



# Between-Hospital Variation in Care Practices and Risk of Mortality or Neurodevelopmental Impairment in Extremely Preterm Infants

Vivek V. Shukla, MD, Barry Eggleston, MSc, Ananta Bangdiwala, MSc, Abhik Das, PhD, Arie Nakhmani, PhD, Colm P. Travers, MD, Matthew A. Rysavy, MD, PhD, Viral Jain, MD, Myriam Peralta, MD, Neha Kumbhat, MD, MSEpi, Ravi M. Patel, MD, Edward F. Bell, MD, Jon E. Tyson, MD, Susan R. Hintz, MD, Namasivayam Ambalavanan, MD, Waldemar A. Carlo, MD



# Disclosures

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- This presentation will not involve discussion of unapproved or off-label, experimental or investigational use of a drug.

# Background

- Alleman et al., NRN, 2013,
    - Five-fold between-hospital differences in mortality for extremely preterm infants (2006-2009)
    - Rates of antenatal corticosteroid administration, cesarean delivery, respiratory support, and NICU admission accounted for some variation
  - Rysavy et al., NRN, 2015,
    - Rates of initiating active treatment explain 78% of between-hospital differences in survival at 22-23 weeks and 22% at 24 weeks (2006-2011)
- Alleman et al., 2013, PMID: 23753096
  - Rysavy et al., 2015, PMID: 25946279

# Background

- Other studies have also shown similar between-hospital variation in survival and other outcomes.
- It remains uncertain , How care practices relate with between-hospital variation in mortality or severe neurodevelopmental impairment (NDI).
- Research in this domain can provide insights and inform care practices associated with outcomes in extremely preterm infants.

- Vohr et al., 2004,  
PMID: 15060228;
- Rysavy et al., 2020,  
PMID: 32119065;
- Lee et al., 2000,  
PMID: 11061777;

- Simpson et al., 2003,  
PMID: 12897358;
- Kusuda et al., 2006,  
PMID: 16950943;
- Almeida et al., 2008,  
PMID: 18528584

# Objective

- To identify care practices associated with between-hospital variations in mortality or severe neurodevelopmental impairment (NDI) in extremely preterm infants.

# Methods

- Inclusion: All actively treated infants 22<sup>0/7</sup> to 26<sup>6/7</sup> weeks gestation born at the NICHD NRN hospitals from 2008-2019 with available outcomes of mortality or NDI at 18-26 months corrected age.
- Exclusion: Those with syndromes or major malformations.
- Primary Outcome: Mortality or severe NDI at 18-26 months.

# Definitions

- Severe NDI: Any of the following –
  - Bayley III Cognitive Composite < 70,
  - Bayley III Motor Composite <70,
  - GMFCS level 4-5,
  - Bilateral blindness,
  - Bilateral hearing impairment.
- Active treatment: Receiving any of the following interventions –
  - Surfactant,
  - Tracheal intubation,
  - Ventilatory support,
  - Parenteral nutrition,
  - Epinephrine,
  - Chest compressions.
- Status: Until discharge home, transfer, mortality, or 120 days.

# Primary Analysis

- Generalized Linear Mixed Models (GLMMs, random effects logistic regression models with a random intercept for hospital) were built adjusting for infant-level predictors (gestational age, birthweight, multiple birth, and sex), called the infant level adjusted model.
- We computed care practice rates for each hospital and included these hospital care practice rates one at a time in the infant level adjusted model.
- The percent decrease in hospital-level random intercept variance associated with each care practice as compared to the infant level adjusted model was noted.
- Practices were ranked by percent reduction in variance.
- Analyses were conducted for 3 time periods (2008-2011, 2012-2015, 2016-2019).



