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Trends of Outcomes Among Extremely Preterm Infants from Neonatal Research Network of Japan Database 2003-2016

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Abstract

The database of Neonatal Research Network of Japan (NRNJ) included 60,695 infants below 1,500g from 2003-2016. The annual trends of mortality of whole subjects decreased OR: 0.939, 95% CI [0.931, 0.947]. In infants at 22 weeks of gestation, the mortality decreased from 74% to 43%, OR: 0.890, 95% CI [0.859, 0.923], but the rates of cerebral palsy (CP), developmental quotient (DQ)<70 and blindness did not change in the study period. Prophylactic indomethacin significantly correlated with the reduction of pulmonary hemorrhage, and the prophylactic indomethacin has shown its effectiveness in the reduction of periventricular leukomalacia (PVL) and CP. Chronic lung disease (CLD) type 3 of Japanese CLD classification correlated with bronchial asthma. BPD36w showed adverse effects on cognitive outcomes at 3 years whereas CLD 3 did not. These findings suggest CLD type 3 better predict outcomes of preterm infants.

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Background

Survival in very preterm infants has been reported in an international comparison of 10 national neonatal networks, in which Japan was shown the largest survival rate in each gestation <29 weeks [1]. In 2012 in Japan 46.3% of total births were born in the obstetric clinic. For very low birthweight infants <1500g, a total of 7,985 infants were born and 5,287 (66.2%) were registered to NRNJ database. The aim of this study was to describe trends of survival and the neurodevelopmental and respiratory outcomes of extremely preterm infants at 3 years of age in a multicenter cohort in Japan. The outcomes of infants born at 22 weeks of gestation were of our special interests because improvements in survival have been the most significant among these infants at the limit of viability.

Subjects & Methods

Subjects of study were 60,695 infants below 1,500g from 2003 to 2016 registered in the NRNJ [2, 3]. Infants with congenital anomalies were excluded. The follow-up of children after discharge was made by each NICU with NRNJ follow-up manual. DQ was assessed by psychologists at 3 years by chronological age [4].

Statistical analysis

Fisher's exact test was used to examine categorical variables, while the Mann–Whitney nonparametric U-test was used to examine continuous variables. The outcomes were examined by logistic regression analysis. EZR (developed by Saitama Medical Center, Jichi Medical University, Saitama, Japan) was used for all statistical analyses [5] which is a graphical user interface for R software (The R Foundation for Statistical Computing, Vienna, Austria, version 4.1.0). All reported p values are two-sided, and p<0.05 was considered statistically significant.

Results

Participants

Characteristics of subjects studied are shown in Table 1. Antenatal steroid for threatened preterm labor has not been labeled until 2009, and the antenatal steroid rate was 60.0% for 2018. The outborn infants who were born elsewhere and transported to NICU after birth consists 7.0% of the database.

Mortality

Annual trends of mortality for 22w, 23w, 24w & 25w (inborn and outborn) are shown in Figure 1. Since 2003-2016 in 14 years mortality nearly halved in each gestational groups both for inborn and outborn infants. Perinatal factors for death to discharge were analyzed with logistic regression analysis, and the results are shown comparing (a) the whole infants of <1500g and (b) infants of 22-23w in Figure 2. Top three factors correlated with death were necrotizing enterocolitis (NEC), pulmonary hemorrhage and persistent pulmonary hypertension of newborn (PPHN) both for <1500g and 22-23 weeks. Factors with odds ratio and 95% confidence interval (CI) below 1 indicate the beneficial effect for reduction of mortality.

Annual trends of delivery room (DR) death and endotracheal intubation (ET) were analyzed for groups of gestational weeks. Majorities are "No DR death–ET" (increase in annual rate) and "No DR death– No ET" (decrease in annual rate). In Figure 3, Rate of "DR death – ET" group (red) and "DR death – No ET" group (green) are larger in infants 22~23 weeks than infants >23w, and this proportions decreased toward 2016. For 22, 23 weeks since 2003 to 2014 there can be seen the trend of decrease in the number of delivery room deaths both with ET and without ET.

The viability of 22 weeks in gestation has been the focus of concern in perinatal care. In NRNJ database since 2003 the number of birth of 22 weeks increased from 34 to 80/year (Table 2). The mortality decreased from 74% to 37% (2003-2013), but there was no improvement after 2014.

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	0: No, 1: Yes	n	%				
Antenatal steroid	0	30,516	51.3%				
	1	28,942	48.7%				
Cesarean section	0	12,806	21.4%				
	1	47,027	78.6%				
Cord blood transfusion	0	37,401	79.8%				
	1	9,485	20.2%				
Inborn	0	56,449	93.0%				
Outborn	1	4,246	7.0%		%C/section		
Gestational weeks	<24w	3,647	6.0%	<24w	49.4%		
	<26w	7,951	13.1%	<26w	74.9%		
	<28w	10,908	18.0%	<28w	79.2%		
	28w-	38,108	62.9%	28w-	82.0%		
5 minutes Apgar score	<4	3,762	6.3%				
	<7	12,240	20.6%				
	7-10	43,318	73%				
Respiratory distress syndrome	0	25,881	43.8%		%No RDS	%RDS	
	1	33,256	56.2%	No PH	44.8%	55.2%	
Pulmonary hemorrhage PH	0	57,106	96.8%	PH	13.8%	86.2	P<0.001
	1	1,917	3.2%				
Intraventricular hemorrhage	0	51,561	87.2%				
all IVH	1	1,917	12.8%				
IVH grade 3		1,189	2%				
IVH grade 4		1,415	2.5%				
Periventricular leukomalacia	0	57,025	96.8%		%No PVL	%PVL	
	1	1,855	3.2%	No PH	96.2%	3.0%	
Specticemia	0	54,316	92.3%	PH	92.4%	6.2%	P<0.001
	1	4,546	7.7%				
Necrotizing enterocolitis	0	58,018	98.4%				
	1	966	1.6%				
Congenital anomaly	0	57,751	92.9%				
	1	4,154	7.1%				
NICU death to discharge	0	56,161	92.6%				
	1	4,467	7.4%				

