Epidemiology of birth defects in very low birth weight infants in Japan

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Objective: To evaluate the mortality and morbidity of very low birth weight (VLBW) preterm infants with birth defects in Japan.

Study design: Data were collected prospectively for infants weighing <1,501 grams and born at <37 weeks of gestation admitted to centers of the Neonatal Research Network of Japan during 2003-2016. We compared outcomes of infants with and without birth defects using Pearson's chi-square test, Wilcoxon rank sum test, log-rank test, nominal logistic regression analysis, and stratified analysis by birth defect subgroups. This study was approved by the Ethics Committee of Kyoto University Graduate School and Faculty of Medicine.

Results: Among 57,730 VLBW preterm infants, 3,557 infants (6.2%) were born with birth defects. Chromosomal abnormalities, congenital heart defects, and congenital malformation of the digestive system were the most common categories. Among diseases, trisomy 18, Down syndrome, and cleft palate were the most prevalent. There were significant differences between perinatal characteristics of infants with and without birth defects. Most categories of morbidity occurred more frequently in infants with birth defects compared with those without birth defects. The adjusted odds ratio for mortality during the NICU admission was 10.6 (95%CI: 9.5–11.7) for infants with birth defects. A stratified analysis identified birth defect categories with good, moderate, and poor prognoses.

Conclusions: This detailed information about mortality and morbidity of preterm VLBW infants with birth defects should be useful for genetic counseling as well as prenatal and neonatal care, with the limitation that we lacked information about the timing of diagnosis, abortion or stillbirth.

The mortality of preterm and low birth weight infants has improved in the past few decades, leading to a neonatal mortality rate of 0.9 per 1,000 live births in Japan in 2017.(1) The Neonatal Research Network of Japan (NRN-J) was established in 1998 to conduct nationwide systematic clinical research on neonates, and the NRN-J initiated a database for very low birth weight (VLBW) infants in 2003.(2) This database now encompasses 192 neonatal intensive care units (NICUs) throughout Japan and approximately 5,000 VLBW infants are registered annually. Data from the NRN-J showed that the mortality rate of VLBW infants during NICU admission decreased from 11% at 2003 to 5% at 2016.(3) the primary goal of treatment for preterm infants has been replaced from life-saving to survival without sequelae.(4)

An estimated 3-5% of liveborn infants have birth defects.(5) In VLBW infants, the incidence of major birth defects has been reported as 4.8%.(6, 7) Although the natural course of full term normal birth weight infants with birth defects is well known, little is known about premature infants with birth defects. There are a few reports of prognosis when prematurity and low body weight are combined with birth defects, with most studies focusing on chromosomal abnormalities or congenital heart defects.(6-11) In Japan there are several single-center reports on this topic,(12-14) but no national survey exists to date. Even minor birth defects that do not lead to a poor prognosis in full term infants with normal birth weights may have an impact on the outcome of VLBW preterm infants, because of their immaturity and technical difficulty in surgical repair.

Methods

The study period was 1/2003-12/2016. In total, 60,136 infants whose birth weights were <1,501 grams and who were admitted to an NICU of an NRN-J center within 28 days after birth were included in this study. We excluded infants born at >36 weeks of gestation. For 57,730 VLBW preterm infants, maternal and neonatal data were collected prospectively. In NRN-J, the infants were followed until 3 years of age.

Maternal data included maternal age at delivery; gravidity and parturition; whether primipara or multipara; comorbidities: diabetes mellitus, hypertensive disorders of pregnancy, chorioamnionitis, preterm premature rupture of membranes; antenatal steroid administration; non-reassuring fetal status diagnosed by fetal heart rate monitoring; delivery mode; and cord blood transfusion. Diabetes mellitus was defined as impaired glucose tolerance during pregnancy, including gestational diabetes. A hypertensive disorder of pregnancy was defined if hypertension was observed after 20 weeks of gestation and resolved within 12 weeks after delivery. Chorioamnionitis was histologically examined using Blanc's classification. Preterm premature rupture of membranes was coded with apparent leakage of amniotic fluid. No data were collected about the timing and frequency of antenatal steroid administration.

Neonatal data included information collected at birth, during the neonatal intensive care unit (NICU) stay and at discharge. Birth information included year, sex, inborn/outborn, gestational age, Apgar score at 1 and 5 minutes after birth, oxygen use and intubation during resuscitation,

measurements, and birth defects. Information collected the during the NICU admission included mortality, morbidity, duration of intubation, transfers, and surgical repair. Discharge information included discharge date, measurements, home oxygen therapy, and tracheostomy. Specific morbidities of prematurity that were collected are shown and defined in the supplement (available at www.jpeds.com). Final discharge status was defined as the earliest of the following conditions: death, discharge from the NICU, or the infant's first birthday.

We defined birth defects as one or more of the disorders listed in Q00–Q99 of ICD-10; which are the codes for congenital malformations, deformations and chromosomal abnormalities.(15) These are listed in Table 1 (available at www.jpeds.com). Metabolic disorders with ICD-10 codes of E70–E90 were excluded from the birth defects group, and these infants were included in the group without birth defects.

We compared the infants with and without birth defects using Pearson's chi-square test and Wilcoxon rank sum test; and generated Kaplan-Meier curves and conducted log-rank tests for comparison. For multivariable analysis, we used nominal logistic regression analysis fit to each outcome, including maternal age (<25, 25–29, 30–34, 35–39, ≥40 years), multiple birth, antenatal steroid, sex, gestational age (22–24, 25–28, 29–32, 33–36 weeks), birth weight small for gestational age, and birth defects. Furthermore, we undertook stratified analysis by birth defect subgroups. We compared mortality during the NICU admission of each birth defect subgroup with that of the other birth defect subgroups by log-rank test; and divided the birth defect subgroups into three; i.e. (A) the

good prognosis group showing significantly better prognosis than the other birth defect groups, (B) the moderate prognosis group showing equivalent prognosis to the other birth defect groups, and (C) the poor prognosis group showing significantly poor prognosis than the other birth defect groups.

JMP Pro 14.3.0 was used for these statistical analyses and the significance level was set at $p<0.05$. This study was approved by the Ethics Committee of Kyoto University Graduate School and Faculty of Medicine.

Results

57,730 infants with birth weights <1,501 grams and gestational ages <37 weeks were registered. Birth defects were identified in 3,557 infants (6.2%). Table 1 (available at www.jpeds.com) shows the number and types of birth defects identified in our cohort. The most frequent disease categories were chromosomal abnormalities (*n*=1,020: 28.7%), circulatory system malformations (*n*=584: 16.4%), digestive system malformations (*n*=409: 11.5%), urinary system malformations (*n*=184: 5.2%), and musculoskeletal system malformations (*n*=173: 4.9%). The most common single diseases were Trisomy 18 (*n*=453: 12.7%), Trisomy 21 (*n*=321: 9.0%), cleft palate (*n*=152: 4.3%), esophageal atresia without fistula (*n*=139: 3.9%), and ventricular septal defect (*n*=108: 3.0%).

Table 2 (available at www.jpeds.com) shows characteristics of the two groups. Infants with birth defects were born to older mothers than infants without birth defects. Maternal complications associated with pregnancy were significantly less frequent in infants with birth defects, except for

maternal diabetes. More infants with birth defects had birth weights small for gestational age and infants with birth defects were born at older gestational ages than infants without birth defects (31.1±3.7 and 28.9±3.2 weeks; $p<0.001$).

Table 3 shows mortality and morbidity in the NICU. Figure 1 shows survival curve of the infants with and without birth defects until 120 days after birth. Complications associated with prematurity; i.e. respiratory distress syndrome, chronic lung disease, late circulatory collapse, severe intraventricular hemorrhage, cystic periventricular leukomalacia, and retinopathy of prematurity were significantly less frequent in the infants with birth defects, except for chronic lung disease. Other complications; i.e. air leak, pulmonary hemorrhage, persistent pulmonary hypertension, operation for patent ductus arteriosus, late onset sepsis, necrotizing enterocolitis, localized intestinal perforation, and hearing impairment, were significantly more frequent in the infants with birth defects. The overall mortality during NICU admission was five times higher in the infants with birth defects compared with infants without birth defects (28.0% and 5.8%; $p<0.001$).

Table 4 shows the result of nominal logistic regression analysis. Infants with birth defects had increased risk for mortality and most of the categories of NICU morbidity except for respiratory distress syndrome, localized intestinal perforation, cystic periventricular leukomalacia, and retinopathy of prematurity. The odds ratio of mortality at all studied timepoints was approximately 10 for infants with birth defects compared with those without birth defects. The odds ratio of surgery during the NICU admission was very high (480, 95%CI: 350–660) for infants with birth defects

compared with those without birth defects.

Figure 2 shows survival curves of each birth defect category until day 120, classified into three groups based on prognosis. The good prognosis group (with a better prognosis than the other birth defect groups) consisted of infants with facial malformation, genital organ malformation and cleft lip and cleft palate. The moderate prognosis group showed a similar prognosis to the other birth defects groups, consisted of infants with digestive, circulatory and nervous system malformation. The poor prognosis group (showing a poorer prognosis than the other birth defect groups) consisted of infants with musculoskeletal, urinary and respiratory system malformations, and chromosomal abnormalities. Log-rank tests were performed for the disease categories included in each prognosis group; and p-values were 0.013, 0.631, and 0.139 for the good, moderate, and poor prognosis groups, respectively, shown in each graph of Figure 2.

