

1 **External model validation of binary clinical risk prediction models in**
2 **cardiovascular and thoracic surgery**

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30 External validation of binary clinical risk-prediction models is vital. We provide
31 strategies for accomplishing this.

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34 **INTRODUCTION**

35 Clinical risk-prediction models (CRPMs, also known as prognostic models or
36 risk score models) serve an important role in healthcare,¹ particularly for binary
37 adverse events (in-hospital, 30-day, or operative mortality) after cardiac, thoracic,
38 and vascular surgery. These models may be applied to 3 different objectives: 1) to
39 assess patient risk, which surgeons and patients can then factor in to healthcare
40 decisions; 2) to stratify risk, both for clinical decision-making and inclusion criteria in
41 a controlled randomized trial,² and 3) to assess and compare healthcare outcomes
42 among providers (benchmarking). The comparison of observed with expected
43 outcomes, accounting for statistical uncertainty, can identify underperforming
44 healthcare providers for quality improvement interventions.³

45 The wide-ranging importance of CRPMs in the cardiovascular specialty
46 means that stakeholders must have confidence in them. A poorly performing model
47 can lead to suboptimal decision-making, misinformed patients, false reassurance of
48 a healthcare provider's performance, or false stigmatization of the provider.
49 Confidence is established by validating the model.⁴

50 Model validation can be internal, temporal, or external. Internal model
51 validation is one element of CRPM development, usually published alongside the
52 model to confirm the model performs well for the training data. External validation,
53 which evaluates the generalizability (or transportability) of the model to other groups
54 of patients, is fundamental to demonstrating a model is appropriate for adoption in
55 clinical practice.⁴ In cardiovascular and thoracic surgery, the majority of CRPMs
56 encountered will predict binary outcomes, which were created using multivariable
57 regression techniques, in particular logistic regression. Therefore, we focus our
58 discussion to this area. However, the general principles and need for external

59 validation apply to other outcome types and models, e.g. time-to-event data,^{5,6} as
60 well as to non-regression techniques, e.g. machine learning approaches.⁷

61

62 **MODEL PERFORMANCE CONCEPTS**

63 Performance of CRPMs is typically based on assessing two important
64 features: calibration and discrimination.⁶

65 **Calibration** is the accuracy of the model for predicting events relative to
66 observed events in groups of patients. For example, if the mean predicted event
67 occurrence is 5% in a patient group, but the observed event occurrence is 10%, then
68 we conclude the model is not well calibrated because it underpredicts.

69 **Discrimination** is the ability of a model to distinguish between patients who
70 experienced the event and those who did not. Discrimination is measured using the
71 area under the receiver-operating-characteristic curve (AUROC), also referred to as
72 the concordance (c-)statistic or c-index.⁵ This value has a meaningful interpretation.
73 If we randomly select 2 patients, 1 who experienced the event and 1 who did not,
74 then the AUROC is equivalent to the probability that the risk score attributed to the
75 former is greater than that attributed to the latter. An AUROC of 1 indicates perfect
76 classification; a value of 0.5 is equivalent to tossing a fair coin.

77 Other aspects of performance assessment include clinical usefulness,
78 impact,⁸ and overall performance measures such as the Brier score⁹ and
79 concordance index, particularly for time-related events.

80

81 **DESIGNING AND REPORTING AN EXTERNAL VALIDATION**

82 When designing a validation study, thought must be given to several key
83 elements.

84 **Selection of patients.** The selection of patients used to externally validate a
85 CRPM might differ from those used to develop the model. These differences might
86 be temporal or geographical, or related to clinical setting, inclusion or exclusion
87 criteria, definitions, diagnostic techniques, or inherent baseline case-mix differences
88 between the two populations. It is important to highlight any differences that might
89 affect model transportability between the validation and original study sample,
90 particularly with validation of general all-surgery models (e.g. the EuroSCORE)
91 within procedural¹⁰ or operative subgroups.¹¹

92 **Risk factor data.** It goes without saying that calculating a risk score requires
93 access to all variables that comprise the risk score. One potential issue is conflict in
94 variable definitions. For example, a registry that only collects binary data on whether
95 pulmonary artery (PA) systolic pressure is >60 mmHg (a risk factor in the logistic
96 EuroSCORE model) would not be able to compute the EuroSCORE II risk score,
97 which includes model coefficients for PA systolic pressures of 31 – 55 mmHg and
98 >55 mmHg. This is primarily an issue for retrospective validation studies, as clinical
99 registries can be updated to capture contemporary risk-score data.

