A calibration hierarchy for risk models: strong calibration occurs only in utopia

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Abstract

Objective. Calibrated risk models are vital for valid decision support. We define four levels of calibration and describe implications for model development and external validation of predictions.

Study Design and Setting. We present results based on simulated datasets.

Results. A common definition of calibration is "having an event rate of *R*% among patients with a predicted risk of *R*%", which we refer to as 'moderate calibration'. Weaker forms of calibration only require the average predicted risk (mean calibration) or the average prediction effects (weak calibration) to be correct. 'Strong calibration' requires that the event rate equals the predicted risk for every covariate pattern. This implies that the model is fully correct for the validation setting. We argue that this is unrealistic: the model type may be incorrect, at model development the linear predictor is only asymptotically unbiased, and all nonlinear and interaction effects should be correctly modeled. In addition, we prove that moderate calibration guarantees non-harmful decision-making. Finally, results indicate that a flexible assessment of calibration in small validation datasets is problematic.

Conclusion. Strong calibration is desirable for individualized decision support, but unrealistic and counter-productive by stimulating the development of overly complex models. Model development and external validation should focus on moderate calibration.

Keywords

Calibration; Decision curve analysis; External validation; Loess; Overfitting; Risk prediction models

What is new?

Key Findings

- We defined a new hierarchy of four increasingly strict levels of calibration, referred to as mean, weak, moderate, and strong calibration.
- Strong calibration of risk prediction models implies that the model was correct given the included predictors. We argue that this is unrealistic.
- Moderate calibration of risk prediction models guarantees that decision-making based on the model does not lead to harm.
- The reliability of calibration assessments, most notably of flexible calibration plots, is highly dependent on the sample size of the validation dataset.

What this adds to what is known

- The evaluation of risk prediction models in terms of calibration is often described as a crucial aspect of model validation. However, a systematic framework for levels of calibration for risk prediction models was lacking, and the characteristics of different levels were unclear.
- We find that strong calibration of risk models occurs only in utopia, while moderate calibration does not and is sufficient from a decision-analytic point of view.

Implications of the findings

- At model development, researchers should not aim to develop the correct model. This is practically impossible and may backfire by developing overly complex models that overfit the available data. Our focus should be on achieving moderate calibration, for example by controlling model complexity and shrinking predictions towards the average.
- At model validation, sufficiently large datasets should be available to reliably assess moderate calibration. We suggest a minimum of 200 events and 200 non-events.

1. Introduction

There is increasing attention for the use of risk prediction models to support medical decision-making. Discriminatory performance is commonly the main focus in the evaluation of performance, while calibration commonly receives less attention [1]. A prediction model is calibrated in a given population if the estimated risks are reliable, i.e. correspond to observed proportions of the event. Commonly, calibration is defined as 'for patients with an estimated risk of R%, on average R out of 100 should indeed suffer from the disease or event of interest'. Calibration is a pivotal aspect of model performance [2-4]: "For informing patients and medical decision making, calibration is the primary requirement" [2], "If the model is not […] well calibrated, it must be regarded as not having been validated. […] To evaluate classification performance […] is inappropriate" [4].

Recently, a stronger definition of calibration has been emphasized in contrast to the definition of calibration given above [4,5]. Models are considered strongly calibrated if estimated risks are accurate for each and every covariate pattern. In this paper, we aim to define different levels of calibration and describe implications for model development, external validation of predictions, and clinical decision-making. We focus on predicting binary endpoints (event vs no event), and assume that a logistic regression model is developed in a derivation sample with performance assessment in a validation sample. We expand on examples used in recent work by Vach [5].

2. Assessing calibration at external validation

2.1.Methods

We assume that the predicted risks are obtained from a previously developed prediction model for outcome Y (1=event, 0=non-event), e.g. based on logistic regression analysis. The model provides a constant (model intercept) and a set of effects (model coefficients). The linear combination of the coefficients with the covariate values in a validation set defines the linear predictor L: $L = a + b_1 \times x_1 + b_2 \times x_2 + \cdots + b_i \times x_i$, where a is the model intercept, b_1 to b_i a set of regression coefficients, and x_1 to x_i the predictor values that define the patient's covariate pattern. Ideally the observed proportions in the validation set equal the predicted risks, resulting in a diagonal line in the plot (e.g. Figure 1A).

Calibration of risk predictions is often visualized in calibration plots. These plots show the observed proportion of events associated with a model's predicted risk [6]. The observed proportions per level of estimated risk cannot be directly observed. We consider their estimation in three ways. First, the observed event rates can be obtained after categorizing the predicted risks, for example using deciles. This is commonly done for the Hosmer-Lemeshow test [7]. Then, for each group the average predicted risk can be plotted versus the observed event rate to obtain a calibration curve, see [8] for an example. Second, the logistic recalibration framework can be used [9,10], where a logistic model is used for the outcome Y as a function of L. More technically, the logistic recalibration framework fits the following model: $logit(Y) = a + b_L \times L$. Using the results of this model to estimate the observed proportions results in a logistic calibration curve. If $b_L = 1$ and $a = 0$, the logistic calibration curve coincides with the diagonal line. The coefficient b_L is the calibration slope that gives an indication of the level of overfitting ($b_L < 1$) or underfitting ($b_L > 1$). Overfitting is most

common, reflected in a linear predictor that gives too extreme values for the validation data: high risks are overestimated and low risks are underestimated. The intercept a can be interpreted when fixing $b_L$at 1, i.e. $a|b_L{=}1$. This calibration intercept is obtained by fitting the model $logit(Y) = a + offset(L)$, where the slope b_L is set to unity by entering L as an offset term to the model. Predicted risks are on average underestimated if $a|b_L{=}1 > 0$, and overestimated if $a|b_L{=}1 < 0$.

