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Intermediate vs. High Oxygen Saturation Targets in Preterm Infants: A National Cohort Study

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Abstract
Introduction: Optimal oxygen saturation targets remain unknown for extremely preterm infants. ***Methods:*** Cohort analysis of eligible preterm infants born <29 weeks' gestation admitted between 2011 and 2018 to centers submitting data to the Canadian Neonatal Network (CNN) database. Site questionnaires to determine saturation targets, alarm settings, and date of change, allowed assignation of centers to intermediate (88–93%) or high (90–95%) saturation targets. A 6-month washout period was applied to sites which switched targets during the study period. Our primary outcome was survival free of major morbidity. Secondary outcomes were death, necrotizing enterocolitis (NEC), bronchopulmonary dysplasia (BPD), treated retinopathy of prematurity, and evidence of brain injury during admission. Generalized estimating equations were applied to compensate for demographic differences and site practices. ***Results:*** There were 2,739 infants in the high (mean gestational age [GA] 26 ± 1.6 weeks) and 6,813 infants in the intermediate (mean GA 26.2 ± 1.6 weeks) saturation target group. Survival without morbidity was higher in the intermediate target group (adjusted odds ratio [aOR] 1.59; 95% CI: 1.04, 2.45). There was no difference in mortality between groups (aOR 0.81; 95% CI: 0.59, 1.11), in NEC, treated retinopathy, or brain injury. On subgroup analysis, restricting data to sites which switched targets during the study, intermediate saturation targets were associated with lower rates of BPD (aOR 0.45; 95% CI: 0.28, 0.72). ***Conclusion:*** For neonates <29 weeks' gestation, intermediate saturation target was associated with higher odds of survival without major morbidity compared to higher oxygen saturation target.

A complete list of Canadian Neonatal Network Site Investigators can be found in the Acknowledgements.

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Introduction

Since unrestricted oxygen was found to cause retrolental fibroplasia (now called retinopathy of prematurity [ROP]) [1], oxygen targets for preterm newborns have been controversial. With changes in neonatal care, clinical signs were replaced with blood and tissue oxygen partial pressure measurement in the 1970s and by the late 1980s continuous pulse oximetry became a standard of care in developed countries [2]. Oxygen therapy in preterm infants needs to balance the benefits of tissue oxygenation with the harms of oxygen toxicity. Thus, the optimal range of SpO_2 targets should balance the potential risk from higher saturation targets (ROP and bronchopulmonary dysplasia [BPD]) with risk from low saturation targets (necrotizing enterocolitis [NEC] and death). At the turn of the 21st century, some published cohort studies found an association between lower saturation targets and improved outcomes [3–5]. Then, between 2005 and 2007, five randomized clinical trials, known collectively as the Neonatal Oxygen Prospective Meta-analysis (NeOProM) collaboration, compared the effects of a lower SpO_2 target range (85 to 89%) versus a higher target range (91 to 95%) in infants born at <28 weeks' gestation [6–8] by randomizing eligible newborns to pulse oximeters that were offset either positively or negatively while within the 85–95% saturation range. An increase in the risk of death and NEC in the low target arm after a change in the computer software algorithm for lower saturations led to a halt in Benefits of Oxygen Saturation Targeting (BOOST II) trials in the UK and Australia [8]. In the final meta-analysis, the rates of death before discharge and NEC were both significantly higher in the low target arm, whereas the rates of ROP treatment and BPD were higher in the high target group (rated as high-quality evidence). There was no statistically significant difference in the primary composite outcome of death or major neurological disability at a corrected age of 18–24 months [9, 10]. Manja et al. [11] reviewing the same data have qualified evidence as "low certainty." Although the NeOProM Meta-analysis favored high SpO_2 targets (91 to 95%) over low SpO_2 targets (85 to 89%) due to better survival in the high target arm, until now there is limited evidence on whether an intermediate SpO_2 target range provides a better balance between the competing risks of high and low oxygenation levels. Foglia et al. [12] compared 10 hospitals which made a change in saturation alarm policy to 9 hospitals which did not make a change and reported that BPD increased in hospitals that switched to a higher target; however, there was no difference in severe ROP or NEC between epochs in either group.

