Prognostic models for mortality after cardiac surgery in patients with infective endocarditis: a systematic review and aggregation of prediction models

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Abstract

Background: Several prognostic models have been developed trying to estimate the risk of mortality after surgery for active infective endocarditis (IE). However, these models incorporate different predictors and their performance is uncertain.

Objective: We aimed to systematically review and critically appraise all available prediction models of post-operative mortality in patients with IE, and to synthesize them into a meta-model.

Data sources: We searched Medline and EMBASE databases from inception to June 2020 to identify post-operative prognostic models.

Study eligibility criteria: We included studies that developed or updated a prognostic model of post-operative mortality in patient with IE.

Methods: We assessed the risk of bias of the models using PROBAST (Prediction model Risk Of Bias ASsessment Tool) and we synthesized them into an aggregate meta-model based on stacked regressions and optimized it for a nationwide registry of IE patients. The meta-model performance was assessed using bootstrap validation methods and adjusted for optimism.

Results: We identified 9 studies reporting the development of 11 prognostic models for post-operative mortality. Eight models were rated as high risk of bias. The meta-model included weighted predictors from the remaining three models (i.e. EndoSCORE, specific ES-I and specific ES-II), which were not rated as high risk of bias and provided full model equation. Additionally, two variables (i.e. age and infectious agent) which had been modelized differently across studies, were estimated from scratch based on the nationwide registry. The meta-model performance was better than that of initial three models, with the corresponding performance measures: C-statistics 0.79 (95% CI 0.76 to 0.82), calibration slope 0.98 (95% CI 0.86 to 1.13) and calibration-in-the-large -0.05 (95% CI -0.20 to 0.11).

Conclusions: The meta-model outperformed published models and showed a robust predictive capacity for predicting the individualized risk of post-operative mortality in patients with IE.

Protocol Registration: PROSPERO (registration number CRD42020192602)

Key words: Prognostic models, systematic review, meta-model, aggregation, validation, infective endocarditis.

Background

Infective endocarditis (IE) is an uncommon but severe disease with a high mortality rate. Its current estimated incidence is 3-10 episodes per 100.000 person-years, while its in-hospital mortality rate ranges between 15% and 40% (1,2). Management of IE is often complex and, although indications for surgery are established in current guidelines (3), the decision whether to perform surgery remains a challenge because of the high mortality rate associated with the procedure. For that reason, it is estimated than less than half of the patients with surgical indication finally undergo cardiac surgery (4)leading to a significant decreased chance of survival (5). In this context, there has been a great interest on modeling prognosis of patients with IE to accurately estimate the risk of mortality and to help in the decision-making processes.

In the last decade, several IE prognostic models using preoperative patient´s-related and IE-specific factors, have been proposed (6). Unfortunately, these models have not been implemented in guidelines or applied in clinical practice. In fact, clinicians seldomly trust these models because they have usually been built in relatively small cohorts and have not been externally validated. Consequently, researchers carry on developing new models from their own data without considering prior knowledge, which leads to an scenario with multiple prognostic models of dubious validity. Therefore, we aimed to systematically review and critically appraise all available prediction models for post-operative mortality in patients with IE, and to synthesize them into a meta-model based on stacked regressions.

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Methods

The protocol for this study was registered on PROSPERO (registration number CRD42020192602). We designed this systematic review according to the recent guidance by Debray et al.(7,8), and reported its results following PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) (9) and TRIPOD (Transparent Reporting of a Multivariable Prediction Model for Individual Prognosis or Diagnosis) (10,11) recommendations.

Literature search

We searched Medline through Ovid and Embase through Elsevier from inception to 01/06/2020. We conducted a literature search to identify all potential studies for inclusion. We applied no restriction considering language or publication dates. We used the methodologic filter developed by Geersing et al. for prediction models research in MEDLINE (12), which was adapted for EMBASE. We added terms related to cardiac surgery and endocarditis. We further searched bibliographic references of included articles to identify other potential eligible studies. Complete search strings are shown in **Supplementary Material: S1.**

Eligibility criteria

We included original studies that developed prognostic models, with or without external validation, to predict the risk of post-operative mortality after cardiac surgery in patient with IE, as well as studies that updated previously published models. We accepted the authors` definition of post-operative mortality (either 30 days and/or in-hospital mortality), but excluded models that predicted mortality as part of a composite adverse outcome. Titles, abstracts, and full texts were screened for eligibility in pairs by three reviewers independently (BMFF, LVB, ACP) using EPPI-Reviewer 4 (13). Discrepancies were resolved by consensus.

