Methodological challenges in the development and validation of a prognostic prediction model for time-to-birth in patients admitted for threatened preterm birth at a tertiary care centre

Objectives – The goal of this study was to illustrate the development and validation of a preterm birth prognostic prediction model for symptomatic patients admitted at a gestational age between 24 and 34 weeks' gestation at a tertiary care centre. We aimed to highlight the importance of adequately handling loss-to-follow up and not restricting analyses to complete cases or cases selected on outcome.

Methods – We developed an univariate (intra-uterine transfer) and multivariate (intra-uterine transfer, singleton/multiple, gestational age at admission, reason for admission, history of preterm birth) Cox proportional hazards model based on a prospective (509 patients), a complete cases (415) and an outcome-dependent cohort (preterm deliveries between 24 and 34 weeks)(645). We performed internal and external temporal (144) and geographical (259) validation by calculating the integrated Brier score and drawing prediction error curves based on Brier scores. We applied inverse probability of censoring weighting to correct for informative censoring in the prospective development set and the external validation sets.

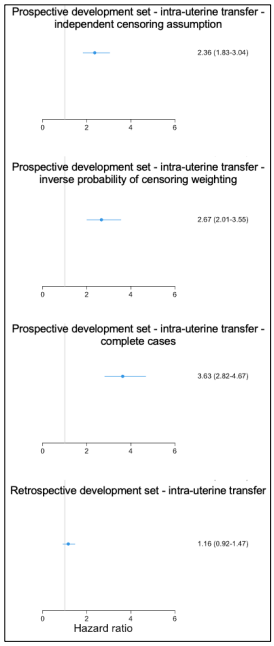
Results – The analyses on the complete cases and outcome-dependent dataset proved to be biased. This was not apparent during internal validation, though the performance measures calculated during external validation indicated that the models were useless, or even harmful. The impact of informative censoring appeared to be low in this study.

Conclusion – For prediction of time-to-(preterm) birth, a time-to-event analysis is indicated. It should be performed on a cohort including all patients for whom prediction is intended. Complete cases analyses and analyses of preterm birth cases are biased.

Preference: oral presentation

Figure 1: Coefficients of the Cox proportional hazards models

Abbreviations: iut = intra-uterine transfer, ga_adm_d: gestational age at admission, in days, spl = spontaneous preterm labour, iatro = iatrogenic threatened preterm birth, pprom = preterm prelabour rupture of membranes, pb_history = preterm birth history



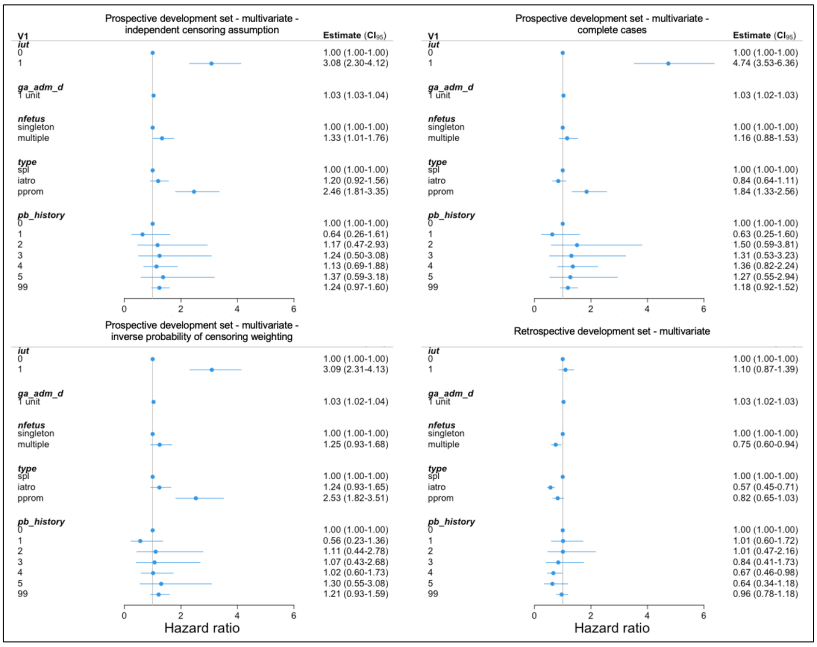


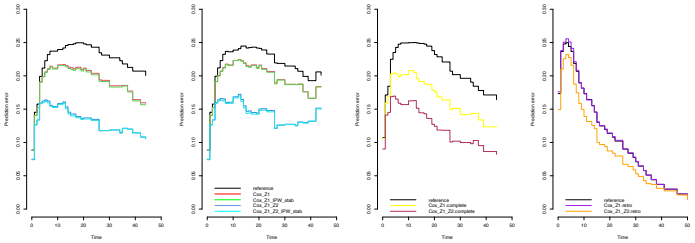
Figure 2: Prediction error curves (Brier scores)

Internal validation. Graph 1: validation in the prospective test set, independent censoring assumption; Graph 2: validation in the prospective test set, inverse probability of censoring weighting; Graph 3: validation in the complete cases analysis; Graph 4: validation in the outcome-dependent retrospective test set

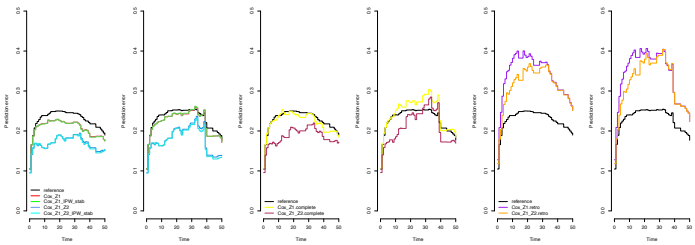
External validation. Graph 1: validation of the prospective model with independent censoring assumption in the external test set; Graph 2: validation of the prospective model with inverse probability of censoring weighting in the external test set; Graph 3: validation of the complete cases model with independent censoring assumption in the external test set; Graph 4: validation of the complete cases model with inverse probability of censoring weighting in the external test set; Graph 5: validation of the outcome-dependent retrospective model with independent censoring assumption in the external test set; Graph 6: validation of the outcome-dependent retrospective model with inverse probability of censoring weighting in the external test set

Abbreviations: Cox_Z1 = univariate Cox model (independent censoring assumption in the development set), Cox_Z1_IPW_stab = univariate Cox model with inverse probability of censoring weighting in the development set, Cox_Z1_Z2 (independent censoring assumption in the development set), Cox_Z1_Z2_IPW_stab = multivariate Cox model with inverse probability of censoring weighting in the development set, reference = Kaplan-Meier curve

Internal validation



External temporal validation



External geographical validation