Table 5 (available at www.jpeds.com) compares the perinatal characteristics between infants from each birth defect category. The proportion of cesarean deliveries was significantly lower in the infants with urinary system malformations. Although the genital and urinary system malformation group had male preponderance, the chromosomal abnormality group had female preponderance. The proportion of outborn infants was significantly higher in conditions that needed special care or operation from the neonatal period; i.e. digestive and circulatory system malformation groups, and chromosomal abnormality.

Table 6 (available at www.jpeds.com) compares the mortality and morbidity between infants from

each birth defect category. The group with facial malformations, including cleft lip and cleft palate, had higher morbidity due to localized intestinal perforation and hearing impairment despite their low mortality. Infants with digestive system malformation had high morbidity due to late onset sepsis, necrotizing enterocolitis, and localized intestinal perforation with higher rates of surgical procedures and tracheostomy placement. The infants with circulatory system malformations had high morbidity due to necrotizing enterocolitis and localized intestinal perforation but the incidence of late circulatory collapse was significantly lower. Infants with nervous system malformations had higher morbidity due to air leak and late onset sepsis, with a high rate of tracheostomy placement. Infants with musculoskeletal system malformations had high morbidity due to persistent pulmonary hypertension and late onset sepsis. The group with urinary system malformation had higher morbidity due to air leak and persistent pulmonary hypertension. Table 7 (available at www.jpeds.com) shows mortality in the NICU by ICD-10 code.

Discussion

Among 57,730 VLBW preterm infants from the NRN-J database, the proportion of birth defects was 6.2%. The mortality and morbidity of the infants with birth defects was significantly higher than infants without birth defects, except for respiratory distress syndrome, late circulatory collapse, cystic periventricular leukomalacia, and retinopathy of prematurity, when the background characteristics were adjusted. The adjusted odds ratio for mortality during the NICU admission was 10.6 (95%CI:

9.5–11.7) for infants with birth defects. We identified three prognostic groups: infants with a good prognosis (facial malformation including cleft lip and cleft palate, and genital organ malformation); infants with a moderate prognosis (digestive, circulatory and nervous system malformations); and infants with a poor prognosis (musculoskeletal, urinary and respiratory system malformations, and chromosomal abnormalities).

No nationwide survey of VLBW infants with birth defects has been published previously in Japan. We used the NRN-J database that collects data for VLBW infants with birth weights <1,501 grams. In Japan, about 8,000 VLBW infants are born every year.(1) The NRN-J database contains about 5,000 infants every year; therefore, about two-thirds of VLBW infants born in Japan are contained in this database.

Adams-Chapman et al. reported that the risk ratio of mortality during the NICU admission of infant with birth defects was 3.66 (95%CI: 3.41–3.92) compared with infants without birth defects, a lower OR than in our study. However, in that study, mortality was higher in infants without birth defects than in the present study (18.3% in Adams-Chapman vs. 5.8% in our report).(7) Improvements in prognosis have been seen for infants without birth defects due to the development of neonatal medicine technology, but improvements in prognosis appear to be lagging for infants with birth defects and birth defects are major prognostic factors along with prematurity and VLBW.

A limitation of our study is that no data exists for the timing of diagnosis or about fetuses who are aborted or stillborn. However, our results still should be useful for prenatal genetic counseling and

postnatal care. It may be possible in the future to conduct a more detailed study using prenatal data as Morisaki linked the NRN-J database with the obstetric database of the Japanese Society of Obstetrics and Gynecology in 2016, using the method proposed by Fellegi and Sunter.(16, 17)

The background characteristics of infants with birth defects differed fundamentally from those without birth defects, due to older gestational ages and higher rates of birth weight small for gestational age. Whereas maternal complications were more common in infants without birth defects, infants with birth defects showed significantly higher rates of non-reassuring fetal status and severe neonatal asphyxia. This suggests that infants with birth defects were born prematurely because of a fetal indication, but infants without birth defects were born prematurely because of a maternal indication as discussed in other studies.(18, 19) Although we had data about the administration of antenatal steroids, no data existed about the timing and frequency of antenatal steroids, which may affect the results of the study.

We identified some unique characteristics of specific types of birth defects. For example, the group with renal malformations showed a lower proportion of cesarean delivery than seen for the other categories of birth defects. We speculate this may reflect prenatal counselling of a fatal diagnosis. Because there are many types of birth defects with differing prognoses, further investigation is needed on specific disorders.

A limitation of the study is that the database does not include information about the timing of diagnosis. If the diagnosis was made before delivery, this may influence decision-making on abortion,

the method of delivery, decisions about emergent delivery, the plan for resuscitation, and all of these may influence an infant's prognosis.

This database also does not include information on fetuses who were aborted or stillborn. These factors may cause biases, which may misdirect the prognosis of birth defects. More severe birth defects may have a greater likelihood of prenatal diagnosis, and greater proportion of spontaneous or induced abortion. This will increase the rates of intrauterine fetal death, thereby decreasing the population of infants with severe birth defects. Finally, because we investigated only VLBW preterm infants with birth defects, we cannot generalize our data to normal birth weight full term infants with birth defects.

We examined data from 14 years of surveillance of VLBW infants in Japan (2003-2016). We found that complications of prematurity tended to be less frequent in infants with birth defects, as a result of the difference in gestational age between VLBW infants with and without birth defects. The overall survival rate in the NICU was 71% for VLBW infants with birth defects and 94% for infants without birth defects, which was significantly higher than a previous report from the United States covering the years 1998-2007.(7) Nominal logistic regression analysis showed that although the presence of a birth defects increases the odds of short-term mortality and morbidity, different types of birth defects have differing prognoses. This information should be useful for planning care and counseling parents.

List of abbreviations:

CI: Confidence interval, NICU: Neonatal intensive care unit, NRN-J: Neonatal Research Network of Japan, OR: Odds ratio, VLBW: Very low birth weight

References

1. Vital Statistics of Japan. Ministry of Health, Labour and Welfare; 2017.

2. Special Report of the Neonatal Research Network of Japan - Summary of the first 10 years of the network database Neonatal Research Network of Japan, The Japan Society for Neonatal Health and Development; 2018.

3. Neonatal Research Network Database Japan [Available from: http://plaza.umin.ac.jp/nrndata/indexe.htm.

4. Isayama T. The clinical management and outcomes of extremely preterm infants in Japan: past, present, and future. Translational pediatrics. 2019;8(3):199-211.

5. Nussbaum RL, McInnes RR, Willard HF. Thompson & Thompson Genetics in Medicine. 8th ed: Elsevier; 2015.

6. Boghossian NS, Horbar JD, Carpenter JH, Murray JC, Bell EF. Major chromosomal anomalies among very low birth weight infants in the Vermont Oxford Network. J Pediatr. 2012;160(5):774-80.e11.

7. Adams-Chapman I, Hansen NI, Shankaran S, Bell EF, Boghossian NS, Murray JC, et al. Ten-year review of major birth defects in VLBW infants. Pediatrics. 2013;132(1):49-61.

8. Boghossian NS, Hansen NI, Bell EF, Stoll BJ, Murray JC, Laptook AR, et al. Survival and morbidity outcomes for very low birth weight infants with Down syndrome. Pediatrics. 2010;126(6):1132-40.

9. Boghossian NS, Hansen NI, Bell EF, Stoll BJ, Murray JC, Carey JC, et al. Mortality and morbidity of VLBW infants with trisomy 13 or trisomy 18. Pediatrics. 2014;133(2):226-35.

10. Anderson AW, Smith PB, Corey KM, Hill KD, Zimmerman KO, Clark RH, et al. Clinical outcomes in very low birth weight infants with major congenital heart defects. Early Hum Dev. 2014;90(12):791-5.

11. Laas E, Lelong N, Ancel PY, Bonnet D, Houyel L, Magny JF, et al. Impact of preterm birth on infant mortality for newborns with congenital heart defects: The EPICARD population-based cohort study. BMC Pediatr. 2017;17(1):124.

12. Kumasaka S, Yoda H, Ishida F, Mizogami M, Kodama H, Saito K, et al. Clinical characteristics of very low birth weight infants with trisomy 21 [in Japanese]. Journal of Japan Society for Premature and Newborn Medicine. 2011;23(1):83-7.

13. Yamada T, Majima H, Nakamura Y, Togawa Y, Suginmoto M, Kouwaki M, et al. Prognosis of very low birth weight infants with trisomy 18 [in Japanese]. Journal of Japan Society of Perinatal and Neonatal Medicine. 2015;51(3):954-9.

14. Nakashima Y, Mori Y, Kaneko S, Inoue N, Murakami T, Isozaki K, et al. Congenital heart disease in very low-birth-weight infants: A single-center experience [in Japanese]. Acta cardiologica paediatrica Japonica. 2016;32(2):160-7.

15. World Health Organization. ICD-10 : international statistical classification of diseases and related health problems : 10th revision version for 2003. [Available from:

http://apps.who.int/classifications/apps/icd/icd10online2003/fr-icd.htm]

16. Morisaki N. Promotion of perinatal epidemiological research by data linkage [in Japanese]. The Uehara Memorial Foundation Research Reports. 2016;30:1-3.

17. Fellegi IP, Sunter AB. A Theory for Record Linkage. Journal of the American Statistical Association. 1969;64(328):1183-210.

