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International Variation and Trends of Intraventricular Hemorrhage in Very Preterm Infants

Georgia Hollens[a] Tim Schindler[a, b] Malcolm Battin[c] Gil Klinger[d] Mark Adams[e] Maximo Vento[f] Antonino Santacroce[g] Stellan Håkansson[h] Tetsuya Isayama[i] Mikael Norman[j, k] Satoshi Kusuda[l] Liisa Lehtonen[m, n] Kjell Helenius[m, n] Neena Modi[o] Prakesh S. Shah[p, q] Kei Lui[a, b] on behalf of the iNeo Neonatal Network

[a]School of Clinical Medicine, University of New South Wales, Sydney, NSW, Australia; [b]Royal Hospital for Women, Sydney, NSW, Australia; [c]Newborn Services, Auckland City Hospital, Grafton, New Zealand; [d]Department of Neonatal Intensive Care, Schneider Children's Medical Center of Israel, Petah Tikva, and Tel Aviv University, Tel Aviv, Israel; [e]Department of Neonatology, University and University Hospital Zurich, Zurich, Switzerland; [f]Division of Neonatology, Health Research Institute Hospital La Fe, Valencia, Spain; [g]Department of Women and Children, University Hospital, Siena, Italy; [h]Department of Clinical Sciences/Pediatrics, Umeå University Hospital, Umeå, Sweden; [i]Division of Neonatology, National Center for Child Health and Development, Tokyo, Japan; [j]Department of Neonatal Medicine, Karolinska University Hospital, Stockholm, Sweden; [k]Division of Pediatrics, Department of Clinical Science, Intervention and Technology, Karolinska Institutet, Stockholm, Sweden; [l]Neonatal Research Network of Japan, Kyorin University, Tokyo, Japan; [m]Department of Pediatrics and Adolescent Medicine, Turku University Hospital, Turku, Finland; [n]Department of Clinical Medicine, University of Turku, Turku, Finland; [o]Section of Neonatal Medicine, School of Public Health, Imperial College London, London, UK; [p]Department of Pediatrics, Mount Sinai Hospital, University of Toronto, Toronto, ON, Canada; [q]Department of Pediatrics, University of Toronto, Toronto, ON, Canada

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Abstract

Introduction: We aimed to investigate international variation in gestational age (GA) specific severe intraventricular hemorrhage (IVH) rates, among infants of <30 weeks' GA from the neonatal networks of 11 high-income countries/region. ***Methods:*** Retrospective cohort study of outcomes of grade 3/4 IVH rates and composite of g3/4 IVH or death in GA groups of 22–23, 24–25, 26–27, and 28–29 weeks infants admitted to networks of Australia and New Zealand, Canada, Finland, Israel, Italy (Tuscany), Japan, Spain, Sweden, Switzerland, and the UK. Their risk adjusted trends across 3 epochs (2007-11, 2012-15, and 2016-19) were also evaluated. ***Results:*** Outcomes of 165,329 infants (median GA 27 weeks, birthweight 950 g) were analyzed. Overall, the lowest grade 3/4 IVH rate was observed in Japan (6.4%) and the highest in Israel (16.1%). The overall gestation-specific rate of IVH grade 3/4 were 25.8%, 18.6%, 9.0%, and 3.8% and composite outcome of grade 3/4 IVH/death rates 52.2%, 33.6%, 15.6%, and 6.7% for the 22–23, 24–25, 26–27, and 28–29 weeks' GA groups, respectively. These

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Correspondence to:
Prakesh S. Shah, prakeshkumar.shah@sinaihealth.ca

inter-network variations were greater at lower GA. In epoch comparisons, almost all networks showed significant decreases in GA specific composite outcome rates, particularly in the 26–27 week' GA group. Japan and Canada demonstrated significant decreases in each GA group while Spain demonstrated significant decreases in each GA group except for 22–23 weeks' gestation. ***Conclusions:*** Rates of grade 3/4 IVH and composite outcome rates varied internationally and have decreased over time. Identification of the driving factors behind variations may allow for opportunities for practice review and improvement.

Introduction

Increasing rates of preterm births and neonatal survival increases rates of severe gestation-related morbidities such as intraventricular hemorrhage (IVH) [1]. The pathophysiology of IVH is theorized to be due to a combination of physiological and environmental factors [2, 3]. Prematurity exacerbates this risk due to greater vulnerability and instability of the microvasculature in the germinal matrix [4]. Risk factors for IVH include lower GA, male sex, low Apgar scores, postnatal transfer, outborn status and other comorbidities [5, 6]. The incidence of IVH is inversely related to GA and birthweight [7, 8]. Antenatal corticosteroid is a known significant protective factor [9, 10]. IVH is a common and significant morbidity in preterm infants and a major prognostic indicator for adverse neurodevelopmental outcomes, particularly post-hemorrhagic hydrocephalus and cerebral palsy [11, 12].

The incidence of IVH has been reported to be decreasing since the 1980s; though becoming more stagnant in recent times [7, 8]. It has been reported that significant variation may exist between countries regarding the incidence and severity of IVH [7, 8, 13]. However, the reasons for this variation are not well understood, especially with little evidence in relation to how the lowest gestational ages (GAs) impact these rates. Exploring GA-specific IVH rates in relation to survival could be useful to better understand international variations.

Methods

Data Source

Data were extracted from the combined dataset of the International Network for Evaluation of Outcomes in neonates (iNeo). The iNeo collaboration was established in 2013 to compare international neonatal outcomes in high-income countries. Included networks were: Australia and New Zealand (ANZNN), Canada (CNN), Finland (FinMBR), Israel (INN), Japan (NRNJ), Spain (SEN1500), Sweden (SNQ), Switzerland (SwissNEONET), Tuscany (Italy) (TuscNN), and the United Kingdom (UKNC). The iNeo Network provide a platform for comparative evaluation of outcomes of very preterm neonates to generate evidence for outcome improvements. All participating networks have obtained ethics/regulatory approval or the equivalent from their local granting agencies to allow for de-identified data to be sent to the iNeo Coordinating Centre. The Coordinating Centre has Research Ethics Board approval for the development, compilation, and hosting of the iNeo dataset, and all networks have signed data transfer agreements with the iNeo Coordinating Centre. Description and development of harmonized dataset is published previously [14].

Population

Infants reported by 10 neonatal networks who were <30 weeks' gestation and were admitted into any of the contributing neonatal units, between January 2007 and December 2019 were included in analysis. Liveborn neonates who were not offered intensive care on admission or those born with serious major congenital anomalies were excluded. Neonates who did not receive cranial ultrasonography were also excluded from analysis. IVH grades were harmonized and classified according to the Papile grading system where grade 3 defined as ventricles distended or enlarged by blood and grade 4 as cerebral parenchymal hemorrhage or hemorrhagic infarction. IVH were categorized to the highest unilateral or bilateral grade.

Outcomes

The co-primary outcomes were gestation specific grade 3 or 4 IVH rates and composite adverse outcomes of grade 3 or 4 IVH or death categorized by GA subgroups of 2-week intervals (22–23, 24–25, 26–27, and 28–29 weeks). Rates of each network were compared in 3 epochs: 2007–2011, 2012–2015, and 2016–2019 to determine trends over time.

Statistical Analysis

Data were reported as a median (quartiles) or as a percentage for categorical variables where appropriate. Significance was set at $p < 0.05$. Outcomes were analyzed as a total population and by network, stratified by GA at birth.

Multivariate logistic regression analysis and risk-adjusted standardized ratios were applied to analyze

Table 1. Maternal and perinatal characteristics of iNEO study infants (2007–2019) among 10 neonatal networks

	Eligible infants with U/S scans	Maternal hypertension	Antenatal steroids	Caesarean section	Outborn	Multiple gestation
ANZNN	24,850	3,839 (15.4)	22,410 (90.2)	15,049 (60.5)	3,354 (13.5)	6,684 (26.9)
CNN	24,172	3,922 (16.2)	20,968 (86.7)	14,392 (59.5)	3,955 (16.4)	6,591 (27.3)
FinMBR	2,784	170 (6.1)	2,652 (95.3)	1,703 (61.2)	106 (3.8)	786 (28.2)
INN	9,574	1,221 (12.8)	7,683 (80.2)	6,795 (71.0)	81 (0.8)	3,659 (38.2)
NRNJ	32,941	4,820 (14.6)	19,286 (58.5)	25,099 (76.2)	1,901 (5.8)	6,665 (20.2)
SEN1500	17,144	2,498 (14.6)	13,402 (78.2)	11,055 (64.5)	1,010 (5.9)	6,174 (36.0)
SNQ	6,806	994 (14.6)	5,733 (84.2)	4,411 (64.8)	730 (10.7)	1,794 (26.4)
SwissNEONET	5,362	NA	4,903 (91.4)	4,315 (80.5)	277 (5.2)	1,693 (31.6)
TuscNN	1,547	268 (17.3)	1,335 (86.3)	1,038 (67.1)	183 (11.8)	496 (32.1)
UKNC	40,149	4,273 (10.6)	34,991 (87.2)	19,440 (48.4)	NA	10,185 (25.4)
All	16,5329	22,005 (13.3)	133,363 (80.7)	103,297 (62.5)	11,597 (7.0)	58,788 (35.6)

Data presented as *n*/*N* (%) unless otherwise stated. ANZNN, Australia and New Zealand Neonatal Network; CNN, Canadian Neonatal Network; FinMBR, Finnish Medical Birth Record; iNEO, International Network for Evaluation of Outcomes of Neonates; INN, Israel Neonatal Network; NRNJ, Neonatal Research Network Japan; SEN1500, Socieda espanoloa de Neonataologia; SNQ, Swedish Neonatal Quality Registry; SwissNEONET, Switzerland Neonatal Network; TuscNN, Tuscany Neonatal Network; UKNC, United Kingdom Neonatal Collaborative.

differences in outcomes by network across epochs. GA specific odds ratio trends comparing grade 3 or 4 IVH/death across the networks were analyzed. Characteristics included in the adjustment were birthweight, sex, multiple pregnancies and outborn status. Harmonization and analysis of data sets were conducted by a statistician based at iNeo coordination Center at Mount Sinai Hospital, Toronto.

Results

A total of 172,701 infants with no major congenital abnormalities were eligible for the study. Of these, 3, 228 infants died prior to cranial ultrasound and 4, 144 infants survived without having a head ultrasound reported. The percentage of infants excluded due to the absence of head ultrasound data was 4.3% among all networks (online suppl. Table 1; for all online suppl. material, see https://doi.org/10.1159/000546714; categorized to those who died or survived without validated ultrasound). A total of 165, 329 infants with head ultrasound scans were included in the study.

Maternal, perinatal, and neonatal characteristics are reported in Table 1. Most infants (62.5%) were born by Caesarean section (ranging from 48.4% in UK to 80.5% in Switzerland). Antenatal steroid use varied from 58.5% in Japan to 95.4% in Finland. At least one-fifth of study infants pertained to multiple gestations (20.2% in Japan to 38.2% in Israel). Mothers with hypertension in pregnancy varied (6.1% in Finland to 17.3% in Italy). Overall, less than 10% of the study infants were outborn (0.8% in Israel to 16.4% in Canada).

The median GA was 27 (quartiles 26, 28) weeks and the median birthweight was 950 g (quartiles 750, 1,174). Japan and Sweden had the largest proportion of infants in the 22–23 week' GA group at 10.3% and 8.9% of their total study population, respectively. In all networks, the proportion of infants that were male, small for GA or had low Apgar scores (5 min Apgar score <3) did not differ significantly between networks. Surfactant use varied between networks and ranged from 63.2% in Sweden to 82.8% in Finland. Rates of intubation at delivery also varied from 37.7% in Canada to 76.6% in Japan (Table 2). In-hospital death by all causes was overall 11.7%, ranging from 6.8% in Sweden to 18.5% in Spain.

