Survival in Very Preterm Infants: An International Comparison of 10 National Neonatal Networks

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abstract

OBJECTIVES: To compare survival rates and age at death among very preterm infants in 10 national and regional neonatal networks.

METHODS: A cohort study of very preterm infants, born between 24 and 29 weeks' gestation and weighing <1500 g, admitted to participating neonatal units between 2007 and 2013 in the International Network for Evaluating Outcomes of Neonates. Survival was compared by using standardized ratios (SRs) comparing survival in each network to the survival estimate of the whole population.

RESULTS: Network populations differed with respect to rates of cesarean birth, exposure to antenatal steroids and birth in nontertiary hospitals. Network SRs for survival were highest in Japan (SR: 1.10; 99% confidence interval: 1.08–1.13) and lowest in Spain (SR: 0.88; 99% confidence interval: 0.85–0.90). The overall survival differed from 78% to 93% among networks, the difference being highest at 24 weeks' gestation (range 35%–84%). Survival rates increased and differences between networks diminished with increasing gestational age (GA) (range 92%–98% at 29 weeks' gestation); yet, relative differences in survival followed a similar pattern at all GAs. The median age at death varied from 4 days to 13 days across networks.

CONCLUSIONS: The network ranking of survival rates for very preterm infants remained largely unchanged as GA increased; however, survival rates showed marked variations at lower GAs. The median age at death also varied among networks. These findings warrant further assessment of the representativeness of the study populations, organization of perinatal services, national guidelines, philosophy of care at extreme GAs, and resources used for decision-making.

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WHAT'S KNOWN ON THIS SUBJECT: Survival rates of very preterm infants vary among regions. International collaborations have been established to compare outcomes, but population-based comparisons have been difficult to accomplish.

WHAT THIS STUDY ADDS: This study shows variations in survival and age at death among very preterm infants in 10 national neonatal networks and provides insight into differences that affect comparisons. The findings warrant investigation of the organization of perinatal care in participating networks.

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Preterm birth remains the major cause of infant mortality in high-income countries.[1] Studies published in the last decade have shown variability in survival rates and outcomes among health care settings as well as within countries.[2–12] Results from the Euro-Peristat project showed that neonatal survival among very preterm infants improved by 29% between 2004 and 2010 in 18 European countries, including those with high baseline survival.[13] Such comparisons of different health care organizations worldwide can deliver important benchmarking information and potentially provide impetus for reviewing clinical practices, norms, and guidelines.

The International Network for Evaluating Outcomes of Neonates (iNeo) is a nonprofit collaboration among 10 national and regional neonatal networks: the Australian and New Zealand Neonatal Network (ANZNN), the Canadian Neonatal Network (CNN), the Finnish Medical Birth Register (FinMBR), the Israel Neonatal Network (INN), Neonatal Research Network Japan (NRNJ), the Spanish Neonatal Network (SEN1500), Sweden's National Quality Registry for Neonatal Care (SNQ), the Swiss Neonatal Network (SwissNeoNet), Tuscany Neonatal Network (TuscanNN), and the United Kingdom Neonatal Collaborative (UKNC). The overarching aim of the iNeo collaboration is to compare outcomes of very preterm infants, understand reasons for variations, and, if possible, identify areas for improvement in care practices based on findings.[14]

By using the iNeo data set, the objective of this study was to compare gestational age (GA)-specific survival rates for very preterm infants in all neonatal networks currently participating in the iNeo partnership and to explore variations in postnatal age at death among the very preterm population.

METHODS

Population and Study Design

This cohort study included infants born at 24 to 29 weeks' gestation, weighing <1500 g at birth, and registered in participating network databases from 2007 to 2013 (2008–2013 for UKNC, 2009–2013 for TuscanNN). The criterion of 1500 g was used because some networks limited their data collection to infants with a birth weight <1500 g. Stillborn infants and delivery room deaths were not included because all networks do not routinely collect data on these infants. Because of variability in practices and philosophy of care provision at <24 weeks' GA, we only included neonates born at ≥24 weeks' gestation. Infants admitted for the first time to neonatal care after 36 weeks' corrected GA were excluded. Data on infant characteristics and outcomes were extracted, as previously described.[14] Transferred infants were included only once.

Population coverage of networks deviate from national birth statistics for various reasons. All neonatal units in Finland, New Zealand, and Tuscany participate in their national and regional neonatal networks; however, in Australia, apart from all tertiary neonatal units, only a few lower-level units participate in the ANZNN. In Canada, only tertiary neonatal units participate in the CNN. In Israel, all neonatal units participate, but infants with a birth weight >1500 g are not included. In Japan and Spain, not all neonatal units participate in the national networks. In Sweden, all neonatal units presently participate in the SNQ; however, the Skåne region is not included in this study because it joined in 2011. In Switzerland, all tertiary and large secondary (level IIB) neonatal units participate in SwissNeoNet. In the United Kingdom, all neonatal units in England, Wales, and Scotland participate in the UKNC; however, a number of neonatal units have not consented for participation in iNeo.

