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NEONATAL RESEARCH NETWORK



Cerebral Injury and Retinopathy as Risk Factors for Blindness in Extremely Preterm Infants

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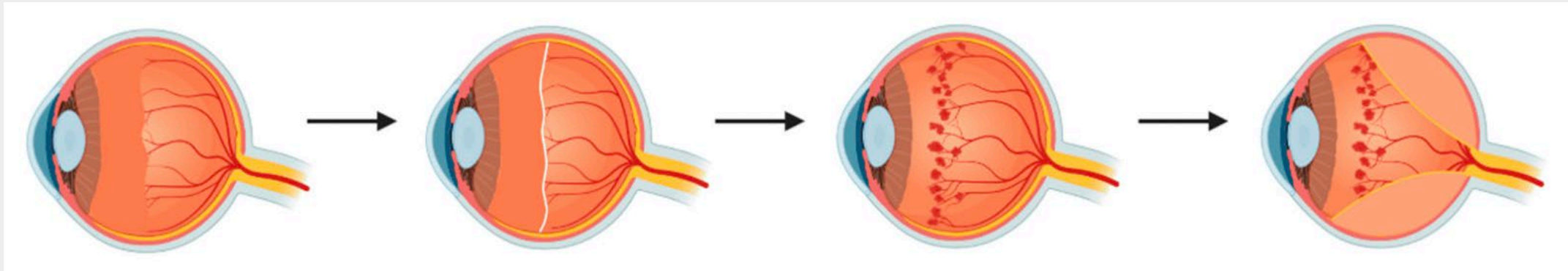


Disclosures

- We have no financial relationships to disclose or Conflicts of Interest to resolve. Any real or apparent conflicts of interest related to the content of this presentation have been resolved.
- This presentation will not involve discussion of unapproved or off-label, experimental or investigational use of a drug.

Blindness and Retinopathy of Prematurity

- 1% of extremely preterm infants develop severe visual impairment.



- 13% of extremely preterm infants develop severe ROP needing treatment.
 - Among infants with severe ROP, 6.4% develop bilateral blindness with no functional vision.

Blindness and Cerebral Injury

Cerebral Visual Impairment (CVI), in term and preterm infants, a result of:

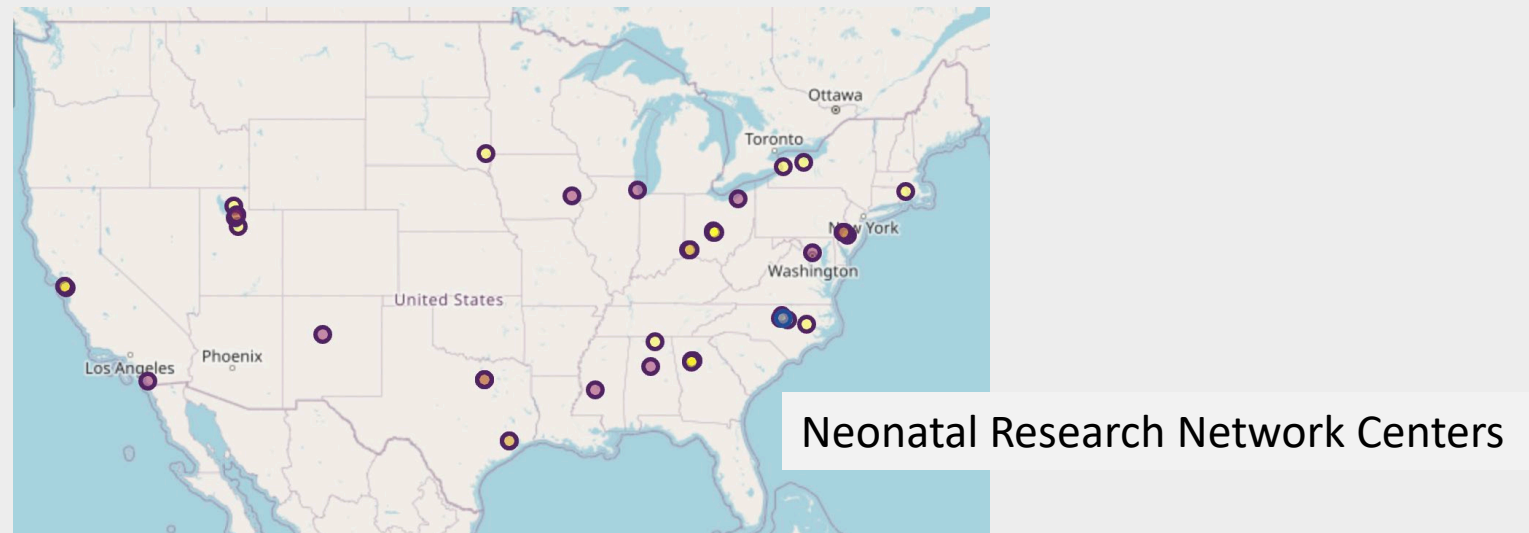
- Hypoxic ischemic encephalopathy (HIE)
 - Periventricular leukomalacia (PVL)
 - Hydrocephalus
-
- Preterm infants are especially vulnerable to:
 - cerebral hemorrhage with ventricular extension
 - White matter ischemia and/or inflammation manifesting as PVL

Hypothesis

Cerebral injury is independently associated with bilateral blindness in extremely preterm infants, in addition to severe ROP alone.

