Stillbirth and neonatal mortality in pregnancies complicated by major congenital anomalies

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What's already known on this topic?

- There are no large-size studies regarding natural course of pregnancy in cases with congenital anomalies.
- Most studies concern small single center series with limited generalizability.

What does this study add?

- By using the EUROCAT Network, representing a large number of European registries and a wide range of anomalies, we were able to perform detailed analyses of the course of pregnancy in terms of stillbirth, early or late neonatal mortality for categories of anomalies, by gestational age and for a large number of isolated anomalies.
- Our data show that the course of these pregnancies differs significantly according to type of congenital anomaly

ABSTRACT

Objective

To provide prognostic information to help parents to reach an informed decision about termination or continuation of the pregnancy and to shape peripartum policy based on a large European cohort.

Method

Thirteen registries from the European Surveillance of Congenital Anomalies (EUROCAT) network contributed data from January 1, 1998 to December 31, 2011. Terminations for fetal anomalies were excluded. Chromosomal anomalies, syndromes and isolated anomaly groups were distinguished according to EUROCAT guidelines. Perinatal mortality, stillbirths, and early and late neonatal mortality rates (NMR)were analyzed by anomaly group and gestational age.

Results

Among 73,337 cases, perinatal mortality associated with congenital anomaly was 1.27 per 1,000 births (95% CI 1.23–1.31). Average stillbirth rate was 2.68%, (range 0–51.2%). Early and late NMR were 2.75% (range 0–46.7%) and 0.97% (range 0-17.9%), respectively. Chromosomal anomalies and syndromes, and most isolated anomalies, had significant differences regarding timing of fetal demise compared to the general population. Chromosomal and central nervous system anomalies had higher term stillbirth rates.

Conclusions

We found relevant differences between anomalies regarding rates of stillbirth, NMR and timing by gestational age. Our data can help parents to decide about their unborn child with a congenital anomaly and help inform maternal-fetal medicine specialists regarding peripartum management.

INTRODUCTION

Prenatal ultrasound screening for congenital anomalies (CA) has been implemented in many countries in Europe and around the world.(1-4) It has provided parents with the option of informed choice for delivery in a neonatal center or termination of the pregnancy in the case of a serious fetal anomaly (TOPFA) in countries where this option is available.(5,6) Clinical geneticists and obstetricians play an important role in this decision by providing accurate information regarding the prognosis of the fetus during the counseling process. However, despite modern ultrasound technology not all congenital anomalies can be detected early, and situations remain where an anomaly is discovered beyond the time window during which termination is legally allowed or at birth or soon after birth. In such cases, or in cases where the decision was made to continue the pregnancy despite the presence of an anomaly, it is important to have information about the probability of fetal demise associated with a specific anomaly. This will help parents and health care professionals to reach a decision in time, taking into account the prognosis of the newborn after birth and the probability of stillbirth during the remainder of the pregnancy. In addition, prognostic information may help to determine peripartum policy, e.g. in terms of abstaining from lifesaving interventions in case of an anomaly with a very poor prognosis, or to reassure parents in case of an anomaly with a good prognosis.

Studies have shown that the presence of CA is associated with an increased risk of stillbirth.(7,8) Overall, CA are found in up to 20% of stillbirths, with or without chromosomal anomalies.(9-11) In a large cohort of stillbirth cases, classification of the cause of death revealed that 4.7% of stillbirths in normally formed fetuses has been attributed to severe or lethal CA.(12) However, recent data on stillbirth risk and pregnancy outcomes for specific anomalies are scarce or fragmented and do not allow comparative evaluation of fetal survival in pregnancies complicated by CA.(13-18)

We have used detailed data from national and regional registries participating in the EUROCAT network to assess the course of pregnancies complicated by CA in cases where TOPFA is not performed. We determined the prevalence of stillbirth and early and late neonatal mortality by

gestational age, specifically investigating the most common chromosomal anomalies (i.e. trisomy 21, trisomy 18 and trisomy 13), other syndromes such as monogenic anomalies and skeletal dysplasias, and specific isolated anomalies according to the EUROCAT classification.(19) Our research questions were:

- In pregnancies complicated by CA, what is the probability of stillbirth and early and late neonatal mortality for common chromosomal anomalies, other syndromes and specific isolated CA?
- At what gestational or neonatal age does mortality occur in these cases?

