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Major Congenital Anomalies in Korean Livebirths in 2013–2014: Based on the National Health Insurance Database

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ABSTRACT

Background: In Korea, there have been no reports comparing the prevalence of major congenital anomalies with other countries and no reports on surgical treatment and long-term mortality. We investigated the prevalence of 67 major congenital anomalies in Korea and compared the prevalence with that of the European network of population-based registries for the epidemiological surveillance of congenital anomalies (EUROCAT). We also investigated the mortality and age at death, the proportion of preterm births, and the surgical rate for the 67 major congenital anomalies.
Methods: Korean National Health Insurance claim data were obtained for neonates born in 2013–2014 and admitted within one-year-old. Sixty-seven major congenital anomalies were defined by medical diagnoses classified by International Classification of Diseases-10 codes according to the EUROCAT definition version 2014. Mortality and surgery were defined if any death or surgery claim code was confirmed until 2020. Poisson distribution was used to calculate the 95% confidence interval of the congenital anomaly prevalence.
Results: The total prevalence of the 67 major anomalies was 433.5/10,000 livebirths. When compared with the prevalence of each major anomaly in EUROCAT, the prevalence of spina bifida, atrial septal defect (ASD), congenital megacolon, hip dislocation and/or dysplasia and skeletal dysplasia were more than five times higher in Korea. In contrast, the prevalence of aortic atresia/interrupted aortic arch and gastroschisis was less than one-fifth in Korea. The proportion of preterm births was 15.7%; however, more than 40% of infants with anencephaly, annular pancreas and gastroschisis were preterm infants. Additionally, 29.2% of the major anomalies were admitted to the neonatal intensive care units at birth, and 25.6% received surgical operation. The mortality rate was 1.7%, and 78.2% of the deaths occurred within the first year of life. However, in neonates with tricuspid valve atresia and stenosis, duodenal atresia or stenosis, and diaphragmatic hernia, more than half died within their first month of life. ASD and ventricular septal defect were the most common anomalies, and trisomy 18 and hypoplastic left heart syndrome were the most fatal anomalies. All infants

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Disclosure
The authors declare no conflict of interest with NHIS.

Author Contributions
Conceptualization: Lee JA, Lee SM, Lim JW, Chang YS. Data curation: Lee SM. Formal analysis: Lee SM, Lee JA. Funding acquisition: Chang YS. Investigation: Lee JA, Lee SM. Methodology: Lee JA. Software: Lee SM. Validation: Lee SM, Lee JA. Visualization: Lee JA. Writing - original draft: Lee JA. Writing - review & editing: Lee SM, Chung SH, Lee JH, Shim JW, Lim JW, Kim CY, Chang YS.

with aortic atresia/interrupted aortic arch and conjoined twins received surgery.
Conclusion: The proportion of surgeries, preterm births and mortality was high in infants with major congenital anomalies. The establishment of a national registry of congenital anomalies and systematic support by national medical policies are needed for infants with major congenital anomalies in Korea.

Keywords: Congenital Anomaly; Korea; Prevalence; Mortality; Surgery

INTRODUCTION

Congenital anomalies or birth defects are one of the leading causes of neonatal deaths, and multidisciplinary medical support with high medical expenses is required during the whole life of neonates with congenital anomalies. The prevalence of congenital anomalies varies according to country, race and era, and various results have been reported depending on how the study subjects were included and which research method was used. Europe and the United States (U.S.) have examined the prevalence of major congenital anomalies through a nationwide or international surveillance system of fetuses and infants which is approximately 3% of all livebirths.[1,2] However, there is no nationwide registry of congenital anomalies in Korea; therefore, only a small number of single-center and multi-center studies in which only a few institutions participated have been published about congenital anomalies in Korea.[3,4] And all reports on the prevalence of congenital anomalies in Korea have been based on the Korean National Health Insurance Service (NHIS) database which shows that the prevalence of major congenital anomalies was 287 per 10,000 livebirths in 2005–2006 to 548 per 10,000 livebirths in 2009–2010.[5,6] Additionally, the prevalence of 69 selected major congenital anomalies increased from 336 per 10,000 livebirths in 2008 to 564 per 10,000 livebirths in 2014.[7] Recently, research was published on major congenital anomalies in very-low-birthweight (VLBW) infants using the Korean Neonatal Network (KNN) Database which showed the prevalence of major congenital anomalies in VLBW as 349 per 10,000 livebirths.[8] However, there are no reports comparing the prevalence of congenital anomalies in Korea with other countries.

Mortality associated with congenital anomalies accounts for approximately 20% of all infant deaths.[9] According to the European network of population-based registries for the epidemiological surveillance of congenital anomalies (EUROCAT) database, the average infant mortality for congenital anomalies was 11 per 10,000 births, and the rate of stillbirths with congenital anomalies was 6 per 10,000.[10] Moreover, congenital anomalies were associated with a high proportion of low birthweight and prematurity.[5,11] However, no data are available on the long-term mortality, the surgical treatment of congenital anomalies and the use of neonatal intensive care unit (NICU) care in Korea. It will be important to know the current status of the prevalence and medical treatments of infants with major congenital anomalies in Korea for establishing national medical policies to support them.

This study investigated the prevalence of 67 major congenital anomalies in Korea using the Korean NHIS claim database. The prevalence of each anomaly was compared with that in the EUROCAT database. Additionally, information was collected for the 67 major congenital anomalies in Korea on mortality, preterm birth, surgery rate and NICU admissions.

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METHODS

The Korean NHIS claim data were used to investigate the population born in 2013 and 2014 which were obtained from the Korean NHIS. In Korea, the NHIS covers approximately 95% of the total population in Korea, and the Korean NHIS database contains all claim data covered by the National Healthcare Insurance program and Medical Aid program. Among the population born in 2013 and 2014, we included neonates diagnosed with any of the 67 major congenital anomalies classified by the International Classification of Diseases (ICD)-10 at admission during the first year after birth in the analysis. Each of the 67 major congenital anomalies was defined by the ICD-10 codes which were selected by the EUROCAT definition version 2014 (**Supplementary Table 1**). Infants diagnosed with a major congenital anomaly after one year of age or any infants with a major congenital anomaly who were not admitted within their first year of life were also excluded. In our analysis, we included all the diagnoses registered in the Korean NHIS claim database which does not discriminate and exclude rule-out diagnoses.