Table 1: Characteristics of subjects studied
(sub-tables)
Cesarean section rate vs gestational category
RDS vs pulmonary hemorrhage
PVL vs pulmonary hemorrhage

Chronic lung disease

We studied the outcome of preterm infants with chronic lung disease (CLD). Since 1992 we used the Japanese classification of CLD [6] (Figure 4). This classification weighs the role of inflammation in utero and evaluate the presence or absence of RDS, chorioamnionitis, and cystic/bubbly chest x-ray >28 days.

CLD type 3 is smallest in gestation among CLDs and characterized with cystic/bubbly chest x-ray >28 days. They do not develop RDS and associate with high serum IgM within 72 hours of birth and/or placental signs of chorioamnionitis. CLD type 3 account for 23% in infants of 22, 23 weeks, and because of this large number CLD type 3 has been recognized by neonatologists in Japan. CLD type 3 is compatible with Wilson-Mikity syndrome [7-9]. This syndrome rarely reported in the last decades except in Japan, and the discrepancy in the incidence remains to be elucidated.

Home oxygen therapy (HOT) rate at discharge of 32% for CLD3 is significantly larger than other CLD types. HOT rate of BPD36w is 24% at discharge and 6% at 3 years, and these HOT rates are smaller than CLD3 (Figure 5).

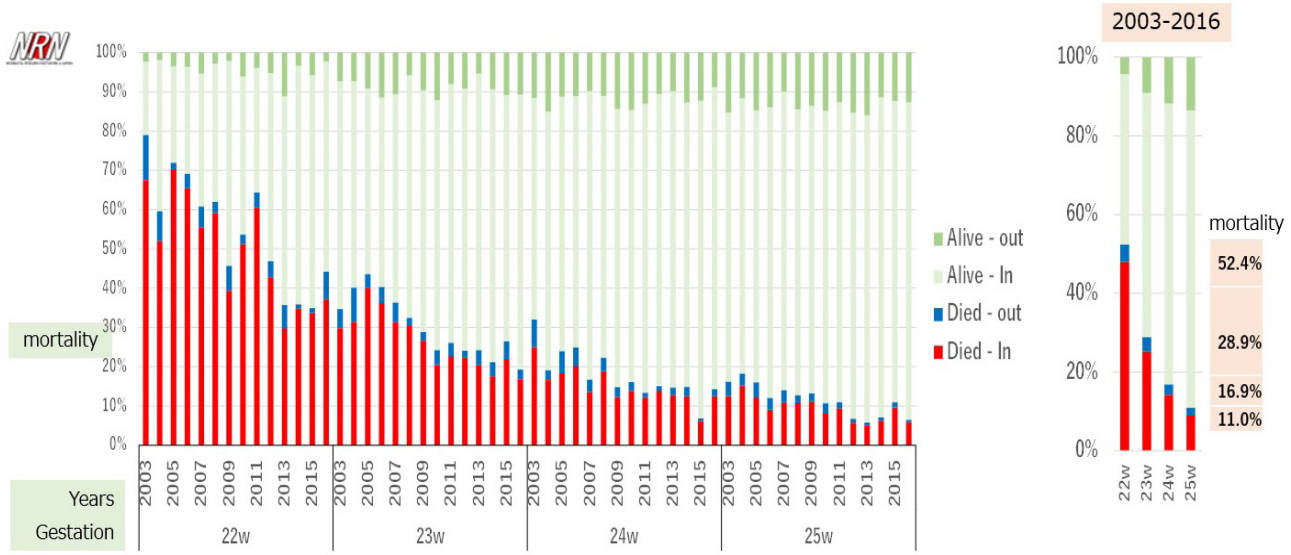
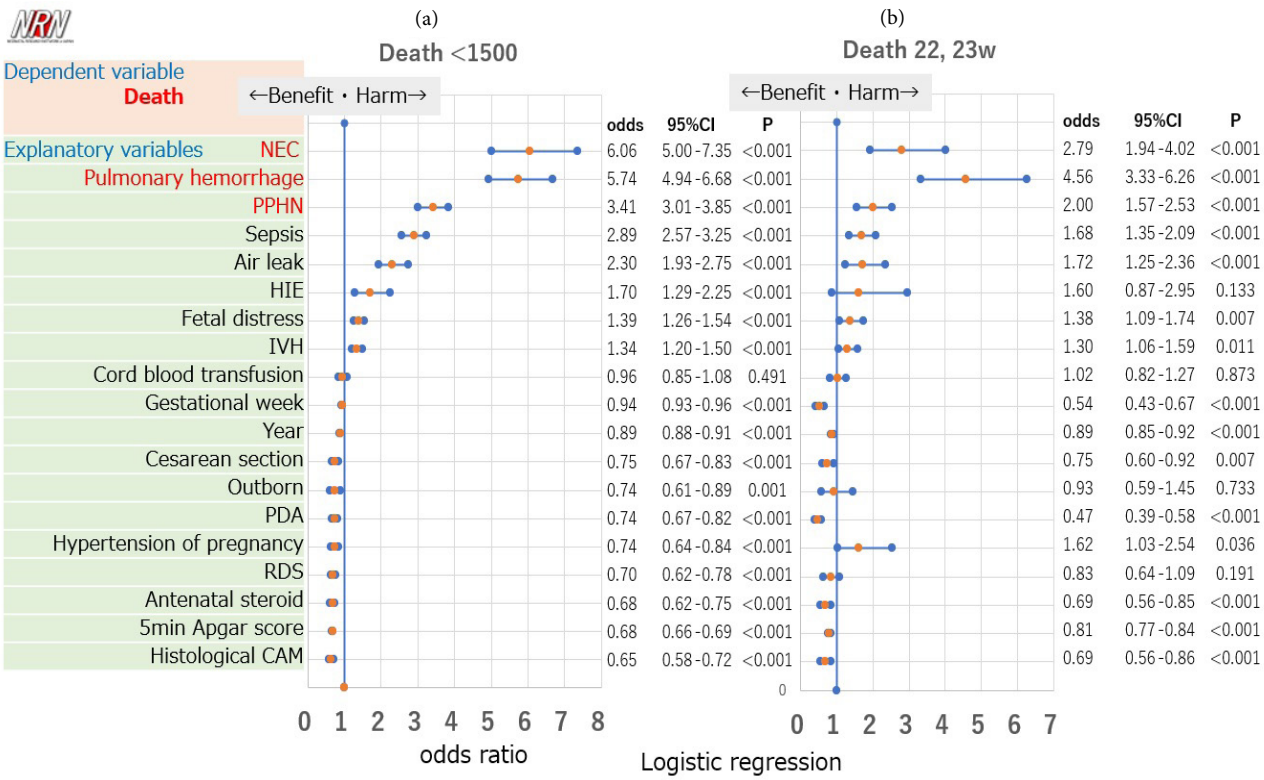


