

The Evidence from NRNJ database for VLBW Vol 2

(2021 revision)

(2003-2016)

Definitions
Annual trend of ex-preterm/ gestation
Limit of viability for extremely preterm infants
Mortality for certain disorders; Overview
Neuro-developmental disabilities (<28w, 3 years)

Masanori Fujimura, Satoshi Kusuda, Yumi Kono, Hidehiko Nakanishi, Shinya Hirano, Naohiro Yonemoto, for the Neonatal Research Network of Japan

Neonatal Research Network of Japan 2020



The Neonatal Research Network of Japan

OBJECTIVES

The objectives of this study were to describe the characteristics and morbidity of very low birth weight infants, to identify the medical intervention for these infants, and to evaluate the factors affecting the outcome of these infants ^{1, 2)}.

METHODS

A large multicenter neonatal research network that included level III NICUs from throughout Japan was established. The network included 202 centers and 60,632 infants weighing at or below 1,500 g, born or admitted to the centers in 2003-2016. Multivariate analyses using logistic regression for variables of VLBW were performed to calculate odds ratio of perinatal factors. All the factors included in the model are presented in the figure or table. Statistical analyses were performed using EZR.

The NRNJ was supported by the Research Grant of Ministry of Health, Labor and Welfare of Japan, 2003-2016.

- 1. Satoshi Kusuda, Masanori Fujimura, Izumi Sakuma, Hirofumi Aotani, Kazuhiko Kabe, Yasufumi Itani, Hiroyuki Ichiba, Katsura Matsunami, Hiroshi Nishida and for the Neonatal Research Network of Japan. Morbidity and Mortality of Infants With Very Low Birth Weight in Japan: Center Variation. Pediatrics 2006;118;e1130-e1138; originally published online Sep 1, 2006
- 2. Kono Y, Yonemoto N, Nakanishi H, et al. Changes in survival and neurodevelopmental outcomes of infants born at <25 weeks' gestation: a retrospective observational study in tertiary centres in Japan. BMJ Paediatrics Open 2018;2:e000211. doi:10.1136/bmjpo-2017-000211



Definitions

We compiled a network database operation manual to define the patient characteristics. In the manual, the day of birth was defined as day 0. **Neonatal mortality** was defined as death within 28 days of birth and mortality before discharge as death occurring before discharge from a participating NICU. **Gestational age** (GA) was determined in the following order: obstetric examination with ultrasonography, obstetric history based on last menstrual period, and then postnatal physical examinations of neonates. Infants weighing 10th percentile of the normal birth weight curve at each GA were defined as light for GA.2 Maternal diabetes mellitus (DM) or gestational DM (GDM) and maternal hypertension were determined according to the diagnostic criteria. **Premature rupture of** membranes (PROM) was defined as rupture of membranes before an onset of labor. Clinical chorioamnionitis was diagnosed based on the clinical findings, such as maternal fever, leukocytosis, and local pain. Histologic chorioamnionitis was defined according to the criteria reported by Blanc. **Antenatal steroid** (ANS) usage was defined as the administration of any corticosteroids to accelerate fetal lung maturity. **Surfactant** therapy meant pulmonary surfactant (Surfacten) given during the acute phase of respiratory problems. Respiratory distress syndrome was diagnosed based on the clinical and radiographic findings. Chronic lung disease (CLD) was defined when an infant received supplemental oxygen on the 28th day after birth (Page 70 for definition), and 36-week CLD was defined when an infant received supplemental oxygen at the 36th week postmenstrual age. **Postnatal steroid** (PNS) usage meant any steroids given during the hospital stay for the prevention or treatment of CLD. Symptomatic patent ductus arteriosus (PDA) was diagnosed based on both the echocardiographic findings and clinical evidence of a volume overload because of a left-to-right shunt. **Persistent pulmonary hypertension** of the newborn (PPHN) was defined as right-to-left shunt at the foramen ovale and/or ductus arteriosus without any anatomic malformations as detected by cardiac echocardiography. **Intraventricular hemorrhage** (IVH) was reported according to the classification of Papile et al. **Necrotizing enterocolitis** (NEC) was defined according to the classification of Bell et al: stage II or greater. Gastrointestinal perforation was diagnosed if free air was detected in the abdominal cavity by radiograph examination regardless of cause. **Sepsis** meant culture-proven septicemia or bacteremia at any time during the stay in the NICU. A **cystic** periventricular leukomalacia (PVL) diagnosis was made by using either head ultrasound or cranial MRI scans, performed either at 2 weeks of age or later. **Intrauterine infection** was diagnosed if any inflammatory response was detected in the infants at birth. **Retinopathy of prematurity** (ROP) was diagnosed if the infants were treated with laser coagulation, cryocoagulation therapy, or both. Patients were classified into adrenal insufficiency of prematurity (AOP) when any steroids were administered during the hospital stay for the treatment of a late-onset circulatory collapse of premature infants because of an impaired adrenal function. Major congenital **anomalies** did not include external malformation.

• Morbidity and Mortality of Infants With Very Low Birth Weight in Japan: Center Variation Satoshi Kusuda, MDa, Masanori Fujimura, MDb, Izumi Sakuma, MDa, Hirofumi Aotani, MDc, Kazuhiko Kabe, MDd, Yasufumi Itani, MDe, Hiroyuki Ichiba, MDf, Katsura Matsunami, MDb, Hiroshi Nishida, MDa, for the Neonatal Research Network, Japan. PEDIATRICS Volume 118, Number 4, October 2006