After the BOOST II study was halted, based on the interim analysis, a recommendation was made to cease targeting low (85–89%) saturation targets [13]. Further recommendations were made later for Europe and the USA, specifically advising saturation targets of between 90 and 95% with suggested upper alarm limits of 95% [14–16]. However, the Canadian Oxygen Trial (COT) [7] had reported no statistically significant difference in death before discharge. No data were collected for intermediate targets. Thus, in Canada, no official recommendation was made. Following COT, most centers in Canada initially continued to apply intermediate saturation goals (consistent with infants that were not enrolled in the COT study) with alarm settings of 85–95% with a subsequent partial switch to higher SpO_2 targets. This change in site practice provided an opportunity to investigate the effects of high (90–95%) versus intermediate (88–93%) SpO_2 targets on neonatal outcomes. In this cohort study, our planned objective was to compare outcomes in preterm infants of <29 weeks' gestation admitted to tertiary neonatal intensive care units (NICUs) with declared saturation targets and/or alarm limits, participating in the Canadian Neonatal Network (CNN) database.

Methods

The CNN database contains health information of infants admitted to 30 tertiary NICUs across Canada. At all affiliated sites, demographics and outcome data were collected from patient charts by trained research assistants using a computerized data entry program according to standardized outcome definitions [17]. Data were collected for each infant until death or discharge from the NICU and were transmitted electronically to the CNN coordinating center, where they were stored in a database which has been shown to have very high internal reliability and consistency [18]. The study proposal required supplementary data on site oxygenation targets. A one-page questionnaire was sent out on July 5, 2019, to all the CNN site investigators asking for their center oxygen saturation targets, alarm limits, and any date of change since 2010. There were three email reminders sent out, if no response was received. Sites who did not respond were excluded from the study. Sites with lower oxygen saturation goals (declared targets below 88–92% or a lower alarm limit below 83%) were also excluded. The study exposure of interest was high (90–95%) versus intermediate SpO_2 targets (88–93%). We also separately compared high (88–97%) with intermediate (83–96%) alarm limits based on survey results. For centers that switched targets and/or alarm limits during the study period, a 6-month washout period (3 months before and after) was applied during which data were not included for the purpose of this study. Infants born at <29

Table 1. Demographic characteristics of included patients based on saturation target groups

	High SpO_2 target group (90–95%)	Intermediate SpO_2 target group (88–93%)	*p* value
	N = 2,739	*N* = 6,813	
Antenatal steroids, *n* (%)	2,403 (89)	5,936 (89)	0.66
Maternal antibiotics, *n* (%)	2,035 (78)	4,553 (70)	<0.01
Cesarean section, *n* (%)	1,550 (57)	3,970 (58)	0.12
Outborn, *n* (%)	422 (15)	1,081 (16)	0.57
Singleton, *n* (%)	2,011 (73)	4,977 (73)	0.72
Gestational age at birth, weeks, mean (SD)	26.0 (1.6)	26.2 (1.6)	<0.01
Gestational age 22^0–23^6 weeks, *n* (%)	225 (8)	410 (6)	<0.01
Gestational age 24^0–26^6 weeks, *n* (%)	1,303 (48)	3,135 (46)	
Gestational age 27^0–28^6 weeks, *n* (%)	1,211 (44)	3,268 (48)	
Birth weight, grams, mean (SD)	900 (248)	925 (255)	<0.01
Birth weight <500 grams, *n* (%)	59 (2)	159 (2)	<0.01
Birth weight 500–1,000 grams, *n* (%)	1,790 (65)	4,153 (61)	
Birth weight >1,000 grams, *n* (%)	887 (32)	2,500 (37)	
Male, *n* (%)	1,455 (53)	3,711 (55)	0.25
Small for gestational age, *n* (%)	242 (9)	591 (9)	0.79
Apgar score at 5 min, median (IQR)	7 (5, 8)	7 (5, 8)	0.06
Surfactant, *n* (%)	2,005 (73)	4,764 (70)	<0.01
SNAP-II >20, *n* (%)	760 (28)	2,055 (31)	0.03
Time to start feeds, days, median (IQR)	2 (1, 2)	2 (1, 3)	<0.01
PDA requiring treatment, *n* (%)	924 (34)	2,582 (39)	<0.01
Late-onset sepsis, *n* (%)	671 (25)	1,294 (19)	<0.01

weeks' gestational age (GA) between January 1, 2011, and December 31, 2018, and admitted to CNN NICUs were eligible. Infants with major congenital malformations or that were moribund at birth were excluded. No direct observation was made regarding adherence to saturation targets or limits. Our primary outcome for both comparisons was survival without any of the following morbidities: (1) ROP receiving treatment, (2) BPD defined as respiratory support or an oxygen requirement at 36 weeks of postmenstrual age or at the time of transfer to level 2 units, (3) brain injury was defined as grade 3 or 4 intraventricular hemorrhage or periventricular leukomalacia, and (4) NEC (Bell stage 2 or worse) by discharge from hospital.

