ORIGINAL ARTICLE
Pediatrics

JKMS

http://dx.doi.org/10.3346/jkms.2015.30.S1.S25 • J Korean Med Sci 2015; 30: S25-34

Changes in Survival Rate for Very-Low-Birth-Weight Infants in Korea: Comparison with Other Countries

Jae Won Shim,[1]* Hyun-Seung Jin,[2]* and Chong-Woo Bae[3]

Department of Pediatrics, [1]Kangbuk Samsung Hospital, Sungkyunkwan University School of Medicine, Seoul; [2]Gangneung Asan Hospital, University of Ulsan College of Medicine, Gangneung; [3]Kyung Hee University School of Medicine, Seoul, Korea

*Jae Won Shim and Hyun-Seung Jin contributed equally to this work.

Received: 7 May 2015
Accepted: 31 July 2015

Address for Correspondence:
Chong-Woo Bae, MD
Department of Pediatrics, Kyung Hee University Hospital at Gangdong, 892 Dongnam-ro, Gangdong-gu, Seoul 05278, Korea
Tel: +82.2-440-6130, Fax: +82.2-440-7175
E-mail: baecw@khnmc.or.kr

Funding: This work was supported by the Reseach Program funded by the Korea Centers for Disease Control and Prevention (2013-E63008-01).

Recently the Korean Neonatal Network (KNN) was established in order to enhance treatment outcomes further through the registration of very-low-birth-weight infants (VLBWI) data. The present study was conducted on 2,606 VLBWI, 2,386 registered and 220 un-registered, in the KNN participating centers, with the objective of reporting on recent survival rates of VLBWI in Korea and verifying the changing trends in survival rates with data from the 1960s and beyond. The study also aimed to compare the premature infants' survival rate in Korea with those reported in neonatal networks of other countries. The recent survival rate of VLBWI increased more than twice from 35.6% in the 1960s to 84.8%, and the survival rate of the extremely low birth weight infants (ELBWI) increased by more than 10 times, indicating improvement of the survival rate in premature infants with lower birth weight and gestational age. Comparison of VLBWI between countries showed improved survival rates according to each birth weight group in Canada, Australia-New Zealand, and European countries with Japan at the head, but in terms of comparison based on gestational age, differences, except for Japan, have been reduced. Efforts to increase the survival rate of premature infants in Korea with low birth rate are inevitable, and they should be the foundation of academic and clinical development based on its network with advanced countries.

Keywords: Infant, Newborn; Infant, Extremely Low Birth Weight; Mortality; Survival Rate; Gestational Age; Intensive Care, Neonatal

INTRODUCTION

Recently, the survival rate of high risk infants, especially premature infants has increased due to the use of antenatal steroids, pulmonary surfactant treatment, and development of perinatal health care such as respiratory and nutritional management (1-4). Even in Korea, the survival rate of very-low-birth-weight infants (VLBWI) has been reported to be constantly increasing in the past half century (5-7). However, the crude birth rate is decreasing in Korea and the level of decrease became even greater in the past years, with 1.19 per 1,000 fertile women of total fertility rate in 2013, marking the lowest in the world (8). At the same time, births of low birth weight infants, premature infants, and multiple births are increasing due to the increase of maternal age from late marriage and development of assisted reproductive technology (9,10). In fact, VLBWI whose birth weight is lower than 1,500 g or extremely low birth weight infants (ELBWI) whose birth weight is lower than 1,000 g require professional and intensive care after birth in many cases, and still have high mortality and morbidity despite such treatments (11,12). If they do not receive proper treatment, it negatively affects them, their families, and their countries economically and mentally for the rest of their lives, and the relevant social costs also increase later on. Therefore, improvement of their treatment outcomes is an important issue that Korea faces with the era of low birth rate. Although U.S. and Japan exhibit relatively high crude birth rates compared to Korea, they have recognized the importance of intensive care for infants from early on, and are collecting data by organizing a network centered on neonatal intensive care units (NICU). By sharing network data obtained from such processes, they are attempting to achieve quality improvement (QI) (13-15). Also in Korea, the Korean Society of Neonatology along with Korea Center for Diseases Control and Prevention established the Korean Neonatal Network (KNN) database based on the web-based registration system for VLBWI, among those receiving inpatient treatment in NICUs, in order to improve the survival rate of high risk infants and reduce major complications (16).

Therefore, we aimed to examine the current survival rate of VLBWI in Korea during the hospitalization in the NICU according to birth weight and gestational age, investigate the changes in the survival rate of VLBWI and ELBWI previously reported in Korea, and compare the VLBWI survival rate of Korea with those from the networks of Japan, U.S., Canada, Australia-New Zealand, and European countries.

pISSN 1011-8934
eISSN 1598-6357

MATERIALS AND METHODS

Data collection

In this study, in order to obtain the current survival rate of VLBWI in Korea based on the KNN database, data were obtained from medical records of 2,386 VLBWIs who were born or transferred within 28 days from birth to 55 medical institutes participating in the KNN study with an agreement to KNN registration and received treatment during the hospitalization at a NICU from January 2013 to June 2014. In order to reduce skew of mortality, the unregistered data of 220 patients who were admitted to a NICU participating in the KNN study with only birth weight, gestational age, and cause of death before discharge known due to parent refusal, were added after the approval of institutional review board, and a total of 2,606 VLBWIs were selected. Infants who were stillborn or died before admission to NICUs after birth were excluded from this study.

To examine the trend in survival rate of VLBWI in Korea, data from 43 survival rate report analyses covering the years 1959 to 2011 (17,18) were used as the basis and then data were added from subsequent nationwide investigations (5-7) and the current KNN study. The data were classified based on a time window on a time according to the birth year and birth weight. Then, the numbers of survival and mortality in VLBWI and ELBWI were examined and were retrospectively and comparatively analyzed (19). In addition, in order to accurately assess the trend of survival rate changes in the recent 10 yr, data on NICU survival rates previously published in 2002 (10,814 cases), 2007 (8,739 cases), and 2009 (11,864 cases), when nationwide investigations of NICU survival rates were conducted, were conducted (5-7), were compared with KNN data (2,606 cases) obtained from this study.

