

Comparison of predictive models for postoperative nausea and vomiting

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Background. In order to identify patients who would benefit from prophylactic antiemetics, six predictive models have been described for the risk assessment of postoperative nausea and vomiting (PONV). This study compared the validity and practicability of these models in patients undergoing general anaesthesia.

Methods. Data were analysed from 1566 patients who underwent balanced anaesthesia without prophylactic antiemetic treatment for various types of surgery. A systematic literature search identified six predictive models for PONV. These models were compared with respect to validity (discriminating power and calibration characteristics) and practicability. Discriminating power was measured by the area under the receiver operating characteristic curve (AUC) and calibration was assessed by weighted linear regression analysis between predicted and actual incidences of PONV. Practicability was assessed according to the number of factors to be considered for the model (the fewer factors the better), and whether the score could be used in combination with a previously applied cost-effective concept.

Results. The incidence of PONV was 600/1566 (38.1%). The discriminating power (AUC) obtained by the models (named according to the first author) using the risk classes from the recommended prophylactic concept were as follows: Apfel, 0.68; Koivuranta, 0.66; Sinclair, 0.66; Palazzo, 0.63; Gan, 0.61; Scholz, 0.61. For four models, the following calibration curves (expressed as the slope and the offset) were plotted: Apfel, $y=0.82x+0.01$, $r^2=0.995$; Koivuranta, $y=1.13x-0.10$, $r^2=0.999$; Sinclair, $y=0.49x+0.29$, $r^2=0.789$; Palazzo, $y=0.30x+0.30$, $r^2=0.763$. The numbers of parameters to be considered were as follows: Apfel, 4; Koivuranta, 5; Palazzo, 5; Scholz, 9; Sinclair, 12; Gan, 14.

Conclusion. The simplified risk scores provided better discrimination and calibration properties compared with the more complex risk scores. Therefore, simplified risk scores can be recommended for antiemetic strategies in clinical practice as well as for group comparisons in randomized controlled antiemetic trials.

Br J Anaesth 2002; **88**: 234–40

Keywords: vomiting, nausea, postoperative; anaesthesia, general; statistics, risk score

Accepted for publication: September 25, 2001

Today, the incidence of postoperative nausea and vomiting (PONV) still appears to be about 30%.^{1–3} Despite this, the benefit of routine prophylactic antiemetic treatment has been questioned because antiemetics may have side-effects⁴ and therefore patient satisfaction may not necessarily improve.⁵ The number of patients needed to be treated (NNT) to prevent one patient from suffering PONV is at best in the range of five when the event rate is relatively

high,⁶ so that unnecessary costs may arise if patients are receiving prophylactic compared with therapeutic antiemetic treatment. However, totally neglecting the potential of prophylactic antiemetics is by no means acceptable: PONV may lead to severe medical complications with sudden airway compromise,⁷ for example. The cost of prophylactic treatment may be contained by keeping the number of patients needed to be treated small through

the use of a multimodal approach for identifying patients at high risk.⁸ Patient satisfaction may well improve if patients with a high risk of PONV are treated.⁵ In contrast, not using prophylactic treatment in these patients may result in considerable costs, far exceeding the costs of prophylactic antiemetic treatment.⁹

In order to identify patients at high risk who would benefit from a cost-effective antiemetic treatment,^{10 11} several models and scores have been proposed. As one of the risk scores predicting the probability of PONV has been developed by our centre, we decided to compare its validity and practicability with all other published models in patients from a different centre.

Patients and methods

The study was approved by the local ethics committee and informed consent was obtained from every patient.

All patients received balanced anaesthesia with isoflurane, enflurane, sevoflurane or desflurane in nitrous oxide/oxygen (ratio 2:1). Propofol, thiopental or etomidate was used for induction at clinically required doses. None of the patients included in the study received perioperatively (at least 24 h before and after anaesthesia) any drug with potential antiemetic properties. Vecuronium, atracurium or mivacurium was used to facilitate intubation and repeat doses were only given if needed, so that the need for antagonizing neuromuscular blockade (atropine 0.5 mg and pyridostigmine 0.1 mg kg⁻¹) was rare (approximately 3%). The most frequently used anaesthetic technique (60% of cases) consisted of propofol, fentanyl and vecuronium for induction followed by desflurane in nitrous oxide/oxygen for maintenance and additional doses of fentanyl as required.