The Evidence from NRNJ database for VLBW (2003-2016) -Vol 2-

Contents

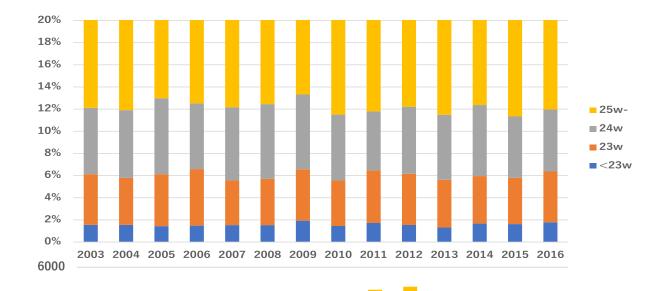
60,632 infants ≤1,500 g

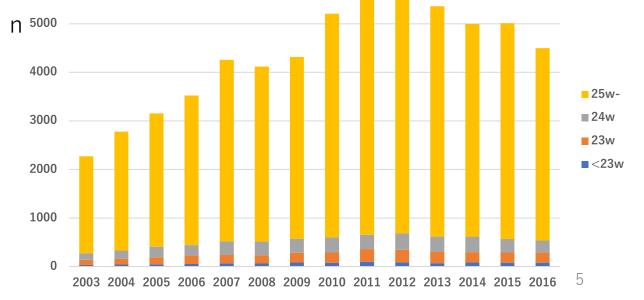
page	SUBJECT
5	Annual trend of extremely preterm/ gestation
6	Vital statistics of Japan vs NRNJ data-base
7-13	Limit of viability for extremely preterm infants
15-21	 Mortality of extremely preterm infants for certain disorders Place of birth, Gender, Fetal monitoring, Presentation, Umbilical transfusion SFD, Mode of delivery, Zygocity, DM, PIH, CAM, PROM, Antenatal steroid Seizure, IVH, PVL, HIE CLD, PDA, Adrenal insufficiencySepsis NEC, TPN, Intestinal perforation, Surgical operation, Blood transfusion, ROP treatment, Congenital malformation Oxygen therapy, CPAP, IPPV
22-30	Neuro-developmental disabilities (<28w, 3 years) 2003-2016



NRNJ Database 2003-2016 Annual trend of ex-preterm/ gestation

NRNJ0522	<23w	23w	24w	25w-	Total
2003	35	104	136	1,995	2,270
2004	43	118	170	2,449	2,780
2005	45	148	216	2,744	3,153
2006	52	180	209	3,082	3,523
2007	65	172	281	3,741	4,259
2008	63	172	278	3,608	4,121
2009	83	200	292	3,741	4,316
2010	75	214	310	4,607	5,206
2011	95	263	295	4,885	5,538
2012	86	259	339	4,915	5,599
2013	70	231	315	4,745	5,361
2014	83	214	321	4,378	4,996
2015	81	210	277	4,444	5,012
2016	80	206	252	3,960	4,498
Total	956	2,691	3,691	53,294	60,632







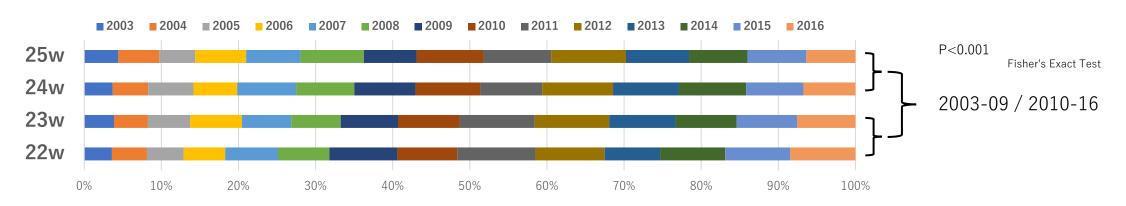
Vital statistics of Japan vs NRNJ data-base

◆ NRNJ data-base comprises approximately 65% of very low birthweight infants of Japanese census born in 2015/2016.

Year	Birth weight	Vital statistics of Japan	NRNJ	NRNJ/Japan
2015	-999g	3,084	2,083	0.675
	1000-1499g	4,426	2,927	0.661
2016	-999g	2,891	1,830	0.633
	1000-1499g	4,124	2,614	0.634

◆ A significant increase of smaller gestations(22, 23w) comparing those of (24, 25w) between 2003-09 with 2010-16.

Annual trend of gestational ratio





Limit of viability for extremely preterm infants



Limit of viability for extremely preterm infants *

```
1. Take an example gestation (for example 24 weeks at birth),
    and analyze annual trend of:
      (1)Survival rate (2)Major disability rate (for example 3 years)
2. How is the expected result of following questions?
Q ①: What is the survival rate?
                         Decreasing survival
                                                      Inappropriate to care for this gestation.
   Type 1
   Type 2
                         No change in survival
                                                   ⇒ Need to re-examine the care for this gestation.
            Improving the survival
                                      \Rightarrow Go to \bigcirc
   Type 3
Q 2: What is the major disability rate among the survivors?
                                                        Inappropriate to care for this gestation.
   Type A
                         Increasing
   Type B
            No change
                                                        Near to the limit for this gestation, but acceptable.
                                         The limit of viability may still be lower gestation.
   Type C
            Decreasing
Definition of viablity
  Type 3 B or C NICU is entitled for care of extremely preterm infants"
```

Let's apply this proposal to extremely preterm infants cared for in NRNJ 2003-2016.