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Data extraction

Data extraction of included articles was done by three reviewers independently (pairs from BMFF, LVB, ACP). Reviewers used a standardized data extraction form based on CHARMS (CHecklist for critical Appraisal and data extraction for systematic Reviews of prediction Modelling Studies) (8), and discrepancies were solved by consensus. We extracted data on the following items: general information of the study, source of data, participants´ characteristics, outcome definition and time of occurrence, candidate predictors, and analysis methods. (**Supplementary Material: S2)**. When the completed model equation or relevant data were not provided, we contacted the correspondence authors to require this information.

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Risk of bias assessment

We used a standardized form based on PROBAST (PRediction model risk of Bias ASsessment Tool) (14,15) to evaluate risk of bias (RoB) and applicability. We defined the presence of RoB as the existence of deficiencies in the study design or analysis that may have led to systematically distorted estimates of the model performance or its composition. Concerns regarding the applicability of a primary study would arise when the population, predictors, or outcomes of the study differed from those specified in our review question. RoB and applicability were assessed by two independent reviewers (pairs from BMFF, LVB, ACP). We evaluated the relevant items on the following domains: Participants, predictors, outcome and analysis. Each domain was rated according to our review question as having a *high*, *low* or *unclear* RoB, and as providing *high*, *low* or *unclear* concerns regarding applicability. Any discrepancies were discussed between reviewers and resolved through discussion. The supplementary material provides details on critical appraisal and applicability (**Supplementary Material: S3**).

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GAMES registry

We used the infective endocarditis nationwide Spanish registry (GAMES) as the validation dataset, to estimate existing model` weights for the meta-model development and its validation, and to externally validate the previously published models. Since January 2008, all consecutive episodes of IE in 34 Spanish hospitals were prospectively registered in GAMES using a standardized form. Regional and local ethics committees approved the study, and patients gave their informed consent in each center. For the present study, we selected all the infective episodes (n=1,453) registered in the GAMES cohort involving adult patients (aged ≥18 years) who had undergone cardiac surgery with preoperative diagnosis of active IE. From these, 354 (24.4%) died after surgery (273 in the first 30 days and the remaining 81 during hospitalization). **Supplementary Material: Table S1** shows the main descriptive characteristic of patients in the validation nationwide registry.

Statistical analyses

The validation dataset was depurated for the outcomes and predictors included in the prognostic models included in the systematic review.

Model aggregation was based on stacked regressions (16), which allows the synthesis of literature models in a meta-model using the prior evidence optimized for the validation dataset (17,18). Only the models that reported the full model equation and were not flagged as high risk of bias were considered for aggregation. Stacked regressions used the linear predictor of each model as a co-variable in the meta-model, and subsequently created a linear combination of model predictions. That is, the original coefficients of each model are weighted by an independent parameter estimated in the meta-model, so that the models with worse performance in the validation dataset are penalized more. When aggregation of the coefficients was not

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possible, either because the definition of the predictor from primary studies was too heterogeneous or because predictors had been modeled differently in the published models (for instance, a numerical variable treated as a continuous predictor in one model and being categorized at different cut-points in the others), these predictors were dropped, and were included in the meta-model as independent covariables to re-estimate their coefficients entirely from scratch based on the validation dataset. Non-linear relationships for continuous predictors were tested using fractional polynomials (19).

Predictors with missing data in the validation dataset were imputed under the missing at random assumption using multiple imputation with chained equations (20). We included all predictors and the outcome in the imputation models to ensure compatibility. (**Supplementary Material: S4**). Imputation checks were completed by looking at the distributions of imputed values to ensure plausibility. We generated 10 multiple imputed datasets and all primary analyses were performed in each imputed dataset. Pooled parameters were estimated both in the aggregation and validation processes using Rubin's rules (21).