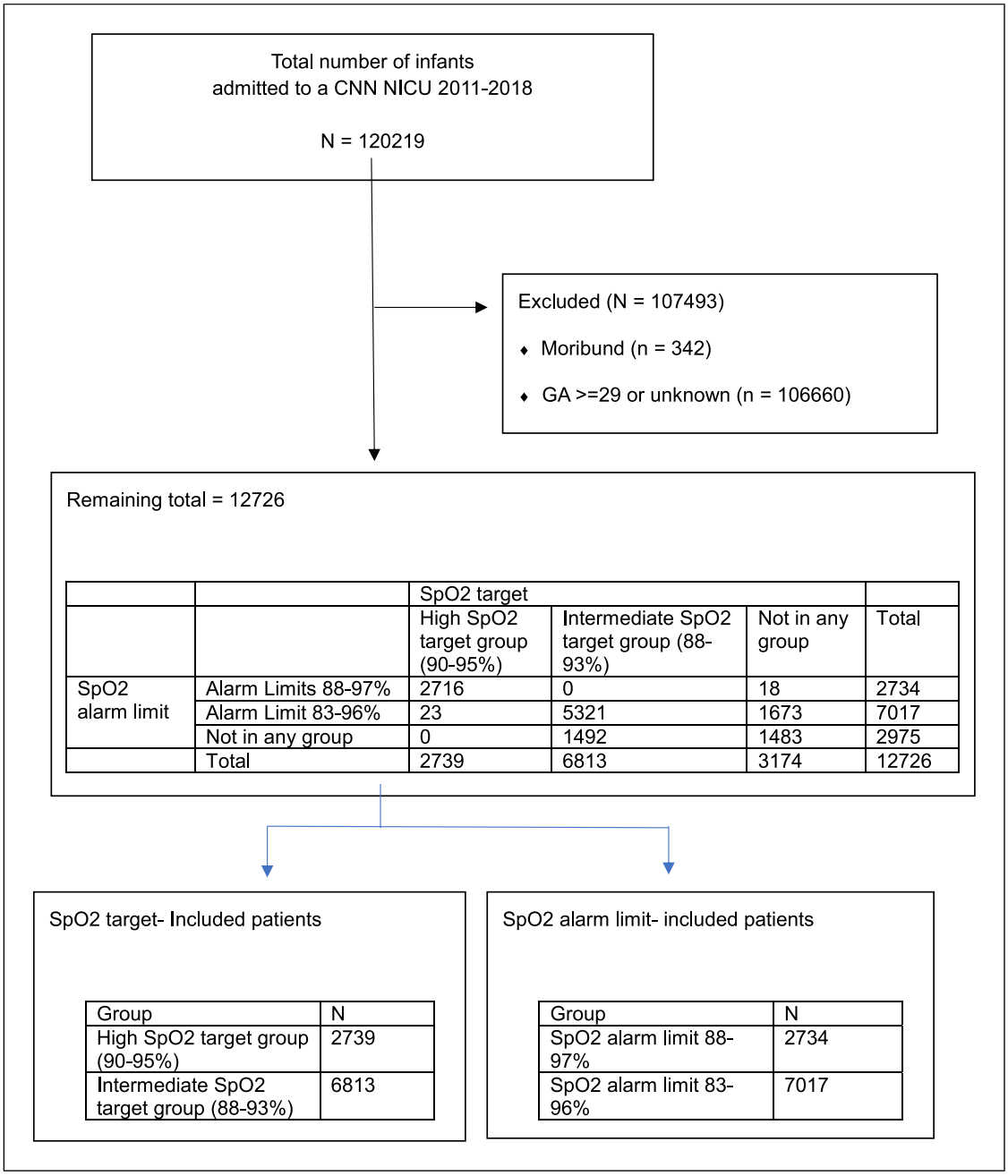
Analyses

Baseline characteristics between groups were compared using univariate comparison appropriate for distribution of variables. Adjusted odds ratio (aOR) and 95% confidence interval (CI) were estimated after adjusting for receipt of any antenatal steroids, maternal systemic antibiotics, sex, multiple births, outborn, GA, SNAP-II >20, and surfactant. We chose not to correct for prophylactic probiotics or human milk use. Generalized estimating equation was applied for each model to account for the correlations among neonates within the same site. All analyses were conducted using Statistical Analysis Software (SAS) version 9.4 (Cary, NC). A p value of <0.05 was considered significant. No adjustments were made for multiple comparisons. We also performed a subgroup analysis, only using data from centers which changed oxygen targets during the study period, again applying a 6-month washout period.

Results

A total of 26 centers from 30 participating CNN sites responded to the survey and were included: 12 centers continued to target intermediate saturations, 6 centers switched targets during the study period, and 8 centers had used high targets throughout the study period. The demographic characteristics based on saturation targets are described in Table 1.

There was center variability in alarm settings, with some sites using narrow and others broader limits. As expected, there was a large overlap between higher targets and higher alarm limits. We performed a separate analysis, comparing centers by stated alarm limits, assigned as intermediate and high. Twenty-five centers were included for this analysis (online suppl. Information, suppl. Tables 4, 5; for all online suppl. material, see https://doi.org/10.1159/000540278). The patient flow in



		SpO2 target			
		High SpO2 target group (90-95%)	Intermediate SpO2 target group (88-93%)	Not in any group	Total
SpO2 alarm limit	Alarm Limits 88-97%	2716	0	18	2734
	Alarm Limit 83-96%	23	5321	1673	7017
	Not in any group	0	1492	1483	2975
	Total	2739	6813	3174	12726

Group	N
High SpO2 target group (90-95%)	2739
Intermediate SpO2 target group (88-93%)	6813

Group	N
SpO2 alarm limit 88-97%	2734
SpO2 alarm limit 83-96%	7017

Fig. 1. Patient flowchart.