Third, a flexible, non-linear, calibration curve can be considered using the model $logit(Y) = a + f(L)$. Here, f may be a continuous function of the linear predictor L, such as loess or spline transformations [6,11]. We used a loess smoother in this paper. Whereas pointwise confidence intervals are easy to obtain in closed form for logistic curves, flexible curves will often require advanced methods such as bootstrapping [12].

2.2. Illustration: Examples 1-5

For illustration, we consider five simulated examples, as previously presented [5]. We randomly generate four independent predictor variables x_1 to x_4. These predictor variables are ordinal with three categories (-1, 0, and 1) that each have 33% prevalence in order to visualize calibration by covariate pattern. Let outcome Y be generated by an underlying logistic regression model with the true linear predictor $L = 0.21 \times x_1 + 0.37 \times x_2 + 0.64 \times x_3 + 0.77 \times x_4$, hence the intercept equals 0, and x_1 to x_4 are assumed to have linear main effects [5]. In simulations, the true probability of event $P(Y = 1|L)$ is calculated using the linear predictor and the observed outcome Y is generated as a Bernoulli variable from $P(Y = 1|L)$. Then, we develop a model to predict Y based on x_1 to x_4, which means that we are using the correct model formulation. Finally, we validate on a new dataset that is generated with the exact same procedure. We repeat this process four times to illustrate the influence of random variability: (1) using 100 simulated patients for development and 100 for validation, (2) using

100 for development and 10,000 for validation, (3) using 10,000 for development and 100 for validation, (4) using 10,000 for development and 10,000 for validation, and (5) using 10 million for development and 10 million for validation. Estimation of model coefficients was unstable when the development data contains only 100 patients (Table 1), despite having more than 10 events per variable (4 parameters, 44 non-events, 56 events). Risk estimates were overfitted, as evidenced by the calibration slope and calibration curves at validation (Example 2 in Table 1, and Figure 1B) as well as the calibration curves. Further, the calibration intercept was negative which is suggestive of general overestimation. Enlarging the development dataset alleviated the problems (Example 4 in Table 1, Figure 1D). Similar issues emerge when using a small validation dataset (Figures 1A and 1C. Calibration results for Examples 1 and 3 are unstable, in particular the flexible calibration curve. With 10 million patients the coefficient estimates and calibration results were perfect (Table 1, Figure 1E).

3. A hierarchy of risk calibration

In the following we propose a hierarchy of increasingly strict levels of calibration, starting with the basic level of 'calibration-in-the-large', followed by weak, moderate, and strong calibration (Table 2). Higher levels of calibration require stronger conditions and imply that the conditions of lower levels are satisfied.

3.1.Level 1: mean calibration (Calibration-in-the-large)

The most basal type of calibration simply evaluates whether the observed event rate in the data equals the average estimated risk as a measure of the estimated event rate. There was some miscalibration in mean risk for Examples 1-2 where the development sample was small, even though the correct underlying model formulation was estimated. For larger development datasets the disagreement between observed and predicted risks disappeared (Examples 3-5).

The logistic recalibration framework can be used to investigate calibration-in-the-large by estimating the calibration intercept $a|b_L{=}1$, and if desired by testing the null hypothesis that $a|b_L{=}1 = 0$ using a likelihood ratio test with 1 degree of freedom [9,10]. Fixing b_L at 1 implies that we keep the relative risks fixed. Calibration-in-the-large is insufficient as the sole criterion. For example, it is satisfied when the estimated risk for each patient would equal the true event rate.

3.2.Level 2: weak calibration

The next level is to have weak calibration of predictions, defined as a calibration intercept ($a|b_L{=}1$) of 0 and a calibration slope of 1. As explained above, these values indicate that there is no over- or underfitting and no systematic over- or underestimation of predicted risks. Deviations from the ideal calibration values can readily be evaluated using confidence intervals, or tested by a Cox recalibration test, a likelihood ratio test with 2 degrees of freedom for the null hypethesis that $a|b_L{=}1 = 0$ and $b_L = 1$ [10]. In Examples 1-2, the prediction model suffers from overfitting and overestimation due to the small development sample (Figure 1A-B). We consider logistic calibration to be only a weak form of calibration for two reasons. First, this approach lacks flexibility because the calibration curve is summarized by only two parameters through a logistic model. Second, this level of calibration is by definition achieved on the dataset on which the prediction model was developed if standard estimation methods are used, such as maximum likelihood for logistic regression models. For example, it generally does not matter whether and how nonlinear effects of continuous predictors were accounted for or whether important interaction terms were included. Nevertheless, this approach can be useful at external validation because the calibration intercept and slope provide a general and concise summary of potential problems with risk calibration. In addition, when dealing with relatively small validation samples a

simple calibration assessment may be preferred over more flexible alternatives (see Example 1) [13].

3.3. Level 3: moderate calibration

Moderate calibration refers to the common definition of calibration: a risk model is moderately calibrated if, among patients with the same predicted risk, the observed event rate equals the predicted risk [4,14,15] For example, among patients with an estimated risk of 25%, 1 in 4 should have the disease. Moderate calibration can be investigated using flexible calibration curves or using categorizations of predicted risk, preferably with the addition of confidence limits. These approaches are more flexible and can reveal miscalibration that is not picked up by the logistic calibration framework. For example, strong interactions or nonlinearities may lead to miscalibration in the development sample although weak calibration is perfect [11].

3.4. Missing non-linearity or interaction: examples 6-7

We simulate patient outcomes with the same procedure as above. For Example 6 we assume that the outcome is generated by a logistic regression formula with the following true linear predictor: $0.21 \times x_1 + 0.37 \times x_2 + 0.64 \times x_3 + 1.2 \times log(x_4)$, where x_1 to x_3 are ordinal variables as defined above and x_4 is a continuous variable with a lognormal distribution (e.g. a biomarker). We develop a model to predict Y based on x_1 to x_4 (without log-transformation) using 10,000 simulated patients, with calibration curves for the development data (Figure 2A). By definition, the logistic calibration curve is perfect. The flexible calibration is not, because the effect of x_4 is not appropriately addressed. Thus, the model is weakly but not moderately calibrated on the development data.