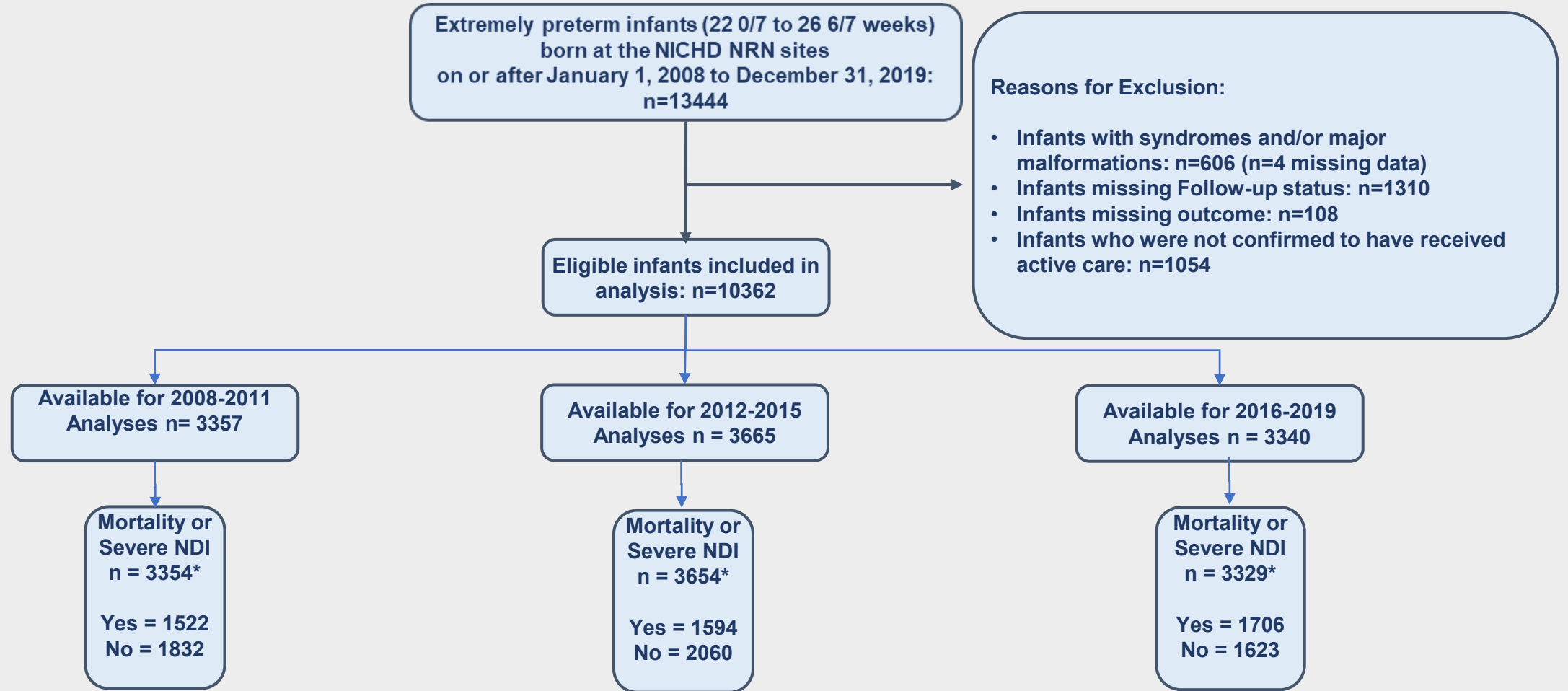
# Secondary Analysis

- Top 20 practices were used in machine learning model (gradient boosted ensemble, with 2016-2019 data, and using a 10-fold cross-validation to train and test) to identify whether the infant-level care practice exposures were associated with infant-level outcomes.
- To avoid collinearity of some of the care practices that were related to discharge, the outcome of severe NDI was selected for prediction in the machine learning model.

# Results

- A total of 10,362 extremely preterm infants were included.

# Participant Flow Diagram



\* Data used in analysis of specified outcome in predictive models. For mortality or severe NDI and