MATERIALS

We used data provided by thirteen EUROCAT registries (http://www.eurocat-network.eu) for the years 1998 – 2011 or for part of this period (see Table 1 for details). Only registries that had information about the date of death for more than 80% of cases were selected to participate in the study. Anomalies had to be within the ICD9 range 740-759 or the ICD10 Q chapter (International Classification of Diseases, 9th revision (ICD-9) and 10th revision (ICD-10), www.who.int) and only major anomalies according to EUROCAT coding were included. (20) Perinatal mortality was defined as either stillbirth or early neonatal mortality, with stillbirth defined as at least 20 weeks of completed gestation and no signs of life at birth according to EUROCAT definitions and early neonatal mortality defined as death within seven completed days after birth in accordance with WHO definitions.(21) Late neonatal mortality was defined as death between 7 and 27 days after live birth. EUROCAT data on the pregnancy outcome (i.e. TOPFA, stillbirth, survival more than or less than 1 week after live birth) were used to determine perinatal and early neonatal mortality. Late neonatal mortality was determined using the date of death, which was recorded in cases of known mortality beyond one week after birth up to 27 days. For the current analysis, we examined the course of pregnancies with a known pregnancy outcome. TOPFA cases were excluded. We divided the cases into three mutually exclusive categories according to EUROCAT guidelines.(19) The first category consisted of trisomies and other chromosomal anomalies. The second category consisted of syndromes: genetic syndromes

or microdeletions, monogenic anomalies, sequences, teratogenic anomalies, skeletal dysplasias and other unclassified syndromes. The third category consisted of isolated non-syndromal anomalies defined as the absence of chromosomal anomalies, multiple anomalies and syndromes. A case was classified as a multiple anomaly when two or more unrelated, major structural malformations were present that could not be explained by an underlying syndrome or sequence. Isolated anomalies were identified using EUROCAT's multiple malformation algorithm[19] and included the following main groups of anomalies: central nervous system, eye, ear, face and neck; congenital heart defects (CHD) with severe CHD specified separately; respiratory system; digestive system; orofacial clefts; abdominal wall defects; urinary tract; genital tract; limb defects and other anomalies. For all main groups, the most prevalent CA were specified. In addition, two distinct entities, neural tube defects and severe congenital heart defects, were also tabulated. Gestational age at birth was categorized according to the WHO criteria (www.who.int) into extreme preterm (less than 28 weeks), very preterm (from 28 to less than 32 weeks), moderate-late preterm (from 32 to less than 37 weeks) and term (37 weeks or longer).

The prevalence of CA and the 95% confidence intervals were calculated using counts of CA and total births provided by the registries. The distribution of mortality and timing of mortality were examined using chi-square tests, comparing cases with the respective CA versus all other cases. A p-value of less than 0.05 was considered statistically significant. All analyses were performed using SPSS version 23 (IBM Corp, Armonk, USA).

Patient involvement, ethics and originality

Patients were not involved in the design of this study. The data used in this study are registry-based and anonymized; no additional consent for this study was required. Results of EUROCAT studies are disseminated through their website which is freely accessible. This work is original and has not been published elsewhere.

RESULTS

Thirteen registries provided data for a total of 84,795 cases of CA over the 14-year study period (Table 1). The total number of births was more than 3 million, resulting in an overall prevalence of CA of 27.3 per 1000 births, ranging between registries from 19.1 to 39.3 per 1000 births. The pregnancy outcome was known for 99.4% of pregnancies (408 were unknown). Of the pregnancies with known outcome (n=84, 387), 2.33% (n=1968, range 0.91% – 6.6%) concerned stillbirths, 2.37% (n=2015, range 0.68% – 7.6%) early and 0.84% (n=710, range 0.09% – 2.26%) late neonatal mortality. In 13.1% of cases (n=11,050), the pregnancy ended in a TOPFA.