18. Auger N, Le TU, Park AL, Luo ZC. Association between maternal comorbidity and preterm birth by severity and clinical subtype: retrospective cohort study. BMC pregnancy and childbirth. 2011;11:67.

19. Dolan SM, Gross SJ, Merkatz IR, Faber V, Sullivan LM, Malone FD, et al. The contribution of birth defects to preterm birth and low birth weight. Obstetrics and gynecology. 2007;110(2 Pt 1):318-24.

Figure legends

Figure 1. Kaplan-Meier curves until 120 days after birth of infants with birth defects and those without birth defects

Figure 2. Kaplan-Meier curves of each birth defect category

(A) Good prognosis group, (B) Moderate prognosis group, and (C) Poor prognosis group

Table 1. Details of Birth Defects by ICD-10 Code

ICD-10	Categories/diseases	*n*	(%)
Q00–Q07	**Congenital malformations of the nervous system**	**132**	**(3.7)**
Q000	Anencephaly	5	(0.1)
Q01	Encephalocele	2	(0.1)
Q02	Microcephaly	1	(0.0)
Q031	Atresia of foramina of Magendie and Luschka	1	(0.0)
Q039	Congenital hydrocephalus, unspecified	48	(1.3)
Q040	Congenital malformations of corpus callosum	2	(0.1)
Q042	Holoprosencephaly	24	(0.7)
Q043	Other reduction deformities of brain	10	(0.3)
Q044	Septo-optic dysplasia	1	(0.0)
Q046	Congenital cerebral cysts	2	(0.1)
Q048	Other specified congenital malformations of brain	1	(0.0)
Q05	Spina bifida	44	(1.2)
Q078	Other specified congenital malformations of nervous system	1	(0.0)
Q10–Q18	**Congenital malformations of eye, ear, face and neck**	**15**	**(0.4)**
Q100	Congenital ptosis	1	(0.0)
Q120	Congenital cataract	2	(0.1)
Q131	Absence of iris	1	(0.0)
Q134	Other congenital corneal malformations	1	(0.0)
Q148	Other congenital malformations of posterior segment of eye	1	(0.0)
Q161	Congenital absence, atresia and stricture of auditory canal (external)	5	(0.1)
Q170	Accessory auricle	1	(0.0)
Q172	Microtia	4	(0.1)
Q173	Other misshapen ear	1	(0.0)
Q20–Q28	**Congenital malformations of the circulatory system**	**584**	**(16.4)**
Q200	Common arterial trunk	14	(0.4)
Q201	Double outlet right ventricle	93	(2.6)
Q203	Discordant ventriculoarterial connection	28	(0.8)
Q204	Double inlet ventricle	10	(0.3)
Q210	Ventricular septal defect	108	(3.0)
Q211	Atrial septal defect	32	(0.9)
Q212	Atrioventricular septal defect	32	(0.9)
Q213	Tetralogy of Fallot	87	(2.4)
Q214	Aortopulmonary septal defect	2	(0.1)
Q220	Pulmonary valve atresia	60	(1.7)

Q221	Congenital pulmonary valve stenosis	3	(0.1)
Q224	Congenital tricuspid stenosis	11	(0.3)
Q225	Ebstein anomaly	4	(0.1)
Q228	Other congenital malformations of tricuspid valve	1	(0.0)
Q230	Congenital stenosis of aortic valve	2	(0.1)
Q231	Congenital insufficiency of aortic valve	2	(0.1)
Q234	Hypoplastic left heart syndrome	29	(0.8)
Q251	Coarctation of aorta	62	(1.7)
Q253	Stenosis of aorta	3	(0.1)
Q254	Other congenital malformations of aorta	2	(0.1)
Q256	Stenosis of pulmonary artery	8	(0.2)
Q258	Other congenital malformations of great arteries	2	(0.1)
Q262	Total anomalous pulmonary venous connection	24	(0.7)
Q263	Partial anomalous pulmonary venous connection	1	(0.0)
Q265	Anomalous portal venous connection	1	(0.0)
Q270	Congenital absence and hypoplasia of umbilical artery	1	(0.0)
Q30–Q34	**Congenital malformations of the respiratory system**	**24**	**(0.7)**
Q311	Congenital subglottic stenosis	2	(0.1)
Q315	Congenital laryngomalacia	2	(0.1)
Q320	Congenital tracheomalacia	4	(0.1)
Q321	Other congenital malformations of trachea	2	(0.1)
Q322	Congenital bronchomalacia	1	(0.0)
Q330	Congenital cystic lung	3	(0.1)
Q332	Sequestration of lung	1	(0.0)
Q336	Hypoplasia and dysplasia of lung	9	(0.3)
Q35–Q37	**Cleft lip and cleft palate**	**158**	**(4.4)**
Q35	Cleft palate	152	(4.3)
Q37	Cleft palate with cleft lip	5	(0.1)
Q38–Q45	**Other congenital malformations of the digestive system**	**409**	**(11.5)**
Q390	Atresia of esophagus without fistula	139	(3.9)
Q392	Congenital tracheo-esophageal fistula without atresia	24	(0.7)
Q399	Congenital malformation of esophagus	1	(0.0)
Q400	Congenital hypertrophic pyloric stenosis	2	(0.1)
Q410	Congenital absence, atresia and stenosis of duodenum	61	(1.7)
Q411	Congenital absence, atresia and stenosis of jejunum	31	(0.9)
Q412	Congenital absence, atresia and stenosis of ileum	44	(1.2)
Q419	Congenital absence, atresia and stenosis of small intestine, part unspecified	2	(0.1)

Q423	Congenital absence, atresia and stenosis of anus without fistula	94	(2.6)
Q429	Congenital absence, atresia and stenosis of large intestine, part unspecified	7	(0.2)
Q430	Meckel diverticulum	2	(0.1)
Q431	Hirschsprung disease	6	(0.2)
Q432	Other congenital functional disorders of colon	1	(0.0)
Q433	Congenital malformations of intestinal fixation	4	(0.1)
Q437	Persistent cloaca	2	(0.1)
Q438	Other specified congenital malformations of intestine	1	(0.0)
Q442	Atresia of bile ducts	4	(0.1)
Q444	Choledochal cyst	1	(0.0)
Q447	Other congenital malformations of liver	1	(0.0)
Q50–Q56	**Congenital malformations of genital organs**	**87**	**(2.4)**
Q53	Undescended testicle	2	(0.1)
Q54	Hypospadias	87	(2.4)
Q60–Q64	**Congenital malformations of the urinary system**	**184**	**(5.2)**
Q600	Renal agenesis, unilateral	4	(0.1)
Q601	Renal agenesis, bilateral	8	(0.2)
Q605	Renal hypoplasia, unspecified	1	(0.0)
Q606	Potter’s syndrome	48	(1.3)
Q61	Cystic kidney disease	34	(1.0)
Q620	Congenital hydronephrosis	87	(2.4)
Q631	Lobulated, fused and horseshoe kidney	1	(0.0)
Q641	Exstrophy of urinary bladder	1	(0.0)
Q642	Congenital posterior urethral valves	1	(0.0)
Q644	Malformation of urachus	3	(0.1)
Q647	Other and unspecified congenital malformations of bladder and urethra	1	(0.0)
Q65–Q79	**Congenital malformations and deformations of the musculoskeletal system**	**173**	**(4.9)**
Q66	Congenital deformity of feet	4	(0.1)
Q682	Congenital deformity of knee	1	(0.0)
Q688	Other specified congenital musculoskeletal deformities	1	(0.0)
Q69	Polydactyly	13	(0.4)
Q702	Fused toes	1	(0.0)
Q704	Polysyndactyly, unspecified	3	(0.1)
Q713	Congenital absence of hand and finger	3	(0.1)
Q72	Reduction defects of lower limb	2	(0.1)
Q740	Other congenital malformations of upper limb(s), including shoulder girdle	1	(0.0)
Q742	Other congenital malformations of lower limb(s), including pelvic girdle	1	(0.0)

Q743	Arthrogryposis multiplex congenita	2	(0.1)
Q750	Craniosynostosis	3	(0.1)
Q753	Macrocephaly	1	(0.0)
Q76	Congenital malformations of spine and bony thorax	5	(0.1)
Q773	Chondrodysplasia punctata	2	(0.1)
Q774	Achondroplasia	2	(0.1)
Q780	Osteogenesis imperfecta	1	(0.0)
Q781	Polyostotic fibrous dysplasia	1	(0.0)
Q790	Congenital diaphragmatic hernia	51	(1.4)
Q792	Exomphalos	39	(1.1)
Q793	Gastroschisis	38	(1.1)
Q795	Other congenital malformations of abdominal wall	1	(0.0)
Q798	Other congenital malformations of musculoskeletal system	1	(0.0)
Q80–Q89	**Other congenital malformations**	**33**	**(0.9)**
Q81	Epidermolysis bullosa	1	(0.0)
Q825	Congenital non-neoplastic nevus	4	(0.1)
Q828	Other specified congenital malformations of skin	1	(0.0)
Q851	Tuberous sclerosis	2	(0.1)
Q870	Congenital malformation syndromes predominantly affecting facial appearance	3	(0.1)
Q871	Congenital malformation syndromes predominantly associated with short stature	8	(0.2)
Q873	Congenital malformation syndromes involving early overgrowth	1	(0.0)
Q878	Other specified congenital malformation syndromes, not elsewhere classified	2	(0.1)
Q891	Congenital malformations of adrenal gland	3	(0.1)
Q893	Situs inversus	1	(0.0)
Q897	Multiple congenital malformation, not elsewhere classified	6	(0.2)
Q90–Q99	**Chromosomal abnormalities, not elsewhere classified**	**1,020**	**(28.7)**
Q90	Down syndrome (Trisomy 21)	321	(9.0)
Q911	Trisomy 18, mosaicism	1	(0.0)
Q913	Edwards syndrome (Trisomy 18), unspecified	453	(12.7)
Q917	Patau syndrome (Trisomy 13), unspecified	58	(1.6)
Q921	Whole chromosome trisomy, mosaicism (mitotic nondisjunction)	1	(0.0)
Q933	Wolff-Hirschhorn syndrome	2	(0.1)
Q935	Other deletions of part of a chromosome	3	(0.1)
Q938	Other deletions from the autosomes	1	(0.0)
Q969	Turner syndrome	1	(0.0)
Q970	Karyotype 47,XXX	1	(0.0)
Q984	Klinefelter syndrome	2	(0.1)