To compare the survival rate of VLBWIs between Korea and other countries, recent annual reports of the national neonatal networks of Japan, Canada, Australia-New Zealand, and European countries were used: Neonatal Research Network of Japan (NRNJ, 2012, 5,214 cases) (20), Canadian Neonatal Network (CNN, 2013, 2,876 cases) (21), Australia-New Zealand Neonatal Network (ANZNN, 2012, 2,981 cases) (22) and European Neonatal Network (EuroNeoNet, 2012, 5,103 cases) (23). In the cases of the U.S., data published in 2009 from Vermont Oxford Network (VON, birth weight 501-1,500 g) for birth weight (11), and data published in 2008-2011 from National Institute of Child Health and Human Development Neonatal Research Network (NICHD, gestational age 22-28 weeks) for gestational age were cited and presented (1). Birth weight and gestational age reported from each country were comparatively analyzed with Korea's KNN data for each section of birth weight and gestational age (Fig. 1).

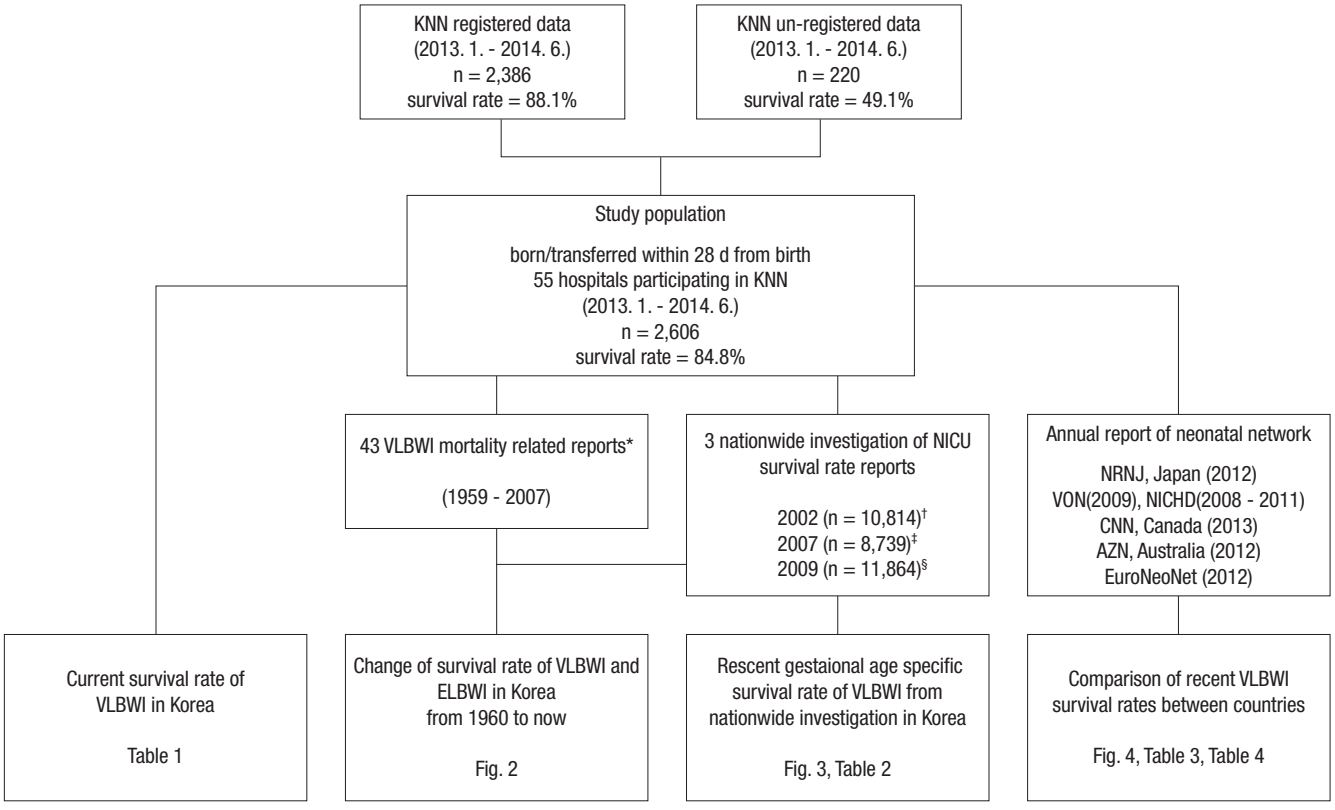

Fig. 1. Flow chart depicting the process of study. *Data acquisition from Kim et al., *Korean J Pediatr 2008* (reference 17); †data acquisition from Park et al., *J Korean Soc Neonatol 2004* (reference 5); ‡data acquisition from Hahn et al., *J Korean Soc Neonatol 2009* (reference 6); §data acquisition from Hahn et al., *J Korean Med Sci 2011* (reference 7).

http://dx.doi.org/10.3346/jkms.2015.30.S1.S25

Data analysis

For the survival rate trend of VLBWIs and ELBWIs in Korea, the total number of survivors in VLBWIs and ELBWIs and the total number of subjects were evenly distributed for each year according to study period for the data collected from each of the 46 previously published reports. Here, KNN data from 2013 to June 2014 were added, and the classified data were organized with time parameters with 5 yr intervals for presentation of the results. Thereby analyzed survival rate trend for each year with 5 yr interval was presented, and the year which showed a statistically significant difference in the survival rate compared to that from late 1960s was obtained. Regression analysis was performed for data from recent 10 yr when nationwide investigation on treatment outcomes was conducted, and after evaluating whether effects of the birth year and the gestational weeks and their correlation were significant, survival rates for each gestational age according to year was compared. Moreover, in order to verify which gestation periods showed improved survival rates based on birth year, the differences in the survival rates between adjacent gestation periods (e.g.; 23 weeks vs. 24 weeks, 24 weeks vs. 25 weeks) within the same birth year were compared. For the comparative analysis between countries, survival rate according to birth weight and gestational age addressed in the annual report of each country's network were compared with KNN data, and after evaluating whether the differences between countries, statistical differences in each gestational age and birth weight were compared to the KNN reference. In the case of the U.S., as data on the number of survivals and the total number could not be obtained, survival rate was presented but statistical comparison could not be performed.