mortality, differences between available data and data used in analysis is due to missing predictor data. For Severe NDI, differences between available data and data used in analysis is missing predictor data or infant did not survive through FU.

# Results (Baseline Characteristics)

- The overall
  - Gestational age (mean +/- SD) was 25.1 +/- 1.2 weeks,
  - Birthweight (mean +/- SD) was 717 +/- 170 grams,
  - 26% were multiple gestation,
  - 51% were male
- The baseline characteristics and care practices exposure varied as expected among survivors without severe NDI, those who died, and survivors with severe NDI.

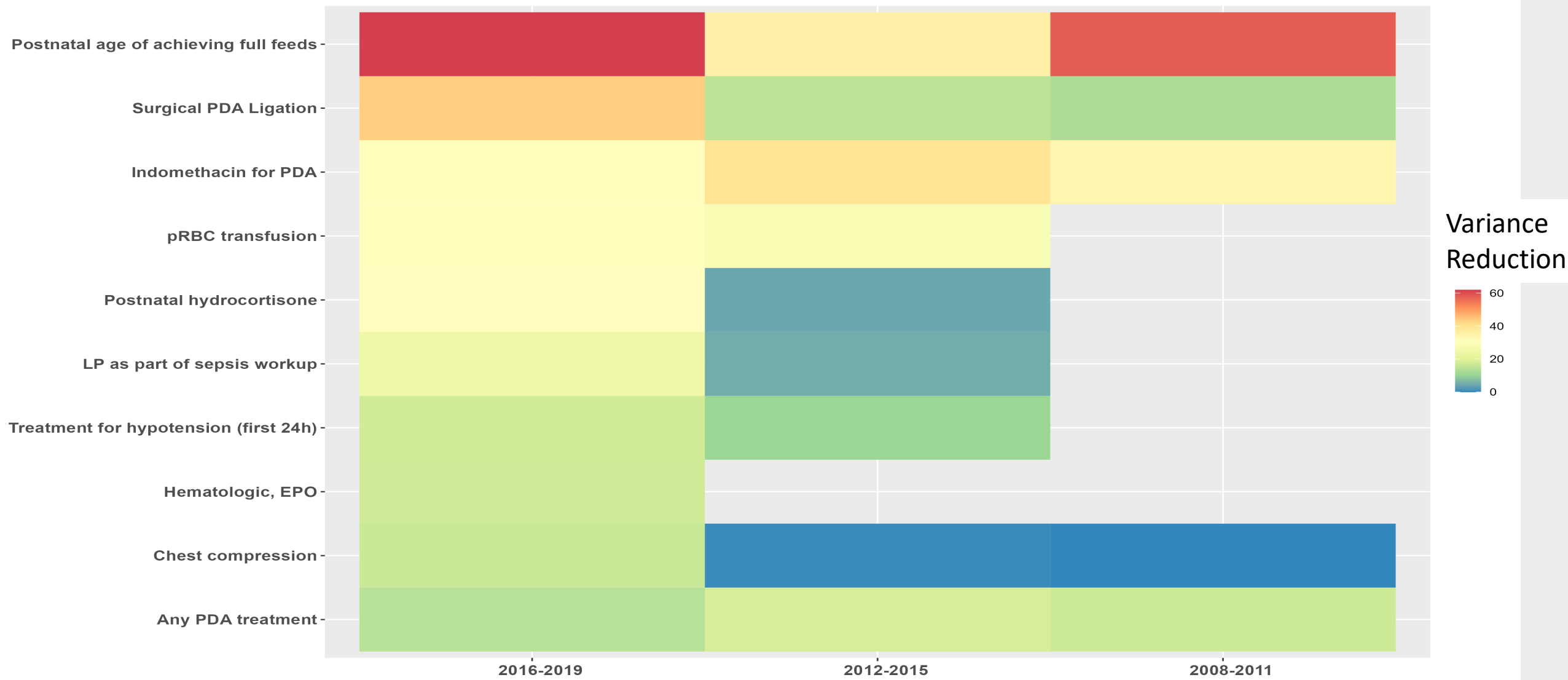
# Results (Between-Hospital Variation)