Table 1 to be placed here.

The first column in table 2 shows the total number and percentage of anomalies by subgroup for the 73,337 cases with known mortality outcome (after exclusion of TOPFA). For the isolated anomalies (n=44,991), the second column shows the total number and percentage of all isolated anomalies for the sake of comparison to the subgroups in the first column. No relevant over- or underrepresentation of anomaly subgroups in the isolated cohort was apparent, except for bilateral renal agenesis (0.3% versus 0.01%). The time of discovery of the anomaly was recorded for 99.6% of all cases. Apart from the main categories 'At birth ' (34.8%) and 'Prenatal' (20.2%), the largest categories were 'Within 1 week' (11.4%) and '1-12 months' (11.5%). In 9.8% of cases, time of discovery was recorded as 'Unknown'. Discovery within 4 weeks occurred in 4.4% and discovery more than one year after birth occurred in 3.8%. Postnatal diagnosis but with unknown age occurred in 3.7% of cases (data not shown).

Table 2 to be placed here.

Among the chromosomal anomalies, representing 8.6% of all CA, trisomy 21 was by far the most prevalent. The subgroup "other syndromes" represented 30.1% of anomalies and consisted mainly of unclassified syndromes (23.2%). The most common isolated CA were CHD (severe congenital heart

defects, ventricular septal defect without severe CHD, and atrial septal defect without severe CHD), limb defects (hip dislocation/dysplasia), urinary tract anomalies (congenital hydronephrosis) and hypospadias.

Table 2 also presents the distribution of stillbirth, early and late neonatal mortality cases for all CA. Overall, stillbirth and early neonatal mortality rates were comparable, while late neonatal mortality occurred less frequently. Figure 1 shows clear differences in causes of mortality among the main categories of anomalies. Stillbirth was most prevalent in chromosomal anomalies while early and late neonatal mortality were more prevalent in chromosomal anomalies and in syndromes.

The highest rates of stillbirth and early neonatal mortality were observed for isolated central nervous system anomalies, respiratory system anomalies, diaphragmatic hernia and abdominal wall defects, while the lowest rates were observed for isolated urinary tract anomalies and limb defects. Significant differences compared to overall mortality patterns were observed for most anomaly groups, with the exception of ear, face, and neck anomalies; Tetralogy of Fallot; aortic valve atresia/stenosis; choanal atresia; renal dysplasia and limb reduction.

Table 3 shows stillbirth by gestational age. Thirteen cases were excluded from this analysis because the gestational age was missing. The overall distribution according to gestational age showed that stillbirth predominately occurred at extreme preterm gestational age (37.9%) and was less frequent between 28 and 32 weeks of gestation (16.1%), while 21.5% of stillbirths occurred at term. A summary of the distribution of stillbirth by gestational age is shown in Figure 2.

Table 3 to be placed here.

Extreme preterm stillbirth occurred in 0% to 68.2% of stillbirths among specific anomaly subgroups. The highest prevalence concerned 15 of 22 cases of clubfoot/talipes equinovarus, which is less than 1% of total clubfoot/talipes cases (n=2,018). Very preterm stillbirth occurred in 0% to 46.2% (renal dysplasia). Patterns significantly deviating from the overall distribution were observed for trisomies

21 and 18, suggesting higher prevalences of stillbirth at higher gestational ages (P<0.001). For neural tube defects and anencephaly in particular, a similar pattern was observed. Stillbirth occurred predominantly at extreme preterm gestation (P<0.001) in the categories other chromosomal anomalies and other syndromes. For many subgroups of anomalies, the numbers were too small to allow reliable statistical evaluation.