Statistical analysis

For group comparisons of survival rate from various sources of summary data, generalized estimating equation (GEE) was conducted to incorporate dependent structures of available data, which were correlated within measurement periods. As well, unlike the comparison of the independent experimental group and the control group, survival rate data according to certain period or birth weight/gestational age of each country are repeatedly-measured data and thereby show within-subject correlation (24). If such a dependent structure within subjects are ignored and the test is performed for each time point or section to compare the means between the groups, information of changes within subjects are lost and the tests of multiple time points are performed repeatedly, thereby causing the problem of multiple comparison in which type I error increases. Therefore in this study, the survival rate of each group was compared using a generalized estimating equation, which is a regression analysis method for categorical outcomes considering within-subject correlation (25), and examined whether there were differences in the survival rate based on birth year, birth weight, and gestational age in Korea, and further analyzed the difference in the survival rates based on birth weight and gestational age between different countries. P value < 0.05 was defined as statistical significance, and significance was adjusted with the number of tests when a multiple test was needed. Statistical analyses were performed using SAS (version 9.4, SAS Institute, Cary, NC) program.

Ethics statement

The KNN registry was approved by the institutional review board at each participating hospital and informed consent was obtained from the parents at enrollment by the NICUs participating in KNN.

RESULTS

Current survival rate of VLBWI in Korea, 2013-2014. 6.

According to KNN data, the survival rate of VLBWI in Korea from January 2013 to June 2014 based on the point of discharge from the NICU was 84.8% (88.1% in KNN registered, 49.1% in un-registered), and the survival rate of ELBWI was 69.6% (76.3% in KNN registered, 19.8% in un-registered). When classified according to the gestational age, the survival rate was 13.8% at 22 weeks, 59.6% at 24 weeks, 70.4% at 25 weeks, and over 90% after 29 weeks (Table 1). The survival rate was higher as birth weight and gestational age increased, and more than two-thirds of the premature infants survived whose birth weight was higher than 700g and gestational age more than 25 weeks.

Changes of survival rate of VLBWI and ELBWI in Korea from 1960s to now

The survival rate of premature infants in Korea according to time showed a constant increase as shown in Fig. 2. From the analysis period from 1959 to June 2014 with 5 yr intervals, the VLBWI survival rate showed an increase up to 84.8% recently after a rapid increase from 35.6% in the early 1960s to 51.3% in the early 1990s. The ELBWI survival rate showed even more rapid improvement at 69.6% recently after a gradual increase from 6.5% in the 1960s to 26% in the early 1990s, showing marked improvement of survival rate within the same period compared to VLBWI. When a statistical difference in the survival rate according to each period with 5 yr intervals was analyzed based on the survival rate of the 1960s, in the early stage of the study, both VLBWI and EBLWI showed significantly rapid improvement of survival rate from the early 1990s ($P = 0.05$ for VLBWI, $P = 0.013$ for ELBWI).

Changes of recent survival rate of VLBWI and ELBWI from nationwide investigation

Three sets of data from 2002, 2007, and 2009, when nationwide investigation of VLBWI survival rate against total NICUs was con-

Table 1. Neonatal survival rates of very-low-birth-weight infants (VLBWI) and extremely low birth weight infants (ELBWI) in the Korea by the 2013-2014. 6. Korean Neonatal Network

Birth weight (g)	No* (A)	No of live† (B)	Survival rate (B/A) (%)	Gestational age (week)	No* (A)	No of live† (B)	Survival rate (B/A) (%)
< 400	15	5	33.3	21	6	0	0.0
400-499	55	22	40.0	22	29	4	13.8
500-599	119	56	47.1	23	107	44	41.1
600-699	146	90	61.6	24	156	93	59.6
700-799	220	151	68.6	25	226	159	70.4
800-899	222	182	82.0	26	229	181	79.0
900-999	267	221	82.8	27	276	238	86.2
1,000-1,099	258	237	91.9	28	332	297	89.5
1,100-1,199	252	236	93.7	29	332	314	94.6
1,200-1,299	303	281	92.7	30	273	255	93.4
1,300-1,399	375	363	96.8	31	234	228	97.4
1,400-1,499	374	366	97.9	32	127	123	96.9
Total	2,606	2,210	84.8	33	120	117	97.5
				34	75	74	98.7
				35	57	56	98.2
ELBWI	**1,044**	**727**	**69.6**	≥ 36	27	27	100.0
VLBWI	**2,606**	**2,210**	**84.8**	Total	2,606	2,210	84.8

*Total number of admission in neonatal intensive care units (NICUs): 2,386 data-locked cases + 220 unregistered cases = 2,606 cases; †Number of survived infants at time of discharge from NICU.

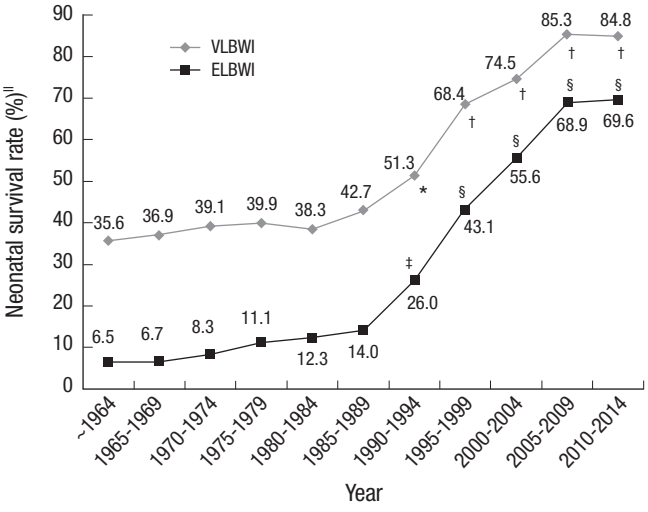

Fig. 2. Changes of neonatal survival rates for very-low-birth-weight infants (VLBWI) and extremely low birth weight infants (ELBWI) in Korea (1960-2014. 6.). *$P < 0.05$ vs. late 1960s; †$P < 0.001$ vs. late 1960s; ‡$P < 0.05$ vs. late 1960s; §$P < 0.001$ vs. late 1960s; ‖data acquisition from Kim et al., *Korean J Pediatr 2008* (reference 17); Park et al., *J Korean Soc Neonatol 2004* (reference 5); Hahn et al., *J Korean Soc Neonatol 2009* (reference 6) and Hahn et al., *J Korean Med Sci 2011* (reference 7). ELBWI, extremely low birth weight infants; VLBWI, very-low-birth-weight infants.