- For the 2016-2019 period, there were a total of 46 hospitals
- The raw estimates of risk of death or severe NDI at the hospital-level ranged from 21% to 74%.
- Adjusting for infant level covariates, the average model-based estimates for risk of death or severe NDI at hospital-level ranged from 28% to 70%.
- This reduction in range is due to adjustment for infant level covariates and the shrinkage tendencies seen with the use of generalized mixed models.

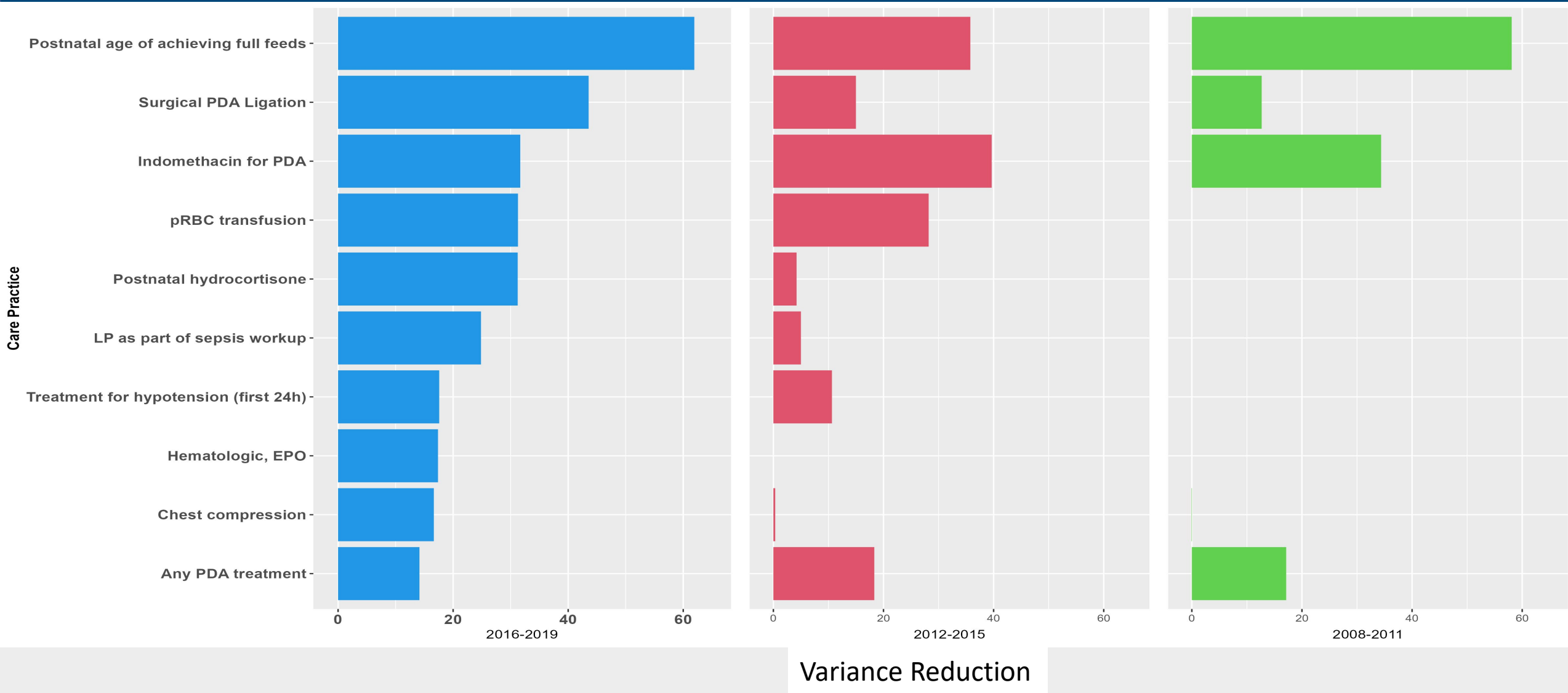
# Results (Care Practices and Between-Hospital Variation)