Table 4 shows early and late neonatal mortality rates by type of CA. Overall, early and late neonatal mortality occurred mainly in children born at term. This could be expected due to the majority of births occurring at term, but data on total births were not available by gestational age, so this could not be verified. The highest early neonatal mortality rates were observed for central nervous system (CNS) anomalies (24.1%) and CHD. These anomalies also showed significantly different distributions, with less predominance at term for CNS anomalies (43.6% versus 54.6% overall, P<0.05) but stronger predominance at term for CHD (76.2% versus 54.6% overall, P<0.005). Some other anomalies such as chromosomal anomalies, genetic syndromes, respiratory and digestive anomalies, urinary tract anomalies and some limb defects also differed significantly from the general distribution. The small number of cases showing late neonatal mortality did not allow for meaningful analysis for many subgroups of anomalies. In general, most of the late neonatal mortality occurred in pregnancies at or near term. Significant differences indicating a stronger predominance of mortality at term were observed for CHD and severe cases in particular (P<0.005), as well as for non-chromosomal syndromes (P<0.001), digestive (P<0.05) and urinary anomalies (P<0.001).

Table 4 to be placed here.

DISCUSSION

This study provides accurate information about the prognosis for counseling parents faced with the decision of whether to continue their pregnancy following antenatal diagnosis of a congenital anomaly or in situations where an anomaly is discovered beyond the time window during which termination is legally allowed or in case of discovery at or soon after birth. Using multicenter data from the EUROCAT network, we found distinct and clinically relevant differences between anomalies with respect to the occurrence of stillbirth and early and late neonatal mortality, and also with respect to the timing of these events by categorized gestational age.

Strengths

We were able to use a large database of CA cases from the EUROCAT network, representing a large number of European registries and a wide range of anomalies. We selected registries with the highest degree of completeness of mortality data and excluded pregnancies that resulted in a TOPFA. The participating registries showed a wide geographic distribution across Europe and a mix of practice and legal status regarding TOPFA. Coding of anomalies was performed according to EUROCAT guidelines, improving the quality and standardization of the data.(22,23)

Limitations

Unfortunately, EUROCAT data do not include information regarding type of delivery, i.e. induced or spontaneous, or about active or non-active management during delivery. The latter may influence whether a baby is eventually registered as stillbirth or as an early neonatal death. Also, we cannot distinguish intrapartum death from prepartum death, which are both coded as stillbirth. Of the pregnancies that we analyzed, about 50% of mortality occurred in the first or second day of life, and about 50% concerned stillbirths. Participation of more registries would have been preferable but might have impacted the completeness and quality of the data. Finally, EUROCAT contains only

anomaly cases; no data on pregnancies without anomalies is available. Therefore, we could only calculate relative risk of mortality compared to all other anomalies, not absolute risk.

Interpretation

The participating registries differ with respect to some important aspects of our study, most obviously regarding the availability and practice of TOPFA. Other factors that could affect the rate of perinatal mortality, including differences in perinatal clinical practice between registry regions (e.g. abstinence from active intervention during labor or immediately post-partum) are not captured in our data. Overall, 20.2% of the anomalies in our database were discovered prenatally, and 34.8% at birth. Thus, although policy differences could have determined whether the outcome was coded as stillbirth or early or late neonatal mortality, this would not have affected the majority of cases. On the other hand, about 50% of mortality occurred on the first or second day after birth.

The prevalence of perinatal mortality in our data (1.27 per 1000 births) is representative of the European population (European Perinatal Health Report 2010, www.europeristat.com). The causes of the differences in overall perinatal mortality figures between countries have been debated (European Perinatal Health Report 2010, www.europeristat.com). Our data suggest that 2-3 CA cases per 1000 births contribute to overall perinatal mortality in countries with high perinatal mortality due to CA and low TOPFA. In countries with low perinatal mortality due to CA and high TOPFA, the contribution of CA to overall perinatal mortality would be expected to be less than 1%.