We compared the prevalence of each of the 67 major congenital anomalies in 2013 and 2014 in Korea with those in the EUROCAT from 2013 to 2019. The prevalence was calculated as the number of congenital anomalies registered in the NHIS database among 10,000 livebirth infants.

We also showed the total prevalence of the 67 major congenital anomalies in Korea if infants had any of the 67 major congenital anomalies. The prevalence of all major congenital anomalies in the EUROCAT from 2013 to 2019 was also shown which was defined as Q chapter, D215, D821, D1810, P350, P351, P354, P358, and P371. Minor anomalies were excluded as specified in Guide 1.5, section 3.3 of the EUROCAT.[12]

We searched for the proportion of male gender, multiple anomalies and preterm infants of the total infants with any of the 67 major congenital anomalies. Multiple anomalies were defined as more than one disease code for major congenital anomalies in the same person. Preterm infant was defined as any diagnosis code with a gestational age at birth less than 37 weeks. We also searched for the proportion of NICU admissions, surgeries, mortalities and age at death of the total infants. NICU admission was defined when there is any insurance claim code related to NICU admission was confirmed. Surgery was defined if any surgical code for claim from birth till the year of 2020 in the Korean NHIS database. Mortality was defined as any death recorded from birth till the year of 2020 in the Korean NHIS database.

We searched for the proportion of male gender, preterm infants, NICU admissions, surgical rate, mortality and age at death for each of the 67 major congenital anomalies. Finally, the top 5 rankings of the prevalence, mortality, and surgical rate were investigated in our study.

Statistical analysis

We used the Poisson distribution to calculate the 95% confidence intervals of the prevalences of the major congenital anomalies. Statistical analysis was performed using R version 3.6.3.

Ethics statement

We used NHIS - National Sample Cohort data (NHIS-2021-4-007) maintained by the NHIS. All identifiable variables including claim, individual, and organizational-level identification numbers were randomly re-generated by the NHIS database to protect the patient privacy. The study protocol was reviewed and approved by the Institutional Review Board (IRB) of the Samsung Medical Center (approval No. SMC 2020-12-059). Informed consent was waived by the IRB.

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Table 1. Characteristics of a total of 67 major congenital anomalies and the major congenital anomalies in the nervous system, head, eye, ear and neck, and orofacial clefts in 2013–2014

Congenital anomalies	Prevalence of 2013–2019 EUROCAT (/10,000 live births)	2013–2014 Korea (total birth = 884,759)		Male (%)	Preterm infant (%)	NICU admission (%)	Surgery (%)	Mortality (%)			
		Number	Prevalence (/10,000 livebirths)					Total (%)	Died < 1 mon (%)	Died 1 mon–1 yr (%)	Died > 1 yr (%)
Major congenital anomalies	203.70 (202.47–204.93)[a]	38,354	433.50 (429.17–437.86)	19,993 (52.1)	6,059 (15.7)	11,204 (29.2)	9,830 (25.6)	655 (1.7)	140 (21.4)	372 (56.8)	143 (21.8)
Nervous system											
Anencephaly	0.20 (0.17–0.25)	10	0.11 (0.05–0.21)	4 (40.0)	4 (40.0)	6 (60.0)	4 (40.0)	3 (30.0)	0 (0.0)	2 (66.7)	1 (33.3)
Encephalocele	0.32 (0.27–0.37)	51	0.58 (0.43–0.76)	28 (54.9)	4 (7.8)	15 (29.4)	27 (52.9)	1 (2.0)	0 (0.0)	0 (0.0)	1 (100.0)
Spina bifida	1.64 (1.53–1.76)	832	9.40 (8.78–10.07)	390 (46.9)	43 (5.2)	155 (18.6)	232 (27.9)	8 (1.0)	1 (12.5)	5 (62.5)	2 (25.0)
Microcephaly	2.08 (1.95–2.20)	226	2.55 (2.23–2.91)	101 (44.7)	55 (24.3)	69 (30.5)	52 (23.0)	12 (5.3)	1 (8.3)	4 (33.3)	7 (58.3)
Congenital hydrocephalus	2.54 (2.40–2.68)	314	3.55 (3.17–3.96)	184 (58.6)	113 (36.0)	180 (57.3)	146 (46.5)	34 (10.8)	5 (14.7)	18 (52.9)	11 (32.4)
Arhinencephaly/ holoprosencephaly	0.28 (0.23–0.33)	14	0.16 (0.09–0.27)	3 (21.4)	5 (35.7)	6 (42.9)	5 (35.7)	3 (21.4)	1 (33.3)	1 (33.3)	1 (33.3)
Eye, ear, face and neck											
Anophthalmos/ microphthalmos	0.60 (0.54–0.67)	47	0.53 (0.39–0.71)	22 (46.8)	14 (29.8)	19 (40.4)	13 (27.7)	4 (8.5)	0 (0.0)	3 (75.0)	1 (25.0)
Congenital cataract	1.32 (1.23–1.43)	119	1.34 (1.11–1.61)	57 (47.9)	13 (10.9)	23 (19.3)	53 (44.5)	6 (5.0)	1 (16.7)	2 (33.3)	3 (50.0)
Congenital glaucoma	0.30 (0.25–0.35)	68	0.77 (0.60–0.97)	43 (63.2)	20 (29.4)	34 (50.0)	37 (54.4)	6 (8.8)	0 (0.0)	5 (83.3)	1 (16.7)
Anotia	0.23 (0.20–0.30)	40	0.45 (0.32–0.62)	28 (70.0)	9 (22.5)	8 (20.0)	12 (30.0)	2 (5.0)	0 (0.0)	1 (50.0)	1 (50.0)
Oro-facial clefs											
Cleft palate without cleft lip	5.40 (5.20–5.60)	806	9.11 (8.49–9.76)	388 (48.1)	81 (10.0)	265 (32.9)	288 (35.7)	28 (3.5)	4 (14.3)	12 (42.9)	12 (42.9)
Cleft lip with or without cleft palate	7.46 (7.23–7.70)	630	7.12 (6.58–7.70)	384 (61.0)	47 (7.5)	175 (27.8)	442 (70.2)	11 (1.7)	0 (0.0)	7 (63.6)	4 (36.4)

EUROCAT = European network of population-based registries for the epidemiological surveillance of congenital anomalies, NICU = neonatal intensive care unit.
[a]All Q+D21.5, D82.1, D18.10, P35.0, and P37.1 of International Classification of Diseases-10 code except minor anomaly.[10]

RESULTS

The number of births registered in the Korean NHIS database was 442,418 in 2013 and 442,341 in 2014 for a total of 884,759. The number of infants with at least one of the 67 major congenital anomalies who were admitted within their first year of life in 2013 was 18,785 and 19,569 in 2014 with an average prevalence of 433.5/10,000 livebirths (**Table 1**). The number of infants with multiple anomalies was 3,035 (16.1%) in 2013 and 3,159 (16.1%) in 2014 for an average of 16.1% of the total population with the 67 major congenital anomalies.