- Using additional GLMMs and the 2016-2019 data, we were able to explain about 75% of between-hospital variation in mortality or severe NDI while accounting for infant level covariates and simultaneously accounting for the following 5 care practices:
  - Postnatal age of achieving full feeds (Adjusted OR = 0.87, p-value = 0.008)
  - Postnatal hydrocortisone (Adjusted OR = 0.89, p-value = 0.011)
  - LP as part of sepsis workup (Adjusted OR = 0.92, p-value = 0.053)
  - Hematologic, Erythropoietin (Adjusted OR = 1.13, p-value = 0.015)
  - Any PDA treatment (Adjusted OR = 0.87, p-value = 0.006)

# Heat Map of Top Care Practices and Between-Hospital Variation

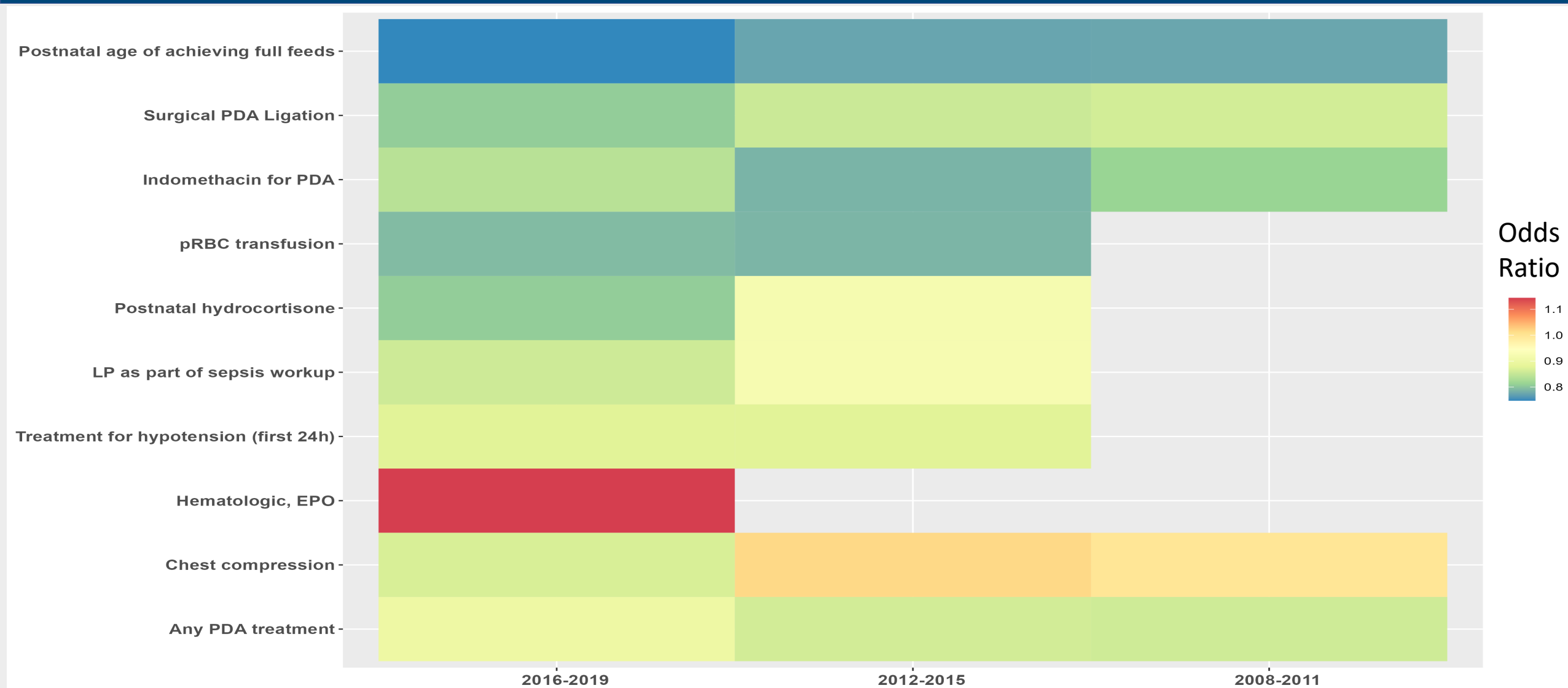


# Trends of Top Care Practices explaining Between-Hospital Variation





# Heat Map of Top Care Practices and Odds Ratio for Outcome



# Hospital-Level Care Practices and Outcome

- Based on the analyses discussed so far, it appears that differences in care practices may account for between-hospital variation in the risk of death or severe NDI.

# Care Practices and Infant-Level Outcomes

- The machine learning model for prediction of severe NDI using infant level predictors (birthweight, gestational age, sex, and multiple birth) had:
  - an AUC of **66%**,
- Adding the top 20 care-practices associated with reduction in between-hospital variation resulted in model AUC improvement to:
  - an AUC of **72%**

# Strengths

- Multicenter research database collected by trained research nurses with several quality checks.
- Large sample size over 12 years allowing for trends identification.

