INTRODUCTION

Post-operative nausea and vomiting (PONV) occurs in approximately 20%–40% of patients after general anaesthesia (GA). Patients can experience their first episode of PONV either early at the post-anaesthesia care unit (PACU) or later at the wards or at home in ambulatory settings. There is no consistent definition of early PONV in the literature. Some studies report early PONV as PONV observed within a specified post-operative time interval2-5 (ie, 0-2 hours or 0-4 hours),...
whereas others report it as PONV during the entire PACU stay.\textsuperscript{6-9} The risk of early PONV in prospective trials is reportedly around 20%,\textsuperscript{10,11} In a randomised controlled trial with 1180 patients, volatile anaesthetics were reported to have a high risk for early PONV (0-2 hours) as compared with propofol anaesthesia, whereas being a child, early PONV and the use of post-operative opioids were the risks for delayed PONV (2-24 hours).\textsuperscript{2} Further, studies reporting early PONV are often controlled trials evaluating interventions and using a specified cohort of patients.\textsuperscript{3-5,8}

At the PACU, patients are extensively monitored, and resources are available to evaluate PONV. Further, many hospitals include PONV at PACU in quality registries, and analysis of PONV can be easily accessible. Around half of patients that experience any PONV have PONV at PACU,\textsuperscript{10-12} and as early PONV is a risk for delayed PONV,\textsuperscript{2} early PONV might be considered an important indicator to identify procedures and factors with high overall PONV risks on an institutional level.

The aims of this retrospective exploratory study were to estimate the risk of early PONV after surgical procedures under GA and identify factors associated with early PONV in a mixed-patient cohort. We hypothesised that in a large mixed-case cohort, patients and perioperative factors associated with early PONV could be identified.

2 | MATERIALS AND METHODS

The study was a retrospective observational review of patients’ medical records and was approved by the Regional Ethical Review Board in Umeå (2018-06-12, 2018/233-3, Chairman Anders Iacobeus). The need for informed consent from the patients was waived by the board.

Inclusion criteria were age ≥18 years, surgical procedures conducted under GA and/or mixed GA + regional anaesthesia in the departments of general surgery, orthopaedic surgery, gynaecology, urology, ophthalmology, ear, nose and throat at Sundsvall’s hospital, Sweden, between 1 January 2017 and 30 June 2017. GA was defined as the use of either volatile or intravenous anaesthesia or a combination of these two anaesthetics. Patients who underwent surgery solely with regional anaesthesia or light sedation with propofol were excluded. Further criteria for exclusion were procedures with sensitive patient data (ie, abortions), insufficient data from perioperative medical records, patients with re-operation during the same hospitalisation and inaccessibility of the medical records due to a high level of confidentiality.

The departmental routine for premedication involves a basic analgesic, that is, paracetamol and/or a cyclooxygenase-2 inhibitor (etoricoxib), provided that the patient has no contraindications. Further, for procedures expected to result in increased pain severity, long-acting opioids (peroral controlled-release oxycodone) could be included in the premedication regimen; alternatively, a regional block (epidural analgesia, intrathecal analgesia, upper or lower extremity nerve blocks) was performed. The choice of anaesthesia was based on the type of procedure and local tradition. There were no major changes in this routine during the study period.

A list of all patients scheduled to undergo procedures during the study period was obtained from the local surgical registry (Orbit\textsuperscript{8} Version 5, Evry Healthcare System AB). Patients under 18 years of age; patients undergoing sensitive procedures (abortions), not requiring PACU stays, undergoing psychiatric procedures (ie, electroconvulsive therapy) and undergoing procedures outside the operating room (OR); and patients who underwent procedures under local anaesthesia were removed from the list. After selecting the eligible patients, study variables were obtained from the surgical registry, medical records, patient’s health declaration form, anaesthesia charts and PACU charts.

Based on the known risk factors for PONV,\textsuperscript{13,14} variables collected from the sources were preoperative: age, sex, height, weight, body mass index (BMI), American Society of Anaesthesiologists (ASA) physical status, smoking status, history of PONV or motion sickness, same-day surgery or inpatient surgery and elective or emergency surgery; perioperative: surgical procedure and type of anaesthesia, administered PONV prophylaxis, long-acting opioids during anaesthesia (ie, morphine towards the end of the procedure) and the duration of surgery and anaesthesia; and post-operative: time at the recovery unit, events of nausea/vomiting, pain assessments registered on the PACU chart, administered PONV rescue treatment (antiemetics), administered opioids, registration of PONV and data on pain relief obtained in the surgical registry.

The simplified PONV score (Apfel score) was used to estimate the individual risk for PONV. The score was the sum of the factors of the female gender, history of PONV or motion sickness, non-smoking status and anticipated need for post-operative opioids.\textsuperscript{15} Anticipated need for post-operative opioids was specific for each type of surgical procedure and was based on the clinical routine at the department.

The PONV prophylaxis was defined as interventions during anaesthesia to reduce the risk of PONV. The departmental routine for PONV prophylaxis was based on the PONV score and published guidelines\textsuperscript{13,15} and consisted of utilising total intravenous anaesthesia (TIVA) when possible, ondansetron (4 mg IV), betamethasone (4-8 mg IV) and droperidol (0.5 mg IV). The selection of prophylactic treatment was decided by the attending anaesthesiologist.