Nausea and vomiting were assessed in the postanaesthetic care unit by specially instructed nurses or anaesthesiologists. Vomiting or retching was considered as an emetic episode. Nausea was assessed on a four-point verbal rating scale (none, mild, moderate, severe) and patients were interviewed explicitly before transfer to the ward. During the afternoon of the same day (at least 6 h postoperatively) and during the following day (at least 24 h postoperatively), further standardized postoperative visits were performed. A patient was considered to have had PONV if any degree of nausea and/or any emetic episodes occurred in at least one of the periods investigated.

A systematic search of a literature database (<http://www.nlm.nih.gov/databases/freemodl.html>) revealed 11 studies dealing with risk models and PONV^{1 2 12-19} when the following search terms were used: 'postoperative' together with (=logical AND) 'score' AND ('nausea' OR 'vomiting') AND 'risk'. However, we excluded five studies because they did not present a predictive model or were validations of previous scores^{1 13 16 18 19} and two further studies from our centre because they dealt only with postoperative vomiting and not with PONV.^{15 16} Thus, four

scores for predicting PONV were identified initially.^{2 12 14 17} Additional hand searching of abstracts and other sources revealed two additional models,^{20 21} so that a total of six models/scores were found for the prediction of PONV.

For each patient, four probabilities of PONV were calculated according to the four scores.^{2 12 14 17} The remaining two models allowed classification of patients only into those with low (less than 30%) and high (more than 30%) risk.^{20 21} Either probability of PONV or classification into low or high risk was used to create so-called receiver operating characteristic (ROC) curves, as described previously.²

In short, a predictive model provides for an individual a probability of an event between 0 and 1. In practice, a decision is needed about whether this event will occur. Depending on the value of the probability that an event is expected to occur (decision criterion), the sensitivity and specificity of a predictive model vary. The ROC curve displays the correlation between the sensitivity and the specificity for all possible decision criteria. Therefore, the area under the ROC curve (AUC) is an overall measure of a risk score/model to discriminate patients with PONV from those without PONV (discriminating power) and is frequently used to compare different risk scores/models.

However, it should be noted that most scores and models have a limited number of outcome variables, resulting in a limited number of possible decision criteria. As ROC curves are constructed by direct lines between the data pairs of specificity and sensitivity, scores/models with fewer risk classes may result in a smaller AUC. Thus, the AUCs of the different scores/models were compared in three ways.

First, the AUC was calculated from the ROC curve that was given by the original scores/models.

Secondly, the four scores that allowed the calculation of the probability of PONV were adapted to the risk classes (<10%, low risk; 10–30%, mild to moderate risk; 30–60%, high risk; >60%, extremely high risk) recommended by White and Watcha.^{10 11} This resulted in three risk classes for the scores from Koivuranta and colleagues and Apfel and colleagues and four risk classes for the scores from Palazzo and Evans and from Sinclair and colleagues, so that all scores had a similar number of decision criteria and were directly comparable. Thirdly, ROC curves with their AUC were calculated for the recommendation of Gan or Scholz and colleagues to apply prophylactic antiemetic treatment if three or more points were obtained²⁰ or if the risk was greater than 30%.²¹ The latter also applied to the risk scores with more than one decision criterion,^{2 12 14 17} i.e. the information was collapsed to a dichotomous outcome so that a direct comparison of all scores was possible.

Differences between the AUC of $P < 0.05$ were considered to be statistically significant.

For the four scores for which the probability of PONV could be determined,^{2 12 14 17} the predicted incidences were compared with the real incidences and weighted linear regression analysis was applied across the recommended

Table 1 Patient characteristics with frequencies and odds ratio for PONV. Data are presented as number of patients (%) except age and duration, which are given in years and minutes (25th and 75th percentiles), and the calculated odds ratios using multiple logistic regression analysis for each factor, with the 95% confidence interval. The surgical categories refer to the categories used in some risk models. Some patients fitted more than one classification, whereas 292 patients did not fit any. * $P < 0.001$; all other P values are > 0.1 .