Figure 1: Annual trend of mortality for 22w, 23w, 24w & 25w (In/Out born).

In 14 years mortality nearly halved in each gestational groups both for inborn and outborn infants.



Explanatory variables	odds	95%CI	P	odds	95%CI	P
NEC	6.06	5.00-7.35	<0.001	2.79	1.94-4.02	<0.001
Pulmonary hemorrhage	5.74	4.94-6.68	<0.001	4.56	3.33-6.26	<0.001
PPHN	3.41	3.01-3.85	<0.001	2.00	1.57-2.53	<0.001
Sepsis	2.89	2.57-3.25	<0.001	1.68	1.35-2.09	<0.001
Air leak	2.30	1.93-2.75	<0.001	1.72	1.25-2.36	<0.001
HIE	1.70	1.29-2.25	<0.001	1.60	0.87-2.95	0.133
Fetal distress	1.39	1.26-1.54	<0.001	1.38	1.09-1.74	0.007
IVH	1.34	1.20-1.50	<0.001	1.30	1.06-1.59	0.011
Cord blood transfusion	0.96	0.85-1.08	0.491	1.02	0.82-1.27	0.873
Gestational week	0.94	0.93-0.96	<0.001	0.54	0.43-0.67	<0.001
Year	0.89	0.88-0.91	<0.001	0.89	0.85-0.92	<0.001
Cesarean section	0.75	0.67-0.83	<0.001	0.75	0.60-0.92	0.007
Outborn	0.74	0.61-0.89	0.001	0.93	0.59-1.45	0.733
PDA	0.74	0.67-0.82	<0.001	0.47	0.39-0.58	<0.001
Hypertension of pregnancy	0.74	0.64-0.84	<0.001	1.62	1.03-2.54	0.036
RDS	0.70	0.62-0.78	<0.001	0.83	0.64-1.09	0.191
Antenatal steroid	0.68	0.62-0.75	<0.001	0.69	0.56-0.85	<0.001
5min Apgar score	0.68	0.66-0.69	<0.001	0.81	0.77-0.84	<0.001
Histological CAM	0.65	0.58-0.72	<0.001	0.69	0.56-0.86	<0.001

Figure 2: Perinatal factors for Death (comparing <1500g and 22-23w).

Perinatal factors for death were analyzed with logistic regression analysis, and the results are shown comparing (a) the whole infants of <1500g and (b) infants of 22-23w. Factors with odds ratio and confidence interval (CI) below 1 indicating the beneficial effect for reduction of mortality are listed

Concerning the outcome of chronic lung disease, we analyzed the relationship between chronic lung disease and bronchial asthma at 3 years (Figure 6a). Bronchial asthma as the dependent variable in the logistic regression analysis CLD type 3 showed significant odds ratio of OR: 1.36, 95% CI [1.10, 1.69], P < 0.01. Recurrent upper respiratory infection at 3 years as the dependent variable, CLD type 3 had significant odds ratio of OR: 1.54, 95% CI [1.21, 1.97], and BPD36w had OR: 1.72, 95% CI [1.40-2.12], both significantly correlated with upper respiratory infection (Figure 6b). DQ<70 at 3 years of age as the dependent variable, the odds ratio of CLD type 3 was OR:1.01, 95% CI [0.84, 1.21], whereas BPD36w showed significant odds ratio of 1.45, 95%CI [1.26, 1.66] (Table 3). We concluded that CLD type 3 significantly correlates with bronchial asthma, and BPD36w showed adverse effects on cognitive outcome at 3 years whereas CLD 3 did not.

