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DIGIROP Prediction models for severe retinopathy of prematurity

Akademisk avhandling

Som för avläggande av medicine doktorsexamen vid Sahlgrenska akademin, Göteborgs universitet kommer att offentligen försvaras i R-aulan, Länsmansgatan 28 i Mölndal, den 26 maj 2023, klockan 09:00, av

Aldina Pivodic

Fakultetsopponent:

J. Peter Campbell, Associate Professor of Ophthalmology

Department of Ophthalmology, Oregon Health and Science University, Portland, USA

Avhandlingen baseras på följande delarbeten

I. **Pivodic A**, Hård AL, Löfqvist C, Smith LEH, Wu C, Bründer MC, Lagrèze WA, Stahl A, Holmström G, Albertsson-Wikland K, Johansson H, Nilsson S, Hellström A. Individual Risk Prediction for Sight-Threatening Retinopathy of Prematurity Using Birth Characteristics. *JAMA Ophthalmol. 2020 Jan 1;138(1):21-29.*

II. **Pivodic A**, Johansson H, Smith LEH, Hård AL, Löfqvist C, Yoder BA, Hartnett ME, Wu C, Bründer MC, Lagrèze WA, Stahl A, Al-Hawasi A, Larsson E, Lundgren P, Gränse L, Sunnqvist B, Tornqvist K, Wallin A, Holmström G, Albertsson-Wikland K, Nilsson S, Hellström A. Development and validation of a new clinical decision support tool to optimize screening for retinopathy of prematurity. *Br J Ophthalmol. 2021 May 12:bjophthalmol-2020-318719.*

III. **Pivodic A**, E H Smith L, Hård AL, Löfqvist C, Almeida AC, Al-Hawasi A, Larsson E, Lundgren P, Sunnqvist B, Tornqvist K, Wallin A, Holmstrom G, Gränse L. Validation of DIGIROP models and decision support tool for prediction of treatment for retinopathy of prematurity on a contemporary Swedish cohort. *Br J Ophthalmol. 2022 Mar 11:bjophthalmol-2021-320738.*

IV. **Pivodic A**, Holmström G, Smith LEH, Hård AL, Löfqvist C, Al-Hawasi A, Larsson E, Lundgren P, Gränse L, Sunnqvist B, Tornqvist K, Wallin A, Johansson H, Albertsson-Wikland K, Nilsson S, Hellström A. Duration of Parenteral Nutrition and Risk for Retinopathy of Prematurity – Development and Validation of the Revised DIGIROP Clinical Decision Support Tool. *Accepted with some revisions*.

SAHLGRENSKA AKADEMIN
INSTITUTIONEN FÖR NEUROVETENSKAP OCH FYSIOLOGI

GÖTEBORGS UNIVERSITET

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Background: Retinopathy of prematurity (ROP), a preventable, potentially blinding eye disease, is primarily diagnosed in extremely preterm infants. Gestational age (GA) and birth weight (BW) are the most prominent risk factors. Routine ROP examinations are performed to identify the low proportion of infants who progress to needing treatment. In Sweden, ~30% of all screened infants are diagnosed with ROP, and 6% require treatment. Safe ROP prediction models can improve infant well-being and make screening efficient by identifying low- and high-risk infants.

Aim: The overall aim of the thesis was to develop and validate prediction models for severe ROP requiring treatment and propose a clinical decision support tool for safe and effective release of low-risk infants from ROP screening examinations. In addition, the natural course of the disease was described, and the prognostic value of the parenteral nutrition duration (PND) on ROP was demonstrated.

Materials and Methods: The model development data originated from the Swedish national ROP register (SWEDROP). External validations included data from SWEDROP, Germany, and the US. *Paper I* included 6947 infants in the model development and 2122 in the external validation cohort. Corresponding figures for *Paper II* were 6991 and 1241, and for *Paper IV*, 8814 and 2325, respectively. *Paper III* included 1082 infants in its external validation. Extended Poisson models were used to develop DIGIROP-Birth requiring GA, BW, and sex in version 1.0, and PND ≥14 days in version 2.0 as input variables. Logistic regression models were used to develop DIGIROP-Screen, including the status and the age at the first ROP diagnosis besides DIGIROP-Birth risk estimates. GA-specific cut-offs were identified for the clinical decision support tool.

Results: The instantaneous risk for ROP peaked around 12 weeks postnatal age, irrespective of GA at birth. Longer PND was strongly correlated to ROP severity, and faster progression. The risk for ROP differed for boys and girls over GA and PND. DIGIROP models released ~50% of infants from all ROP screening examinations and additionally ~25% during the screening process, while maintaining 100% sensitivity.

Conclusion: DIGIROP models may safely and efficiently release infants from unnecessary ROP examinations. The models appear superior to other currently available ROP models and are freely available as an online application (www.digirop.com).

Keywords: preterm birth, retinopathy of prematurity, prediction models, screening, clinical decision support tool

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