Among the 67 congenital anomalies, the prevalence of spina bifida, atrial septal defect (ASD), congenital megacolon, hip dislocation and/or dysplasia and skeletal dysplasia in Korea was more than five times higher than the prevalence of each anomaly in the EUROCAT. However, the prevalence of aortic atresia/interrupted aortic arch and gastroschisis was less than one-fifth in Korea when compared with that of the EUROCAT data.

When we searched for the proportion of male gender and preterm infants in infants with major congenital anomalies, 52.1% were male, and 15.7% were preterm infants. However, more than 40% of the infants with anencephaly, annular pancreas, and gastroschisis were preterm infants. Among the 67 major congenital anomalies, the number of infants who died up to 2020 was 655, which comprised 1.7% of the deaths. Most of the deaths occurred within the first year of life (78.2% of all mortalities), especially between 1 and 12 months of age (56.8%). However, more than half of the infants with tricuspid valve atresia and stenosis, duodenal atresia or stenosis, and diaphragmatic hernia died within one month after birth. When we searched for NICU admissions, 29.2% of the major congenital anomalies were admitted to the NICU. When we assessed the rate of surgery in congenital anomalies, 25.6% of the major congenital anomalies received surgical operation (**Table 1**). When we searched for the subtype of congenital anomalies, the operation rate and NICU admission rate of infants with congenital heart defects and digestive system anomalies were higher than those of other anomalies (**Tables 2** and **3**).

Congenital anomalies of the central nervous system (CNS), head, eye, ear, face and neck, and orofacial clefts

In congenital anomalies of the CNS, the prevalences of anencephaly and arhinencephaly/holoprosencephaly were

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Table 2. Characteristics of the major congenital anomalies in the respiratory system and major congenital heart defects in 2013–2014

Congenital anomalies	Prevalence of 2013–2019 EUROCAT (/10,000 live births)	2013–2014 Korea (total birth = 884,759)		Male (%)	Preterm infant (%)	NICU admission (%)	Surgery (%)	Mortality (%)			
		No.	Prevalence (/10,000 livebirths)					Total (%)	Died < 1 mon (%)	Died 1 mon–1 yr (%)	Died > 1 yr (%)
Respiratory system											
Cystic adenomatoid malformation of lung	1.10 (1.01–1.19)	37	0.42 (0.29–0.58)	21 (56.8)	5 (13.5)	15 (40.5)	7 (18.9)	1 (2.7)	0 (0.0)	0 (0.0)	1 (100.0)
Choanal atresia	0.88 (0.80–0.96)	54	0.61 (0.46–0.80)	31 (57.4)	8 (14.8)	27 (50.0)	16 (29.6)	3 (5.6)	0 (0.0)	1 (33.3)	2 (66.7)
Congenital heart defects											
Common arterial truncus	0.42 (0.37–0.48)	34	0.38 (0.27–0.54)	17 (50.0)	5 (14.7)	23 (67.6)	26 (76.5)	6 (17.6)	1 (16.7)	2 (33.3)	3 (50.0)
Double outlet right ventricle (Taussig-Bing syndrome)	1.20 (1.11–1.30)	192	2.17 (1.87–2.50)	113 (58.9)	28 (14.6)	144 (75.0)	169 (88.0)	31 (16.1)	6 (19.4)	17 (54.8)	8 (25.8)
Transposition of great vessels	3.02 (2.87–3.18)	177	2.00 (1.72–2.32)	125 (70.6)	7 (4.0)	143 (80.8)	167 (94.4)	28 (15.8)	7 (25.0)	16 (57.1)	5 (17.9)
Tetralogy of Fallot	2.92 (2.76–3.08)	385	4.35 (3.93–4.81)	222 (57.7)	45 (11.7)	262 (68.1)	293 (76.1)	31 (8.1)	5 (16.1)	21 (67.7)	5 (16.1)
Atrial septal defect	15.97 (15.60–16.34)	17,871	201.99 (199.04–204.97)	9,025 (50.5)	4,410 (24.7)	7,168 (40.1)	4,974 (27.8)	273 (1.5)	54 (19.8)	166 (60.8)	53 (19.4)
Ventricular septal defect	36.59 (36.03–37.15)	5,677	64.16 (62.51–65.86)	2,688 (47.3)	580 (10.2)	1,385 (24.4)	1,713 (30.2)	142 (2.5)	30 (21.1)	79 (55.6)	33 (23.2)
Atrioventricular septal defect	3.18 (3.02–3.35)	274	3.10 (2.74–3.49)	137 (50.0)	53 (19.3)	161 (58.8)	161 (58.8)	35 (12.8)	8 (22.9)	23 (65.7)	4 (11.4)
Tricuspid valve atresia and stenosis	0.42 (0.36–0.48)	23	0.26 (0.17–0.39)	11 (47.8)	3 (13.0)	20 (87.0)	19 (82.6)	2 (8.7)	2 (100.0)	0 (0.0)	0 (0.0)
Ebstein's anomaly	0.41 (0.35–0.47)	78	0.88 (0.70–1.10)	41 (52.6)	9 (11.5)	50 (64.1)	33 (42.3)	7 (9.0)	2 (28.6)	3 (42.9)	2 (28.6)
Aortic valve stenosis/atresia	1.24 (1.14–1.35)	75	0.85 (0.67–1.06)	44 (58.7)	7 (9.3)	42 (56.0)	54 (72.0)	12 (16.0)	2 (16.7)	7 (58.3)	3 (25.0)
Hypoplastic left heart syndrome	1.21 (1.11–1.32)	48	0.54 (0.40–0.72)	26 (54.2)	6 (12.5)	40 (83.3)	46 (95.8)	23 (47.9)	8 (34.8)	14 (60.9)	1 (4.3)
Coarctation of aorta	3.74 (3.56–3.92)	333	3.76 (3.37–4.19)	190 (57.1)	40 (12.0)	237 (71.2)	279 (83.8)	43 (12.9)	14 (32.6)	21 (48.8)	8 (18.6)
Single ventricle	0.40 (0.35–0.46)	108	1.22 (1.00–1.47)	53 (49.1)	9 (8.3)	92 (85.2)	102 (94.4)	33 (30.6)	5 (15.2)	24 (72.7)	4 (12.1)
Pulmonary valve stenosis	4.19 (4.01–4.37)	661	7.47 (6.91–8.06)	296 (44.8)	58 (8.8)	146 (22.1)	192 (29.0)	11 (1.7)	2 (18.2)	6 (54.5)	3 (27.2)
Pulmonary valve atresia	0.91 (0.83–0.99)	151	1.71 (1.45–2.00)	95 (62.9)	26 (17.2)	129 (85.4)	138 (91.4)	31 (20.5)	8 (25.8)	18 (58.1)	5 (16.1)
Hypoplastic right heart syndrome	0.32 (0.28–0.38)	14	0.16 (0.09–0.27)	8 (57.1)	1 (7.1)	12 (85.7)	13 (92.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Total anomalous pulmonary venous return	0.68 (0.61–0.75)	113	1.28 (1.05–1.54)	71 (62.8)	14 (12.4)	80 (70.8)	110 (97.3)	29 (25.7)	9 (31.0)	19 (65.5)	1 (3.4)
Mitral valve anomalies	1.28 (1.18–1.38)	126	1.42 (1.19–1.70)	56 (44.4)	20 (15.9)	44 (34.9)	58 (46.0)	9 (7.1)	1 (11.1)	7 (77.8)	1 (11.1)
Aortic atresia/interrupted aortic arch	0.39 (0.34–0.45)	4	0.05 (0.01–0.12)	2 (50.0)	0 (0.0)	4 (100.0)	4 (100.0)	1 (25.0)	0 (0.0)	1 (100.0)	0 (0.0)

