**External validation of prognostic models to predict stillbirth using the International Prediction of Pregnancy Complications (IPPIC) Network database: An individual participant data meta- analysis**

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**Abstract**

**Objective**

Stillbirth is a potentially preventable complication of pregnancy. Identifying women at risk can guide decisions on closer surveillance or timing of birth to prevent fetal death. Prognostic models have been developed to predict the risk of stillbirth, but none have yet been externally validated. We externally validated published prediction models for stillbirth using individual participant data (IPD) meta-analysis to assess their predictive performance.

**Methods**

We searched Medline, EMBASE, DH-DATA and AMED databases from inception to December 2020 to identify stillbirth prediction models. We included studies that developed or updated prediction models for stillbirth for use at any time during pregnancy. IPD from cohorts within the International Prediction of Pregnancy Complication (IPPIC) Network were used to externally validate the identified prediction models whose individual variables were available in the IPD. We assessed the risk of bias of the models and IPD using PROBAST, and reported discriminative performance using the C-statistic, and calibration performance using calibration plots, calibration slope and calibration-in-the-large. We estimated performance measures separately in each study, and then summarised across studies using random-effects meta-analysis. Clinical utility was assessed using net benefit.

**Results**

We identified 17 studies reporting the development of 40 prognostic models for stillbirth. None of the models were previously externally validated, and only a fifth (20%, 8/40) reported the full model equation. We were able to validate three of these models using the IPD from 19 cohort studies (491,201 pregnant women) within the IPPIC Network database. Based on evaluating their development studies, all three models had an overall high risk of bias according to PROBAST. In our IPD meta-analysis, the models had summary C-statistics ranging from 0.53 to 0.65; summary calibration slopes of 0.40 to 0.88, and generally with observed risks predictions that were too extreme compared to observed risks; and little to no clinical utility as assessed by net benefit. However, there remained uncertainty in performance for some models due to small available sample sizes

**Conclusion**

The three validated models generally showed poor and uncertain predictive performance in new data, with limited evidence to support their clinical application. Findings suggest methodological shortcomings in their development including overfitting of models. Further research is needed to further validate these and other models, identify stronger prognostic factors, and to develop more robust prediction models.

## **Study registration**

PROSPERO ID: CRD42018074788

**Keywords:** stillbirth, intra-uterine death, prediction model, individual participant data, external validation

**Word count:** 376

**INTRODUCTION**

Stillbirth continues to be a major burden globally, accounting for almost two thirds of perinatal mortality.1,2 In the UK, stillbirth rates were largely unchanged from 2000 – 2015, and at 4.2 stillbirths/1,000 births in 2017 had one of the highest rates in Europe.3-5 Prediction and individualisation of risk remain key priorities for stillbirth research,6,7 because accurate identification of women at risk of stillbirth can guide decisions on closer surveillance, or timing of birth to prevent fetal death. A recent review that identified existing prediction models for stillbirth reported that none had been externally validated.8 As a result, no prediction models are routinely used in clinical practice and none have been recommended by any national or international guidelines.

An independent, external validation and comparison of existing multivariable stillbirth prediction models is important to help identify which prediction model (if any) performs best and is potentially applicable in clinical practice. However, the relative rarity of this devasting outcome limits rigorous investigation of existing stillbirth prediction models in single cohort studies. An individual participant data (IPD) meta-analysis that combines the raw data from multiple studies, has great potential for use in externally validating existing models, by increasing the sample size beyond what is feasible in a single study, thereby increasing the number of events observed.9-12 It also allows us to evaluate the generalisability and transportability of the predictive performance of the models across a range of clinical settings being considered for their application.

We therefore set out to identify, critically appraise and externally validate existing multivariable prognostic models for stillbirth prediction using IPD meta-analysis within the independent International Prediction of Pregnancy Complication (IPPIC) Network database, and to assess the clinical utility of the models using decision curve analysis.

**Methods**

This study was based on a prospective protocol registered on PROSPERO (registration number CRD42018074788), and reported in line with TRIPOD recommendations for reporting risk prediction model validation studies.13

*Literature search and selection of prediction models for external validation using the IPPIC network database*

We systematically searched Medline, EMBASE, DH-DATA and AMED databases from inception to December 2020 to identify all studies that developed or updated prognostic models for stillbirth for use at any time during pregnancy. We also hand searched reference lists of relevant articles and systematic reviews to identify potentially eligible studies. Our search included terms for stillbirth, intrauterine fetal death and perinatal mortality, and study selection was done independently by two researchers. The complete search strategy is provided in appendix 1.