For Example 7 we assume that the outcome is generated by a logistic regression formula with the following true linear predictor: $0.21 \times x_1 + 0.37 \times x_2 + 0.64 \times x_3 + 0.77 \times x_4 - 1 \times x_2 \times x_4$, so with a strong interaction effect between x_2 and x_4. Variables x_1 to x_4 are ordinal variables as defined above. We develop a model to predict Y based on x_1 to x_4, without the interaction, using 10,000 simulated patients, with calibration curves for the development sample (Figure 2B). Again, only the flexible calibration curve reveals that calibration is problematic.

3.5.Level 4: strong calibration

The most stringent definition of calibration requires predicted risks to correspond to observed event rates for each and every covariate pattern [4,5]. This definition of strong calibration disentangles different covariate patterns that may be associated with the same predicted risk. Requiring strong calibration is sensible from a clinical point of view [5]. If a model is moderately but not strongly calibrated, we may provide biased risk estimates depending on an individual patient's covariate values. Note that calibration is always assessed relative to the predictors in the model. Thus, if a model is strongly calibrated it is still possible that patients with the same covariate pattern have different observed event rates after stratification for another variable that is not included as a predictor. This would not invalidate the strong calibration of the model.

3.6. Model misspecification: Examples 8-9

Figure 3 presents three calibration plots to illustrate strong calibration. Each plot contains a logistic calibration curve, a flexible calibration curve, and results per covariate pattern. Figure 3A represents the validation for Example 5 (model developed on 10 million patients and validated on another 10 million patients). This model exhibits perfect strong calibration: both

calibration curves and all covariate patterns coincide with the diagonal. Example 8 (Figure 3B) uses the same validation data as Example 5, but now a model with the following linear predictor is validated: $0.40 \times x_1 + 0.31 \times x_2 + 0.68 \times x_3 + 0.63 \times x_4$. Two coefficients are overestimated and two underestimated relative to the true values (Table 1). This model exhibits perfect moderate calibration but lacks strong calibration because results per covariate pattern are scattered around the diagonal. Example 9 (Figure 3C) uses the same validation data to validate a model with the following linear predictor: $0.40 \times x_1 + 0.04 \times x_2 - 0.06 \times x_3 + 1.62 \times x_4$. The calibration curves show that this model is not weakly calibrated due to overfitting. Results per covariate pattern are scattered around the calibration curves. (This last plot is based on the third example in [5].)

3.7.Can strong calibration be assessed?

Ideally, we would check for strong calibration as in Figure 3 by calculating the observed event rate for every covariate pattern observed in the data, and construct a plot where every covariate pattern is represented by its estimated risk vs observed event rate. In practice this approach is hardly ever feasible because of limited sample size and/or the presence of continuous predictors: in such situations there may be as many patients as there are distinct covariate patterns. The impact of sample size is illustrated in Figure 4 for Examples 1-5. Figure 4A-B present the validation of the same model on a small or large dataset. In the small dataset there were 100 patients for 81 covariate patterns, hence many covariate patterns contained a single patient. These cells had an observed event rate of 0 or 1. For the model developed on 10,000 patients and validated on a different but equally large sample (Example 4, Figure 4D), the covariate patterns still did not lie on the diagonal line. Only when the

development and validation datasets were extremely large (Example 5, Figure 4E, 10M patients), results were near perfect.

An approach that may be considered as an attempt to assess calibration beyond moderate calibration involves the categorization of patients based on (combinations of) predictor values rather than on predicted risk. For different subgroups defined by values of one or more predictors, the average predicted risk may be compared with the observed event rate [16]. This is an insightful exercise, but the 'curse of dimensionality' is still looming: increasingly detailed categorizations will inevitably lead to small subgroups and hence unreliable results.

A recent measure that bears resemblance to Harrell's Emax and Brier score [6] is the estimated calibration index (ECI) [17]. This measure builds upon a flexible calibration analysis by computing the average squared difference between predicted risk and observed risk, and transforming to obtain a value between 0 and 1. ECI averages miscalibration on the patient level and therefore quantifies lack of strong calibration. If predicted risks are fully accurate, ECI equals 0. If a model is moderately yet not strongly calibrated, then ECI>0. Because ECI summarizes a flexible calibration curve into a single number, it was mainly suggested as a measure to easily compare calibration between competing models [17].

4. Calibration, decision-making, and clinical utility

Strong calibration implies that an accurate risk estimate is obtained for every covariate pattern. Hence a strongly calibrated model allows the communication of accurate risks to every individual patient. In contrast, a moderately calibrated model allows the communication of a reliable average risk for patients with the same estimated risk: among patients with an

estimated risk of 70% on average 70 out of 100 have the event, although there may exist relevant subgroups with different covariate patterns and different event rates.

Previous work has shown that miscalibration decreases clinical utility compared to moderate calibration [18]. Clinical utility was evaluated with the Net Benefit measure. This is a simple and increasingly adopted summary measure that appropriately takes the relative clinical consequences of true and false positives into account [19,20]. Net Benefit accounts for the different consequences of true and false positives through the risk threshold, i.e. the risk at which one is indifferent about classifying a patient as having the event (and providing treatment) or not. The odds of the risk threshold is the harm-to-benefit ratio, i.e. the ratio of the harm of a false positive and the benefit of a true positive classification [21]. For example, a threshold of 0.2 implies a 1:4 odds, suggesting that one true positive is worth four false positives. Net Benefit at threshold *t* equals $(N_{TP} - odds(t) \times N_{FP})/N$, with N_{TP} the number of true positives, N_{FP} the number of false positives, and N the sample size. Plotting Net Benefit for different choices for the risk threshold yields a decision curve. The model's Net Benefit need to be compared with the Net Benefit of two default strategies in which either all patients are classified as having the event (treat all) or as not having the event (treat none). If the model's Net Benefit is lower than that of a default strategy, then using the model to support decision-making can be considered as clinically harmful.