100.0%

Total

100.0%

100.0%

100.0%

100.0%

100.0%

100.0%

100.0%

100.0%

100.0%

100.0%

100.0%

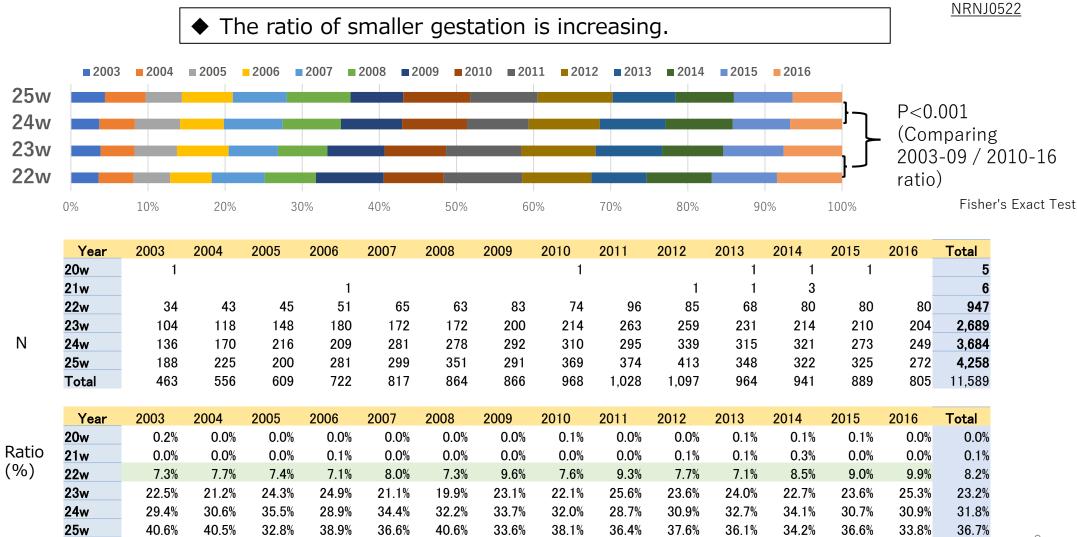
100.0%

100.0%

100.0%

Annual trend of admissions (2003-2016) 22w, 23w, 24w & 25w

Database20200122





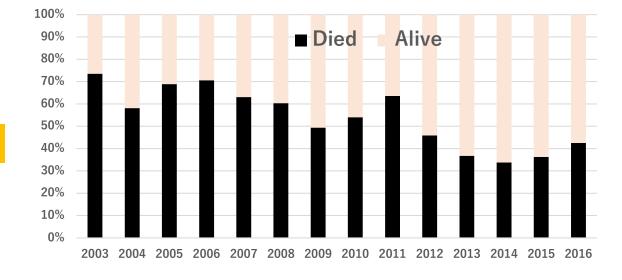
22w

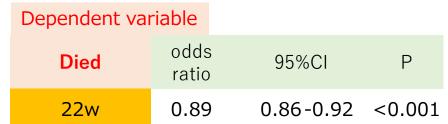
Annual trend of mortality for 20w, 21w, 22w (2003-2016)

◆ There were 2/3 infants of 20w died/alive, 2/4 infants of 21w died/alive, and 947 infants of 22w. (The Cinderella effect)

	20w					21w				22w														22w Total
	20032	20102	0132	0142	015	20062	012	2013	2014	20032	20042	20052	20062	2007	20082	20092	2010	20112	2012	20132	20142	2015	2016	
Died	1	1							2	25	25	31	36	41	38	41	40	61	39	25	27	29	34	492
Aive			1	1	1	1	1	1	1	9	18	14	15	24	25	42	34	35	46	43	53	51	46	455
Total	1	1	1	1	1	1	1	1	3	34	43	45	51	65	63	83	74	96	85	68	80	80	80	947
Mortality(%	5)									74%	58%	69%	71%	63%	60% 4	49% !	54% (64% 4	16% 3	37% 3	4% 3	6% 4	-3%	52.0%

◆ Between 2003 to 2016 the mortality for 22w has significantly decreased 2% every year.



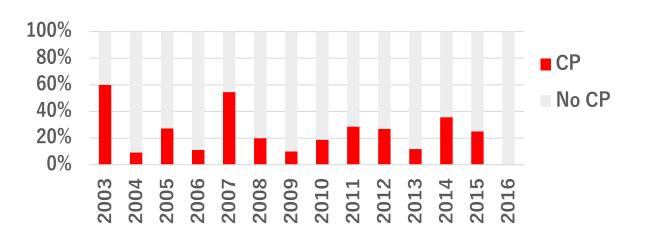


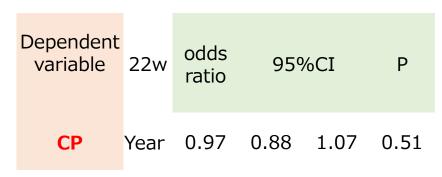
Logistic regression adjusted for gestation



Annual trend of Cerebral Palsy (22w)

◆In 14 years 2003-2016, no significant change of CP rate for 22w.





Logistic regression adjusted for gestation

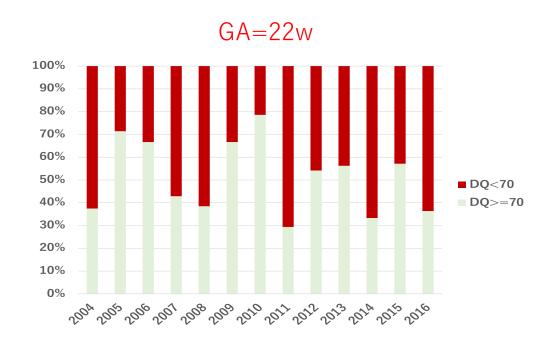
\sim \wedge	_	٦.	
GΑ	=2	Z١	w

Year	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	Total
СР	3	1	3	1	6	3	2	3	6	7	2	5	4	0	46
No CP	2	10	8	8	5	12	18	13	15	19	15	9	12	7	153
Total	5	11	11	9	11	15	20	16	21	26	17	14	16	7	199
%CP	60%	9%	27%	11%	55%	20%	10%	19%	29%	27%	12%	36%	25%	0%	23%



Annual trend of DQ<70 (22w)

♦In 14 years 2003-2016, no significant change of DQ<70 rate for 22w.



Dependent	variable	22w		
DQ<70	odds	95%	Р	
Year	1.04	0.94	1.14	0.45

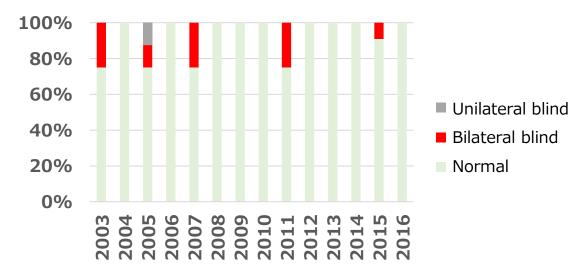
Logistic regression adjusted for gestation

2	22w	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	Total
DO	Q>=70	3	5	4	3	5	12	11	5	13	9	4	8	4	86
D	Q<70	5	2	2	4	8	6	3	12	11	7	8	6	7	81
_	Total	8	7	6	7	13	18	14	17	24	16	12	14	11	167
%[OQ<70	63%	29%	33%	57%	62%	33%	21%	71%	46%	44%	67%	43%	64%	49%



Annual trend of Visual Impairment (3 yrs)

◆ For children of 22w, visual impairment (3 yrs) decreased 2008 – 2016



22w Blind	Odds ratio	959	Р	
Year	0.723	0.523	-1.000	<0.05

Logistic regression

22w

Year	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016
Normal	3	8	6	5	3	4	6	5	3	5	7	3	10	3
Bilateral blind	1		1		1				1				1	
Unilateral blind			1											
Total	4	8	8	5	4	4	6	5	4	5	7	3	11	3



Limit of viability for extremely preterm infants Summary of annual trend

Taking 22 week of NRNJ data as an example,

 \times ; No, \bigcirc ; Yes

Q ①: What is the survival rate?