The overall rate of grade 3 or 4 IVH in the cohort was 9.6%, from 6.4% in Japan to 16.1% in Israel. This rate was higher in the 22–23 week' GA group at 25.8% and decreased to 18.6%, 9.0%, and 3.8% in the 24–25 weeks, 26–27 weeks, and 28–29 weeks GA groups, respectively. There were substantial variations of grade 3 or 4 IVH by

Table 2. Neonatal characteristics of iNEO study infants (2007–2019) among 10 neonatal networks

	Total eligible infants	Mean GA weeks (SD)	Mean BW gram (SD)	Male	SGA <10th centile	5 min APGAR <3	Surfactant treatment	Intubation at delivery
ANZNN	24,850	26.9 (1.7)	1,012 (286)	13,527 (54.4)	2,283 (9.2)	607 (2.4)	18,422 (74.1)	13,331 (53.6)
CNN	24,172	26.8 (1.8)	1,002 (289)	13,187 (54.6)	1,972 (8.2)	1,156 (4.8)	15,728 (65.1)	9,119 (37.7)
FinMBR	2,784	26.8 (1.9)	991 (300)	1,492 (53.6)	312 (11.2)	163 (5.9)	2,304 (82.8)	1,569 (56.4)
INN	9,574	27.0 (1.7)	975 (251)	5,169 (54.0)	787 (8.2)	167 (1.7)	7,030 (73.4)	4,727 (49.5)
NRNJ	32,941	26.4 (2.0)	886 (277)	17,522 (53.2)	4,431 (13.5)	1,606 (4.9)	25,128 (77.2)	25,249 (76.6)
SEN1500	17,144	27.0 (1.7)	980 (288)	9,129 (53.2)	2,028 (11.8)	268 (1.6)	11,586 (67.6)	8,090 (47.2)
SNQ	6,806	26.6 (2.0)	976 (311)	3,740 (55.0)	686 (10.1)	317 (4.7)	4,300 (63.2)	2,651 (39.0)
SwissNEONET	5,362	27.0 (1.7)	971 (278)	2,852 (53.2)	527 (9.8)	192 (3.6)	3,565 (67.7)	2,718 (50.7)
TuscNN	1,547	26.8 (1.9)	943 (293)	809 (52.3)	141 (9.1)	19 (1.2)	1,257 (81.3)	715 (46.2)
UKNC	40,149	26.8 (1.8)	987 (236)	21,148 (52.7)	5,636 (14.0)	988 (2.5)	30,802 (76.7)	27,492 (68.5)
All	165,329	26.8 (1.8)	972 (235)	88,575 (53.6)	18,803 (11.4)	5,483 (3.3)	120,122 (72.7)	95,661 (57.9)

Data presented as *n*/*N* (%) unless otherwise stated. Eligible infants were those with a head U/S scan. APGAR, APGAR Score; ANZNN, Australia and New Zealand Neonatal Network; BW, birthweight CNN, Canadian Neonatal Network; FinMBR, Finnish Medical Birth Record; GA, gestational age iNEO, International Network for Evaluation of Outcomes of Neonates; INN, Israel Neonatal Network; NRNJ, Neonatal Research Network Japan; SEN1500, Socieda espanoloa de Neonataologia; SGA, Small for gestational age; SNQ, Swedish Neonatal Quality Registry; SwissNEONET, Switzerland Neonatal Network; TuscNN, Tuscany Neonatal Network; UKNC, United Kingdom Neonatal Collaborative.

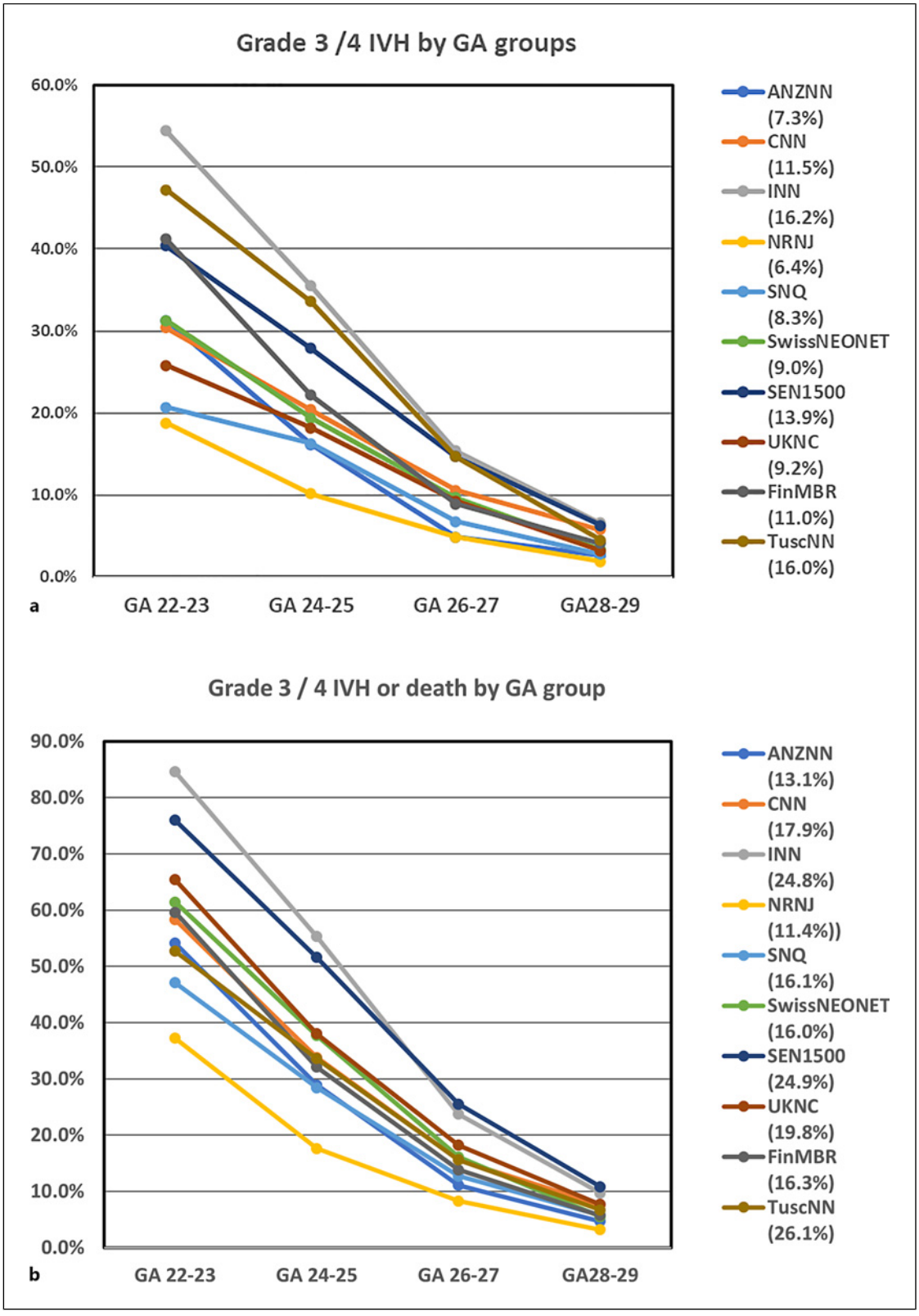
gestation groups among the 10 networks. The ratios of IVH grade 3 to grade 4 were similar across all networks. The overall iNeo grade 3 rate is 3.7%, which is on average 38% of the overall grade 3/4 rate of 9.6% (online suppl. Table 2).

Figure 1a shows that grade 3 or 4 IVH rates varied between networks from 6.4% of included infants in Japan to 16.1% in Israel. There was an inverse relationship between lower GA and higher rates of grade 3 or 4 IVH observed in all networks. Greater variation between networks existed in the lower GA groups and it reduced with increasing GA. The composite outcome of grade 3 or 4 IVH or death, with an average rate of 17.4%, similarly decreased as GA group increased in each network (shown in Fig. 1b). Overall, it ranged from 11.4% in Japan to 26.1% in Tuscany, Italy. The gestation specific composite outcome variations narrowed as gestation increased. Their corresponding details of gestation specific outcomes rates for the 10 networks are detailed in online supplementary Table 2.

Figure 2a showed a significant reduction of grade 3 or 4 IVH in the 3 Epoch comparisons 2007–2011, 2012–2015, and 2016–2019, only in Canada, Japan, and Israel, but an increased crude rate in the UK. Conversely, reduction of death was seen in almost all networks except in Sweden that had a low death rate (shown in Fig. 2b). While there were little changes in the perinatal characteristics across all 3 epochs (online suppl. Table 3), there was an overall increase in the number of 22–23 weeks gestation infants and a reduced outborn status in almost all networks. The crude gestation-specify IVH and death rates are summarized in online supplementary Table 4. The risk adjusted odds of grade 3 or 4 IVH or death for each network decreased over time in the 3 Epoch comparisons (Table 3). In particular, the 26–27 week' GA group showed statistically significant improvements in most networks. Japan and Canada demonstrated significant decreases in each GA group while Spain demonstrated significant decreases in each GA group except for 22–23 weeks' gestation. UK has also shown an overall significant decreased in adjusted odds, particularly in the 22-23- and 24–25-week gestation groups.

Discussion

We identified significant variation in grade 3 or 4 IVH rates and composite outcome rates of grade 3 or 4 IVH or death between 10 international neonatal networks,



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despite similar population characteristics. Previous studies regarding grade 3 or 4 IVH generally focus on singular country's outcomes, stratified by other measures such as birthweight [15]. Previous meta-analysis has reported on IVH variation between different countries, with the range of grade 3 or 4 IVH rate between 6 and 22% [7, 8]. Reports from the USA predominate the amalgamated study data and high heterogeneity in the included population characteristics and time period amongst studies from other countries limits interpretations [7, 8]. Our study fills a data gap by comparing IVH rates internationally with harmonized definitions. The large sample size allows for stratification of outcomes by GA. Rates of grade 3 or 4 IVH were higher at lower GA across all networks which reaffirms low GA as a significant risk factor for all IVH [6, 8].

In a meta-analysis of 2010–2020 publications, Lai et al. [8] reported the international incidence of grade 3 or 4 IVH of 23.7% for <25 weeks' GA, 15% for <28 weeks' GA, 4.6% for 28–31 weeks' GA, 3.3% for 32–33 weeks and 1.8% for 34–36 weeks' GA. Our study builds upon these data by further refining the data into smaller GA groups. For example, in ANZNN the rate of IVH grade IV in all <30 weeks' GA infants (as typically reported) was 5%, masked by the large proportion of higher gestation infants. Indeed, this rate was 23.8% in the 22–23 weeks' GA group and 11.8%, 3.9%, and 1.4% in the 24–25 weeks, 26–27 weeks, and 28–29 weeks' GA groups, respectively.

The difference in IVH incidence between networks was wider in the younger GA groups and became narrower in the higher GA group. The composite outcome of grade 3 or 4 IVH or death exhibited a parallel variation. Similar variations in survival rates of 24–29 weeks' GA amongst iNeo member networks were previously reported [16]. By analyzing IVH rates by specific GA groups, there is a clearer understanding of trends and rates at specific GAs which could be beneficial for parental counseling, education, and benchmarking purposes.

The variations in IVH cannot be easily explained by the differences in perinatal characteristic data available for analysis such as antenatal steroid and outborn status. Japan had the lowest (6.4%) IVH grade 3/4 rate (outborn rate 5.8%, antenatal steroid 58%, surfactant treatment rate 78%) and Israel had the highest (16%) rate (outborn rate 0.8%, antenatal steroid 80%, surfactant treatment 73%). Of note, Japan has long been proactive in caring for less than 24-week gestation infants and has developed some unique clinical management [17]. Antenatal steroid use in Japan has increased from 50% in Epoch 1–68% in Epoch 3 (online suppl. Table 3) and in Israel from 75% to 87%.