Our data show that only a few anomaly types are lethal in the majority of cases. These include trisomy 18 (77.8%), trisomy 13 (75.5%) and anencephaly (99.6%). On the other hand, some anomalies in our data are associated with a relatively good prognosis, such as monogenic anomalies and CHD. Some of the large subgroups of anomalies, such as the trisomies, CNS anomalies, and CHD, have previously been studied individually with respect to mortality outcomes.(7,13,17,24-28) However, these studies generally focused on either stillbirth or neonatal mortality, not both.

For trisomies, our study is one of the largest series focused on survival published to date. Previous papers have reported stillbirth rates of 5.4% - 6.2% of all pregnancies for trisomy 21, equivalent to 7% - 8% if TOPFA is taken into account(17,29), and 49% - 72% in cases of trisomy 13 and 18, respectively.(30,31) Smaller case series have reported even higher figures.(27) In a relatively small series, early neonatal mortality in trisomy 13 and 18 was between 54% and 64%, higher than our results.(30) Few previous reports specified stillbirth and neonatal mortality in relation to gestational age. Frey and colleagues reported on stillbirth by gestational age in a population of selected major anomalies in the USA but did not separate their cases by type of anomaly.(7) They showed that the overall occurrence of stillbirth was equal before and after 32 weeks. Our data for chromosomal anomalies, including both trisomies and chromosomal anomalies in general, show that stillbirths occurred more often before 28 weeks and after 32 weeks of gestation than in the intermediate stage of 28 - 32 weeks.

With respect to isolated anomalies, CHD are widely studied, with some large series based on EUROCAT data(32,33) or data from other registries.(25,26) Reported stillbirth rates ranged between 1% and 3%, with perinatal and neonatal mortality of 3% and 6%, respectively. These rates are slightly higher than in our rates, which may be explained by the fact that we only included isolated CHD, which may represent relatively uncomplicated cases.

Among isolated CNS anomalies, only relatively small series on neural tube defects have been published to date.(34-36) Stillbirth (4-19%) and neonatal mortality rates (7-20%) reported by these studies are variable, partly due to small numbers of cases, but are in the same range as those found in our results.

Generalizability

Our data were extracted from the EUROCAT registry based on the voluntary participation of registry leaders and availability of survival data. Overall, EUROCAT surveys over 1.7 million births per year,

covering approximately 29% of the European birth population and offering high-quality data(22). Our data are therefore not expected to be strongly biased by selection and are the best possible source to study questions related to CA on a large scale.

Conclusion

Our data show that the prognosis of pregnancies differs significantly according to CA. For most types of anomalies, we had much larger numbers of cases than have been reported in the literature so far. Our results provide more support for the decision making process of parents and healthcare professionals confronted with the presence of a congenital anomaly.

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Figures

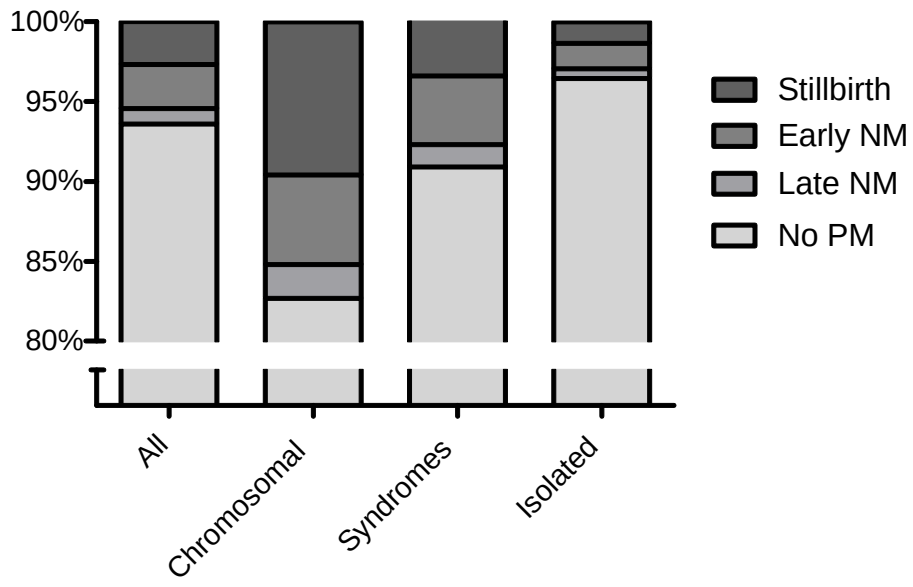

Figure 1: Causes of mortality among main categories of congenital anomalies. Note that the Y-axis scale starts at 80%.

