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Original Article

Refining evidence-based retinopathy of prematurity screening guidelines: The SCREENROP study

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Abstract

Purpose: Retinopathy of prematurity (ROP) is a potentially blinding condition affecting premature infants for which less than 10% of babies undergoing screening require treatment. This study assessed and validated predictors of developing clinically significant ROP (type 2 or worse) and ROP requiring treatment.
Design: Nationwide retrospective cohort study.
Methods: This study included infants born between January 2014 and June 2016, admitted to level 3 neonatal intensive care units across Canada who underwent ROP screening. Data were derived from the Canadian Neonatal Network database. Predefined ≥ 1% risk for clinically significant retinopathy or prematurity and ROP requiring treatment was set as threshold for screening. Thirty-two potential predictors were analyzed, to identify and validate the most important ones for predicting clinically significant ROP. The predictors were determined on a derivation cohort and tested on a validation cohort. Multivariable logistic regression modeling was used for analysis.
Results: Using a sample of 4,888 babies and analyzing 32 potential predictors, capturing babies with ≥1% risk of developing clinically significant ROP equated to screening babies with birth weight (BW) <1,300 g or gestational age (GA) <30 weeks while capturing babies with ≥1% risk of requiring ROP treatment equated to screening babies with BW <1,200 g or GA <29 weeks.
Conclusions: The Canadian ROP screening criteria can be modified to screen babies with BW <1,200 g or GA <30 weeks. Using these criteria, babies requiring treatment would be identified while reducing the number of babies screened unnecessarily.

Keywords: *Birth weight; Extremely premature; Eye; Gestational age; Infant; Premature; Retina*

In premature Canadian neonates, 40 to 50% will develop retinopathy of prematurity (ROP), with 5 to 6% requiring treatment (1). Severity of ROP depends on three factors: stage (1 to 5) with 1 being mild and 5 being the most severe; presence or absence of plus disease (dilation and tortuosity of retinal vasculature) and zone (1–3). Attempting to improve on the timing

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of when to treat ROP, the Early Treatment for Retinopathy of Prematurity (ETROP) (2) study looked at high-risk prethreshold ROP cases, which were defined as any ROP with a ≥ 15% risk of leading to unfavourable visual outcome if untreated. In conclusion, the ETROP study defined two new types of ROP: Type 1 (which requires urgent treatment) and Type 2 (which requires close monitoring in case it progresses to Type 1 when treatment is required). Type 1 ROP is defined as any stage 3 or plus disease in zone 1, or stage 3 and plus disease in zone 2. Type 2 ROP is defined as zone 1, stage 1 or 2 without plus disease or zone 2, stage 3 without plus. In our study, Type 2 or worse ROP is collectively referred to as clinically significant retinopathy of prematurity (CSROP).

Many national guidelines (3–7) aim to predict which newborns will develop severe ROP. British guidelines recommend screening infants <32 weeks gestational age (GA) or <1,501 g birth weight (BW) (4). In Canada, current recommendations are to screen infants with GA <31 weeks or BW <1,251 g (8) while in USA recommend screening is for infants with GA <30 weeks or BW ≤1,500 g as well as infants with BW of 1,500 to 2,000 g who have an unstable clinical course (9).

Limitations of existing recommendations include the smaller sample sizes as well as differences between the populations used to develop the guidelines (10). The primary aim of this study was to identify and validate the most important predictors of CSROP and to determine if these predictors also predicted ROP treatment. The findings from this study would allow for an informed decision-making process to minimize the number of babies missed with CSROP while reducing the overall number of babies (and ensuing health care costs) enrolled into ROP screening unnecessarily.

METHODS

Study design

SCREENROP (Seminal Canadian Recommendations for Evidence-Based Examination of Neonates for Retinopathy of Prematurity) is a population-based nationwide study. Institutional ethics approval was obtained from the Hamilton Integrated Research Ethics Board as well as from each tertiary care neonatal intensive care unit (NICU) in Canada.

Canadian Neonatal Network (CNN) database

This study collected data from the CNN (11), which houses clinical and demographic information on all infants admitted to all level 3 NICUs across Canada. Throughout the study period, the SCREENROP team contacted all ophthalmologists in Canada involved in ROP treatment on a monthly basis in order to collect data on all babies that they had treated for ROP over the previous month. This information was then cross-checked with the CNN database to ensure that no ROP-treated neonates were missed.

Study population

Infants born January 1, 2014 through June 30, 2016, admitted to level 3 NICUs Canada wide, who underwent ROP screening. See Figure 1 for exclusion criteria.

Data extraction

Data collected through CNN database, including details of every ROP eye examination received by every child during their level 3 NICU stay.

Outcome measures

The primary outcomes were (1) CSROP and (2) ROP requiring treatment. Diagnosis and classification of ROP and decisions relating to timing of screening and initiation of treatment (including retinal laser application or intraocular anti-VEGF injection) were based on the individual practices at each centre (9,10). There may have been circumstances where treatment was administered before reaching Type 1.