Further, PONV prophylaxis aimed at being administered in relation to the PONV risk. To classify if the prophylaxis given to each individual was adequate, we used the relationship between the simplified PONV score and the number of prophylaxis given. We considered that a patient was given optimal prophylaxis when the number
of prophylaxis given was at least one less than the PONV score. Suboptimal prophylaxis was considered when, for example, a patient with a PONV score of three (factors) was given only one prophylaxis. If the number of prophylaxis given exceeded the optimal amount, we considered it as more than optimal. Our model is a linear simplification of the recommendations of the third consensus guidelines from 2014, with the difference being that with four risk factors, we considered three prophylactic measures as a minimum, whereas the guidelines recommend a minimum of two.

The clinical routine in the PACU was to administer alfentanil or morphine for post-operative rescue treatment of pain and ondansetron for established PONV. All administered drugs were documented on the PACU chart.

2.1 | Definition of outcome variables

Early PONV was defined as any documented event of nausea and/or vomiting OR the administration of PONV treatment at the PACU OR the registration of PONV events in the surgical registry. Further, we limited early PONV to the first four post-operative hours in the PACU.

2.2 | Data analysis and statistics

Our sample size was primarily based on the resources available for the review of patient records, and we considered that analysis of a 6-month period, with potentially 2000-3000 patients undergoing GA, as feasible. To justify the sample size, first, we estimated the minimal number of patients needed to describe the 95% confidence interval (CI) of the primary outcome variable (PONV risk) with an absolute 2% marginal error. As the number of patients is dependent on the outcome in the binominal distribution, the minimal number of patients needed, in the PONV risk interval 10%-25%, was 864-1801 patients. Furthermore, for the logistic regression, we retrieved a minimal number of 800-2000 patients for the same PONV risks using the criterion with 10 or more events per variable (EPV) and with a minimal number of 800-2000 patients undergoing GA, as feasible. To justify the sample size, first, we estimated the minimal number of patients needed to describe the 95% confidence interval (CI) of the primary outcome variable (PONV risk) with an absolute 2% marginal error. As the number of patients is dependent on the outcome in the binominal distribution, the minimal number of patients needed, in the PONV risk interval 10%-25%, was 864-1801 patients. Furthermore, for the logistic regression, we retrieved a minimal number of 800-2000 patients for the same PONV risks using the criterion with 10 or more events per variable (EPV) and with a minimal number of 800-2000 patients for the same rea-son not included in the primary model. We used a backward elimination approach with \( P > .1 \) as the significance level for exclusion of the variables from the model. For the multivariate models, the adjusted odds ratio (aOR) with the corresponding 95% CIs is presented.

Additionally, as suboptimal prophylaxis was a highly significant factor in the univariate analysis, we constructed an alternative multivariate model, based on the primary analysis including this variable, and excluded the variables on which suboptimal prophylaxis was based.

3 | RESULTS

Data from 4680 procedures were retrieved from the surgical registry, and a total of 2847 eligible patients were identified and screened for inclusion; among them, 86 had received local anaesthesia/sedation, 557 had received regional anaesthesia, 99 had no medical records, 39 had incomplete data and 36 had undergone a re-operation within the same hospitalisation period. After exclusions, the final cohort included 2030 patients (Data S1).

3.1 | Patient and perioperative characteristics

The mean age of the patients was 56 ± 18 years, and the majority were female (59%). Approximately 70% of patients (\( n = 1416 \)) received volatile anaesthetics; 53% of the patients (\( n = 1066 \)) underwent endotracheal intubation, with 40% of outpatient surgeries (518 of 1297) and 75% of inpatient surgeries (548 of 733) intubated.

A high risk of PONV (PONV score >2) was seen in 31% of all patients, and 116 patients (5.7%) received suboptimal PONV prophylaxis. For further characteristics of the cohort, including missing values, see Table 1.

3.2 | Post-anaesthesia care unit

The mean time spent at the PACU was 96 ± 98 minutes. There were documented assessments of pain in 89% of the patients, and 15% of the patients had maximal pain intensity ≥5 on the numerical rating scale (NRS) or the visual analogue scale (VAS). Opioids were administered to 662 patients (33%) in the PACU (Table 2).

3.3 | Early PONV

Early PONV was found in 194 patients (9.6%; CI: 8.3%-11%). Administration of PONV treatment was the main source for identifying early PONV (9.0%; Figure 1 and Table 2).
### TABLE 1  Patient and perioperative characteristics (n = 2030)