*Stillbirth model eligibility criteria, data extraction and risk of bias assessment*

We included studies that reported the development or update of a multivariable model with at least three variables to predict the risk of stillbirth in pregnant women and reported the model equation in the publication. No attempts were made to contact authors of studies that did not publish their model equation. Given the wide international variation in definitions of stillbirth, we accepted the authors’ definition of stillbirth (both antepartum and intrapartum), and included models developed for use at any time in pregnancy. We excluded models that: predicted stillbirth as part of a composite adverse outcome; contained predictors that were not measured in any of the cohorts within the IPPIC IPD; or if there were too few outcomes (<10 stillbirths) reported across the IPPIC IPD cohorts with the same predictors as the model, to allow for its external validation.

We extracted data on the definition of stillbirth, number of participants and events, population type, predictors in the final model, and the reported model performance. Based on information in the original articles, we assessed the risk of bias of included models using the Prediction study Risk of Bias Assessment tool (PROBAST),14 across the four domains of participant selection, predictors, outcome and analysis, and this was done independently by two researchers. Disagreement were resolved through discussions with a third researcher. We classified the risk of bias to be low, high or unclear for each domain, as well as an overall risk of bias. Each domain included signalling questions rated as “yes”, “probably yes”, “probably no”, “no” or “no information”. Domains with any signalling question rated as “probably no” or “no” were considered to have potential for bias and classed as high risk. The overall risk of bias was considered to be low if it scored low in all domains, high if any one domain had a high risk of bias, and unclear for any other classifications.

*International Prediction of Pregnancy Complications (IPPIC) Network*

We identified cohorts for the IPPIC Network by systematically reviewing evidence for risk of pregnancy complications including pre-eclampsia, stillbirth and fetal growth restriction (FGR), and inviting research groups that had undertaken the primary studies to join the IPPIC Network and share their primary IPD. We also searched major databases and repositories and contacted researchers within the IPPIC Network to identify relevant studies or datasets that may have been missed, including unpublished research and birth cohorts. We formatted, cleaned and harmonised datasets received and assessed the quality of each cohort using the participants, predictors and outcome domains of the PROBAST tool.14 Study population could vary from low to high risk of development of complications. The network includes nearly 150 collaborators from 26 countries, contributing IPD of over 4 million pregnancies, and contains data on maternal characteristics, obstetric history, clinical assessment and tests, as well as various maternal and offspring outcomes. The database is a living repository and is regularly being enriched with additional studies. We consider the predictor variables contained within the IPPIC Network to represent measures which are easy to obtain in a clinical setting, reflecting their availability in routine practice. Methods on how cohorts within the IPPIC Network database were identified and harmonised have previously been published.15-17

**Statistical analysis for external validation using IPPIC network database**

*Data harmonisation and set-up*

Predictors or outcomes of existing prediction models that were partially missing for <95% of individuals in any cohort were multiply imputed under the missing at random assumption using multiple imputation by chained equations.18,19 We used linear regression to impute for approximately normally distributed continuous variables, logistic regression for binary variables, and multinomial logistic regression for categorical variables. We carried out multiple imputation for each individual cohort separately and generated fifty imputed datasets for each. We also included other predictors that were available within the cohort as auxiliary variables in the imputation models. Imputation checks were completed by looking at histograms, summary statistics and tables of values across imputations, as well as checking trace plots for convergence issues.