In terms of decision-making the question is whether strong calibration improves clinical utility over a moderately calibrated model? Let us consider Example 9 (Figure 3C). The model presented is not calibrated in a weak sense. We derived decision curves to assess the clinical utility of (1) the original miscalibrated model, (2) a recalibrated model to ensure moderate calibration, and (3) the strongly calibrated true model (Figure 5). Moderate

recalibration was obtained by replacing original risk estimates with those from a flexible recalibration analysis based on 10 million patients. The original model has Net Benefit below that of treat all or treat none for a subset of risk thresholds (Figure 5). The moderately recalibrated version does not have that problem anymore: Net Benefit is now at least as high as that of the default strategies. Nevertheless, the decision curve for the true model is the best one. This suggests that moderate calibration prevents the model from becoming harmful [18] but that strong calibration may further enhance the model's clinical utility. More specifically, we prove (see Appendix) that clinical utility in terms of Net Benefit will not be lower than the default strategies that either classify everyone as having the event or as not having the event.

5. Strong calibration: realistic or utopic?

In line with Vach's work [5], we find that moderate calibration does not imply that the prediction model is 'valid' in a strong sense. In principle, we should aim for strong calibration since this makes predictions accurate at the individual patient's level as well as at the group level leading tobetter decisions on average. However, we consider four problems in empirical analyses. First, strong calibration requires that the model form (e.g. a generalized linear model such as logistic regression) is correct. Such model formulations are often sensible approximations, but in reality, the true model is unknown, may not have a generalized linear form, or may not even exist [22]. Second, using maximum likelihood estimation, as is done for logistic regression and Cox proportional hazards regression for time to event outcomes, yields only asymptotically unbiased estimates of individual coefficients [23]. However, even when the model coefficients are estimated without bias there is a tendency for overfitting: their combination in the linear predictor leads to too extreme risk prediction, resulting in a calibration slope smaller than one when the model is internally or externally validated.

Ensuring sufficient events per variable (EPV) is important to control the amount of overfitting [24]. Also, for predictive purposes, estimators that impose shrinkage to reduce variance at the expense of inducing bias to the individual coefficients have been shown to be superior to standard maximum likelihood [25-27]. Such shrinkage methods include uniform shrinkage, ridge regression, LASSO, elastic net, and the Garotte [2,27].

Third, strong calibration not only requires correctly estimated regression coefficients for the main effects of model predictors, but also requires fully correct modeling of all nonlinear and non-additive effects. For a limited number of categorized predictors we can imagine fitting a 'full model' including all first- and higher-order interaction terms, but the use of continuous predictors makes finding the correct model unrealistic. We stress that calibration is assessed relative to the predictors included in the model. Failing to include relevant predictors is therefore not an argument for stating that strong calibration is unrealistic, although the fact that many relevant covariates may exist outside of the model should make us modest in claiming that we can define a "true model".

Fourth, measurement error of the predictors is in practice often ignored although it is known that this is a common phenomenon that can bias regression coefficients [28]. Moreover, measurement error may not be transportable across various settings [29]. This means that at least part of the measurement error is systematic, and further thwarts the concept of the existence of a true model.

In sum, aiming for strong calibration requires the assumption that the model formulation is fully correct, and that unbiased model coefficients as well as unbiased linear predictors are obtained. Such a true model can only be identified in an infinitely large dataset: in utopia. As

Vach [30] writes: “the idea to identify the “true” model by statistical means is just a great wish which cannot be fulfilled” (p202).

6. Moderate calibration: a pragmatic guarantee for non-harmful decision-making

Focusing on finding at least moderately calibrated models has several advantages. First, it is a realistic goal in epidemiologic research, where empirical data sets are often of relatively limited size, and the signal to noise ratio is unfavorable [31]. Second, moderate calibration guarantees that decision-making based on the model is not clinically harmful. Conversely, it is an important observation that calibration in a weak sense may still result in harmful decision-making [18]. Third, simpler models can be aimed for, although it is still advisable to have sufficient events per variable (EPV) to appropriately investigate important deviations from linearity for continuous predictors, and to assess whether some (preferably prespecified) interaction terms are indispensable. We emphasize that continuous predictors should not be categorized in a naïve attempt to achieve strong calibration. The disadvantages of categorization are too numerous to summarize here [32]. Examining nonlinear and interaction terms may help to reduce the deviation from strong calibration and obtain better individual risk estimates, but at the risk of overfitting. While still providing sensible risk predictions, simple models that are for example moderately but not strongly calibrated often have many practical advantages such as transparency or ease of use [33].

7. A link with model updating

In model updating, we adapt a model that has poor performance at external validation [34]. Basic updating approaches include, in order of complexity, intercept adjustment, recalibration,

and refitting [34,35]. There are parallels between updating methods and levels of calibration. Intercept adjustment updates the linear predictor L to $a + L$. This will only address calibration-in-the-large, but does not guarantee weak calibration. A more complex updating method involves logistic recalibration, where the linear predictor L is updated to $a + b_L \times L$. This method addresses lack of weak calibration, but does not guarantee moderate calibration unless all coefficients were biased by the same rate. In model refitting, model coefficients for the predictors are re-estimated. Refitting should lead to moderate calibration, although this may also require reassessment of nonlinear effects.