EUROCAT = European network of population-based registries for the epidemiological surveillance of congenital anomalies, NICU = neonatal intensive care unit.

lower and the prevalence of spina bifida was more than five times higher in Korea compared to those of the EUROCAT. The proportion of preterm infants and the NICU admission rate, surgical rate, and mortality rate in anencephaly were relatively higher than other CNS anomalies.

In congenital anomalies of orofacial clefts, the prevalence of cleft palate without cleft lip was higher in Korea than that of the EUROCAT. The surgical rate of cleft lip with or without cleft palate was 70% which was higher than that of the other anomalies (**Table 1**).

Congenital anomalies of the respiratory system and congenital heart defects

In congenital anomalies of the respiratory system, the prevalence of congenital cystadenoid malformation was lower in Korea compared to that in the EUROCAT.

In congenital heart defects, the NICU admission rate and surgical rate were relatively higher than those of the other system anomalies. Especially, the prevalence of ASD was twelve times higher in Korea than in the EUROCAT, and the prevalence of ventricular septal defect (VSD) was also higher in Korea than in the EUROCAT. In contrast, the prevalences of tricuspid atresia and stenosis, hypoplastic left heart syndrome, hypoplastic right heart syndrome, and aortic atresia/interrupted aortic arch were lower in Korea than those in the EUROCAT. All deaths of infants with tricuspid atresia and stenosis occurred within one month after birth. The proportion of preterm infants with transposition of great arteries was only 4% (**Table 2**).

Congenital anomalies of the digestive system, genitourinary system and abdominal wall defects

The prevalences of esophageal atresia and diaphragmatic hernia were lower in Korea compared with those in the EUROCAT; however, the prevalences of congenital megacolon, atresia of bile ducts, atresia or stenosis of other parts of the small intestine were higher in Korea than in the EUROCAT. The proportions of preterm infants, NICU admission rate, and surgical rate were much higher in gastrointestinal (GI) anomalies

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Table 3. Characteristics of the major congenital anomalies in the digestive system, genitourinary system, and abdominal wall defects in 2013–2014