 \times Type 1 Decreasing survival \Rightarrow Inappropriate to care for this gestation.

 \times Type 2 No change in survival \rightarrow Need to re-examine the care for this gestation.

OType 3 Improving the survival

Go to ②

Q 2: What is the major disability rate among the survivors?

 \times Type A Increasing \Rightarrow Inappropriate to care for this gestation.

CP DQ<70 VI

Type B No change \bigcirc \Rightarrow Near to the limit for this gestation, but acceptable.

Type C Decreasing $\bigcirc \Rightarrow$ The limit of viability may still be at lower gestation.

Conclusions

22 week meets the criteria of Type 3- B or C.

22 week is near to the limit of viability but acceptable for active intervention



Mortality of extremely preterm infants for certain disorders

The results of NRNJ database 2003-2016

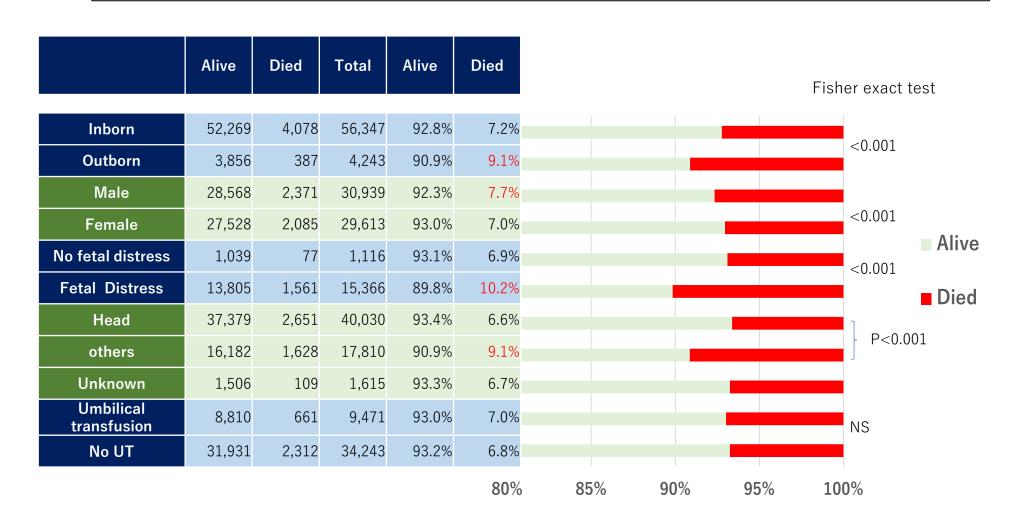
Simple correlation in mortality with and without morbidity.

- 1. Place of birth, Gender, Fetal monitoring, Presentation, Umbilical transfusion
- 2. SFD, Mode of delivery, Zygocity, DM, PIH, CAM, PROM, Antenatal steroid
- 3. Seizure, IVH, PVL, HIE
- 4. CLD, PDA, Adrenal insufficiencySepsis
- 5. NEC, TPN, Intestinal perforation, Surgical operation, Blood transfusion, ROP treatment, Congenital malformation
- 6. Oxygen therapy, CPAP, IPPV



