Dose-response relationship of dexamethasone for postoperative nausea and vomiting: A retrospective stratified analysis based on Apfel score

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Research Article

Keywords:

Posted Date: November 20th, 2025

DOI: https://doi.org/10.21203/rs.3.rs-7614826/v1

Additional Declarations: No competing interests reported.

Abstract

Objective

To determine the dose-response relationship of dexamethasone for PONV prophylaxis, considering the patient's Apfel risk score.

Methods

A retrospective study analyzed a sample of 99 adult surgical patients receiving dexamethasone for PONV prophylaxis, stratified by Apfel score. Data were extracted from electronic medical records, including demographics, anesthetic and surgical variables, and PONV outcomes. A logistic regression model was used to evaluate the interaction between dexamethasone dose and Apfel score on PONV incidence.

Results

The PONV incidence was 34% overall. A significant interaction was found between dexamethasone and Apfel score ($p = 0.0325$), with 10 mg demonstrating superior efficacy in high-risk patients (Apfel scores 3–4). No ceiling effect was observed t this dose. Low-risk patients (Apfel scores 0–2) showed minimal benefit from dexamethasone.

Conclusion

Dexamethasone's antiemetic efficacy follows a dose-dependent relationship, with maximal benefit observed at 10 mg in high-risk patients (Apfel scores 3–4), while offering minimal advantage in low-risk populations (Apfel scores 0–2).

Background

Postoperative nausea and vomiting (PONV) is a common complication after surgery, contributing to prolonged recovery times in the post-anesthesia care unit (PACU), increased healthcare costs, and a higher risk of unplanned hospital readmissions [1–3]. Studies estimate that PONV-related costs can reach several hundred dollars per affected patient [4, 5]. Furthermore, PONV negatively impacts patient satisfaction and, in severe cases, can lead to serious medical complications such as electrolyte imbalances, aspiration pneumonia, and wound dehiscence [6]. The significant effects of PONV on healthcare costs and patient outcomes highlight the necessity for effective prevention and management strategies during the perioperative care of patients.

The Apfel simplified risk score is a widely used tool for predicting the likelihood of PONV in adult patients. It is based on four independent risk factors: female sex, non-smoking status, a history of PONV or motion sickness, and postoperative opioid use. Patients with a score greater than two are considered high-risk, warranting more aggressive prophylactic measures. The Fourth Consensus Guidelines for the Management of Postoperative Nausea and Vomiting recommends administering two antiemetics for low- to moderate-risk patients, while high-risk patients should receive three to four antiemetics to optimize prevention strategies [7].

Dexamethasone is an effective prophylactic agent for PONV, showing results similar to those of 5-HT3 receptor antagonists like ondansetron. While studies suggest no significant difference in antiemetic efficacy between lower (4–5 mg) and higher (8–10 mg) doses in the general population [7], certain populations might benefit more from higher doses of dexamethasone. Therefore, optimizing dosing requires a patient-specific approach that balances benefits against potential risks, including hyperglycemia and delayed wound healing [7, 8].

Stratifying patients based on risk factors, such as those identified by the Apfel score, may allow for a more targeted and effective dosing strategy, maximizing prophylactic efficacy in those most at risk. This study aims to determine the dose-response relationship of dexamethasone for PONV prophylaxis, considering the patient's Apfel risk score.

Methods

Study design and patient population

This was a retrospective observational study conducted to evaluate the effect of dexamethasone on PONV and its interaction with the risk of developing PONV as assessed by the Apfel score. Data were extracted from the perioperative database of the Electronic Medical Record (EMR) system of a tertiary care hospital, covering the period from January 2023 to April 2023. Collected variables included demographic, anesthetic, and surgical information. The study population comprised adult patients (aged >18 years) with American Society of Anesthesiologists (ASA) physical status I, II, or III who underwent elective surgery, had at least one risk factor for PONV, and received intraoperative antiemetic prophylaxis with dexamethasone.

PONV risk factors included female sex, non-smoking status, a history of motion sickness or prior PONV, and the intraoperative use of opioids or inhaled anesthetics. The Apfel simplified risk score, which assigns one point for each of the following risk factors: female sex, non-smoking status, history of PONV or motion sickness, and use of postoperative opioids, was used to stratify patients, with a maximum score of four. Patients were excluded if they had incomplete information, were pregnant, had altered mental status, were admitted to the intensive care unit, or underwent rapid sequence induction. The study protocol was reviewed and approved by the Institutional Review Board (IRB) of Augusta University.