Covariates

GA was determined by the best estimate based on either early ultrasound, the timing of the last menstrual period, or physical examination after birth, in that order. Antenatal steroid use was defined as maternal receipt of antenatal steroids at any time before birth. Birth weight *z* scores were calculated according to birth weight references appropriate for each country.[15–17] Mode of delivery was recorded as vaginal or cesarean. Multiple births included twins and higher-order multiples.

Outcomes

The primary outcome was survival to discharge from the hospital for infants admitted to neonatal care. Survival to transfer to a step-down hospital was used when follow-up was available only until the transfer. We analyzed survival in 1-week GA increments. As a secondary outcome, we compared postnatal age at death among nonsurvivors. Neonatal morbidities among iNeo survivors have been recently published.[18]

Data Management

For most networks, defined data elements were either collected from patient records by designated abstractors according to network policies or entered directly into a central online database by participating units. For the UKNC, data were obtained from the National Neonatal Research Database managed by the Neonatal Data Analysis Unit, which contains a predefined extract from electronic patient records used in UK neonatal units. Finnish data were collected from the Medical Birth Register kept at the National Institute for Health and Welfare.

Statistical Analyses

Background characteristics of infants were compared by using the Pearson χ^2 test for categorical variables and the analysis of variance F test for continuous variables. Standardized ratios (SRs) were computed by using the indirect standardization approach. The pooled estimate of survival for the whole population was used as a standard. Each network was then compared with this standard, computed as the sum of predicted probabilities from a multivariable logistic regression model with adjustment for GA (linear), birth weight *z* score (linear and quadratic), multiple births, and sex. SR estimates were displayed graphically to identify countries with survival rates greater than and less than the average rate of all others with 99% confidence intervals (CIs). Because the SR estimate is calculated in relation to all other networks combined, it is not directly comparable among networks. No adjustment was made for the administration of antenatal steroids, cesarean birth, or birth in a nontertiary hospital because these are practice-related elements, and adjustment of these variables can lead to biased estimates in favor of underperforming systems. Missing data were not imputed. All statistical analyses and plots were conducted by using SAS version 9.3 (SAS Institute Inc, Cary, NC) or R version 2.2.

Research Ethics Approval

All iNeo collaborators hold relevant research ethics approvals for their data collection. Separate data sharing agreements were obtained from the executive committees of each network and the iNeo Coordinating Center in Toronto, Canada. Ethics approval for the iNeo collaboration was obtained from the Research Ethics Board at Mount Sinai Hospital in Toronto, Canada.

RESULTS

A total of 91 835 infants born between 24 and 29 weeks' gestation were identified in the iNeo database during the study period. After excluding infants with a birth weight >1500 g (*N* = 3070) and infants admitted to neonatal care after 36 weeks' corrected GA (*N* = 438), the final population consisted of 88 327 infants. The variations in care provision and organization of care among the networks are provided in Table 1, as reported by network directors. Table 2 describes characteristics of infants in each participating network. The population coverage of iNeo networks compared with national birth statistics ranged from 61% in Japan (NRNJ) to 100% in Sweden (SNQ), Switzerland (SwissNeoNet), and Tuscany (TuscanNN). Infant characteristics (including exposure to antenatal steroids, cesarean birth, and birth in a nontertiary hospital) were markedly different among networks.

Survival

Of the 88 327 included infants, 77 172 (87%) survived to discharge. Overall survival rates varied from 78% in SEN1500 to 93% in NRNJ (Table 3). The differences in percentage points between networks with the lowest and highest survival rates were 49% at 24 weeks' gestation (INN 35%, NRNJ 84%), 32% at 25 weeks (INN 57%, NRNJ 89%), 20% at 26 weeks (73% SEN1500, 93% NRNJ), 12% at 27 weeks (82% SEN1500, 94% NRNJ), 8% at 28 weeks (89% SEN1500, 97% NRNJ), and 6% at 29 weeks (92% SEN1500, 98% SwissNeoNet). Survival increased as GA increased in all networks. Internetwork ranking of the survival rate followed a similar pattern at all GAs. The GA-specific survival rates are presented graphically in Fig 1.

Estimated SRs comparing survival in each network to all other networks were higher in NRNJ (SR: 1.10; 99% CI: 1.08–1.13) and lower in INN (SR: 0.91; 99% CI: 0.87–0.95) and SEN1500 (SR: 0.88; 99%: CI 0.85–0.90) and overlapped with the 99% CI in ANZNN (SR: 1.01; 99% CI: 0.99–1.04), CNN (SR: 1.01; 99% CI: 0.99–1.04), FinMBR (SR: 1.01; 99% CI: 0.94–1.08), SNQ (SR: 1.03; 99% CI: 0.98–1.08), SwissNeoNet (SR: 0.99; 99% CI: 0.94–1.04), TuscanNN (SR: 0.95; 99% CI: 0.85–1.05), and UKNC (SR: 0.99; 99% CI: 0.97–1.01) (Fig 2). Pairwise comparisons among networks are presented in Supplemental Table 5.