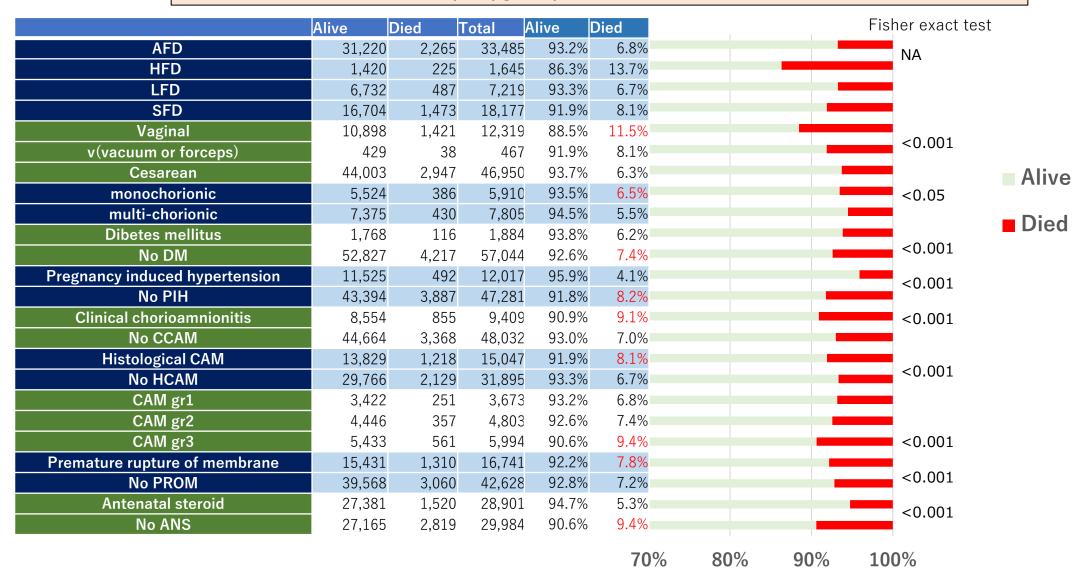
Mortality for certain disorders

1. Place of birth, Gender, Fetal monitoring, Presentation, Umbilical transfusion





2. SFD, Mode of delivery, Zygocity, DM, PIH, CAM, PROM, Antenatal steroid

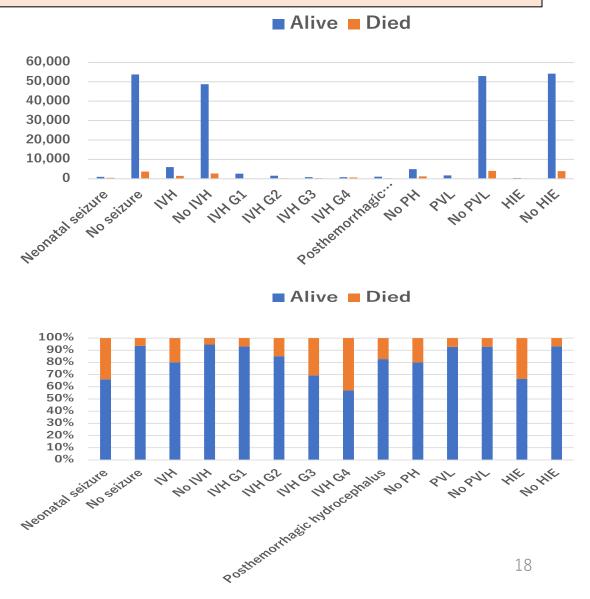




3. Seizure, IVH, PVL, HIE

		- ·		
	Alive	Died	Total	
Total	56125	4465	60590	Р
Neonatal seizure	1,015	519	1,534	< 0.001
No seizure	53,814	3,714	57,528	
IVH	6,050	1,503	7,553	< 0.001
No IVH	48,778	2,720	51,498	
IVH G1	2,634	198	2,832	< 0.001
IVH G2	1,560	273	1,833	
IVH G3	824	364	1,188	
IVH G4	828	623	1,451	
Posthemorrhagic hydrocephalus	1,063	222	1,285	0.025
No PH	4,912	1,230	6,142	
PVL	1,716	134	1,850	NS
No PVL	52,946	4,016	56,962	
HIE	369	186	555	< 0.001
No HIE	54,167	3,940	58,107	

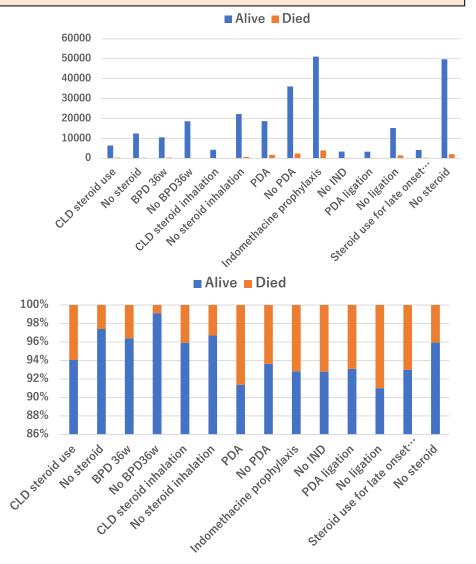
Fisher exact test





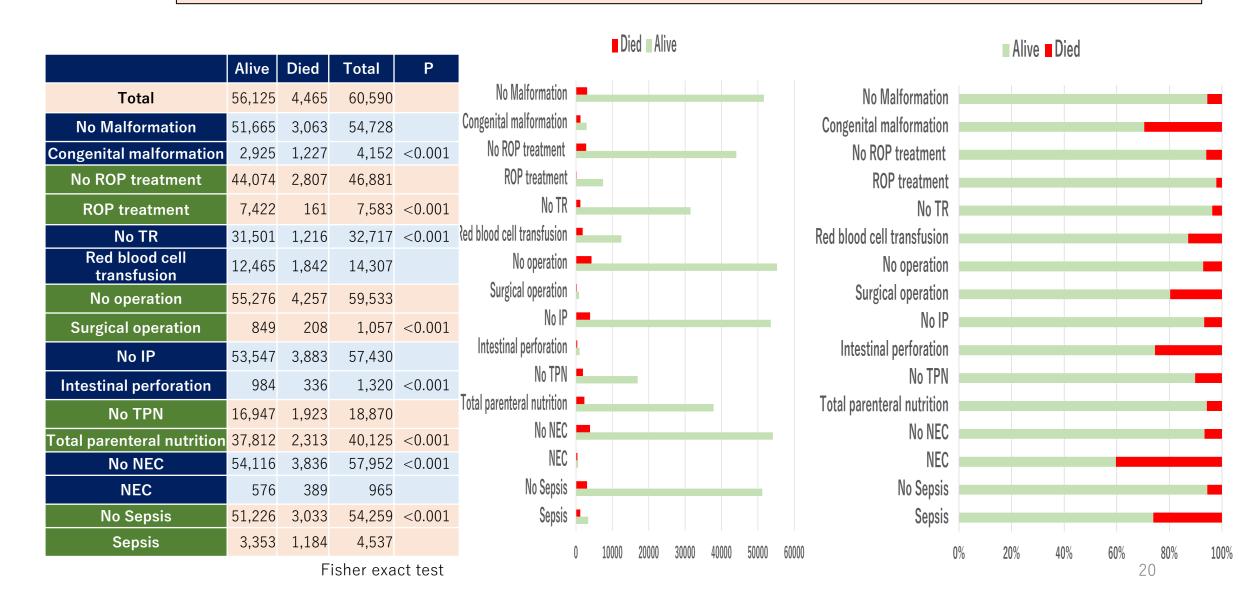
4. CLD, PDA, Adrenal insufficiency

	Alive	Died	Total	Р
Total	56,125	4,465	60,590	
CLD steroid use	6,495	411		<0.001
No steroid	12,459	332	12,791	
BPD 36w	10,563	395	10,958	
No BPD36w	18,607	167	18,774	<0.001
CLD steroid inhalation	4,348	185	4,533	0.008
No steroid inhalation	22,253	757	23,010	
PDA	18,706	1,767	20,473	<0.001
No PDA	36,090	2,452	38,542	
Indomethacine prophylaxis	51,075	3,947	55,022	NS
No IND	3,453	268	3,721	
PDA ligation	3,335	247	3,582	<0.001
No ligation	15,233	1,506	16,739	
Steroid use for late onset adrenal insuff	4,215	317	4,532	
No steroid	49,676	2,106	51,782	<0.001