Statistical analysis

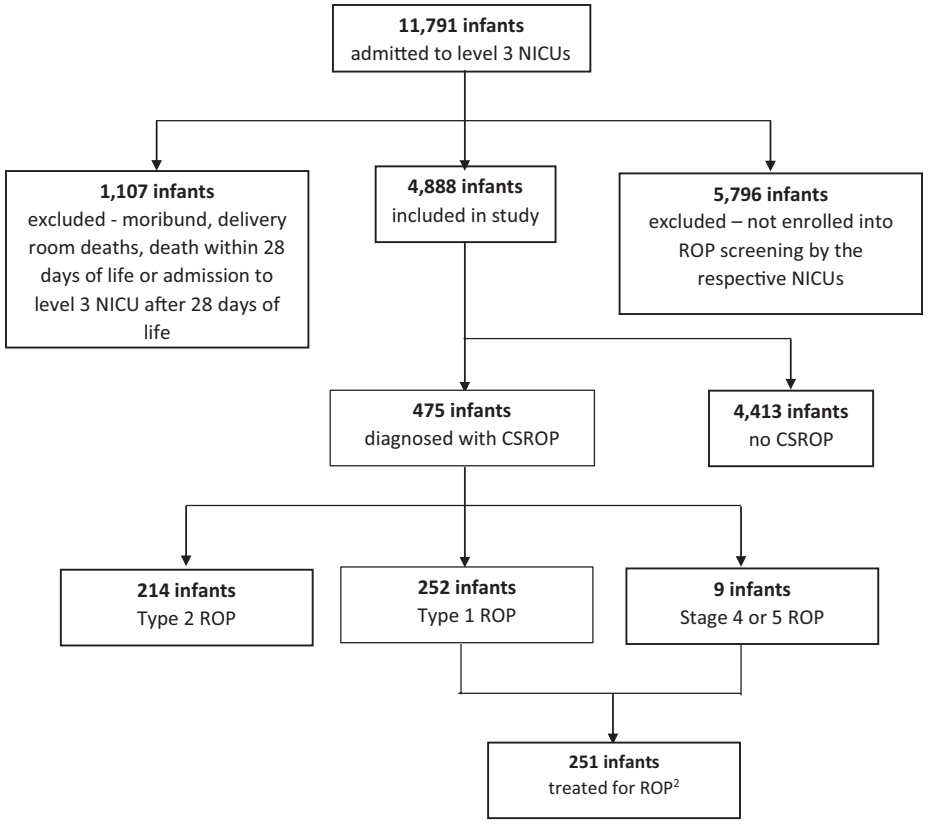
Using results of a comprehensive literature review (6,12–27), 32 clinical factors associated with CSROP were selected for prediction regression models. Using Peduzzi et al. recommendations a priori, at least 10 events per covariable were required to avoid poor estimation of Wald-based confidence intervals (CI) and Wald-test of coefficients (28). Therefore, a minimum of 320 CSROP (events) were required to maintain at least 80% power.

Phase 1—(determination and validation of CSROP predictors)

Threshold for screening was fixed a priori at probability of 0.01 (1%) for developing CSROP. In other words, a baby would be screened if the risk of developing CSROP was 1% or higher. The low threshold of 1% was chosen by consensus among the study collaborators during the planning stages of the study. Given the understandably risk-averse nature of clinicians, fixing the probability of developing CSROP at 0% would be ideal, but this was not possible due to statistical estimation problems. The predictive models were developed from the derivation cohort (two-third of data) and tested on validation cohort (one-third of data).

Derivation cohort (two-third of the sample size)

Two-thirds of the available data were randomly selected. Univariable analyses of the CSROP were performed to identify the candidate variables for inclusion in the multivariable logistic regression analysis. Categorical data were reported as frequencies and relative frequencies and compared using Chi-square or Fisher's exact test as appropriate. Continuous data were reported as mean with standard deviation and compared using Student's t-test. One step logistic regression model was



[1] Abbreviations: CSROP- Clinically Significant Retinopathy of Prematurity (Type 2 or worse); NICU – Neonatal Intensive Care Unit; ROP – Retinopathy of Prematurity
[2] The treatment total according to our data is 251 infants, as treatment of type 1 ROP while recommended, is ultimately at the discretion of the responsible physicians for said patient.

Figure 1. Overall study population details and severity of ROP[1] developed. [1]CSROP Clinically significant retinopathy of prematurity (Type 2 or worse); NICU Neonatal intensive care unit; ROP Retinopathy of prematurity. [2]The treatment total according to our data is 251 infants, as treatment of type 1 ROP while recommended, is ultimately at the discretion of the responsible physicians for said patient.

conducted including all variables with P-value of ≤0.1 from univariable analyses. Coefficients, 95% CI and P-values were estimated for the variables.

Validation cohort (one-third of sample size)

First, all variables with P-value of <0.05 as predictors of CSROP identified from the derivation cohort were included in the multivariable logistic regression analysis using CSROP as the dependent variable. The variables that likely introduced collinearity (Max FI O2%, O2 and intubation and ventilation) did not have significant association and were removed from the model. Then, a backward step-wise approach was used and variables with larger p-values were removed one at a time. Coefficients, 95% CI, and P-values were estimated and reported for each model. Using the predefined threshold of 1% risk for CSROP as screening criteria, the number of missed CSROP cases for each model was estimated. The most optimal prediction model as final model was selected based on minimizing the number of missed CSROP cases and reducing the overall number of infants subjected to screening.

Phase 2—(validation of predictors of ROP requiring treatment)

The predictors from the Final Model from Phase 1 were included in the one-step logistic regression analysis using ROP treatment versus no treatment as dependent variable on validation cohort. The objective was to test if these factors also predicted which babies will require ROP treatment, using the same threshold probability of 0.01 (1%) and statistical approach. Sensitivity analysis for outliers was not performed to avoid unwarranted assumptions.