Outcome

The primary outcome was the incidence of postoperative nausea and vomiting (PONV) documented in the medical record during the patient's stay in the post-anesthesia care unit (PACU). We assessed the dose-response relationship between dexamethasone and PONV reduction, stratified according to the patient's Apfel score.

Exposure and covariates

This study focused on two exposure variables: the administered dose of dexamethasone and the Apfel score, a validated clinical tool for assessing risk of PONV, ranging from 0 to 4. Sociodemographic covariates included patient age and sex. Relevant medical history variables included smoking status and a prior history of motion sickness or PONV. Body mass index (BMI) was included as an anthropometric measure. Anesthetic-related covariates included ASA physical status classification, use of inhalational agents, intraoperative opioids, propofol, ondansetron, and the total duration of anesthesia. PACU variables included postoperative administration of opioids and antiemetics, as well as PACU length of stay. Surgical variables included the type of procedure and the corresponding surgical specialty.

Statistical Analysis

The sample size was determined based on the primary objective of assessing a potential interaction between dexamethasone dose and Apfel score on the likelihood of PONV. Given an anticipated PONV incidence of 35% [9], a minimum sample size of 86 patients was estimated to yield approximately 30-35 events, ensuring sufficient power for a logistic regression model including the key predictors dexamethasone dose, Apfel score, and their interaction. To account for potential exclusions or missing data, we collected information from 99 patients, representing ~15% oversampling margin. Based on this specification, the study achieves an event-per-variable (EPV) ratio of approximately 11, which exceeds the commonly recommended minimum of 10 EPV for stable coefficient estimates in logistic regression. Power calculations indicated that with 99 observations and a binary incidence of 35%, the study would have approximately 80% power and a two-sided $\alpha = 0.05$ to detect an interaction effect corresponding to an odds ratio (OR) of 0.2-0.3, assuming balanced distribution of Apfel scores and dexamethasone doses. All calculations were performed using standard formulas for power analysis in logistic regression models.

Continuous variables with normal and non-normal distributions are presented as mean (SD) or median (interquartile range), respectively, while for categorical variables, percent of frequency was used. Normality of quantitative data was tested with Shapiro-Wilk test. Univariate comparisons for continuous variables were performed with Student's t test and Mann-Whitney U test for normally and non-normally distributed data, respectively. Comparisons for categorical variables were performed with Chi-square test or Fisher's exact test if cell counts < 5 observations. A logistic regression model was fitted with PONV as the outcome variable. The primary predictor was dexamethasone dose, with an interaction term between dexamethasone and the Apfel score to assess whether the antiemetic effect of dexamethasone varied depending on PONV risk factors. Predicted probabilities were computed to visualize the dose-response effect of dexamethasone across Apfel scores. Interaction plots were

generated with probability of PONV stratified by Apfel scores and by dexamethasone dose. All analyses were conducted using R software (version 4.4.0; R Foundation for Statistical Computing, Vienna, Austria). $P < 0.05$ was considered as statistically significant.

Results

Baseline characteristics

The baseline characteristics of the study population are presented in Table 1. A total of 99 patients were included in the analysis. The group that experienced PONV was comparable with the group that did not, with no significant differences in most baseline characteristics. However, the PONV group was more likely to have received intraoperative propofol and a higher dose of ondansetron in PACU ($p = 0.035$ and 0.003, respectively).