# Limitations

- Observational study design
- Cannot determine causality
- Limited by recorded care practices

# Conclusion

- In extremely preterm infants, hospital-level care practices were associated with between-hospital variations in mortality or severe NDI.
- Given care practice rates at the hospital-level are associated with hospital-level variations in death or severe NDI, and care practice exposure at the infant-level helps increase the predictive ability of the models for severe NDI, we can speculate that there might be possible opportunities for optimization of the care practices to improve outcomes for extremely preterm infants, which could be further tested in controlled studies.

# Neonatal Research Network Centers



- Brown University<sup>a,b,c</sup>
- Case Western Reserve University<sup>a,b,c,d</sup>
- Children's Mercy Hospitals and Clinics, University of Missouri-Kansas City<sup>b</sup>
- Cincinnati Children's Medical Center<sup>a,b,c,d</sup>
- Duke University<sup>a,b,c,d</sup>
- Emory University<sup>a,b,c,d</sup>
- Indiana University<sup>a,b</sup>
- Lurie Children's/Northwestern<sup>d</sup>
- Nationwide Children's Hospital, Ohio State University<sup>b,c</sup>
- RTI International<sup>a,b,c,d</sup>
- Sharp Memorial Hospital/UCSD<sup>d</sup>
- Stanford University<sup>a,b,c</sup>
- Tufts Medical Center<sup>a</sup>
- University of Alabama at Birmingham<sup>a,b,c,d</sup>
- University of California – Los Angeles<sup>b</sup>
- University of Iowa<sup>a,b,c,d</sup>
- University of Mississippi<sup>d</sup>
- University of New Mexico<sup>a,b,c,d</sup>
- University of Pennsylvania<sup>b,c,d</sup>
- University of Rochester<sup>b,c</sup>
- University of Texas Southwestern<sup>a,b,c,d</sup>
- University of Texas Health Science Center at Houston<sup>a,b,c,d</sup>
- University of Utah<sup>a,c,d</sup>
- Wayne State University<sup>a,b</sup>
- Yale University<sup>a</sup>

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

# Appendix Slides



# Baseline Characteristics

	Overall	Survived follow-up	Died before follow-up	P-value (survived vs died)	Survived without Severe NDI	Survived with Severe NDI	P-value (no SNI vs SNI)	Overall P-value
N	N=10362	N= 7074	N= 3288		N= 5523	N= 1551		
Gestational age (weeks), Mean (SD)	25.1 (1.2)	25.3 (1.1)	24.5 (1.2)	<.001	25.4 (1.0)	24.9 (1.1)	<.001	<.001
Birthweight (grams), Mean (SD)	717 (170)	755 (160)	636 (162)	<.001	770 (158)	701 (159)	<.001	<.001
Multiples, n/N (%)	2695/10362 (26%)	1740/7074 (25%)	955/3288 (29%)	<.001	1334/5523 (24%)	406/1551 (26%)	0.102	<.001
SGA, n/N (%)	894/10350 (9%)	415/7070 (6%)	479/3280 (15%)	<.001	278/5521 (5%)	137/1549 (9%)	<.001	<.001
Male sex, n/N (%)	5326/10358 (51%)	3487/7070 (49%)	1839/3288 (56%)	<.001	2566/5521 (46%)	921/1549 (59%)	<.001	<.001
Race				0.033			0.034	0.009
Black, n/N (%)	4338/10362 (42%)	2942/7074 (42%)	1396/3288 (42%)		2255/5523 (41%)	687/1551 (44%)		
White, n/N (%)	5141/10362 (50%)	3558/7074 (50%)	1583/3288 (48%)		2806/5523 (51%)	752/1551 (48%)		
Other/missing, n/N (%)	883/10362 (9%)	574/7074 (8%)	309/3288 (9%)		462/5523 (8%)	112/1551 (7%)		
Hispanic or Latino, n/N (%)	1608/10140 (16%)	1142/6951 (16%)	466/3189 (15%)	0.020	890/5433 (16%)	252/1518 (17%)	0.838	0.066
Limited or no prenatal care, n/N (%)	3203/3330 (96%)	2184/2276 (96%)	1019/1054 (97%)	0.312	1568/1623 (97%)	616/653 (94%)	0.013	0.022
Maternal insurance				0.020			<.001	<.001
Private, n/N (%)	5799/10286 (56%)	3955/7042 (56%)	1844/3244 (57%)		2998/5498 (55%)	957/1544 (62%)		
Public, n/N (%)	3942/10286 (38%)	2740/7042 (39%)	1202/3244 (37%)		2228/5498 (41%)	512/1544 (33%)		
Other, n/N (%)	444/10286 (4%)	277/7042 (4%)	167/3244 (5%)		220/5498 (4%)	57/1544 (4%)		
Maternal education				<.001			<.001	<.001
Less than high school, n/N (%)	1617/8042 (20%)	1114/5710 (20%)	503/2332 (22%)		847/4447 (19%)	267/1263 (21%)		
High school degree, n/N (%)	2388/8042 (30%)	1660/5710 (29%)	728/2332 (31%)		1255/4447 (28%)	405/1263 (32%)		
Partial college/trade/tech, n/N (%)	2109/8042 (26%)	1566/5710 (27%)	543/2332 (23%)		1229/4447 (28%)	337/1263 (27%)		
College degree or higher, n/N (%)	1928/8042 (24%)	1370/5710 (24%)	558/2332 (24%)		1116/4447 (25%)	254/1263 (20%)		
Diabetes								
Maternal diabetes pre-pregnancy, n/N (%)	144/3338 (4%)	98/2279 (4%)	46/1059 (4%)	0.954	67/1627 (4%)	31/652 (5%)	0.498	0.794
Maternal gestational diabetes, n/N (%)	114/3310 (3%)	83/2264 (4%)	31/1046 (3%)	0.303	61/1618 (4%)	22/646 (3%)	0.677	0.536
Hypertension during pregnancy, n/N (%)	2432/10342 (24%)	1677/7067 (24%)	755/3275 (23%)	0.450	1271/5520 (23%)	406/1547 (26%)	0.009	0.023
Prolonged rupture of membranes, n/N (%)	2752/10111 (27%)	1911/6907 (28%)	841/3204 (26%)	0.136	1513/5401 (28%)	398/1506 (26%)	0.224	0.156
Chorioamnionitis, n/N (%)	1836/10315 (18%)	1235/7056 (18%)	601/3259 (18%)	0.247	978/5507 (18%)	257/1549 (17%)	0.285	0.291
Apgar score at 1 minute < 4, n/N (%)	5909/10282 (57%)	3552/7034 (50%)	2357/3248 (73%)	<.001	2598/5496 (47%)	954/1538 (62%)	<.001	<.001
Apgar score at 5 minutes < 4, n/N (%)	2277/10298 (22%)	1021/7047 (14%)	1256/3251 (39%)	<.001	689/5504 (13%)	332/1543 (22%)	<.001	<.001