The variations in IVH rates and other outcomes between networks [16, 18, 19] could be related to many differences in health systems, infrastructure, staffing resources, clinician and community attitudes toward redirection of care [20] and clinical practice differences [16, 17]. Canada and ANZNN having the geographic similarity of a vast country had the highest outborn rates. Supported by efficient neonatal retrieval systems [21], both had very low IVH rates.

The current literature suggests that severe IVH rates and mortality are decreasing [6, 13, 22]. We found overall reductions in the rates of severe IVH as well as death of all causes from 2007 to 2019 in <30 weeks gestation infants. When adjusted for multiple factors, an overall reduction in IVH grade III/IV or death was observed in each network. Japan observed statistically significant reductions in all GA groups while Canada and Spain had statistically significant reductions in all GA groups except for 22–23 weeks' GA. Interestingly, the 26–27 weeks' GA group particularly experienced a significant reduction in most networks. This may partly relate to the combination of a consistent larger magnitude of improvement in this gestation range with an adequate sample size in achieving statistical significance. Only two networks reported significant improvements in the 22–23 weeks' GA group, the UK and Japan, both of which had a very large sample size.

Differences in the clinical practices toward considering redirection of care between networks could contribute to the variation in grade 3 or 4 IVH or death rates observed in this study. Helenius et al. [20] identified that ANZNN had the highest inclination toward offering redirection of care while Tuscany, Spain, and Israel had lower rates. Obviously, future studies of neurodevelopmental outcomes of these infants, particularly those survived with grade 3 or 4, could identify whether variation in outcomes among networks is consequent to redirection and care practices.

Fig. 1. Variation in IVH rates by GA groups across 10 neonatal networks. **a** Rates of IVH III/IV by GA groups with mean rate for each network listed in legend side bar. **b** Rates of IVH III and IV/death by GA groups with mean rate for each network listed in legend side bar. ANZNN, Australia and New Zealand Neonatal Network; BW, birthweight; CNN, Canadian Neonatal Network; FinMBR, Finnish Medical Birth Record; INN, Israel Neonatal Network; NRNJ, Neonatal Research Network Japan; SEN1500, Socieda espanoloa de Neonataologia (Spain); SNQ, Swedish Neonatal Quality Registry; SwissNEONET, Switzerland Neonatal Network; TuscNN, Tuscany Neonatal Network; UKNC, United Kingdom Neonatal Collaborative.

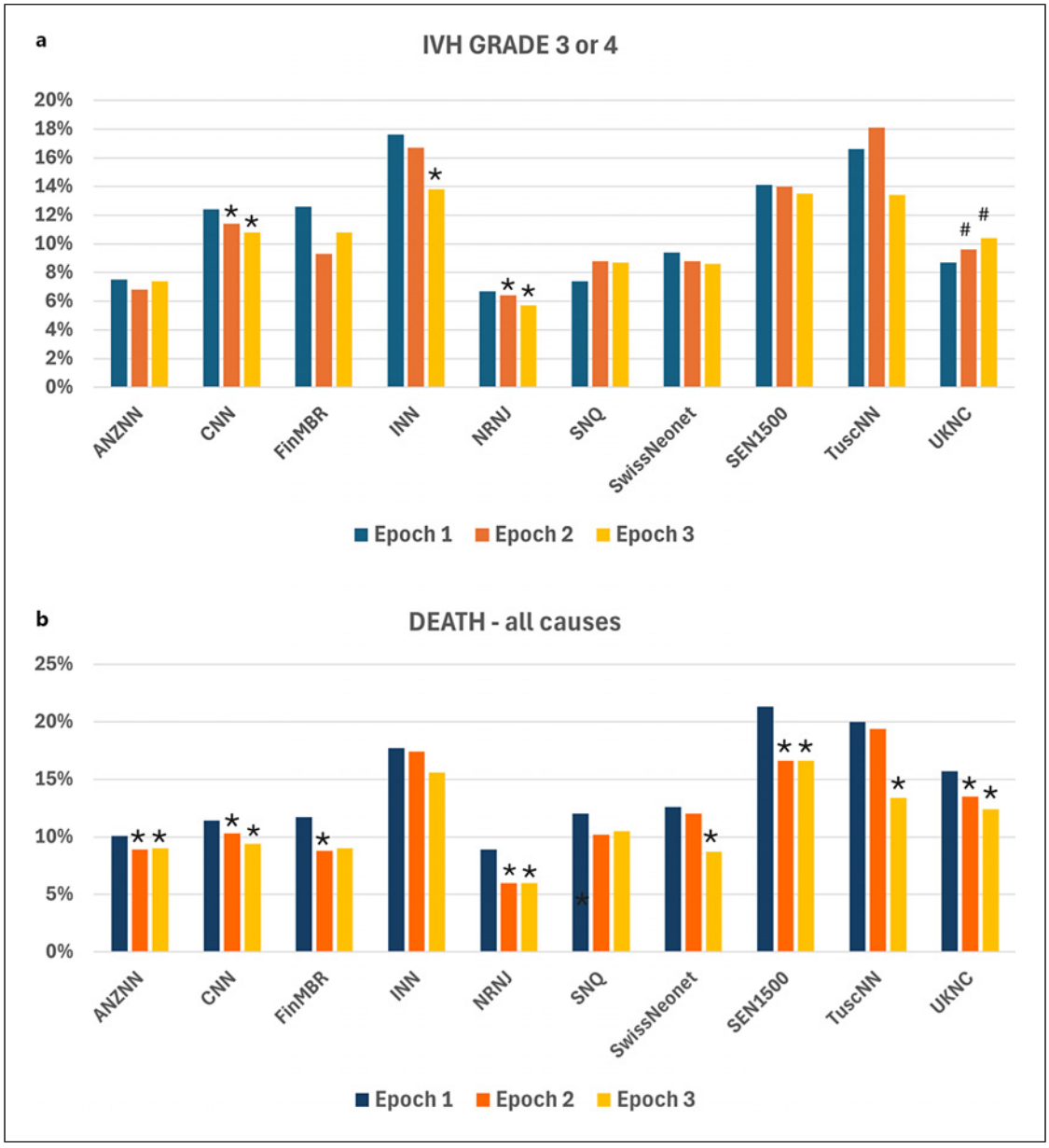

Fig. 2. Trend of changes in IVH and mortality rates by GA groups across 3 epochs in the 10 neonatal networks (Epoch 1 2007–2011; Epoch 2 2012–2015; Epoch 3 2016–2019). **a** Rate of grade 3 or grade 4 across the 3 epochs. **b** Rate of death of all causes across the 3 epochs. Compared with Epoch 1; * denotes reduction of crude rate $p < 0.05$; # increase in crude rate $p < 0.05$. ANZNN, Australia and New Zealand Neonatal Network; BW, birthweight; CNN, Canadian Neonatal Network; FinMBR, Finnish Medical Birth Record; INN, Israel Neonatal Network; NRNJ, Neonatal Research Network Japan; SEN1500, Socieda espanoloa de Neonataologia (Spain); SNQ, Swedish Neonatal Quality Registry; SwissNEONET, Switzerland Neonatal Network; TuscNN, Tuscany Neonatal Network; UKNC, United Kingdom Neonatal Collaborative.

While this is the largest study to investigate GA specific IVH rates in 11 similar high-income countries, there are some limitations. Infants that did not have head ultrasounds performed were excluded, accounting for 4.3% of the total population. Among the 1.9% who died without validated reports, most (2,243/3,228; 70%) were born before 26 weeks GA. It is likely due to very early death. However, 2.4% of the survivors did not have routine validated cranial ultrasound report for data extraction. Of note, 80% (3,390/4,144) of these survivors without

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Table 3. GA specific adjusted OR and trend comparison of grade 3/4 IVH or death across 10 neonatal networks and 3 epochs 2007–2011, 2012–2015, and 2016–2019

GA	ANZNN			CNN			INN			NRNJ			SNQ		
	EPOCH 2v1 (95% CI)	EPOCH 3v1 (95% CI)	*p* value for Trend	EPOCH 2v1 (95% CI)	EPOCH 3v1 (95% CI)	*p* value for Trend	EPOCH 2v1 (95% CI)	EPOCH 3v1 (95% CI)	*p* value for Trend	EPOCH 2v1 (95% CI)	EPOCH 3v1 (95% CI)	*p* value for Trend	EPOCH 2v1 (95% CI)	EPOCH 3v1 (95% CI)	*p* value for Trend
22–23 weeks	1.11 (0.76–1.61)	0.92 (0.79–1.07)	0.60	0.84 (0.59–1.21)	0.79 (0.69–0.91)	0.07	0.66 (0.26–1.66)	1.05 (0.84–1.33)	0.26	0.67 (0.56–0.79)	0.73 (0.64–0.84)	<0.01	0.93 (0.62–1.38)	0.66 (0.49–0.89)	0.21
24–25 weeks	0.92 (0.79–1.07)	0.90 (0.78–1.05)	0.18	0.79 (0.69–0.91)	0.65 (0.56–0.74)	<0.01	1.05 (0.84–1.33)	0.87 (0.69–1.09)	0.25	0.73 (0.64–0.84)	0.72 (0.62–0.84)	<0.01	0.66 (0.49–0.89)	0.91 (0.69–1.21)	0.53
26–27 weeks	0.75 (0.63–0.89)	0.71 (0.60–0.85)	<0.01	0.84 (0.72–0.97)	0.71 (0.61–0.83)	<0.01	0.89 (0.73–1.09)	0.71 (0.57–0.87)	<0.01	0.84 (0.71–0.99)	0.75 (0.62–0.90)	<0.01	1.25 (0.91–1.72)	0.97 (0.70–1.37)	0.93
28–29 weeks	0.93 (0.76–1.14)	0.80 (0.64–1.00)	0.05	0.82 (0.69–0.97)	0.71 (0.59–0.85)	<0.01	0.89 (0.70–1.13)	0.80 (0.63–1.02)	0.07	0.80 (0.64–1.01)	0.60 (0.46–0.79)	<0.01	0.92 (0.63–1.35)	0.81 (0.54–1.21)	0.30
ALL	0.88 (0.80–0.97)	0.90 (0.82–0.99)	0.02	0.85 (0.79–0.93)	0.76 (0.70–0.82)	<0.01	0.94 (0.83–1.06)	0.81 (0.72–0.92)	<0.01	0.75 (0.69–0.82)	0.69 (0.63–0.75)	<0.01	0.91 (0.77–1.08)	0.91 (0.77–1.07)	0.24
GA	SwissNEONET			SEN1500			UKNC			FinMBR			TuscNN		
	EPOCH 2v1 (95% CI)	EPOCH 3v1 (95% CI)	*p* value for Trend	EPOCH 2v1 (95% CI)	EPOCH 3v1 (95% CI)	*p* value for Trend	EPOCH 2v1 (95% CI)	EPOCH 3v1 (95% CI)	*p* value for Trend	EPOCH 2v1 (95% CI)	EPOCH 3v1 (95% CI)	*p* value for Trend	EPOCH 2v1 (95% CI)	EPOCH 3v1 (95% CI)	*p* value for Trend
22–23 weeks	0.45 (0.08–2.37)	0.79 (0.58–1.08)	0.62	0.89 (0.46–1.7)	0.90 (0.77–1.07)	0.10	0.79 (0.64–0.99)	0.86 (0.77–0.95)	0.01	0.84 (0.37–1.93)	0.60 (0.38–0.93)	0.48	0.92 (0.25–3.33)	1.11 (0.63–1.97)	0.10
24–25 weeks	0.79 (0.58–1.08)	0.48 (0.35–0.66)	<0.01	0.90 (0.77–1.07)	0.78 (0.65–0.92)	<0.01	0.86 (0.77–0.95)	0.91 (0.80–1.03)	0.05	0.60 (0.38–0.93)	0.73 (0.46–1.17)	0.10	1.11 (0.63–1.97)	1.10 (0.60–2.01)	0.75
26–27 weeks	0.82 (0.60–1.12)	0.79 (0.58–1.09)	0.14	0.74 (0.64–0.86)	0.69 (0.59–0.80)	<0.01	0.98 (0.88–1.09)	1.00 (0.88–1.14)	0.95	0.83 (0.53–1.31)	0.52 (0.31–0.88)	0.02	0.59 (0.34–1.04)	0.46 (0.26–0.81)	0.01
28–29 weeks	0.75 (0.50–1.12)	0.54 (0.35–0.83)	<0.01	0.75 (0.63–0.89)	0.8 (0.67–0.95)	<0.01	0.98 (0.86–1.11)	0.86 (0.74–1.01)	0.09	0.96 (0.55–1.67)	0.74 (0.39–1.41)	0.39	1.19 (0.61–2.33)	0.66 (0.31–1.4)	0.30
ALL	0.82 (0.69– 0.99)	0.67 (0.55–0.81)	<0.01	0.79 (0.72–0.86)	0.77 (0.70–0.84)	<0.01	0.94 (0.88–0.99)	0.92 (0.85–0.99)	0.01	0.81 (0.63–1.05)	0.76 (0.58–0.99)	0.03	0.94 (0.69–1.29)	0.64 (0.46–0.89)	0.01