5. Sepsis, NEC, TPN, Intestinal perforation, Surgical operation, Blood transfusion, ROP treatment, Congenital malformation

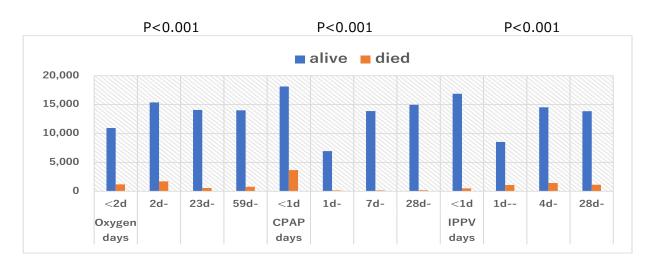


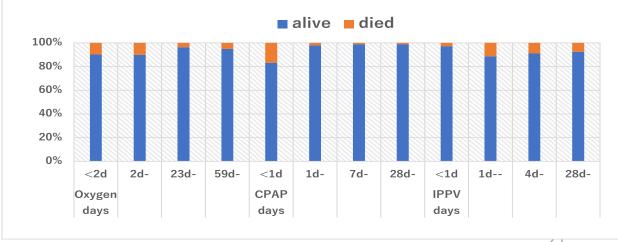


6. Oxygen therapy, CPAP, IPPV

		alive	died
Total		56,125	4,465
Oxygen days	<2d	10,948	1,190
	2d-	15,377	1,719
	23d-	14,079	547
	59d-	14,017	768
CPAP days	<1d	18,133	3,654
	1d-	6,952	151
	7d-	13,882	151
	28d-	14,957	176
IPPV days	<1d	16,874	494
	1d	8,525	1,085
	4d-	14,519	1,426
	28d-	13,856	1,126

	alive	died
<2d	90.2%	9.8%
2d-	89.9%	10.1%
23d-	96.3%	3.7%
59d-	94.8%	5.2%
<1d	83.2%	16.8%
1d-	97.9%	2.1%
7d-	98.9%	1.1%
28d-	98.8%	1.2%
<1d	97.2%	2.8%
1d	88.7%	11.3%
4d-	91.1%	8.9%
28d-	92.5%	7.5%







Neuro-developmental disabilities (<28w, 3 years)

NRNJ database 2003-2016



Disability of extremely preterm infants (<28w, 3 years)

◆ Children of ex-preterm infants (<28w) at 3 years are shown with and without major disabilities.

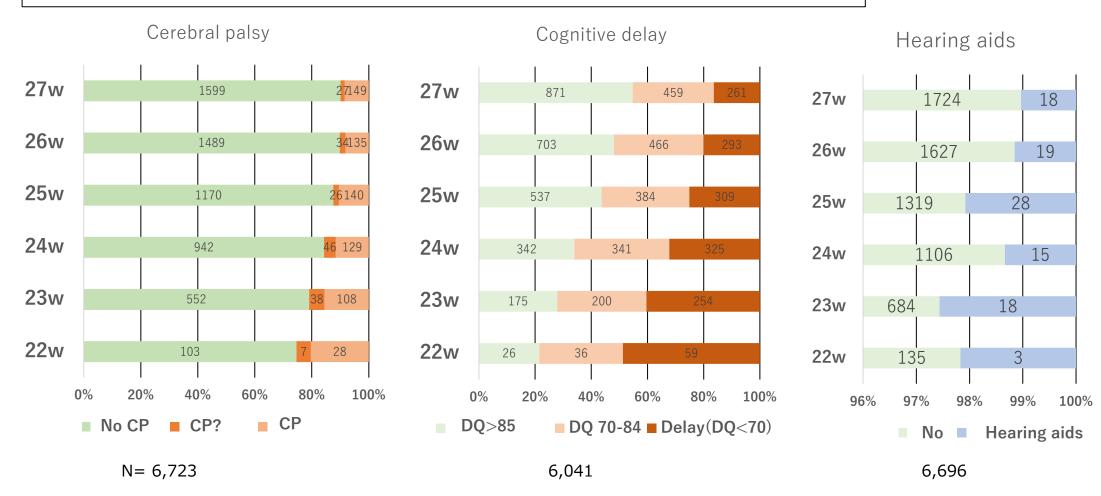
	Cerebral palsy	No CP	СР	Total	Visual impairment	No VI	VI	Total
	22w	57	6	63	22w	46	17	63
	23w	319	53	372	23w	298	74	372
	24w	545	73	618	24w	525	93	618
()	25-27w	3543	323	3866	25-27w	3612	254	3866
(N)	Total	4464	455	4919	Total	4481	438	4919
	DQ<70	No DQ<70	DO<70	Total	Hearing aid	No HA	HA	Total
	22w	36	27	63	22w	63		63
	23w	222	150	372	23w	369	3	372
	24w	415	203	618	24w	610	8	618
	25-27w	3209	657	3866	25-27w	3830	36	3866
	Total	3882	1037	4919	Total	4872	47	4919
			27			N. 17		
	СР	No CP	СР	Total	VI	No VI	VI	Total
	22w	90.5%	9.5%	100%	22w	73.0%	27.0%	100%
	23w	85.8%	14.2%	100%	23w	80.1%	19.9%	100%
	24w	88.2%	11.8%	100%	24w	85.0%	15.0%	100%
(0.1)	25w-	91.6%	8.4%	100%	25w-	93.4%	6.6%	100%
(%)	Total	90.8%	9.2%	100%	Total	91.1%	8.9%	100%
	DQ<70	No DQ<70	DO<70	Total	HA	No HA	HA	Total
	22w	57.1%	42.9%	100%	22w	100.0%	0.0%	100%
	23w	59.7%	40.3%	100%	23w	99.2%	0.8%	100%
	24w	67.2%	32.8%	100%	24w	98.7%	1.3%	100%
	25-27w	83.0%	17.0%	100%	25-27w	99.1%	0.9%	100%
	Total	78.9%	21.1%	100%	Total	99.0%	1.0%	100%

... 23



Cerebral palsy, Cognitive delay, Hearing aids and Gestational age

- ◆ The proportion of disabilities according to gestational weeks of birth are shown.
- ◆ Large proportion of cognitive delay is the characteristic disability in extreme preterm births.