Table 2. Characteristics of Infants With and Without Birth Defects

Characteristic	Birth Defects (*n*=3,557)		No Birth Defects (*n*=54,173)		p-value
Maternal age (y), mean±S.D.	32.6±5.7		31.6±5.4		<0.001
<25, *n* (%)	293	(8.5)	5,304	(10.1)	<0.001
25−29, *n* (%)	715	(20.6)	12,390	(23.5)	
30−34, *n* (%)	1,102	(31.8)	18,438	(34.9)	
35−39, *n* (%)	973	(28.1)	13,198	(25.0)	
≥40, *n* (%)	382	(11.0)	3,436	(6.5)	
Multiple birth, *n* (%)	638	(17.9)	13,332	(24.6)	<0.001
Maternal diabetes (including gestational diabetes), *n* (%)	136	(3.9)	1,673	(3.1)	0.014
Hypertensive disorders of pregnancy, *n* (%)	594	(16.9)	11,080	(20.6)	<0.001
Histological chorioamnionitis, *n* (%)	605	(21.7)	14,056	(32.9)	<0.001
Preterm premature rupture of membranes, *n* (%)	777	(22.1)	15,414	(28.6)	<0.001
Antenatal steroid, *n* (%)	1,422	(40.9)	26,725	(49.9)	<0.001
Non-reassuring fetal status, *n* (%)	1,309	(38.2)	13,447	(25.5)	<0.001
Cesarean delivery, *n* (%)	2,900	(81.8)	42,320	(78.4)	<0.001
Cord blood transfusion, *n* (%)	440	(16.6)	8,767	(22.1)	<0.001
Male, *n* (%)	1,877	(52.9)	27,659	(51.1)	0.037
Outborn, *n* (%)	376	(10.6)	3,634	(6.7)	<0.001
Gestational age (wk), mean±S.D.	30.7±3.4		28.9±3.2		<0.001
22−24, *n* (%)	212	(6.0)	6,842	(12.6)	<0.001
25−28, *n* (%)	866	(24.4)	20,227	(37.3)	
29−32, *n* (%)	1,447	(40.7)	21,330	(39.4)	
33−36, *n* (%)	1,032	(29.0)	5,774	(10.7)	
Apgar Score 1 min. < 4, *n* (%)	1,310	(37.2)	13,622	(25.4)	<0.001
Apgar Score 5 min. < 4, *n* (%)	451	(12.9)	3,128	(5.9)	<0.001
O_2 use at resuscitation, *n* (%)	2,977	(85.3)	46,066	(86.1)	0.167
Intubation at resuscitation, *n* (%)	1,972	(55.9)	30,158	(56.0)	0.893
Birth weight (g), mean±S.D.	1054.6±305.1		1033.6±306.9		<0.001
≤500, *n* (%)	160	(4.6)	2,202	(4.1)	<0.001
501−750, *n* (%)	528	(15.1)	9,827	(18.4)	
751−1000, *n* (%)	733	(21.0)	11,747	(22.0)	
1001−1250, *n* (%)	925	(26.5)	13,043	(24.5)	
1251−1500, *n* (%)	1,150	(32.9)	16,520	(31.0)	
Small for gestational age, *n* (%)	2,145	(61.4)	15.362	(28.8)	<0.001

Table 3. Mortality and morbidity in the NICU

Mortality and morbidity in NICU	Infants With Birth Defects (*n*=3,557)		Infants Without Birth Defects (*n*=54,173)		p-value
Respiratory distress syndreom, *n* (%)	1,571	(44.9)	30,971	(57.4)	<0.001
Air leak, *n* (%)	137	(3.9)	1,454	(2.7)	<0.001
Pulmonary hemorrhage, *n* (%)	140	(4.0)	1,720	(3.2)	0.011
Persistent pulmonary hypertension of the newborn, *n* (%)	330	(9.5)	2,700	(5.0)	<0.001
Intubation period (d), mean±S.D.	35.8±97.0		19.8±48.6		<0.001
Chronic lung disease, *n* (%)	590	(38.0)	10,288	(35.8)	0.083
Patent ductus arteriosus ligation, *n* (%)	267	(7.5)	3,222	(6.0)	<0.001
Late circulatory collapse, *n* (%)	206	(5.9)	4,232	(7.9)	<0.001
Severe intraventricular hemorrhage, *n* (%)	127	(3.7)	2,450	(4.6)	0.010
Cystic periventricular leukomalacia, *n* (%)	73	(2.1)	1,726	(3.2)	<0.001
Late onset sepsis, *n* (%)	239	(6.9)	2,828	(5.3)	<0.001
Necrotizing enterocolitis, *n* (%)	77	(2.2)	864	(1.6)	0.009
Localized intestinal perforation, *n* (%)	111	(3.2)	1,177	(2.2)	<0.001
Hearing impairment, *n* (%)	494	(23.4)	3,258	(7.4)	<0.001
Retinopathy of prematurity, *n* (%)	256	(8.6)	7,214	(14.2)	<0.001
Transfer at acute phase, *n* (%)	187	(5.3)	903	(1.7)	<0.001
Operation during NICU admission, *n* (%)	958	(26.9)	43	(0.1)	<0.001
Died at day 0, *n* (%)	188	(5.4)	424	(0.8)	<0.001
Died till 3 days of age, *n* (%)	390	(11.3)	1,053	(2.0)	<0.001
Died in hospital, *n* (%)	996	(28.0)	3,137	(5.8)	<0.001
Day of death at hospital (d), mean±S.D.	60.5±116.0		39.6±88.8		0.132
Alive at discharge, *n* (%)	2,561	(72.0)	51,017	(94.2)	<0.001
Alive discharge date (d), mean±S.D.	123.6±101.9		94.3±62.0		<0.001
Final discharge status					
Dead, *n* (%)	976	(34.1)	3,096	(6.5)	<0.001
Discharge, *n* (%)	1,869	(65.2)	44,735	(93.5)	
Still hospitalized at 1 year, *n* (%)	20	(0.7)	41	(0.1)	
Weight at discharge in survivors (g), mean±S.D.	3043±1048		2841±710		<0.001
Home oxygen therapy at discharge, *n* (%)	283	(9.4)	2,784	(5.3)	<0.001
Tracheostomy at discharge, *n* (%)	99	(3.3)	364	(0.7)	<0.001

Table 4. Odds of mortality and morbidity in the NICU for infants with birth defects

Mortality and morbidity	Adjusted OR (95% CI)
Respiratory distress syndrome	1.08 (0.99−1.18)
Air leak	2.03 (1.68−2.46)
Pulmonary hemorrhage	1.61 (1.33−1.94)
Persistent pulmonary hypertension	2.79 (2.44−3.18)
Chronic lung disease	1.64 (1.45−1.86)
Patent ductus arteriosus ligation	2.22 (1.92−2.57)
Localized intestinal perforation	1.07 (0.91−1.25)
Severe intraventricular hemorrhage	1.28 (1.05−1.56)
Cystic periventricular leukomalacia	0.82 (0.64−1.06)
Late onset sepsis	1.80 (1.55−2.09)
Necrotizing enterocolitis	1.93 (1.51−2.48)
Localized intestinal perforation	2.00 (1.61−2.48)
Hearing impairment	4.21 (3.76−4.72)
Retinopathy of prematurity	0.87 (0.75−1.01)
Transfer at acute phase	4.06 (3.40−4.84)
Surgery during NICU admission	480 (350−660)
Died at day 0	10.6 (8.61−13.0)
Died till 3 days of age	9.34 (8.07−10.8)
Died in hospital	10.6 (9.55−11.7)
Home oxygen therapy at discharge	2.77 (2.40−3.19)
Tracheostomy at discharge	5.64 (4.43−7.18)

Adjusted ORs and CIs were calculated using nominal logistic regression analysis fit to each outcome which included maternal age (<25, 25–29, 30–34, 35–39, ≥40 years), multiple birth, antenatal steroid, sex, gestational age (22–24, 25–28, 29–32, 33–36 weeks), birth weight small for gestational age, and birth defects.