Table 1. Demographic Characteristics of Patient Population			
Variable	**PONV**	**No PONV**	**p-value**
Age (mean, SD)	52.26 (19.24)	56.27 (16.64)	0.307
Female sex (n, %)	26 (76.47)	46 (71.87)	0.713
BMI (mean, SD)	32.67 (7.22)	30.81 (6.75)	0.218
Intraoperative ondansetron (n, %)			0.980
0 mg	1 (2.95)	1 (1.54)	
4 mg	33 (97.05)	62 (95.39)	
8 mg	0 (0.00)	2 (3.07)	
Smoking (n, %)	5 (14.71)	10 (15.38)	0.948
ASA score (n, %)			0.642
I	2 (5.88)	2 (3.08)	
II	16 (47.06)	27 (41.54)	
III	16 (47.06)	36 (55.38)	
Inhalational anesthetic (n, %)	30 (88.23)	56 (86.15)	0.980
Propofol (n, %)	29 (85.29)	42 (64.62)	0.035
Surgical specialty (n, %)			0.036
ENT	9 (26.47)	6 (9.23)	
General surgery	5 (14.71)	14 (21.53)	
Gynecology	2 (5.88)	5 (7.69)	
Neurosurgery	2 (5.88)	8 (12.31)	
Surgical Oncology	3 (8.82)	14 (21.54)	
Ophthalmology	3 (8.82)	1 (1.54)	
Orthopedic surgery	9 (26.47)	9 (13.85)	
Pulmonology	1 (2.95)	2 (3.08)	
Urology	0 (0.00)	6 (9.23)	
Intraoperative morphine equivalents (median, IQR)	9 (1.87, 30.00)	9 (0, 75.8)	0.976
Anesthesia duration minutes (median, IQR)	110.5 (70, 165.5)	138 (89, 198)	0.103

PACU LOS minutes	132 (96-201)	135 (93, 172)	0.813
PACU ondansetron (n, %)			0.003
0 mg	25 (73.53)	62 (95.38)	
4 mg	9 (26.47)	3 (4.62)	
Postoperative morphine equivalents (median, IQR)	9 (0, 18)	7.5 (0, 15)	0.263

PONV, postoperative nausea and vomiting. SD, standard deviation. BMI, body mass index. ASA, American Society of Anesthesiologists physical status. ENT, ear, nose, and throat surgery. PACU, post-anesthesia care unit. LOS, length of stay.

Interaction between dexamethasone and Apfel score and dose-response relationship

The logistic regression model demonstrated a significant association between duration of anesthesia PONV (Table 2). Regarding surgical specialties, general surgery and gynecology were significantly associated with PONV with lower risk when compared to ENT surgery. Notably, a significant interaction between dexamethasone and Apfel score ($\beta = -0.509$, $p = 0.0325$), suggesting that the effect of dexamethasone on reducing PONV was more pronounced in patients with higher Apfel scores. Figure 1 illustrates the probability of PONV across Apfel scores, stratified by dexamethasone dose. The predicted probability of PONV increased with Apfel score, but higher dexamethasone doses were associated with lower probabilities, particularly for Apfel scores 3 and 4. Figure 2 presents the probability of PONV across dexamethasone doses, stratified by Apfel score. Apfel scores (0, 1) demonstrated minimal change in PONV probability with increasing dexamethasone doses. In contrast, patients with Apfel scores of 3 and 4 exhibited a more pronounced dose-dependent reduction in PONV probability.

Table 2. Association between exposure, covariates, and PONV			
Variable	**OR**	**CI 95% Lower**	**CI 95% Upper**
Age	0.98	0.61	1.58
Sex	0.97	0.01	176
BMI	1.11	0.99	1.24
Intraoperative ondansetron	0.73	0.28	1.91
Intraoperative opioids	1.01	0.99	1.02
Specialty			
General Surgery	0.03	0.01	0.49
Gynecology	0.01	0.001	0.65
Neurosurgery	3.70	0.13	107
Surgical Oncology	0.21	0.02	1.79
Ophthalmology	1.06	0.03	35.77
Orthopedic surgery	0.37	0.04	3.49
Inhalational anesthetic	2.53	0.36	17.61
Intraoperative propofol	2.80	0.52	15.17
Intraoperative opioids	1.00	0.99	1.01
Anesthesia duration	0.98	0.97	0.99
Dexamethasone: Apfel interaction	0.59	0.37	0.96
PONV, postoperative nausea and vomiting. CI, confidence interval. BMI, body mass index.			

Discussion

This study examined the interaction between dexamethasone and Apfel score, demonstrating that dexamethasone's antiemetic effect is more pronounced in patients at high risk for PONV. When stratified for PONV risk, the dose-response analysis revealed that dexamethasone had minimal impact on PONV reduction in patient with low Apfel scores (0-1). In contrast, among high-risk patients (Apfel scores 3-4), a 10 mg dose of dexamethasone was associated with a significantly lower incidence of PONV.