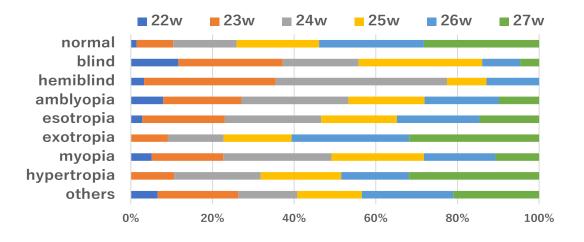


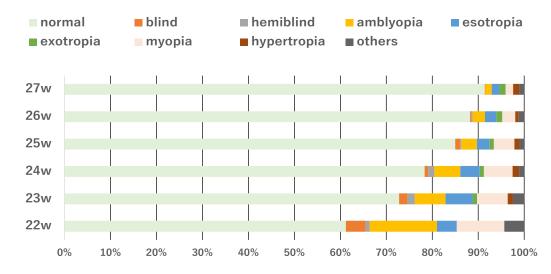


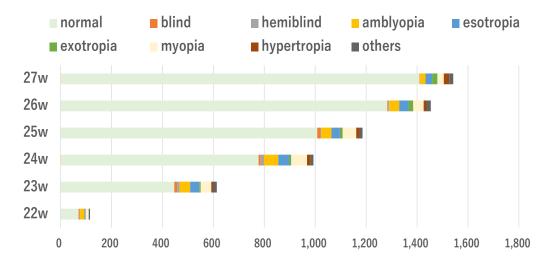
Visual impairment (3 yrs)

- ◆ Details of visual impairments are shown according to gestational weeks of birth.
- ◆ 1.3% are blind or hemi-blind in extreme preterm infants <28w.

	22w	23w	24w	25w	26w	27w	Total
normal	71	447	778	1,008	1,283	1,410	4,997
blind	5	11	8	13	4	2	43
hemiblind	1	10	13	3	4		31
amblyopia	17	41	56	40	39	21	214
esotropia	5	36	42	33	36	26	178
exotropia		6	9	11	19	21	66
myopia	12	41	62	53	41	25	234
hypertropia		7	14	13	11	21	66
others	5	15	11	12	17	16	76
Total	116	614	993	1,186	1,454	1,542	5,905



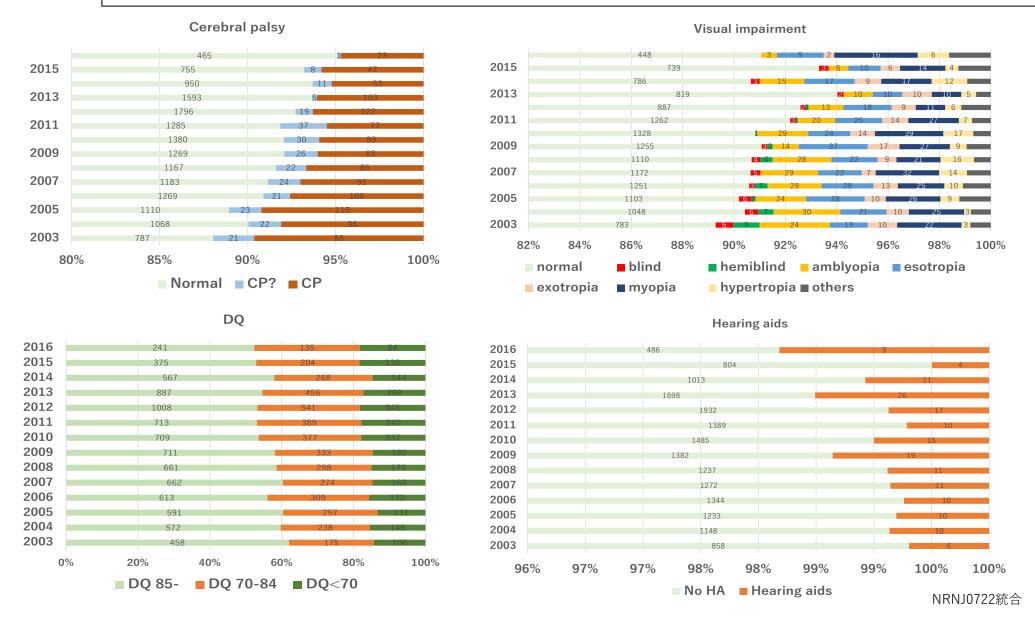






Yearly Trend of Neurological Impairment

◆ The incidence of CP and visual impairments are decreasing, whereas small DQ and need of HA are increasing.





Proportion of gestation in multiple disabilities (<28w, 3 years)

◆ Definition by NRN(delay : DQ<70, border : DQ70-84)