Table 5. Maternal and admission characteristics by ICD-10 code and prognosis groupings

Characteristic	(A) Good prognosis group			(B) Moderate prognosis group			(C) Poor prognosis group			
	Q10–Q18: Eye, ear, face, neck (*n*=15)	Q50–Q56: Genital organs (*n*=87)	Q35–Q37: Cleft lip and cleft palate (*n*=158)	Q38–Q45: Digestive system (*n*=409)	Q20–Q28: Circulatory system (*n*=584)	Q00–Q07: Nervous system (*n*=132)	Q65–Q79: Musculoskeletal system (*n*=173)	Q90–Q99: Chromosomes (*n*=1,020)	Q60–Q64: Urinary system (*n*=184)	Q30–Q34: Respiratory system (*n*=24)
Maternal age (y), mean±S.D.	30.7±4.6	32.4±5.6	32.4±4.8	32.5±5.4	32.3±5.7	32.0±5.7	30.7±6.7 ***	34.6±5.6 ***	31.6±5.3 *	30.2±6.1
<25, *n* (%)	0 (0.0)	7 (8.1)	10 (6.5)	29 (7.3)	49 (8.6)	15 (11.5)	35 (20.7) ***	43 (4.3) ***	18 (9.9) **	5 (21.7)
25–29, *n* (%)	8 (53.3)	21 (24.1)	32 (20.8)	81 (20.4)	125 (22.0)	28 (21.5)	36 (21.3)	154 (15.6)	37 (20.4)	5 (21.7)
30–34, *n* (%)	4 (26.7)	29 (33.3)	61 (39.6)	144 (36.3)	184 (32.4)	38 (29.2)	44 (26.0)	244 (24.7)	75 (41.4)	7 (30.4)
35–39, *n* (%)	2 (13.3)	22 (25.3)	43 (27.9)	97 (24.4)	147 (25.9)	40 (30.8)	39 (23.1)	340 (34.3)	41 (22.7)	4 (17.4)
≥40, *n* (%)	1 (6.7)	8 (9.2)	8 (5.2)	46 (11.6)	63 (11.1)	9 (6.9)	15 (8.9)	209 (21.1)	10 (5.5)	2 (8.7)
Multiple birth, *n* (%)	5 (33.3)	14 (16.1)	36 (22.8)	79 (19.3)	119 (20.4)	37 (28.0) **	36 (20.8)	60 (5.9) ***	34 (18.5)	4 (16.7)
Maternal diabetes, *n* (%)	0 (0.0)	3 (3.5)	5 (3.2)	15 (3.8)	38 (6.6) ***	3 (2.3)	7 (4.2)	34 (3.4)	7 (3.8)	0 (0.0)
Hypertensive disorder of pregnancy, *n* (%)	1 (6.7)	28 (32.2) ***	29 (18.5)	55 (18.8)	114 (19.8) *	18 (14.0)	23 (13.6)	116 (11.5) ***	27 (14.8)	4 (17.4)
Histological chorioamnionitis, *n* (%)	3 (27.3)	13 (18.1)	29 (24.6)	55 (17.9)	88 (19.8)	30 (27.3)	33 (24.6)	130 (16.4) ***	38 (24.5)	11 (52.6) **
Preterm premature rupture of membranes, *n* (%)	2 (13.3)	10 (11.5) *	35 (22.4)	109 (27.1) *	116 (20.1)	31 (23.7)	36 (21.2)	159 (15.7) ***	57 (31.3) **	7 (29.2)
Antenatal steroid, *n* (%)	7 (46.7)	48 (55.2) **	72 (47.1)	154 (39.4)	232 (41.0)	60 (46.5)	63 (38.0)	292 (29.2) ***	87 (47.8)	11 (45.8)
Non-reassuring fetal status, *n* (%)	3 (21.4)	35 (41.7)	49 (32.7)	127 (33.2) *	202 (36.2)	48 (37.2)	61 (37.2)	487 (49.2) ***	47 (26.6) **	9 (37.5)
Cesarean delivery, *n* (%)	9 (60.0) *	79 (91.9) *	135 (85.4)	309 (76.3) **	490 (83.9)	102 (77.9)	144 (83.2)	810 (79.5) *	134 (72.8) **	20 (83.3)
Cord blood transfusion, *n* (%)	1 (10.0)	15 (22.4)	12 (10.7)	56 (19.1)	66 (14.8)	14 (15.7)	15 (11.2)	89 (11.8) ***	20 (14.1)	6 (28.6)
Male, *n* (%)	8 (53.3)	86 (100.0) ***	80 (50.6)	210 (51.5)	283 (48.5) *	66 (50.0)	83 (48.0)	477 (46.9) ***	118 (64.1) **	11 (45.8)
Outborn, *n* (%)	1 (6.7)	5 (5.8)	12 (7.6)	86 (21.0) ***	80 (13.7) **	14 (10.6)	13 (7.5)	101 (9.9)	9 (4.9) *	2 (8.3)
Gestational age (wk), mean±S.D.	30.5±3.8	31.1±3.0	30.6±3.5	30.8±3.4	30.9±3.4	30.1±3.7	31.0±3.4	32.0±3.2 ***	30.3±3.2	28.8±2.8 **
22–24, *n* (%)	2 (13.3)	2 (2.3)	10 (6.3)	29 (7.1)	28 (4.8)	13 (9.9)	13 (7.5)	20 (2.0) ***	12 (6.5) *	3 (12.5) *
25–28, *n* (%)	2 (13.3)	23 (26.4)	44 (27.9)	89 (21.8)	132 (22.6)	35 (26.5)	34 (19.7)	175 (17.2)	37 (20.1)	10 (41.7)
29–32, *n* (%)	6 (40.0)	35 (40.2)	55 (34.8)	173 (42.3)	237 (40.6)	51 (38.6)	71 (41.0)	376 (36.9)	95 (51.6)	10 (41.7)
33–36, *n* (%)	5 (33.3)	27 (31.0)	49 (31.0)	118 (28.9)	187 (32.0)	33 (25.0)	55 (31.8)	449 (44.0)	40 (21.7)	1 (4.2)
Apgar Score 1 min. < 4, *n* (%)	3 (20.0)	19 (22.1) **	38 (24.5) ***	128 (32.0) *	175 (30.2) ***	56 (43.4)	81 (47.7) **	498 (49.4) ***	66 (35.9)	12 (50.0)
Apgar Score 5 min. < 4, *n* (%)	0 (0.0)	2 (2.4) **	16 (10.3)	40 (10.2)	58 (10.0) *	18 (14.1)	34 (20.1) **	165 (16.6) ***	39 (21.4) ***	8 (33.3) **
O_2 use at resuscitation, *n* (%)	10 (71.4)	66 (77.7) *	130 (85.5)	350 (88.2)	466 (81.3) **	108 (83.1)	149 (87.1)	864 (86.8)	156 (86.7)	22 (91.7)
Intubation at resuscitation, *n* (%)	6 (40.0)	39 (44.8) *	73 (46.8) *	227 (56.1)	317 (54.3)	68 (52.3)	119 (69.6) ***	551 (54.5)	107 (58.5)	20 (83.3) **
Birth weight (g), mean±S.D.	1122.3±305.8	933.1±325.6 ***	1060.6±300.5	1086.1±312.1 *	1064.5±298.5	1048.0±304.6	1122.9±283.6 *	1086.4±294.4 ***	1141.4±297.6 ***	911.5±328.6 *
≤500, *n* (%)	0 (0.0)	9 (10.3) **	5 (3.2)	20 (4.9) *	28 (4.9)	7 (5.3)	5 (2.9)	39 (3.9) **	6 (3.4) ***	3 (12.5)
501–750, *n* (%)	2 (13.3)	21 (24.1)	29 (18.5)	50 (12.3)	72 (12.5)	22 (16.8)	20 (11.8)	120 (11.9)	17 (9.5)	5 (20.8)
751–1000, *n* (%)	4 (26.7)	19 (21.8)	27 (17.2)	82 (20.2)	122 (21.2)	20 (15.3)	27 (15.9)	210 (20.8)	26 (14.5)	6 (25.0)
1001–1250, *n* (%)	1 (6.7)	18 (20.7)	44 (28.0)	95 (23.4)	170 (29.6)	40 (30.5)	53 (31.2)	285 (28.2)	44 (24.5)	6 (25.0)
1251–1500, *n* (%)	8 (53.3)	20 (23.0)	52 (33.1)	159 (39.2)	183 (31.8)	42 (32.1)	65 (38.2)	356 (35.3)	86 (48.0)	4 (16.7)
Small for gestational age, *n* (%)	7 (46.7)	78 (89.7) ***	95 (60.5)	227 (55.9) *	359 (62.4)	70 (53.4)	98 (57.7)	821 (81.3) ***	86 (48.0) ***	13 (54.2)

*: $p<0.05$ compared with the other birth defect group; **: $p<0.01$ compared with the other birth defect group; ***: $p<0.001$ compared with the other birth defect group

The significant differences are calculated comparing the characteristic of each ICD-10 code group from that of the other ICD-10 code groups via Pearson's chi-square test or Wilcoxon rank sum test.