Age at Death

A total of 11 155 infants did not survive to discharge. Age at death was available for 10 839 (97%) neonates, which is presented as a function of postnatal age in Fig 3 and Supplemental Fig 4. Median age at death for the entire population was 8 days, varying from 4 days to 13 days in the FinMBR and NRNJ, respectively (Table 4). Among deaths, 14.6% occurred before 24 hours of age (6.9% TuscanNN, 26.8% FinMBR), 29.7% at 1 to 6 days of age (23.8% NRNJ, 44.4% SwissNeoNet), 32.1% at 7 to 27 days of age (21.6% FinMBR, 37.3% TuscanNN), and 23.6% after 28 days of age (14.4% SwissNeoNet, 32.7% NRNJ). Overall, the median postnatal age at death for the entire population remained stable at 8 days to 9 days over the study duration.

DISCUSSION

In this large, multinational study, we identified significant differences in the survival of very preterm infants, particularly at 24 to 27 weeks' gestation. Survival increased and differences in survival between networks decreased with increasing GA, whereas internetwork ranking of survival remained relatively unchanged at each gestation. The median postnatal age at death ranged from 4 days to 13 days within networks.

TABLE 1 Characteristics of the 10 National Neonatal Networks Participating in the iNeo

	ANZNN	CNN	Fin MBR	INN	NRNJ	SEN1500	SNQ[a]	SwissNeoNet	TuscanNN[b]	UKNC[c]	Total
Approximate no. of births per year	360 000	380 000	60 000	160 000	1 080 000	480 000	90 000	80 000	30 000	690 000	3 410 000
Units from which data are included in iNeo[b]	56	28	30	27	73	61	28	12	24	131	470
Tertiary neonatal units in the country or region	29	28	5	23	93	50	7	9	7	49	300
Delivery room deaths included in database	No	Partial	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Partial	—
Data from step-down units included	Yes	No	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	—
Proportion of infants in network compared with national birth statistics[d]	92.5%	92.5%	99.1%	95.0%	61.1%	76.1%[e]	100%	99.7%	100%	73.5%	75.6%

—, not applicable.
[a] Sweden, excluding the Skåne region.
[b] 2009–2013.
[c] 2008–2013.
[d] Proportion of infants born at 24–29 weeks' gestation in each network compared with corresponding numbers in national birth statistics.
[e] Of all infants born at <28 weeks' GA.

The iNeo networks reached survival ranging from 78% to 93% in the very preterm infant population. Other international studies have shown similar survival rates: 77% to 91% for infants born at 22 to 31 weeks' gestation in the European Health Care Outcomes, Performance and Efficiency (study in 2006–2008,[9] 83% for infants born at 24 to 28 weeks' gestation in the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development Neonatal Research Network (NICHD NRN) in 2008–2012,[2] and 74% to 94% for infants born at 24 to 29 weeks' gestation in the Effective Perinatal Intensive Care in Europe (EPICE) study in 2011.[19] The European Health Care Outcomes, Performance and Efficiency study can also be used to validate our ranking order related to 3 countries because the ranking order of Sweden, Finland, and Italy was the same in both studies.

Some differences have to be noted in the study designs, such as the inclusion of delivery room deaths and limitation to tertiary hospitals in the NICHD NRN. The EPICE study also included stillborn infants and delivery room deaths, but the proportion of live-born infants could be extracted from their data. Including nontertiary hospitals is likely to decrease overall survival rates, but excluding delivery room deaths is likely to overestimate survival.

Internetwork differences in survival were largest among infants born at 24 weeks' gestation and decreased with increasing GA. However, networks with the lowest survival rates among 24-week infants continued to display low survival rates in relation to the other networks at almost all GA groups. Similarly, Berger et al[4] reported that among Swiss university hospitals, survival differences were most pronounced among infants born at 23 to 25 weeks' gestation, and the

TABLE 2 Population Characteristics of Infants (24–29 Weeks' Gestation, Birth Weight <1500 g) Born Between 2007 and 2013 and Admitted to Neonatal Care in iNeo Contributing Networks