The model validation was assessed in terms of discrimination (i.e. through the use of the C-statistic, with values from 1 indicating perfect discrimination to 0.5 no discrimination) and calibration (i.e. through the calibration slope and calibration-in-the-large [CITL], with 1 and 0 as ideal values, respectively; as well as with calibration plots). Calibration plots represent the average predicted probability for risk groups categorized using deciles of predicted probability against observed proportion in each group, and fitting a less smoother to show calibration across the entire range of predicted probabilities at the individual-level (22,23). For the calibration plots we used the average predicted probabilities for individuals by pooling the imputed datasets using Rubin's rules (21). Because the meta-model was optimized to the validation dataset, we assessed its optimism-corrected performance measures by applying bootstrap validation with 500 replicates. As sensitivity analyses, we tested all model

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performance regardless of their critical appraisal. In addition, the meta-model performance was assessed only for 30-days mortality to investigate the meta-model robustness.

All analyses were performed using Stata software version 16 (24).

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Results

Literature search and study selection

We retrieved 4,862 titles through our systematic search combining Medline and Embase. From these, 684 duplicate references were identified. Of 4,178 titles assessed by title and abstract, 34 studies were retained for full text screening, and 2 additional studies were detected in the bibliographic references of these articles. Nine studies describing 11 prediction models met the inclusion criteria (**Figure 1 and Supplementary Table S2**).

Source of data and participants

All prognostic model development studies were carried out in the last decade. Six used data from a study cohort (three of them from a single center (25–27) and three from multiple centers (28–30)); two studies used data from multicenter registries (6,31); and one study used data from both a multicenter cohort and a local clinical registry (32). Eight studies used data from patients in Europe (Spain, Italy, France or Portugal) and one from patients in North America. Participants were recruited between 1980 and 2015. (**Supplementary Table S3**).

Outcomes

Three models were developed to predict any death occurring before discharge or within 30 days of surgery (6,25,27), five models were built to predict any death occurring before discharge (26,30–32), and the remaining three models predicted death within 30 days of surgery (28, 29). The incidence of deaths varied between 8.2% and 29.2% (**Table 1**).

Predictors

The number of candidate predictors considered in the models varied from 15 to 57 and included patient-, clinical-, surgery- and IE-related factors. The number of parameters retained in the final models ranged from 2 to 15 (**Table 1**): The most common factors were critical preoperative state (n=9), renal failure (n = 7), age (n = 6), New York Heart Association (NYHA)

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classification (n = 6), paravalvular complications (n = 6) and infection etiology (n = 5). The predictor definitions and the models' composition are shown in the **Supplementary Table S4 and Table S5**.

Model development and presentation

Sample sizes for models' development varied between 128 and 13,617 patients, and the number of events ranged from 21 and 1,117. Only two models from the same study adequately informed the handling of missing data (29), and these used complete data analyses. Logistic regression analysis was the most common modelling technique (n = 9), while logistic mixed effects (28) and logistic GEE (Generalized Estimating Equation) models (6) were only used in one model development each. Nine models used univariable analyses to select the candidate predictors. In nine out of eleven models the number of events per parameter (EPP) assessed for inclusion in the final model were lower than the minimum required for development of a new prediction model, based on the sample size estimation proposed by Riley et al.(33,34) (**Supplementary Table S6**). The method of predictors selection during multivariable modelling was backward selection in three models (26,32), stepwise selection in two models (30,31), and an automatic algorithm based on Akaike information criteria in multiple bootstrap samples in the other two models, with predictors selected in at least 70% of the bootstrapped samples being included in the final model (29). Four models did not inform about the method used to select predictors. (**Table 1**)

In seven out of 11 models the authors did not inform the complete model equation, and five of them did not respond when were asked for further details (**Supplementary Table S7**). Nine models were presented as a scoring system, and two of them included nomograms.

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Model performance

The model performance was assessed in terms of discrimination in all models through the C-statistic. Nevertheless calibration was often wrongly assessed using the Hosmer-Lemeshow test (37) in six models. Only three models (27,29) used calibration slopes and CITL. Eight models were internally validated: three models were evaluated by bootstrapping with correction for optimism (28,29), one was assessed through the 0.632 bootstrap method (26), two used temporal split samples (32) and two used random split samples (6,30). Three models only estimated the apparent performance (25,27,31). Three models were externally validated in the same development study using very small sample sizes, with only 18 events in the Olmos' model (30) and 21 in the Gatti's model (32). Clinical utility of the models was never assessed.