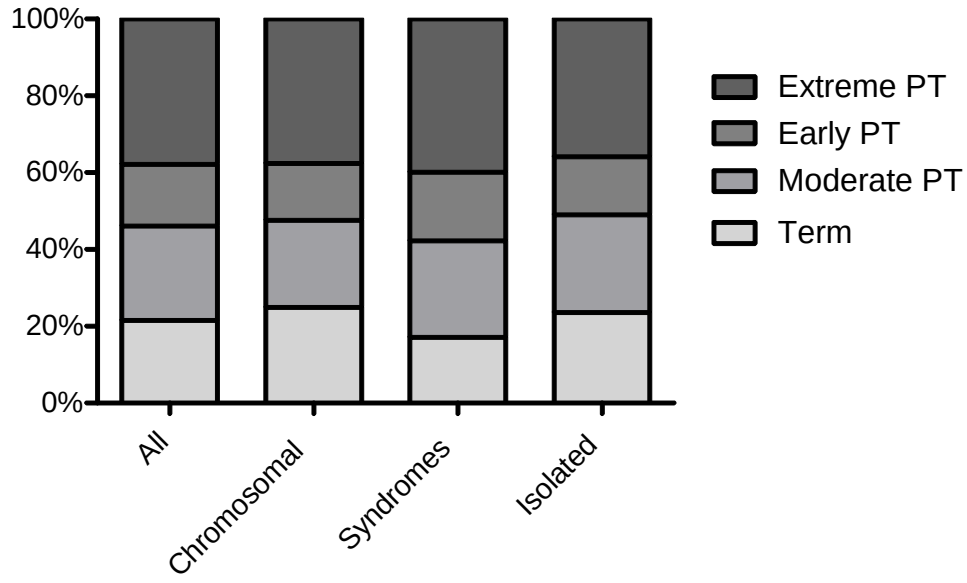

Figure 2: Distribution of stillbirth by gestational age. Extreme PT: extreme preterm; very PT: very preterm; moderate PT: moderate-late preterm.

Table 1. Total number of births, number of congenital anomalies (CA), CA prevalence, terminations of pregnancy for fetal anomaly (TOPFA), stillbirth, early and late neonatal mortality and perinatal mortality associated with CA per EUROCAT registry, 1998-2011*