| Factor                              | Values  | Missing values |
|-------------------------------------|---------|----------------|
| **Age, years**                      | 56 (18) | 0 (0%)         |
| **Females**                         | 1203 (59%) | 0 (0%)       |
| **Height, cm**                      | 171 (9.6) | 269 (13%)    |
| **Weight, kg**                      | 80 (18.3) | 262 (13%)    |
| **BMI, kg m\(^{-2}\)**             | 27.3 (5.4) | 288 (14%)    |
| **Smokers**                         | 216 (11%) | 0 (0%)        |
| **ASA physical status**             | 641 (32%) | 0 (0%)        |
| **History of PONV**                 | 80 (4%) | NA            |
| **History of motion sickness**      | 323 (16%) | NA            |
| **Apfel score**                     | 58 (3%) | 0 (0%)         |
| **Type of care**                    | 1297 (64%) | 0 (0%)       |
| **Procedure timeline**              | 504 (25%) | 0 (0%)        |
| **Department**                      | 1526 (75%) | 0 (0%)       |
| **Type of surgery**                 | 477 (23%) | 0 (0%)        |
| **Surgical approach**               | 497 (24%) | 0 (0%)        |
| **Duration of surgery, min**        | 63 (54) | 2 (0%)        |
| **Duration of anaesthesia, min**    | 118 (68) | 0 (0%)        |
| **Type of general anaesthesia**     | 1416 (70%) | 0 (0%)       |
| **Airway management**               | 68 (3%) | 0 (0%)        |
| **Mask**                            | 896 (44%) | 0 (0%)        |
| **Laryngeal mask**                  | 1066 (53%) | 0 (0%)       |
| **Endotracheal intubation**         | 294 (14%) | NA            |
| **Opioids given as part of a central block** | 158 (8%) | NA            |
| **Intrathecal opioids**             | 84 (4%) | NA            |
| **Epidural opioids**                | 74 (4%) | NA            |
| **Long-acting opioids during surgery** | 393 (19%) | NA            |
| **Anticipated need for post-operative opioids and/or the use of long-acting perioperative opioids** | 739 (36%) | NA            |
| **PONV prophylaxis**                | 614 (30%) | NA            |
| **TIVA**                            | 1839 (91%) | 0 (0%)       |
| **Betamethasone**                   | 1307 (64%) | 0 (0%)        |
| **Ondansetron**                     | 250 (12%) | 0 (0%)        |
| **Droperidol**                      | 54 (3%) | 0 (0%)         |
| **Number of PONV prophylaxis administered** | 546 (27%) | 0 (0%)        |
| **Suboptimal**                      | 508 (25%) | 0 (0%)        |
| **Optimal**                         | 1390 (68%) | 0 (0%)       |
| **More than optimal**               | 116 (6%) | 0 (0%)        |
| **Prophylaxis in relation to PONV risk** | 524 (26%) | 0 (0%)        |
| **Note:**                           | Continuous variables are presented with mean values (±standard deviation), and dichotomous variables with numbers of patients (% of the total number). Major surgery includes intra-abdominal surgery (both laparoscopic and open), intrathoracic surgery, spinal surgery and amputation above the knee. Intermediate surgery includes breast surgery, ENT surgery, orthopaedic surgery of the upper and lower extremities, hernial repair, endoscopic interventional procedures and gynaecologic surgery from a vaginal approach. Minor surgery includes endoscopic examination, closed reduction of fractures/joint luxations, incision of abscesses, extraction of osteosyntheses, excisions/biopsies, perianal procedures, gynaecological ablations/hysteroscopies and insertion/removal of catheters.**

Abbreviations: ASA physical status, American Society of Anaesthesiologists physical status classification system; BMI, body mass index; GA, general anaesthesia; NA, not available, as the variables were counted only in the presence of the factor; PONV, post-operative nausea and vomiting; RSI, rapid sequence induction; TIVA, total intravenous anaesthesia.
The relationship between the number of PONV prophylaxes, PONV risk (Apfel score) and early PONV is presented in Data S2.

Factors associated with early PONV in the univariate analysis included suboptimal prophylaxis (OR 3.43), rescue opioids at the recovery unit (OR 3.04), NRS/VAS score ≥5 for pain (OR 2.81), duration of anaesthesia (OR 2.59), long-acting opioids administered during anaesthesia (OR 2.12), major surgery (OR 2.34) and BMI >35 kg m\(^{-2}\) (OR 2.15). Further details and other associated factors are presented in Table 3.

In the multivariate model, the strongest independent factors associated with early PONV were rescue opioids in the PACU (aOR 2.52), major surgery (aOR 2.44), female sex (aOR 2.16), anaesthesia time >60 minutes (aOR 2.15), long-acting opioids administered during anaesthesia (aOR 2.10) and PONV prophylaxis: ondansetron (aOR 0.28) and droperidol (aOR 0.36). Further details and other associated factors are presented in Table 4.

In the alternative multivariate model, when suboptimal prophylaxis was entered as an independent variable, the strongest independent factors associated with early PONV were suboptimal prophylaxis (aOR 4.11), rescue opioids at the recovery unit (aOR 2.55) and BMI >35 kg m\(^{-2}\) (aOR 2.08). Further details and other associated factors are presented in Table 5.

4 | DISCUSSION

In this mixed-patient cohort, we found that every 10th patient undergoing GA experienced early PONV in the PACU. Several factors associated with early PONV were identified. Suboptimal PONV prophylaxis, in addition to previously acknowledged risk factors for PONV, was associated with early PONV.