ANZNN, Australia and New Zealand Neonatal Network; CI, confidence interval; CNN, Canadian Neonatal Network; FinMBR, Finnish Medical Birth Record; INN, Israel Neonatal Network; NRNJ, Neonatal Research Network Japan; OR, odds ratio; SEN1500, Socieda espanoloa de Neonataologia (Spain); SNQ, Swedish Neonatal Quality Registry; SwissNEONET, Switzerland Neonatal Network; TuscNN, Tuscany Neonatal Network; UKNC, United Kingdom Neonatal Collaboration. Data presented as adjusted OR (95% confidence intervals). *p* value for trend was determined by two-tailed test and result deemed significant when $p < 0.05$. ANZNN, Australia and New Zealand Neonatal Network; CI, confidence interval; CNN, Canadian Neonatal Network; FinMBR, Finnish Medical Birth Record; INN, Israel Neonatal Network; NRNJ, Neonatal Research Network Japan; OR, odds ratio; SEN1500, Socieda espanoloa de Neonataologia (Spain); SNQ, Swedish Neonatal Quality Registry; SwissNEONET, Switzerland Neonatal Network; TuscNN, Tuscany Neonatal Network; UKNC, United Kingdom Neonatal Collaboration.

validated ultrasound reports were born from 26 weeks GA and their likelihood of IVH grade 3/4 would be low. It is possible that some neonates who died in earlier period could have had major IVH, resulting in undercalculation of grade 3 or 4 IVH rates. Conversely, excluding those higher GA surviving infants without scans, may likely result in an overestimation of grade 3 or 4 IVH rates. Our results may also have been influenced by variation in ultrasound interpretation. Studies have shown variations in reporting, particularly in the low grade IVH and white matter injuries, but less so for the high IVH grades [23]. At a large neonatal network level, a multicentre independent blinded review found there was little variation in the reporting of IVH between the reviewers and the reports to ANZNN [24].

Conclusion

We identified GA specific variation in grade 3 or 4 IVH rates in 11 high-income countries. Substantial variation of grade 3 or 4 IVH or death among networks could be partly accounted for by the considerable difference in survival after severe IVH. There is a significant decrease in IVH and death rates in all networks during this study period. These data can act as a tool for benchmarking and further studies to evaluate differences in health system, infrastructure, resources, and clinical practices and to identify and benchmark clinical practices that are associated with lower rates of grade 3 or 4 IVH. Long-term neurodevelopmental outcome data are needed to quantify the impact of this observed variation of grade 3 or 4 IVH rates.

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List of contributing neonatal units and site investigators: Australian and New Zealand Neonatal Network (ANZNN): Kei Lui* Chair of ANZNN. Flinders Medical Centre, SA: Scott Morris. Gold Coast University Hospital, QLD: Peter Schmidt, Manbir Chauhan*. Blacktown District Hospital, NSW: Anjali Dhawan*. John Hunter Children's Hospital, NSW: Larissa Korostenski. King Edward Memorial and Perth Children's Hospitals, WA: Mary Sharp, Tobias Strunk*. Liverpool Hospital, NSW: Jacqueline Stack. Mater Mothers' Hospital, QLD: Pita Birch, Tori Oliver*. Neonatal Retrieval Emergency Service Southern Queensland, QLD: Lucy Cooke. Mercy Hospital for Women, VIC: Dan Casalaz and Jim Holberton*. Monash Medical Centre, VIC: Alice Stewart, Rod Hunt*, Kenneth Tan*. Nepean Hospital, NSW: Lyn Downe. Paediatric Infant Perinatal Emergency Retrieval (VIC): Michael Stewart. NSW Newborn and Paediatric Emergency Transport Service: Andrew Berry. Royal Children's Hospital, VIC: Leah Hickey. Royal Darwin Hospital, NT: Mantho Kgosiemang, Laura Prado*. Royal Hobart Hospital, Tasmania: Tony De Paoli, Naomi Spotswood*. Royal Hospital for Women, NSW: Srinivas Bolisetty, Kei Lui*. Royal North Shore Hospital, NSW: Eveline Staub. Royal Prince Alfred Hospital, NSW: Mark Greenhalgh. Royal Brisbane and Women's Hospital, QLD: Pieter Koorts. Royal Women's Hospital, VIC: Risha Bhatia. SAAS MedSTAR Emergency Medical Retrieval Services: Bron Hennebry. Sydney Children's Hospital, NSW: Hari Ravindranathan. The Canberra Hospital, ACT: Hazel Carlisle. The Children's Hospital at Westmead, NSW: Nadia Badawi, Himanshu Popat. The Townsville Hospital, QLD: Gary Alcock. Neonatal Emergency Transport Service of Western Australia: Jonathan Davis. Westmead Hospital, NSW: Melissa Luig*. Women's and Children's Hospital, SA: Michael Stark. Australian College of Neonatal Nurses: Margaret Broom*. National Perinatal Epidemiology and Statistics Unit, University of New South Wales: Georgina Chambers*. Consumer representative: Natalie Merida*. New Zealand: Christchurch Women's Hospital: Bronwyn Dixon. University of Otago, Christchurch: Brian Darlow. Dunedin Hospital: Jason Wister. Middlemore Hospital: Kristin O'Connor. Auckland City Hospital: Mariam Buksh, Malcolm Battin*. Waikato Hospital: Jutta van den Boom. Wellington Women's Hospital: Angelica Allermo-Fletcher, Helen Miller. Whangarei Hospital: David Barker*. Neonatal Nurses College Aotearoa: Claire Jacobs*. Singapore: Singapore General Hospital: Woei Bing Poon, Vijay R. Baral. KK Women's and Children's Hospital: Rajadurai V. Samuel, Mei Chien Chua. Hong Kong: Hong Kong Children's Hospital, Rosanna Wong, Prince of Wales Hospital: Simon Lam*. Queen Elizabeth Hospital: Kiu Lok Siu. Queen Mary Hospital: Mabel Wong, *denotes the ANZNN Executive Committee.

Canadian Neonatal Network (CNN): Marc Beltempo, MD (Director, Canadian Neonatal Network and Site Investigator), Montreal Children's Hospital at McGill University Health Centre, Montréal, Québec; Prakesh S. Shah, MD, MSc, Mount Sinai Hospital, Toronto, Ontario; Thevanisha Pillay, MD, Victoria General Hospital, Victoria, British Columbia; Jonathan Wong, MD, British Columbia Women's Hospital, Vancouver, British Columbia; Miroslav Stavel, MD, Royal Columbian Hospital, New Westminster, British Columbia; Rebecca Sherlock, MD, Surrey Memorial Hospital, Surrey, British Columbia; Ayman Abou Mehrem, MD, Foothills Medical Centre, Calgary, Alberta; Jennifer Toye, MD, and Joseph Ting, MD, Royal Alexandra Hospital and University of Alberta Hospital, Edmonton, Alberta; Carlos Fajardo, MD, Alberta Children's Hospital, Calgary, Alberta; Andrei Harabor, MD, Regina General Hospital, Regina, Saskatchewan; Lannae Strueby, MD, Jim Pattison Children's Hospital, Saskatoon, Saskatchewan; Mary Seshia, MBChB, and Deepak Louis, MD, Winnipeg Health Sciences Centre, Winnipeg, Manitoba; Chelsea Ruth, MD, and Ann Yi, MD, St. Boniface General Hospital, Winnipeg, Manitoba; Amit Mukerji, MD, Hamilton Health Sciences Centre, Hamilton, Ontario; Orlando Da Silva, MD, MSc, London Health Sciences Centre, London, Ontario; Sajit Augustine, MD, Windsor Regional Hospital, Windsor, Ontario; Kyong-Soon Lee, MD, MSc, Hospital for Sick Children, Toronto, Ontario; Eugene Ng, MD, Sunnybrook Health Sciences Centre, Toronto, Ontario; Brigitte Lemyre, MD, The Ottawa Hospital, Ottawa, Ontario; Brigitte Lemyre, MD, Children's Hospital of Eastern Ontario, Ottawa, Ontario; Faiza Khurshid, MD, Kingston General Hospital, Kingston, Ontario; Victoria Bizgu, MD, Jewish General

Hospital, Montréal, Québec; Keith Barrington, MBChB, Anie Lapointe, MD, and Guillaume Ethier, NNP, Hôpital Sainte-Justine, Montréal, Québec; Christine Drolet, MD, Centre Hospitalier Universitaire de Québec, Sainte Foy, Québec; Martine Claveau, MSc, LLM, NNP, Montreal Children's Hospital at McGill University Health Centre, Montréal, Québec; Marie St-Hilaire, MD, Hôpital Maisonneuve-Rosemont, Montréal, Québec; Valerie Bertelle, MD, and Edith Masse, MD, Centre Hospitalier Universitaire de Sherbrooke, Sherbrooke, Québec; Caio Barbosa de Oliveira, MD, Moncton Hospital, Moncton, New Brunswick; Hala Makary, MD, Dr. Everett Chalmers Hospital, Fredericton, New Brunswick; Gabriela de Carvalho Nunes, MD, and Wissam Alburaki, MD, Saint John Regional Hospital, Saint John, New Brunswick; Jo-Anna Hudson, MD, Janeway Children's Health and Rehabilitation Centre, St. John's, Newfoundland; Jehier Afifi, MB BCh, MSc, IWK Health Centre, Halifax, Nova Scotia; Andrzej Kajetanowicz, MD, Cape Breton Regional Hospital, Sydney, Nova Scotia; Bruno Piedboeuf, MD (Chairman, Canadian Neonatal Network), Centre Hospitalier Universitaire de Québec, Sainte Foy, Québec.

Finnish Medical Birth Register (FinMBR): Marjo Metsäranta, MD, Helsinki University Hospital, Helsinki; Liisa Lehtonen, MD, Turku University Hospital, Turku; Päivi Korhonen, MD, Tampere University Hospital, Tampere; Ulla Sankilampi, MD, Kuopio University Hospital, Kuopio; Timo Saarela, MD, Oulu University Hospital, Oulu.