# Care Practices for entire cohort

Care Practices	Overall	Survived follow-up	Died before follow-up	P-value (survived vs died)	Survived without Severe NDI	Survived with Severe NDI	P-value (no SNDI vs SNDI)	Overall P-value
N	N=10362	N= 7074	N= 3288		N= 5523	N= 1551		
Antenatal corticosteroids, n/N (%)	9109 (88%)	6399 (90%)	2710 (82%)	<.001	5018 (91%)	1381 (89%)	0.031	<.001
Betamethasone, n/N (%)	8918 (86%)	6272 (89%)	2646 (80%)	<.001	4918 (89%)	1354 (87%)	0.055	<.001
Dexamethasone, n/N (%)	137 (1%)	94 (1%)	43 (1%)	0.931	79 (1%)	15 (1%)	0.159	0.368
Cesarian delivery, n/N (%)	6497 (63%)	4602 (65%)	1895 (58%)	<.001	3580 (65%)	1022 (66%)	0.410	<.001
Vaginal delivery, n/N (%)	3852 (37%)	2463 (35%)	1389 (42%)	<.001	1937 (35%)	526 (34%)	0.410	<.001
Bag and mask/ PPV, n/N (%)	8962 (86%)	5992 (85%)	2970 (90%)	<.001	4618 (84%)	1374 (89%)	<.001	<.001
Intubation, n/N (%)	8306 (80%)	5475 (77%)	2831 (86%)	<.001	4183 (76%)	1292 (83%)	<.001	<.001
CPAP, n/N (%)	3809 (37%)	2973 (42%)	836 (25%)	<.001	2419 (44%)	554 (36%)	<.001	<.001
Epinephrine, n/N (%)	620 (6%)	234 (3%)	386 (12%)	<.001	176 (3%)	58 (4%)	0.282	<.001
Chest compression, n/N (%)	1030 (10%)	498 (7%)	532 (16%)	<.001	365 (7%)	133 (9%)	0.007	<.001
Surfactant ever received, n/N (%)	9185 (89%)	6336 (90%)	2849 (87%)	<.001	4865 (88%)	1471 (95%)	<.001	<.001
Nitric oxide, n/N (%)	1404 (14%)	715 (10%)	689 (21%)	<.001	447 (8%)	268 (17%)	<.001	<.001
Days to nitric oxide, Mean (SD)	19.4 (27.5)	22.4 (28.5)	16.3 (26.0)	<.001	19.8 (25.9)	26.8 (31.9)	0.013	<.001
Postnatal corticosteroids, n/N (%)	2243 (22%)	1837 (26%)	406 (12%)	<.001	1244 (23%)	593 (38%)	<.001	<.001
Respiratory support by status								
No. of days HFV was highest support used, Mean (SD)	7.6 (13.7)	8.0 (14.0)	6.8 (13.1)	<.001	6.5 (12.3)	13.1 (17.9)	<.001	<.001
Prop. of days (birth to status) HFV was highest support used, Mean (SD)	0.164 (0.293)	0.071 (0.122)	0.366 (0.424)	<.001	0.059 (0.109)	0.112 (0.152)	<.001	<.001
No. of days CV was highest support used, Mean (SD)	18.2 (22.6)	22.0 (23.0)	10.1 (19.5)	<.001	18.4 (19.6)	34.8 (28.6)	<.001	<.001
Prop. of days (birth to status) CV was highest support used, Mean (SD)	0.244 (0.274)	0.200 (0.197)	0.337 (0.375)	<.001	0.172 (0.173)	0.302 (0.240)	<.001	<.001
No. of days nasal ventilation was highest support used, Mean (SD)	5.9 (10.4)	8.0 (11.3)	1.5 (6.1)	<.001	7.8 (11.0)	8.7 (12.4)	0.084	<.001
Prop. of days (birth to status) nasal ventilation was highest support used, Mean (SD)	0.061 (0.161)	0.076 (0.107)	0.028 (0.236)	<.001	0.076 (0.107)	0.078 (0.111)	0.495	<.001
No. of days CPAP was highest support used, Mean (SD)	15.0 (17.8)	20.9 (18.0)	2.2 (7.7)	<.001	21.1 (17.6)	20.3 (19.1)	<.001	<.001
Prop. of days (birth to status) CPAP was highest support used, Mean (SD)	0.156 (0.186)	0.208 (0.181)	0.045 (0.140)	<.001	0.214 (0.182)	0.185 (0.177)	<.001	<.001
No. of days supplemental O2, Mean (SD)	59.1 (43.8)	76.6 (36.5)	21.6 (33.5)	<.001	72.0 (36.2)	92.9 (32.5)	<.001	<.001
Prop. of days supplemental O2, Mean (SD)	0.738 (0.612)	0.720 (0.295)	0.779 (0.995)	<.001	0.692 (0.300)	0.818 (0.254)	<.001	<.001
Culture negative LOS with ≥ 5 days antibiotics, n/N (%)	4454 (43%)	3562 (50%)	892 (27%)	<.001	2581 (47%)	981 (63%)	<.001	<.001
Number of Culture negative LOS with ≥ 5 days treatment, Mean (SD)	0.7 (1.0)	0.8 (1.1)	0.5 (0.9)	<.001	0.7 (1.0)	1.2 (1.3)	<.001	<.001
Prophylactic indomethacin, n/N (%)	3822 (37%)	2715 (38%)	1107 (34%)	<.001	2067 (37%)	648 (42%)	0.002	<.001
Anti-convulsant > 72 hours, n/N (%)	404 (4%)	219 (3%)	185 (6%)	<.001	108 (2%)	111 (7%)	<.001	<.001
Retinal ablation, n/N (%)	642 (6%)	591 (8%)	51 (2%)	<.001	360 (7%)	231 (15%)	<.001	<.001
PDA, n/N (%)	5235 (51%)	4077 (58%)	1158 (35%)		3097 (56%)	980 (63%)		
Ligation, n/N (%)	1082 (10%)	961 (14%)	121 (4%)	<.001	677 (12%)	284 (18%)	<.001	<.001
Indomethacin, n/N (%)	2156 (21%)	1786 (25%)	370 (11%)	<.001	1404 (25%)	382 (25%)	0.526	<.001
Ibuprofen, n/N (%)	1035 (10%)	816 (12%)	219 (7%)	<.001	610 (11%)	206 (13%)	0.015	<.001
Day, first enteral feeds, Mean (SD)	5.3 (14.1)	5.1 (12.0)	6.0 (20.7)	<.001	4.9 (13.0)	6.1 (7.6)	<.001	<.001
Day, 120 ml/kg feeds, Mean (SD)	27.3 (20.0)	27.3 (20.1)	27.9 (18.6)	0.530	25.8 (19.7)	32.9 (20.6)	<.001	<.001
TPN duration, Mean (SD)	26.4 (23.9)	31.6 (22.7)	15.2 (22.4)	<.001	28.7 (19.6)	42.2 (29.2)	<.001	<.001
No discharge medications, n/N (%)	2942 (28%)	2916 (41%)	26 (1%)	<.001	2591 (47%)	325 (21%)	<.001	<.001
Discharged on diuretics, n/N (%)	609 (6%)	594 (8%)	15 (0%)	<.001	511 (9%)	83 (5%)	<.001	<.001
Discharged on bronchodilators, n/N (%)	170 (2%)	169 (2%)	1 (0%)	<.001	144 (3%)	25 (2%)	0.023	<.001
Discharged on anticonvulsants, n/N (%)	21 (0%)	21 (0%)	0 (0%)	0.002	14 (0%)	7 (0%)	0.206	0.002
Discharged on anti-reflux medications, n/N (%)	442 (4%)	434 (6%)	8 (0%)	<.001	383 (7%)	51 (3%)	<.001	<.001

