil dosage (ng/kg/min)	(> 89.0 vs. ≤ 89.0)	1.024	2.785	1.188–6.529	0.018**
Alb (g/dL)	(≤ 3.5 vs. > 3.5)	0.916	2.498	1.065–5.860	0.035**
eGFR (mL/min/1.73m^2)	(< 60 vs. ≥ 60)	1.246	3.477	1.234–9.793	0.018**

VATS-E video-assisted thoracic surgery esophagectomy, *PONV* postoperative nausea and vomiting, *OR* odds ratio, *CI* confidence interval, *Alb* albumin, *eGFR* estimated glomerular filtration rate, *ABCB1* ATP(adenosine tri-phosphate) binding cassette subfamily B member 1, **: < 0.05
Alb ≤ 3.5 g/dL, eGFR < 60 mL/min/1.73m^2, *ABCB1* 2677 polymorphism, Apfel score, and remifentanil dosage > 89.0 ng/kg/min were entered into multivariate analysis.

A low eGFR is an independent risk factor for PONV. In this study, none of the patients received renally excreted drugs preoperatively or intraoperatively, suggesting that the effect of renally excreted drugs on the incidence of PONV was low. For other reasons, we considered that intraoperative intravenous hydration might have affected the incidence of PONV. Large volumes of intraoperative intravenous hydration have been reported to increase the risk of PONV (de Souza et al. 2016). Large volumes of intravenous hydration increase atrial natriuretic peptide levels, breakdown the vascular endothelial glycocalyx, increase vascular permeability, and cause intestinal edema (Myburgh and Mythen 2013). Generally, intraoperative intravenous hydration is 1–1.5 mL/kg/h (Voldby and Brandstrup 2016); however, intravenous hydration in patients who underwent VATS-E was as high as 8–10 mL/kg/h. Intraoperative intravenous hydration of > 10 mL/kg/h has been reported to increase the risk of PONV (de Souza et al. 2016). Additionally, patients with decreased renal function often experience impaired body fluid excretion, which leads to a tendency towards increased body fluid. Therefore, we considered that patients with a low eGFR had increased body fluid volume due to large volumes of intravenous hydration, leading to an increased incidence of PONV.

A high dosage of remifentanil per unit body weight per min was an independent risk factor for PONV. In this study, total remifentanil dosage, operative duration, and anesthesia duration were not significantly associated with the incidence of PONV. We hypothesized that a high dosage of anesthesia through a long operative duration for VATS-E might have increased the incidence of PONV; however, the results were different. The reason for this could be the difference in the surgical methods used. In previous studies, many patients had a short operative time (< 60 min). In contrast, the patients in this study underwent only VATS-E; therefore, all patients' operative duration was long. These results suggest that the remifentanil dosage per unit body weight per min may strongly affect the incidence of PONV, regardless of the operative and anesthesia durations. This is the first study to show that remifentanil dosage per unit body weight per min may affect the incidence of PONV.

A low Alb level is an independent risk factor for PONV. The participants in this study were administered fentanyl preoperatively and intraoperatively, which has a high plasma protein-binding ratio. Generally, drugs with high plasma protein-binding rates are strongly influenced by low Alb level. However, the hepatic first-pass metabolism of fentanyl was < 0.7, suggesting that the effect of free drug concentration on the incidence of PONV was low. Therefore, risk factors other than fentanyl use may affect the incidence of PONV. Sarcopenia may also affect the incidence of PONV. Most patients who underwent VATS-E in this study had esophageal cancer, and the incidence of sarcopenia in patients with esophageal cancer is as high as 50.3–74.9% (Nishigori et al. 2016; Matsunaga et al. 2019). Therefore, patients with sarcopenia may have decreased muscle mass in the head and neck, causing swallowing disorders and vomiting. Additionally, the inappropriate management of Enhanced Recovery after Surgery (ERAS) increases the risk of postoperative complications, including PONV (Fearon et al. 2005). The ERAS program also includes preoperative nutritional management. Therefore, patients with low Alb level may have an increased risk of PONV owing to concurrent sarcopenia and inappropriate ERAS management.