Congenital anomalies	Prevalence of 2013–2019 EUROCAT (/10,000 livebirths)	2013–2014 Korea (total birth = 884,759)		Male (%)	Preterm infant (%)	NICU admission (%)	Surgery (%)	Mortality (%)			
		No.	Prevalence (/10,000 livebirths)					Total (%)	Died < 1 mon (%)	Died 1 mon–1 yr (%)	Died > 1 yr (%)
Digestive system											
Esophageal atresia with/without tracheoesophageal fistula	2.47 (2.33–2.60)	155	1.75 (1.49–2.05)	95 (61.3)	58 (37.4)	147 (94.8)	148 (95.5)	26 (16.8)	7 (26.9)	15 (57.7)	4 (15.4)
Anorectal atresia and stenosis	2.75 (2.61–2.89)	430	4.86 (4.41–5.34)	221 (51.4)	64 (14.9)	317 (73.7)	375 (87.2)	18 (4.2)	5 (27.8)	9 (50.0)	4 (22.2)
Duodenal atresia or stenosis	1.27 (1.17–1.37)	120	1.36 (1.13–1.62)	53 (44.2)	35 (29.2)	107 (89.2)	108 (90.0)	7 (5.8)	4 (57.1)	2 (28.6)	1 (14.3)
Hirshsprung's disease (congenital megacolon)	1.42 (1.31–1.52)	713	8.06 (7.48–8.67)	382 (53.6)	94 (13.2)	474 (66.5)	335 (47.0)	12 (1.7)	0 (0.0)	8 (66.7)	4 (33.3)
Atresia of bile ducts	0.33 (0.28–0.38)	166	1.88 (1.60–2.18)	84 (50.6)	19 (11.4)	47 (28.3)	118 (71.1)	12 (7.2)	1 (8.3)	7 (58.3)	4 (33.3)
Atresia or stenosis of other parts of small intestine	0.92 (0.84–1.01)	167	1.89 (1.61–2.20)	92 (55.1)	54 (32.3)	155 (92.8)	159 (95.2)	12 (7.2)	5 (41.7)	6 (50.0)	1 (8.3)
Annular pancreas	0.16 (0.13–0.20)	17	0.19 (0.11–0.31)	8 (47.1)	7 (41.2)	14 (82.4)	15 (88.2)	2 (11.8)	0 (0.0)	0 (0.0)	2 (100.0)
Diaphragmatic hernia	2.15 (2.03–2.28)	135	1.53 (1.28–1.81)	72 (53.3)	23 (17.0)	120 (88.9)	125 (92.6)	22 (16.3)	11 (50.0)	8 (36.4)	3 (13.6)
Abdominal wall defects											
Gastroschisis	2.09 (1.96–2.22)	32	0.36 (0.25–0.51)	16 (50.0)	14 (43.8)	30 (93.8)	30 (93.8)	2 (14.3)	0 (0.0)	1 (50.0)	1 (50.0)
Omphalocele	1.25 (1.16–1.35)	514	5.81 (5.32–6.33)	334 (65.0)	51 (9.9)	90 (17.5)	111 (21.6)	8 (1.6)	1 (12.5)	6 (75.0)	1 (12.5)
Genitourinary system											
Bilateral/renal agenesis including Potter syndrome	0.24 (0.20–0.29)	5	0.06 (0.02–0.13)	2 (40.0)	1 (20.0)	5 (100.0)	4 (80.0)	1 (20.0)	1 (100.0)	0 (0.0)	0 (0.0)
Bladder exstrophy and/or epispadia	0.40 (0.35–0.46)	23	0.26 (0.17–0.39)	19 (82.6)	7 (30.4)	14 (60.9)	12 (52.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Renal dysplasia	3.53 (3.37–3.69)	191	2.16 (1.86–2.49)	83 (43.5)	18 (9.4)	49 (25.7)	27 (14.1)	3 (1.6)	0 (0.0)	3 (100.0)	0 (0.0)
Congenital hydronephrosis	12.27 (11.97–12.57)	3,320	37.52 (36.26–38.82)	2,516 (75.8)	270 (8.1)	614 (18.5)	467 (14.1)	13 (0.4)	2 (15.4)	7 (53.8)	4 (30.8)
Posterior urethral valve and/or prune belly	1.17 (1.08–1.27)	31	0.35 (0.24–0.50)	31 (100.0)	7 (22.6)	19 (61.3)	23 (74.2)	1 (3.2)	0 (0.0)	0 (0.0)	1 (100.0)
Indeterminate sex	0.35 (0.30–0.40)	138	1.56 (1.31–1.84)	69 (50.0)	34 (24.6)	64 (46.4)	60 (43.5)	9 (6.5)	0 (0.0)	7 (77.8)	2 (22.2)
Hypospadias	17.98 (17.62–18.35)	612	6.92 (6.38–7.49)	611 (99.8)	181 (29.6)	229 (37.4)	248 (40.5)	7 (1.1)	1 (14.3)	4 (57.1)	2 (28.6)

EUROCAT = European network of population-based registries for the epidemiological surveillance of congenital anomalies, NICU = neonatal intensive care unit.

compared with the other system anomalies. The mortalities of esophageal atresia and diaphragmatic hernia were higher than those of other GI anomalies. Especially, more than half of the mortalities of duodenal atresia or stenosis and diaphragmatic hernia occurred within one month after birth. In infants with an annular pancreas, 41.2% were preterm infants.

In abdominal wall defects, the prevalence of gastroschisis was lower; however, the prevalence of omphalocele was higher in Korea than in the EUROCAT. The proportion of preterm infants and the NICU admission rate, surgical rate, and mortality were higher in gastroschisis when compared with other GI anomalies.

The prevalence of a genitourinary anomaly was relatively lower in Korea than in the EUROCAT; however, the prevalence of congenital hydronephrosis was three times higher in Korea than in the EUROCAT. The surgical rate was about 80% for Potter syndrome and posterior urethral valve (**Table 3**).

Limb anomalies, chromosomal anomalies and other congenital anomalies

In limb anomalies, the prevalences of hip dislocation, polydactyly, and syndactyly were higher in Korea than in the EUROCAT. However, the prevalence of clubfoot was lower in Korea.

The prevalence of chromosomal anomalies was relatively lower in Korea than in the EUROCAT. The NICU admission rate, surgical rate, and mortality were high in trisomy 13 and trisomy 18, and the proportion of preterm infants for trisomy 18 was also high.

In other anomalies, the prevalences of congenital skin disorders, skeletal dysplasia, and craniosynostosis were higher in Korea than in the EUROCAT. All conjoined twins received surgical operations (**Table 4**).

Top 5 rankings of major congenital anomalies

We also ranked the top 5 anomaly cases that were the most common and had the highest mortality and surgical rates. ASD and VSD were the most common congenital anomalies. Trisomy 18, hypoplastic left heart syndrome and trisomy 13 were the most fatal congenital anomalies. Among the 67 major congenital anomaly subgroups, the surgical rate was highest for aortic atresia/interrupted aortic arch, conjoined twins and total anomalous pulmonary venous return (**Table 5**).