In order to decrease sampling error and ensure balanced groups, the splitting of the study population into derivation and validation cohorts as well as all steps of the analysis were repeated through 1,000 independent randomizations (29).

Table 1. Baseline characteristics and potential predictors of retinopathy of prematurity among the total study population, derivation (two-third of sample) and validation (one-third of sample) cohorts

Characteristics	Total	Derivation cohort	Validation cohort	P-value
Number of infants	**4,888**	**3,259**	**1,629**	
Severity of ROP				
No/Mild ROP	90.3% (4,413/4,888)	89.9% (2,929/3,259)	91.1% (1,484/1,629)	0.48
Type 2 ROP	4.4% (214/4,888)	4.5% (145/3,259)	4.2% (69/1,629)	
Type 1 ROP	5.2% (252/4,888)	5.5% (179/3,259)	4.5% (73/1,629)	
Stage 4 or 5 ROP	0.2% (9/4,888)	0.2% (6/3,259)	0.2% (3/1,629)	
ROP requiring treatment	5.1% (251/4,888)	5.5% (179/3,259)	4.4% (72/1,629)	0.13
Clinical Predictors				
Prenatal Period				
Antenatal Steroids (Yes), %(n/N)	89% (4,132/4,642)	89.2% (2,769/3,103)	88.6% (1,363/1,539)	0.52
Rupture of membranes <24 h (Yes), %(n/N)	79% (3,615/4,575)	79.1% (2,420/3,060)	78.9% (1,195/1,515)	0.90
Postnatal Life (first 24 h of life)				
Gestational age (weeks), mean (SD)	27.8 (2.30)	27.9 (2.33)	27.8 (2.35)	0.87
Birth Weight (grams), mean (SD)	1,095 (335.23)	1,094.3 (336.25)	1,096.3 (332.92)	0.85
Number of births >1, %(n/N)	15.5% (756/4,888)	15.2% (496/3,259)	16% (260/1,629)	0.53
Small gestational age (Yes), %(n/N)	13.9% (683/4,888)	14.4% (449/3,259)	13.8% (234/1,629)	0.61
Gender				0.79
Male, %(n/N)	53.9% (2,637/4,888)	53.6% (1,747/3,259)	54.6% (890/1,629)	
Female, %(n/N)	45.9% (2,242/4,888)	46.2% (1,506/3,259)	45.2% (736/1,629)	
Unknown or Ambiguous, %(n/N)	0.2% (9/4,888)	0.2% (6/3,259)	0.2% (3/1,629)	
Mode of delivery (vaginal), %(n/N)	37% (1,804/4,871)	37.4% (1,214/3,246)	36.3% (590/1,625)	0.48
Location of Birth (Out born), %(n/N)	17.8% (868/4,888)	17.3% (565/3,259)	18.6% (303/1,629)	0.29
Apgar score <7 at 5 min (Yes), %(n/N)	33.6% (1,582/4,713)	33.5% (1,051/3,139)	33.7% (531/1,574)	0.89
Max FI O2 >21% (Yes), % (n/N)	72.3% (3,534/4,888)	72.1% (2,349/3,259)	72.7% (1,185/1,629)	0.65
SNAPII score >20 (Yes), %(n/N)	18.9% (923/4,882)	19.1% (622/3,257)	18.5% (301/1,625)	0.66
Postnatal Life (first 28 days of life)				
Postnatal systemic steroids (Yes), %(n/N)	11.7% (574/4,888)	12.1% (395/3,259)	11% (179/1,629)	0.27
Surfactant use (Yes), %(n/N)	54.8% (2,680/4,888)	54.9% (1,789/3,259)	54.7% (891/1,629)	0.92
Inotropes (Yes), %(n/N)	14.5% (711/4,888)	14.1% (459/3,259)	15.5% (252/1,629)	0.21
iNO (Yes), %(n/N)	4.9% (241/4888)	5.0% (164/3259)	4.7% (77/1629)	0.69
Transfusions: PRBC or Platelets, %(n/N)	33.9% (1,656/4,888)	34.3% (1,097/3,259)	33.7% (559/1,629)	0.67
Pneumothorax, %(n/N)	3.5% (172/4,887)	3.3% (109/3,259)	3.9% (63/1,628)	0.39
Culture Positive Sepsis, %(n/N)	14.5% (710/4,888)	14.3% (466/3,259)	15% (244/1,629)	0.55
NEC stage 2 or above, %(n/N)	3.4% (164/4,880)	3.4% (110/3,252)	3.3% (54/1,628)	0.97
PDA, %(n/N)	42% (2,040/4,860)	41.2% (1,343/3,239)	43% (697/1,621)	0.32
Caffeine, %(n/N)	84.9% (4,152/4,888)	85.2% (2,776/3,259)	84.5% (1,376/1,629)	0.54
IVH grade 3 or above, %(n/N)	9.7% (473/4,888)	8.8% (285/3,259)	11.5% (188/1,629)	<0.0001
O2_Dt1stExp mean (±SD; N)	1.7 (±4.83; 4,299)	1.6 (±4.66; 3,078)	1.9 (±5.02; 1,221)	0.55
≥14 days of Intubation and ventilation, %(n/N)	78.7% (3847/4888)	79.5% (2590/3259)	77.2% (1257/1629)	0.07
Duration of Intubation and ventilation, mean (±SD)	6.5 (±9.43)	6.5 (±9.33)	6.8 (±9.67)	0.29
Birth weight gain, mean (±SD)	25.4 (±8.63)	25.3 (±8.63)	25 (±8.64)	0.29
HFV_Dt1stExp mean (±SD; N)	5.5 (± 6.61; 1,132)	5.5 (±6.64; 778)	4.8 (±6.48; 354)	0.16
IPPV_Dt1stExp mean (±SD; N)	2.5 (±5.74; 2,635)	2.5 (±5.74; 1,771)	2.6 (±5.72; 864)	0.73