different groups is described in Figure 1. On unadjusted comparison, the high saturation target groups had less mature infants (average GA at birth; 26.0 vs. 26.2), the intermediate SpO_2 group had sicker (SNAP-II >20; 31% vs. 28%) infants at admission, with more infants subsequently treated for patent ductus arteriosus (PDA). The incidence of late-onset sepsis was significantly higher in the high SpO_2 group. The demographic characteristics for analysis, when comparing high versus intermediate SpO_2 alarm limits were similar to the baseline characteristics comparing high versus intermediate SpO_2 targets (online suppl. Table 4).

On unadjusted analysis, survival at discharge without major morbidity was higher in the intermediate SpO_2 target group (Table 2). Death prior to discharge, BPD, and home oxygen therapy were lower in the intermediate

Table 2. Outcome comparison according to oxygen saturation targets

Outcomes/characteristics	High SpO_2 target group (90–95%)	Intermediate SpO_2 target group (88–93%)	*p* value
	N = 2,739	*N* = 6,813	
Survival at discharge without major morbidities[a], *n* (%)	822 (30)	2,683 (39)	<0.01
Death prior to discharge, *n* (%)	456 (17)	924 (14)	<0.01
Retinopathy stage 3 or higher or treated, *n* (%)	290 (14)	690 (16)	0.06
Stage 2 or 3 necrotizing enterocolitis, *n* (%)	234 (9)	522 (8)	0.14
Bronchopulmonary dysplasia, *n* (%)	1,375 (60)	2,879 (49)	<0.01
Severe brain injury, *n* (%)	317 (12)	700 (11)	0.13
Any retinopathy[b], *n* (%)	1,180 (57)	2,741 (63)	<0.01
Late-onset sepsis, *n* (%)	667 (24)	1,463 (21)	<0.01
Duration of mechanical ventilation, days, median (IQR)	5 (1, 23)	5 (1, 23)	0.75
Home oxygen therapy, *n* (%)	138 (5)	141 (2)	<0.01
Length of hospital stay, days, median (IQR)	70 (38, 102)	68 (36, 100)	<0.01
Infants z-score for weight at the time of discharge, mean (SD)	0.05 (1.06)	−0.02 (0.96)	<0.01

[a]Survival without any of the major morbidities included survival without treated retinopathy, or bronchopulmonary dysplasia, or grade 3 or 4 intraventricular hemorrhage or periventricular leukomalacia, or stage 2 or 3 necrotizing enterocolitis. [b]For "ALL ROP," the percentage was calculated out of those who had eye exam done, but the babies whose results were "immature" were excluded from the calculation.