Methods

- **Design:** Retrospective analysis of prospectively collected data – Neonatal Research Network multicenter preterm infant registry



- **Participants:** Extremely preterm infants of gestational age 22 0/7 to 28 6/7 weeks, born from 1994 to 2021, who received care at NICHD Neonatal Research Network centers and participated in follow-up at 18-26 months with visual assessment.

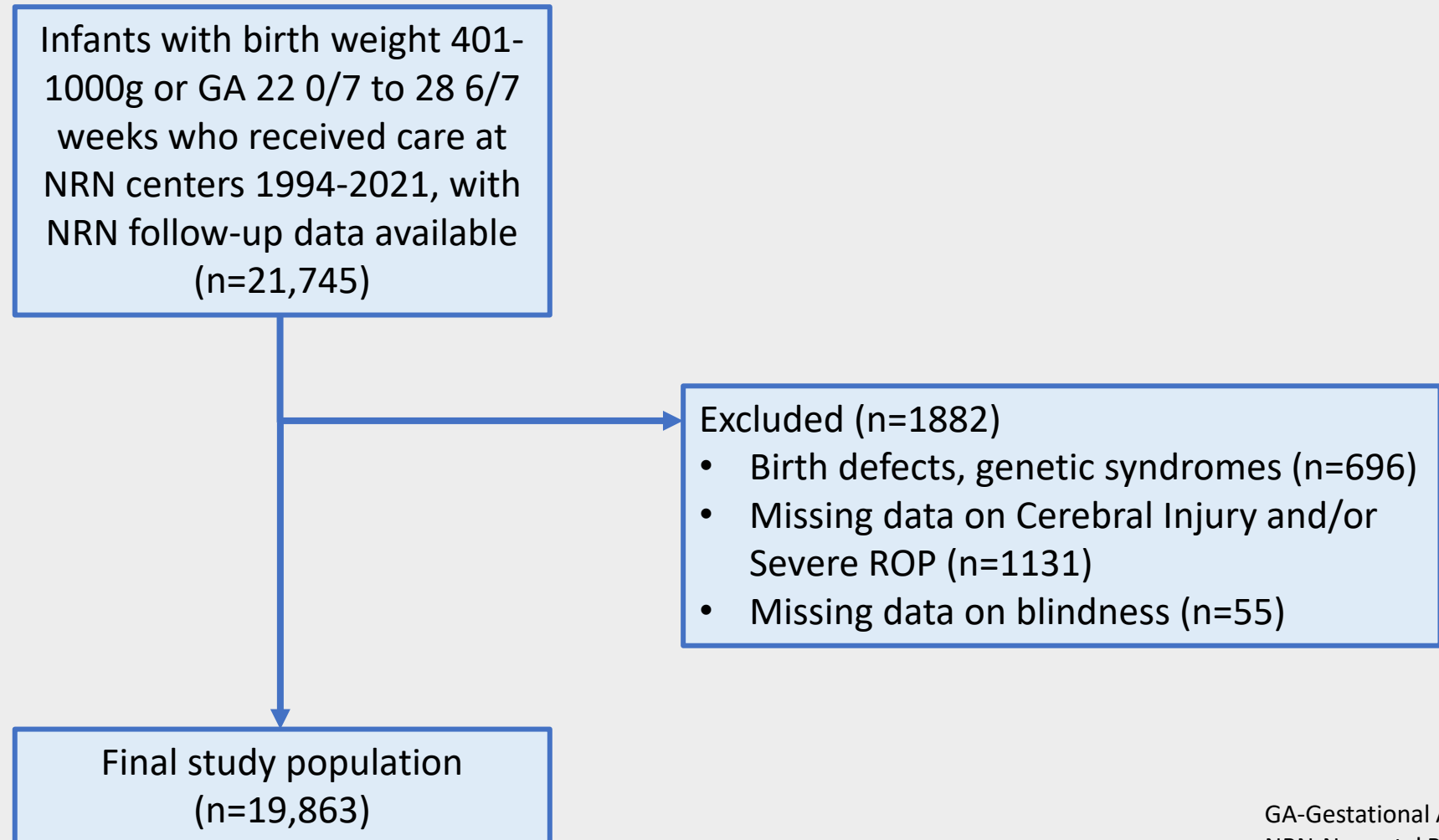
Methods

- **Exposures:**
 - Severe ROP, defined as any of the following:
 - either eye with stage 3 ROP or worse
 - retinal detachment
 - Plus disease
 - receipt of peripheral retinal laser ablation, scleral buckling, vitrectomy, and/or treatment with anti-VEGF drugs
 - Cerebral injury, defined as any of the following on cranial imaging:
 - blood/increased echogenicity in the parenchyma
 - ventriculomegaly with or without hydrocephalus
 - cystic periventricular leukomalacia
- **Outcome:** Bilateral blindness was defined as a follow-up examination meeting criteria of “blind – some functional vision” or “blind – no useful vision” in both eyes.

Methods

- **Statistical Analysis:** A logistic regression model compared the presence of bilateral blindness among infants with severe ROP and/or cerebral injury.
- We adjusted for baseline factors that differed between groups and tested for interaction between ROP and cerebral injury.