8. Sample size at external validation

Our simulations have shown the impact of sample size on how reliably calibration can be assessed (Figures 1 and 4). It is clear that observed calibration curves will easily deviate from the diagonal line even when the model is moderately or strongly calibrated. We have extended our simulations by validating the correct (and hence strongly calibrated) model from Examples 1-5 on datasets with sample size between 100 and 1000. Given an overall event rate of 50%, the number of events and non-events varied from 50 to 500, yet the observed number of events per simulated dataset may vary due to random variation. Figure A1 shows flexible calibration curves for 50 randomly drawn validation datasets per sample size, Figure A2 shows boxplots of the calibration slope and ECI for 200 randomly drawn validation datasets. Given that we know that the model is correct, ECI can be used to quantify the variability of the flexible calibration curve around the true line. The results suggest that the flexible calibration curve is more variable and hence requires more data than the calibration slope for a stable assessment. This is in line with related work on this topic [11,13,36]. Confidence intervals are useful to properly interpret the obtained results.

9. Statistical testing for calibration

We mainly focused on conceptual issues in assessing calibration of predictions from statistical models. We did not consider statistical testing in detail, and in this area the assessment of statistical power needs further study. In previous simulations, the Hosmer-Lemeshow test showed such poor performance that it may not be recommended for routine use [7,37]. In practice, indications of uncertainty such as confidence intervals are far more important than a statistical test.

10. Conclusion and recommendations

We conclude that strong calibration, although desirable for individual risk communication, is unrealistic in empirical medical research. Focusing on obtaining prediction models that are calibrated in the moderate sense is a better attainable goal, in line with the most common definition of the notion of 'calibration of predictions'. In support of this view, we proved that moderate calibration guarantees that clinically non-harmful decisions are made based on the model. This guarantee cannot be given for prediction models that are only calibrated in the weak sense. Based on these findings, we make the following recommendations. When externally validating prediction models, (1) perform a graphical assessment for moderate calibration including pointwise 95% confidence limits, and (2) provide the summary statistics for weak calibration, specifically the calibration slope (b_L) for the overall effect of the predictors and the calibration intercept ($a|b_L=1$). If sample size is limited, flexible calibration curves may become highly unstable and can be omitted [11]. In line with related work, we recommend at least 100 events and 100 non-events to assess the calibration intercept and

slope, and at least 200 events and 200 non-events to derive flexible calibration curves [11,13,36].

At internal validation, e.g. using cross-validation or bootstrapping, we recommend to focus on the calibration slope to provide a shrinkage factor for the estimated risks. The calibration intercept is not relevant because internal validation implies that the model is validated for the same setting, where the mean of predictions matches the mean event rate according to standard statistical estimation methods such as maximum likelihood. When developing or updating prediction models, we recommend to focus on simple models and, to avoid overfitting, to focus more on non-linearity than on interaction terms, but always in balance with the effective sample size. In addition, flexible calibration curves on the development or updating dataset are important to evaluate moderate calibration.

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Conflict of interest

None.

Table 1. Development and validation results for Examples 1 to 5. Results are shown for a single random draw.

	True model	**Example 1. N_D=100 N_V=100**	**Example 2. N_D=100 N_V=10,000**	**Example 3. N_D=10,000 N_V=100**	**Example 4. N_D=10,000 N_V=10,000**	**Example 5. N_D=10M N_V=10M**
Development results, shown as estimate or estimate (SE)						
C statistic	0.724	0.694		0.718		0.724
Intercept	0	0.24 (0.22)		0.01 (0.02)		0.00 (0.0007)
Coefficient x_1	0.21	-0.12 (0.27)		0.17 (0.03)		0.21 (0.0008)
Coefficient x_2	0.37	0.74 (0.28)		0.38 (0.03)		0.37 (0.0008)
Coefficient x_3	0.64	0.23 (0.26)		0.59 (0.03)		0.64 (0.0009)
Coefficient x_4	0.77	0.59 (0.27)		0.77 (0.03)		0.77 (0.0009)
Validation results, shown as estimate or estimate (SE)						
C statistic	0.724	0.623	0.668	0.673	0.717	0.724
$a \mid b_L = 1$	0	-0.18 (0.21)	-0.28 (0.02)	0.03 (0.21)	-0.04 (0.02)	0.00 (0.0007)
b_L	1	0.71 (0.29)	0.80 (0.03)	0.75 (0.27)	1.00 (0.03)	1.00 (0.0009)
Event rate	0.50	0.49	0.49	0.49	0.49	0.50
Average risk	0.50	0.53	0.55	0.48	0.50	0.50

N_D: development sample size; N_V: validation sample size; 10M: ten million; SE: standard error; $a \mid b_L = 1$: calibration intercept; b_L: calibration slope

Table 2. A hierarchy of calibration levels for risk prediction models.

Level	**Definition**	**Assessment**
Mean	Observed event rate equals average risk estimate; "calibration-in-the-large"	* Compare event rate with average predicted risk; * evaluate $a\|b_L{=}1$ (with 1 df test $a\|b_L{=}1 = 0$)
Weak	No systematic over- or underfitting and/or over- or underestimation of risks; "logistic calibration"	Logistic calibration analysis to evaluate $a\|b_L{=}1$ and b_L (with Cox recalibration test: a 2 df test of the null hypothesis that $a\|b_L{=}1 = 0$ and $b_L = 1$)
Moderate	Predicted risks correspond to observed event rates	Calibration plot (e.g. using loess or splines), or analysis by grouped predictions (including Hosmer-Lemeshow test)
Strong	Predicted risks correspond to observed event rates for each and every covariate pattern	Scatter plot of predicted risk and observed event rate per covariate pattern; impossible when continuous predictors are involved

FIGURES

Figure 1. Calibration curves on the validation data for examples 1 to 5, with pointwise 95% confidence limits for flexible curves: (A) trained on 100, validated on 100; (B) trained on 100, validated on 10,000; (C) trained on 10,000, validated on 100; (D) trained and validated on 10,000; (E) trained and validated on 10 million patients.