SpO_2 target group. Severe brain injury, NEC, and ROP treatment were not significantly different between the two groups. Results were similar when analyzed for high versus intermediate SpO_2 alarm limits, except severe brain injury which was lower in the intermediate SpO_2 alarm limit group (online suppl. Table 5).

After adjustment, survival at discharge without major morbidity remained significantly higher both in the intermediate saturation target group (aOR 1.59, 95% CI: 1.04, 2.45) and in SpO_2 alarm limit of 83–96% group (aOR 1.67, 95% CI: 1.05, 2.65) (Table 3). There was no statistically significant difference in any other outcomes in both comparisons.

We then performed a subgroup analysis, only using data from the six sites which declared a change in oxygen saturation targets during the study period: five sites increased their targets. These sites had pre-change and post-change data for comparison. One site increased its target for 1 year and then reverted to mid targets. Average birth weight and gestation decreased slightly, with increased SNAP-II >20 in association with increased targets. There was an increased receipt of human milk, no significant change in probiotic use, and a decrease in treatment for PDA (online suppl. Table 6) in neonates in the higher target group. Adjusted results for this subgroup (online suppl. Table 7) also showed increased survival without morbidity in association with intermediate saturation targets (aOR 1.92, 95% CI: 1.30, 2.84) with a statistically significant lower BPD rate (aOR 0.45; 95% CI: 0.28, 0.72). NEC and death before discharge were not significantly different between groups.

Discussion

We identified an association between intermediate oxygen saturation targets and higher odds of survival without morbidity, compared to high oxygen saturation targets. This could be due to a higher BPD rate (unadjusted) in infants exposed to higher targets. There was no significant difference in NEC or death before discharge, in contrast to the NeoPRoM meta-analysis. Possible reasons for these differences include lower oxygen saturation targets in the low arm of NeoPRoM studies, generally lower low alarm limits (except COT which used a lower limit of 85%), as well as more recently introduced practice interventions for reducing NEC.

The NeOProM group had three definitions for NEC, including "severe confirmed, including death." However, both CNN and COT defined NEC as Bell stage 2 (or worse)/confirmed by pathology. In the COT study, the

Table 3. Multivariable adjusted results

Outcomes	Adjusted[a] odds ratio (95% CI) for intermediate SpO_2 target group compared to high SpO_2 target	Adjusted[a] odds ratio (95% CI) for SpO_2 alarm limit 83–96% compared to alarm limit of 88–97%
Survival at discharge without major morbidities	1.59 (1.04, 2.45)	1.67 (1.05, 2.65)
Death prior to discharge	0.81 (0.59, 1.11)	0.87 (0.65, 1.17)
Retinopathy stage 3 or higher or treated	1.26 (0.80, 1.97)	1.00 (0.77, 1.31)
Stage 2 or 3 necrotizing enterocolitis	0.90 (0.69, 1.18)	0.87 (0.70, 1.08)
Bronchopulmonary dysplasia	0.63 (0.38, 1.03)	0.58 (0.34, 1.01)
Severe brain injury	0.93 (0.73, 1.19)	0.86 (0.72, 1.02)
All ROP	1.31 (0.61, 2.81)	1.04 (0.54, 1.99)

[a]Adjusted for GA, maternal systemic antibiotics, SNAP-II >20, surfactant, antenatal steroids, sex, multiple births, outborn.

NEC rate was 12.3% in the low target group and 9.3% in the high target group [7]. Our cohort study included more mature infants (<29 weeks' gestation), and our NEC rate was 7.7% in the intermediate group and 8.5% in the high target group. The improvement in Canada's NEC rate since the COT study may be due to an increase in the use of human milk as well as prophylactic probiotics [19].