	<i>n</i>	%	Odds ratio	95% confidence interval
Total	1566	100	–	–
Age (yr), odds ratio per decade	46.1	30–61	0.96	0.90–1.02
Female	699	44.6	2.91*	2.30–3.70
Previous history of PONV	569	36.3	1.71*	1.36–2.15
Previous history of motion sickness	134	8.6	1.73*	1.17–2.57
Previous history of PONV or motion sickness	634	40.5	1.83*	1.46–2.29
Obesity (body mass index > 30)	214	13.7	0.82	0.59–1.13
Anxiety (assessed preoperatively)	336	21.5	1.25	0.95–1.63
Non-smoking status	1098	70.1	1.83*	1.41–2.37
Duration of anaesthesia (min), odds ratio (per h)	123	84–165	1.36*	1.22–1.51
Gynaecological operations, all (no curettages)	52	3.3	1.11	0.57–2.20
Gynaecological laparoscopies	47	3	1.63	0.86–3.09
Orthopaedic procedures, shoulder	146	9.3	1.37	0.93–2.02
Orthopaedic procedures, knee	201	12.8	1.10	0.77–1.55
Orthopaedic procedures, others	538	34.4	0.93	0.72–1.21
Ophthalmic operations, no strabismus surgery	75	4.8	1.36	0.78–2.37
ENT operations, all	93	5.9	1.00	0.62–1.63
ENT operations, middle ear operations	21	1.3	1.56	0.61–4.00
Abdominal surgery, all (including all laparoscopies)	217	13.9	1.23	0.83–1.83
Laparoscopic cholecystectomies	42	2.7	2.85*	1.40–5.81
Use of intraoperative opioids	1559	99.6	1.86	0.32–10.78
Use of postoperative opioids	1078	68.8	1.32	1.01–1.73
Use of perioperative opioids	1563	99.8	1.85	0.15–22.45
Patients with PONV	600	38.3	N/A	N/A

classes. This regression analysis resulted in calibration curves for which a slope of 1.00 or 45° with no offset would represent a perfect fit. A deviation from the slope of less than 25% was defined to be clinically acceptable.

The risk calculations were performed using Excel 2000 (Microsoft, USA). Logistic regression analysis was performed with SPSS 9.0 (SPSS, Chicago, IL, USA). The area under the ROC curve was calculated using MedCalc 4.2 (Mariakerke, Belgium).

Results

An average of 38.3% (600/1566) patients suffered from PONV (Table 1). The population analysed represented 885 orthopaedic, 75 ophthalmic, 93 ENT, 170 gastrointestinal abdominal and 52 gynaecological surgical procedures and 292 procedures of other types. Of the 885 orthopaedic patients, 146 had shoulder, 201 knee, 89 hip and 449 other types of orthopaedic procedures. However, Table 1 does not display all numbers for all types of procedure. The selection was based on the types that were considered in at least one of the risk models. For example, one score¹⁷ considered an odds ratio of 5.91 for shoulder, 2.82 for knee and 2.57 for all other orthopaedic surgery. The odds ratio in this population, however, revealed no significant effect of orthopaedic surgery on PONV (Table 1). Another score defined surgery involving the abdominal cavity as a risk factor for PONV.²¹ This included all laparoscopic surgery, so that 170