Dexamethasone is a well-studied prophylactic agent for PONV. A meta-analysis including four studies (n = 490) found dexamethasone significantly more effective than placebo to prevent PONV (risk ratio [RR] = 0.46, 95% CI 0.3, 0.7, p = 0.0003)[10]. However, its use may be associated with perioperative hyperglycemia and impaired wound healing. A larger meta-analysis of 23 RCTs (n = 11,154) reported a

mean glucose rise ranging between 6.7 and 29.4 mg/dL, which may be clinically insignificant in most cases but potentially relevant in high-risk populations[11]. Although a single dose does not appear to increase postoperative infection rates, delayed would healing, particularly in hyperglycemic patients, cannot be entirely excluded, as supported by a Cochrane review and meta-analysis of 38 studies [12]. Given these potential risks, the risk-benefit ratio of dexamethasone should be carefully weighed when considering PONV prophylaxis. Our findings suggest that the benefit of dexamethasone to prevent PONV is maximized in high-risk patients (Apfel score $\geq$ 3). In contrast, for patients with low Apfel scores (0-2), the absolute risk reduction of PONV may be too small to justify dexamethasone's potential metabolic and wound-healing effects.

Multimodal PONV prophylaxis, including dexamethasone, is standard practice for high-risk patients [13]. Our results demonstrate that dexamethasone's antiemetic efficacy increases with dose escalation up to 10 mg in patients with high Apfel scores (3-4), corroborating findings by Ye et al., who reported significant PONV reduction and decreased requirement for additional medications with 8-10 mg doses [14]. We may argue that given dexamethasone's safety profile, higher doses in high-risk PONV patients may reduce reliance on polypharmacy and its cumulative side effects. Importantly, our dose-response analysis revealed no ceiling effect at 10 mg, with this dose proving superior to 8 mg in this group of patients. Furthermore, higher dexamethasone doses may extend the therapeutic window, particularly beneficial for patients receiving long-acting opioids, by prolonging PONV protection [15].

Our study has limitations. First, the retrospective design may introduce confounding. However, we mitigated this by controlling for key covariates (e.g. opioids, anesthetic medications, surgical specialty) in the logistic regression model. Second, the generalizability of our findings may be limited by being a single-center study. Nonetheless, the incidence type of patient and surgical procedures align with larger multicenter studies. Third, PONV was only assessed during PACU stay. Although future studies may address a longer observation window, the peak incidence of PONV occurs during the first few postoperative hours. The study also has several strengths. By leveraging the Apfel score, we demonstrated a clear dose-response relationship, with 10 mg dexamethasone offering superior efficacy in high-risk patients, while minimizing unnecessary exposure in low-risk patients. The retrospective designed allowed for efficient evaluation of real-world clinical practice. Prospective randomized trials are necessary to validate our dose-stratified approach, particularly comparing 8 mg vs. 10 mg dexamethasone in high-risk patients. Finally, pharmacodynamic studies might clarify the molecular basis of the dose-response relationship of dexamethasone.

Conclusion

This study demonstrates that dexamethasone's antiemetic efficacy follows a dose-dependent relationship, with maximal benefit observed at 10 mg in high-risk patients (Apfel scores 3–4), while offering minimal advantage in low-risk populations (Apfel scores 0–2). These findings support an approach to PONV prophylaxis that balances efficacy and minimization of the side effects associated

with polypharmacy. Future prospective trials should validate these results and focus on the pharmacodynamic nature of the dose-response relationship of dexamethasone.

Abbreviations

ASA: American Society of Anesthesiologists

BMI: Body mass index

CI: Confidence interval

EMR: Electronic medical record

ENT: Ear, nose, and throat

EPV: Events per variable

IRB: Institutional Review Board

IQR: Interquartile range

LOS: Length of stay

OR: Odds ratio

PACU: Post-anesthesia care unit

PONV: Postoperative nausea and vomiting

RCT: Randomized controlled trial

RR: Risk ratio

SD: Standard deviation

Declarations

Ethics approval and consent to participate

This study was approved by the Augusta University Institutional Review Board and it was conducted in accordance with the 1964 Declaration of Helsinki and its later amendments. The requirement for informed consent was waived by the Augusta University Committee A in accordance with U.S. federal regulations (45 CFR 46.116).