	ANZNN	CNN	FinMBR	INN	NRNJ	SEN1500	SNQ[a]	SwissNeoNet	TuscanNN[b]	UKNC[c]	Total
No. of neonates included in database	14 043	13 688	1728	5441	18 431	10 695	3346	2775	737	20 951	91 835
Infants excluded due to birth weight >1500 g, *n* (%)	778 (5.5)	717 (5.2)	95 (5.5)	0 (0)	5 (0.03)	148 (1.4)	222 (6.6)	97 (3.5)	32 (4.3)	976 (4.7)	3070 (3.3)
Admitted at >36 wks' gestation, *n* (%)	26 (0.2)	83 (0.6)	0 (0)	0 (0)	5 (0.03)	321 (3.0)	0 (0)	3 (0.1)	0 (0)	0 (0)	438 (0.5)
Study infants, *n* (%)	13 239 (94.3)	12 888 (94.2)	1633 (94.5)	5441 (100)	18 421 (99.9)	10 226 (95.6)	3124 (93.4)	2675 (96.4)	705 (95.7)	19 975 (95.3)	88 327 (96.2)
GA (wks), mean (SD)[d]	27.0 (1.6)	26.9 (1.6)	27.0 (1.6)	27.0 (1.6)	26.9 (1.7)	27.1 (1.6)	27.0 (1.6)	27.1 (1.6)	27.0 (1.7)	27.0 (1.6)	27.0 (1.6)
Proportion of infants 24 wks' GA, *n* (%)[d]	1229 (9.3)	1191 (9.2)	156 (9.6)	482 (8.9)	2082 (11.3)	866 (8.5)	292 (9.3)	186 (7.0)	94 (13.3)	2053 (10.3)	8631 (9.8)
Birth weight (g), mean (SD)[d]	993 (251)	986 (246)	980 (259)	972 (247)	927 (256)	978 (247)	986 (256)	961 (254)	940 (257)	976 (243)	969 (251)
Birth weight *z* score, mean (SD)[d]	0.01 (0.95)	−0.09 (0.83)	−0.18 (0.91)	−0.10 (0.83)	−0.17 (0.99)	−0.08 (0.98)	−0.12 (0.86)	−0.17 (0.82)	0.07 (0.97)	−0.18 (0.93)	−0.11 (0.93)
Multiple births, *n* (%),[d] [missing data]	3758 (28.4) [11]	3706 (28.8) [9]	484 (29.6)	2133 (39.2)	3809 (20.7)	3071 (30.0)	898 (28.7)	802 (30.0)	222 (31.5) [1]	5305 (26.6) [7]	24 188 (27.4) [28]
Male sex, *n* (%), [missing data]	7064 (53.4) [9]	6985 (54.2) [22]	862 (52.8)	2952(54.3)	9877 (53.6) [8]	5461 (53.4)	1697 (54.3) [2]	1401 (52.4) [1]	363 (51.5)	10 740 (53.8) [9]	47 402 (53.7) [51]
Any antenatal steroid, *n* (%),[d] [missing data]	11 818 (89.3) [185]	10 994 (85.3) [429]	1537 (94.1) [17]	4098 (75.3) [3]	9901 (53.7) [556]	8700 (85.1) [170]	2616 (83.7)	2400 (89.7) [42]	607 (86.1) [5]	16 585 (83.0) [1018]	69 256 (78.4) [2425]
Cesarean birth, *n* (%),[d] [missing data]	8101 (61.2) [61]	7703 (59.8) [96]	1144 (70.1) [4]	3877 (71.3)	14 132 (76.7) [262]	6592 (64.5)	2159 (69.1)	2146 (80.2)	492 (69.8)	9903 (49.6) [1725]	56 249 (63.7) [2151]
Born in nontertiary hospital, *n* (%),[d] [missing data]	1791 (13.5)	2234 (17.3) [16]	79 (4.8)	63(1.2)	1193 (6.5)	562 (5.5)	321 (10.3) [13]	127 (4.7)	115 (16.3)	Not applicable	6485 (9.5) [29]

[a] Sweden, excluding the Skåne region.
[b] 2009–2013.
[c] 2008–2013.
[d] $P < .001$.

interunit rank remained consistent for more mature infants. We do not have detailed data for an in-depth explanation of these differences, but in addition to variable population coverage, they may be related to organizational factors, such as regionalization, staffing, philosophy of care provision, willingness to offer palliative care, and withdrawal of intensive support and other resources.[20,21] Furthermore, it is well recognized that the approach to active care largely explains differences in survival in infants at extremely low GAs.[7,22] We only included infants born at 24 to 29 weeks' gestation, assuming that participating neonatal units would provide active care to these neonates. It has been suggested by researchers in other studies that adopting a more active approach to extremely low GAs also results in increased survival in higher-GA groups.[23–25]

The nonsurvivors died later (median of 8 days) in our study compared with those in the NICHD NRN (median of 3 days) from 2008 to 2011.[26] However, it must be acknowledged that the infants in the NICHD NRN study were more immature (median GA of 25.7 weeks for all live births). Mohamed et al[27] found a significant increase in the mean age at death (from 6.6 days to 8.7 days) in very low birth weight infants in a large, national sample in the United States between 1997 and 2004. They also showed that infants with a birth weight of <500 g died earlier than others.