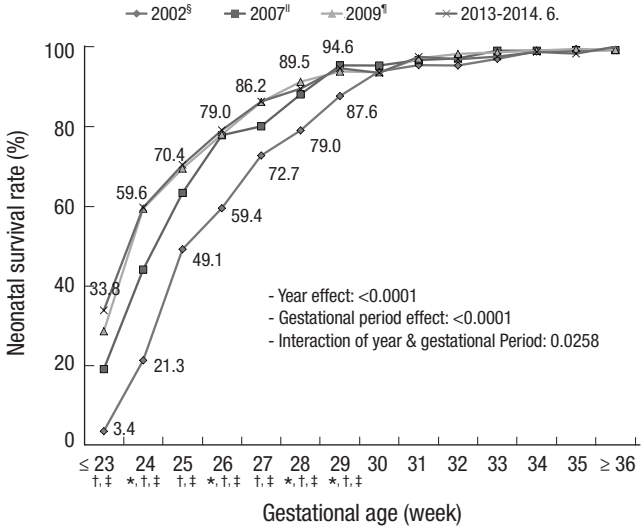

Fig. 3. Changes of neonatal survival rates by gestational period in Korea (2002-2014. 6). *$P < 0.015$, 2007 vs. 2002; †$P < 0.015$, 2009 vs. 2002; ‡$P < 0.015$, 2013-2016.6 vs. 2002; §data acquisition from Park et al., *J Korean Soc Neonatol 2004* (reference 5); ‖data acquisition from Hahn et al., *J Korean Soc Neonatol 2009* (reference 6); ¶data acquisition from Hahn et al., *J Korean Med Sci 2011* (reference 7).

ducted in Korea, and recent survival data of premature infants obtained from January 2013 to June 2014 through KNN data were classified according to gestational age to compare the changes of recent survival rate. Generalized estimating equation analysis of repeatedly measured data for gestational age according to time showed a significant difference in the corresponding year and gestational age ($P < 0.001$), and significant interaction between the year and gestational age ($P < 0.026$). Because such interaction indicates changes of survival rate in each gestational age according to time parameters, multiple comparisons of survival rates in each gestational stage according to each year was performed. When type I error was adjusted with the number of tests and compared, survival rate of premature infants with gestational age lower than 29 weeks in 2002, when the annual nationwide investigation first began, was lower than the survival rates of three investigated later ($P < 0.002$). There were no differences in the survival rate in each gestational age in 2007, 2009, and between 2013 to June 2014 (Fig. 3). When the survival rate was compared among years by paring with the contiguous ges-

http://dx.doi.org/10.3346/jkms.2015.30.S1.S25

Table 2. Comparison of neonatal survival rates of very-low-birth-weight infants (VLBWI) between adjacent gestational age in Korea

GA week	2002*			2007†			2009‡			2013-2014. 6.§		
	SR (%)	N	*P*	SR (%)	N	*P*	SR (%)	N	*P*	SR (%)	N	*P*
≤ 23	3.4	(58)		19.0	(42)		28.6	(84)		33.8	(142)	
			0.009			0.007			< 0.001			< 0.001
24	21.3	(80)		44.0	(84)		59.3	(123)		59.6	(156)	
			0.000			0.005			0.064			0.030
25	49.1	(116)		63.3	(139)		69.4	(206)		70.4	(226)	
			0.082			0.004			0.038			0.037
26	59.4	(180)		77.8	(207)		78.0	(254)		79.0	(229)	
			0.006			0.558			0.012			0.033
27	72.7	(216)		80.0	(260)		86.1	(310)		86.2	(276)	
			0.101			0.011			0.036			0.224
28	79.0	(290)		88.0	(284)		91.2	(386)		89.5	(332)	
			0.003			0.001			0.157			0.067
29	87.6	(355)		95.3	(341)		93.8	(450)		94.6	(332)	
			0.002			0.980			0.898			0.545
30	93.8	(484)		95.3	(444)		93.6	(545)		93.4	(273)	
			0.262			0.288			0.004			0.040
31	95.4	(582)		96.7	(478)		97.1	(715)		97.4	(234)	
			0.946			0.689			0.132			0.747
≥ 32	95.3	(678)		97.1	(715)		98.2	(941)		96.9	(127)	

*Data acquisition from Park et al., *J Korean Soc Neonatol 2004* (reference 5); †data acquisition from Hahn et al., *J Korean Soc Neonatol 2009* (reference 6); ‡data acquisition from Hahn et al., *J Korean Med Sci 2011* (reference 7); §current KNN study. GA, gestational age; SR, survival rate.

tational age of the corresponding year, difference in the survival rate according to gestational age was statistically significant between contiguous gestational ages under 30 weeks in 2002, under 29 weeks in 2007, under 28 weeks in 2009, and under 27 weeks from 2013 to June 2014, and this shows that improvement in the survival rate was observed at younger gestational age over time (Table 2).

Comparison of recent VLBWI and ELBWI survival rates between countries

When the difference of survival rates in each country was compared according to birth weight, total survival rates of VLBWI were 93.8% (4,892/5,214), 90.2% (2,593/2,872), 92.2% (2,749/2,981) and 89.4% (4,562/5,103) in Japan, Canada, Australia-New Zealand, and European countries, respectively, which were higher than 84.8% of Korea. Their survival rates of ELBWI were also higher than that of Korea (Japan 89.4%, Canada 79.6%, Australia-New Zealand 83.3%, and European countries 78.2% vs. Korea 69.6%, Fig. 4). When the survival rates were compared according to each section of birth weight, survival rates of 500-1,000 g in Australia-New Zealand and Europe were higher than that of Korea, but there was no difference in the survival rate for groups below 500 g and over 1,000 g. Survival rates in all sections of birth weight lower than 1,200 g in Japan and lower than 1,250 g in Canada were higher than that of Korea, and especially in Japan, survival rates in all sections with birth weight below 1,000 g were markedly higher than that of Korea (Table 3). However, when survival rates of these countries and Korea were compared according to gestational age, it showed a different trend