Israel Neonatal Network (INN): Iris Morag, MD, Assaf Harofeh Medical Center, Tzrifin; Omer Globus MD, Assuta Hospital, Ashdod; Shmuel Zangen, MD, Barzilai Medical Center, Ashkelon; Tatyana Smolkin, MD, Baruch Padeh Medical Center, Poriya; Yaron Nave, MD, Bikur Cholim Hospital, Jerusalem; Arieh Riskin, MD, Bnai Zion Medical Center, Haifa; Karen Lavie-Nevo, MD, Carmel Medical Center, Haifa; Zipora Strauss, Chaim Sheba Medical Center, Ramat Gan; Clari Felszer, MD, Emek Medical Center, Afula; Hussam Omari, MD, French Saint Vincent de Paul Hospital, Nazareth; Smadar Even Tov-Friedman, MD, Hadassah University Hospital-Ein Karem, Jerusalem; Smadar Even Tov-Friedman, MD, Hadassah University Hospital-Har Hazofim, Jerusalem; Amit Hochberg, MD, Hillel Yaffe Medical Center, Hadera; Nizar Saad, MD, Holy Family (Italian) Hospital, Nazareth; Orna Flidel-Rimon, MD, Kaplan Medical Center, Rehovot; Aryeh Simmonds, MD, Laniado Hospital, Netanya; Bernard Barzilay, MD, Mayanei Hayeshua Medical Center, Bnei Brak; Sofia Bauer, MD, Meir Medical Center, Kfar Saba; Amir Kugelman, MD, Rambam Medical Center; Eric Shinwell, MD, Rivka Ziv Medical Center, Safed; Gil Klinger, MD, Schneider Children's Medical Center of Israel, Rabin Medical Center (Beilinson Campus), Petah Tikva; Yousif Nijim, MD, Scottish (EMMS) Hospital, Nazareth; Yaron Nave, MD, Shaare-Zedek Medical Center, Jerusalem; Eilon Shani, MD, Soroka Medical Center, Beersheba; Dror Mandel, MD, Sourasky Medical Center, Tel Aviv; Vered Fleisher-Sheffer, MD, Western Galilee Medical Center, Nahariya; Anat Oron, MD, Wolfson Medical Center, Holon; Lev Bakhrakh, MD, Yoseftal Hospital, Eilat.

Neonatal Research Network of Japan (NRNJ): Yukiteru Tachibana, MD, Abashiri Kosei Hospital, Abashiri, Hokkaido; Ayumu Noro, MD, JCHO Hokkaido Hospital, Sapporo, Hokkaido; Toshihiko Mori, MD, NTT East Sapporo Hospital, Sapporo, Hokkaido; Ken Nagaya, MD, Asahikawa Medical University, Asahikawa, Hokkaido; Masaru Shirai, MD, Asahikawa Kosei Hospital, Asahikawa, Hokkaido; Toru Ishioka, MD, Engaru Kosei Hospital, Engaru, Hokkaido; Toshiya Saito, MD, Iwamizawa City Hospital, Iwamizawa, Hokkaido; Yosuke Kaneshi, MD, Kushiro Red Cross Hospital, Kushiro, Hokkaido; Masaki Kobayashi, MD, Sapporo Prefecture Medical University, Sapporo, Hokkaido; Nobuko Shiono, MD, Sapporo City Hospital, Sapporo, Hokkaido; Nobuhiro Takahashi, MD, Tenshi Hospital, Sapporo, Hokkaido; Yusuke Ohkado, MD, Tomakomai Chity Hospital, Tomakomai, Hokkaido; Tatsuro Satomi, MD, Nikko Kinen Hospital, Sapporo, Hokkaido; Mika Nakajima, MD, Hakodate Central Hospital, Hakodate, Hokkaido; Eiki Nakamura, MD, Nayoro City Hospital, Nayoro, Hokkaido; Tomofumi Ikeda, MD, Aomori Prefecture Central Hospital, Aomori, Aomori; Genichiro Sotodate, MD, Iwate Medical University, Morioka, Iwate; Mari Ishii, MD, Iwate Prefecture Kuji Hospital, Kuji, Iwate; Toru Huchimukai, MD, Iwate Prefecture Ohfunato Hospital, Ohfunato, Iwate; Takahide Hosokawa, MD, Iwate Prefecture Ninohe Hospital, Ninohe, Iwate; Rikio Suzuki, MD, Sendai City Hospital, Sendai, Miyagi; Masatoshi Sanjo, MD, Sendai Red Cross Hospital, Sendai, Miyagi; Michiya Kudo, MD, Osaki City Hospital, Osaki, Iwate; Takushi Hanita, MD, Tohoku University, Sendai, Miyagi; Hirokazu Arai, MD, Akita Red Cross Hospital, Akita, Akita; Masato Ito, MD, Akita University, Akita, Akita; Satoshi Niwa, MD, Odate City Hospital, Odate, Akita; Masanari Kawamura, MD, Hiraka General Hospital, Hiraka, Akita; Satoshi Watanabe, MD, Yamagata Prefecture Central Hospital, Yamagata, Yamagata; Yousuke Sudo, MD, Yamagata University, Yamagata, Yamagata; Hiroshi Yoshida, MD, Tsuruoka City Shonai Hospital, Tsuruoka, Yamagata; Tsutomu Ishii, MD, National Fukushima Hospital, Sukagawa, Fukushima; Takashi Imamura, MD, Takeda General Hospital, Aizuwakamatsu, Fukusima; Maki Sato, MD, Fukusima Prefecture Medical University, Fukushima, Fukushima; Yoshiya Yukitake, MD, Ibaraki Children's Hospital, Mito, Ibaraki; Yayoi Miyazono, MD, Tsukuba University, Tsukuba, Ibaraki; Goro Asada, MD, Tsuchiura Kyodo Hospital, Tsuchiura, Ibaraki; Yumi Kono, MD, Jichi Medical University, Oyama, Tochigi; Yasuaki Kobayashi, MD, Ashikaga Red Cross Hospital, Ashikaga, Tochigi; Hiroshi Suzuki, MD, Dokkyo Medical University, Shimotsugagun, Tochigi; Yasushi Oki, MD, Kiryu Kosei General Hospital, Kiryu, Gunma; Kenji Ichinomiya, MD, Gunma Prefecture Children's Hospital, Maebashi, Gunma; Toru Fujiu, MD, Gunma University, Maebashi, Gunma; Hideaki Fukushima, MD, Ohta General Hospital, Ota, Gunma; Hideshi Fujinaga, MD, National Nishisaitama Central Hospital, Tokorozawa, Saitama; Tetsuya Kunikata, MD, Saitama Medical University, Iruma, Saitama; Fumihiko Namba, MD, Saitama Medical University Medical Center, Kawagoe, Satitama; Masaki Shimizu, MD, Saitama Prefecture Children's Hospital, Omiya, Saitama; Shigeharu Hosono, MD, Jichi Medical University Saitama Medical Center, Omiya, Saitama; Chika Morioka, MD, Kawaguchi City Medical Center, Kawaguchi, Saitama; Motoichiro Sakurai, MD, Kameda General Hospital, Kameda, Chiba; Hiroshi Matsumoto, MD, Asahi Central Hospital, Asahi, Chiba; Naoto Nishizaki, MD, Juntendo University Urayasu Hospital, Urayasu, Chiba; Satoshi Toishi, MD, Narita Red Cross Hospital, Narita, Chiba; Harumi Otsuka, MD, Chiba City Kaihin Hospital, Chiba, Chiba; Masahiko Sato, MD, Tokyo Women's Medical University Yachiyo Medical Center, Yachiyo, Chiba; Kenichiro Hirakawa, MD, Aiiku Hospital, Minato, Tokyo; Kenichiro Hosoi, MD, Kyorin Univesity, Mitaka, Tokyo; Keiji Goishi, MD, National International Medical Center, Shinjuku, Tokyo; Yuji Ito, MD,