22 weeks		2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016
Mortality	Died	25	25	31	36	41	38	41	40	61	39	25	27	29	34
	Alive	9	18	14	15	24	25	42	34	35	46	43	53	51	46
	Total	34	43	45	51	65	63	83	74	96	85	68	80	80	80
	Mortality	74.0%	58.0%	69.0%	71.0%	63.0%	60.0%	49.0%	54.0%	64.0%	46.0%	37.0%	34.0%	36.0%	43.0%
CP	CP	3	1	3	1	6	3	2	3	6	7	2	5	6	1
	No CP	2	10	8	8	5	12	18	13	14	19	15	9	13	12
	Total	5	11	11	9	11	15	20	16	20	26	17	14	19	13
	%CP	60.0%	9.1%	27.3%	11.1%	54.5%	20.0%	10.0%	18.8%	30.0%	26.9%	11.8%	35.7%	31.6%	7.7%
DQ	DQ<70	0	5	2	2	4	8	6	3	12	11	7	8	6	7
	DQ>=70	0	3	5	4	3	5	12	11	5	13	9	4	8	4
	Total	0	8	7	6	7	13	18	14	17	24	16	12	14	11
	DQ<70(%)	-	62.5%	28.6%	33.3%	57.1%	61.5%	33.3%	21.4%	70.6%	45.8%	43.8%	66.7%	42.9%	63.6%
Blindness	Bi-lateral blind	1		1		1				1				1	
	Hemi-lateral blind			1											
	Total	4	8	8	5	4	4	6	5	4	5	7	3	11	3

Table 2: Annual trends of mortality, cerebral palsy, cognition and blindness of infants of 22 weeks.

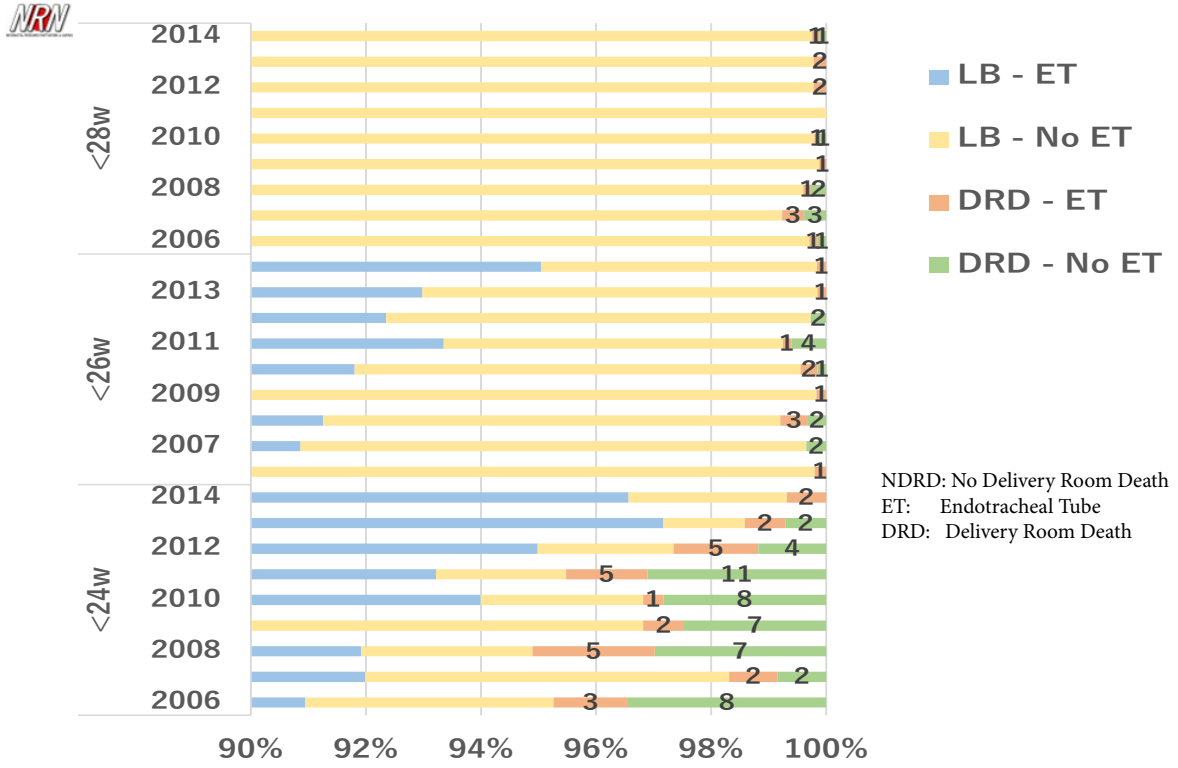


Figure 3: Relations of Delivery room death/ Endotracheal intubation / by the groups of gestational weeks.

Majorities are "No delivery room (DR) death– endotracheal tube (ET)" group (increase) and "No DR death– No ET" group (decrease). Rate of "DR death – ET" group and "DR death – No ET" group are larger in infants 22~23 weeks than infants >23w, and this proportions decreased toward 2016. For 22, 23 weeks since 2003 to 2016 there can be seen the trend of decrease in the number of delivery room deaths without endotracheal intubation.

＊Oxygen therapy >28days of age

Type of CLD	n	(%)	Gestation		RDS	High serum IgM Chorioamnionitis Funicitis	Cystic/bubbly chest X-ray >28days
			mean	SD			
1	4612	23.9%	25.7	2.1	+	—	+
2	7859	40.8%	26.9	2.2	+	—	—
3	2949	15.3%	25.2	2.0	—	+	+
4	473	2.4%	26.6	2.4	—	Unknown	+
3′	1751	9.1%	26.1	2.1	—	+	—
5	946	4.9%	27.9	2.6	—	—	—
6	700	3.6%	25.9	2.7			