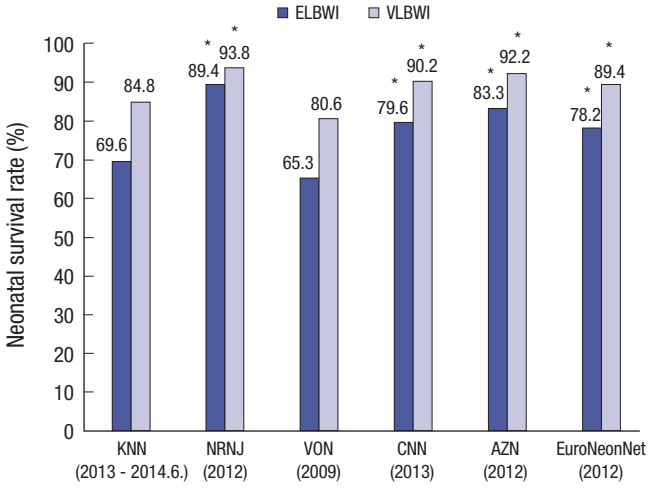

Fig. 4. Comparison of neonatal survival rate in Korea, Japan, Europe, Canada, and Autralia-New Zealand by very-low-birth-weight infants (VLBWI) and extremely low birth weight infants (ELBWI). *$P < 0.05$ comparison to the KNN reference birth weight specific survival rates. KNN, Korean Neonatal Network; NRNJ, Neonatal Research Network of Japan (reference 20); NICHD, National Institute of Child Health and Human Development Neonatal Research Network (U.S., reference 11); CNN, Canadian Neonatal Network (reference 21); AZN, Australia-New Zealand Neonatal Network (reference 22); EuroNeoNet, European Neonatal Network (reference 23); ELBWI, extremely low birth weight infants; VLWBI, very-low-birth-weight infants.

from the differences in the survival rate according to birth weight. In all countries except for Japan, differences in the survival rate with that of Korea decreased. Survival rates for 23 weeks and less, which is considered as a week for limited survival in most countries, showed no difference between Korea and all countries except for Japan. Most countries including Korea showed

Table 3. Comparison of survival rates according to birth weight for very-low-birth-weight infants (VLBWI) in networks from Korea, Japan, USA, Canada, Australia-New Zealand and European countries

Birth weight (g)	KNN	NRNJ	Birth weight (g)	KNN	VON	CNN	AZN	EuroNeoNet
	2013-2014. 6.	2012		2013-2014. 6.	2009	2013	2012	2012
< 500	38.6	69.4†	< 500	38.6		61.1*	47.4	34.2
500-599	47.1	81.6†	500-749	58.3	63.4	69.6†	74.1†	65.0*
600-699	61.6	87.9†						
700-799	68.6	92.2†						
800-899	82.0	94.9†	750-999	80.7	88.3	87.3*	90.2†	88.5†
900-999	82.8	96.7†						
1,000-1,099	91.9	94.8	1,000-1,249	92.6	94.3	95.1*	97.1†	93.4
1,100-1,199	93.7	97.2*						
1,200-1,299	92.7	98.1†						
1,300-1,399	96.8	97.6	1,250-1,499	96.7	96.5	98.4*	97.4	97.4
1,400-1,499	97.9	97.4						
ELWBI	69.6	89.4†			65.3	79.6†	83.3†	78.2†
VLBWI	84.8	93.8†			80.6	90.2†	92.2†	89.4†

*$P < 0.05$ comparison to the KNN reference birth weight specific survival rates; †$P < 0.001$ comparison to the KNN reference birth weight specific survival rates. ELBWI; extremely low birth weight infants, VLWBI; very-low-birth-weight infants, KNN; Korean Neonatal Network, NRNJ; Neonatal Research Network of Japan (reference 20), VON; Vermont Oxford Network (reference 11), CNN; Canadian Neonatal Network (reference 21), AZN; Australia-New Zealand Neonatal Network (reference 22), EuroNeoNet; European Neonatal Network (reference 23).

Table 4. Comparison of neonatal survival rate according to gestational age for very-low-birth-weight infants in 6 networks form Korea, USA, Canada, Australian-New Zealand, and Europe countries

GA	KNN	NRNJ	NICHD	CNN	AZN	GA	KNN	EuroNeonNet
	2013-2014. 6.	2012	2008-2011	2013	2012		2013-2014. 6.	2012
22	11.4	55.3†	5.2	25.0		≤ 23	33.8	20.8
23	41.1	73.8†	30.9	51.3	50.0			
24	59.6	84.2†	61	67.5	70.3*	24-25	66.0	63.2
25	70.4	93.3†	75.7	78.9*	79.9*			
26	79.0	94.6*	83.2	85.4	92.3†	26-27	83.0	86.2
27	86.2	95.6†	89	92.4*	92.9*			
28	89.5	97.0†	93.5	94.2*	94.7*	28-29	92.0	94.4*
29	94.6	96.8		96.5	95.8			
30	93.4	97.4†		98.2†	98.7†	30-31	95.3	96.9
31	97.4	98.0		98.8	98.0			
≥ 32	97.8	95.8		98.7	97.6	≥ 32	97.8	98.1
22-28 weeks	74.7	90.6†	74.4	83.9†	87.3†			
Total	84.8	93.8†		92.9†	95.2†		84.8	90.4†

*$P < 0.05$ comparison to the KNN reference birth weight specific survival rates; †$P < 0.001$ comparison to the KNN reference birth weight specific survival rates. GA, gestational age, KNN; Korean Neonatal Network, NRNJ; Neonatal Research Network of Japan (reference 20), NICHD; National Institute of Child Health and Human Development Neonatal Research Network (U.S. (reference 1), CNN; Canadian Neonatal Network (reference 21), AZN; Australia-New Zealand Neonatal Network (reference 22), EuroNeoNet; European Neonatal Network (reference 23).

60%-70% survival rate for 24-25 weeks while Japan showed a more than 80% survival rate. The survival rate of Japan showed a tendency to be maintained higher than the survival rates of other countries according to gestational age up to 28 weeks (Table 4).

DISCUSSION

According to our current KNN study, the latest VLBWI and ELBWI survival rates until NICU discharge in South Korea were 84.8% and 69.6%, respectively, indicating clear improvements (approximately two- and ten-fold, respectively) over the past half century. These improved premature infant survival rates from Korea are approaching those of the United States, Canada, Australia, and the European Union but are still far from those of Japan, which exhibits best-in-the-world treatment outcomes. In Korea, where modernized premature infant treatments started later than in other countries, there has been a pattern of low survival rates from the 1960s and gradually increasing until the 1980s, then showing dramatic increase in the 1990s that continued until the late 2000s and plateauing in the 2010s. These results are similar to those of a previous study by Kim et al. (17), who reported that improvements in survival rates of premature infants in Korea were dramatic during the early 1990s, and studies from the United States and Canada reporting that continued improvements in VLBWI survival rates were no longer seen