In univariate analysis, *ABCB1* 2677 G > T/A was significantly associated with the incidence of PONV. Particularly, the *ABCB1* 2677 GT/GA genotype was significantly associated with an increased incidence of PONV. However, the mechanism through which the *ABCB1* 2677 GT/GA genotype affects the incidence of PONV remains unclear. In contrast, the proportion of patients with *ABCB1* 2677 TT genotype was higher in the non-PONV group than in the PONV group (8.6% vs. 17.8%; data not shown). Therefore, patients with the *ABCB1* 2677 TT genotype may have a reduced risk of developing PONV. This is because *ABCB1* genetic polymorphisms may affect the ability to excrete antiemetics. *ABCB1*, also known as P-glycoprotein or MDR1, is an ATP-binding cassette (ABC) transporter expressed in several blood–organ barriers and is related to the excretion of drugs, such as ondansetron and dexamethasone. Patients with the *ABCB1* 2677 TT genotype have decreased activity of the *ABCB1* transporter and a higher concentration of ondansetron in the central nervous system, leading to a decreased risk of PONV (Choi et al. 2010). Most patients in this study received dexamethasone as an antiemetic. Therefore, patients with the *ABCB1* 2677 TT genotype may have decreased *ABCB1* transporter activity and increased dexamethasone concentrations in the central nervous system, which may reduce the risk of developing PONV. Thus, the *ABCB1* 2677 G > T/A polymorphism may be a useful indicator for predicting the effects of antiemetics.

This study had three limitations. First, the number of prophylactic antiemetics administered increased during the study period. Although ondansetron was indicated during the study period, the number of patients receiving ondansetron was small; therefore, it did not significantly affect the incidence of PONV. Second, the type, dosage, and timing of the intraoperative antiemetic administration were left to the discretion of the anesthesiologist. Therefore, the effect of intraoperative antiemetic administration on PONV could not be analyzed. Finally, the history of motion sickness and/or PONV could not be adequately collected from all patients. This may have resulted in an underestimation of the Apfel score.

In conclusion, eGFR < 60 mL/min/1.73 m^2, remifentanil dosage > 89.0 ng/kg/min, and Alb ≤ 3.5 g/dL were independent risk factors for PONV after VATS-E. Moreover, the incidence of PONV increased as the number of these risk factors increased. Therefore, these risk factors are useful indicators for selecting patients at a high risk of developing PONV after VATS-E. In patients at high risk of developing PONV, avoiding the development of PONV will be possible by performing appropriate risk management of PONV.

4. Experimental

4.1. Patients and study design

We performed a prospective cohort study of 155 patients who underwent VATS-E at the Showa University Hospital between April 1st, 2020 and November 30th, 2022. The exclusion criteria were as follows: postoperative mechanical ventilation management and reoperation within 24 h after surgery. Of the 155 patients, two were excluded, and 153 were included in the final analysis (Fig. 2).

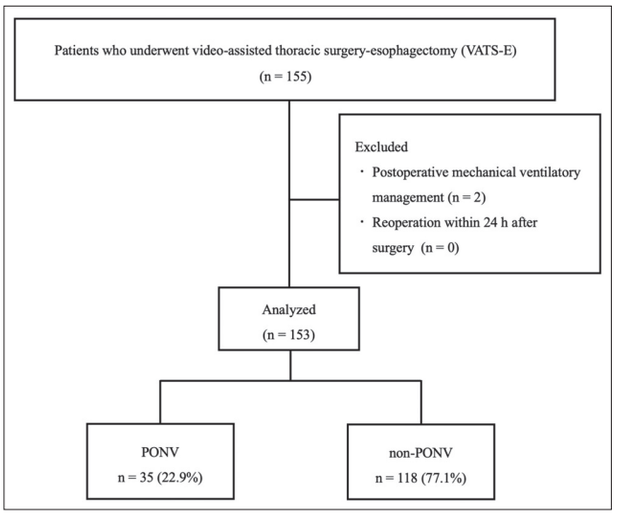

Fig. 2: Flowchart of patients. PONV postoperative nausea and vomiting.

4.2. Anesthetic and perioperative management

Anesthesia and perioperative management were appropriately performed by an anesthesiologist. Prophylactic antiemetic medications were administered by an anesthesiologist according to the Apfel score.

Anesthesia was induced using 1–2 μg/kg fentanyl and 1–2.5 mg/kg propofol, or 0.1–0.3 mg/kg midazolam, or 12 mg/kg/h remimazolam. Anesthesia was maintained using 2–4 μg/mL propofol under the target controlled infusion (TCI), sevoflurane 0–2% in oxygen, and desflurane 0–6% in oxygen. Analgesia was achieved by admin-

istering 0.05–0.5 μg/kg/min remifentanil and 1–5 μg/kg fentanyl. Anesthesia was adjusted to maintain a bispectral index (BIS) value of 40–60 during its maintenance.

4.3. Postoperative medications

Fentanyl was used with a patient-controlled epidural analgesia (PCEA) or intravenous patient-controlled analgesia (IV-PCA) for postoperative pain relief. Metoclopramide was used to relieve nausea and vomiting.