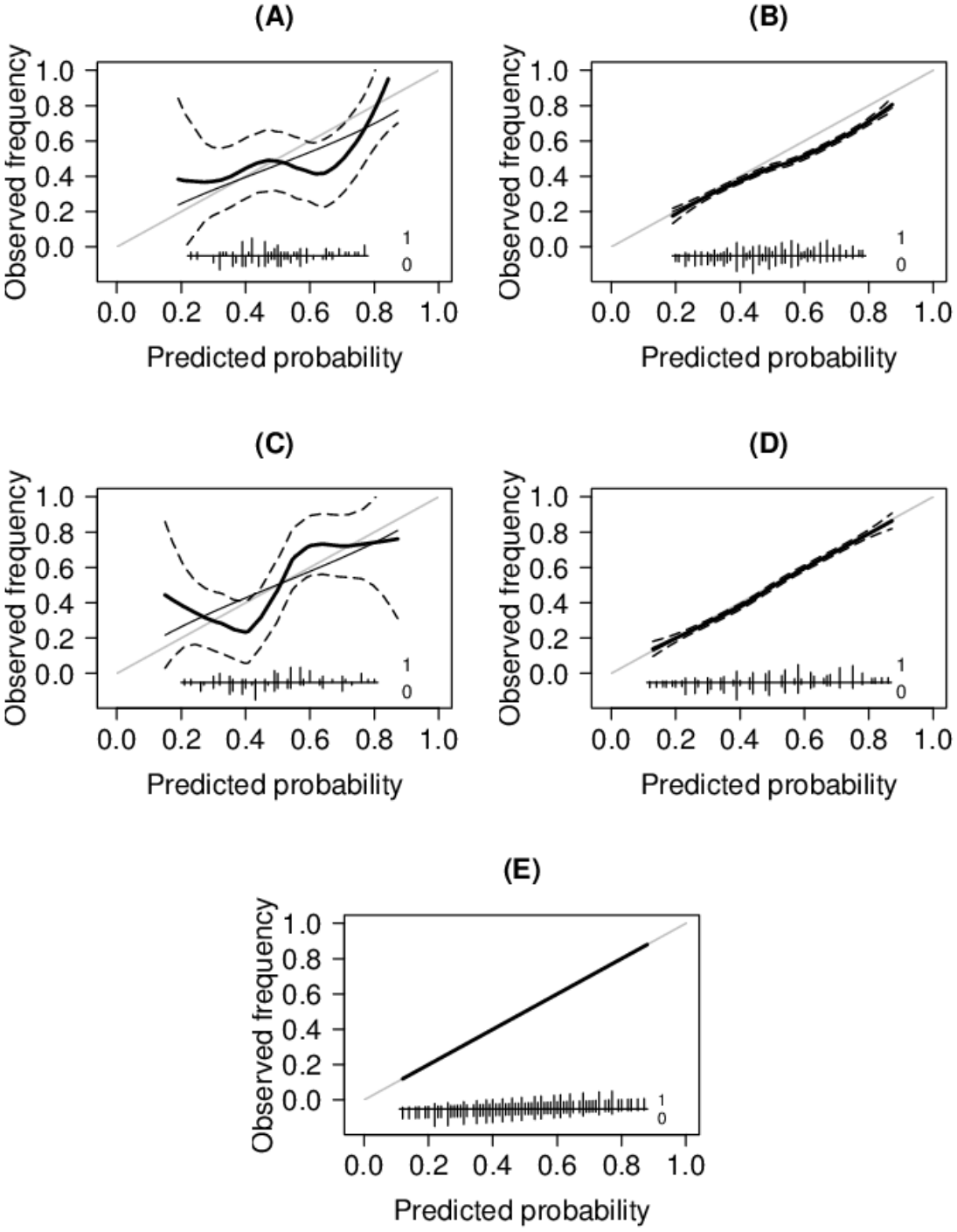


Figure 2. Calibration plots on the development data for (A) example 6 in which a true nonlinear effect is ignored and (B) example 7 in which a true interaction effect is ignored.