Finally, we also identified differences in the age at death of nonsurvivors among the iNeo networks. The reasons for death vary at different postnatal ages. In the NICHD NRN study,[26] the predominant causes of death were reported to be immaturity in the first 12 hours of life, followed by respiratory distress syndrome during the first 2 weeks to 4 weeks, necrotizing enterocolitis between 0.5 months and 2 months,

TABLE 3 GA-Specific Survival Rates Among Infants (24–29 Weeks' Gestation, Birth Weight <1500 g) Born Between 2007 and 2013 and Admitted to Neonatal Care in the iNeo Networks

	ANZNN *n*/*N* (%)	CNN *n*/*N* (%)	FinMBR *n*/*N* (%)	INN *n*/*N* (%)	NRNJ *n*/*N* (%)	SEN1500 *n*/*N* (%)	SNQ[a] *n*/*N* (%)	SwissNeoNet *n*/*N* (%)	TuscanNN[b] *n*/*N* (%)	UKNC[c] *n*/*N* (%)	Total *n*/*N* (%)
GA $24^{0/7}$–$24^{6/7}$	793/1229 (64.5)	736/1191 (61.8)	110/156 (70.5)	168/482 (34.9)	1743/2082 (83.7)	312/866 (36.0)	205/292 (70.2)	107/186 (57.5)	50/94 (53.2)	1308/2053 (63.7)	5532/8631 (64.1)
GA $25^{0/7}$–$25^{6/7}$	1321/1655 (79.8)	1445/1829 (79.0)	155/197 (78.7)	381/664 (57.4)	2155/2413 (89.3)	714/1200 (59.5)	335/395 (84.8)	214/319 (67.1)	58/81 (71.6)	1815/2366 (76.7)	8593/11 119 (77.3)
GA $26^{0/7}$–$26^{6/7}$	1853/2117 (87.5)	1777/2043 (87.0)	196/231 (84.8)	659/847 (77.8)	2658/2850 (93.3)	1147/1568 (73.2)	450/509 (88.4)	384/458 (83.8)	60/78 (76.9)	2626/3091 (85.0)	11 810/13 792 (85.6)
GA $27^{0/7}$–$27^{6/7}$	2163/2346 (92.2)	2208/2412 (91.5)	295/329 (89.7)	809/947 (85.4)	3116/3301 (94.4)	1507/1842 (81.8)	539/582 (92.6)	434/478 (90.8)	107/127 (84.3)	3289/3657 (89.9)	14 467/16 021 (90.3)
GA $28^{0/7}$–$28^{6/7}$	2785/2939 (94.8)	2559/2703 (94.7)	336/362 (92.8)	1063/1156 (92.0)	3714/3850 (96.5)	1959/2210 (88.6)	624/672 (92.9)	551/581 (94.8)	140/148 (94.6)	4068/4383 (92.8)	17 799/19 004 (93.7)
GA $29^{0/7}$–$29^{6/7}$	2870/2953 (97.2)	2626/2710 (96.9)	347/358 (96.9)	1270/1345 (94.4)	3806/3925 (97.0)	2348/2540 (92.4)	650/674 (96.4)	637/653 (97.5)	170/177 (96.0)	4247/4425 (96.0)	18 971/19 760 (96.0)
GA $24^{0/7}$–$29^{6/7}$	11 785/13 239 (89.0)	11 351/12 888 (88.1)	1439/1633 (88.1)	4350/5441 (79.9)	17 192/18 421 (93.3)	7987/10 226 (78.1)	2803/3124 (89.7)	2327/2675 (87.0)	585/705 (83.0)	17 353/19 975 (86.9)	77 172/88 327 (87.4)

[a] Sweden, excluding the Skåne region.
[b] 2009–2013.
[c] 2008–2013.

and bronchopulmonary dysplasia after 2 months of age. Corchia et al[28] reported that respiratory causes and intraventricular hemorrhage were the predominant causes of death within the first 2 weeks of life, and late-onset infections and gastrointestinal causes became more prevalent after the first week. We did not have data on the causes of death, and therefore, we were unable to find reasons for differences in postnatal age at death. However, we believe that these differences are important to know and understand from health services and administrative perspectives. Other possible causes of differences in postnatal age at death can be related to the care and diagnostics during pregnancy, in addition to perinatal and neonatal care. For instance, a region with a restrictive pregnancy termination policy had a higher proportion of deaths because of congenital anomalies in the Models of OrganiSing Access to Intensive Care for very preterm births study.[29] In addition, policies and attitudes regarding redirection of care can be different in different countries and regions.[30]

Our study has several acknowledgeable strengths. We used a large, multinational, population-based cohort of very preterm infants. Data collection was standardized by using a common data set and providing clear definitions for variables before analysis. Including data from 7 consecutive years decreased the influence of random variations. All iNeo contributors have well-established data gathering systems, conduct benchmarking and quality-improvement activities, have similar antenatal health care resources, and contain nearly universal access to antenatal follow-up and public delivery hospitals. Finally, survival as the primary outcome is objective and not biased by complex definitions.