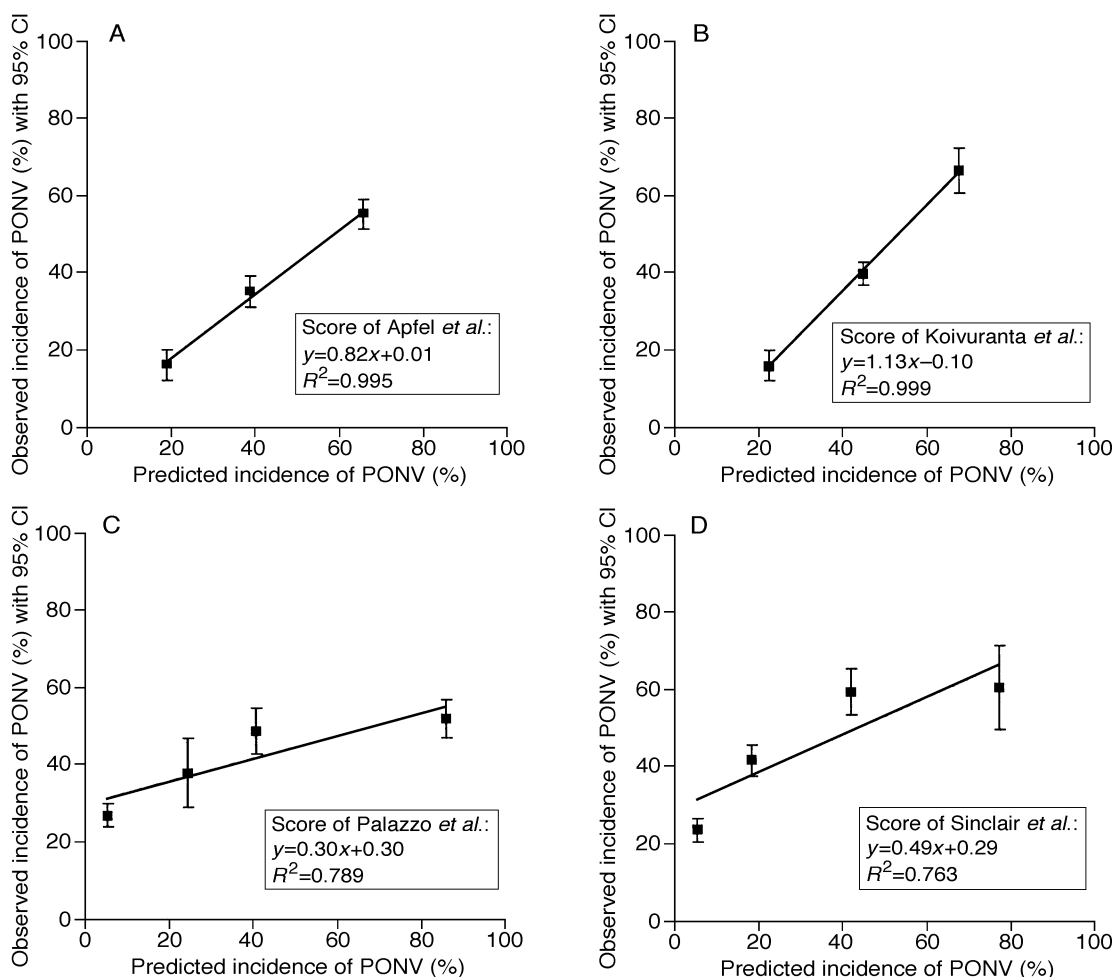
gastrointestinal procedures [laparotomies and laparoscopies (42)] plus 47 gynaecological laparoscopies resulted in 217 procedures involving the abdominal cavity. Again, as in all other types of surgeries investigated here, procedures involving the abdominal cavity had no significant effect on PONV (Table 1).

The discriminating power of the original scores from Apfel, Koivuranta and Sinclair and their colleagues was significantly higher than that of the scores from Palazzo and colleagues, Gan, and Scholz and colleagues (Table 2; all $P < 0.05$). The application of the four scores to the classes recommended by White and Watcha did not lead to a significant decrease in the AUC ($P > 0.05$). When the classification was made according to low-risk patients (less than 30%), in whom no prophylaxis should be given, or high-risk patients, in whom prophylactic antiemetic strategies should be considered (more than 30%), all predictions of the scores which enabled calculation of the probability decreased significantly ($P < 0.05$).

No calibration curve was possible with the models that simply classified patients into two risk groups without giving an expected incidence.^{20 21} The scores from Apfel and Koivuranta and their colleagues showed a good correlation between the predicted and actual incidences of PONV (Fig. 1A and B). This was not the case for the scores from Palazzo and Sinclair and their colleagues, for which the incidence of patients classified as having a low risk ($< 10\%$) was above 20% (Fig. 1C and D).

Table 2 Area under the ROC curve (AUC) for the six risk scores. Three applications were defined according to (A) the original description of the authors, (B) the four categories suggested by Watcha *et al.* and (C) a binary decision with a limit of 30%. CI=confidence interval; N/A=not applicable.

Authors	(A) Original model		(B) Watcha model		(C) Binary model	
	AUC	95% CI	AUC	95% CI	AUC	95% CI
Apfel <i>et al.</i> ²	0.68	0.66–0.71	0.68	0.65–0.70	0.64	0.62–0.66
Gan ²⁰	0.61	0.58–0.63	N/A	–	0.61	0.58–0.63
Koivuranta <i>et al.</i> ¹⁴	0.70	0.67–0.72	0.66	0.64–0.69	0.60	0.58–0.63
Palazzo and Evans ¹²	0.64	0.62–0.67	0.63	0.60–0.65	0.62	0.59–0.64
Scholz <i>et al.</i> ²¹	0.61	0.58–0.63	N/A	–	0.61	0.58–0.63
Sinclair <i>et al.</i> ¹⁷	0.68	0.66–0.71	0.66	0.64–0.69	0.61	0.59–0.63

**Fig 1** Calibration curves, i.e. correlations between predicted (x) and actual (y) incidences, for the scores adapted to the risk classes suggested by White and Watcha to allow direct comparisons.^{10 11} (A) Score of Apfel *et al.*² (B) Score of Koivuranta *et al.*¹⁴ (C) Score of Palazzo *et al.*¹² (D) Score of Sinclair *et al.*¹⁷ The calibration curves are weighted according to the number of patients per group.