CLD type 3;
Cystic/bubbly appearance on chest X-ray

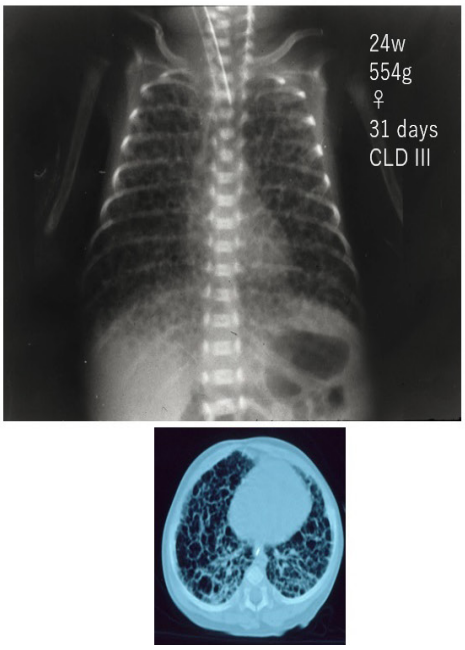
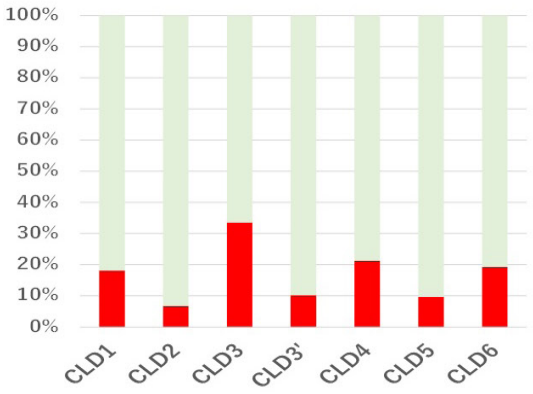
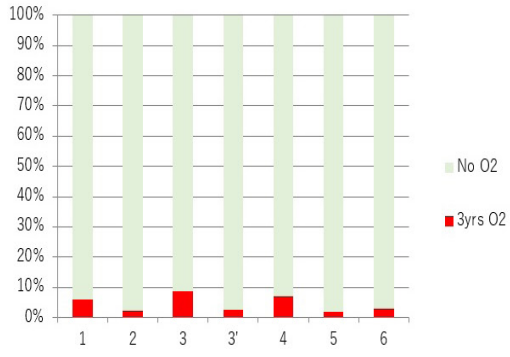


Figure 4: Japanese Classification of Chronic Lung Disease.

CLD is defined by the use of oxygen therapy >28days of age. The types of CLD is classified according to the presence or absence of RDS, signs of inflammation at birth, and cystic/bubbly chest x-ray >28 days.





Significance of differences (p)

	CLD2	CLD3	CLD4	CLD5	CLD2	CLD6
CLD1	<0.0001	<0.0001	<0.0001	NS	<0.0001	NS
CLD2	-	<0.0001	0.0075	<0.0001	.00874	<0.0001
CLD3	-	-	<0.0001	0.00286	<0.0001	<0.0001
CLD3"	-	-	-	<0.0001	NS	<0.0001
CLD4	-	-	-	-	0.00062	NS
CLD5	-	-	-	-	-	0.00229

Mann-Whitney U test

CLD type	1	2	CLD3	3′	4	5	6	BPD36w
HOT at discharge	17%	6%	32%	9%	20%	10%	18%	24%
HOT at 3 years	5%	2%	8%	2%	7%	2%	3%	6%

Figure 5: Home oxygen therapy.

HOT rate of 32% for CLD3 is significantly larger than other CLD types,
HOT rate of BPD36w is 24% at discharge and 8% at 3 years. These HOT rates are smaller than CLD3.

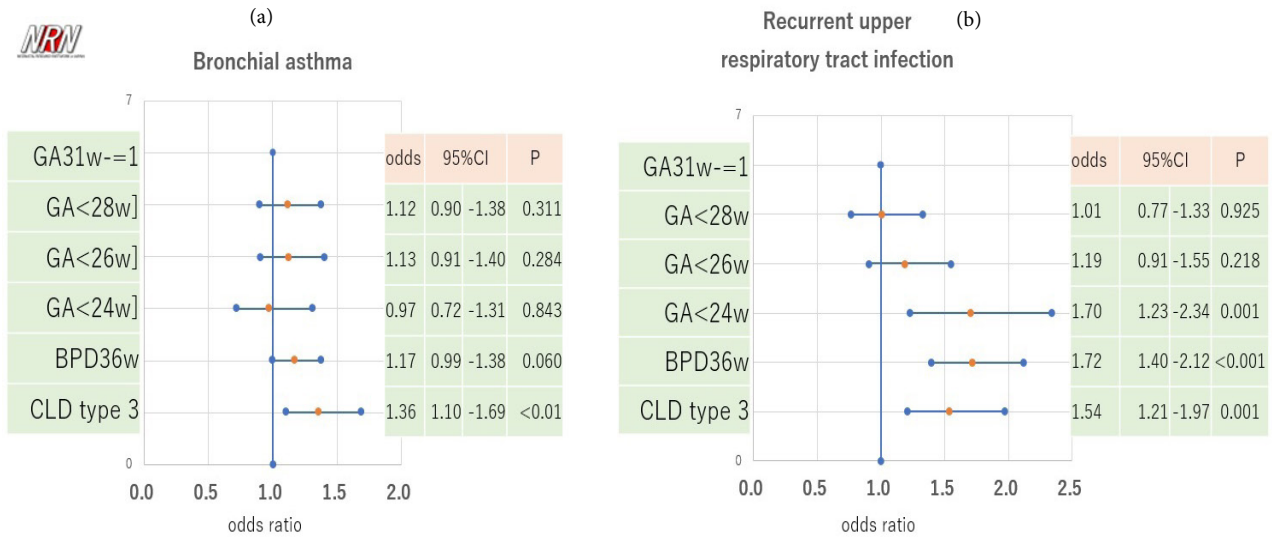


Figure 6: Bronchial asthma, Recurrent upper respiratory infection at 3 years for infants with BPD36w or CLD type 3 during the neonatal period.