Table 6. Mortality and morbidity in the NICU by ICD-10 code and prognosis groupings

Mortality and morbidity in NICU	(A) Good prognosis group			(B) Moderate prognosis group			(C) Poor prognosis group			
	Q10–Q18: Eye, ear, face, neck (*n*=15)	Q50–Q56: Genital organs (*n*=87)	Q35–Q37: Cleft lip and cleft palate (*n*=158)	Q38–Q45: Digestive system (*n*=409)	Q20–Q28: Circulatory system (*n*=584)	Q00–Q07: Nervous system (*n*=132)	Q65–Q79: Musculoskeletal system (*n*=173)	Q90–Q99: Chromosomes (*n*=1,020)	Q60–Q64: Urinary system (*n*=184)	Q30–Q34: Respiratory system (*n*=24)
Respiratory distress, *n* (%)	4 (26.7)	34 (39.1)	70 (45.8)	179 (44.6)	254 (44.0)	61 (48.8)	80 (49.4)	376 (37.4)***	85 (47.0)	13 (54.2)
Air leak, *n* (%)	0 (0.0)	2 (2.3)	5 (3.3)	12 (3.0)	17 (3.0)	10 (8.0)*	6 (3.7)	30 (3.0)	22 (12.2)***	3 (12.5)*
Pulmonary hemorrhage, *n* (%)	0 (0.0)	2 (2.3)	3 (2.0)	12 (3.0)	22 (3.8)	4 (3.2)	5 (3.1)	59 (5.9)***	7 (3.9)	1 (4.2)
Persistent pulmonary hypetension of the newborn, *n* (%)	0 (0.0)	2 (2.3)*	7 (4.6)*	26 (6.5)*	34 (5.9)**	4 (3.2)*	31 (19.1)***	119 (11.9)**	34 (19.0)***	7 (29.2)***
Intubation period (d), mean±S.D.	13.9±25.9	11.3±19.2***	32.2±90.1	42.6±106.7***	36.5±84.5*	37.2±116.2	47.9±131.4*	50.3±132.6	11.7±28.4***	118.1±230.7
Chronic lung disease, *n* (%)	1 (14.3)	14 (36.8)	32 (45.1)	54 (34.0)	26 (33.2)	18 (35.3)	24 (31.6)	170 (44.6)**	18 (26.9)	6 (60.0)
Ligation of patent ductus arteriosus, *n* (%)	1 (6.7)	3 (3.5)	11 (7.0)	32 (7.8)	54 (9.3)	4 (3.0)*	7 (4.1)	95 (9.3)**	8 (4.4)	2 (8.3)
Late circulatory collapse, *n* (%)	2 (14.3)	9 (10.3)	10 (6.5)	22 (5.5)	23 (4.1)*	11 (8.9)	6 (3.7)	37 (3.7)***	9 (5.1)	0 (0.0)
Severe intraventricular hemorrhage, *n* (%)	0 (0.0)	0 (0.0)	4 (2.6)	17 (4.3)	25 (4.4)	9 (7.4)*	7 (4.3)	39 (3.9)	5 (2.8)	0 (0.0)
Cystic periventricular leukomalacia, *n* (%)	0 (0.0)	0 (0.0)	3 (2.0)	11 (2.8)	12 (2.1)	1 (0.8)	6 (3.7)	17 (1.7)	4 (2.3)	2 (8.7)*
Late onset sepsis, *n* (%)	1 (6.7)	6 (6.9)	7 (4.6)	34 (8.6)	34 (6.0)	15 (12.1)*	19 (11.7)*	59 (6.0)	11 (6.2)	1 (4.2)
Necrotizing enterocolitis, *n* (%)	0 (0.0)	1 (1.2)	3 (2.0)	15 (3.8)*	24 (4.2)***	3 (2.4)	2 (1.2)	20 (2.0)	1 (0.6)	0 (0.0)
Localized intestinal perforation, *n* (%)	2 (13.3)*	2 (2.3)	1 (0.7)	25 (6.3)***	23 (4.1)	1 (0.8)	6 (3.7)	30 (3.0)	3 (1.7)	0 (0.0)
Hearing impairment, *n* (%)	7 (58.3)**	10 (12.8)*	40 (33.1)*	44 (19.2)	49 (17.3)**	21 (28.0)	13 (14.0)*	221 (51.2)***	11 (10.7)**	1 (9.1)
Retinopathy of prematurity, *n* (%)	3 (21.4)	6 (7.3)	17 (12.8)	31 (9.3)	39 (8.5)	7 (6.4)	13 (9.9)	27 (3.4)***	7 (4.7)	1 (5.3)
Transfer at acute phase, *n* (%)	0 (0.0)	1 (1.2)	10 (6.3)	30 (7.3)*	74 (12.7)***	5 (3.8)	4 (2.3)	55 (5.4)	6 (3.3)	1 (4.2)
Operation during NICU admission, *n* (%)	2 (13.3)	5 (5.8)***	15 (9.5)***	316 (77.3)***	211 (36.1)***	55 (41.7)***	87 (50.3)***	208 (20.4)***	14 (7.6)***	11 (45.8)*
Died at day 0, *n* (%)	0 (0.0)	0 (0.0)*	6 (3.9)	15 (3.8)	21 (3.7)	10 (7.9)	18 (10.7)**	74 (7.4)***	24 (13.2)***	1 (4.4)
Died till 3 days of age, *n* (%)	0 (0.0)	0 (0.0)***	10 (6.5)	33 (8.6)	53 (9.5)	18 (14.3)	32 (19.2)***	165 (16.7)***	48 (26.4)***	7 (30.4)**
Died in hospital, *n* (%)	0 (0.0)*	1 (1.2)***	22 (13.9)***	109 (26.7)	159 (27.2)	34 (25.8)	62 (35.8)*	484 (47.5)***	74 (40.2)***	9 (37.5)
Day of death at hospital (d), mean±S.D.	N.A.	67	59.5±80.5	79.6±140.7*	64.6±94.2*	41.9±89.9*	50.4±100.2*	66.6±114.9***	18.4±61.9***	2.8±4.4*
Alive at discharge, *n* (%)	15 (100.0)*	86 (98.9)***	136 (86.1)***	300 (73.4)	425 (72.8)	98 (74.2)	111 (64.2)*	536 (52.6)***	110 (59.8)***	15 (62.5)
Alive discharge date (d), mean±S.D.	79.0±38.0*	94.3±58.4#	114.4±77.9	146.2±97.7***	122.7±86.9	164.3±210.1**	129.5±115.4	146.1±124.4***	92.1±69.4***	250.7±158.8***
Final discharge status										
Dead, *n* (%)	0 (0.0)*	1 (1.3)***	22 (16.4)***	104 (33.8)	158 (41.9)**	33 (32.0)	60 (39.7)	476 (55.7)***	73 (42.4)	9 (47.4)
Discharge, *n* (%)	15 (100.0)	78 (98.7)	112 (83.6)	199 (64.6)	218 (57.8)	69 (67.0)	89 (58.9)	371 (43.4)	98 (57.0)	10 (52.6)
Still hospitalized at 1 year, *n* (%)	0 (0.0)	0 (0.0)	0 (0.0)	5 (1.6)	1 (0.3)	1 (0.1)	2 (1.3)	8 (0.9)	1 (0.6)	0 (0.0)
Weight at discharge for survivors (g), mean±S.D.	2823±508	2681±639***	2960±905	3100±1017	2916±878*	3630±1535***	2969±1069	3228±1260***	2869±762	4063±1213***
Home oxygen at discharge, *n* (%)	1 (6.7)	4 (4.7)	10 (7.0)	27 (7.9)	47 (9.8)	8 (7.0)	10 (7.7)	120 (15.3)***	10 (6.6)	3 (16.7)
Tracheostomy at discharge, *n* (%)	0 (0.0)	0 (0.0)	2 (1.4)	21 (6.2)**	6 (1.3)**	7 (6.0)	3 (2.3)	39 (5.0)**	1 (0.7)	5 (27.8)***

*: $p<0.05$ compared with the other birth defect group; **: $p<0.01$ compared with the other birth defect group; ***: $p<0.001$ compared with the other birth defect group

The significant differences are calculated comparing the characteristic of each ICD-10 code group from that of the other ICD-10 code groups via Pearson's chi-square test or Wilcoxon rank sum test.

Table 7. Death in hospital for each category/disease

ICD-10	Categories/diseases	*Deaths*, n* (%)	Relative Risk (95% CI)
Q00–Q07	**Congenital malformations of the nervous system**	**34 (25.8)**	**4.45 (3.32–5.95)**
Q000	Anencephaly	5 (100.0)	17.3 (16.7–17.9)
Q039	Congenital hydrocephalus, unspecified	5 (10.4)	1.80 (0.78–4.13)
Q042	Holoprosencephaly	15 (62.5)	10.8 (7.90–14.7)
Q043	Other reduction deformities of brain	3 (30.0)	5.18 (2.01–13.4)
Q05	Spina bifida	7 (15.9)	2.75 (1.39–5.42)
Q10–Q18	**Congenital malformations of eye, ear, face and neck**	**0 (0.0)**	**N.A.**
Q20–Q28	**Congenital malformations of the circulatory system**	**159 (27.2)**	**4.70 (4.10–5.39)**
Q200	Common arterial trunk	6 (42.9)	7.40 (4.04–13.6)
Q201	Double outlet right ventricle	39 (41.9)	7.24 (5.69–9.22)
Q203	Discordant ventriculoarterial connection	9 (32.1)	5.55 (3.24–9.51)
Q204	Double inlet ventricle	7 (70.0)	12.1 (8.04–18.2)
Q210	Ventricular septal defect	8 (7.4)	1.28 (0.66–2.49)
Q211	Atrial septal defect	2 (6.3)	1.08 (0.28–4.13)
Q212	Atrioventricular septal defect	10 (31.3)	5.39 (3.22–9.03)
Q213	Tetralogy of Fallot	14 (16.1)	2.78 (1.72–4.49)
Q220	Pulmonary valve atresia	28 (46.7)	8.06 (6.13–10.6)