The risk of early PONV in this study cohort was in the lower range compared with previous studies, where risks of 10%–45% have been reported.\(^3\)\(^,\)\(^8\)\(^,\)\(^10\)\(^,\)\(^11\) PONV risk is dependent on the case mix of the cohort, and the higher risks observed in other studies can be explained by the selection of patients/procedures at a higher risk for PONV. In addition, the majority of patients in our study cohort were

| TABLE 2 | Outcome variables as numbers (% of total numbers) or mean values (standard deviation) |
|-----------------|---------------------------------|-------------------------------|
| Value | Missing values |
| Time spent in the PACU, min | 96 (99) | 0 (0%) |
| PONV at PACU, number of patients | 194 (10%) | NA |
| Documentation of nausea and/or vomiting in the medical records | 28 (1%) | NA |
| Documentation of PONV treatment in the medical records | 182 (9%) | NA |
| Registration of PONV in the local surgical registry | 71 (3%) | NA |

Pain at the PACU

| Documentation of opioids given, in the medical records, number of patients | 662 (33%) | NA |
| Documentation of the highest pain level in the medical records, NRS | 1.4 (2.5) | 227 (11%) |
| Pain level NRS ≥5, number of patients | 274 (15%) | NA |
| Registration of [need for pain relief] in the local surgical registry, numbers of patients | 389 (19%) | NA |

Note: PONV at PACU was defined as PONV up to 4 h.
Abbreviations: NA, not available, as the variable was counted only in the presence of the factor; NRS, numeric rating scale; PACU, post-anaesthesia care unit; PONV, post-operative nausea and vomiting.

FIGURE 1 Sources for identification of patients with early post-operative nausea and vomiting (PONV) (9.0%, 194 of 2030)


**TABLE 3** Risk of PONV during the first 24 h after surgery with unadjusted odds ratios for variables that have the potential to be associated with PONV

| Variables                          | Number of patients | Number of patients with PONV (%) | Unadjusted OR (CI) | P-value (chi-square test) |
|------------------------------------|--------------------|----------------------------------|---------------------|---------------------------|
| **Patient characteristics**        |                    |                                  |                     |                           |
| BMI                                |                    |                                  |                     |                           |
| >35 kg m⁻²                         | 148                | 26 (18)                          | 2.21 (1.40-3.50)    | <.001                     |
| ≤35 kg m⁻²                         | 1594               | 140 (9)                          |                     |                           |
| Gender                             |                    |                                  |                     |                           |
| Female                             | 1203               | 135 (11)                         | 1.65 (1.19-2.27)    | .002                      |
| Male                               | 827                | 59 (7)                           |                     |                           |
| Age                                |                    |                                  |                     |                           |
| <50 years                          | 695                | 73 (11)                          | 1.18 (0.87-1.60)    | .30                       |
| ≥50 years                          | 1335               | 121 (9)                          |                     |                           |
| History of PONV                    |                    |                                  |                     |                           |
| Yes                                | 80                 | 6 (8)                            | 0.76 (0.33-1.77)    | .52                       |
| No                                 | 1950               | 188 (10)                         |                     |                           |
| History of motion sickness         |                    |                                  |                     |                           |
| Yes                                | 323                | 36 (11)                          | 1.23 (0.84-1.80)    | .29                       |
| No                                 | 1707               | 158 (9)                          |                     |                           |
| Smoking                            |                    |                                  |                     |                           |
| Yes                                | 216                | 23 (11)                          | 1.15 (0.72-1.81)    | .56                       |
| No                                 | 1814               | 171 (9)                          |                     |                           |
| ASA physical status                |                    |                                  |                     |                           |
| 1-2                                | 1626               | 145 (9)                          | 0.69 (0.49-0.98)    | .035                      |
| 3-4                                | 395                | 49 (12)                          |                     |                           |
| Simplified PONV score              |                    |                                  |                     |                           |
| 0-1                                | 626                | 45 (7)                           | Reference           | .008                      |
| 2                                  | 782                | 72 (9)                           | 1.31 (0.89-1.93)    |                           |
| 3-4                                | 622                | 77 (12)                          | 1.82 (1.24-2.68)    |                           |
| Intraoperative variables           |                    |                                  |                     |                           |
| Type of surgery                    |                    |                                  |                     |                           |
| Inpatient                          | 733                | 89 (12)                          | 1.57 (1.16-2.11)    | .003                      |
| Outpatient                         | 1297               | 105 (8)                          |                     |                           |
| Acute                              | 504                | 48 (10)                          | 1.01 (0.71-1.41)    | .98                       |
| Elective                           | 1526               | 146 (10)                         |                     |                           |
| Major                              | 477                | 79 (17)                          | 2.33 (1.67-3.24)    | <.001                     |
| Intermediate                       | 1056               | 83 (8)                           | Reference           |                           |
| Minor                              | 497                | 32 (6)                           | 0.81 (0.53-1.23)    |                           |
| Conventional                       | 1124               | 96 (9)                           | Reference           | .0012                     |
| Laparoscopic                       | 387                | 56 (14)                          | 1.81 (1.27-2.58)    |                           |
| Endoscopic                         | 519                | 42 (8)                           | 0.94 (0.65-1.37)    |                           |
| Time of surgery                    |                    |                                  |                     |                           |
| ≥60 min                            | 809                | 106 (13)                         | 1.94 (1.44-2.61)    | <.001                     |
| <60 min                            | 1218               | 88 (7)                           |                     |                           |
| Time of anaesthesia                |                    |                                  |                     |                           |
| ≥60 min                            | 1735               | 181 (10)                         | 2.53 (1.42-4.50)    | .0011                     |