 http://dx.doi.org/10.3346/jkms.2015.30.S1.S25

after the 2000s (3,4,26). Actually, confirming the age-based survival rates according to previously published reports without collecting continuous treatment outcome data can create a significant amount of errors (3,13,14,27-29). Particularly in Korea, nationwide surveys on premature infant survival rates prior to the 2000s did not exist, and mostly treatment outcomes from single institutes (including four multi-center studies) of varying sizes and levels had been reported with some overlapping survey periods. Previous papers on survival rate trends simply divided the total number and the survival number of VLBWI and ELBWI reported by each institute into five-year intervals and compared them narratively (17,30). However, this method can created problems of having overlapping durations between individual studies and ignoring effect size. The present study used the number of premature infant participants and survivors reported in the study by Kim et al. (17) as the basis and added data from reports published thereafter (5-7,18) and the current KNN study for our analysis. The number of participants and survivors between each study was divided into the study duration and evenly distributed to the corresponding study year. The data evenly distributed by each year were summed according to sequential year order from 1960 to 2014, spanning the entire survey period for considering the effect size (19). Then, the data were organized by time variables of five-year increments, resolving the above mentioned problems and enabling more accurate statistical analysis. The dramatic increases in survival rates in the early 1990s in Korea that were analyzed in this manner were consistent with the timing of when Korea first began using surfactants while the number of hospitals with neonatal intensive care units equipped with incubators and artificial ventilators slowly increased (31). It is believed that the establishment of the Korean Society of Neonatology, the Korean government's expansion of support programs for premature infants, the emergence of large level III units as in developed countries, and nation-wide expansion of systematic education of neonatal cardiopulmonary resuscitation played significant roles in the dramatic increases in survival rates from the 1990s to today (31).

We confirmed that improvements in survival rates at gestational age below 29 weeks were mainly made in 2007 by performing multiple comparisons by year on three nation-wide surveys on premature infant survival rates performed in the most recent 10 yr and the survival rates per gestational age from this KNN study. Moreover, GEE statistics revealed a statistical significance in the corresponding year and gestational age, and significant interaction between the year and gestational age (Fig. 3). As a result of confirming the gestational age (statistical differences between adjacent gestational ages) in which survival rates improved for each survey year, improved survival rates were found in gestational ages of 30 weeks in 2002, 29 weeks in 2007, 28 weeks in 2009, and 27 weeks in 2013-June 2014, suggesting that survival rates in extremely premature infants are continuing to show increases in Korea, albeit slowly. This finding was in accord with the study by Kusuda et al., who reported that mortality rates for gestational age 28 weeks or higher were already sufficiently reduced and that more efforts should be made in the future for survival of smaller and more premature infants with threshold viability (32). The same study reported that survival rates of premature infants with marginal viability increased between 2003 and 2008 in Japan through a constant attitude of resuscitation. It can be inferred from the increases in the numbers and rates of registered premature infants under 28 weeks in the three nationwide retrospective studies and within the study period of the current KNN study that aggressive treatment of younger and smaller infants is also being attempted in Korea, just as in Japan (Table 2).

Although most countries have reported recent improvements in premature infant survival rates (1-4), there are still discrepancies in the survival rates between the countries, which appear prominently between developed and developing countries but also exist among developed countries (13-15,32-35). Therefore, comparing the differences in premature infant survival rates between countries and analyzing the possible causes are very meaningful and significant. However, the presence of confounding factors must be considered when comparing survival rates between countries or regions (27,28). These confounding factors include not only the biomedical domains like premature infant enrollment rate and inclusion criteria but also social domains, such as racial, economic, and political differences (37). In order to reduce these confounding factors, the current 2013-June 2014 KNN study prospectively collected data by matching the inclusion/exclusion criteria from other countries' networks as much as possible (20-23). Moreover, in order to reduce the distortion in the mortality rates, analysis included de-identified data of 220 VLBWI patients who received in-hospital treatments in the KNN participating NICU but whose guardians did not consent to participation in the study (early death was the most common reason for the non-consent, because of which the survival rates of these 220 VLBWI patients was low at 49.1% while ELBWI was 19.8%). In the present study, the survival rates of VLBWI and ELBWI in Korea were marginally lower than in most countries with which statistical comparison was possible, with the exception of the United States. Further comparisons by dividing them into more detailed birth weight groups showed that these differences can be attributed to survival rates of smaller infants below 1,000 g. However, it was discovered that comparing the survival rates between countries based on gestational age showed reduced differences in the survival rates, with the exception of Japan. Analysis of survival rates by gestational age compares birth weight-specific data to reduce the skewing caused by more mature infants based on growth restriction and is known to have the advantage of providing the doctors and parents with appropriate information before measuring the weight

prior to birth (2,3,33). As found from this comparison of the survival rate through the network data of developed countries, the reduced difference in the survival rate according to gestational age compared to that according to birth weight, but it was not analyzed in this study due to limited data whether it was because Korea had fewer cases of small for gestational age infants that had lower birth weight but somewhat more matured or because statistical power dropped due to division into smaller segments than that for birth weight. However, considering the fact that current comparative studies on premature infant survival rates regard gestational age to be more important than birth weight (33,36), the small differences in survival rates based on gestation between countries appeared to be a more favorable outcome. In the present study, statistical comparison with the United States was not possible since only the survival rates and not the number of registered infants for both birth weight and gestational age were used, but the overall survival rate was low. However, Rossen et al.'s report (38) that there was a major difference in survival rates between Caucasians and African Americans stemming from socioeconomic and racial differences points out the need for future comparisons of racial and socioeconomic differences with more detailed network data. Another interesting fact not listed in the table is that, among VLBWI, the rate of gestational age below 25 weeks was higher in Japan and Korea than in Canada and Australia. According to international comparative studies after 2000, treatment approaches for extremely premature infants can be divided into comfort (palliative) and active (intensive) care (36). The studies also reported that attempting active management on those exhibiting marginal viability resulted in increased survival rates and reduced the complication rates in infants with higher gestational ages, and continuing such effort also increased the survival rates of lower gestational ages (2,36). Considering that Japan, an exemplary country that has implemented active care for extremely premature infants, actually has the best treatment outcomes in the world, the fact that the rate of extreme premature infants being treated in Korea is high is an encouraging sign for future improvements of their survival rates. Moreover, in the case of Japan with the highest survival rate of premature infants in international comparative studies, all-out governmental support has been reported with government-supported special care for premature infants starting from 1958 followed by implementation of government support and localization of perinatal care in 1979. Moreover, a maternal-fetal ICU started operating by 1984 and it was expanded to tertiary central perinatal care centers and secondary regional perinatal care centers; moreover, and from 1996 onwards, networks were combined for each prefecture (33). As of 2012, when an annual report was published, there were 92 tertiary central perinatal care centers and 284 regional perinatal care centers (20), and the outstanding perinatal care system that covers the entire country is believed to be related to maintaining good treatment outcomes.