Participant Flow Diagram



GA-Gestational Age
NRR-Neonatal Research Network
ROP-Retinopathy of Prematurity

Baseline Characteristics

	Neither (N=12,459)	Cerebral Injury (N=2836)	Severe ROP (N=3130)	Both (N=1438)	Total (N=19,863)
Maternal age — yr ^c	N=12458 27.8 ± 6.6	N=2833 27.2 ± 6.5	N=3130 27.7 ± 6.5	N=1438 27.6 ± 6.6	N=19859 27.7 ± 6.6
Race — no./total no. (%) ^{a,c}	N=12,295	N=2788	N=3091	N=1412	N=19586
Black	5590 (45%)	1270 (46%)	1112 (36%)	507 (36%)	8479 (43%)
White	6175 (50%)	1427 (51%)	1772 (57%)	834 (59%)	10208 (52%)
Other	530 (4.3%)	91 (3.3%)	207 (6.7%)	71 (5.0%)	899 (4.6%)
Hispanic or Latino ethnic group — no./total no. (%) ^{a,c}	N=12186 1871 (15%)	N=2771 441 (16%)	N=3050 568 (19%)	N=1404 317 (23%)	N=19411 3197 (16%)
Mother's education — no./total no. (%)	N=12459	N=2836	N=3130	N=1438	N=19863
Less than high school diploma	2888 (23%)	656 (23%)	737 (24%)	359 (25%)	4640 (23%)
High school diploma	3659 (29%)	875 (31%)	854 (27%)	421 (29%)	5809 (29%)
Partial college/trade/technical	2972 (24%)	656 (23%)	776 (25%)	313 (22%)	4717 (24%)
College degree or more	2716 (22%)	594 (21%)	700 (22%)	311 (22%)	4321 (22%)
Unknown	224 (1.8%)	55 (1.9%)	63 (2.0%)	34 (2.4%)	376 (1.9%)
Received any antenatal glucocorticoids — no./total no. (%) ^c	N=12437 10813 (87%)	N=2824 2246 (80%)	N=3118 2652 (85%)	N=1432 1118 (78%)	N=19811 16829 (85%)
Public maternal medical insurance — no./total no. (%) ^b	N=12457 7100 (57%)	N=2833 1681 (59%)	N=3130 1726 (55%)	N=1436 822 (57%)	N=19856 11329 (57%)
Prenatal care — no./total no. (%)	N=12452 11797 (95%)	N=2830 2660 (94%)	N=3124 2954 (95%)	1434 1344 (94%)	N=19840 18755 (95%)
Diabetes prior to pregnancy (2016+) — no./total no. (%)	N=2151 100 (4.6%)	N=456 15 (3.3%)	N=509 22 (4.3%)	N=238 12 (5.0%)	N=3354 149 (4.4%)
Insulin-dependent diabetes — no./total no. (%)	N=12420 510 (4.1%)	N=2827 102 (3.6%)	N=3117 110 (3.5%)	N=1429 46 (3.2%)	N=19793 768 (3.9%)
Gestational diabetes mellitus (2016+) — no./total no. (%)	N=2126 101 (4.8%)	N=454 27 (5.9%)	N=504 17 (3.4%)	N=238 12 (5.0%)	N=3322 157 (4.7%)
Maternal hypertension — no./total no. (%) ^c	N=12443 3719 (30%)	N=2827 575 (20%)	N=3123 696 (22%)	N=1433 250 (17%)	N=19826 5240 (26%)

- Mean gestational age: 25.6 ± 1.7 weeks

- Mean birth weight: 782 ± 158 grams

Children who had cerebral injury:

- shorter gestation
- lower birth weight
- less likely to be small for gestational age, to have received antenatal glucocorticoids, antenatal magnesium sulfate, and to be born to mothers with hypertension

^a Plus-minus values are means ±SD. Percentages may not total 100 because of rounding.

^b Race and ethnic group were reported by the parent or guardian. "Other" includes American Indian or Alaska Native, Asian, Native Hawaiian or Other Pacific Islander, or more than one race.

^c Significant at p<0.05 (Chi-square test).

^d Significant at p<0.01 (Chi-square, Wilcoxon, or Median test).

^e Chorioamnionitis as documented in the mother's medical record.

Missing data: Maternal age=4, Race=277, Hispanic or Latino ethnic group=452, Mother's education=376 (Unknown), Antenatal glucocorticoids=52, Gestational age=2, Sex=3, 5-min Apgar score=155, SGA=8, Public maternal medical insurance=7, Prenatal care=23, Diabetes prior to pregnancy=18509, Insulin-dependent diabetes=70, Gestational Diabetes Mellitus=16541, HTN=37, Chorioamnionitis=9517, Histologic chorioamnionitis=10713, Antenatal antibiotic exposure=110, Mg sulfate exposure=12994, Mode of delivery=28.