Q224	Congenital tricuspid stenosis	4	6.28
		(36.4)	(2.87–13.7)
Q225	Ebstein anomaly	2	8.63
		(50.0)	(3.24–23.0)
Q234	Hypoplastic left heart syndrome	20	11.9
		(69.0)	(9.30–15.2)
Q251	Coarctation of aorta	22	6.13
		(35.5)	(4.37–8.58)
Q254	Other congenital malformations of aorta	1	8.63
		(50.0)	(2.16–34.5)
Q258	Other congenital malformations of great arteries	1	8.63
		(50.0)	(2.16–34.5)
Q262	Total anomalous pulmonary venous connection	8	5.75
		(33.3)	(3.26–10.1)
Q30–Q34	**Congenital malformations of the respiratory system**	**9**	**6.47**
		(37.5)	**(3.86–10.9)**
Q321	Other congenital malformations of trachea	1	8.63
		(50.0)	(2.16–34.5)
Q330	Congenital cystic lung	1	5.75
		(33.3)	(1.16–28.5)
Q336	Hypoplasia and dysplasia of lung	7	13.4
		(77.8)	(9.45–19.1)
Q35–Q37	**Cleft lip and cleft palate**	**22**	**2.40**
		(13.9)	**(1.63–3.55)**
Q35	Cleft palate	22	2.50
		(14.5)	(1.70–3.68)
Q38–Q45	**Other congenital malformations of the digestive system**	**109**	**4.60**
		(26.7)	**(3.90–5.42)**
Q390	Atresia of esophagus without fistula	57	7.08
		(41.0)	(5.78–8.67)
Q392	Congenital tracheo-esophageal fistula without atresia	12	8.63
		(50.0)	(5.78–12.9)
Q410	Congenital absence, atresia and stenosis of duodenum	6	1.70
		(9.8)	(0.79–3.63)
Q411	Congenital absence, atresia and stenosis of jejunum	11	6.13
		(35.5)	(3.81–9.86)
Q412	Congenital absence, atresia and stenosis of ileum	10	3.92

		(22.7)	(2.27–6.77)
Q423	Congenital absence, atresia and stenosis of anus without fistula	16	2.94
		(17.0)	(1.88–4.60)
Q429	Congenital absence, atresia and stenosis of large intestine, part unspecified	1	2.47
		(14.3)	(0.40–15.1)
Q437	Persistent cloaca	1	8.63
		(50.0)	(2.16–34.5)
Q438	Other specified congenital malformations of intestine	1	17.3
		(100.0)	(16.7–17.9)
Q444	Choledochal cyst	1	17.3
		(100.0)	(16.7–17.9)
Q50–Q56	**Congenital malformations of genital organs**	**1**	**0.20**
		(1.2)	**(0.03–1.39)**
Q54	Hypospadias	1	0.20
		(1.2)	(0.03–1.39)
Q60–Q64	**Congenital malformations of the urinary system**	**74**	**6.94**
		(40.2)	**(5.80–8.31)**
Q601	Renal agenesis, bilateral	8	17.3
		(100.0)	(16.7–17.9)
Q606	Potter's syndrome	45	16.2
		(93.8)	(14.9–17.5)
Q61	Cystic kidney disease	14	7.11
		(41.2)	(4.75–10.6)
Q620	Congenital hydronephrosis	8	1.59
		(9.2)	(0.82–3.07)
Q644	Malformation of urachus	1	5.75
		(33.3)	(1.16–28.5)
Q647	Other and unspecified congenital malformations of bladder and urethra	1	17.3
		(100.0)	(16.7–17.9)
Q65–Q79	**Congenital malformations and deformations of the musculoskeletal system**	**62**	**6.19**
		(35.8)	**(5.05–7.57)**
Q713	Congenital absence of hand and finger	1	5.75
		(33.3)	(1.16–28.5)
Q743	Arthrogryposis multiplex congenita	1	8.63
		(50.0)	(2.16–34.5)
Q781	Polyostotic fibrous dysplasia	1	17.3
		(100.0)	(16.7–17.9)

Q790	Congenital diaphragmatic hernia	35	11.2
		(64.7)	(9.10–13.7)
Q792	Exomphalos	17	7.54
		(43.6)	(5.26–10.8)
Q793	Gastroschisis	9	4.09
		(23.7)	(2.31–7.24)
Q798	Other congenital malformations of musculoskeletal system	1	17.3
		(100.0)	(16.7–17.9)
Q80–Q89	**Other congenital malformations**	**3**	**1.57**
		(9.1)	**(0.53–4.62)**
Q878	Other specified congenital malformation syndromes, not elsewhere classified	1	8.63
		(50.0)	(2.16–34.5)
Q891	Congenital malformations of adrenal gland	1	5.75
		(33.3)	(1.16–28.5)
Q897	Multiple congenital malformation, not elsewhere classified	1	2.88
		(16.7)	(0.48–17.2)
Q90–Q99	**Chromosomal abnormalities, not elsewhere classified**	**484**	**8.19**
		(47.5)	**(7.62–8.81)**
Q90	Down syndrome (Trisomy 21)	72	3.17
		(22.4)	(2.58–3.89)
Q913	Edwards syndrome (Trisomy 18), unspecified	330	11.0
		(72.9)	(10.3–11.7)
Q917	Patau syndrome (Trisomy 13), unspecified	44	10.7
		(75.9)	(9.22–12.4)
Q970	Karyotype 47,XXX	1	14.0
		(100.0)	(13.6–14.4)

Denominators are shown in Table 1. Diseases with no death during NICU admission are excluded from this table. Relative risk compared with infants with no birth defects.

Figure 1. Kaplan-Meier curves until 120 days after birth of infants with birth defects and those without birth defects

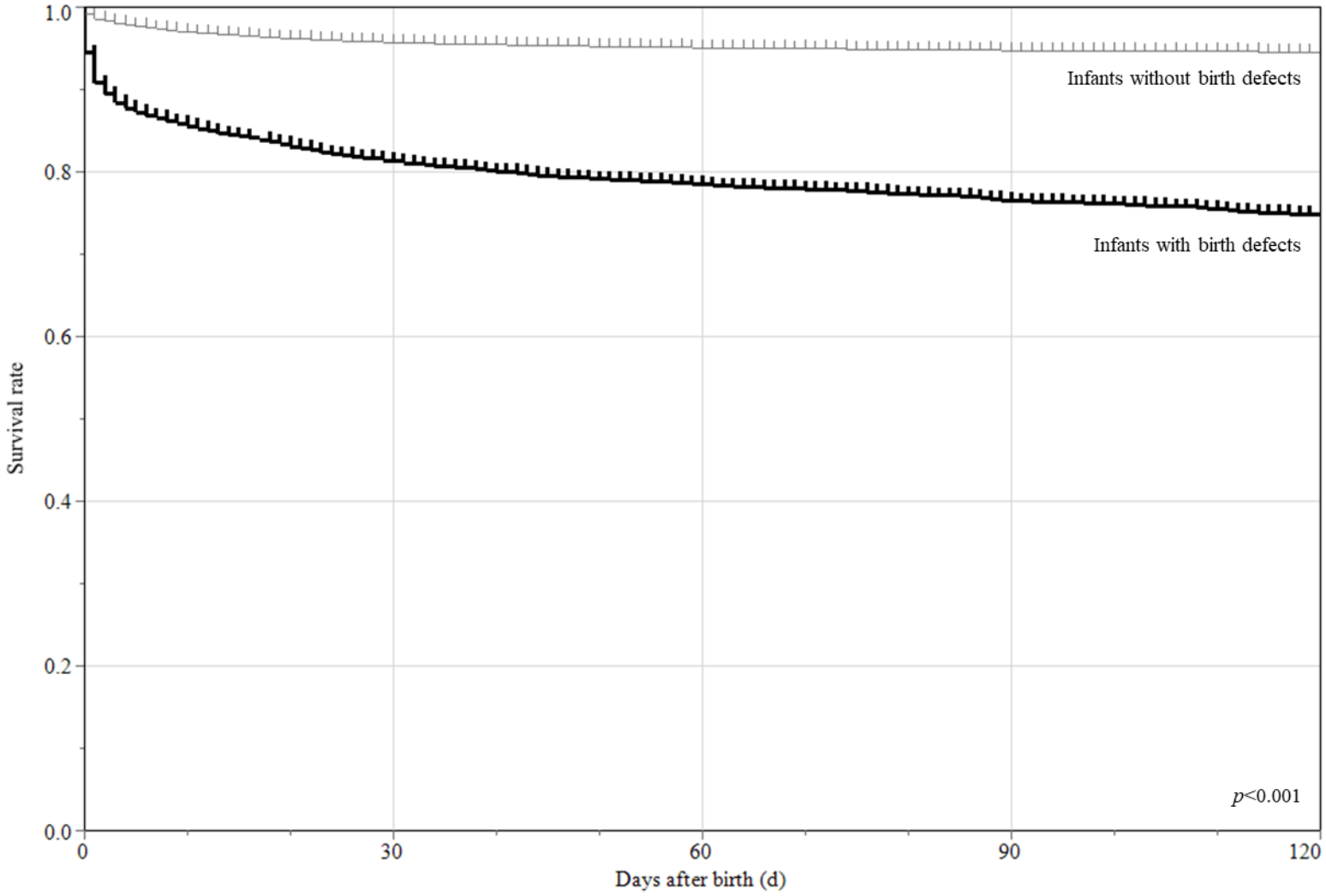
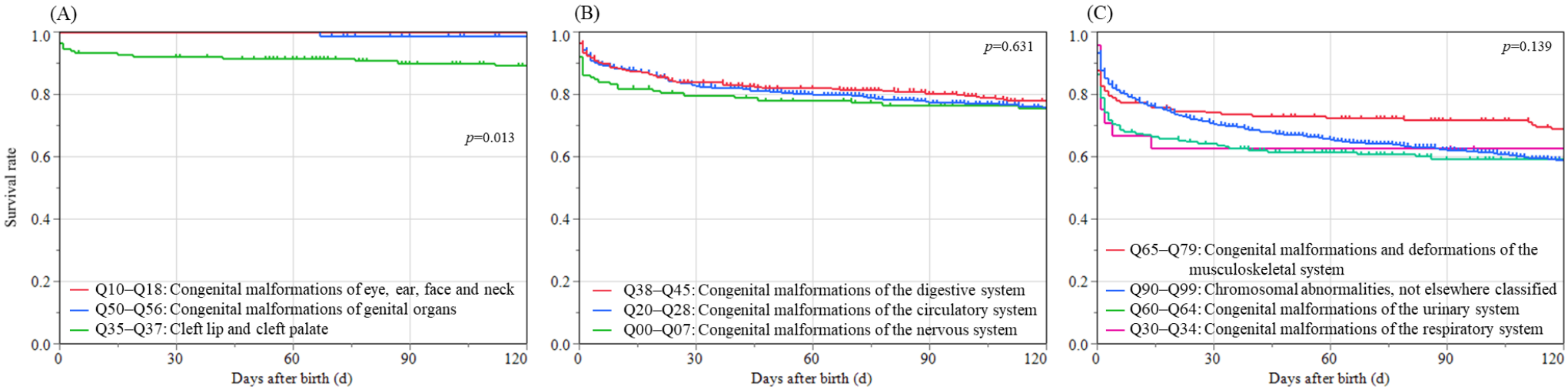