However, we must also recognize our limitations. First, varying national coverage of births in participating networks might have influenced our results. It is likely that units not participating or not providing data may have lower survival rates compared with participating units. Preliminary data from Japan suggest that units not contributing to the NRNJ have mortality rates that are 1.1- to 1.5-fold higher than NRNJ contributors for infants of <27 weeks' gestation (N.M., unpublished observations). Some networks limited their data collection to infants with a birth weight of <1500 g, which led us to restrict our whole data set accordingly. This might introduce bias because some well-grown infants in the higher-GA range are excluded. However, this bias is similar in all networks, and the results were adjusted for country-specific birth weight z scores. Likewise, some networks collect data only from tertiary neonatal units, which is likely to introduce a bias because very preterm infants born in nontertiary hospitals have

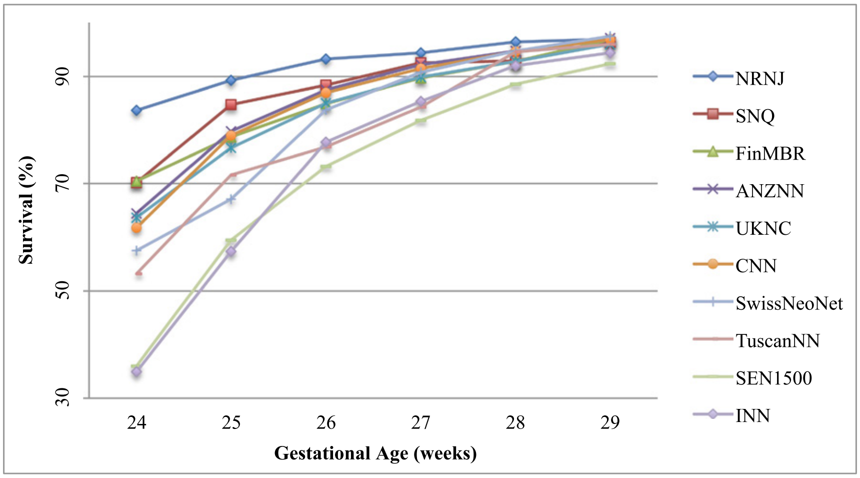

FIGURE 1
GA-specific survival for infants (24–29 weeks' gestation, birth weight <1500 g) born between 2007 and 2013 and admitted to neonatal care in the iNeo networks.

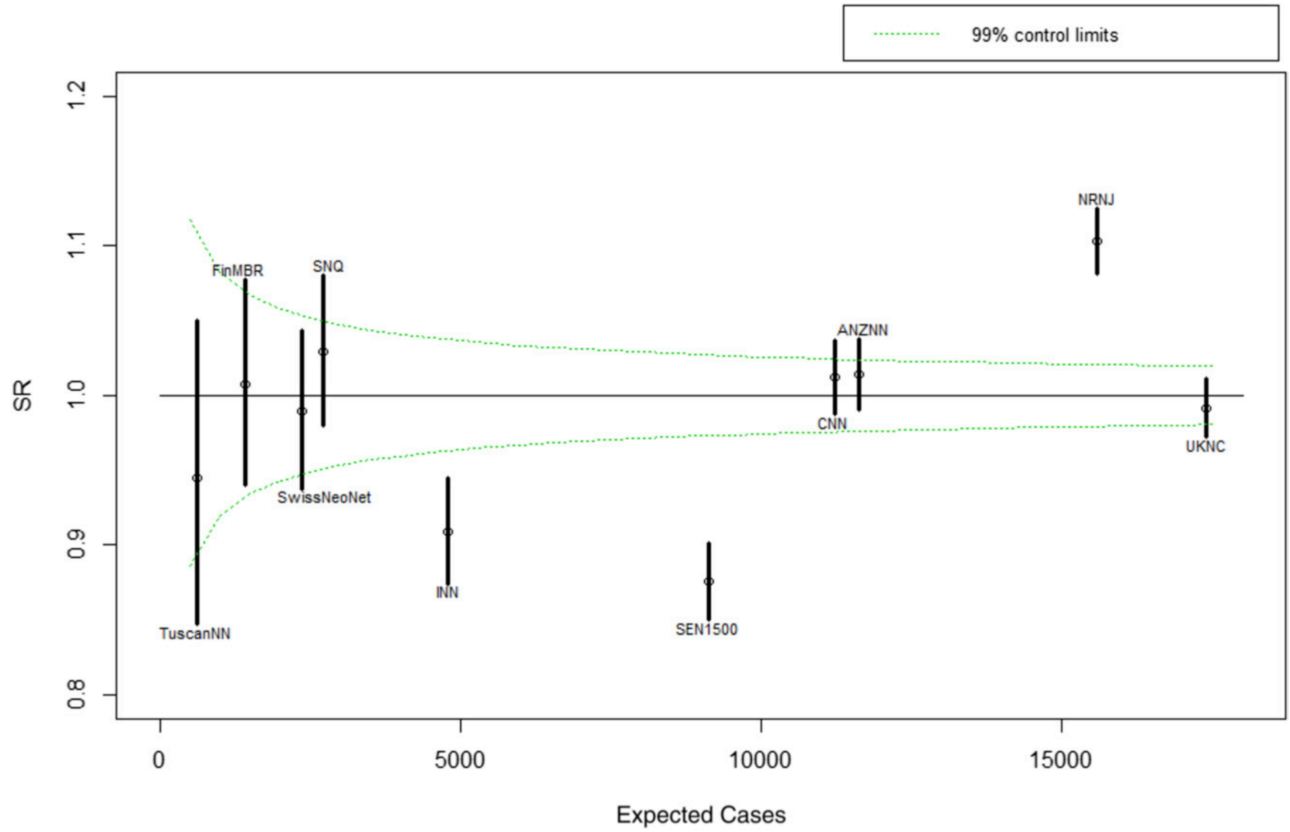

FIGURE 2
SRs of survival for infants (24–29 weeks' gestation, birth weight <1500 g) born during the study period (2007–2013) and admitted to neonatal care in each iNeo network. [a] SRs comparing the survival in each network to all other networks combined. Vertical bars are the estimated 99% CIs of the SRs. The dotted curves represent the 99% control limits expected under the null hypothesis of similar outcome rates (SR = 1).