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Baseline Characteristics

	Neither (N=12,459)	Cerebral Injury (N=2836)	Severe ROP (N=3130)	Both (N=1438)	Total (N=19,863)
Chorioamnionitis (2006+) — no./total no. (%) ^d	N=6620 1055 (16%)	N=1453 271 (19%)	N=1569 265 (17%)	N=704 127 (18%)	N=10346 1718 (17%)
Histologic chorioamnionitis (2006+) — no./total no. (%) ^c	N=5867 3090 (53%)	N=1258 737 (59%)	N=1403 743 (53%)	N=622 371 (60%)	N=9150 4941 (54%)
Antenatal antibiotic exposure — no./total no. (%) ^b	N=12400 8789 (71%)	N=2816 2016 (72%)	N=3110 2277 (73%)	N=1427 1042 (73%)	N=19753 14124 (72%)
Magnesium sulfate exposure (2011+) — no./total no. (%) ^c	N=4466 3746 (84%)	N=923 728 (79%)	N=1019 817 (80%)	N=461 344 (75%)	N=6869 5635 (82%)
Mode of delivery — no./total no. (%) ^c	N=12443	N=2831	N=3126	N=1435	N=19835
Vaginal vertex	3655 (29%)	1028 (36%)	949 (30%)	509 (35%)	6141 (31%)
Vaginal breech	433 (3.5%)	154 (5.4%)	201 (6.4%)	101 (7.0%)	889 (4.5%)
C-section	8355 (67%)	1649 (58%)	1976 (63%)	825 (57%)	12805 (65%)
Birth weight — g ^c	N=12459 812 ± 155	N=2836 790 ± 154	N=3130 696 ± 136	N=1438 699 ± 136	N=19863 782 ± 158
Gestational age — wk ^c	N=12457 26.0 ± 1.7	N=2836 25.4 ± 1.6	N=3130 24.8 ± 1.4	N=1438 24.5 ± 1.3	N=19861 25.6 ± 1.7
Sex — no (%) ^c	N=12458	N=2836	N=3129	N=1437	N=19860
Male sex	5774 (46%)	1458 (51%)	1614 (52%)	801 (56%)	9647 (49%)
Female sex	6675 (54%)	1376 (49%)	1514 (48%)	636 (44%)	10201 (51%)
Ambiguous sex	9 (0.1%)	2 (0.1%)	1 (0.03%)	0 (0%)	12 (0.1%)
Small for gestational age — no. (%) ^c	N=12456 1585 (13%)	N=2836 218 (7.7%)	N=3129 340 (11%)	N=1436 91 (6.3%)	N=19857 2234 (11%)
Multiple birth — no. (%) ^c	N=12459 2872 (23%)	N=2836 661 (23%)	N=3130 785 (25%)	N=1438 391 (27%)	N=19863 4709 (24%)
Median 5-min Apgar score (5th to 95th percentile) ^c	N=12377 7 (6-8)	N=2798 7 (5-8)	N=3111 7 (5-8)	N=1422 6 (4-7)	N=19708 7 (6-8)
5-min Apgar score ≤5 — no./total no. (%) ^c	N=12377 2508 (20%)	N=2798 875 (31%)	N=3111 913 (29%)	N=1422 550 (39%)	N=19708 4846 (25%)

Of all children included:

- 23% (4568/19,863) had severe ROP
- 22% (4274/19,863) had cerebral injury
- 1% (213/19,863) had bilateral blindness

Plus-minus values are means ±SD. Percentages may not total 100 because of rounding.

^a Race and ethnic group were reported by the parent or guardian. "Other" includes American Indian or Alaska Native, Asian, Native Hawaiian or Other Pacific Islander, or more than one race.

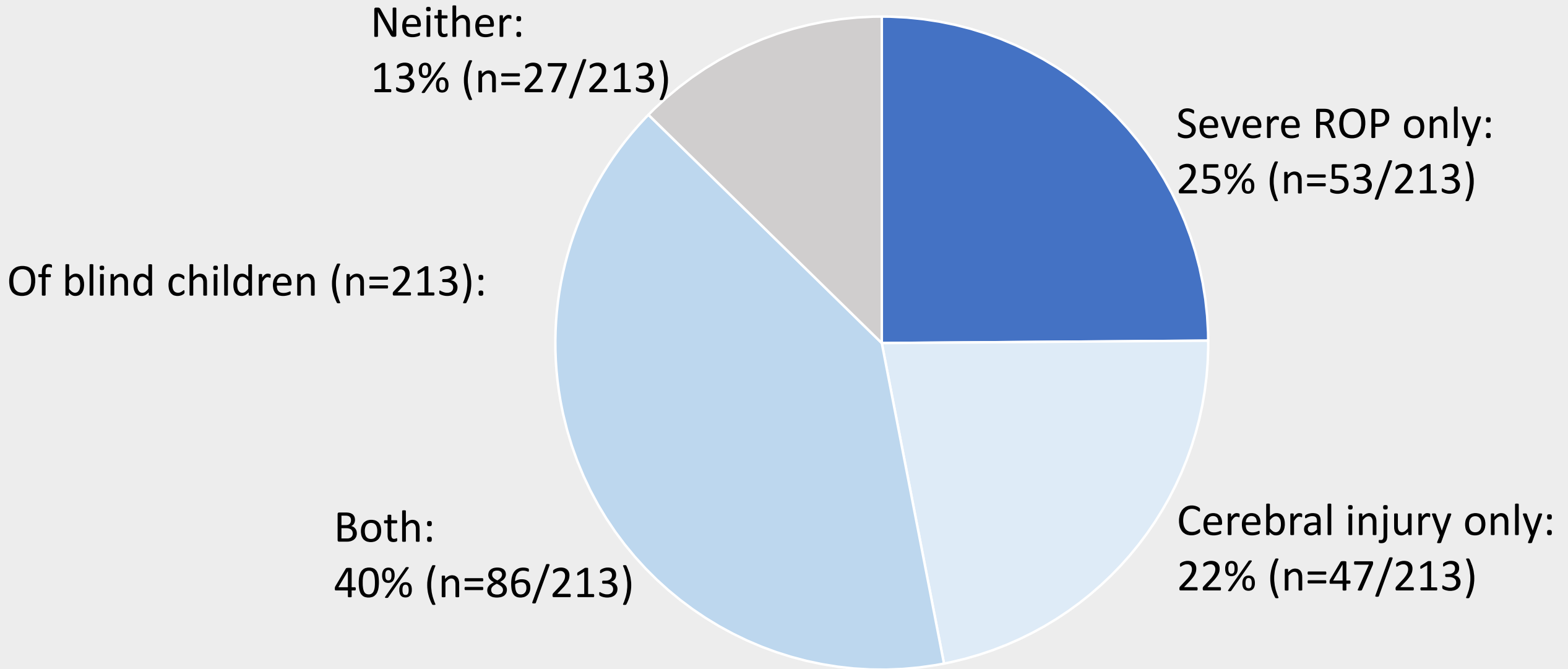
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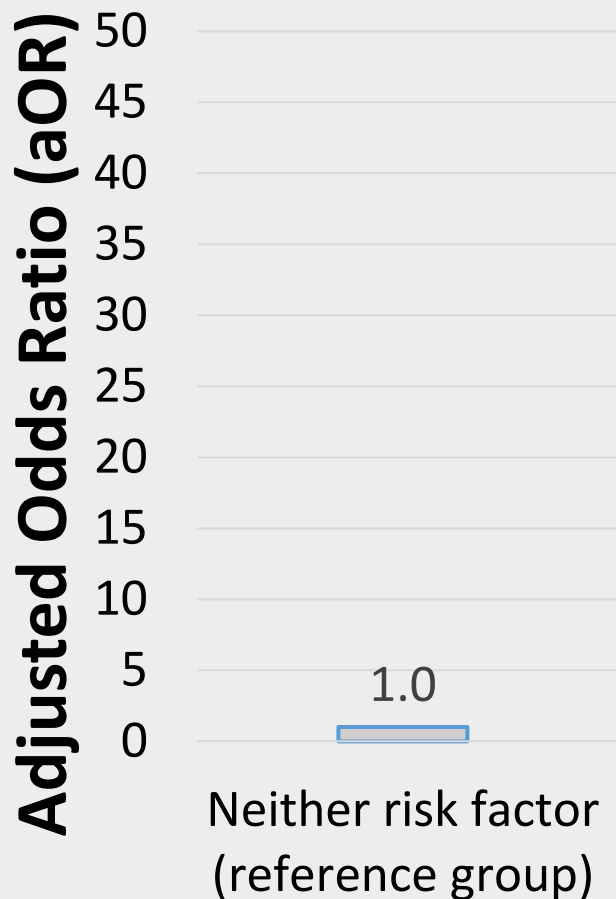
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Risk Factors for Blindness