Discussion

A comparison of all currently available models for predicting the probability of PONV in patients undergoing balanced anaesthesia revealed significant differences concerning their validity and practicability. Among these models, the simplified scores from Apfel and Koivuranta and their colleagues^{2 14} appeared to be suitable tools for

clinicians to put the rational and cost-effective antiemetic concept into practice¹⁰ and for researchers to perform group comparisons in randomized controlled trials.^{11 22}

Palazzo and Evans were the first to apply logistic regression analysis to patients undergoing minor orthopaedic surgery under well-defined conditions.¹² Although they did not originally intend to develop a score with universal applicability for predicting PONV, the first

Table 3 Comparison of the six scores. Note that the simplified models by Apfel *et al.*² and Koivuranta *et al.*¹⁴ have the best discrimination and calibration despite considering just four or five risk factors. AUC=area under the receiver operating characteristic curve

	Apfel <i>et al.</i> ²	Gan ²⁰	Koivuranta <i>et al.</i> ¹⁴	Palazzo and Evans ¹²	Scholz <i>et al.</i> ²¹	Sinclair <i>et al.</i> ¹⁷
Discriminating properties >0.65 (AUC)	+ (0.68)	– (0.61)	+ (0.70)	– (0.64)	– (0.61)	+ (0.68)
Risk can be calculated as percentage (yes/no)	+ (yes)	– (no)	+ (yes)	+ (yes)	– (no)	+ (yes)
Risk calculated in percent with acceptable calibration (yes/no, slope and offset)	+ (yes) (0.82 and 0.01)	– (N/A)	+ (yes) (1.13 and –0.10)	– (no) (0.30 and 0.30)	– (N/A)	– (no) (0.49 and 0.29)
Applicable to Watcha's recommendations	+ (yes)	– (no)	+ (yes)	+ (yes)	– (no)	+ (yes)
Ease of use I (simplified model possible)	+ (yes)	+ (yes)	+ (yes)	– (no)	+ (yes)	– (no)
Ease of use II (number of predictors needed)	+ (4)	– (14)	+ (5)	+ (5)	– (9)	– (12)

validation with 400 patients suggested that their model could well be transferred to other types of surgery.¹³ However, in this validation, the calibration curve presented a flattened slope of 0.3 and an offset of 30%. Thus, patients who were classified as having a low risk showed a much higher incidence, while patients who were really at low risk were not identified. The reason for this difficulty may lie in the extremely high odds ratio of 53.0 for a positive history of PONV in the data from Palazzo and Evans, because of the smaller study population,¹² while the odds ratio of this risk factor was between 2.27 and 3.13 in all other studies^{1 2 13 14 17} and 1.71 in this population (Table 1). Although this calibration makes this score less suitable for clinical practice, we would like to point out that this model for the prediction of PONV has stimulated several other investigators to apply this method on a larger scale.

The score from Koivuranta and colleagues appeared to be one of the best models in the population investigated.¹⁴ First, they identified all significant factors and calculated the corresponding AUC. Interestingly, the type of operation did not have any significant effect on PONV in their original multivariable model, i.e. when corrections for the other predictors were considered. Secondly, they reduced the number of predictors from eight to five and found no effect on overall discriminating power. Thirdly, they observed that the coefficients of the predictors were all quite similar. Thus, they investigated whether a model which was based only on the simple number of risk factors resulted in a similar AUC compared with the rather complicated logit model, which considers different coefficients for each factor. They found that such a score can be simplified without a significant decrease in the AUC. In our view, simplification is an important characteristic for a score suitable for daily practice (Table 3).

The calibration curve of the model of Sinclair and colleagues appeared to have an offset of about 30%, which is corroborated by a recent study that revealed a similar offset of 27%.²³ Therefore, like the score of Palazzo and Evans, patients classified as low-risk (<10%) showed a much higher incidence (25%), while true low-risk patients were not appropriately identified. Ascribing this discrepancy to the fact that the score of Sinclair and colleagues was developed for ambulatory surgical patients conflicts with