*External validation of models*

Each model was validated by applying the model equation to each participant in the cohort to calculate the linear predictor for that participant ($LP\_{i}$, value of the linear combination of predictors in the model equation for individual $i$), as well as the predicted probability of stillbirth (inverse logit transformation of $LP\_{i}$). For each prediction model, the distribution of $LP\_{i}$ values were summarised for each cohort, and performance statistics were calculated in each imputed dataset and then averaged across imputations using Rubin’s rules to obtain one estimate and standard error (SE) for each performance statistic in each cohort.20

The discriminatory performance of models were assessed using the C-statistic (summarised as the area under receiver operating characteristic curve, where 1 indicates perfect discrimination and 0.5 indicates no discrimination beyond chance), and calibration statistics of the calibration slope (slope of the regression line fitted between predicted and observed risk probabilities on the logit scale, with 1 being the ideal value), and calibration-in-the-large (the extent that model predictions are systematically too low or too high across the cohort, ideal value of 0).21 22 Model calibration was also visually assessed using calibration plots representing the average predicted probability for risk groups categorised using deciles of predicted probability against the observed proportion in each group, in cohorts with at least 100 events. A lowess smoother curve was applied to show calibration across the entire range of predicted probabilities at the individual-level (i.e. without categorisation). For the calibration plots, average predicted probabilities were obtained for individuals by pooling their linear predictor values across imputed datasets using Rubin’s rules, and then transforming to the probability scale.

Performance measures of prediction models that were validated in more than two independent cohorts were summarised using a random effects meta-analysis to calculate a summary estimate for the model’s discrimination and calibration performance. Model performance was summarised for each statistic as the average and 95% confidence interval (CI) calculated using the Hartung-Knapp-Sidik-Jonkman approach.23,24 Between-study heterogeneity ($τ^{2}$) and the proportion of variability due to between-study heterogeneity ($I^{2}$)25 were summarised. We also reported the approximate 95% prediction intervals, for potential predictive performance in a new study, as calculated using the approach of Higgins et al.26

*Decision curve analysis*

We performed decision curve analysis (DCA) to assess the clinical value of the models on cohorts with at least 100 events. This analysis allowed us to determine the net benefit of the models across a range of clinically plausible threshold probabilities (which included any values up to 0.1, given the generally very low risk of stillbirth), compared to either simply classifying all women as having the outcome or no women as having the outcome.27 The strategy with the highest net benefit at a particular threshold has the highest clinical value.28 The net benefit is represented as a function of the decision threshold in decision curve plots.

All statistical analyses were performed using Stata software version 15.

**RESULTS**

From 5055 citations we identified 17 articles describing the development of 40 stillbirth prediction models published between 2007 and 2020 (Appendix 2). Three studies reporting three prediction models - Smith 2007,29 Yerlikaya 2016,30 and Trudell 201731 met our inclusion criteria for external validation in the IPPIC IPD datasets (Figure 1).

## Characteristics of included models

All three models were developed using binary logistic regression in unselected populations of pregnant women,29-31 and the definition of stillbirth varied between the studies. Two models included only maternal clinical characteristics as predictors,30,31 while one model additionally included ultrasound markers.29 Only one study had at least 10 events per predictor for model development,30 the others did not justify whether their sample size was sufficient. Using the PROBAST tool, the overall risk of bias for all three models was high, with all models assessed as being at high risk of bias in the analysis domain. The characteristics of included studies and models are described in Table 1.

**Characteristics of the IPPIC validation cohorts**

Of the 78 cohorts in the IPPIC data repository, 19 cohorts (24%) contained relevant data that could be used to externally validate at least one of the three prediction models identified. Only women with singleton pregnancies in the cohorts were used for external validation. The prevalence of stillbirth ≥24 weeks gestation in the cohorts ranged from 0.1% - 1.6%. A quarter of the studies used for external validation included only low risk (26%, 5/19) women, while a fifth (21%, 4/19) included only high-risk women in the cohorts. Seventy-five percent (14/19) of the cohorts used for external validation had an overall low risk of bias as assessed by PROBAST, 21% (4/19) were assessed as high risk and one cohort as unclear (appendix 3). Summary maternal characteristics and outcomes of women in the validation cohort are provided in table 2, and a summary of missing data for each predictor and outcome is provided in appendix 4.

## External validation and meta-analysis of predictive performance

The Smith 2007 model29 was validated in 3 cohorts, Yerlikaya 2016 model30 in 4 cohorts and the Trudell 2017 model31 in 17 cohorts. Two of the cohorts used to validate the Smith 2007 model and all four of the cohorts used to validate the Yerlikaya 2016 model were also used to validate the Trudell 2017 model. A direct comparison of performance of the prediction models was not possible due to differences in outcomes of each model. The distribution of the linear predictor and predicted probability for each model and validation cohort are shown in appendix 5.