Adjusted Odds Ratios (aOR) for Blindness



Possible Risk Factor

Conclusions

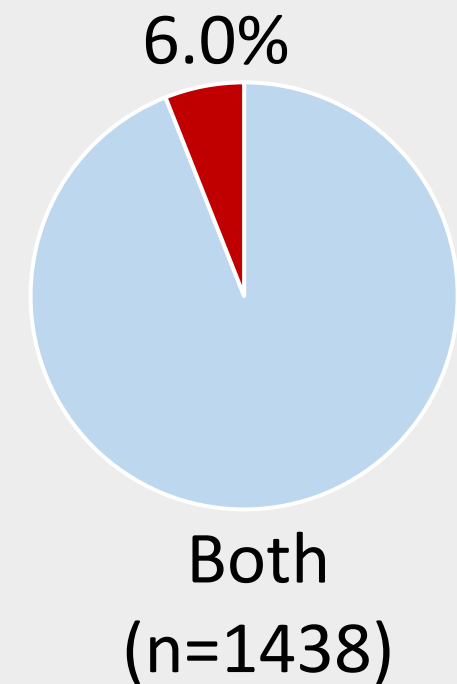
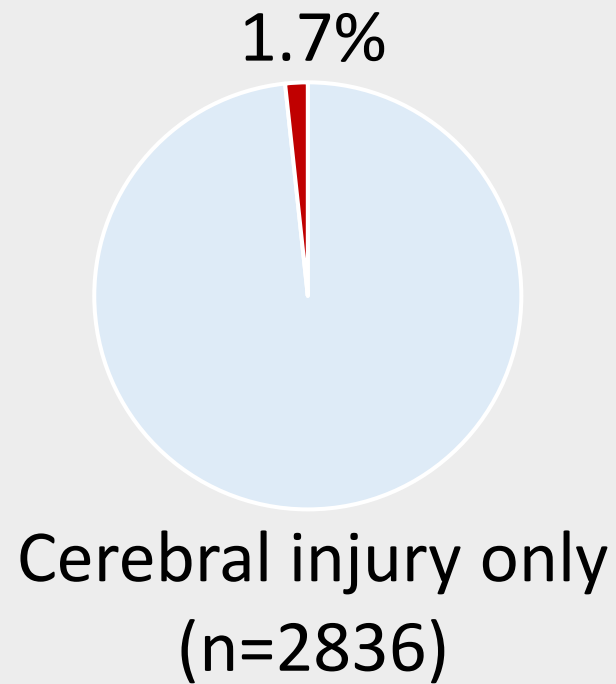
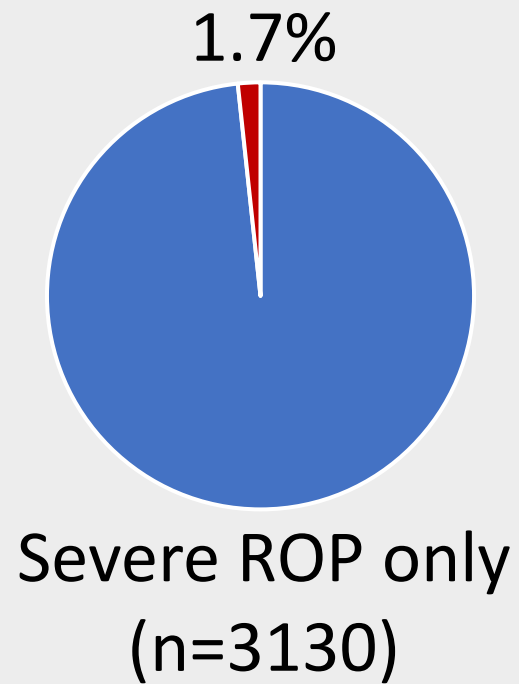
- Cerebral injury is associated with blindness and accounts for variance not explained severe ROP alone.
- Cerebral injury and severe ROP are equally important risk factors for blindness (aOR 8.38 vs 8.14).
- Likely diverse mechanisms for blindness in extremely preterm infants; some blindness is likely cerebral in nature.
- Shared mechanisms of ROP and cerebral injury are possible.