Table 1. *Continued*

Characteristics	Total	Derivation cohort	Validation cohort	P-value
Number of infants	**4,888**	**3,259**	**1,629**	
O2 for 7 days	47.8% (2,338/4,888)	48.2% (1,570/3,259)	47.2% (768/1,629)	0.52
O2 for 28 days	12.5% (610/4,888)	12.5% (407/3,259)	12.5% (203/1,629)	1.00
Max FI O2 %, mean (±SD)	55.7 (±32.30)	55.7 (±32.27)	55.7 (±32.36)	1.00

Birth weight gain Weight on day 28 – weight at birth in grams; HFV_Dt1stExp mean Age of infant in days when first exposed to High Frequency Ventilation; iNO Inhaled nitric oxide; IPPV_Dt1stExp mean Age of infant in days when first exposed to Intermittent positive pressure ventilation; IVH Intraventricular hemorrhage; Max FI O2 >21% (Yes), % (n/N) The infant received supplementary oxygen >21% during resuscitation within the first 30 minutes of life ; Max FI O2 %, mean (+SD) The maximum oxygen concentration provided on day 28 of life; NEC Necrotizing enterocolitis; O2_Dt1stExp mean Age of infant in days when were first exposed to oxygen; O2 for 7 days Having supplemental oxygen for 7 days or more in the first 28 days of life; O2 for 28 days Having supplemental oxygen for 28 out of 28 days in the first 28 days of life; PBRC Packed red blood cells; PDA Patent ductus arteriosus; ROP Retinopathy of prematurity; SNAPII Score for neonatal acute physiology.

A P-value of 0.05 was set for statistical significance. R software (https://www.r-project.org/) was used for statistical analysis.

RESULTS

Figure 1 shows that from the 11,791 infants admitted to level 3 NICUs in the study period, 4,888 babies were screened for ROP and therefore included in the study. Table 1 provides characteristics of the study patients, as well as the 32 potential clinical predictors assessed for the overall study sample, derivation, and validation cohort.

Phase 1—(determination and validation of CSROP predictors)

Table 2 presents univariable analysis and comparison between babies with and without CSROP in the derivation cohort using the 32 clinical predictors. Twenty-one of these predictors identified with P<0.1 from univariable analysis were then included in the multivariable logistic regression model (Table 3). The odds ratios with 95% confidence intervals are reported. Nine of these 21 predictors with P-value of <0.05 were identified as potential risk factors for CSROP. These final nine predictors were GA, BW, IVH, max FI O_2%, inotropes, inhaled nitric oxide, mode of delivery, O_2_7, and patent ductus arteriosus.

These nine predictors with P-value of <0.05 were tested on the validation cohort using backward step-wise logistic regression analysis, whereby the least significant variable was removed one at a time (Table 4). Table 4 (part A) presents the first, middle, last three and final recommended models for predicting CSROP. Using the predefined risk threshold of ≥1% for ROP screening, the number of screened babies and missed CSROP cases were calculated for each model. Compared to the models with more variables (i.e., models 1A to 8A), models 9A and 10A result in the fewest missed babies with CSROP but with a smaller drop in the overall number of babies screened.

Model 8A compared to models 9A (GA) and 10A (BW) included both GA and BW, reducing the overall number of babies screened to 1,082 (66.4%) but missing 7 babies with CSROP. Models including only GA or BW, led to 3 and 4 babies with CSROP being missed, but less reduction in number of the babies screened. However, when models 9 and 10 were applied independently to any given baby (Final Model A), only one baby with CSROP was missed, while still reducing the overall number of babies screened to 1,346 (82.6%). This one missed baby was an outlier with higher GA and BW, who did not require ROP treatment.

Using model 9A, a ≥1% risk of developing CSROP equates to being born with GA of ≤29.5 weeks. Using model 10A, a ≥1% risk of developing CSROP equates to being born with BW of ≤1,300.

Phase 2—(validation of predictors of ROP requiring treatment)

Table 4, part B relates to predicting ROP that requires treatment. These models are based on various combinations of the two main predictors emerging from the previous predictive models on CSROP, namely GA and BW. While the greatest reduction in overall number of babies enrolled in screening is achieved with Model 1B, two babies requiring treatment would be missed with this model. Models 2B and 3B included GA or BW as single variables and led to 3 and 2 missed treated ROP, cases respectively. However, when models 2B and 3B were applied independently to any given baby (Final Model B), only one baby requiring ROP treatment would have been missed, while still reducing the overall number of babies screened to 1,191 (70.9%). This one missed baby was an outlier with BW >1,799 g and GA >32 weeks, who was identified to require ROP screening by the treating neonatologists due to his/her complicated morbidities. Due to the CNN's confidentiality rules surrounding analysis and discussion of individual patient level data, we are not able to discuss the individual medical history of this patient further.