Bronchial asthma as the dependent variable in the logistic regression analysis CLD type 3 showed significant odds ratio of OR:1.36,95%CI [1.10,1.69]P<0.01. Recurrent upper respiratory infection at 3 years as the dependent variable, CLD type 3 had significant odds ratio of OR:1.54,95%CI [1.21,1.97], and BPD36w had OR:1.72,95%CI [1.40-2.12], both significantly correlated with upper respiratory infection.

Dependent variable: DQ<70 at 3 years	odds ratio	95%CI		P
Gestational age weeks	0.86	0.83	0.88	<0.001
CLD type 3	1.01	0.84	1.21	NS
BPD36w	1.45	1.26	1.66	<0.001

Logistic regression analysis

Table 3: Logistic regression analysis of DQ<70 at 3 years as with CLD type 3 and BPD36w independent variables.

BPD36w showed adverse effects on cognitive outcome at 3 years whereas CLD 3 did not.

Prophylactic indomethacin, pulmonary hemorrhage, and periventricular leukomalacia

We analyzed the annual trend of PVL, and the results are shown in Figure 7. The number of PVL significantly decreased in infants of 24-27w. The incidence and relationships of RDS, PH and PVL are shown in Table 1. The rate of PVL significantly correlates with pulmonary hemorrhage.

In a randomized controlled trial for the prevention of intraventricular hemorrhage in Japan, we have found that the prophylactic indomethacin significantly reduced pulmonary hemorrhage for infants <1000g (indomethacin /placebo; 10/27: 235/234, P<0.004) [10]. (For prophylactic indomethacin, starting within 6 hours of birth, 3 doses of indomethacin were given with 6 hours' continuous i.v. infusion every 24 hours. Indomethacin was given at the dose of 0.1 mg/kg-wt/dose.). In the trial the rate of pulmonary hemorrhage in prophylactic indomethacin group was 4.3% which was significantly low compared with placebo group (11.5%). Since 2006 in Japan the prophylactic indomethacin has been the recommended use for preterm infants <1000gm. We then had the opportunity to study the effect of prophylactic indomethacin on pulmonary hemorrhage and PVL in the NRNJ database. The rate of pulmonary hemorrhage in prophylactic indomethacin group was 3.5% (37/1023: 24, 25w)~ 4.7% (23/464: 22, 23w), being very close to the rate noted in RCT. PVL significantly correlated with pulmonary hemorrhage in a multivariate-analysis of perinatal factors with odds ratio 1.70, 95% CI [1.40, 2.07].

In Table 4 with CP as a dependent variable the results of logistic regression analysis of gestational weeks, prophylactic indomethacin, pulmonary hemorrhage, and periventricular leukomalacia are shown. Prophylactic indomethacin is a beneficial factor for CP, and pulmonary hemorrhage and PVL are adverse factors to CP. In the real data evidence, therefore, the prophylactic indomethacin has shown its effectiveness in the prevention of CP.

dependent variable		
Cerebral palsy (3 years)	odds ratio	95%CI
Gestational age weeks	0.83	0.81-0.85
prophylactic indomethacin	0.76	0.60-0.96
pulmonary hemorrhage	2.33	1.83-2.96
periventricular leukomalacia	14.6	12.50-16.90

Logistic regression analysis

Table 4: Logistic regression analysis of CP with gestation, prophylactic indomethacin, pulmonary hemorrhage, and periventricular leukomalacia as independent variables.

Prophylactic indomethacin is a beneficial factor for CP, and pulmonary hemorrhage and PVL are adverse factors to CP.

Neurodevelopmental outcomes

Figure 8 summarizes the annual trends of disabilities including cerebral palsy (CP), cognitive development, visual impairment and use of hearing aids at 3 years. Data were available for CP in 57% and for the cognitive assessment 30%. CP decreased from 10% to 5% in 14 years. The rates of DQ < 70 and < 85 have not improved. Annual change of visual impairment shows gradual improvement. The blindness has decreased, but myopia and other impairments remain in similar rate. There was no change in the use of hearing aids.

The annual trends of 22 weeks for the CP rate decreased (OR: 0.96 [0.88, 1.06]), the rate of DQ < 70 increased (OR: 1.05 [0.95, 1.15]), and the rate of blindness decreased (OR: 0.87 [0.69, 1.10]) in 14 years (Table 2).