Figure 2. Kaplan-Meier curves of each birth defect category

(A) Good prognosis group, (B) Moderate prognosis group, and (C) Poor prognosis group



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University, Teikyo University, Showa University, Japan Red Cross Medical Center, National Center for Child Health and Development, Tokyo Metropolitan Otsuka Hospital, Toho University, Tokyo Metropolitan Bokuto Hospital, Tokyo Jikei Medical University, Tokyo Medical and Dental University, Saint Luke's International Hospital, Juntendo University, Sanikukai Hospital, Katsushika Red Cross Hospital, Yokohama Rosai Hospital, Yokohama City University Medical Center, St. Marianna University School of Medicine Hospital, Kanagawa Children's Medical Center, Tokai University, Kitazato University, Odawara Municipal Hospital, Nippon Medical School Musashi Kosugi Hospital, Saiseikai Yokohamashi Tobu Hospital, National Hospital Organization Yokohama Medical Center, Yamanashi Prefectural Central Hospital, Nagano Children's Hospital, Shinshu University, Iida Municipal Hospital, National Hospital Organization Shinshu Ueda Medical Center, Saku General Hospital, Niigata University, Niigata Prefectural Central Hospital, Niigata Municipal Hospital, Nagaoka Red Cross Hospital, Koseiren Takaoka Hospital, Toyama Prefectural Central Hospital, Toyama University, Ishikawa Medical Center for Maternal and Child Health, Kanazawa Medical University, Kanazawa Medical Center, Fukui Prefectural Hospital, Fukui University, Gifu Prefectural General Medical Center, National Hospital Organization Nagara Medical Center, Takayama Red Cross Hospital, Seirei Hamamatsu Hospital, Shizuoka Saiseikai Hospital, Shizuoka Children's Hospital, Hamamatsu Medical University, Numazu Municipal Hospital, Yaizu City Hospital, Fujieda Municipal General Hospital, Nagoya Red Cross Daini Hospital, Nagoya University, Nagoya Red Cross Daiichi Hospital, Toyohashi Municipal Hospital, Nagoya City West Medical Center, Anjo kosei Hospital, Tosei

General Hospital, Komaki Municipal Hospital, TOYOTA Memorial Hospital, Okazaki Municipal Hospital, Konan Kosei Hospital, National Mie Central Medical Center, Ise Red Cross Hospital, Yokkaichi Municipal Hospital, Otsu Red Cross Hospital, Shiga University of Medical Science Hospital, Nagahama Red Cross Hospital, Uji Tokushukai Hospital, The Japan Baptist Hospital, Kyoto University, Kyoto Red Cross Daiichi Hospital, National Maizuru Medical Center, Fukuchiyama City Hospital, Kyoto Prefectural University of Medicine Hospital, Kyoto City Hospital, Mitsubishi Kyoto Hospital, Yodogawa Christian Hospital, Osaka Medical Center and Research Institute for Maternal and Child Health, Osaka University, Takatsuki General Hospital, Kansai Medical University, Osaka City General Hospital, Osaka City Sumiyoshi Hospital, Aizenbashi Hospital, Toyonaka Municipal Hospital, National Cerebral and Cardiovascular Center, Kitano Hospital, Saiseikai Suita Hospital, Chifune Hospital, Bellland General Hospital, Rinku General Medical Center, Osaka Red Cross Hospital, Yao Municipal Hospital, Osaka General Medical Center, Osaka City University, Hyogo Prefectural Kobe Children's Hospital, Kobe University, Kakogawa West City Hospital, Saiseikai Hyogoken Hospital, Kobe City Medical Center General Hospital, Hyogo College of Medicine Hospital, Himeji Red Cross Hospital, Toyooka Public Hospital, Hyogo Prefectural Awaji Medical Center, Nara Medical University, Wakayama Medical University, Tottori Prefectural Central Hospital, Tottori University, Shimane Prefectural Central Hospital, Matsue Red Cross Hospital, Kurashiki Central Hospital, Tsuyama Central Hospital, Kawasaki Medical School Hospital, National Hospital Organization Okayama Medical Center, Okayama Red Cross Hospital, Hiroshima City Hiroshima Citizens Hospital, Hiroshima

Prefectural Hospital, Hiroshima University, Tsuchiya General Hospital, National Hospital Organization Kure Medical Center, Yamaguchi University, Yamaguchi Grand Medical Center, Tokushima University, Tokushima Municipal Hospital, Kagawa University, National Hospital Organization Kagawa Children's Hospital, Matsuyama Red Cross Hospital, Ehime Prefectural Central Hospital, Kochi Health Science Center, St. Mary's Hospital, National Kyushu Medical Center, Kurume University, Kitakyushu Municipal Medical Center, University of Occupational and Environmental Health, Fukuoka University, Kyushu University, Iizuka Hospital, National Hospital Organization Kokura Medical Center, National Hospital Organization Saga Hospital, National Hospital Organization Nagasaki Medical Center, Kumamoto City Hospital, Kumamoto University, Oita Prefectural Hospital, Almeida Memorial Hospital, Nakatsu Municipal Hospital, Miyazaki University, National Hospital Organization Miyakonojo Medical Center, Kagoshima City Hospital, Imakiire General Hospital, Okinawa Prefectural Nanbu Medical Center and Children's Medical Center, Okinawa Prefectural Chubu Hospital, Naha City Hospital, Okinawa Red Cross Hospital.

Appendix 2

Definition of Neonatal Morbidities.

Morbidities included respiratory distress syndrome, air leak, pulmonary hemorrhage, persistent pulmonary hypertension of newborn, chronic lung disease, operation for patent ductus arteriosus, late-onset circulatory collapse, intraventricular hemorrhage and its severity, cystic periventricular leukomalacia, sepsis and its onset, necrotizing enterocolitis, localized intestinal perforation, hearing impairment detected by neonatal screening, and retinopathy of prematurity.

Respiratory distress syndrome was diagnosed with reference to clinical symptoms, chest X-ray findings, and stable microbubble tests. Pulmonary hemorrhage, necrotizing enterocolitis and localized intestinal perforation were diagnosed clinically. Persistent pulmonary hypertension of the newborn was diagnosed when right to left shunt was proven by cardiac ultrasonography or by clinical findings. Chronic lung disease was defined as supplemental oxygen administration or respiratory support at corrected age of 36 weeks. Late-onset circulatory collapse was defined only when steroid administration was required for late-onset circulatory collapse. Intraventricular hemorrhage was diagnosed by cranial ultrasound and was classified using the Papile grading system. Severe intraventricular hemorrhage was defined as grade 3 or 4. Cystic periventricular leukomalacia was diagnosed by cranial ultrasound or brain magnetic resonance imaging. Sepsis was defined only when blood culture was positive and late-onset sepsis was defined as sepsis whose onset was after 7 days of age. Retinopathy of prematurity was defined when treatment; i.e. retinal photocoagulation therapy or anti-vascular endothelial growth factor antibody therapy, was undertaken.