(Continues)
| Variables                                                                 | Number of patients | Number of patients with PONV (%) | Unadjusted OR (CI) | P-value (chi-square test) |
|--------------------------------------------------------------------------|--------------------|----------------------------------|--------------------|--------------------------|
| <60 min                                                                  | 295                | 13 (4)                           |                    |                          |
| Rapid sequence induction                                                |                    |                                  |                    |                          |
| Yes                                                                      | 294                | 41 (14)                          | 1.68 (1.16-2.43)    | .0056                    |
| No                                                                       | 1736               | 153 (9)                          |                    |                          |
| Anticipated need for post-operative opioids including long-acting opioids given before and during anaesthesia |                    |                                  |                    |                          |
| Yes                                                                      | 739                | 90 (12)                          | 1.58 (1.17-2.13)    | .0024                    |
| No                                                                       | 1291               | 104 (8)                          |                    |                          |
| Long-acting opioids given during anaesthesia                             |                    |                                  |                    |                          |
| Yes                                                                      | 393                | 63 (16)                          | 2.19 (1.59-3.03)    | <.001                    |
| No                                                                       | 1637               | 131 (8)                          |                    |                          |
| Regional blockade in combination with GA                                 |                    |                                  |                    |                          |
| Yes                                                                      | 304                | 39 (13)                          | 1.49 (1.03-2.17)    | .035                     |
| No                                                                       | 1726               | 155 (9)                          |                    |                          |
| Intrathecal (spinal) opioids                                            |                    |                                  |                    |                          |
| Yes                                                                      | 84                 | 13 (15)                          | 1.79 (0.97-3.29)    | .059                     |
| No                                                                       | 1946               | 181 (9)                          |                    |                          |
| Epidural opioids                                                         |                    |                                  |                    |                          |
| Yes                                                                      | 74                 | 9 (12)                           | 1.33 (0.65-2.71)    | .44                      |
| No                                                                       | 1956               | 185 (9)                          |                    |                          |
| Total intravenous anaesthesia (TIVA)                                     |                    |                                  |                    |                          |
| Yes                                                                      | 614                | 67 (11)                          | 1.24 (0.91-1.70)    | .17                      |
| No                                                                       | 1416               | 127 (9)                          |                    |                          |
| PONV prophylaxis used                                                   |                    |                                  |                    |                          |
| Ondansetron                                                              |                    |                                  |                    |                          |
| Yes                                                                      | 1307               | 96 (7)                           | 0.51 (0.38-0.68)    | <.001                    |
| No                                                                       | 723                | 98 (13)                          |                    |                          |
| Betamethasone                                                            |                    |                                  |                    |                          |
| Yes                                                                      | 1839               | 171 (9)                          | 0.75 (0.47-1.19)    | .22                      |
| No                                                                       | 191                | 23 (12)                          |                    |                          |
| Droperidol                                                               |                    |                                  |                    |                          |
| Yes                                                                      | 250                | 13 (5)                           | 0.48 (0.27-0.86)    | .012                     |
| No                                                                       | 1780               | 181 (10)                         |                    |                          |
| Number of prophylaxis                                                   |                    |                                  |                    |                          |
| 0-1                                                                      | 600                | 73 (12)                          | 1.50 (1.10-2.04)    | .010                     |
| 2                                                                        | 1430               | 121 (8)                          |                    |                          |
| Suboptimal prophylaxis                                                  |                    |                                  |                    |                          |
| Yes                                                                      | 116                | 28 (24)                          | 3.35 (2.13-5.28)    | <.001                    |
| No                                                                       | 1914               | 166 (9)                          |                    |                          |
| Post-operative pain                                                      |                    |                                  |                    |                          |
| Max NRS ≥5 at PACU                                                       |                    |                                  |                    |                          |
| Yes                                                                      | 274                | 48 (18)                          | 2.79 (1.93-4.04)    | <.001                    |
| No                                                                       | 1529               | 108 (7)                          |                    |                          |
| Rescue opioids at PACU                                                   |                    |                                  |                    |                          |
| Yes                                                                      | 662                | 109 (16)                         | 2.98 (2.20-4.02)    | <.001                    |

(Continues)
scheduled for surgery under GA. Thus, the results of this study may reflect the general risk of early PONV more reliably than that of previous reports. Because we identified early PONV most commonly from PONV treatment noted in medical charts, we cannot rule out an underestimation of a true PONV incidence.

Opioids, both long acting administered during the procedure and those given at the PACU, are known to increase the PONV risk. In line with these reports, opioids were found to be among the strongest factors associated with early PONV, in both the univariate and multivariate models even in our study cohort.

Volatile anaesthesia is a known risk factor for early PONV, and by using TIVA, the risk can be reduced. However, patients anaesthetised with TIVA did not show a reduced PONV risk compared with patients administered volatile agents. There is an obvious risk of selection bias with our retrospective study design, and if there was an overall higher PONV risk for patients receiving TIVA in our cohort, we might not find any differences. Further, it is possible to compensate for the higher PONV risk of volatile agents by providing more prophylaxis. Therefore, our results may also indicate that PONV prophylaxis was given correctly according

### Variables

| Variables                                      | Number of patients | Number of patients with PONV (%) | Unadjusted OR (CI) | P-value (chi-square test) |
|-----------------------------------------------|--------------------|---------------------------------|--------------------|--------------------------|
| No                                            | 1368               | 85 (6)                          |                    |                          |
| Suboptimal prophylaxis                        |                    |                                 |                    |                          |
| Yes                                           | 116                | 28 (24)                         | 3.35 (2.13-5.28)   | <.001                    |
| No                                            | 1914               | 166 (9)                         |                    |                          |

Note: The number of patients is the total number of patients in the subgroup.