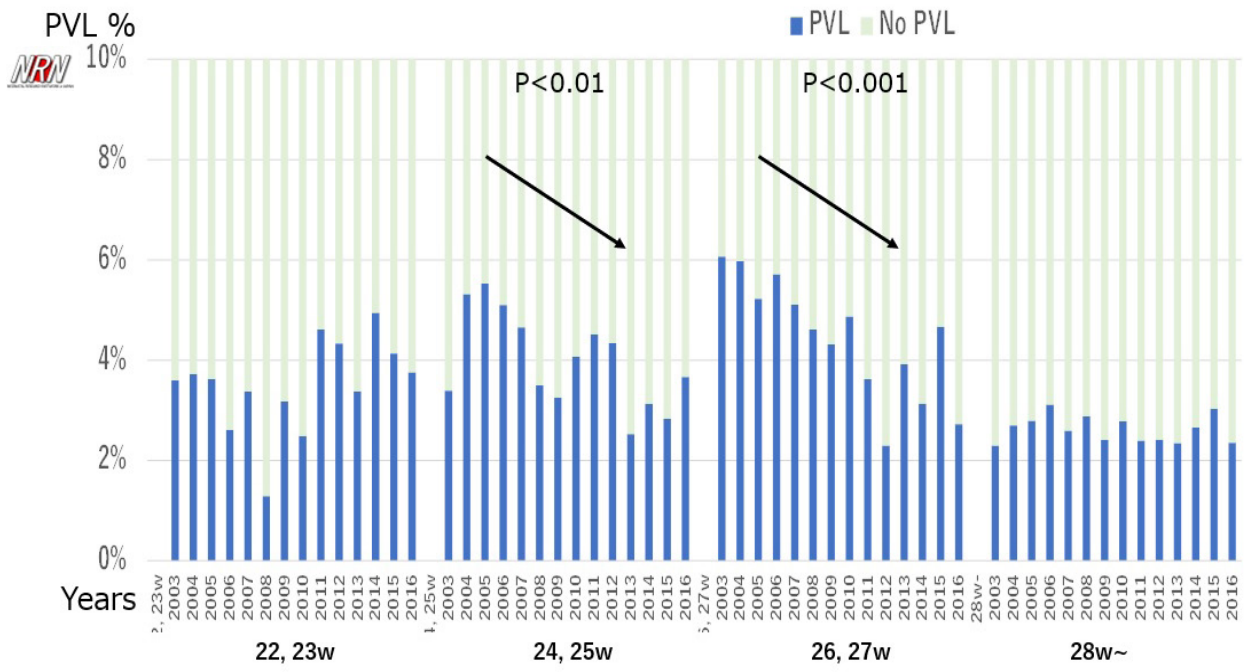


Figure 7: PVL number significantly decreased in infants of 24, 25w, 26w and 27w.

The number of PVL significantly decreased in infants of 24-27w. PVL significantly increased with pulmonary hemorrhage with odds ratio 1.70 (1.40-2.07).

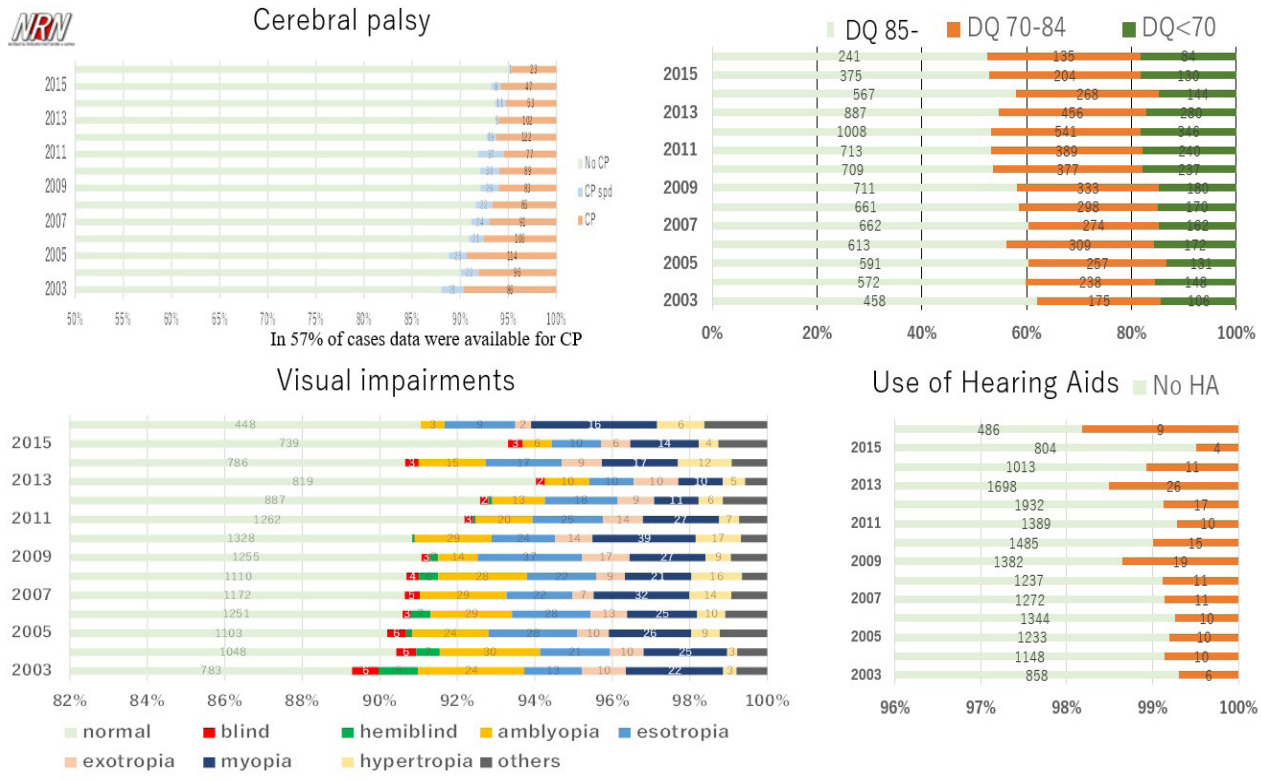


Figure 8: Annual Trends of Neurodevelopmental Impairments.

CP decreased from 10% to 5% in 14 years. The rate of DQ<70 and <85 have not improved. Annual change of visual impairment shows gradual improvement. There was no change in the use of hearing aids.