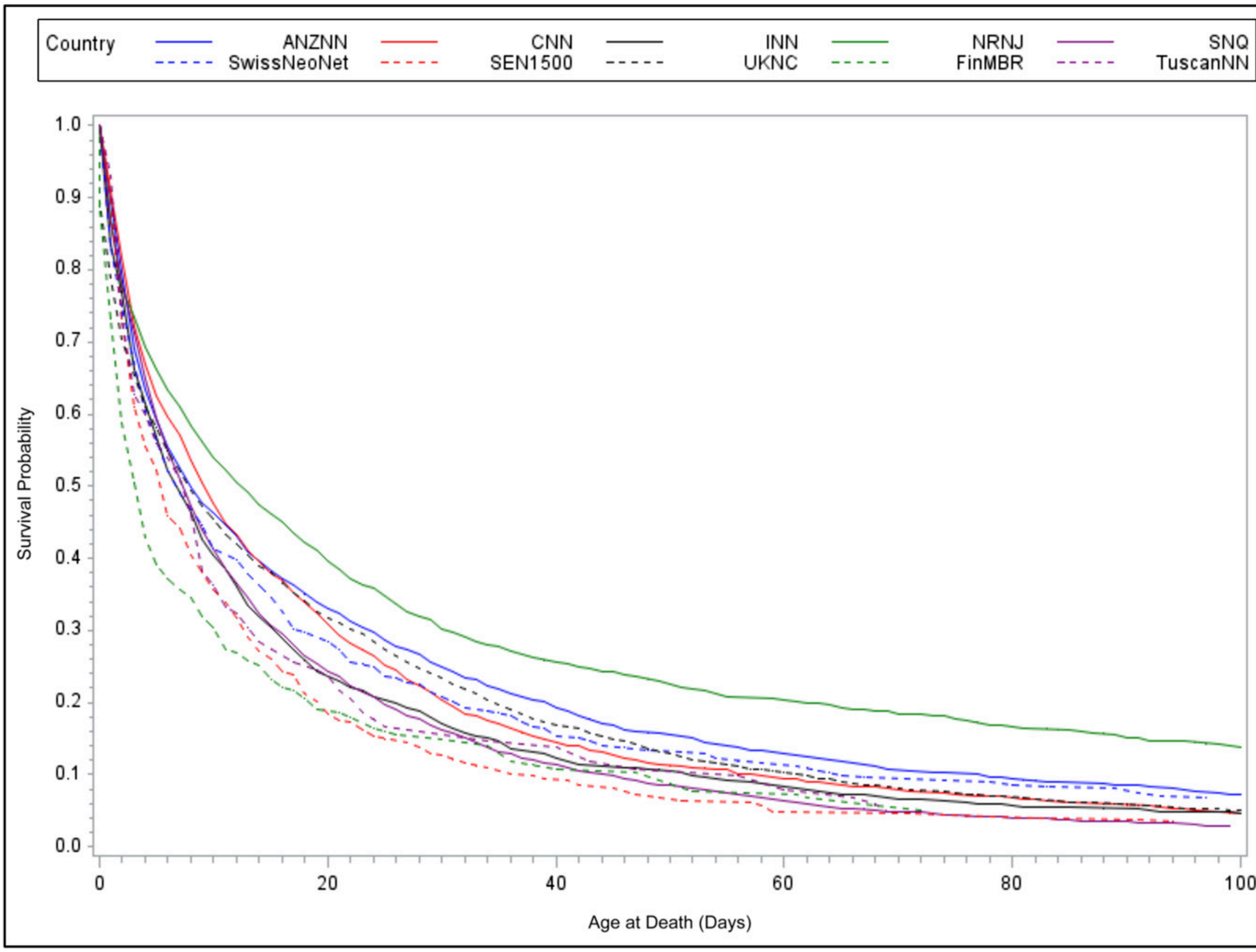

FIGURE 3

Age at death among nonsurviving infants (24–29 weeks' gestation, birth weight <1500 g) born between 2007 and 2013 and admitted to neonatal care in each iNeo network. [a] Truncated to 100 days.