# Care Practices since 2011 and since 2016

Care Practices	Overall	Survived follow-up	Died before follow-up	P-value (survived vs died)	Survived without Severe NDI	Survived with Severe NDI	P-value (no SNDI vs SNDI)	Overall P-value
<b>Additional care practices available since 2011</b>	<b>N= 7883</b>	<b>N= 5454</b>	<b>N= 2429</b>		<b>N= 4190</b>	<b>N= 1264</b>		
Magnesium sulfate, n/N (%)	5973 (76%)	4296 (79%)	1677 (69%)	<.001	3327 (79%)	969 (77%)	0.037	<.001
Use of thermal products, n/N (%)	5796 (74%)	4068 (75%)	1728 (71%)	0.001	3112 (74%)	956 (76%)	0.330	0.004
Vitamin A, n/N (%)	1470 (19%)	1098 (20%)	372 (15%)	<.001	801 (19%)	297 (23%)	<.001	<.001
Dexamethasone, n/N (%)	1347 (17%)	1139 (21%)	208 (9%)	<.001	732 (17%)	407 (32%)	<.001	<.001
Hydrocortisone, n/N (%)	593 (8%)	466 (9%)	127 (5%)	<.001	337 (8%)	129 (10%)	0.016	<.001
LP for sepsis evaluation, n/N (%)	1983 (25%)	1728 (32%)	255 (10%)	<.001	1308 (31%)	420 (33%)	0.178	<.001
EEG confirmed seizures, n/N (%)	114 (1%)	72 (1%)	42 (2%)	0.160	40 (1%)	32 (3%)	<.001	<.001
Anti-convulsant > 72 hours among those EEG confirmed, n/N (%)	69 (61%)	44 (61%)	25 (60%)	0.867	19 (48%)	25 (78%)	0.008	0.030
Avastin/anti-VEGF, n/N (%)	444 (6%)	391 (7%)	53 (2%)	<.001	213 (5%)	178 (14%)	<.001	<.001
Treatment for hypotension (first 24h), n/N (%)	2356 (30%)	1453 (27%)	903 (37%)	<.001	1033 (25%)	420 (33%)	<.001	<.001
Transfused with pRBC, n/N (%)	6744 (86%)	5001 (92%)	1743 (72%)	<.001	3795 (91%)	1206 (95%)	<.001	<.001
Lowest Hct before first transfusion, n/N (%)	10.5 (2.4)	10.5 (2.4)	10.5 (2.5)	0.989	10.6 (2.4)	10.3 (2.1)	0.016	0.060
Transfused with platelets, n/N (%)	2218 (28%)	1207 (22%)	1011 (42%)	<.001	703 (17%)	504 (40%)	<.001	<.001
<b>Additional care practices available since 2016</b>	<b>N= 3340</b>	<b>N= 2280</b>	<b>N= 1060</b>		<b>N= 1627</b>	<b>N= 653</b>		
Antenatal corticosteroids -Repeat courses, n/N (%)	287 (9%)	239 (10%)	48 (5%)	<.001	179 (11%)	60 (9%)	0.201	<.001
Delayed cord clamping, n/N (%)	961 (29%)	719 (32%)	242 (23%)	<.001	533 (33%)	186 (28%)	0.047	<.001
Cord milking, n/N (%)	273 (8%)	182 (8%)	91 (9%)	0.554	135 (8%)	47 (7%)	0.381	0.577
Baby received surfactants, n/N (%)	2918 (87%)	610 (93%)	924 (87%)					
If baby received surfactant, first dose in DR, n/N (%)	1184 (41%)	857 (43%)	327 (35%)	<.001	584 (42%)	273 (45%)	0.288	<.001
PDA, n/N (%)	1774 (53%)	417 (64%)	388 (37%)					
Cath Closure, n/N (%)	87 (3%)	84 (4%)	3 (0%)	<.001	46 (3%)	38 (6%)	<.001	<.001
Acetaminophen, n/N (%)	254 (8%)	197 (9%)	57 (5%)	<.001	139 (9%)	58 (9%)	0.795	0.004
EPO, n/N (%)	204 (6%)	155 (7%)	49 (5%)	0.015	106 (7%)	49 (8%)	0.396	0.034
Probiotics, n/N (%)	267 (8%)	230 (10%)	37 (3%)	<.001	177 (11%)	53 (8%)	0.048	<.001
Discharged on antihypertensive medications, n/N (%)	60 (2%)	60 (3%)	0 (0%)	<.001	29 (2%)	31 (5%)	<.001	<.001
Discharged on methylxanthines, n/N (%)	27 (1%)	27 (1%)	0 (0%)	<.001	20 (1%)	7 (1%)	0.754	0.002
Discharged receiving any Mother's milk, n/N (%)	279 (8%)	276 (12%)	3 (0%)	<.001	201 (12%)	75 (11%)	0.565	<.001

# Secondary Analysis

- The primary analysis identified care practice measures that were associated with reductions in site-to-site variation in the outcomes. In the primary analysis, the care practice was entered into the models as a site-level variable. This secondary analysis studied whether or not exposure to select care practices would enhance predictability of outcomes beyond gestational age, birthweight, multiple birth, and sex.
- Top 20 practices were used in machine learning model (gradient boosted ensemble, with 2016-2019 data, and using a 10-fold cross-validation to train and test models) to identify whether the infant-level care practice exposures were predictive of infant-level outcomes. This machine learning model used individual level data for the outcome and the care practice measures, which in this analysis represented exposure to a care practice.
- To avoid collinearity of some of the care practices that were related to discharge, the outcome of severe NDI was selected for prediction in the machine learning model.
- If the primary GLMM analysis shows differences in outcomes across sites can be explained by variations in care practice rates and these secondary machine learning models show that accounting for individual care practice exposures enhance predictive performance beyond gestational age, birthweight, multiple birth, and sex, then the two analyses jointly support further prospective studies to standardize care practices across sites to best practice protocols.