4.4. Outcome

The primary outcome was the incidence of PONV within 24 h after surgery, defined as nausea and/or vomiting. The incidence of PONV was defined as the occurrence of at least one episode of nausea or vomiting. The development of PONV was evaluated by anesthesiologists, nurses, and pharmacists during postoperative rounds.

4.5. Data collection

Data were collected from medical records before and during VATS-E. Patient background data included age, sex, body mass index (BMI), American Society of Anesthesiologists (ASA) physical status, alcohol use, Apfel score (female sex, history of motion sickness and/or PONV, smoking history, and postoperative opioid use), disease, history of surgery, blood pressure, and heart rate. Blood test data included white blood cells (WBC), hemoglobin (Hb), platelets (PLT), alanine aminotransferase (ALT), D-dimer, serum albumin (Alb), estimated glomerular filtration rate (eGFR), serum sodium (Na), serum potassium (K), C-reactive protein (CRP), and glycated hemoglobin A1c (HbA_{1c}). Drug-related data included the type of prophylactic and therapeutic antiemetics (dexamethasone, ondansetron, and metoclopramide), intravenous anesthetics (propofol, fentanyl, remifentanil, remimazolam, and midazolam), and the dosage of each medication, including peripheral nerve block medications (mepivacaine and bupivacaine). Additionally, data on anesthetic techniques (inhalational and total intravenous anesthesia), PCEA, IV-PCA, operative duration, and anesthesia duration were collected.

4.6. Definition

The Apfel score is scored on the four following risk factors, with each scoring one point: female sex, history of motion sickness and/or PONV, non-smoking status, and postoperative opioid use (Apfel et al. 1999). The operative duration, anesthesia duration, and dosage of intravenous anesthetics were divided into two groups using the Youden index. The WBC, Hb, and PLT levels were divided into two groups according to the lower limit of the reference range. ALT, D-dimer, Na, K, CRP, and HbA_{1c} levels were divided into two groups according to the upper limits of the reference range levels. The patients were divided into two groups based on the cut-off albumin level of 3.5 g/dL, according to the criteria for hypoalbuminemia in clinical practice, as well as based on the cut-off eGFR level of 60 mL/min/1.73 m^2, according to the criteria for mild renal impairment established in the chronic kidney disease guidelines (Kidney Disease: Improving Global Outcomes Blood Pressure Work 2021).

4.7. Genotyping of single-nucleotide polymorphisms (SNPs)

Genomic DNA was extracted from the blood using NucleoSpin Tissue (Takara Bio, Shiga, Japan), as per manufacturer's instructions. Subsequently, genotyping was performed using the TaqMan Single-Nucleotide Polymorphism (SNP) Genotyping Assay (Thermo Fisher Scientific, Waltham, MA) in a Step One Plus Real-Time Polymerase Chain Reaction System (Thermo Fisher Scientific, Waltham, MA). The patients were genotyped for *LAMB3* rs2076222, *TRPC3* rs1465040, *OPRM1* rs1799971, *KCNJ6* rs2070995, *KCNJ6* rs2835859, *CHRM3* rs2165870, *TACR1* rs3771836, *TACR1* rs3755468, *DRD3* rs6280, *DRD2* rs1800497, *ABCB1* rs1045642, *ABCB1* rs2032582, and *5HT3A* rs1176713. Amplification conditions were as follows: 95 °C for 5 min, followed by 40 cycles of 95 °C for 5 s and 60 °C for 30 s.

4.8. Statistical analysis

4.8.1. Sample size

We estimated that a sample size of 136 patients was required to detect an odds ratio (OR) of 1.7 with 80% statistical power at a significance level of 0.05, assuming a PONV rate of 30% (Gan et al. 2020). Therefore, the sample size of this study was sufficient to arrive at a valid conclusion.

4.8.2. Risk factors for PONV

The baseline characteristics were compared between the PONV and non-PONV groups. Univariate analysis was performed using the chi-squared test or Fisher's exact test for categorical variables. Variables with $p < 0.05$ in the univariate analysis and Apfel scores (as a covariate that affected the incidence of PONV) were entered into the multivariate analysis. A multivariate analysis was performed using logistic regression analysis. Significant independent variables contributing to the incidence of PONV were identified using a stepwise selection method. The association between the number of risk factors for PONV and its incidence was analyzed using the chi-squared test. Allele frequencies were tested for Hardy–Weinberg equilibrium using the chi-squared test. All statistical analyses were performed using SPSS software version 27 (IBM, Tokyo, Japan). A p-values < 0.05 was considered statistically significant.

4.9. Ethical approval

This study was approved by the Ethics Committee of Showa University (Approval No. 291; June 20th, 2019). In accordance with the principles of the Declaration of Helsinki, written informed consent was obtained from all patients prior to collection of blood samples and medical records.

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