higher mortality rates.[31] These issues should be considered when interpreting the results. Ideally, survival rates for each network should be calculated by using all deliveries of live fetuses at presentation to the hospital as the denominator, as done by the Extremely Preterm Infants in Sweden Study Group[12]; however, such data are not available to all iNeo contributors. Second, in some networks, data were only available until transfer to a step-down hospital. Nonetheless, death rates for very preterm infants after transfer to step-down hospitals were low in Finland because only 0.4% of the infants died after transfer but before discharge from the hospital. In Canada, Synnes et al[32] reported a 0.7% death rate between discharge from tertiary neonatal care and 18 months to 24 months of age. Third, data on delivery room deaths and stillbirths were not available; therefore, the results may not be comparable to other groups and should be used cautiously for counseling. Fourth, data on maternal conditions (eg, hypertensive disorders, preterm rupture of membranes, and perinatal infections) and reasons for prematurity (spontaneous preterm birth versus maternal or fetal indication for preterm birth) were not available in sufficient detail to be used in the analyses. However, as shown by the EPICE group, maternal factors have little effect on the variations in outcomes.[19]

In the future, similar comparisons should attempt to include all deliveries of live fetuses at presentation to the hospital. Meanwhile, networks should aim to increase the number of participating neonatal units to achieve complete population coverage, enable a comprehensive assessment of outcomes, and avoid selection biases in their evaluations.

CONCLUSIONS

Large variations in the survival of very preterm infants were evident among iNeo networks. Internetwork

TABLE 4 Age at Death Among Nonsurviving Infants (GA 24–29 Weeks' Gestation, Birth Weight <1500 g) Born Between 2007 and 2013 and Admitted to Neonatal Care in Each iNeo Network

	ANZN N, *N* = 1450	CNN, *N* = 1531	FinMBR, *N* = 194	INN, *N* = 1091	NRNJ, *N* = 1206	SEN1500, *N* = 1986	SNQ, *N* = 311	SwissNeoNet, *N* = 347	TuscanNN,[a] *N* = 102	UKNC,[b] *N* = 2621	All, *N* = 10 839
Median (IQR) age at death, d	8 (3–30)	10 (3–26)	4 (1–15)	7 (3–19)	13 (3–42)	8 (3–20)	7 (2–24)	6 (2–16)	8 (2–19)	8 (2–28)	8 (3–26)
No. missing	4	6	0	0	23	253	10	1	18	1	316
Age at death <1 d,[c] *n* (%)	146 (10.0)	139 (9.1)	52 (26.8)	179 (16.4)	155 (12.9)	266 (13.4)	52 (16.7)	34 (9.8)	7 (6.9)	554 (21.1)	1584 (14.6)
Age at death 1–6 d, *n* (%)	499 (34.4)	478 (31.2)	70 (36.1)	343 (31.4)	287 (23.8)	627 (31.6)	97 (31.2)	154 (44.4)	40 (39.2)	627 (23.9)	3222 (29.7)
Age at death 7–27 d, *n* (%)	409 (28.2)	558 (36.5)	42 (21.6)	358 (32.8)	370 (30.7)	732 (36.9)	92 (29.6)	109 (31.4)	38 (37.3)	771 (29.4)	3479 (32.1)
Age at death[c] ≥28 d, *n* (%)	396 (27.3)	356 (23.3)	30 (15.5)	211 (19.3)	394 (32.7)	361 (18.2)	70 (22.5)	50 (14.4)	17 (16.7)	669 (25.5)	2554 (23.6)
Median age at death in days according to years											
2007	8	9.5	4	7.5	11	7	4	5	—	—	8
2008	9	11.5	3	8	14	10	4	5	—	9	9
2009	7	7	3	6.5	15	8	16	6	4	9	8
2010	10	11	3.5	9	12	7	8	5	24	8	9
2011	7	9	3	7	12.5	9	13	6	5	8	8
2012	10	10	16	6	11	7	9	9	3	8	8
2013	8	10	8	6	21	8	5	6	8	7	8

—, not applicable.
[a] 2009–2013.
[b] 2008–2013.
[c] Percentage of all nonsurvivors in each network.

differences in survival were largest at 24 weeks' gestation, and relative network ranking of the survival rate persisted across the studied GAs. For nonsurvivors, the median age at death varied from 4 days to 13 days among the networks. Our results warrant further assessment of the organization of perinatal services, national guidelines, philosophy of care, and resources used for decision-making.

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ABBREVIATIONS

ANZNN: Australian and New Zealand Neonatal Network
CI: confidence interval
CNN: Canadian Neonatal Network
EPICE: Effective Perinatal Intensive Care in Europe
FinMBR: Finnish Medical Birth Register
GA: gestational age
iNeo: International Network for Evaluating Outcomes of Neonates
INN: Israel Neonatal Network
NICHD NRN: *Eunice Kennedy Shriver* National Institute of Child Health and Human Development Neonatal Research Network
NRNJ: Neonatal Research Network Japan
SEN1500: Spanish Neonatal Network
SNQ: Sweden's National Quality Registry for Neonatal Care
SR: standardized ratio
SwissNeoNet: Swiss Neonatal Network
TuscanNN: Tuscany Neonatal Network
UKNC: United Kingdom Neonatal Collaborative

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Survival in Very Preterm Infants: An International Comparison of 10 National Neonatal Networks

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