Abbreviations: BMI, body mass index; CI, 95% confidence interval; NRS, numerical rating scale; PACU, post-operative care unit; PONV, post-operative nausea and vomiting.

### Variables

| Variables                                      | Adjusted odds ratio | 95% CI          | P-value |
|-----------------------------------------------|---------------------|-----------------|---------|
| Ondansetron administered during anaesthesia    | 0.29                | 0.19-0.42       | <.001   |
| Droperidol administered during anaesthesia     | 0.36                | 0.19-0.69       | .002    |
| Rescue opioids at the recovery unit            | 2.41                | 1.68-3.46       | <.001   |
| Major surgery                                  | 2.36                | 1.49-3.75       | <.001   |
| Female gender                                  | 2.26                | 1.26-3.48       | <.001   |
| Long-acting opioids administered during anaesthesia | 2.20                | 1.27-3.73       | .005    |
| Anaesthesia time ≥60 min                       | 2.10                | 1.05-4.20       | .035    |
| BMI >35 kg m⁻²                                  | 2.10                | 1.26-3.48       | .004    |
| Laparoscopic procedure                         | 0.49                | 0.27-0.91       | .024    |
| Betamethasone administered during anaesthesia  | 0.53                | 0.31-0.91       | .022    |
| History of motion sickness                     | 1.84                | 1.16-2.90       | .009    |
| Outpatient surgery                             | 1.41                | 0.96-2.07       | .076    |

Note: Variables entered in the logistic regression model: BMI >35 kg m⁻², female sex, age < 50 years, history of motion sickness, history of PONV, smoking status, ASA class, outpatient surgery (ambulatory), major surgery, laparoscopic surgery, time of anaesthesia ≥60 min, rapid sequence induction, anticipated need for post-operative opioids, long-acting opioids administered during anaesthesia, regional block, spinal opioids, total intravenous anaesthesia, ondansetron as PONV prophylaxis and betamethasone as PONV prophylaxis; droperidol as PONV prophylaxis; rescue opioids at the recovery unit. Variables were excluded one by one if P > .10. Variables entered in the logistic regression model: BMI >35 kg m⁻², female sex, age < 50 years, history of motion sickness, history of PONV, smoking status, ASA class, outpatient surgery (ambulatory), major surgery, laparoscopic surgery, time of anaesthesia ≥60 min, rapid sequence induction, anticipated need for post-operative opioids, long-acting opioids administered during anaesthesia, regional block, spinal opioids, total intravenous anaesthesia, ondansetron as PONV prophylaxis and betamethasone as PONV prophylaxis; droperidol as PONV prophylaxis; rescue opioids at the recovery unit. Variables were excluded one by one if P > .10.

Abbreviations: BMI, body mass index; CI, confidence interval; PONV, post-operative nausea and vomiting.
to PONV risk and that TIVA may be considered as a prophylactic intervention.

A longer duration of anaesthesia (>60 minutes) was associated with early PONV. Long exposure to surgery and anaesthetic drugs are known to increase the risk of PONV. To reduce the risk of PONV, it is crucial to administer proper PONV prophylaxis in relation to an assessed PONV risk using the Apfel score. With our model stating the minimum amount of PONV prophylaxis in relation to PONV risk, we found that early PONV was associated with suboptimal PONV prophylaxis administered to patients. Other studies indicate that even when PONV risk models are implemented in a clinical setting and accompanied with prophylactic recommendations, the PONV risk is still high due to low adherence to guidelines. We may further speculate that PONV risk would decrease if patients with suboptimal prophylaxis were given adequate prophylaxis; but as there might be other confounding factors involved, our result only indicates that it might be a target for improvements.

Patients with three or four risk factors receiving two prophylactic interventions had a higher risk of early PONV (13-14%), indicating that the recommended routine for PONV prophylaxis may not be enough. Indeed, in the recently published fourth consensus guidelines for the management of PONV, a more liberal administration of PONV prophylaxis in patients with risk factors is recommended. By following these new guidelines, potential reduction of the risk for PONV may occur.

Two thirds of patients were considered to have been given more prophylaxis than standard, and PONV risk was lower among those patients compared with patients with an optimal prophylaxis. This is in accordance with the new recommendations of PONV prophylaxis.

However, as the Apfel score was based on chart reviews, we could have missed factors included in the score leading to a wrong classification of patients and resulting in a lower score.

The majority of our patients (53%) underwent endotracheal intubation during the procedures, which might be considered high for a consecutive flow of patients. However, patients receiving regional anaesthesia only were not included in our study cohort, and 25% of our patients underwent emergency procedures, which may lead to more instances of endotracheal intubations when compared with elective procedures.