Table 2. Univariable analysis of potential clinical predictors between CSROP and non-CSROP cases in derivation cohort (n=3,259)

Characteristics	Non-CSROP (n=2,917)	CSROP (n=342)	OR (95% CI)	P-value
Prenatal Period				
Antenatal Steroids (Yes), %(n/N)	89.24% (2,471/2,769)	89.22% (298/334)	0.99 (0.69–1.44)	1.00
Rupture of membranes <24 h (Yes), %(n/N)	79.22% (2,165/2,733)	77.98% (255/327)	0.93 (0.70–1.23)	0.65
Postnatal Life (first 24 h of life)				
Gestational age, mean (SD)	28.17 (2.19)	25.12 (1.59)	0.89 (0.45–0.99)	<0.001
Birth Weight, mean (SD)	1,134.82 (327.46)	748.83 (171.80)	0.90 (0.85–0.99)	<0.001
Number of births >1, %(n/N)	15.63% (456/2,917)	11.70% (40/342)	0.72 (0.51–1.01)	0.06
Small gestational age (Yes), %(n/N)	13.88% (405/2,917)	12.87% (44/342)	0.92 (0.66–1.28)	0.66
Gender				
Male, %(n/N)	53.72% (1,567/2,917)	52.63% (180/342)	0.96 (0.77–1.20)	0.699
Unknown or Ambiguous, %(n/N)	0.21% (6/2,917)	0% (0/342)	0.65 (0.04–11.63)	0.999
Mode of delivery (vaginal), %(n/N)	36.00% (1046/2906)	49.41% (168/340)	1.74 (1.39–2.18)	<0.001
Location of Birth (Out born), %(n/N)	17.00% (496/2,917)	20.18% (69/342)	1.23 (0.93–1.63)	0.16
Apgar score <7 at 5 min (Yes), %(n/N)	30.27% (883/2,804)	50.15% (168/335)	2.19 (1.74–2.75)	<0.001
Max FI O2 >21% (Yes), % (n/N)	31.49% (2,054/2,917)	86.26% (295/342)	2.64 (1.92–3.62)	<0.001
SNAPII score>20 (Yes), %(n/N)	18.52% (540/2,915)	23.98% (82/342)	1.39 (1.06–1.81)	0.02
Postnatal Life (first 28 days of life)				
Postnatal systemic steroids (Yes), %(n/N)	8.91% (260/2,917)	39.47% (135/342)	6.67 (5.18–8.57)	<0.001
Surfactant use (Yes), %(n/N)	51.66% (1,507/2,917)	82.46% (282/342)	4.40 (3.30–5.87)	<0.001
Inotropes (Yes), %(n/N)	10.73% (313/2,917)	42.69% (146/342)	6.20 (4.85–7.91)	<0.001
iNO (Yes), %(n/N)	3.77% (110/2,917)	15.79% (54/342)	4.79 (3.38–6.77)	<0.001
Transfusions: PRBC or Platelets (Yes), %(n/N)	29.62% (864/2,917)	68.13% (233/342)	5.08 (3.99–6.46)	<0.001
Pneumothorax (Yes), %(n/N)	3.19% (93/2,917)	4.68% (16/342)	1.58 (0.92–2.72)	0.2
Culture Positive Sepsis (Yes), %(n/N)	13.13% (383/2,917)	24.27% (83/342)	2.12 (1.62–2.78)	<0.001
NEC stage 2 or above (Yes), %(n/N)	3.02% (88/2,912)	6.47% (22/340)	0.11 (0.07–0.18)	<0.001
PDA (Yes), %(n/N)	37.74% (1,094/2,899)	73.24% (249/340)	4.52 (3.51–5.81)	<0.001
Caffeine (Yes), %(n/N)	85.09% (2,482/2,917)	85.96% (294/342)	1.07 (0.78–1.48)	0.73
IVH grade 3 or above, %(n/N)	6.92% (202/2,917)	24.27% (83/342)	4.31 (3.24–5.73)	<0.001
O2_Dt1stExp mean (SD-N)	2.02 (5.16–2,183)	1.61 (4.66–274)	0.79 (0.47–1.06)	0.18
Duration of Intubation and ventilation ≥14 days, %(n/N)	15.15% (442/2,917)	66.37% (227/342)	11.05 (8.64–14.14)	<0.001
Duration of Intubation and ventilation, mean (SD)	5.14 (8.14)	17.92 (10.90)	3.48 (2.15–4.12)	<0.001
Birth weight gain, mean (SD)	25.42 (8.73)	24.70 (7.80)	0.97 (0.60–1.65)	0.13
HFV_Dt1stExp mean (SD-N)	5.68 (6.82–691)	4.74 (5.87–87)	0.83 (0.65–1.60)	0.17
IPPV_Dt1stExp mean (SD-N)	2.49 (5.78–1,555)	3.29 (4.61–216)	1.32 (0.36–1.82)	0.63
O2_7 (True)	44.15% (1,288/2,917)	82.46% (282/342)	5.94 (4.46–7.93)	<0.001
O2_28 (True)	9.15% (267/2,917)	40.94% (140/342)	6.88 (5.36–8.83)	<0.001
Max FI O_2 %, mean (SD)	53.57 (31.74)	73.60 (31.16)	1.37 (1.19–1.58)	<0.005