National Center for Child Health and Development, Setagaya, Tokyo; Kyone Ko, MD, Sanikukai Hospital, Sumida, Tokyo; Hiromichi Shoji, MD, Juntendo University, Bunkyo, Tokyo; Atsuo Miyazawa, MD, Showa University, Shinagawa, Tokyo; Yuko Nagaoki, MD, Saint Luku Hospital, Chuo, Tokyo; Naoki Ito, MD, Teikyo University, Itabashi, Tokyo; Ken Masunaga, MD, Tokyo Metropolitan Otsuka Hospital, Toshima, Tokyo; Reiko Kushima, MD, Tokyo Metropolitan Bokuto Hospital, Sumida, Tokyo; Sakae Kumasaka, MD, Tokyo Katsushika Red Cross Perinatal Center, Katsushika, Tokyo; Manabu Sugie, MD, Tokyo Medical and Dental University, Bunkyo, Tokyo; Daisuke Haruhara, MD, Tokyo Medical University, Shinjuku, Tokyo; Masahiro Kobayashi, MD, Tokyo Jikei Medical University, Minatoku, Tokyo; Satsuki Kakiuchi, MD, Tokyo Women's Medical University, Shinjuku, Tokyo; Riki Nishimura, MD, Tokyo University, Bunkyo, Tokyo; Kaoru Okazaki, MD, Tokyo Metropolitan Children's Medical Center, Fuchu, Tokyo; Hitoshi Yoda, MD, Toho University, Ota, Tokyo; Atsushi Nakao, MD, Japan Red Cross Hospital, Shibuya, Tokyo; Ichiro Morioka, MD, Nihon University, Itabashi, Tokyo; Daisuke Ogata, MD, Yokohama City Hospital, Yokohama, Kanagawa; Fumihiko Ishida, MD, Yokohama City University Medical Center, Yokohama, Kanagawa; Daisuke Nishi, MD, Yokohama Rosai Hospital, Yokohama, Kanagawa; Miho Sato, MD, Yokosuka Kyosai Hospital, Yokosuka, Kanagawa; Ayako Fukuyama, MD, Yokohama Medical Center, Yokohama, Kanagawa; Kuriko Nakamura, MD, Saiseikai Eastern Yokohama Hospital, Yokohama, Kanagawa; Kanji Ogo, MD, Odawara City Hospital, Odawara, Kanagawa; Masahiko Murase, MD, Showa University Northern Yokohama Hospital, Yokohama, Kanagawa; Katsuaki Toyoshima, MD, Kanagawa Children's Medical Center, Yokohama, Kanagawa; Isamu Hokuto, MD, St. Marianna Medical University, Kawasaki, Kanagawa; Maha Suzuki, MD, St. Mariana Medical University Yokohama City Seibu Hospital, Yokohama, Kanagawa; Atsushi Uchiyama, MD, Tokai University, Isehara, Kanagawa; Yoshio Shima, MD, Nippon Medical School Musashi Kosugi Hospital, Kawasaki, Kanagawa; Hidehiko Nakanishi, MD, Kitasato University Hospital, Sagamihara, Kanagawa; Atsushi Nemoto, MD, Yamanashi Prefecture Central Hospital, Kofu, Yamanashi; Akira Shimazaki, MD, National Shinshu Ueda Medical Center, Ueda, Nagano; Tatsuya Yoda, MD, Saku General Hospital, Saku, Nagano; Yukihide Miyosawa, MD, Shinshu University, Matsumoto, Nagano; Takehiko Hiroma, MD, Nagano Children's Hospital, Azumino, Nagano; Yosuke Shima, MD, Iida City Hospital, Iida, Nagano; Gen Kuratsuji, MD, Niigata Central Hospital, Niigata, Niigata; Yoshihisa Nagayama, MD, Niigata City Hospital, Niigata, Niigata; Tohei Usuda, MD, Niigata University, Niigata, Niigata; Rei Kobayashi, MD, Nagaoka Red Cross Hospital, Nagaoka, Niigata; Hiroaki Imamura, MD, Koseiren Takaoka Hospital, Takaoka, Toyama; Takeshi Hutani, MD, Toyama Prefectural Central Hospital, Toyama, Toyama; Taketoshi Yoshida, MD, Toyama University, Toyama, Toyama; Azusa Kobayashi, MD, Kanazawa Medical University, Kanazawa, Kanazawa; Kazuhide Ohta, MD, Kanazawa Medical Center, Kanazawa, Kanazawa; Shuya Nagaoki, MD, Kanazawa University, Kanazawa, Ishikawa; Yasuhisa Ueno, MD, Ishikawa Prefectural Central Hospital, Kanazawa, Ishikawa; Toru Ando, MD, Tsuruga City Hospital, Tsuruga, Fukui; Ritsuyo Taguchi, MD, Fukui Prefectural Hospital, Fukui, Fukui; Takashi Okuno, MD, Fukui University, Fukui, Fukui; Hiroshi Yamamoto, MD, Gifu Prefectural Medical Center, Gifu, Gifu; Takeshi Arakawa, MD, Gifu Prefecture Tajimi Hospital, Tajimi, Gifu; Shinji Usui, MD, Takayama Red Cross Hospital, Takayama, Gifu; Yasushi Uchida, MD, National Nagara Medical Center, Nagara, Gifu; Takashi Tachibana, MD, Oogaki City Hospital, Oogaki, Gifu; Tokuso Murabayashi, MD, Numazu City Hospital, Numazu, Shizuoka; Tadayuki Kumagai, MD, Yaizu City Hospital, Yaizu, Shizuoka; Shigeru Oki, MD, Seirei Hamamatsu Hospital, Hamamatsu, Shizuoka; Reiji Nakano, MD, Shizuoka Children's Hospital, Shizuoka, Shizuoka; Taizo Ueno, MD, Shizuoka Saiseikai Hospital, Shizuoka, Shizuoka; Mitsuhiro Ito, MD, Fujieda City Hospital, Fujieda, Shizuoka; Masami Shirai, MD, Iwata City Hospital, Shizuoka, Shizuoka; Akira Oishi, MD, Hamamatsu Medical University, Hamamatsu, Shizuoka; Hikaru Yamamoto, MD, Toyota Memorial Hospital, Toyota, Aichi; Hiroshi Takeshita, MD, Aichi Medical University, Nagoya, Aichi; Yuichi Kato, MD, Anjokosei Hospital, Anjo, Aichi; Masashi Hayashi, MD, Okazaki City Hospital, Okazaki, Aichi; Kuniko Ieda, MD, Koritsu Tosei Hospital, Toyota, Aichi; Koji Takemoto, MD, Konankosei Hospital, Kona, Aichi; Takako Hirooka, MD, Komaki City Hospital, Komaki, Aichi; Masashi Miyata, MD, Fujita Medical University, Nagoya, Aichi; Makoto Ohshiro, MD, Japanese Red Cross Aichi Medical Center Nagoya Daiichi Hospital, Nagoya, Aichi; Masanori Kowaki, MD, Japanese Red Cross Aichi Medical Center Nagoya Daini Hospital, Nagoya, Aichi; Osamu Shinohara, MD, Handa City Hospital, Handa, Aichi; Yasunori Koyama, MD, Toyohashi City Hospital, Toyohashi, Aichi; Osuke Iwata, MD, Nogoya City University, Nagoya, Aichi; Takahiro Muramatsu, MD, Nagoya City Seibu Medical Cneter, Nagoya, Aichi; Akinobu Taniguchi, MD, Nagoya University, Nagoya, Aichi; Naoki Kamata, MD, Ise Red Cross Hospital, Ise, Mie; Hiroshi Uchizono, MD, National Mie Central Medical Center, Tsu, Mie; Kanemasa Maki, MD, Yokkaichi City Hospital, Yokkaichi, Mie; Takahide Yanagi, MD, Shiga Medical University, Otsu, Shiga; Kenji Nakamura, MD, Otsu Red Cross Hospital, Otsu, Shiga; Masahito Yamamoto, MD, Nagahama Red Cross Hospital, Nagahama, Shiga; Jitsuko Ohira, MD, Uji Tokushukai Hospital, Uji, Kyoto; Machiko Sawada, MD, Kyoto Katsura Hospital, Kyoto, Kyoto; Kozue Shiomi, MD, Kyoto City Hospital, Kyoto, Kyoto; Ryosuke Araki, MD, Kyoto University, Kyoto, Kyoto; Daisuke Kinoshita, MD, Kyoto Red Cross Daiichi Hospital, Kyoto, Kyoto; Ryuji Hasegawa, MD, Kyoto Prefecture Medical University, Kyoto, Kyoto; Akira Nishimura, MD, Kyoto Prefectural Medical University Northern Hospital, Yosagun, Kyoto; Hiroshi Komatsu, MD, National Maizuru Medical Center, Maizuru, Kyoto; Koji Nozaki, MD, Mitubishi Kyoto Hospital, Kyoto, Kyoto; Shinsuke Adachi, MD, Fukuchiyama City Hospital, Fukuchiyama, Kyoto; Toru Yamakawa, MD, Japan Baptist Hospital, Kyoto, Kyoto; Masahiko Kai, MD, Bell Land General Hospital, Sakai, Osaka; Hiroshi Sumida, MD, Rinku General Hospital, Izumisano, Osaka; Hirotaka Minami, MD, Takatsuski General Hospital, Takatsuki, Osaka; Kenji Mine, MD, Kansai Medical University, Hirakata, Osaka; Reiko Negi, MD, National Cerebral and Cardiovascular Center, Suita, Osaka; Satoru Ogawa, MD, Saiseikai Suita Hospital, Suita, Osaka; Ryoko Yoshinare, MD, Hannan Central Hospital, Hannan, Osaka; Yasuyuki Tokunaga, MD, Toyonaka City Hospital, Toyonaka, Osaka; Kiyoaki Sumi, MD, Aizenbashi Hospital, Osaka, Osaka; Akihiro Takatera, MD, Chifune Hospital, Osaka, Osaka; Atsushi Ogihara, MD, Osaka Medical University, Takatsuki, Osaka; Satoshi Onishi, MD, Osaka Metropolitan University, Osaka, Osaka; Taho Kim, MD, Osaka City Sumiyoshi Hospital, Osaka, Osaka; Hiroyuki Ichiba, MD, Osaka City General Hospital, Osaka, Osaka; Misao

Yoshii, MD, Osaka Red Cross Hospital, Osaka, Osaka; Hitomi Okabe, MD, Osaka University, Suita, Osaka; Yoshio Kusumoto, MD, Osaka General Medical Center, Osaka, Osaka; Shinya Hirano, MD, Osaka Women's and Children's Hospital, Izumi, Osaka; Hiroshi Mizumoto, MD, Kitano Hospital, Osaka, Osaka; Yae Michinomae, MD, Yao City Hospital, Yao, Osaka; Makoto Nabetani, MD, Yodogawa Christian Hospital, Osaka, Osaka; Takeshi Morisawa, MD, Kakogawa City Hospital, Kakogawa, Hyogo; Masaaki Ueda, MD, Toyooka General Hospital, Toyooka, Hyogo; Takahiro Okutani, MD, Saiseikai Hyogo Hospital, Kobe, Hyogo; Masaru Yamakawa, MD, Kobe City Medical Center Central Hospital, Kobe, Hyogo; Kazumichi Fujioka, MD, Kobe University, Kobe, Hyogo; Tomoaki Ioroi, MD, Himeji Red Cross Hospital, Himeji, Hyogo; Takeshi Utsunomiya, MD, Hyogo Medical University Hospital, Nishinomiya, Hyogo; Seiji Yoshimoto, MD, Kobe Children's Hospital, Kobe, Hyogo; Tamaki Ohashi, MD, Hyogo Prefectural Awaji Medical Center, Sumoto, Hyogo; Toshiya Nishikubo, MD, Nara Prefecture Medical University, Kashiwara, Nara; Ken Kumagaya, MD, Wakayama Prefecture Medical University, Wakayama, Wakayama; Akiko Tamura, MD, Tottori Prefectural Central Hospital, Tottori, Tottori; Masumi Miura, MD, Tottori University, Yonago, Tottori; Yuki Hasegawa, MD, Matsue Red Cross Hospital, Matsue, Matsue; Rie Kanai, MD, Shimane Prefectural Central Hospital, Izumo, Shimane; Kei Takemoto, MD, Okayama Red Cross Hospital, Okayama, Okayama; Koichi Tsukamoto, MD, Okayama University, Okayama, Okayama; Misao Kageyama, MD, National Okayama Medical Center, Okayama, Okayama; Takashi Nakano, MD, Kawasaki Medical University, Kurashiki, Okayama; Hironobu Tokumasu, MD, Kurashiki Central Hospital, Kurashiki, Okayama; Moriharu Sugimoto, MD, Tsuyama Central Hospital, Tsuyama, Okayama; Rie Fukuhara, MD, Hiroshima Prefectural Hospital, Hiroshima, Hiroshima; Yutaka Nishimura, MD, Hiroshima City Central Hospital, Hiroshima, Hiroshima; Seiichi Hayakawa, MD, Hiroshima University, Hiroshima, Hiroshima; Yasuhiko Sera, MD, National Kure Medical Center, Kure, Hiroshima; Masahiro Tahara, MD, Tsuchiya General Hospital, Hiroshima, Hiroshima; Shinosuke Fukunaga, MD, Saiseikai Shimonoseki General Hospital, Shimonoseki, Yamaguchi; Keiko Hasegawa, MD, Yamaguchi Prefecture Medical Center, Hofu, Yamaguchi; Kazumasa Takahashi, MD, Yamaguchi University, Ube, Yamaguchi; Hiroshi Tateishi, MD, Tokuyama Central Hospital, Tokuyama, Yamaguchi; Tomomasa Terada, MD, Tokushima Prefecture Central Hospital, Tokushima, Tokushima; Takashi Yamagami, MD, Tokushima City Hospital, Tokushima, Tokushima; Takahiko Saijo, MD, Tokushima University, Tokushima, Tokushima; Kosuke Koyano, MD, Kagawa University, Kida, Kagawa; Toru Kuboi, MD, Shikoku Medical Center for Children and Adults, Zentsuji, Kagawa; Osamu Matsuda, MD, Ehime Prefectural Imabari Hospital, Imabari, Ehime; Shinosuke Akiyoshi, MD, Ehime Prefectural Central Hospital, Matsuyama, Ehime; Takahiro Motoki, MD, Uwajima City Hospital, Uwajima, Ehime; Yoichi Kondo, MD, Matsuyama Red Cross Hospital, Matsuyama, Ehime; Yusei Nakata, MD, Kochi Health Science Center, Kochi, Kochi; Hideaki Harada, MD, Kurume University, Kurume, Fukuoka; Masayuki Ochiai, MD, Kyushu University, Fukuoka, Fukuoka; Toshinori Nakashima, MD, National Kokura Medical Center, Kitakyushu, Fukuoka; Toshiharu Hikino, MD, National Kyushu Medical Center, Fukuoka, Fukuoka; Shutaro Suga, MD, University of Occupational and Environmental Health Japan, Kitakyushu, Fukuoka; Mitsuaki Unno, MD, Saint Maria Hospital, Kurume, Fukuoka; Hiroshi Kanda, MD, Iizuka Hospital, Iizuka, Fukuoka; Yasushi Takahata, MD, Fukuoka City Children's Hospital, Fukuoka, Fukuoka; Hiroyasu Kawano, MD, Fukuoka University, Fukuoka, Fukuoka; Takayuki Kokubo, MD, Kitakyushu City Hospital, Kitakyushu, Fukuoka; Toshimitsu Takayanagi, MD, National Saga Hospital, Saga, Saga; Mikio Aoki, MD, National Nagasaki Medical Center, Nagasaki, Nagasaki; Muneichiro Sumi, MD, Sasebo City Hospital, Sasebo, Nagasaki; Fumiko Kinoshita, MD, Nagasaki City Hospital, Nagasaki, Nagasaki; Tsutomu Ogata, MD, Nagasaki University, Nagasaki, Nagasaki; Kei Inomata, MD, Kumamoto City Hospital, Kumamoto, Kumamoto; Masanori Iwai, MD, Kumamoto University, Kumamoto, Kumamoto; Naoki Fukushima, MD, Almeida Memorial Hospital, Oita, Oita; Koichi Iida, MD, Oita Prefectural Hospital, Oita, Oita; Mitsushi Goshi, MD, Nakatsu City Hospital, Nakatsu, Oita; Yuki Kodama, MD, Miyazaki University, Miyazaki, Miyazaki; Shuichi Yanagibe, MD, National Miyakonojo Hospital, Miyakonojo, Miyazaki; Yuko Maruyama, MD, Imakyure General Hospital, Kagoshima, Kagoshima; Takuya Tokuhisa, MD, Kagoshima City Hospital, Kagoshima, Kagoshima; Yoriko Kisato, MD, Okinawa Prefectural Central Hospital, Uruma, Okinawa; Tatsuo Oshiro, MD, Okinawa Prefectural Nanbu Medical Center/Nanbu Child Medical Center, Shimajiri, Okinawa; Kazuhiko Nakasone, MD, Okinawa Red Cross Hospital, Naha, Okinawa; Asao Yara, MD, Naha City Hospital, Naha, Okinawa.