the expectation that, under comparable conditions (same procedures, same anaesthetic techniques, etc.), PONV should occur more frequently in outpatients than in inpatients, as motion sickness may be a contributing factor. In contrast, the incidence reported by Sinclair and colleagues was only 9.1%, which is far below the known average incidence of 20–40% from all other prospective studies on PONV.^{1 2 12 14} Under-reporting of PONV was suggested as a possible problem in the study of Sinclair and colleagues.¹⁷ Another difficulty with this model is the flattened slope of only 0.5 (~30°). Comparison of the odds ratio of our population with those described by Sinclair and colleagues revealed that, in accordance with other multivariable analyses,^{1 13 14} most types of surgery did not affect PONV significantly, while odds ratios from Sinclair and colleagues ranged between 2.57 (orthopaedic surgery) and 6.68 (plastic surgery). If these odds ratios do not apply to other centres, such as the population investigated here, this could result in a flatter calibration curve, as the score would lead to some patients being estimated to have a much higher or lower risk (depending on the type of surgery) while the real incidence would not have been affected to that extent. In addition, the risk can only be estimated using a rather complicated formula, making the use of this score less practical under clinical conditions (Table 3).

The score of Apfel and colleagues² is a result of collaboration between a German and a Finnish centre. Reanalysing their previously published data,^{14–16} the authors investigated whether risk scores were valid for different centres and whether risk scores based on logistic regression coefficients could be simplified without loss of discriminating power. While testing different scores, they developed a final score from a joint data set which consisted of four predictors: female gender, history of motion sickness or PONV, non-smoking status and the use of postoperative opioids. If none, one, two, three or four of these risk factors were present, the incidences of PONV were 10, 21, 39, 61 and 79% respectively. Owing to the definition of a 'low risk' as less than 10%, patients with no risk factor or one risk factor were classified into the mild to moderate risk class. However, for practical purposes it may make more sense to classify patients with no risk factors as low-risk patients. We believe that this will be even more reasonable when the

recommendation of White and Watcha is applied.^{10 11} In the population studied here, the score of Apfel and colleagues gave an acceptable AUC of 0.68 and a slope very close to 1. Similar positive results in favour of the score of Apfel and colleagues² have now been obtained by Pierre and colleagues.²³ In the light of this, and its easy applicability, we suggest that this score and its underlying model provide a tool that can usefully be put into clinical practice (Table 3).

While the other two models are guidelines for the use of prophylactic antiemetics rather than genuine risk scores to estimate the probability of PONV, they were included in this comparison for the sake of completeness.^{20 21} Unfortunately, it is not clear to what extent the weight attributed to their risk factors is based on multivariable analysis. Moreover, they are more complex than the simplified scores of Apfel and Koivuranta and their colleagues, they do not have better discriminating power and do not provide a calibration curve. In addition, they cannot be used for the cost-effective strategy suggested by White and Watcha (Table 3).^{10 11} The overall weak performance may indicate that risk models based on personal conviction yields poorer results than risk scores where the evidence is based on conscientious multivariate analyses of thoroughly collected data.

It seems surprising that models with a higher number of predictors were not superior to those with few predictors. The main reason may be that there are some predictors (e.g. female gender) which appear to be fairly constant in every population and are therefore part of every model, while other predictors included in the more complicated models do not seem to have more general applicability. For example, one model considered orthopaedic procedures to be associated with odds ratios between 2.6 and 5.9,¹⁷ while they had no significant effect on PONV in this data-set (Table 1). Another reason is that the increase in discriminating power with an additional predictor is relatively high when the first predictors are introduced in a model but decreases when four or five predictors are already present, so that further inclusion of predictors is not justified.²⁴

We have demonstrated that the simplified models appear to be easily applicable and to provide a valid concept to predict the probability of PONV in individuals. However, none of the models is able to predict with certainty which individual will actually suffer from PONV. An experiment with a virtual population has shown that this limitation results from the fact that the odds ratio of the risk factors for PONV is at best in the range of 2–3 (when non-reproduced outliers are not considered).²⁴ Therefore, unless significantly stronger predictors are found which appear to be applicable to most centres, it seems unlikely that further risk scores will lead to significantly better predictions.

Despite the above-mentioned limitations, the simplified risk scores can provide a rational basis for an antiemetic strategy. In addition, they may be used for group comparisons of randomized controlled trials of antiemetic strategies.²² If, for example, several risk factors have a tendency

to be more frequent in one group than in the other, although not being statistically significant on their own, this may lead to a significantly different risk, as assessed by a scoring model. Thus, a more cautious interpretation of the results may be needed. On the other hand, when one risk factor is significantly more frequent in one group than in the other, although the overall risk is similar, this finding would be put into perspective. Therefore, we believe that validated scores predicting PONV should be used not only in clinical practice but also in demographic tables for group comparisons in randomized controlled trials.

Acknowledgement

We thank Bernd W. Urban for critically reading this manuscript.

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