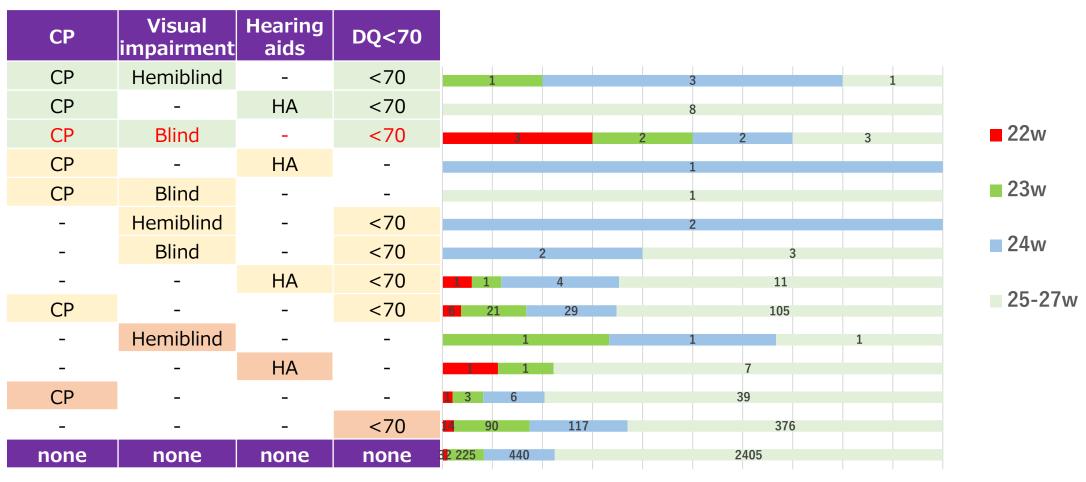
Hearing	Blind	СР	DQ	22w	23w	24w	25-27w	総計	22w	23w	24w	25-27w	Total
_	-	CP	<70	8	26	40	132	206	11.6%	6.5%	5.6%	4.0%	4.6%
_	-	CP	70-84	1	2	7	40	50	1.4%	0.5%	1.0%	1.2%	1.1%
_	-	CP	_		5	11	39	55	0.0%	1.2%	1.5%	1.2%	1.2%
_	_	_	<70	11	79	114	353	557	15.9%	19.6%	15.9%	10.6%	12.4%
_	_	_	70-84	12	95	149	564	820	17.4%	23.6%	20.8%	17.0%	18.2%
	- No Di	sability-		28	171	366	2,112	2,677	40.6%	42.4%	51.0%	63.6%	59.4%
_	Bilateral	CP	<70	4	3	2	5	14	5.8%	0.7%	0.3%	0.2%	0.3%
_	Bilateral	CP	70-84				1	1	0.0%	0.0%	0.0%	0.0%	0.0%
_	Bilateral	_	<70		2	3	3	8	0.0%	0.5%	0.4%	0.1%	0.2%
_	Hemi	CP	70-84		3	3	1	7	0.0%	0.7%	0.4%	0.0%	0.2%
_	Hemi	CP	70-84		1		0	1	0.0%	0.2%	0.0%	0.0%	0.0%
_	Hemi	_	<70		2	4	2	8	0.0%	0.5%	0.6%	0.1%	0.2%
_	Hemi	_	70-84		2	1	1	4	0.0%	0.5%	0.1%	0.0%	0.1%
_	Hemi	_	_	1	1	2	1	5	1.4%	0.2%	0.3%	0.0%	0.1%
Hearing	_	CP	<70	1	3	5	14	23	1.4%	0.7%	0.7%	0.4%	0.5%
Hearing	-	CP	70-84				1	1	0.0%	0.0%	0.0%	0.0%	0.0%
Hearing	_	CP	_			1	1	2	0.0%	0.0%	0.1%	0.0%	0.0%
Hearing	_	_	<70	2	2	4	14	22	2.9%	0.5%	0.6%	0.4%	0.5%
Hearing	_	_	70-84	1	3	3	13	20	1.4%	0.7%	0.4%	0.4%	0.4%
Hearing	_	_	_		2	3	21	26	0.0%	0.5%	0.4%	0.6%	0.6%
Hearing	Bilateral	СР	<70		1		2	3	0.0%	0.2%	0.0%	0.1%	0.1%
Total				69	403	718	3,320	4,510	100.0%	100.0%	100.0%	100.0%	100.0%

NRNJ0722統合



Proportion of gestation in multiple disabilities (<28w, 3 years)

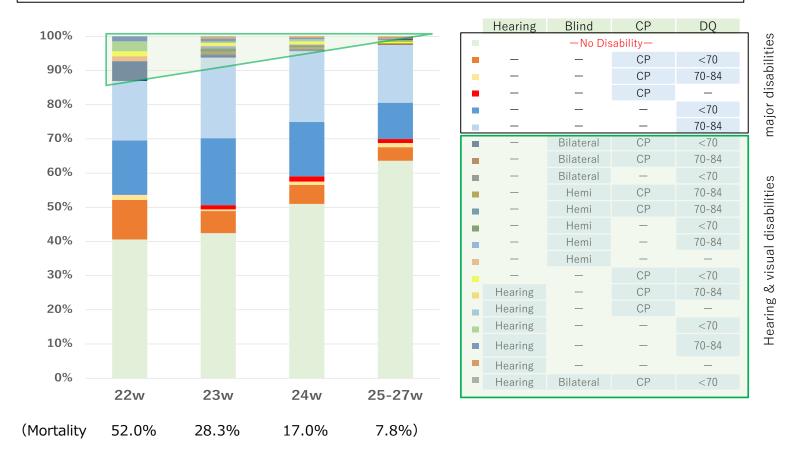
- Proportion of gestation in groups of multiple disabilities are shown in percentage.
- ◆ The CP, Blind, DQ<70 combination is 30% for 22w, followed by 23w, 24w.





Multiple disabilities of extremely preterm infants (<28w, 3 years)

- ◆ Combinations of disabilities of ex-preterm (<28w) with major disabilities at 3 years are illustrated with specific colors.
- ◆ The large mortality of 22w relates to relative small proportion of disabilities comparing to "No disability".





Ratio of gestation and groups of multiple disabilities (<28w, 3 years)

◆ DQ<70 is the largest disability followed by CP and DQ<70. In Isolated CP gestation groups are similar in ratio

CP,		eral, Hearing	g aid, DQ<70							
CP	-unila -	i teral HA	<70	0.3% 8:8%						
CP	Blind	-	<7 <u>0</u>	0.1%	5.1%					
_	Blind	-	<70	0.1% ₇ % 8:8%					25-27w	
_	-	НА	<7 <u>0</u>	0.4% 0.3% 1.7%					■ 24w	
СР	_	-	<70		3.5% _{4.7%} 6.0%	10.2%			■ 23w	
СР	-	НА	_	000% 6:6%		2012/3			■ 22w	
СР	Blind	-		8:8%						
_	_	_		0.070			12.6%	19.0%	23.7% 25.9%	
_	-	НА	_	0.5%					20.170	
	Blind	-		0.1%, 0.6%, 1.7%						
СР	_	_		1.7% 12,1% 1,4%/						
No disab	22w (54.2%	%), 23w (64.79 %), 25-27w (8)		0%	5.0%	10.0%	15.0%	20.0%	25.0%	30.0%