*Model predictive performance*

The C-statistics of models in the different validation cohorts ranged from 0.56-0.82 in the Smith 2007 model, 0.54-0.73 in the Yerlikaya 2016 model and 0.34-0.69 in the Trudell 2017 model (Table 3). The Trudell 2017 model had the lowest overall discrimination across the validation cohorts. Summary C-statistics of the models were 0.65 (95% CI 0.53 to 0.75) for the Smith 2007 model, 0.61 (95% CI 0.43 to 0.77) for the Yerlikaya 2016 model, and 0.53 (95% CI 0.51 to 0.55) for the Trudell 2017 model (Table 4). Confidence intervals for the Smith 2007 and Yerlikaya 2016 models were wide, due to the fewer number of cohorts available for their validation.

Calibration statistics for each model in the different validation cohorts are shown in Table 3. Summary calibration slopes were < 1 for all models, indicative of overfitting during model development; in particular, the 95% confidence intervals for the calibration slope were all below 1 for the Yerlikaya 2016 and Trudell 2017 models, indicating extreme predictions compared to what was observed (Table 4).

Each of the three models were validated in one cohort with at least 100 events. The average calibration plots showed miscalibration of the predicted risk of stillbirth in all three models (Figure 2). However, predicted probabilities were all less than 0.02, therefore absolute risk differences remain small. The 95% CI was wide for the calibration slope of the Smith 2007 model, due to less data on stillbirth outcome in the validation cohorts available for this model, and so further research is needed for this model.

**Net benefit of model use**

The DCA for all three models in cohorts with at least 100 events, showed little or no improvement in the net benefit at any probability threshold compared to a treat all or treat none strategy (Figure 3).

**DISCUSSION**

**Summary of findings**

Only a fifth of published stillbirth prognostic models reported the model equation required for independent external validation. Three models developed in high-income countries could be externally validated using cohorts from the IPPIC data repository. The models were mostly developed using maternal clinical characteristics, but one model additionally included ultrasound markers. PROBAST of the original model development articles suggested risk of bias concerns, and our IPD meta-analysis of model performance showed low discriminatory ability and poor calibration, with calibration slopes mostly <1, indicative of overfitting during model development. The models had no clinical utility as assessed by DCA. Although each of the three models could be validated in at least one cohort with >100 events, confidence intervals of predictive performance were wide for the Smith 2007 model, suggesting further validation is needed for this model.

## Strengths and limitations

To our knowledge, this is the first systematic review and external validation study of stillbirth prediction models.8,32 Our study with its large sample size, allowed for the evaluation of the predictive performance of each model across multiple cohorts, as well as the overall performance through an IPD meta-analysis. We used multiple imputation of predictors and outcomes for each cohort separately, to avoid loss of useful information, and ensure we did not mask any heterogeneity across cohorts.20,33 Although the definition of stillbirth in the validation cohorts were standardised, stillbirth was defined differently in each model, which prevented a head-to-head comparison of model performance.

Our study has some limitations. We were only able to validate three of the 40 identified models , mainly due to the failure of studies to adhere to reporting standards of publishing the model equation.34,35 Only two models were published before release of TRIPOD. Some cohorts used in the external validation had few observed cases of stillbirths, and only two had more than 100 events. Predicted probabilities in the cohorts only went up to 3%, which makes it difficult for the models to discriminate between women who had and did not have the outcome. This further highlights the primary limitation of stillbirth research, which is the comparative rarity of the outcome.

## Comparison to existing studies

External validation of prediction models are needed to confirm generalisability and transportability of a model in populations with different characteristics.36 However, independent data with sufficiently large sample sizes of stillbirth and relevant predictors for external validation of models are not readily available. This is a factor on why none of the published models have been recommended for use in clinical practice.35 Our meta-analysis obtained lower summary estimates for discrimination to that reported in the development datasets, although this might be due to chance as some confidence intervals were wide (e.g. Smith 2007), further research is recommended.29-31 Some published stillbirth models report discrimination of > 0.8,37,38 but these studies either did not report the model equation needed for independent external validation,38 or did not provide enough information on predictors .37 In most cases, the performance of a prediction model is often overestimated when only estimated in the dataset used to develop the model, especially when there are few outcomes relative to the number of predictors considered.39,40 Our study highlighted several methodological shortcomings in the development of stillbirth prediction models, which is further reflected in the risk of bias assessment of the models.