Conclusions

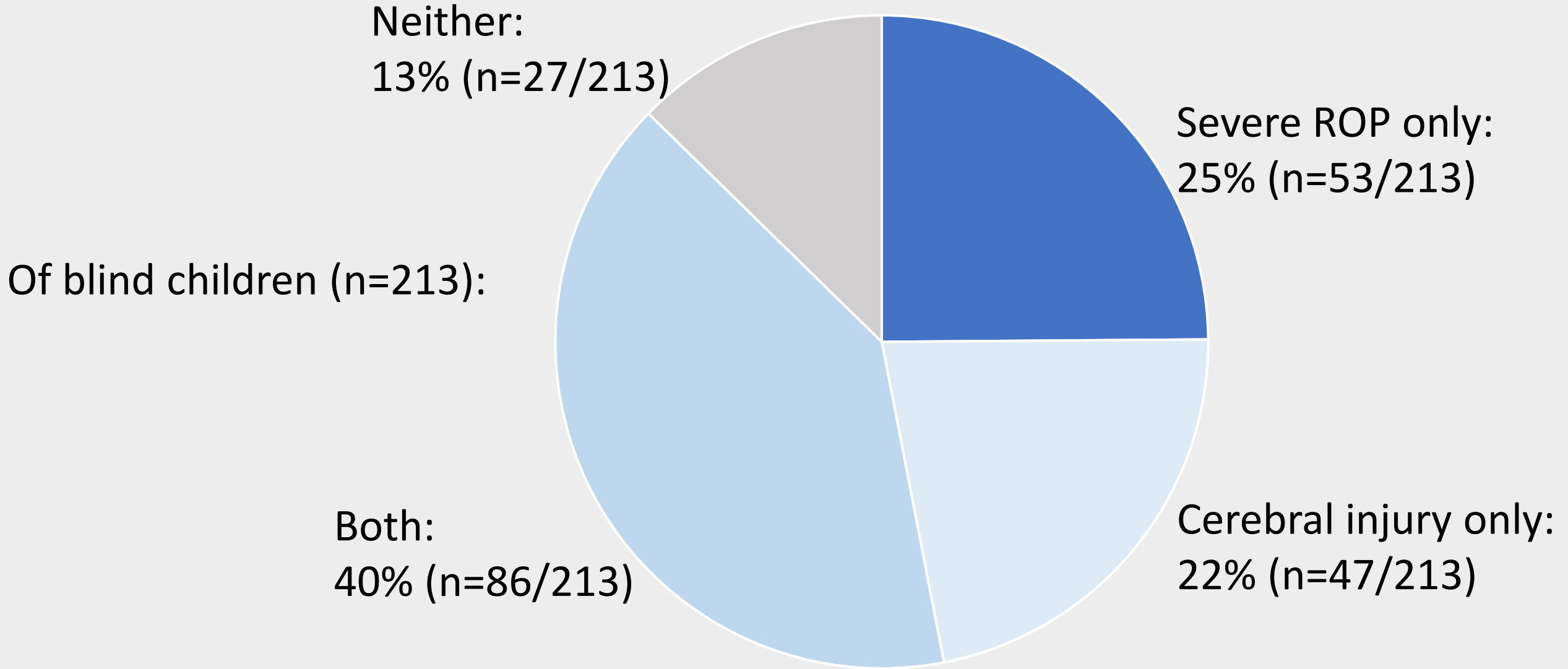
- The multiplicative interaction was significant ($p=0.01$).
- Risk factors are not synergistic:
 - Given cerebral injury, aOR for severe ROP = $28.73/8.14 = 3.53$
 - Given severe ROP, aOR for cerebral injury = $28.73/8.38 = 3.43$

Conclusions

- Actual risk of blindness is low:



Conclusions



Limitations

- No information on pupillary reflexes, location of cerebral injuries
- Challenging to assess vision in young children with severe cerebral injury
- Follow-up vision outcomes based on history and a certified neurologic examiner's observation, but no formal follow-up by an ophthalmologist.

Strengths

- Large database and study population (n=19,863)
- Robust follow-up
- Relatively few excluded infants

Final Conclusions

- Cerebral injury and severe ROP were equally important factors for blindness.
- Besides ROP, clinicians should have a high index of suspicion for cerebral injury when considering causes of blindness in this population.