100 **Missing data.** One cannot calculate a risk score without access to data for
101 variables that comprise the CRPM. If a model contains a risk factor such as
102 preoperative serum creatinine, but these data are sparsely available in the dataset,
103 then in many cases the risk score cannot be calculated. Case-complete analyses—
104 those that delete subjects with missing data for required variables—might lead to
105 bias if those subjects are not representative of the whole population.¹² In certain
106 cases, reasonable estimates and assumptions can be made based on clinical
107 expertise or additional information in the dataset. For example, a number of variables
108 in Society of Thoracic Surgeons (STS) risk models have coefficients set to 0 for

109 some variables in some models; if one is validating such a model, missing data for
110 such a variable is of no consequence. Alternatively, statistical imputation or subset
111 analysis techniques might be applied to compensate.^{13,14} If a validation study
112 specifically excludes certain groups of patients (for example, emergency surgery,
113 reoperations, or endocarditis), imputation of 0 is an accurate and appropriate
114 substitution, but the validation is only partial. In any case, it is always necessary to
115 summarize the frequency of missing data and present methods for managing it and
116 its assumptions.

117 **Sample size.** Considerations regarding sample size should not be limited to
118 randomized control trials. Single-center validation studies will often have a limited
119 pool of subjects, especially for subgroup analyses, and increasing the sample size
120 will require widening the study period, which could come at a price (see comment on
121 calibration drift below). When designing a study, sample size (number of subjects)
122 alone is not enough; one must also consider effective sample size (number of
123 events). Relatively little attention has been given to this matter, but some studies
124 have recommended a minimum of 100 events and 100 non-events for validation
125 studies, and in certain applications, larger effective sizes will be required to obtain
126 adequate power.^{15,16}

127 **Outcome definitions.** Many well-known CRPMs in cardiac surgery predict
128 early or operative mortality, including the logistic EuroSCORE¹⁷ and STS Cardiac
129 Surgery Risk Models.^{18–20} Operative mortality is generally accepted to mean death
130 within 30 days (or later if the patient has not been discharged within 30 days).²¹
131 However, other definitions of mortality exist, such as in-hospital mortality.²² Two
132 large databases reported operative mortality to be 4.63% and 3.57%, compared with
133 in-hospital mortality of 4.02% and 2.94%, respectively.^{23,24} In both cases, in-hospital

134 mortality was approximately 0.6% lower. In-hospital mortality is generally easier to
135 robustly measure, whereas 30-day mortality requires post-discharge follow-up for
136 most patients.²⁵ Therefore, it is common to see models validated against in-hospital
137 mortality. In this example, we would expect the model to over-predict mortality
138 relative to the observed data. It is reasonable to assess the model performance for
139 this similar endpoint; however, this subtlety should be borne in mind when designing
140 a study, particularly if the objective of the study is to compare models that have
141 different outcome definitions. Similar considerations apply to cases where the
142 definition of a major postoperative complication used for model development differs
143 from that in the validation dataset.

144 **Large study windows.** One simple way to increase sample size in a
145 validation study is to widen the study window. However, validation of a CRPM over a
146 substantially wide period can introduce a number of complexities. One potential
147 issue is calibration drift.^{26,27} Multiple studies demonstrated that the ratio of observed
148 mortality to mean logistic EuroSCORE was decreasing with time. Changing risk
149 profiles, other variables influencing mortality, and changes in the association of risk
150 factors with outcome can all contribute to this phenomenon. This prompted the
151 introduction of the EuroSCORE II model²³ and the series of contemporary STS
152 models.^{18–20} Researchers should be aware of this, particularly when validating
153 cardiac surgery CRPMs.

154 **TRIPOD statement.** In recent years, reporting of biomedical research has
155 been improved with guidelines such as the CONSORT statement²⁸ for randomized
156 trials and the PRISMA statement²⁹ for systematic reviews and meta-analyses.
157 Prompted by evidence of poor quality reporting in the CRPM literature, the recent
158 TRIPOD statement describes reporting guidelines for studies developing, validating,

159 or updating a prediction model.³⁰ We strongly encourage researchers to follow these
160 guidelines and make use of the checklist for validating models. Examples of good
161 practice and additional details have been previously published.³¹

162

163 **METHODS FOR ASSESSING CALIBRATION**

164 ***Hosmer-Lemeshow test.*** The Hosmer-Lemeshow test is a frequently
165 reported statistical test for assessing calibration in CRPMs. However, it has a
166 number of drawbacks.^{31–35} First, it is not easily interpreted; that is, it does not provide
167 a measure of the magnitude of any miscalibration. Second, for slight deviations in
168 calibration, the test is sensitive to sample size. Third, the classical version of the test
169 is dependent on arbitrary groupings of patients. In some cases, the Hosmer-
170 Lemeshow test remains a useful adjunct statistic, but should only be included as part
171 of a more comprehensive assessment. Typically, the Hosmer-Lemeshow test refers
172 to a test based on 10 groups composed by deciles of risk. However, authors should
173 be aware that there are variations on the test with regard to groupings (quantiles vs.
174 fixed cut-points), number of groups (g), degrees of freedom of the chi-squared
175 statistic ($g-2$ for internal vs. g for external validation), and software
176 implementations.^{35,36} While g is typically selected to be 10, one must ensure the cell
177 counts are sufficient to justify the distributional approximation. Including a table of
178 observed and expected events by binning group provides a useful summary, and
179 allows for inspection of each term for fit, as recommended by Hosmer and
180 Lemeshow (p. 188).³⁶

181 ***Calibration plot.*** If a standard Hosmer-Lemeshow test is performed, then a
182 simple graph—the calibration plot—is a straightforward next step (**Figure**).⁴ Within
183 each of the g groups, observed events are plotted against expected events. If the

184 model is well calibrated, then these points should be close to the 45° line. The
185 calibration plot can be augmented by overlaying a non-parametric smoothing curve
186 (e.g. loess) through the observed and predicted data³⁷ or a calibration curve.³⁸
187 Contrary to the Hosmer-Lemeshow test and basic calibration plot, these additional
188 fits are not dependent on arbitrary groupings.