CI Confidence interval; CSROP Clinically significant retinopathy of prematurity; HFV_Dt1stExp mean Age of infant in days when first exposed to high frequency ventilation; iNO Inhaled nitric oxide; IPPV_Dt1stExp mean Age of infant in days when first exposed to intermittent positive pressure ventilation; IVH Intraventricular hemorrhage; Max FI O2 >21% (Yes), % (n/N) The infant received supplementary oxygen >21% during resuscitation within the first 30 minutes of life; Max FI O2 %, mean (+SD) The maximum oxygen concentration provided on day 28 of life; NEC Necrotizing enterocolitis; O2_Dt1stExp mean Age of infant in days when were first exposed to oxygen; O2_7 Having supplemental oxygen for 7 days or more in the first 28 days of life; O2_28 Having supplemental oxygen for 28 out of 28 days in the first 28 days of life; OR Odds ratio; PDA Patent ductus arteriosus; PRBC Packed red blood cells; SD Standard deviation; SNAPII Score for neonatal acute physiology.

Table 3. Multivariable logistic regression analysis of clinical predictors with P-value of ≤0.1 from univariable analyses on the derivation cohort

Characteristics	Coefficients (SE)	Odds ratio (95% CI)	P-value
Gestational Age	−0.3554 (0.0587)	0.700 (0.624–0.786)	<0.001
Birth Weight	−0.0034 (0.0004)	0.996 (0.995–0.997)	<0.001
IVH grade 3 or above	0.6269 (0.1883)	1.871 (1.294–2.707)	<0.001
Max FI O2 %	0.0082 (0.0031)	1.008 (1.002–1.014	<0.001
Inotropes (Yes)	0.6793 (0.1745)	1.972 (1.630–2.776)	<0.001
iNO (Yes)	0.6290 (0.2435)	1.875 (1.164–3.022)	<0.01
Mode of Delivery	−0.3377 (0.1518)	0.713 (0.529–0.960)	0.02
O2_7	−0.5103 (0.2247)	0.600 (0.386–0.9324)	0.02
PDA (medical or surgical)	−0.3571 (0.1686)	0.699 (0.502–0.973)	0.03
Postnatal Systemic Steroids (Yes)	0.27484 (0.1742)	1.316 (0.935–1.852)	0.11
Surfactant (Yes)	0.3129 (0.1998)	1.367 (0.924–2.022)	0.12
Number of births	−0.3119 (0.2093)	0.732 (0.485–1.103)	0.14
Apgar Score <7 at 5 min (Yes)	−0.2111 (0.1517)	0.809 (0.601–1.090)	0.16
Duration of Intubation	0.0263 (0.0191)	1.026 (0.989–1.065)	0.17
SNAPII score >20 (Yes)	−0.1556 (0.1659)	0.856 (0.618–1.184)	0.35
NEC stage 2 or above (Yes)	0.2574 (0.3352)	1.293 (0.670–2.495)	0.44
Culture Positive Sepsis (Yes)	−0.1389 (0.1820)	0.870 (0.609–1.243)	0.45
O2_28	−0.1269 (0.1814)	0.881 (0.617–1.256)	0.48
Max FI O2 >21% (Yes)	0.0730 (0.2732)	1.075 (0.629–1.837)	0.79
Intub_Vent_14D	−0.0483 (0.3711)	0.953 (0.460–1.972)	0.9
Transfusions (Yes)	−0.0105 (0.1752)	0.989 (0.709–1.395)	0.95

Omnibus tests were done, and P-values were < 0.05.

Hosmer–Lemeshow tests were done and P-values were > 0.05.

iNO Inhaled nitric oxide; IVH Intraventricular hemorrhage; Max FI O2 >21% (Yes), % (n/N) The infant received supplementary oxygen >21% during resuscitation within the first 30 minutes of life; Max FI O2 %, mean (+SD) The maximum oxygen concentration provided on day 28 of life; NEC Necrotizing enterocolitis; O2_7 Having supplemental oxygen for 7 days or more in the first 28 days of life; O2_28 Having supplemental oxygen for 28 out of 28 days in the first 28 days of life; PDA Patent ductus arteriosus; SE Standard error; SNAPII Score for neonatal acute physiology.

Using model 2B, a ≥1% risk of requiring ROP treatment equates to GA of 28.3 weeks or less. Using model 3B, a ≥1% risk of requiring ROP treatment equates to BW of 1,153 g or less.

Using Final Models A and B derived in Table 4, Figures 2a and 2b show how accepting a higher threshold for risk of developing CSROP (Figure 2a) or ROP requiring treatment (Figure 2b), lead to a reduction in overall number of babies subjected to unnecessary ROP screening, although at the cost of more babies with CSROP or requiring ROP treatment being missed. Moving from left to right, the bars show the decreasing percentage of babies subjected to ROP screening, while the lines show the increasing number of babies with CSROP or requiring ROP treatment that are missed, as one decides to only screen babies with a higher and higher risk.

DISCUSSION

While many risk factors other than GA and BW (12–27) have been implicated as possible predictors of ROP, they have not been previously tested in as rigorous a manner. Model 1A (Table 4) results in the greatest decrease in number of babies screened, but also leads to the greatest number of CSROP cases missed. Furthermore, this model requires data to be gathered over the first 4 weeks of life, before all nine variables are known. Therefore, erring on the side of caution, missing the fewest babies with CSROP while offering an easy to use guideline (increasing uptake by nurseries), the recommended models are based on two variables only: GA at birth and BW (Table 4).