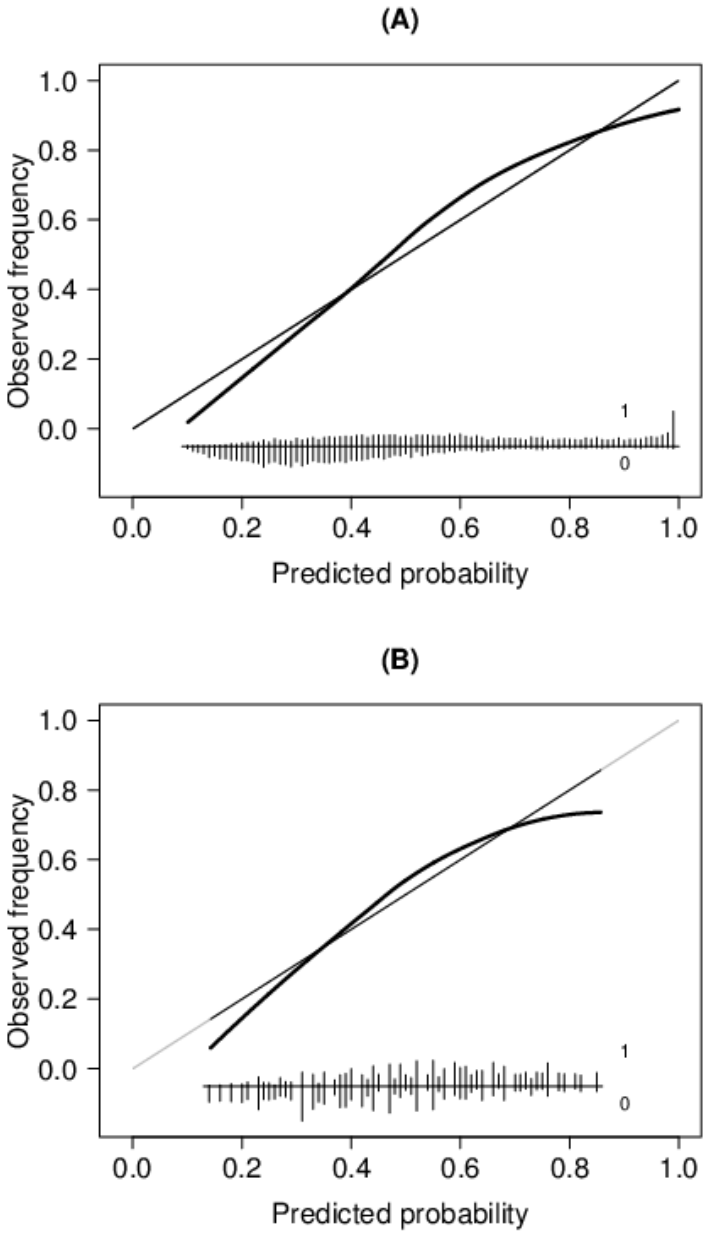


Figure 3. Calibration plots illustrating (A) strong calibration, (B) moderate but not strong calibration, (C) miscalibration.

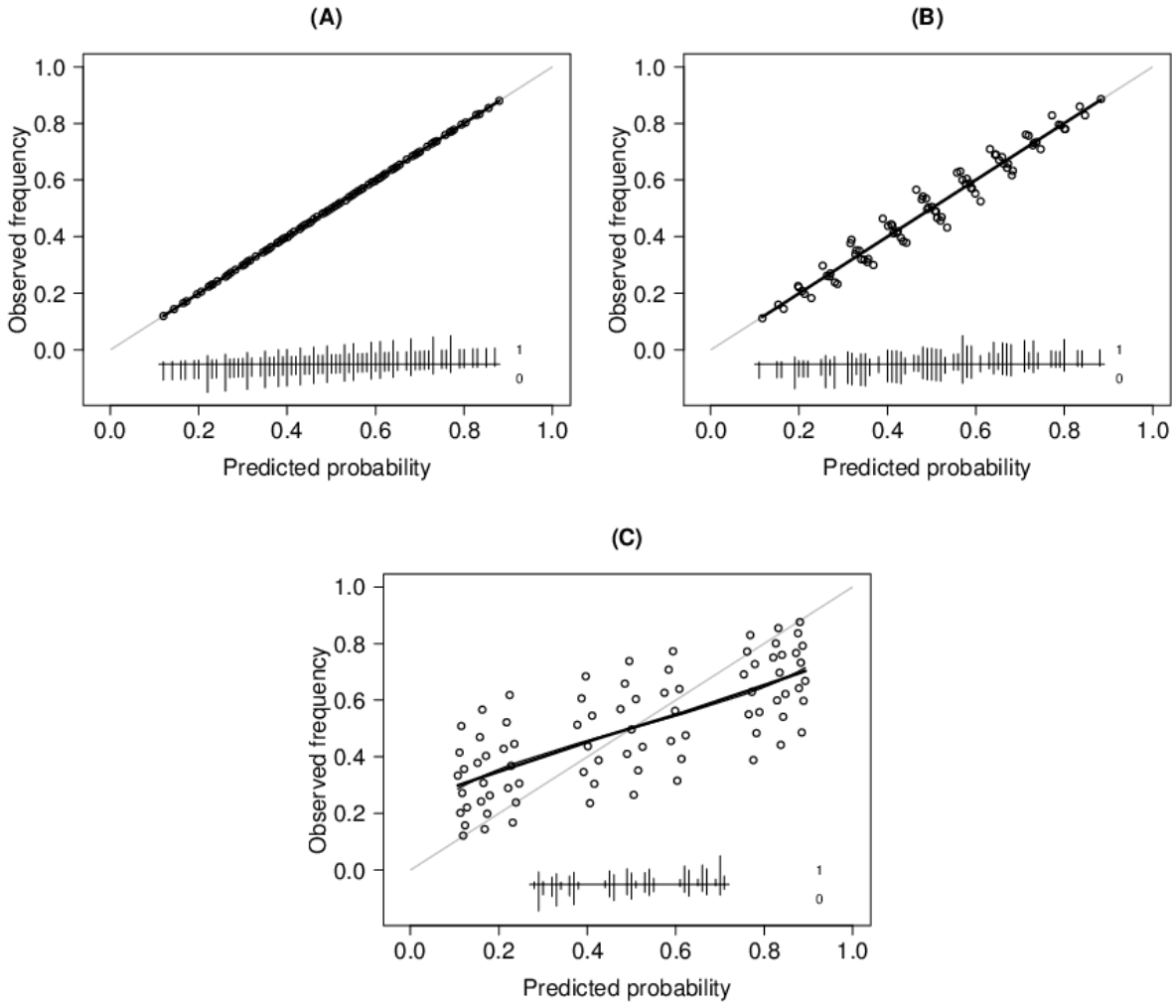


Figure 4. Calibration curves for examples 1 to 5 including results for individual covariate patterns, for examples 1 to 5: (A) Trained on 100, validated on 100; (B) Trained on 100, validated on 10,000; (C) Trained on 10,000, validated on 100; (D) Trained and validated on 10,000; (E) Trained and validated on 10 million patients.