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Table 4. Characteristics of the limb anomalies, chromosomal anomalies, and other major congenital anomalies in 2013–2014

Congenital anomalies	Prevalence of 2013–2019 EUROCAT (/10,000 livebirths)	2013–2014 Korea (total birth = 884,759)		Male (%)	Preterm infant (%)	NICU admission (%)	Surgery (%)	Mortality (%)			
		No.	Prevalence (/10,000 livebirths)					Total (%)	Died < 1 mon (%)	Died 1 mon–1 yr (%)	Died > 1 yr (%)
Limb anomaly											
Reduction deformity of limbs	3.09 (2.94–3.24)	192	2.17 (1.87–2.50)	94 (49.0)	14 (7.3)	21 (10.9)	35 (18.2)	2 (1.0)	0 (0.0)	2 (100.0)	0 (0.0)
Hip dislocation and/or dysplasia	5.96 (5.75–6.18)	4,362	49.30 (47.85–50.79)	1,583 (36.3)	190 (4.4)	298 (6.8)	466 (10.7)	9 (0.2)	0 (0.0)	4 (44.4)	5 (55.6)
Polydactyly	9.79 (9.52–10.06)	1,167	13.19 (12.44–13.97)	672 (57.6)	92 (7.9)	165 (14.1)	441 (37.8)	14 (1.2)	4 (28.6)	3 (21.4)	7 (50.0)
Clubfoot-talipes equinovarus	9.71 (9.44–9.98)	189	2.14 (1.84–2.46)	95 (50.3)	10 (5.3)	17 (9.0)	61 (32.3)	2 (1.1)	0 (0.0)	1 (50.0)	1 (50.0)
Syndactyly	3.41 (3.26–3.58)	658	7.44 (6.88–8.03)	379 (57.6)	55 (8.4)	87 (13.2)	148 (22.5)	8 (1.2)	1 (12.5)	4 (50.0)	3 (37.5)
Chromosomal anomaly											
Patau syndrome/Trisomy 13	0.29 (0.25–0.34)	7	0.08 (0.03–0.16)	3 (42.9)	1 (14.3)	6 (85.7)	4 (57.1)	3 (42.9)	0 (0.0)	2 (66.7)	1 (33.3)
Down syndrome	9.87 (9.60–10.14)	467	5.28 (4.81–5.78)	265 (56.7)	97 (20.8)	252 (54.0)	179 (38.3)	31 (6.6)	3 (9.7)	20 (64.5)	8 (25.8)
Edward syndrome/Trisomy 18	0.71 (0.64–0.79)	41	0.46 (0.33–0.63)	22 (53.7)	16 (39.0)	33 (80.5)	27 (65.9)	23 (56.1)	1 (4.3)	18 (78.3)	4 (17.4)
Turner syndrome	0.63 (0.56–0.70)	35	0.40 (0.28–0.55)	5 (14.3)	1 (2.9)	10 (28.6)	6 (17.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Klinefelter syndrome	0.48 (0.43–0.55)	35	0.40 (0.28–0.55)	35 (100.0)	6 (17.1)	10 (28.6)	6 (17.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Others											
Situs inversus	0.64 (0.57–0.71)	56	0.63 (0.48–0.82)	30 (53.6)	7 (12.5)	25 (44.6)	21 (37.5)	6 (10.7)	2 (33.3)	2 (33.3)	2 (33.3)
Conjoined twins	0.01 (0.00–0.02)	4	0.05 (0.01–0.12)	0 (0.0)	1 (25.0)	2 (50.0)	4 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Congenital skin disorders	1.40 (1.30–1.51)	604	6.83 (6.29–7.39)	300 (49.7)	29 (4.8)	89 (15.7)	93 (15.4)	8 (1.3)	0 (0.0)	6 (75.0)	2 (25.0)
Skeletal dysplasia	1.00 (0.91–1.09)	650	7.35 (6.79–7.93)	320 (49.2)	82 (12.6)	152 (23.4)	128 (19.7)	22 (3.4)	0 (0.0)	11 (50.0)	11 (50.0)
Craniosynostosis	2.66 (2.52–2.81)	890	10.06 (9.41–10.74)	533 (59.9)	68 (7.6)	115 (12.9)	203 (22.8)	10 (1.1)	0 (0.0)	4 (40.0)	6 (60.0)
Congenital constriction bans/amniotic band	0.24 (0.20–0.29)	77	0.87 (0.69–1.09)	40 (51.9)	13 (16.9)	22 (28.6)	29 (37.7)	5 (6.5)	0 (0.0)	4 (80.0)	1 (20.0)
Fetal alcohol syndrome	0.42 (0.36–0.48)	9	0.10 (0.05–0.19)	6 (66.7)	2 (22.2)	6 (66.7)	3 (33.3)	1 (11.1)	0 (0.0)	0 (0.0)	1 (100.0)

EUROCAT = European network of population-based registries for the epidemiological surveillance of congenital anomalies, NICU = neonatal intensive care unit.

Table 5. Top 5 congenital anomalies for prevalence, surgery, and mortality rate in 2013/2014 in Korea

Ranking	Prevalence		Mortality		Surgery	
	Diagnosis	Prevalence (/10,000 livebirths)	Diagnosis	Mortality (%)	Diagnosis	Surgery rate (%)
1	Atrial septal defect	201.99 (199.04–204.97)	Edward syndrome/Trisomy 18	56.1	Aortic atresia/interrupted aortic arch	100.0
2	Ventricular septal defect	64.16 (62.51–65.86)	Hypoplastic left heart syndrome	47.9	Conjoined twins	100.0
3	Hip dislocation and/or dysplasia	49.30 (47.85–50.79)	Patau syndrome/Trisomy 13	42.9	Total anomalous pulmonary venous return	97.3
4	Congenital hydronephrosis	37.52 (36.26–38.82)	Single ventricle	30.6	Hypoplastic left heart syndrome	95.8
5	Polydactyly	13.19 (12.44–13.97)	Anencephaly	30.0	Esophageal atresia with/without tracheoesophageal fistula	95.5

DISCUSSION

In our data, the prevalence of 67 major congenital anomalies in 2013 and 2014 was 434/10,000 livebirths. Males were slightly more than females in infants with major congenital anomalies. The average mortality rate was 1.7% for all major congenital anomalies, and most deaths were between one and 12 months after birth. Preterm infants comprised 15.7% of the infants with major congenital anomalies, and 29.2% were admitted to the NICU. Additionally, 25.6% of the major congenital anomalies received surgical operations.

Our results are meaningful because approximately all the infants born in 2013 and 2014 were included in our analysis. The number of births registered in the Korean NHIS database was 884,759 in this study. Considering that the number of births was 436,455 in 2013 and 435,435 in 2014 according to the data provided by the Korean Statistical Information Service (KSIS),[13] it seems that all the population delivered each year in Korea was included. The difference between the number of births registered in the Korean NHIS database and the KSIS database may be due to the inclusion of neonates with foreign nationality only in the Korean NHIS database and not in the database of the KSIS database.