## Relevance to clinical care

The UK Government and NHS launched a care initiative in a bid to halve stillbirth rates by 2025, which includes risk assessment as part of a wider care-bundle.41 The bundle does not include tools to help determine if a woman is at increased risk of stillbirth, instead individual factors have been identified to categorise women as low, moderate or high risk of FGR, the most frequent cause of stillbirth in the UK. An accurate tool to predict which woman is at increased risk of stillbirth would allow for personalised risk stratification in pregnancy, and enable clinicians to make decisions on closer surveillance, or timing of birth to prevent fetal death. It would also empower mothers to make informed decisions on their risk of stillbirth. This would be a more targeted approach than the currently used system of a generalised population level risk factor to identify women at risk of stillbirth. However, none of the models validated in this study had sufficient performance or clinical utility to be recommended for use in practice.

## Recommendations for further research

Stillbirth prediction models that can be used in routine care would be especially valuable in low-and-middle-income countries, where stillbirth burden is disproportionately high. Models we were unable to externally validate will need to be independently validated before they can be recommended for use. Apart from improvement in the model development process to reduce overfitting by using larger sample sizes and adjusting for optimism of the predictor effects (e.g. by post-estimation shrinkage or penalising the model coefficients), additional work is needed to identify novel prognostic factors for use in model development, to improve the discriminatory performance of prediction models.42 A closer examination of existing stillbirth risk factors could potentially enable us to abandon inaccurate risk predictors and focus clinical care and research on the highest value predictors.

Systematic reviews using aggregate data meta-analysis, currently represent the best available evidence on predictors of stillbirth, and have proposed several risk factors to categorise women as high-risk.43 However, these studies are limited by heterogeneity in the data reported within the primary studies, such as in the definition of stillbirth.43 Existing primary studies are often small with imprecise estimates, and inconsistencies in confounding factors adjusted for in their analysis, which sometimes leads to contradictory factor-outcome associations. Large cohorts are needed to collect richer data on risk factors to enable development and validation of prediction models.

Whilst this study has explored validation of different stillbirth prediction models, stillbirth is the final endpoint of several heterogeneous antecedent pathways, with varying biological mechanisms involved (for example, those involving FGR, and those secondary to diabetes, typically with a large for gestational age infant). It is possible that more than one model will be needed, either for prediction at different gestational ages, or for stillbirths with similar phenotypes.

**CONCLUSION**

This is a comprehensive assessment and independent external validation of published stillbirth prognostic models across multiple cohorts. Findings suggest methodological shortcomings including overfitting of models during development. None of the three previously published stillbirth models that were validated in this study showed sufficient performance or clinical utility to be recommended for use in practice. Although there were differences in predictor and outcome definitions used for the different models, all three models considered similar candidate predictors for model development, which may suggest additional and better predictors (prognostic factors) of stillbirth still need to be identified.

**Abbreviations**

IPD Individual participant data

IPPIC International Prediction of Pregnancy Complications

PROBAST Prediction study Risk of Bias Assessment

SE Standard error

CI Confidence interval

LP Linear predictor

**Declarations**

**Ethics approval and consent to participate**

Not applicable. The study involved secondary analysis of existing anonymised data.

**Consent for publication**

Not applicable

**Availability of data and materials**

The data that support the findings of this study are available from the IPPIC data sharing committee, but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are however available from the authors upon reasonable request and with permission of contributing collaborators.

**Competing interests**

None to declare

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**Authors’ contributions**

ST, AK developed the protocol. RW wrote the statistical analysis plan and performed the analysis, JA produced the first draft of the article and revised the article. RR and KS oversaw the statistical analyses and analysis plan. MS and JA formatted, harmonised and cleaned IPPIC datasets, in preparation for analysis. JA, MS mapped the variables in the datasets, and cleaned and quality checked the data. JA, ST, MS and RT undertook the literature searches, study selection, acquired Individual Participant Data, contributed to the development of all versions of the manuscript and led the project. All authors provided input at all stages of the project and helped revise the article.

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