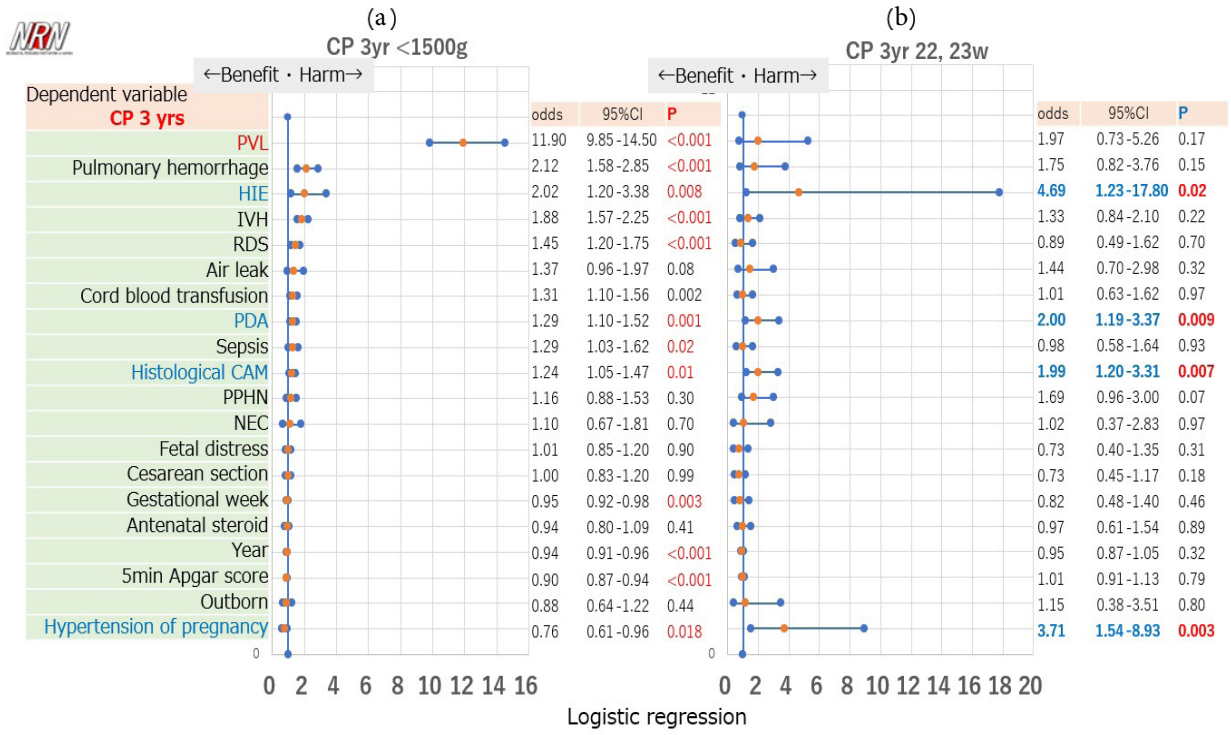


Figura 9: Perinatal factor for CP 3 years (comparing <1500g and 22-23w).

PVL was the strongest factor for birth weight<1500g, but for infants of 22-23 weeks HIE, PDA, CAM and hypertension of pregnancy were significant factors.

In Figure 9 perinatal factors for CP at 3 years were analyzed with logistic regression analysis in (A) all infants with birth weight <1500g and in (B) infants born at 22 or 23 weeks. Annual decrease of CP was shown for infants <1500g. Periventricular leukomalacia (PVL) was the strongest factor for CP in infants with birthweight <1500g. Prophylactic indomethacin was shown to reduce CP through prevention of pulmonary hemorrhage. In infants of 22-23 weeks HIE, patent ductus arteriosus (PDA), histological chorioaminionitis (CAM) and hypertension of pregnancy were significant adverse factors.

Discussion

This study is one of the largest to deal with 22 and 23 weeks in relation with neurodevelopmental and respiratory outcomes (n=3,647). The survival rates were 50% for 22wks and 70% for 23wks, and the neurological, cognitive, visual, and hearing outcomes were presented. Using the accumulated data of 14 years, we could demonstrate either the trend of improvement or no improvement which may reflect the change of neonatal care. Since 2006 more than 70 peer reviewed articles utilized the NRNJ database [11].

During the study period a significant reduction of CP was noted. This study made it clear that prophylactic low dose indomethacin within 72 hours of age significantly reduced pulmonary hemorrhage and correlated with the reduction of PVL. For 22, 23 weeks since 2003 to 2016 there can be seen the trend of decrease in the number of delivery room deaths indicating more active resuscitation for extreme preterm delivery.

Chronic lung disease has been one of the adverse factors for cognitive delay of extreme preterm infants. We have shown that BPD36w significantly correlated with DQ<70 or death at 3 years of age. We have no explanation yet on the reason that CLD type 3 did not correlate with poor cognitive function even though they were smallest in gestation with largest HOT rate among CLDs.

In this study we have shown that the CLD type 3 by the Japanese classification significantly correlated bronchial asthma at 3 years of age, whereas BPD36w did not. CLD type 3 is characterized with cystic/bubbly emphysema during the neonatal period, and Hirata et al reported that the neonatal pulmonary emphysema was associated with obstructive disorder at 8 years of age [12]. We have shown that the CLD type 3 predict the bronchial asthma at 3 years among various CLDs.

Conclusions

The neonatal network database of Japan included 60,000 infants below 1,500 g in 2003-2016. In the infant at 22 weeks of gestation, the mortality decreased from 74% to 43%, the rate of CP, DQ<70 and the blindness did not change. Prophylactic indomethacin significantly reduced pulmonary hemorrhage and was effective in the prevention of PVL and CP. CLD Type 3 at four weeks of age significantly correlated with bronchial asthma at 3 years. BPD36w showed adverse effects on cognitive outcomes at 3 years whereas CLD 3 did not. CLD type 3 of Japanese classification could better predict outcomes of preterm infants. NRNJ database have maintained activities for over 15 years, and aims to be sustainable for real data evidence on a voluntary basis, supported by staff in neonatal care.

Limitations

NRNJ was designed as a database obtained from routine clinical work in the daily intensive care activities. No fulltime personnel were

available for this project, and this resulted relatively large missing follow-up data. In 43% of cases data were not available for CP. In only 30% the cognitive assessment by psychologists were available. Even with these limitations NRNJ database still works as a valuable big data in relation with outcomes of neonatal care as shown by peer reviewed articles [11].

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Competing Interests

The authors declare that they have no competing interests.

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