The limitations of this retrospective observational study are acknowledged. All data were based on routine perioperative documentation; thus, there is a risk for missing or improper data registration. The observed risk of nausea and vomiting depends solely on the documentation of these events; that is, by possible missed documentation, the true PONV risk may be higher than that reported in this study. Further, the definition of PONV was based on three sources, and the administration of PONV treatment was the main source of finding early PONV in our study. Only a few patients had documented post-operative PONV. This is in line with previous observations showing that the routine documentation of PONV might be insufficient. Further, the administration of PONV treatment was not standardised, and there might have been more patients with PONV not receiving treatment. Also, we did not capture PONV after discharge from the PACU, and therefore, the true PONV risk up to 4 hours post-operatively might be further underestimated.

As some variables were only documented on positive reporting (e.g., motion sickness and smoker), there is an obvious risk for false negative values leading to wrong estimations of risks and associations that has to be taken into account in the interpretation of our

### Table 5: Multivariate analysis of independent risk factors associated with early PONV using an alternative model including suboptimal PONV prophylaxis as an independent variable (n = 1734)

| Variables                                           | Adjusted odds ratio | 95% CI       | P-value |
|-----------------------------------------------------|---------------------|--------------|---------|
| Suboptimal PONV prophylaxis                         | 4.05                | 2.51-6.70    | <.001   |
| Rescue opioids at the recovery unit                 | 2.41                | 1.70-3.42    | <.001   |
| BMI >35 kg m⁻²                                       | 2.08                | 1.28-3.39    | .003    |
| Major surgery                                       | 1.94                | 1.21-3.11    | .006    |
| Long-acting opioids administered during anaesthesia | 1.86                | 1.13-3.09    | .015    |
| Regional blockade                                    | 1.57                | 0.97-2.54    | .068    |
| Laparoscopic procedure                              | 0.59                | 0.32-1.08    | .088    |

Note: Variables entered in the logistic regression model: BMI >35 kg m⁻², age <50 years, ASA class, outpatient surgery (ambulatory), major surgery, laparoscopic surgery, time of anaesthesia ≥60 min, rapid sequence induction, long-acting opioids administered during anaesthesia, regional block, spinal opioids, rescue opioids at the recovery unit and suboptimal PONV prophylaxis. Variables were excluded one by one if P > .10. The variable suboptimal prophylaxis was based on the relation between the simplified PONV score and that TIVA may be considered as a prophylactic intervention. The observed ratio 95% CI P-value

Abbreviations: BMI, body mass index; CI, confidence interval; PONV, post-operative nausea and vomiting.
results. To further explore and confirm factors associated with early PONV, we suggest studies to be prospective with a pre-defined standard in the collection of data. With a retrospective design, many of the variables collected may have low accuracies in a mixed-case cohort. Our study was also limited by the variables included, and there are many other possible confounders, for example, analgesic premedication, which might be associated with early PONV.

The strength of our study was that a majority of all adult patients receiving GA in our hospital were included. However, this study describes the PONV risk at only one hospital, thus limiting the generalisability of the results. Furthermore, our study only described the PONV risk up to the first four post-operative hours. Many patients experience their first episode of PONV after discharge from the PACU, and to report PONV during the whole post-operative course, patients should be observed for several days after discharge.10,11

We consider early PONV as potentially an important indicator for the overall PONV risk, and if used in, for example, audits, it may be a valuable tool in PONV-reducing strategies. To further explore the role of early PONV, we plan to confirm our findings of the risk estimates with national data from the Swedish perioperative registry (SPOR). Our results also warrant prospective multicentre studies on the relations between early and late PONV and associated factors.

In conclusion, we found that almost every 10th patient under GA experienced early PONV and we are, to our knowledge, the first to identify risk factors in a mixed-case cohort. Suboptimal PONV prophylaxis, in addition to previously acknowledged risk factors for overall PONV, was associated with early PONV. Our results also highlight the importance of a more liberal approach to PONV prophylaxis and of adhering to PONV guidelines. Further, we suggest future prospective studies evaluating early PONV as an indicator for overall PONV.

CONFLICT OF INTERESTS
JW has received lecture fees from Abbvie Sweden AB. The other authors have no conflicts of interest to declare.

ORCID
Magnus Hultin https://orcid.org/0000-0003-2935-7161
Tomi Myrberg https://orcid.org/0000-0002-8802-2321
Jakob Wallååen https://orcid.org/0000-0002-8171-5184