Comparison with other existent ROP models

The CHOP model (30) was developed using infants from one centre and has 53% specificity and 98% sensitivity. Utilizing infants from a single institution may limit the generalizability of this model.

The WINROP model (31) used GA, BW, and weekly postnatal weight measurements to calculate the likelihood of the baby developing severe ROP. If the risk was high, the WINROP model would give an 'alarm' signal telling the user the baby has high risk of developing severe ROP.

Table 4. Backwards logistic regression on validation cohort for CSROP and ROP requiring treatment models

	Part A - Models for CSROP						Part B - Models for ROP requiring treatment			
	Model 1A	Model 6A	Model 8A	Model 9A	Model 10A	Final Model A	Model 1B	Model 2B	Model 3B	Final Model B
Characteristics	coefficients (SE)*	coefficients (SE)	coefficients (SE)	coefficients (SE)	coefficients (SE)		coefficients (SE)	coefficients (SE)	coefficients (SE)	
Gestational Age	−0.3843 (0.0556), P<0.0001	−0.4399 (0.0516), P<0.0001	0.50051 (0.0502), p<0.0001	−0.8045 (0.0041), P<0.0001		GA or BW from Model 9A and Model 10A	−0.5276 (0.0673), P<0.0001	−0.8327 (0.055), P<0.0001		GA or BW from Model 2B and Model 3B
Birth Weight	−0.0036 (0.0004), P<0.0001	−0.0035 (0.0004), P<0.0001	−0.0364 (0.0004), P<0.0001		−0.0062 (0.0003), P<0.0001		−0.0037 (0.0006), P<0.0001		−0.0064 (0.000), P<0.0001	
Mode of Delivery	−0.3136 (0.1457), P=0.03									
PDA	−0.4371 (0.1564), P=0.005									
Inotropes (Yes)	0.7871 (0.1604), P<0.0001	0.9101 (0.1488), P<0.0001								
iNO (Yes)	0.7152 (0.2316), P=0.002									
IVH grade 3 or above	0.6447 (0.1887), P<0.0001	0.7095 (0.1807), P<0.0001								
Max FI O2 %	0.0067 (0.0022), P=0.002									
O2_7	−0.2227 (0.1887), P=0.24									

Table 4. *Continued*

	Part A - Models for CSROP						Part B - Models for ROP requiring treatment			
	Model 1A	**Model 6A**	**Model 8A**	**Model 9A**	**Model 10A**	**Final Model A**	**Model 1B**	**Model 2B**	**Model 3B**	**Final Model B**
Characteristics	**coefficients (SE)***	**coefficients (SE)**	**coefficients (SE)**	**coefficients (SE)**	**coefficients (SE)**		**coefficients (SE)**	**coefficients (SE)**	**coefficients (SE)**	
Number of babies screened	1,036 (63.60%)	1,075 (65.99%)	1,082 (66.42%)	1,191 (73.11%)	1,186 (72.81%)	1,346 (82.63%)	837 (51.38%)	988 (60.65%)	962 (59.05%)	1,155 (70.90%)
Number of babies saved from unnecessary screening	593 (36.4%)	554 (34.01%)	547 (33.58%)	438 (26.89%)	443 (27.19%)	283 (17.37%)	792 (48.62%)	641 (39.35%)	667 (40.95%)	474 (29.1%)
CSROP cases missed	6	6	7	3	4	1	NA	NA	NA	NA
ROP-treated cases missed	NA	NA	NA	NA	NA	NA	2 (2.78%)	3 (4.17%)	2 (2.78%)	1** (1.39%)

*Alpha = 0.01 (1%) is the predefined risk threshold for developing CSROP.

**Baby had GA of > 32weeks and BW > 1,799 g; NA = not applicable.

BW Birth weight; CSROP Clinically significant retinopathy of prematurity; GA Gestational age; iNO Inhaled nitric oxide; IVH Intraventricular hemorrhage; Max FI O2 %, mean (+SD) The maximum oxygen concentration provided on day 28 of life; O2_7 Having supplemental oxygen for 7 days or more in the first 28 days of life; PDA Patent ductus arteriosus; ROP Retinopathy of prematurity; SE Standard error.