The prevalences seen in our data were higher than those of the EUROCAT database, almost twice those for all the major congenital anomalies in the EUROCAT database although the inclusion criteria of major congenital anomalies were slightly different from each other (433.5 vs. 203.7/10,000 livebirths). The number of neonates with ASD was 17,871 which was almost 46% of the total number of the 67 major congenital anomalies. This result could be why there were such differences in the whole number of major congenital anomalies between Korea and the EUROCAT. When we reviewed the previous reports on ASD in Korea, the prevalence of ASD increased from 66.6/10,000 livebirths in 2005–2006[5] to 117.9/10,000 livebirths in 2009–2010[6] and finally to 202.0/10,000 livebirths in 2013–2014 in our study. This result could be due to the increased accessibility to echocardiography and increased registration of rule-out diagnoses in the database of the medical insurance system. Moreover, quite a number of patent foramen ovale were misclassified as ASD when registering the diagnosis in the medical insurance database.

The prevalences of spina bifida, congenital megacolon, hip dislocation and/or dysplasia, congenital hydronephrosis and craniosynostosis might be exaggerated because they could include rule-out diagnoses for health insurance claims. We could not exclude umbilical hernia from omphalocele which may explain some of the reasons for the high prevalence rate of omphalocele. To determine a more accurate prevalence rate of major congenital anomalies, it is important to exclude the rule-out diagnoses just for medical claims. In preterm infants, if we can make another birth cohort by matching the KNN database with the NHIS database, we can get a more accurate prevalence of congenital anomalies in preterm infants. Moreover, if we can make a nationwide surveillance system of major congenital anomalies such as the EUROCAT, and if we can match such surveillance data using the resident registration number or other information with the NHIS database, KSIS database, medical check-up database, or Korean obstetrics registry database if established, we can get more accurate and detailed data about the prevalence, use of medical resources, medical expenses, mortality and life expectancy of such major congenital anomalies and long-term prognoses. It will also serve as a basis for establishing national policies on congenital anomalies. In Europe, a recent article was already published about ten-year survival of children with major congenital anomalies using such linkage analysis.[14] In some congenital

anomalies that absolutely require specific surgery for survival, we can assume the prevalence rate by matching the diagnosis at admission with the surgical claim code.

In Korea, there have been several reports on congenital anomalies which usually were based on the NHIS claims database. First, a report[15] using the ICD-9 codes to classify congenital anomalies showed that the average prevalence of congenital anomalies in infants aged less than one year was 393/10,000 livebirths in 1993 and 344/10,000 livebirths in 1994. Cardiovascular anomalies were the most common congenital malformations followed by musculoskeletal anomalies and GI anomalies. When they assessed the medical expenses to treat congenital anomalies, the total expenses for the care of infants with VSD were the highest followed by those with congenital coagulation factor VIII disorders and secundum ASD. Second, a report[5] utilizing congenital anomaly survey data connected to the medical insurance claims database of the national health insurance corporation showed the prevalence of congenital anomalies in infants born in 2005–2006 as 286.9/10,000 livebirths. As with the 1993–1994 data, anomalies of the circulatory system were the most common defects followed by musculoskeletal system anomalies and digestive system anomalies. In this report, birth defects in livebirths were associated with a high proportion of low birthweight, prematurity, multiple births and advanced maternal age. The prevalence of congenital anomalies in this report was lower than that shown by our data, however, similar to the prevalence of the EUROCAT database. Lamichhane et al.[6] searched for the prevalence rate of 69 major birth defects in 2009–2010 using the data from seven metropolitan areas (Seoul, Pusan, Daegu, Incheon, Gwangju, Daejeon and Ulsan), which was 548.3/10,000 livebirths. When the same research group searched for the trends in the prevalence of the 69 major birth defects from 2008 to 2014,[7] it showed an increasing trend by year with a prevalence rate ratio of 1.091 (336.4/10,000 livebirths in 2008 to 563.6/10,000 livebirths in 2014). A significant increase in the prevalence was observed for urogenital anomalies in this study. In our study, we searched for 67 major congenital anomalies, and the prevalence was 434/10,000 livebirths which is similar to these previous reports.

There are several surveillance systems for congenital anomalies around the world such as the EUROCAT, the national birth defects prevention network (NBDPN) and the international clearinghouse for birth defects surveillance and research (ICBDSR). The EUROCAT is an European network of population-based registries for the epidemiological surveillance of congenital anomalies. They collect data on illnesses and medications used during pregnancy, stillbirths, smoking and alcohol use and socioeconomic status of the parents. They provide yearly reports on the prevalence rate for total cases, livebirths, stillbirths, and terminations of pregnancy for congenital anomalies. ICBDSR is a voluntary non-profit international organization affiliated with the WHO in 36 countries. NBDPN is a national birth defect prevention network in the U.S. They make an annual report every year which includes population-based data for up to 47 major birth defects using ICD or modified ICD codes. The data also include maternal race/ethnicity, maternal age at birth, infant sex and pregnancy outcomes. The last version of data for major birth defects was for 2010–2014.[16]

There were slightly more male infants than female infants with congenital anomalies in our study which was shown in other studies on congenital anomalies. About 15 percent of the major congenital anomalies were preterm infants, and the rate of preterm birth was higher than the preterm birth rate in whole infants delivered in Korea at 8.4% of the total neonatal births in 2020. In reports on congenital anomalies in VLBW infants using the KNN database,[8] the overall prevalence of major congenital anomalies in VLBW infants was

349/10,000 livebirths. Considering that the number of preterm infants registered in the KSIS was 57,325 in 2013–2014,[13] the prevalence of the 67 major congenital anomalies in preterm infants was 1,057/10,000 livebirths in our data which was higher than that in the KNN data. In the KNN database, only 54 major congenital anomalies are registered and analyzed for that study, and relatively minor and common anomalies such as ASD, spina bifida, congenital megacolon, hypospadias, hip dislocation, polydactyly, syndactyly, congenital skin disorders, skeletal dysplasia, and craniosynostosis were included only in our cohort, not in the KNN cohort. Moreover, rule-out diagnoses were excluded in the KNN database such as umbilical hernia classified as omphalocele which could not be omitted in our study. Additionally, especially in 2013–2014 (half of the inclusion criteria of the KNN study), only 51–58 hospitals were included in the KNN analysis, for which the hospitals were mostly level 3–4 hospitals that deal with serious congenital anomalies requiring surgery. Thus, the prevalence of major congenital anomalies of VLBW infants from 2013–2016 in the KNN database was lower than the prevalence of the 67 major congenital anomalies of preterm infants in 2013–2014 in our data.