Consent for publication

Not applicable.

Availability of data and materials

The data supporting the findings of this study are available from the corresponding author upon reasonable request and at the authors' discretion, in order to protect patient privacy.

Competing interests

None.

Funding

This research received no external funding.

Authors contributions

ERP and SVP conceived the idea and designed the study. JAB and PG collected and processed the dataset. ERP performed the data analysis. ERP and BAM wrote the main manuscript text. ERP prepared figures 1-2. All authors reviewed the manuscript.

Acknowledgments

Not applicable.

References

1. Sizemore DC, Singh A, Dua A, Singh K, Grose BW. Postoperative nausea. *StatPearls [Internet].* StatPearls Publishing; 2022.
2. Habib AS, Chen Y-T, Taguchi A, Henry Hu X, Gan TJ. Postoperative nausea and vomiting following inpatient surgeries in a teaching hospital: a retrospective database analysis. *Curr Med Res Opin.* 2006;22(6):1093-9.
3. Li Z-P, Song Y-C, Li Y-L, Guo D, Chen D, Li Y. Association between operative position and postoperative nausea and vomiting in patients undergoing laparoscopic sleeve gastrectomy. *World J Gastrointest Surg.* 2024;16(7):2088.
4. Carroll NV, Miederhoff PA, Cox FM, Hirsch JD. Costs incurred by outpatient surgical centers in managing postoperative nausea and vomiting. *J Clin Anesth.* 1994;6(5):364-9.
5. Parra-Sanchez I, Abdallah R, You J, Fu AZ, Grady M, Cummings K, et al. Une analyse économique des temps et mouvements pour les nausées et vomissements postopératoires en chirurgie d'un jour. *Can J Anesth.* 2012;59:366-75.

6. Qian Y, Zhu J-k, Hou B-l, Sun Y-e, Gu X-p, Ma Z-l. Risk factors of postoperative nausea and vomiting following ambulatory surgery: A retrospective case-control study. *Heliyon.* 2022;8(12).
7. Gan TJ, Belani KG, Bergese S, Chung F, Diemunsch P, Habib AS, et al. Fourth consensus guidelines for the management of postoperative nausea and vomiting. *Anesth Analg.* 2020;131(2):411-48.
8. Soghomonyan S, Stoicea N, Ackermann W, Bhandary SP. PONV management in patients with QTc prolongation on the EKG. *Front Pharmacol.* 2021;11:565704.
9. Henzi I, Walder B, Tramèr MR. Dexamethasone for the prevention of postoperative nausea and vomiting: a quantitative systematic review. *Anesth Analg.* 2000;90(1):186-94. doi: 10.1097/00000539-200001000-00038.
10. Xu L, Xie X, Gu X. Dexamethasone for preventing postoperative nausea and vomiting after mastectomy. *Medicine (Baltimore).* 2020;99(30):e21417. doi: 10.1097/MD.0000000000021417.
11. Katerenchuk V, Ribeiro EM, Batista AC. Impact of intraoperative dexamethasone on perioperative blood glucose levels: Systematic review and meta-analysis of randomized trials. *Anesth Analg.* 2024;139(3):490-508. doi: 10.1213/ANE.0000000000006933.
12. Polderman JA, Farhang-Razi V, Van Dieren S, Kranke P, DeVries JH, Hollmann MW, Preckel B, Hermanides J. Adverse side effects of dexamethasone in surgical patients. *Cochrane Database Syst Rev.* 2018;8(8):CD011940. doi: 10.1002/14651858.CD011940.pub2.
13. Elvir-Lazo OL, White PF, Yumul R, Cruz Eng H. Management strategies for the treatment and prevention of postoperative/postdischarge nausea and vomiting: an updated review. *F1000Res.* 2020;9:F1000 Faculty Rev-983. doi: 10.12688/f1000research.21832.1.
14. Ye H, Gou J, Li S, Ji Q. Preoperative dexamethasone administration in reducing the incidence of nausea and vomiting after thyroidectomy: a systematic review and meta-analysis of drug dosage. *Gland Surg.* 2024;13(2):189-198. doi: 10.21037/gs-23-260.
15. Grape S, Usmanova I, Kirkham KR, Albrecht E. Intravenous dexamethasone for prophylaxis of postoperative nausea and vomiting after administration of long-acting neuraxial opioids: a systematic review and meta-analysis. *Anaesthesia.* 2018;73(4):480-9. doi: 10.1111/anae.14166.