Risk of bias

The RoB was high in eight models, unclear in one (28) and low in the remaining two (29) (**Table 1, Supplementary Table S8 and Figure S1**). Two of the eight models with high RoB scored at "high risk" in the participants domain. Eight models scored at "high risk" in the analysis domain. Most of the models had small sample sizes and the number of EPP was close to 1 in several models, increasing the risk of overfitting (34). Many studies decided model predictors based on univariable analysis, three reported only the apparent performance and two used random splitting validation. The calibration was sub-optimally assessed in all models classified as high risk of bias, with most of them using the Hosmer-Lemeshow test.

Derivation of the Meta-model

The eight models with high RoB were excluded from the statistical synthesis so that only the EndoScore, Specifics EuroSCORE-I (Specific ES-I and EuroSCORE-II (Specific ES-II) models were aggregated in the meta-model. The model developed by Di Mauro (EndoSCORE) (28) included 15 parameters, while the other two (Specific ES-I and Specific ES-II) developed by Fernández-Hidalgo (29), presented 10 and 9 parameters respectively, from the EuroSCORE

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models predictors (35, 36) and IE-related factors (**Table 2 and Supplementary Table S7**). The dependent variable for the meta-model was mortality (either 30-days or in-hospital).

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To construct the meta-model, we first calculated the linear predictors (LP) from EndoSCORE, Specific ES-I and Specific ES-II for each observation in the validation dataset, after dropping the parameters for age and infection etiology because these variables were modelized differently in the different studies. Subsequently, we adjusted the meta-model using a logistic regression model, which incorporated the LPs as co-variables, to estimate the models' weights for aggregation, as well as the predictors for age (treated as continuous) and infection etiology (categorized into three groups: *Staphylococcus* spp, fungi and other microorganisms) to re-estimate the coefficients from scratch. The meta-model included 18 parameters from the predictors included in at least one of the three original models (**Table 2**).

Validation of the models

The three prediction models considered for aggregation and the meta-model were validated in the GAMES registry. The C-statistics and their 95% confidence intervals (95%CI) for the published models were: 0.76 (95% CI 0.73 to 0.79) for EndoSCORE, 0.76 (95% CI 0.73 to 0.79) for Specific ES-I, and 0.73 (95% CI 0.73 to 0.79) for Specific ES-II. The optimism adjusted C-statistic for the meta-model was 0.79 (95% CI 0.76 to 0.82) (**Figure 2**). Calibration slopes were < 1 for all published models: 0.80 (95% CI 0.69 to 0.92) for EndoScore, 0.82 (95% CI 0.70 to 0.94) for Specific ES-I, and 0.76 (95% CI 0.65 to 0.87) for Specific ES-II. CITL was 0.58 (95% CI 0.44 to 0.71) for EndoSCORE and 0.62 (95% CI 0.48 to 0.76) for Specific ES-II, and -0.02 (95% CI -0.16 to 0.11) for Specific ES-I. Optimism adjusted calibration measures for the meta-model were 0.98 (95% CI 0.86 to 1.13) for the slope and -0.05 (95% CI -0.20 to 0.11) for CITL (**Figure 2**). The calibration plots for the three previously published models and the meta-model are shown in **Figure 3**.

Sensitivity analysis showed that the meta-model had better overall performance than all published models regardless of their quality assessment (**Supplementary Figure S2**). Moreover, even though the meta-model was not fitted for the 30-days mortality outcome, it outperformed the three models used for model aggregation. (**Supplementary Figure S3**)

Discussion

Summary of findings

In this systematic review of prediction models for post-operative mortality in patients with infective endocarditis, we identified and critically appraised 11 models developed in 9 studies. The predicted outcome varied between studies (in-hospital, 30-days or both in-hospital or 30-days mortality). Of the eleven prognostic models, only two had low RoB and one unclear, the remained eight models had high RoB mainly owing to poor statistical methods used, which suggests that their predictive performance when used in practice is probably lower than that reported. The sample sizes used to develop the models were limited and this is a well-known problem that leads to inaccurate predictions and consequently incorrect healthcare decisions in practice (34).