There are some limitations in the present study. First, since it was a retrospective study using published reports that did not include current survival rates in Korea (KNN 2013-June 2014), there may be several confounding factors. In particular, since the survival rates prior to 2000 came from individual institutes that were large hospitals with good treatment outcomes, it is possible that the national survival rates at the time could have been lower than reported. Moreover, because "pre-viable" was not defined, data on stillbirth and miscarriage from each country were missing, and there were differences in the criteria for applying resuscitation during child delivery. Furthermore, the present study did not compare morbidity even though a report on quality improvement of neonatal care indicated that treatment outcomes should be accompanied by investigations on complications or morbidity since improved survival rates in extreme premature infants can lead to increased medical costs due to increased morbidity (2,36,39). However, Japan, which exhibits the best-in-the-world premature infant treatment outcomes despite having a low birth rate similar to that in Korea, has been able to maintain its current low levels of neurological complications such as intraventricular hemorrhage and periventricular leukomalacia, by regularly performing resuscitation and treating premature infants between gestational ages of 22 and 24 weeks, this provides us with significant implications (15, 40).

Korea now has its own neonatal network that accumulates and provides accurate data on premature infants representative on a national level, similar to the Vermont Oxford Network or NICHD in the United States, Neonatal Research Network in Japan, and Canadian Neonatal Network in Canada. This network made possible investigation of survival rates as well as short- and long-term complications in premature infants. Furthermore, it was confirmed through the current KNN data (along with previously published data) that the survival rates of premature infants in Korea is continuing to increase and getting close to those from other developed countries. Moving forward, efforts will be necessary to continue accumulation of data through the Korean network and to share and analyze the data obtained with data from networks of other developed countries so that better treatment approaches can be chosen and quality improvements can be made to bring treatment outcomes in premature infants a step higher.

DISCLOSURE

The authors have no potential conflicts of interest to disclose.

AUTHOR CONTRIBUTION

Conception and design of the study: Shim JW, Jin HS, Bae CW.

http://dx.doi.org/10.3346/jkms.2015.30.S1.S25

Acquisition of data: Shim JW, Bae CW. Statistical analysis: Shim JW. First draft of the manuscript: Shim JW, Jin HS. Manuscript approval: all authors.

ORCID

Jae Won Shim *http://orcid.org/0000-0003-0101-3076*
Hyun-Seung Jin *http://orcid.org/0000-0002-3695-8080*
Chong-Woo Bae *http://orcid.org/0000-0002-0965-5674*

REFERENCES

1. Patel RM, Kandefer S, Walsh MC, Bell EF, Carlo WA, Laptook AR, Sánchez PJ, Shankaran S, Van Meurs KP, Ball MB, et al.; Eunice Kennedy Shriver National Institute of Child Health and Human Development Neonatal Research Network. *Causes and timing of death in extremely premature infants from 2000 through 2011. N Engl J Med 2015; 372: 331-40.*
2. Ancel PY, Goffinet F, Kuhn P, Langer B, Matis J, Hernandorena X, Chabanier P, Joly-Pedespan L, Lecomte B, Vendittelli F, et al.; EPIPAGE-2 Writing Group. *Survival and morbidity of preterm children born at 22 through 34 weeks' gestation in France in 2011: results of the EPIPAGE-2 cohort study. JAMA Pediatr 2015; 169: 230-8.*
3. Stoll BJ, Hansen NI, Bell EF, Shankaran S, Laptook AR, Walsh MC, Hale EC, Newman NS, Schibler K, Carlo WA, et al.; Eunice Kennedy Shriver National Institute of Child Health and Human Development Neonatal Research Network. *Neonatal outcomes of extremely preterm infants from the NICHD Neonatal Research Network. Pediatrics 2010; 126: 443-56.*
4. Agarwal P, Sriram B, Rajadurai VS. *Neonatal outcome of extremely preterm Asian infants ≤28 weeks over a decade in the new millennium. J Perinatol 2015; 35: 297-303.*
5. Park DK, Kil CH, Bae CW. *Neonatal statistics of Korea in 2002: collective results of live-births, and neonatal mortality rates from 62 hospitals. J Korean Soc Neonatol 2004; 11: 122-9.*
6. Hahn WH, Chang JY, Bae CW. *Birth statistics and mortality rates for neonatal intensive care units in Korea during 2007: collective results from 57 hospitals. J Korean Soc Neonatol 2009; 16: 36-47.*
7. Hahn WH, Chang JY, Chang YS, Shim KS, Bae CW. *Recent trends in neonatal mortality in very low birth weight Korean infants: in comparison with Japan and the USA. J Korean Med Sci 2011; 26: 467-73.*
8. Korean Statistical Information Service. *Birth statistics. Available at http://www.kosis.kr/ [accessed on 20 April 2015].*
9. Moon JY, Hahn WH, Shim KS, Chang JY, Bae CW. *Changes of maternal age distribution in live births and incidence of low birth weight infants in advanced maternal age group in Korea. Korean J Perinatol 2011; 22: 30-6.*
10. Choi SH, Park YS, Shim KS, Choi YS, Chang JY, Hahn WH, Bae CW. *Recent trends in the incidence of multiple births and its consequences on perinatal problems in Korea. J Korean Med Sci 2010; 25: 1191-6.*
11. Horbar JD, Carpenter JH, Badger GJ, Kenny MJ, Soll RF, Morrow KA, Buzas JS. *Mortality and neonatal morbidity among infants 501 to 1500 grams from 2000 to 2009. Pediatrics 2012; 129: 1019-26.*
12. Kim TH, Choi MS, Chung SH, Choi YS, Bae CW. *Morbidity of low birth weight infants in Korea (2012): a comparison with Japan and the USA. Neonatal Med 2014; 21: 218-23.*
13. Shah PS, Lee SK, Lui K, Sjörs G, Mori R, Reichman B, Håkansson S, Feliciano LS, Modi N, Adams M, et al.; International Network for Evaluating Outcomes of Neonates (iNeo). *The international network for evaluating outcomes of very low birth weight, very preterm neonates (iNeo): a protocol for collaborative comparisons of international health services for quality improvement in neonatal care. BMC Pediatr 2014; 14: 110.*
14. Kramer MS, Platt RW, Yang H, Haglund B, Cnattingius S, Bergsjo P. *Registration artifacts in international comparisons of infant mortality. Paediatr Perinat Epidemiol 2002; 16: 16-22.*
15. Isayama T, Lee SK, Mori R, Kusuda S, Fujimura M, Ye XY, Shah PS.; Canadian Neonatal Network; Neonatal Research Network of Japan. *Comparison of mortality and morbidity of very low birth weight infants between Canada and Japan. Pediatrics 2012; 130: e957-65.*
16. Chang YS, Ahn SY, Park WS. *The establishment of the Korean Neonatal Network (KNN). Neonatal Med 2013; 20: 169-78.*
17. Kim KS, Bae CW. *Trends in survival rate for very low birth weight infants and extremely low birth weight infants in Korea, 1967-2007. Korean J Pediatr 2008; 51: 237-42.*
18. Kim DH, Shim SY, Kim JR, Shin SH, Kim ES, Joung KE, Kim SD, Lee JA, Choi CW, Kim EK, et al. *Recent outcome of extremely low birth weight infants: the use of CRIB(clinical risk index for babies) II score for analyzing the survival rate. Korean J Pediatr 2006; 49: 952-8.*
19. Egger M, Smith GD. *Meta-analysis. Potentials and promise. BMJ 1997; 315: 1371-4.*
20. Neonatal Research Network Japan. *Available at http:nrn.shiga-med.ac.jp/Englishdefault.htm [accessed on 20 April 2015].*
21. The Canadian Neonatal Network TM. *Available at http://www.canadianneonatalnetwork.org/portal/ [accessed on 20 April 2015].*
22. Australian & New Zealand Neonatal Network (ANZNN). *National Perinatal Epidemiology and Statistics Unit (NPESU). Available at https://npesu.unsw.edu.au/data-collection/australian-new-zealand-neonatal-network-anznn [accessed on 20 April 2015].*
23. European Neonatal Network. *EuroNeoNet Available at http://www.euroneonet.eu/paginas/publicas/euroneo/euroNeoNet/index.html [accessed on 20 April 2015].*
24. Hanley JA, Negassa A, Edwardes MD, Forrester JE. *Statistical analysis of correlated data using generalized estimating equations: an orientation. Am J Epidemiol 2003; 157: 364-75.*
25. Hubbard AE, Ahern J, Fleischer NL, Van der Laan M, Lippman SA, Jewell N, Bruckner T, Satariano WA. *To GEE or not to GEE: comparing population average and mixed models for estimating the associations between neighborhood risk factors and health. Epidemiology 2010; 21: 467-74.*
26. Shah PS, Sankaran K, Aziz K, Allen AC, Seshia M, Ohlsson A, Lee SK; Canadian Neonatal Network. *Outcomes of preterm infants <29 weeks gestation over 10-year period in Canada: a cause for concern? J Perinatol 2012; 32: 132-8.*
27. Evans TA, Seaton SE, Manktelow BN. *Quantifying the potential bias when directly comparing standardised mortality ratios for in-unit neonatal mortality. PLoS One 2013; 8: e61237.*
28. Draper ES, Field DJ. *Epidemiology of prematurity--how valid are comparisons of neonatal outcomes? Semin Fetal Neonatal Med 2007; 12: 337-43.*