Figures

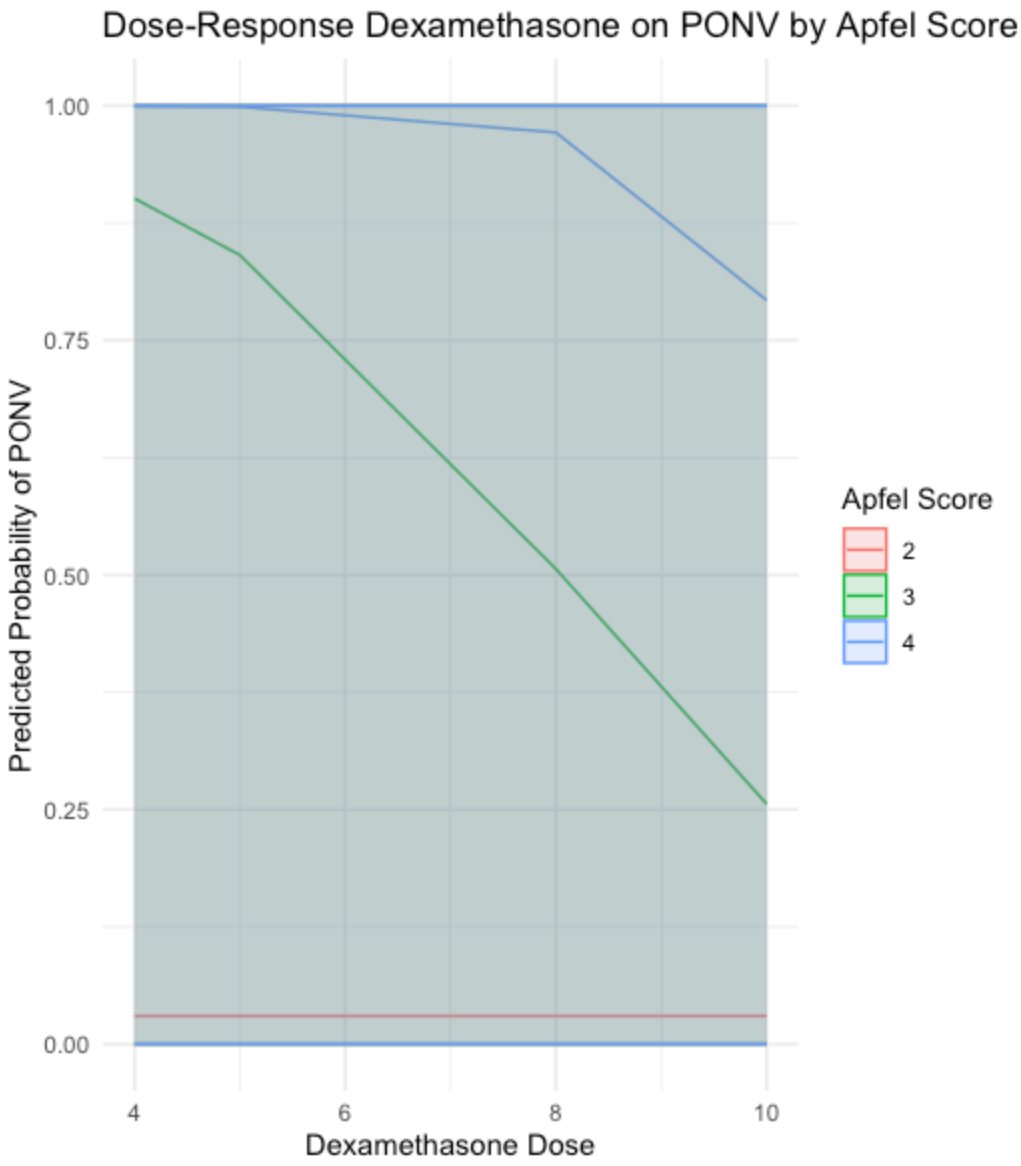

Figure 1

Dose-response relationship between dexamethasone and predicted probability of PONV across Apfel scores (2-4). Higher doses (8-10 mg) show increasing efficacy in high-risk patients (Apfel 3-4).