Neonatal Research Network Centers

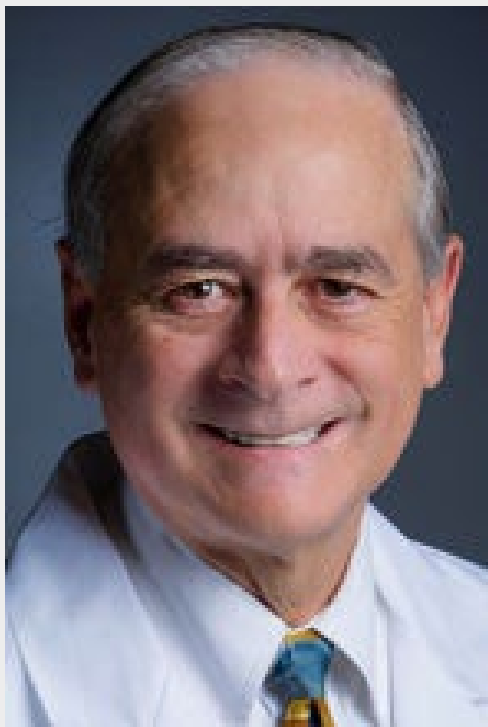
- Brown University^{a,b,c}
- Case Western Reserve University^{a,b,c,d}
- Children's Mercy Hospitals and Clinics, University of Missouri-Kansas City^b
- Cincinnati Children's Medical Center^{a,b,c,d}
- Duke University^{a,b,c,d}
- Emory University^{a,b,c,d}
- Indiana University^{a,b}
- Lurie Children's/Northwestern^d
- Nationwide Children's Hospital, Ohio State University^{b,c}
- RTI International^{a,b,c,d}
- Sharp Memorial Hospital/UCSD^d
- Stanford University^{a,b,c}
- Tufts Medical Center^a



- University of Alabama at Birmingham^{a,b,c,d}
- University of California – Los Angeles^b
- University of Iowa^{a,b,c,d}
- University of Mississippi^d
- University of New Mexico^{a,b,c,d}
- University of Pennsylvania^{b,c,d}
- University of Rochester^{b,c}
- University of Texas Southwestern^{a,b,c,d}
- University of Texas Health Science Center at Houston^{a,b,c,d}
- University of Utah^{a,c,d}
- Wayne State University^{a,b}
- Yale University^a

a: 2006-2011
b: 2011-2016
c: 2016-2023
d: 2023-2030

Thank you!



Waldemar A. Carlo, MD



Scott A. McDonald, BS

Supplemental Slides

Risk Factors for Blindness

Risk Factor	No Cerebral Injury (N=15589)	Cerebral Injury (N=4274)	Total
No Severe ROP (N=15295)	27/12459 (0.2%)	47/2836 (1.7%)	74/15295 (0.5%)
Severe ROP (N=4568)	53/3130 (1.7%)	86/1438 (6.0%)	139/4568 (3.0%)
Total	80/15589 (0.5%)	133/4274 (3.1%)	213/19863 (1.1%)

Adjusted Odds Ratios (aOR) for Blindness

Risk Factor	Adjusted Odds Ratio ^a (95% CI)	p-value
Cerebral Injury, with Severe ROP present	3.53 (2.26-5.50)	<0.0001
Cerebral Injury, with Severe ROP absent	8.38 (5.28-13.28)	<0.0001
Severe ROP, with Cerebral Injury present	3.43 (2.31-5.09)	<0.0001
Severe ROP, with Cerebral Injury absent	8.14 (4.52-14.65)	<0.0001
Cerebral Injury*Severe ROP Interaction	--	0.01
Both Cerebral Injury and Severe ROP vs. Neither ^b	28.73 (15.96-51.71)	<0.0001

In infants without severe ROP, cerebral injury was associated with an 8.38-fold increase in adjusted odds of blindness.

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Cerebral Injury*Severe ROP Interaction	--	0.01
Both Cerebral Injury and Severe ROP vs. Neither^b	28.73 (15.96-51.71)	<0.0001

As compared to infants with neither risk factor, those with both severe ROP and cerebral injury were 28.73 times more likely to be blind.

Secondary Investigation for Visual Outcomes based on Type of Cerebral Injury, Relative to No Cerebral Injury

Possible Risk Factor	Blindness n/N (%)	aOR ^a (95% CI)	p-value
No Cerebral Injury	80/15586 (0.5%)	reference group	
A. Ventricular size enlarged (with or without concurrent/prior blood)	33/2141 (1.5%)	2.23 (1.49-3.33)	<0.0001
B. Blood/echodensity in parenchyma with or without midline shift ^b	0/200 (0%)	N/A	
C. PVL	15/294 (5.1%)	8.94 (4.60-17.4)	<0.0001
D. Combination of ≥2 above Cerebral Injury criteria	45/1149 (3.9%)	5.58 (3.33-9.36)	<0.0001
E. Any of criteria A-D with shunt for hydrocephalus	40/476 (8.4%)	12.7 (8.86-18.2)	<0.0001

None of the 200 infants with blood/echodensity in the parenchyma as the sole abnormality were blind.

Secondary Investigation for Visual Outcomes based on Type of Cerebral Injury, Relative to No Cerebral Injury

Possible Risk Factor	Blindness n/N (%)	aOR ^a (95% CI)	p-value
No Cerebral Injury	80/15586 (0.5%)	reference group	
A. Ventricular size enlarged (with or without concurrent/prior blood)	33/2141 (1.5%)	2.23 (1.49-3.33)	<0.0001
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Among cerebral injuries, cystic PVL was associated with the greatest increase in the risk of blindness.

