BAYESIAN GROWTH CURVE MODELING FOR NEONATAL BILIRUBIN TRAJECTORIES ESTIMATION AND PHOTOTHERAPY THRESHOLDS IDENTIFICATION

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Introduction

Neonatal jaundice is a common physical sign observed in the 60% of term newborn infants and in the 80% of preterm infants [1]. It manifests through the yellowing of the skin and whites of the eyes and is caused by high bilirubin concentration in the blood. The level of bilirubin tends to increase in the first 96 hours of life; if the concentration of bilirubin exceeds the thresholds reported in the guidelines [2], infants undergo phototherapy. The prediction of bilirubin trajectories can help to prevent acute bilirubin encephalopathy and kernicterus in newborns, but also to avoid phototherapy for infants who actually do not need it. The estimation of individual trajectories can be performed with growth curve models which are a family of statistical techniques able to capture within-person change over time [3].

Aims

The aim of this study is to reconstruct the bilirubin trajectory of newborns, enabling the identification of optimal minimum values that indicate the need for phototherapy. The curves of minima will be then compared to those of guidelines for a quality-of-care improvement in the future.

Methods

A total of 198 infants born at Mauriziano Hospital (Torino, Italy) from September to November 2022 were monitored and their clinical data collected. In particular, their bilirubin values during the first 96 hours of life were measured at different time points. 43 of them underwent phototherapy after their bilirubin values were deemed by the medical staff to be above the safe level.

Bayesian growth curve modeling [4] was performed to reconstruct the bilirubin trajectories for infants who underwent phototherapy and the trajectories for those who did not.

The bilirubin value of subject $i=1,\ldots,n$ measured at time $t=1,\ldots,T$ was modelled with a two-level Bayesian growth curve model. The level-1 equation captures the effect of time at the person level: $Y_{it} \sim N(\beta_{i,1} + \beta_{i,2}T_t, \sigma^2)$; the level-2 equations specified the distribution of the parameters to capture the between

person variability: $\beta_{i,1} \sim N\left(\gamma_{00} + \gamma_{10} X_{i,1}, \sigma^2_{\beta_1}\right)$ and $\beta_{i,2} \sim N\left(\gamma_{10} + \gamma_{11} X_{i,1}, \sigma^2_{\beta_2}\right)$. In our case the variable X represents the phototherapy indicator variable for the model considering all the subjects. The vector β is supposed to follow a binormal distribution thus a covariance term $\sigma_{\beta_{1,2}}$ was considered. We assumed: a standard non-informative normal distribution for the coefficients and a standard non-informative uniform distribution for variance, correlation, and standard error terms.

A second model was fitted only on the 43 infants who underwent phototherapy to reconstruct the thresholds curve of Mauriziano Hospital. For this model prior were specified accordingly with the guidelines. The curve of minima was compared to the guidelines to assess how closely they were followed. The advantage of the chosen approach is the capability of managing sparse data: some patient curves can be estimated also with a single observed value.

All the statistical analysis were performed with R version 4.2.1 and JAGS through the *rjags* package.

Results

Bilirubin was measured in a time range between 15 and 92 hours of life with a median value of 50. The number of bilirubin measurement for each infant ranges between 1 and 6 with a median value of 2. In particular, 60 out of 198 infants reported only one measurement, 15 of whom underwent phototherapy. The minimum values of bilirubin for which infants underwent phototherapy range from 9.70 to 17.83 in a time window between 23 and 86 hours of life.

The posterior sample distributions are reported in Figure 1.

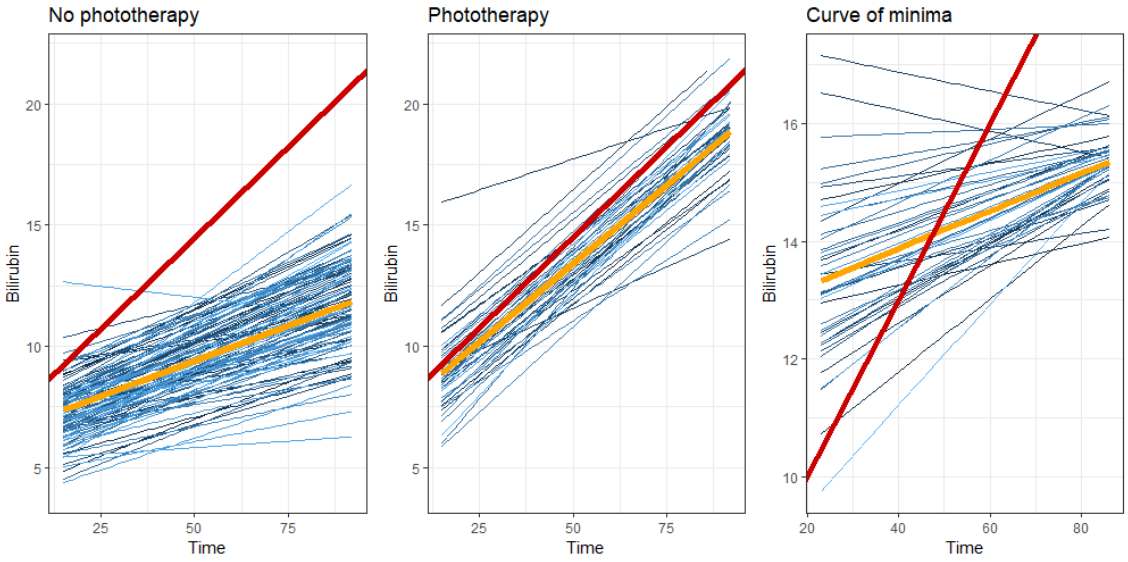

Figure 1. Center and left panels represent the posterior samples trajectories of bilirubin in the first 96 hours of life for infants who underwent phototherapy and who did not respectively. Right panel represents the minimum values of bilirubin for which infants underwent phototherapy. Thick orange lines are the mean posterior trajectories. Thick red line is the guideline threshold curve for deciding to administer phototherapy.

As we expected the posterior trajectories for infants who underwent phototherapy have similar starting values of bilirubin (intercept 6.95 [5.32-8.61]), but a higher increase (slope 0.13 [0.10-0.16]) respect to those who did not (intercept 6.49 [5.47-7.53], slope 0.06 [0.04-0.08]). Infants who underwent phototherapy still have trajectories below the guidelines suggesting that phototherapy was administered to infants who did not need it. This was confirmed by the second model performed on the subjects who underwent phototherapy considering only the bilirubin value for which medical staff decided to intervene. In fact, the posterior mean trajectory was above the guideline thresholds curve (intercept 7, slope 0.15) until the 47 hours of life, then because of the small increasing slope (0.03 [0-0.07]) it continues below the reference curve.

Conclusions

Bayesian growth curve modeling allowed us to reconstruct the trajectories of bilirubin of the newborns at Mauriziano Hospital despite the high sparsity of data and to estimate the posterior distribution of minimum bilirubin values for which infants underwent phototherapy. As the curve of minima is very conservative, phototherapy can be avoided for the 71% of children also reducing the maternal neonate separation that is source of toxic stress [5]. The impact of these findings will be a new planning strategy for the monitoring of neonatal jaundice at Mauriziano Hospital.

Bibliography

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