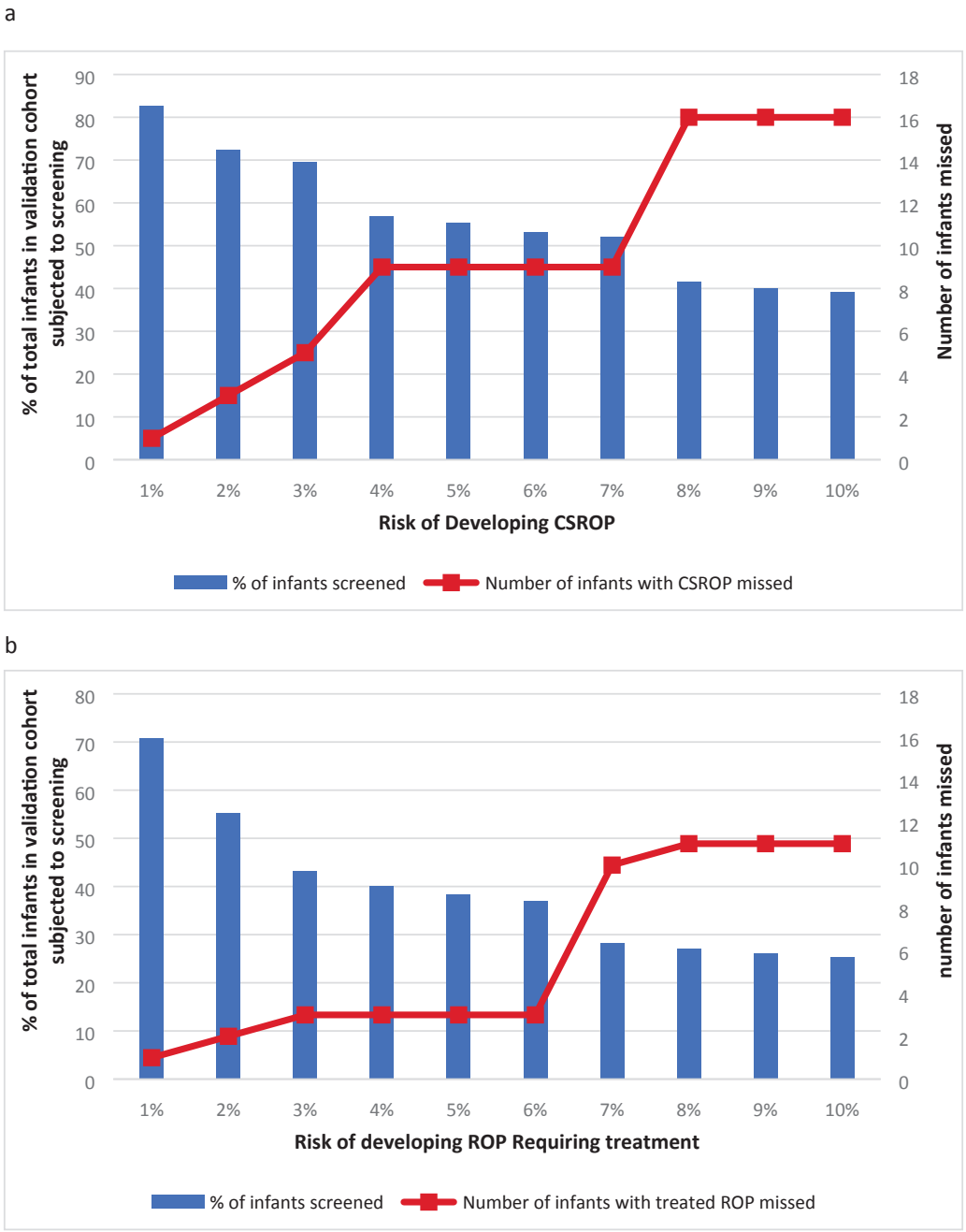


Figure 2. (a) Number of babies screened versus CSROP[1] cases missed in the validation cohort based on accepting increasing risk threshold cut-offs for screening (Final Model A). (b) Number of babies screened versus treated ROP cases missed in the validation cohort based on accepting risk threshold cut-offs for screening (Final Model B). [1]CSROP Clinically significant retinopathy of prematurity; ROP Retinopathy of prematurity.

While this model had 95.7% sensitivity it had only 23.9% specificity.

Owen et al. (32) found the most predictive model of ROP risk to include GA, BW, need for surgery, and maternal magnesium prophylaxis. This study looked at data from only one NICU.

Strengths of SCREENROP

Standardization of practice

SCREENROP guidelines will allow for standardization of ROP screening inclusion criteria across Canada, decreasing the continuing variability seen in screening practices nationally (10).

New, individualized, patient-specific ROP risk profile calculation

Using SCREENROP web-based applications, by entering BW or GA, the exact percentage risk of developing CSROP or requiring ROP treatment can be calculated for any given baby. This individualized, patient-specific information can help physicians in discussing ROP screening with each family.

Decreasing morbidity and health care costs

Tighter screening inclusion criteria will decrease morbidity related to unnecessary screening. ROP examination can cause apnea, bradycardia, desaturation, and red eyes (33,34). Despite the use of telemedicine, the centralization of subspecialized ophthalmologists skilled in screening and treating ROP means that many neonates are still transported across large geographic distances to be screened (35) causing further morbidity.

Cost savings are realized through reductions in the time nursing staff and physicians spend performing ROP examinations.

Limitations

Although the study did not capture ROP examinations conducted outside level 3 NICUs by contacting treating ophthalmologists and the fact that any baby requiring treatment after discharge from level 3 NICU, most likely would be transferred back to level 3 NICU, means it is unlikely that any treated babies were missed during the study period. Certain predictor variables such as frequency of desaturations and maintenance of oxygen saturation within target range were not collected by all NICUs and therefore not analyzed (36).

CONCLUSION

While tightening the ROP screening criteria can reduce the number of babies subjected to unnecessary examinations, it can also raise apprehension among neonatologists regarding babies who fall just outside the screening criteria. It can also raise concern among ophthalmologists who feel that by screening fewer babies they may lose key clinical skills needed for detecting severe ROP. Therefore, being mindful of these competing needs, we recommend the current ROP screening guidelines in Canada be updated to screen babies born with BW <1,200 g or GA <30 weeks. Regardless of screening cut-offs, there remains the option of screening *any* neonate in whom the neonatologists have a high index of suspicion for development of significant ROP. The study team will work closely with the Canadian Paediatric Society, Canadian Ophthalmological Society and individual NICUs to help promote the uptake of the new suggested recommendations.

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