REFERENCES
1. Franck M, Radtke FM, Apfel CC, et al. Documentation of postoperative nausea and vomiting in routine clinical practice. J Int Med Res. 2010;38:1034-1041. https://doi.org/10.1177/03060418103800030
2. 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;88:659-668, https://doi.org/10.1093/bja/88.5.659
3. Geng ZY, Liu YF, Wang SS, Wang DX. Intra-operative dexmedetomidine reduces early postoperative nausea but not vomiting in adult patients after gynaecological laparoscopic surgery: a randomised controlled trial. Eur J Anaesthesiol. 2016;33:761-766. https://doi.org/10.1097/EJA.000000000000491
4. Mraovic B, Simurina T, Gan TJ. Nitrous oxide added at the end of isoflurane anesthesia hastens early recovery without increasing the risk for postoperative nausea and vomiting: a randomized clinical trial. Can J Anaesth. 2018;65:162-169. https://doi.org/10.1007/s12630-017-1013-y
5. Celio A, Bayouth L, Burruss MB, Spaniolas K. Prospective assessment of postoperative nausea early after bariatric surgery. Obes Surg. 2019;29:858-861. https://doi.org/10.1007/s11695-018-3605-1
6. Scuderi PE, James RL, Harris L, Mims GR 3rd. Multimodal antiemetic management prevents early postoperative vomiting after outpatient laparoscopy. Anesth Analg. 2000;91:1408-1414.
7. Visser K, Hassink EA, Bonsel GJ, Moen J, Kalkman CJ. Randomized controlled trial of total intravenous anesthesia with propofol versus inhalation anesthesia with isoflurane-nitrous oxide: postoperative nausea with vomiting and economic analysis. Anesthesiology. 2001;95:616-626. https://doi.org/10.1097/00000542-200109000-00012
8. Gauger PG, Shanks A, Morris M, Greenfield ML, Burney RE, O’Reilly M. Propofol decreases early postoperative nausea and vomiting in patients undergoing thyroid and parathyroid operations. World J Surg. 2008;32:1525-1534. https://doi.org/10.1007/s00268-008-9472-5
9. Gustafsson S, Stromqvist M, Ekblom R, Engstrom A. Factors influencing early postoperative recovery after laparoscopic cholecystectomy. J Perianesth Nurs. 2020;35:80-84.
10. Apfel CC, Philip BK, Cakmakkaya OS, et al. Who is at risk for postdischarge nausea and vomiting after ambulatory surgery? Anesthesiology. 2012;117:475-486. https://doi.org/10.1097/ALN.0b013e318267ef31
11. Wallden J, Flodin J, Hultin M. Validation of a prediction model for post-discharge nausea and vomiting after general anaesthesia in a cohort of Swedish ambulatory surgery patients. Eur J Anaesthesiol. 2016;33:743-749.
12. Dinh KH, McAuliffe PF, Boisen M, et al. Post-operative nausea and analgesia following total mastectomy is improved after implementation of an enhanced recovery protocol. Ann Surg Oncol. 2020;27:4828-4834.
13. Gan TJ, Diemunsch P, Habib AS, et al. Society for ambulatory anesthesia. Consensus guidelines for the management of postoperative nausea and vomiting. Anesth Analg. 2014;118:85-113.
14. Horn CC, Wallisch WJ, Homanics GE, Williams JP. Pathophysiological and neurochemical mechanisms of postoperative nausea and vomiting. Eur J Pharmacol. 2014;722:55-66. https://doi.org/10.1016/j.ejphar.2013.10.037
15. Apfel CC, Laara 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. https://doi.org/10.1097/00000542-199909000-00022
16. Peduzzi P, Concato J, Kemper E, Holford TR, Feinstein AR. A simulation study of the number of events per variable in logistic regression analysis. J Clin Epidemiol. 1996;49:1373-1379. https://doi.org/10.1016/s0895-4356(96)00236-3
17. Barnes NM, Bunce KT, Naylor RJ, Rudd JA. The actions of fentanyl to inhibit drug-induced emesis. Neuropharmacology. 1991;30:1073-1083. https://doi.org/10.1016/0028-3908(91)90136-y
18. Wheeler M, Oderma GM, Ashburn MA, Lipman AG. Adverse events associated with postoperative opioid analgesia: a systematic review. J Pain. 2002;3:159-180. https://doi.org/10.1054/jpam.2002.123652
19. Kranke P, Eberhart LH. Possibilities and limitations in the pharmacological management of postoperative nausea and vomiting. Eur J Anaesthesiol. 2011;28:758-765.
20. Sneyd JR, Carr A, Byrom WD, Bilski AJ. A meta-analysis of nausea and vomiting following maintenance of anaesthesia with propofol
or inhalational agents. *Eur J Anaesthesiol*. 1998;15:433-445. https://doi.org/10.1046/j.1365-2346.1998.00319.x

21. Schaefer MS, Kranke P, Weibel S, Kreysing R, Kienbaum P. Total intravenous anaesthesia versus single-drug pharmacological antiemetic prophylaxis in adults: a systematic review and meta-analysis. *Eur J Anaesthesiol*. 2016;33:750-760. https://doi.org/10.1097/EJA.0000000000000520

22. Apfel CC, Heidrich FM, Jukar-Rao S, et al. Evidence-based analysis of risk factors for postoperative nausea and vomiting. *Br J Anaesth*. 2012;109:742-753. https://doi.org/10.1093/bja/aes276

23. Dewinter G, Staelens W, Veef E, Teunkens A, Van de Velde M, Rex S. Simplified algorithm for the prevention of postoperative nausea and vomiting: a before-and-after study. *Br J Anaesth*. 2018;120:156-163. https://doi.org/10.1016/j.bja.2017.08.003

24. Gan TJ, Belani KG, Bergese S, et al. Fourth consensus guidelines for the management of postoperative nausea and vomiting. *Anesth Analg*. 2020;131:411-448.

**SUPPORTING INFORMATION**

Additional supporting information may be found online in the Supporting Information section.

**How to cite this article:** Johansson E, Hultin M, Myrberg T, Walldén J. Early post-operative nausea and vomiting: A retrospective observational study of 2030 patients. *Acta Anaesthesiol Scand*. 2021;65:1229-1239. https://doi.org/10.1111/aas.13936