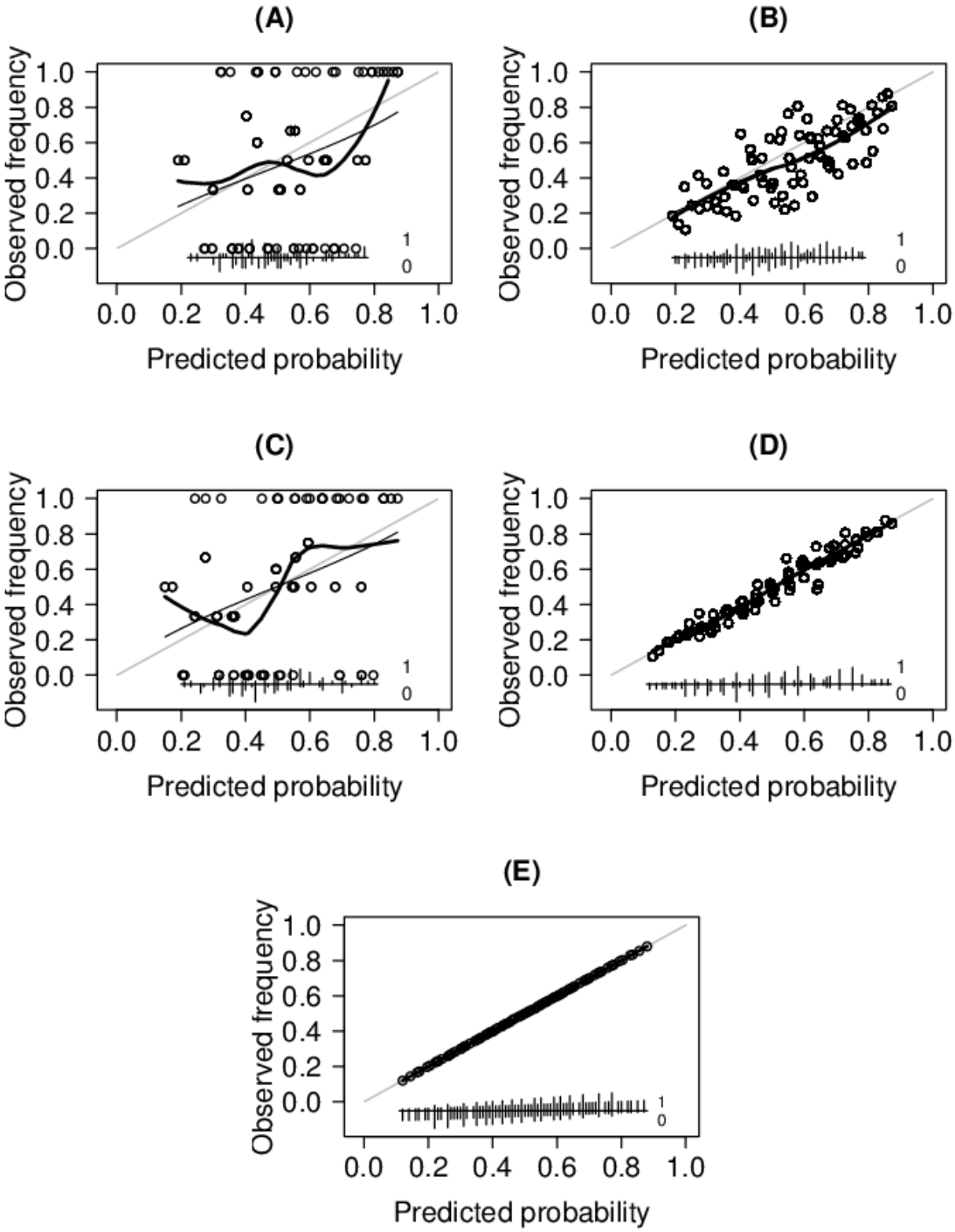
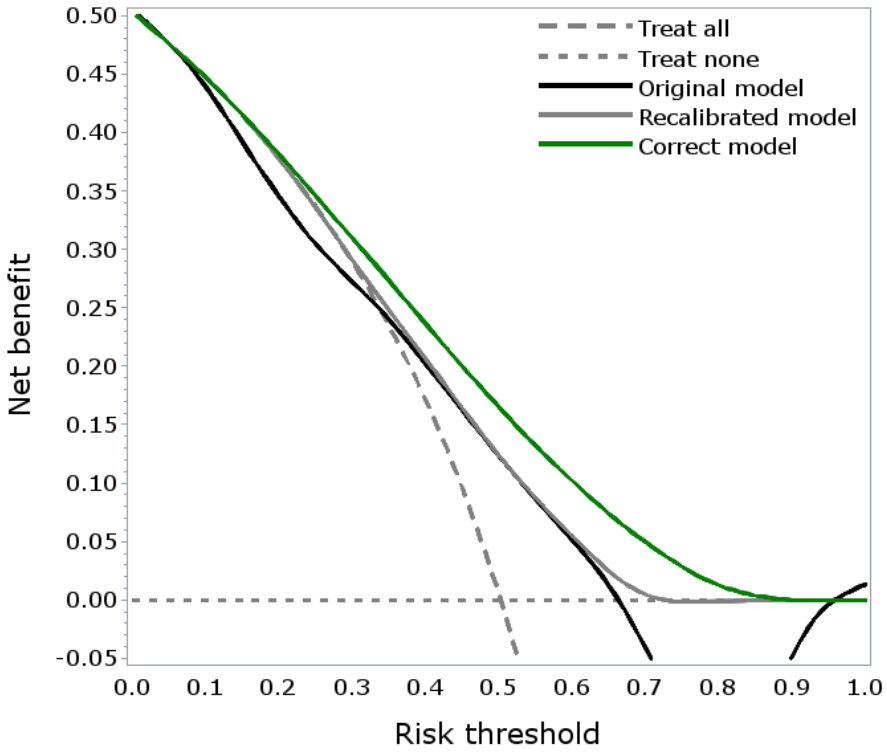


Figure 5. Decision curves for Example 8 to assess clinical usefulness.



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