29. Terzic S, Heljic S. *Assessing mortality risk in very low birth weight infants. Med Arh 2012; 66: 76-9.*
30. Bae YM, Bae CW. *The changes in the mortality rates of low birth weight infant and very low birth weight infant in Korea over the past 40 years. J Korean Med Sci 2004; 19: 27-31.*
31. Choi JH. *Milestones of the History of Neonatal Intensive Care in Korea. Neonatal Med 2013; 20: 236-48.*
32. Kusuda S, Fujimura M, Uchiyama A, Totsu S, Matsunami K; Neonatal Research Network Japan. *Trends in morbidity and mortality among very-low-birth-weight infants from 2003 to 2008 in Japan. Pediatr Res 2012; 72: 531-8.*
33. Su BH, Hsieh WS, Hsu CH, Chang JH, Lien R, Lin CH; Premature Baby Foundation of Taiwan (PBFT). *Neonatal outcomes of extremely preterm infants from taiwan: comparison with Canada, Japan, and the USA. Pediatr Neonatol 2015; 56: 46-52.*
34. Kusuda S, Fujimura M, Sakuma I, Aotani H, Kabe K, Itani Y, Ichiba H, Matsunami K, Nishida H, Neonatal Research Network Japan. *Morbidity and mortality of infants with very low birth weight in Japan: center variation. Pediatrics 2006; 118: e1130-8.*
35. Shim JW, Kim MJ, Kim EK, Park HK, Song ES, Lee SM, Lee JH, Jin HS, Kim ES, Chang YS, et al. *The impact of neonatal care resources on regional variation in neonatal mortality among very low birthweight infants in Korea. Paediatr Perinat Epidemiol 2013; 27: 216-25.*
36. Arnold C, Tyson JE. *Outcomes following periviable birth. Semin Perinatol 2014; 38: 2-11.*
37. Upadhyay RP, Krishnan A, Rai SK, Chinnakali P, Odukoya O. *Need to focus beyond the medical causes: a systematic review of the social factors affecting neonatal deaths. Paediatr Perinat Epidemiol 2014; 28: 127-37.*
38. Rossen LM, Schoendorf KC. *Trends in racial and ethnic disparities in infant mortality rates in the United States, 1989-2006. Am J Public Health 2014; 104: 1549-56.*
39. Goldstein RF, Cotten CM, Shankaran S, Gantz MG, Poole WK; Eunice Kennedy Shriver National Institute of Child Health and Human Development Neonatal Research Network. *Influence of gestational age on death and neurodevelopmental outcome in premature infants with severe intracranial hemorrhage. J Perinatol 2013; 33: 25-32.*
40. Ishii N, Kono Y, Yonemoto N, Kusuda S, Fujimura M, Neonatal Research Network Japan. *Outcomes of infants born at 22 and 23 weeks' gestation. Pediatrics 2013; 132: 62-71.*

 http://dx.doi.org/10.3346/jkms.2015.30.S1.S25