Considering that mortality within one year after birth in Korea was 25/10,000 population in 2020 from the KSIS data,[17] mortality from the major congenital anomalies within one year after birth in our study was 5.8/10,000 livebirths which is almost 24% of the overall mortality for infants one to 12 months old. Recent reports on the ten-year survival of congenital anomalies using the EUROlinkCAT data[14] also showed that the highest mortality with isolated structural congenital anomalies was within infancy which is consistent with our data. Additionally, the ten-year survival rate exceeded 90% for the majority of the specific congenital anomalies in their report. Considering the high mortality rate of congenital anomalies and that most of the deaths occur within the first year of life in our data, more aggressive life support and surgery within the first year after birth if needed could reduce the mortality and improve the quality of life of the infants with congenital anomalies.

The prevalence of subgroups of congenital anomalies varied according to the year reported although the prevalences of congenital anomalies of the circulatory and GI systems were persistently high. In our data, the prevalence of complicated congenital heart diseases was relatively lower in Korea when compared with EUROCAT, which was consistent with other previous reports.[18,19] The recently reported worldwide prevalence of congenital heart disease is about 90/10,000 livebirths with significant geographic difference.[18,19] Genetic, environmental, socioeconomical, or ethnic factors can affect such regional difference in the prevalence of congenital heart defects. Recent meta-analysis differentiated mild lesions (ASD, VSD, and patent ductus arteriosus) from all congenital heart defects.[19] The overall prevalence of congenital heart defects in Europe was lower compared to Asia; mainly because Asia had the highest prevalence of mild congenital heart diseases, almost twice that of Europe. The prevalence of significant congenital heart defects was lower in Asia compared to Europe, same as our results. The increase in mild lesions in recent years is due to improved prenatal and postnatal detection such as fetal echocardiography, antenatal aneuploidy detection methods, and postnatal echocardiography. In contrast, the prevalence of left ventricular outflow tract obstruction was decreased possibly due to improved prenatal diagnoses and the consequent terminations of pregnancies around the world. The higher maternal age for giving birth in Europe could also affect the higher prevalence of significant congenital heart defects when compared with Asia. Because data on stillbirths and the abortion rate of infants with congenital heart defects in Korea were not available, we could not assess the influence of stillbirths or abortions on the prevalence of serious anomalies.

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About chromosomal anomalies, we also compared the prevalence in Korea with the U.S. in 2010–2014,[16] Canada in 2014,[20] and Japan in 2011–2014,[21] The prevalence (per 10,000 livebirths) of trisomy 13 was 1.43 (1.33, 1.54) in the U.S., 1.1 (0.7, 1.5) in Canada, and 0.8 in Japan. The prevalence of trisomy 18 was 3.24 (3.09, 3.40) in the U.S., 2.2 (1.7, 2.8) in Canada, and 4.4 in Japan. The prevalence of trisomy 21 was 14.85 (14.52, 15.19) in the U.S., 12.8 (11.5, 14.1) in Canada, and 15.0 in Japan. When compared with other countries, the lowest prevalence of major chromosomal anomalies in Korea could be due to the lack of or delayed postnatal detection of chromosomal anomalies or death before confirmation of the chromosomal anomalies after birth. We could not determine the influence of stillbirths or abortions due to chromosomal anomalies in our study because those data were not available in Korea. It will be important to get more information about stillbirths or abortions by making a database on stillbirths and abortions due to congenital anomalies as a part of the congenital anomaly surveillance database in Korea.

When we compared with the previous data, the top 5 ranked common anomalies always included ASD, VSD, and hydronephrosis.

There are some limitations in our study. First, in our study using the diagnosis included in the NHIS database, incorrect diagnoses or rule-out diagnoses could be included for the purpose of insurance claims. Additionally, some diagnoses could be missed because they are not required for insurance claims. Major congenital anomalies usually have serious morbidities which require surgery or intensive care. We assumed that relatively reliable diagnoses were included for the 67 major congenital anomalies. Second, regarding surgeries for congenital anomalies, we did not know whether the surgeries were done to treat the congenital anomalies. However, considering the high needs of surgery, especially for congenital heart defects or digestive tract anomalies, delivery in a hospital supported by a pediatric surgeon or pediatric thoracic surgeon should be considered for infants with major congenital anomalies. Third, the rate of NICU admissions was relatively low. Some portion of congenital anomalies requiring surgery could have been cared for in the pediatric intensive care unit under treatment by a pediatric surgeon from birth. Or if there was no need for ventilator care or gastric tube feeding, infants with congenital anomalies could have been cared for in a normal nursery because they could not meet the requirements for NICU admission according to the insurance claim. Fourth, we did not have any information on stillbirths and abortions due to birth defects in our study. The 2005–2009 EUROCAT data showed that terminations of pregnancy due to congenital anomalies were three times more frequent compared to infant deaths and stillbirths from congenital anomalies.[10] In making national support policies for congenital anomalies in Korea, we should not ignore the burden of the hidden problems of congenital anomalies, and more accurate data on stillbirths and abortions from congenital anomalies will be needed and such data should be included in future Korean congenital anomaly surveillance.

In conclusion, the preterm birth rate, surgical rate and mortality were higher in infants with major congenital anomalies. For future research, a comparison of the prevalence of major congenital anomalies in Korea with other countries other than Europe such as the U.S., Canada, and Japan will be necessary. To get more accurate information on congenital anomalies, it will be necessary to make a national surveillance registry such as the EUROCAT as soon as possible. Moreover, linkage analysis between surveillance data and the KSIS database, Korean NHIS database, infant medical check-up database, or Korean obstetrics registry database if established is needed to get more information on the causes and long-

term prognoses of congenital anomalies. Based on such information, systematic support through national welfare policies should be provided for prevention and treatment of major congenital anomalies in Korea.

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SUPPLEMENTARY MATERIAL

Supplementary Table 1

Lists of the ICD-10 codes for the diagnosis of the 67 major congenital anomalies

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