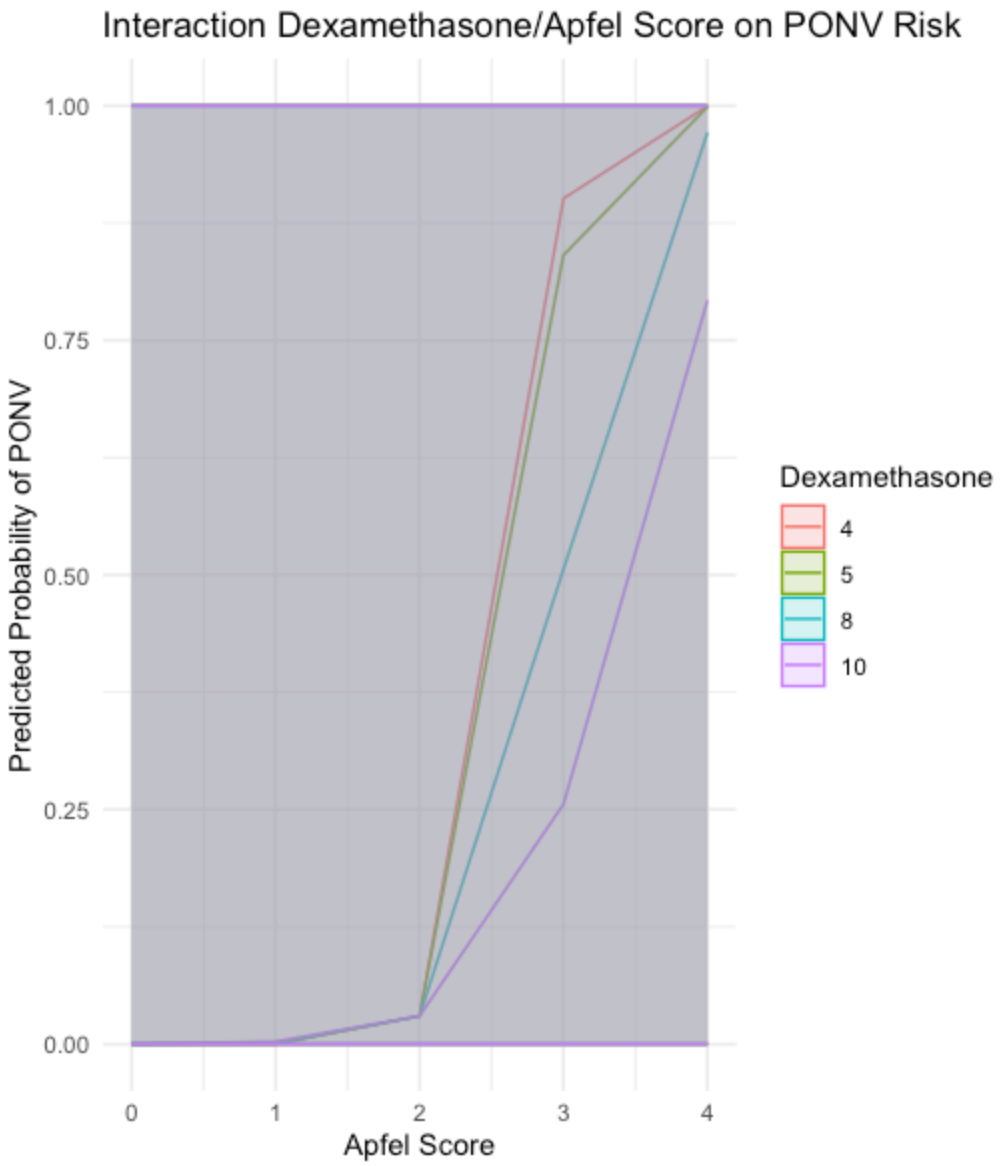

Figure 2

Interaction effect of dexamethasone dose and Apfel score on PONV risk. The antiemetic benefit escalates with both increasing dose and higher baseline PONV risk.