Four out of the 11 published models reported the full model equation required for a models' aggregation and a complete independent external validation as recommended by reporting guidelines (10,11). Two models' equations were recovered asking correspondence authors. Three models that were not flagged as high RoB could be used to create the meta-model.

Our meta-model showed better performance than the existing models. We investigated the internal validity of the meta-model using bootstrap validation, and the results indicate there was no substantial over-optimism and that the validation sample was sufficiently large to combine and update the published models. Therefore, the meta-model is likely less prone to over-optimism and more generalizable to new patient populations or settings, because it was built from the evidence of several patient cohorts and optimized to a nationwide registry.

Strengths and limitations

To our knowledge, this is the first systematic review of prediction models of post-operative mortality in patients with infective endocarditis with a complete external validation. We only

combined the published prediction models with low or unclear RoB and adjusted them to a new patient population. We used multiple imputation of predictors to avoid loss of useful information. The resulting meta-model incorporated prior knowledge optimally and outperformed previously published models.

Our study has some limitations. The outcome definition in the validation dataset was either 30-days or in-hospital post-operative mortality, and the outcome definition in the three models used for aggregation was 30-days mortality. Despite this difference a sensitivity analysis showed that the meta-model outperformed all published models when we explored its performance for the 30-days mortality. The meta-model did not include some predictors that were associated with post-operative mortality from the models with high RoB. Nevertheless, except type-of-valve which was included in several models (27,30,31), the remaining predictors were each only included in one model. Unfortunately, although we identified 11 prediction models in our systematic review, we were only able to validate the models that published the complete model equation. Although the definition of predictors in GAMES registry was standardized, these could differ from definitions of published studies.

Comparison to existing studies

Most studies to develop new prediction models are based on small sample sizes and the modelling strategies are excessively driven by available data without considering the previous knowledge, leading to inefficient models. Other authors carried out external validation studies but none of them made a critical appraisal (38–41). In a previous study, Varela et. al. developed a prognostic meta-model based on a systematic review of pre-operative factors related to in-hospital mortality, however, it was built using multiple univariate meta-analyses of the crude associations, without considering possible covariable correlations (42,43).

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Implications for practice

The decision whether to perform surgery in IE remains a challenge in clinical practice and it should come after a careful balance between the procedural risk and its estimated benefit. Although risk scores in predicting mortality do not offer help in terms of establishing the burdens of surgical futility, they apport a great value helping endocarditis teams to manage that complex disease.

Although in the 2015 IE guidelines the score created by De Feo-Cotrufo et al for native IE is the only one recommended, it would be expected to change with the creation of several new IE specific scores and the generation of a meta-model that outperformed existing models.

Challenges and opportunities

Further external validation studies are necessary to confirm the improvement in predictive ability of the meta-model. We will develop an online calculator to allow a simple and effective use of the meta-model. Given the low incidence of infective endocarditis, available sufficient sample sizes for the adequate development of new predictive models are difficult to come by. We encourage authors to make their data available in order to allow building models based on available data (44).

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Conclusions

The meta-model we built is a robust prognostic model to calculate the individualized risk of post-operative mortality in patients with infective endocarditis. It was developed based on the previous evidence using aggregation methods of the existing models identified from a systematic review and after critical being appraised. This meta-model outperformed existing models; therefore, this preoperative tool can help guide individually tailored choices made by patients and clinicians.

Authors contributions

Conceptualization: BMFF, LVB, JLA, AM, JIP, MR, JRM, EGE, JZ; Search strategies: BMFF, NAD, JLA; Data extraction and Critical appraisal: BMFF, LVB, ACP; Methodology: BMFF, EGE, AM, JZ; Software, Formal analysis: BMFF; Validation: AM, JZ; Data adquisition/curation: BMFF, ENE, PM, MCF, MAG: Writing - Original draft: BMFF, EGE, JZ; Visualization: BMFF, LVB, NFH; Supervision: EGE, JZ; Writing – Review & Editing: All authors.

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