In our study, the incidence of treated ROP was not statistically different between the two arms, possibly due to differences in thresholds for treatment as well as preferred modes of therapy at different sites [20]. For our subgroup analysis, crude rates for ROP treatment in the six sites that switched targets went from 11% for intermediate to 16% with high targets, but after adjustment, this was not statistically significant. Two older studies, STOP ROP [21] and the original BOOST study [22], trialed higher oxygen targets to reduce severe ROP: they found that targeting higher O_2 targets later during an infant's NICU stay did not reduce ROP requiring laser treatment but did increase BPD.

We found a ~60% higher rate of BPD with both higher saturation targets and higher alarm limits, but this was only statistically significant in our subgroup analysis. In the NeoPRoM studies, there was an agreed upper alarm limit of 95/96%, intersecting with higher saturation targets and possibly leading to a narrowing of saturation differences [20] between both arms. In our study, most centers which switched to higher targets also switched to higher alarm limits, likely reflecting a practical difficulty in applying higher targets without changing the high alarm setting. As the hemoglobin oxygen saturation curve flattens at higher values, a slight percentage point increase in oxygen saturation is associated with a far greater increase in arterial partial pressure.

The higher BPD rate in infants exposed to higher saturation targets may have more clinical importance than due to the simple application of those targets to define BPD: there was also an increased duration of hospital length of stay as well as higher home oxygen use in the high target group in our unadjusted results. Possible additional mechanisms for the higher BPD rate in our high target cohort include increased oxygen toxicity, leading to lung injury [23] as well as decreased physiological respiratory drive from oxygen chemoreceptors (such as the carotid body), leading to an increased need for ventilation [24], although we did not see any difference in the duration of mechanical ventilation between the two groups. The strengths of our study are that it was a large multicenter study including most infants treated at tertiary care centers in a single country with a universal health care system. We used standard definitions for all neonatal outcomes. The results represent national data, so may be generalizable.

Our study is limited by being an unblinded cohort comparison, rather than a randomized trial. We did not collect data on actual saturations or adherence. As our report is linking survey data to patient outcomes, it is subject to ecological bias. There was also an overlap between centers which used higher targets and centers which used higher alarm settings. During the study period, there were slight changes in infant admission demographics as well as some practice changes such as management of PDA, fortification, and use of human milk. In unadjusted comparison, there was a statistically significant difference in discharge weight of 0.07 SD favoring neonates who were managed in higher oxygen saturation limits. This difference is likely clinically

less significant and could be due to other changes over time with regard to nutritional practices and cultural change in the approach of these babies. We would like to caution readers that this is an association-finding exercise to generate hypothesis, and no cause-and-effect relationship should be inferred from these observations.

Conclusion

In Canada, for neonates <29 weeks' gestation at birth, intermediate saturation target (88–93%; alarm settings 84–96%) was associated with higher odds of survival without major morbidity compared to a higher oxygen saturation target (90–95%; alarm settings of 88–97%). Higher oxygen saturation targets were not associated with any decrease in mortality, NEC rates, or neurological injury, compared to intermediate saturation targets. Higher O_2 saturation targets were associated with a higher BPD rate and longer hospital length of stay in unadjusted comparison. Moreover, there is great variation in maintaining target SpO_2 and alarm limits for preterm neonates, and without such confirmatory information, the association described could exist for any number of other care patterns in the units. Further studies are warranted to confirm or refute this association.

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Statement of Ethics

The Research Ethics Board at IWK Health Centre (Project #: 1025036) and the CNN Executive Committee both approved the study. Data sharing agreements were approved by local research ethics boards. Waiver of written informed consent was approved by research ethics boards or equivalent bodies at participating sites prior to data transfer to the coordinating center. We also obtained approval from the Mount Sinai Hospital Research Ethics Board.

Conflict of Interest Statement

None of the authors have any conflict of interest to declare.

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Author Contributions

Study design was conceived by R.T., B.S., A.M., J.D., R.A., A.L., W.E., E.Y., and P.S. Database analysis by E.Y. Paper written by R.T., P.S., and B.S. and edited and reviewed and approved by R.T., B.S., A.M., J.D., R.A., A.L., W.E., E.Y., and P.S.

Data Availability Statement

Patient data remain on the CNN database. Center survey responses are held by B.S. Further inquiries can be directed to the corresponding author.

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