Spanish Neonatal Network (SEN1500): Alejandro Avila-Alvarez, MD, and José Luis Fernandez-Trisac, MD, Complexo Hospitalario Universitario De A Coruña, A Coruña; Mª Luz Couce Pico, MD, and María José Fernández Seara, MD, Hospital Clínico Universitario de Santiago, Santiago de Compostela; Andrés Martínez Gutiérrez, MD, Complejo Hospitalario Albacete, Albacete; Carolina Vizcaíno, MD, Hospital General Universitario de Elche, Alicante; Miriam Salvador Iglesias, MD, and Honorio Sánchez Zaplana, MD, Hospital General Universitario de Alicante, Alicante; Belén Fernández Colomer, MD, and José Enrique García López, MD, Hospital Universitario Central de Asturias, Oviedo, Asturias; Rafael García Mozo, MD, and M. Teresa González Martínez, MD, Hospital Universitario de Cabueñes, Gijón, Asturias; Mª Dolores Muro Sebastián, MD, and Marta Balart Carbonell, MD, Clínica Corachán, Barcelona; Joan Badia Barnusell, MD, and Mònica Domingo Puiggròs, MD, Corporacio Parc Taulí, Sabadell, Barcelona; Josep Figueras Aloy, MD, and Francesc Botet Mussons, MD, Hospital Clínic de Barcelona, Barcelona; Israel Anquela Sanz, MD, Hospitalario De Granollers, Granollers; Gemma Ginovart Galiana, MD, H. De La Santa Creu I Sant Pau, Barcelona; W. Coroleu, MD, Hospital Universitari Germans Trias I Pujol, Badalona; Martin Iriondo, MD, Hospital Sant Joan de Déu Barcelona, Esplugues de Llobregat, Barcelona; Laura Castells Vilella, MD, Hospital General de Cataluña, Barcelona; Roser Porta, MD, Institute Dexeus, Barcelona; Xavier Demestre, MD, and Silvia Martínez Nadal, MD, Scias-Hospital Barcelona, Barcelona; Cristina de Frutos Martínez, MD, Hospital Universitario de Burgos, Burgos; María Jesús López Cuesta, MD, H. San Pedro de Alcántara, Cáceres; Dolores Esquivel Mora, MD, and Joaquín Ortiz Tardío, MD, Hospital Jerez, Cádiz; Isabel Benavente, MD, and Almudena Alonso, MD, Hospital Universitario Puerta Del Mar, Cádiz; Ramón Aguilera Olmos, MD, Hospital General de Castellón, Castellón; Miguel A. García Cabezas, MD, and Mª Dolores Martínez Jiménez, MD, Hospital General Universitario de Ciudad Real, Ciudad Real; Mª Pilar Jaraba Caballero, MD, and Mª Dolores

Ordoñez Díaz, MD, Hospital Universitario Reina Sofía, Córdoba; Alberto Trujillo Fagundo, MD, and Lluis Mayol Canals, MD, Hospital Universitari de Girona Dr. Josep Trueta, Girona; Fermín García-Muñoz Rodrigo, MD, and Lourdes Urquía Martí, MD, H.M.I. Las Palmas, Las Palmas, Gran Canaria; María Fernanda Moreno Galdo, MD, and José Antonio Hurtado Suazo, MD, Hospital Universitario Virgen De Las Nieves, Granada; Eduardo Narbona López, and José Uberos Fernández, MD, Hospital Universitario San Cecilio, Granada; Miguel A Cortajarena Altuna, MD, and Oihana Muga Zuriarrain Hospital, MD, Donostia, Gipuzkoa; David Mora Navarro, MD, Hospital Juan Ramón Jiménez, Huelva; María Teresa Domínguez, MD, Hospital Costa De La Luz, Huelva; Mª Yolanda Ruiz del Prado, MD, and Inés Esteban Díez, MD, Hospital San Pedro, Logroño, La Rioja; María Teresa Palau Benavides, MD, and Santiago Lapeña, MD, Hospital de León, León, León; Teresa Prada, MD, Hospital del Bierzo, Ponferrada, León; Eduard Soler Mir, MD, Hospital Arnau De Vilanova, Lleida; Araceli Corredera Sánchez, MD, Enrique Criado Vega, MD, Náyade del Prado, MD, and Cristina Fernández, MD, Hospital Clínico San Carlos, Madrid; Lucía Cabanillas Vilaplana, MD, and Irene Cuadrado Pérez, MD, Hospital Universitario De Getafe, Madrid; Luisa López Gómez, MD, Hospital De La Zarzuela, Madrid; Laura Domingo Comeche, MD, Hospital Universitario de Fuenlabrada, Fuenlabrada, Madrid; Isabel Llana Martín, MD, Hospital Madrid-Torrelodones, Madrid, Madrid; Carmen González Armengod, MD, and Carmen Muñoz Labián, MD, Hospital Universitario Puerta De Hierro, Majadahonda, Madrid; Mª José Santos Muñoz, MD, Hospital Severo Ochoa, Leganés, Madrid; Dorotea Blanco Bravo, MD, and Vicente Pérez, MD, Hospital Gregorio Marañón, Madrid; Mª Dolores Elorza Fernández, MD, Celia Díaz González, MD, and Susana Ares Segura, MD, H.U. La Paz, Madrid; Manuela López Azorín, MD, Hospital Universitario Quirónsalud Madrid, Madrid; Ana Belén Jimenez MD, Hospital Universitario Fundación Jiménez Díaz, Madrid; Tomás Sánchez-Tamayo, MD, and Elías Tapia Moreno, MD, Hospital Carlos Haya, Málaga; María González, MD, and José Enrique Sánchez Martínez, MD, Hospital Parque San Antonio De Málaga, Málaga; José María Lloreda García, MD, Hospital Universitario Santa Lucia De Cartagena, Murcia; Concepción Goñi Orayen, MD, Hospital Virgen Del Camino De Pamplona, Pamplona, Navarra; Javier Vilas González, MD, Complexo Hospitalario Pontevedra, Pontevedra; María Suárez Albo, MD, and Eva González Colmenero, MD, Hospital Xeral De Vigo, Pontevedra; Elena Pilar Gutiérrez González, MD, and Beatriz Vacas del Arco, MD, Hospital Universitario de Salamanca, Salamanca; Josefina Márquez Fernández, MD, and Laura Acosta Gordillo, MD, Hospital Valme, Sevilla; Mercedes Granero Asensio, MD, Hospital Virgen De La Macarena, Sevilla; Carmen Macías Díaz, MD, Hospital Universitario Virgen Del Rocío, Sevilla; Mar Albújar, MD, Hospital Universitari de Tarragona Joan XXIII, Tarragona; Pedro Fuster Jorge. MD, Hospital Universitario De Canarias, San Cristóbal de La Laguna, Santa Cruz de Tenerife; Sabina Romero, MD, and Mónica Rivero Falero, MD, Hospital Universitario Nuestra Señora De Candelaria, Santa Cruz de Tenerife; Ana Belén Escobar Izquierdo, Hospital Virgen De La Salud, Toledo; Javier Estañ Capell, MD, Hospital Clinico Universitario De Valencia, Valencia; Mª Isabel Izquierdo Macián, MD, Hospital Universitari La Fe, Valencia; Mª Mar Montejo Vicente, MD, and Raquel Izquierdo Caballero, MD, Hospital Universitario Río Hortega, Valladolid; Mª Mercedes Martínez, MD, and Aintzane Euba, MD, Hospital de Txagorritxu, Vitoria-Gasteiz; Amaya Rodríguez Serna, MD, and Juan María López de Heredia Goya, MD, Hospital de Cruces, Baracaldo; Alberto Pérez Legorburu, MD, and Ana Gutiérrez Amorós, MD, Hospital Universitario de Basurto, Bilbao; Víctor Manuel Marugán Isabel, MD, and Natalio Hernández González, MD, Hospital Virgen De La Concha – Complejo Asistencial De Zamora, Zamora; Segundo Rite Gracia, MD, Hospital Miguel Servet, Zaragoza; Mª Purificación Ventura Faci, MD, and Mª Pilar Samper Villagrasa, MD, Hospital Clínico Universitario Lozano Blesa, Zaragoza.

Swedish Neonatal Quality Register (SNQ): Zeljka Mustapic, MD, Södra Älvsborgs Sjukhus, Borås; Katarina Strand Brodd, MD, Mälarsjukhuset, Eskilstuna; Andreas Odlind, MD, Falu Lasarett, Falun; Per Friskopp, MD, Gällivare Sjukhus, Gällivare; Sofia Arwehed, MD, Gävle Sjukhus, Gävle; Svetlana Najm, MD, SU/Östra, Göteborg; Anna Kasemo, MD, Länssjukhuset, Halmstad; Karin Nederman, MD, Helsingborgs Lasarett, Helsingborg; Thomas Hägg, MD, Hudiksvalls Sjukhus, Hudiksvall; Fredrik Ingemarsson, MD, Länssjukhuset Ryhov, Jönköping; Henrik Petersson, MD, Länssjukhuset, Kalmar; Ulrik Lindström, MD, Blekingesjukhuset, Karlskrona; Eva Albinsson, MD, Centralsjukhuset, Karlstad; Holger Hövel, MD, Centralsjukhuset, Kristianstad; Carin Widén, MD, Universitetssjukhuset, Linköping; Ingela Heimdahl, MD, Sunderby sjukhus, Luleå; Kristbjorg Sveinsdottir, MD, Skånes Universitetssjukhus, Malmö/Lund; Erik Wejryd, MD, Vrinnevisjukhuset, Norrköping; Johanna Kusima-Löfbom, MD, Skellefteå Lasarett, Skellefteå; Maria Söderberg, MD, Kärnsjukhuset Skaraborg, Skövde; Lars Navér, MD, Karolinska Sjukhuset, Stockholm; Fredrik Stenius, MD, Södersjuhuset, Stockholm; Jens Bäckström, MD, Länssjukhuset, Sundsvall; Peder Helmersson, MD, Norra Älvsborgs Länssjukhus, Trollhättan; Jolanta Wróblewska, MD, Norrlands Universitetssjukhus, Umeå; Erik Normann, MD, Akademiska Barnsjukhuset, Uppsala; Magnus Fredriksson, MD, Visby Lasarett, Visby; Anders Palm, MD, Västerviks Sjukhus, Västervik; Peter Jotorp, MD, Centrallasarettet, Västerås; Bengt Walde, MD, Centrallasarettet, Växjö; Linda Resman, MD, Lasarettet, Ystad; Miriam Pettersson, MD, Universitetssjukhuset, Örebro; Christina Ziegel, MD, Örnsköldsviks Sjukhus, Örnsköldsvik; Kari Arhimaa, MD, Östersunds Sjukhus, Östersund.

Swiss Neonatal Network (SwissNeoNet): Mark Adams, PhD (Network coordinator), University Hospital Zurich; Philipp Meyer, MD, and Rachel Kusche, MD, Cantonal Hospital, Children's Clinic, Aarau; Sven Schulzke, MD, University Children's Hospital, Basel; André Kidszun, MD, University Hospital, Berne; Mathias Gebauer, MD, Children's Hospital, Biel; Bjarte Rogdo, MD, Children's Hospital, Chur; Benedikt Huber, MD, Cantonal Hospital, Fribourg; Riccardo E. Pfister, MD, University Hospital (HUG), Geneva; Jean-François Tolsa, MD, and Juliane Schneider, MD, University Hospital (CHUV), Lausanne; Martin Stocker, MD, Children's Hospital, Lucerne; Ikbel El Faleh, MD, Cantonal Hospital, Neuchatel; Andreas Malzacher, MD, Cantonal Hospital, St. Gallen; André Birkenmaier, MD, Children's Hospital, St. Gallen; Lukas Hegi, MD, Cantonal Hospital, Winterthur; Vera Bernet, Cantonal Hospital, Zollikerberg; Dirk Bassler, MD, and Vincenzo Cannizzaro, MD, University Hospital (USZ), Zurich; Cornelia Hagmann, MD, University Children's Hospital, Zurich; Maren Tomaske, MD, Zurich City Hospital, Zurich.