Secondary Investigation for Visual Outcomes based on Type of Cerebral Injury, Relative to No Cerebral Injury

Possible Risk Factor	Blindness n/N (%)	aOR ^a (95% CI)	p-value
No Cerebral Injury	80/15586 (0.5%)	reference group	
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E. Any of criteria A-D with shunt for hydrocephalus	40/476 (8.4%)	12.7 (8.86-18.2)	<0.0001

Severe hydrocephalus category: defined as placement of a ventricular shunt in the setting of other cerebral injury.

Infants with hydrocephalus requiring shunt in the setting of other defined cerebral injury had a further increased risk of blindness.

Adjusting for Severe Cerebral Palsy and Grade 3 Bronchopulmonary Dysplasia (2006-2021 births)

Risk Factor	(N=10,380)	
	aOR ^a (95% CI)	p-value
Cerebral Injury, with Severe ROP present	1.79 (1.05-3.03)	0.03
Cerebral Injury, with Severe ROP absent	3.72 (1.93-7.17)	<0.0001
Severe ROP, with Cerebral Injury present	2.13 (1.45-3.13)	0.0001
Severe ROP, with Cerebral Injury absent	4.44 (2.57-7.67)	<0.0001
Cerebral Injury*Severe ROP Interaction	--	0.03
Both Cerebral Injury and Severe ROP vs. Neither ^b	7.93 (3.61-17.4)	<0.0001

- Severe CP was found to be a significant risk factor for blindness (aOR=40.6, 95% CI=27.9-58.9, p=0.002).
- There was no association between grade 3 BPD and blindness (p=0.62).

Adjusted Odds Ratios for Blindness, Comparing Cerebral injury vs. Normal imaging

- This excluded 4285 infants who lacked imaging (N=15,578).

Risk Factor	aOR^b (95% CI)	p-value
Cerebral Injury, with Severe ROP present	3.47 (2.20-5.49)	<0.0001
Cerebral Injury, with Severe ROP absent	10.8 (6.11-19.3)	<0.0001
Severe ROP, with Cerebral Injury present	3.41 (2.33-4.98)	<0.0001
Severe ROP, with Cerebral Injury absent	10.6 (5.00-22.6)	<0.0001
Cerebral Injury*Severe ROP Interaction	--	0.01
Both Cerebral Injury and Severe ROP vs. Neither ^c	36.9 (18.7-72.9)	<0.0001

Risk Factors for Blindness, Cerebral Injury vs. Normal Imaging

(N=15,578)	
Risk Factor	Blind
Cerebral Injury	133/4274 (3.1%)
Normal imaging	53/11304 (0.5%)
Severe ROP	122/3544 (3.4%)
No Severe ROP	64/12034 (0.5%)
Cerebral Injury only	47/2836 (1.7%)
Severe ROP only	36/2106 (1.7%)
Both	86/1438 (6.0%)
Neither	17/9198 (0.2%)
If Severe ROP:	N=3544
Cerebral Injury	86/1438 (6.0%)
No Cerebral Injury	36/2106 (1.7%)
If No Severe ROP:	N=12034
Cerebral Injury	47/2836 (1.7%)
No Cerebral Injury	17/9198 (0.2%)
If Cerebral Injury:	N=4274
Severe ROP	86/1438 (6.0%)
No Severe ROP	47/2836 (1.7%)
If Normal imaging:	N=11304
Severe ROP	36/2106 (1.7%)
No Severe ROP	17/9198 (0.2%)

Abbreviation: ROP, Retinopathy of Prematurity.

Adjusted aOR and 95% Confidence Interval for Blindness, with Blood/Echodensity in Parenchyma not in Cerebral Injury Definition

Risk Factor	aOR^a (95% CI)	p-value
Cerebral Injury, with Severe ROP present	3.73 (2.40-5.79)	<0.0001
Cerebral Injury, with Severe ROP absent	8.97 (5.71-14.1)	<0.0001
Severe ROP, with Cerebral Injury present	3.35 (2.26-4.97)	<0.0001
Severe ROP, with Cerebral Injury absent	8.06 (4.50-14.4)	<0.0001
Cerebral Injury*Severe ROP Interaction	--	0.01
Both Cerebral Injury and Severe ROP vs. Neither^b	30.1 (16.8-53.6)	<0.0001

Risk Factors for Blindness, with Blood/Echodensity in Parenchyma not Included in Cerebral Injury Definition

Risk Factor	Blind
Cerebral Injury	133/4074 (3.3%)
No Cerebral Injury	80/15789 (0.5%)
Severe ROP	139/4568 (3.0%)
No Severe ROP	74/15295 (0.5%)
Cerebral Injury only	47/2687 (1.7%)
Severe ROP only	53/3181 (1.7%)
Both	86/1387 (6.2%)
Neither	27/12608 (0.2%)
If Severe ROP:	N=4568
Cerebral Injury	86/1387 (6.2%)
No Cerebral Injury	53/3181 (1.7%)
If No Severe ROP:	N=15295
Cerebral Injury	47/2687 (1.7%)
No Cerebral Injury	27/12608 (0.2%)
If Cerebral Injury:	N=4074
Severe ROP	86/1387 (6.2%)
No Severe ROP	47/2687 (1.7%)
If No Cerebral Injury:	N=15789
Severe ROP	53/3181 (1.7%)
No Severe ROP	27/12608 (0.2%)