189 **Calibration curves.** Cox's calibration regression fits a logistic regression
190 between the observed event and the log-odds transformed predicted values.³⁹ A
191 perfectly calibrated CRPM (deriving from a logistic regression model) yields an
192 intercept = 0 and a slope = 1. These fitted regression models can be superimposed
193 onto a calibration plot, giving an alternative graphical description of the
194 miscalibration. As well as quantifying the degree of miscalibration, one can also
195 simultaneously test whether the estimated parameters reject the null hypothesis of
196 calibration. There are other related null hypotheses that can be tested for assessing
197 calibration also (p. 274).⁶

198 **Other tests.** The Hosmer-Lemeshow is ubiquitous in biomedical CRPM
199 literature. However, researchers can take advantage of a wide variety of statistical
200 tests to assess model validation, such as the aforementioned calibration curve
201 test(s), the Spiegelhalter Z-test,⁴⁰ and methods proposed by Stallard.⁴¹ Most can be
202 calculated using routine software packages.^{6,38} There is no omnibus test of
203 calibration; each approach has different merits and limitations. Therefore, it is
204 important that researchers employ a broad repertoire of methods to address the
205 study questions.

206

207 **MODEL UPDATING**

208 A natural extension to the validation of a CRPM is the concept of updating an
209 existing model. This might involve exploring whether a new biomarker improves a
210 model (e.g. using net reclassification improvement measures⁴²), recalibrating a
211 model,⁴³ and, more recently, assessing whether multiple models can be combined to
212 provide a more accurate prediction (e.g. meta-models and model averaging).⁴⁴ This
213 expanding research area is especially important in an era of personalized
214 medicine.⁴⁵

215

216 **CONCLUSIONS**

217 External validation of CRPMs is necessary to demonstrate their predictive
218 accuracy. Available models have likely been validated internally; however, using
219 them in different settings, locations, and populations can result in relatively poor
220 performance. CRPMs that have been overfitted during development will also often
221 fail to generalise to the external validation sample. Calibration and discrimination
222 must be measured in order to establish validity. There are multiple statistical
223 approaches available to interrogate the calibration, with it being widely accepted that
224 the ubiquitous Hosmer-Lemeshow test has limited utility. Execution of a rigorous
225 CRPM validation study rests in proper study design, application of suitable statistical
226 methods, and transparent reporting.

227

228

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- 361
- 362

363 **FIGURE LEGEND**

364 **Figure.** A calibration plot for simulated data ($n = 500$). The green triangles denote
365 the mean predicted and observed event probabilities for patients grouped into tenths
366 using deciles. The grey dashed line denotes perfect calibration. A smoothing curve
367 (blue dashed line) and the calibration curve (red solid line) are also overlaid. The
368 distribution of calculated predicted probabilities is overlaid along the horizontal axis.
369 A subset of various statistics useful for validating the model are also shown. This
370 figure was generated using standard statistical software: the rms package for R (R
371 Core Team, R Foundation for Statistical Computing, Vienna, Austria; version 3.1.2).
372 Further details are given in Harrell (2001)³⁸ and Harrell (2015).⁴⁶ Code to reproduce
373 this plot is given in the Appendix.

374

APPENDIX

375

376 **R code to produce figure**

```
377 # If 'rms' package not install, run command
378 # install.packages("rms")
379 library(rms)
380 ## Simulate fake data:
381 ##   y = binary outcome
382 ##   x1, x2, x3 = covariates in the risk model
383 ##   n = sample size
384 set.seed(1)
385 n <- 1000 # 500 development + 500 validation
386 x1 <- runif(n) # covariate 1
387 x2 <- runif(n) # covariate 2
388 x3 <- runif(n) # covariate 3
389 logit <- -5 + 0.5*x1 + 2*x2 + 3.5*x3
390 P <- 1 / (1 + exp(-logit))
391 y <- ifelse(runif(n) <= P, 1, 0) # outcomes
392 d <- data.frame(x1, x2, x3, y) # combined dataset
393
394 ## Fit a risk prediction model to first half of the data
395 f <- lrm(y ~ x1 + x2 + x3, subset = 1:500)
396
397 ## Use model to get predictions for second half of data
398 pred.logit <- predict(f, d[501:1000, ])
399 phat <- 1 / (1 + exp(-pred.logit))
400
401 ## Validate prediction
402 val.prob(phat, y[501:1000], g = 10, riskdist = "predicted")
```