Tuscany Neonatal Network (TNN): Carlo Dani, MD, Careggi University Hospital, Florence, Italy; Marco Moroni, MD, Meyer Children's Hospital, Florence, Italy; Luca Filippi, MD, University

Hospital of Pisa, Pisa, Italy; Barbara Tomasini, MD, University Hospital of Siena, Siena, Italy; Elettra Berti, Meyer Children's Hospital, Florence, Italy; Vieri Lastrucci, Meyer Children's Hospital, Florence, Italy.

United Kingdom Neonatal Collaborative (UKNC): Anita Mittal, MBChB, Bedford Hospital, Bedford, Bedfordshire; Jonathan Kefas, MBChB, Lister Hospital, Stevenage, Hertfordshire; Anand Kamalanathan, MBChB, Arrowe Park Hospital, Wirral, Merseyside; Michael Grosdenier, MBChB, Leighton Hospital, Crewe, Cheshire; Christopher Dewhurst, MBChB, Liverpool Women's Hospital, Liverpool, Merseyside; Andreea Bontea, MBChB, Ormskirk District General Hospital, Ormskirk, Lancashire; Delyth Webb, MBChB, Warrington Hospital, Warrington, Cheshire; Ross Garr, MBChB, Whiston Hospital, Prescot, Merseyside; Ahmed Hassan, MBChB, Broomfield Hospital, Chelmsford, Essex; Priyadarshan Ambadkar, MBChB, James Paget Hospital, Gorleston, Norfolk; Mark Dyke, MBChB, Norfolk and Norwich University Hospital, Norwich, Norfolk; Katharine McDevitt, MBChB, Peterborough City Hospital, Peterborough, Cambridgeshire; Glynis Rewitzky, MBChB, Queen Elizabeth Hospital, King's Lynn, Birmingham, West Midlands; Angela D'Amore, MBChB, Rosie Maternity Hospital, Addenbrookes, Cambridge, Cambridgeshire; P. Kamath, MBChB, North Manchester General Hospital, Manchester, Greater Manchester; Paul Settle, MBChB, Royal Bolton Hospital, Bolton, Lancashire; Natasha Maddock, MBChB, Royal Oldham Hospital, Manchester, Greater Manchester; Ngozi Edi-Osagie, MBChB, St Mary's Hospital, Manchester, Greater Manchester; Christos Zipitis, MBChB, The Royal Albert Edward Infirmary, Wrightington, Greater Manchester; Carrie Heal, MBChB, Stepping Hill Hospital, Stockport, Cheshire; Jacqeline Birch, MBChB, Tameside General Hospital, Ashton-under-Lyne, Lancashire; Abdul Hasib, MBChB, Darent Valley Hospital, Dartford, Kent; Aung Soe, MBChB, Medway Maritime Hospital, Gillingham, Kent; Bushra Abdul-Malik, MBChB, Queen Elizabeth the Queen Mother Hospital, Margate, Kent; Hamudi Kisat, MBChB, Tunbridge Wells Hospital, Tunbridge Wells, Kent; Vimal Vasu, MBChB, William Harvey Hospital, Ashford, Kent; Savi Sivashankar, MBChB, Lancashire Women and Newborn Centre, Burnley, Lancashire; Richa Gupta, MBChB, Royal Preston Hospital, Preston, Lancashire; Chris Rawlingson, MBChB, Victoria Hospital, Blackpool, Blackpool, Lancashire; Tim Wickham, MBChB, Barnet Hospital, Barnet, Hertfordshire; Marice Theron, MBChB, The Royal Free Hospital, Hampstead, London; Giles Kendall, MBChB, University College Hospital, Fitzrovia, London; Aashish Gupta, MBChB, Basildon Hospital, Basildon, Essex; Narendra Aladangady, MBChB, Homerton Hospital, Hackney, London; Imdad Ali, MBChB, Newham General Hospital, Newham, London; Neeraj Jain, MBChB, North Middlesex University Hospital, Edmonton, London; Khalid Mannan, MBChB, Queen's Hospital, Romford, Essex; Vadivelam Murthy, MBChB, The Royal London Hospital, Whitechapel, London; Caroline Sullivan, MBChB, Whipps Cross University Hospital, Whipps Cross, London; Shu-Ling Chuang, MBChB, Chelsea and Westminster Hospital, Chelsea, London; Tristan Bate, MBChB, Hillingdon Hospital, Hillingdon, London; Lidia Tyszcuzk, MBChB, Queen Charlotte's Hospital, East Acton, London; Lidia Tyszcuzk, MBChB, St Mary's Hospital, Westminster, London; Geraint Lee, MBChB, Guy's and St Thomas' Hospital, Lambeth, London; Ozioma Obi, MBChB, University Hospital Lewisham, Lewisham, London; John Chang, MBChB, Croydon University Hospital, Croydon, Surrey; Vinay Pai, MBChB, Kingston Hospital, Kingston, London; Charlotte Huddy, MBChB, St George's Hospital, Wandsworth, London; Salim Yasin, MBChB, St. Helier Hospital, Merton, London; Richard Nicholl, MBChB, Northwick Park Hospital, Brent, London; Poornima Pandey, MBChB, Kettering General Hospital, Kettering, Northhamptonshire; Jonathan Cusack, MBChB, Leicester General Hospital, Leicester, Leicestershire; Venkatesh Kairamkonda, MBChB, Leicester Royal Infirmary, Leicester, Leicestershire; Dominic Muogbo, MBChB, Queen's Hospital, Burton On Trent, Burton-on-Trent, Staffordshire; Liza Harry, MBChB, Alexandra Hospital, Redditch, Worcestershire; Pinki Surana, MBChB, Birmingham Heartlands Hospital, Birmingham, West Midlands; Penny Broggio, MBChB, City Hospital, Birmingham, West Midlands; Pinki Surana, MBChB, Good Hope Hospital, Birmingham, West Midlands; Liza Harry, MBChB, Worcestershire Royal Hospital, Worcester, Worcestershire; Tilly Pillay, MBChB, New Cross Hospital, Wolverhampton, West Midlands; Sanjeev Deshpande, MBChB, Princess Royal Hospital, Shrewsbury, Shropshire; Mahadevan, MBChB, Russells Hall Hospital, Dudley, West Midlands; Alison Moore, MBChB, Royal Stoke University Hospital, Hartshill, Staffordshire; Porus Bastani, MBChB, The Jessop Wing, Sheffield, South Yorkshire; Mehdi Garbash, MBChB, Darlington Memorial Hospital, Darlington, County Durham; Mithilesh Lal, MBChB, James Cook University Hospital, Middlesborough, North Yorkshire; Majd Abu-Harb, MBChB, Sunderland Royal Hospital, Sunderland, Tyne and Wear; Mehdi Garbash, MBChB, University Hospital of North Durham, Durham, Durham; Alex Allwood, MBChB, Derriford Hospital, Plymouth, Devon; Michael Selter, MBChB, North Devon District Hospital, Barnstaple, Devon; Paul Munyard, MBChB, Royal Cornwall Hospital, Truro, Cornwall; David Bartle, MBChB, Royal Devon and Exeter Hospital, Exeter, Devon; Siba Paul, MBChB, Torbay Hospital, Torquay, Devon; Graham Whincup, MBChB, Conquest Hospital, St Leonards-on-sea, East Sussex; Sanghavi Rekha, MBChB, Frimley Park Hospital, Frimley, Surrey; Philip Amess, MBChB, Princess Royal Hospital, Telford, Shropshire; Ben Obi, MBChB, Royal Surrey County Hospital, Guildford, Surrey; Philip Amess, MBChB, Royal Sussex County Hospital, Brighton, East Sussex; Peter Reynolds, MBChB, St. Peter's Hospital, Chertsey, Surrey; Indranil Misra, MBChB, Milton Keynes Foundation Trust Hospital, Milton Keynes, Buckinghamshire; Peter De Halpert, MBChB, Royal Berkshire Hospital, Reading, Berkshire; Sanjay Salgia, MBChB, Stoke Mandeville Hospital, Aylesbury, Buckinghamshire; Rekha Sanghavi, MBChB, Wexham Park Hospital, Slough, Berkshire; Nicola Paul, MBChB, Basingstoke and North Hampshire Hospital, Basingstoke, Hampshire; Abby Deketelaere, MBChB, Dorset County Hospital, Dorchester, Dorset; Minesh Khashu, MBChB, Poole Hospital NHS Foundation Trust, Poole, Dorset; Mark Johnson, MBChB, Princess Anne Hospital, Southampton, Hampshire; Charlotte Groves, MBChB, Queen Alexandra Hospital, Portsmouth, Hampshire; Jim Baird, MBChB, Salisbury District Hospital, Salisbury, Wiltshire; Nick Brennan, MBChB, St Richard's Hospital, Chichester, West Sussex; Katia Vamvakiti, MBChB, Worthing Hospital, Worthing, West Sussex; John McIntyre, MBChB, Royal Derby Hospital, Derby, Derbyshire; Jennifer Holman, MBChB, Gloucestershire Royal Hospital, Gloucester, Gloucestershire; Stephen Jones, MBChB, Royal United Hospital, Avon, Somerset; Alison Pike, MBChB, Southmead Hospital, Westbury-on-Trym, Bristol; Pamela Cairns, MBChB, St

Michael's Hospital, Bristol, Bristol; Megan Eaton, MBChB, Yeovil District Hospital, Yeovil, Somerset; Karin Schwarz, MBChB, Calderdale Royal Hospital, Halifax, West Yorkshire; David Gibson, MBChB, Pinderfields General Hospital, Dewsbury, West Yorkshire; Lawrence Miall, MBChB, Leeds Neonatal Service, Leeds, Yorkshire; David Gibson, MBChB, Pinderfields General Hospital, Wakefield, West Yorkshire; Dr Krishnamurthy, MBChB, Walsall Manor Hospital, Walsall, West Midlands; Sankara Narayanan, MBChB, Watford General Hospital, Watford.

Statement of Ethics

Data collection and data transfer from individual networks were approved by the research ethics boards of the participating networks in the respective countries and by the iNeo steering committee. Specific ethics approval for this project was obtained from the Mount Sinai Hospital Research Ethics Board and the iNeo Steering Committee. This study protocol was reviewed and approved by the Research Ethics Board Approval No. 22-0057-C on the 22nd of March 2022. Informed consent from individual patients was waived due to the retrospective nature of this database study.

Conflict of Interest Statement

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Author Contributions

Dr. Georgia Hollens and Prof. Kei Lui conceptualized and designed the study, drafted the initial manuscript, and reviewed and revised the manuscript. Prof. Prakesh S. Shah conceptualized the design, coordinated the study, supervised the data collation and analysis, critically reviewed, and revised the manuscript. Profs. and Drs. Malcolm Battin, Gil Klinger, Mark Adams, Maximo Vento, Antonino Santacroce, Stellan Håkansson, Tetsuya Isayama, Mikael Norman, Satoshi Kusuda, Liisa Lehtonen, Kjell Helenius, and Neena Modi contributed to the data collection instruments, interpretation of results, and critically reviewed and revised the manuscript.

Data Availability Statement

Prakesh S. Shah, Mount Sinai Hospital, Toronto, ON, Canada, has full access to the data. He takes responsibility for the integrity of the data and the accuracy of the data analysis. The data analyses were conducted by Junmin Yang. Data are confidential and not available for public access. Further inquiries can be directed to the corresponding author.

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