Registry	Total births (n)	Number of CA cases (n)	Overall CA prevalence per 1,000 births (95% CI)	TOPFA (n, %)	CA perinatal mortality prevalence per 1,000 births (95% CI)	Perinatal and neonatal mortality		
						Stillbirth (n, %)	Early neonatal mortality (n, %)	Late Neonatal mortality (n, %)
Denmark, Odense	74,398	2,146	28.8 (27.6-30.0)	353 (16.5)	1.25 (1.00-1.50)	50 (2.3)	43 (2.0)	10 (0.47)
Italy, Tuscany	400,976	8,678	21.6 (21.2-22.1)	1605 (18.5)	0.35 (0.29-0.41)	81 (0.93)	61 (0.68)	39 (0.45)
Ireland, Dublin	336,462	6,472	19.2 (18.8-19.7)	0 (0)	2.43 (2.26-2.59)	408 (6.6)	416 (6.6)	96 (1.48)
Northern Netherlands	265,933	7,068	26.6 (26.0-27.2)	631 (8.9)	1.49 (1.34-1.64)	177 (2.5)	219 (3.1)	77 (1.09)
Switzerland, Vaud	104,594	4,110	39.3 (38.1-40.5)	783 (19.1)	0.91 (0.73-1.09)	46 (1.1)	49 (1.2)	16 (0.39)
Germany, Saxony Anhalt	231,698	7,567	32.7 (32.0-33.4)	829 (11.0)	0.86 (0.74-0.98)	127 (1.7)	73 (0.97)	7 (0.09)
Austria, Styria	146,395	4,771	32.6 (31.8-33.6)	525 (10.9)	0.84 (0.69-0.99)	61 (1.3)	64 (1.4)	26 (0.54)
Ireland, Cork and Kerry	126,380	3,325	26.3 (25.4-27.2)	26 (0.79)	2.47 (2.20-2.74)	131 (4.0)	182 (5.5)	49 (1.47)
UK, Wales	466,301	18,249	39.1 (38.6-39.7)	2493 (13.6)	1.31 (1.20-1.41)	344 (1.9)	275 (1.4)	99 (0.54)
Ukraine[#]	208,772	5,085	24.4 (23.7-25.0)	664 (13.1)	1.81 (1.63-1.99)	168 (3.3)	208 (4.2)	115 (2.26)
UK, Northern England[$]	382,900	9,351	24.4 (23.9-24.9)	1982 (21.2)	1.18 (1.07-1.29)	266 (2.8)	185 (2.0)	76 (0.81)
South East Ireland	95,837	1,829	19.1 (18.2-20.0)	3 (0.17)	1.96 (1.68-2.24)	53 (2.9)	137 (7.6)	39 (2.13)
Spain, Valencia region[^]	267,408	6,144	23.0 (22.4-23.5)	1156 (18.8)	0.59 (0.50-0.69)	56 (0.91)	103 (1.7)	61 (0.99)
Total	**3,108,054**	**84,795****	**27.3 (27.1-27.5)**	**11,050 (13.1)**	**1.27 (1.23-1.31)**	**1,968 (2.33)**	**2,015 (2.37)**	**710 (0.84)**

CA: congenital anomaly; TOPFA: termination of pregnancy for fetal anomaly

* Shorter time-period where indicated: [#]: 2005-2011; [$]: 2000-2011; ^: 2007-2011

** Including 408 cases with unknown pregnancy outcome

Table 2. Perinatal and neonatal mortality for chromosomal anomalies, syndromes and isolated anomalies

Anomaly group	Total number excluding TOPFA (n, % of total)	Number isolated (n, % of total)	Stillbirth (n,% of group)	Early neonatal mortality (n, % of group)	Late neonatal mortality (n, % of group)
All anomalies	73,337 (100)	-	1,968 (2.68)	2015 (2.75)	710 (0.97)
Chromosomal anomalies	6,286 (8.6)	-	604 (9.6)	349 (5.6)	131 (2.1)
Trisomy 21	3,684 (5.0)	-	182 (4.9)	51 (1.4)	26 (0.7)[#]
Trisomy 18	482 (0.7)	-	177 (36.7)	149 (30.9)	49 (10.2)[#]
Trisomy 13	212 (0.3)	-	47 (22.2)	85 (40.1)	28 (13.2)[#]
Other	1,908 (2.6)	-	198 (10.4)	64 (3.4)	28 (1.5)[#]
Syndromes	22,060 (30.1)	-	753 (3.4)	945 (4.3)	303 (1.4)[#]
Genetic syndromes/microdeletions	2,704 (3.7)	-	54 (2.0)	67 (2.5)	50 (1.8)
Monogenic anomalies	897 (1.2)	-	15 (1.7)	26 (2.9)	7 (0.8)
Sequences	638 (0.9)	-	66 (10.3)	113 (17.4)	5 (0.8)
Teratogenic anomalies	425 (0.6)	-	19 (4.5)	6 (1.4)	6 (1.4)
Skeletal dysplasias	348 (0.5)	-	22 (6.3)	47 (13.5)	3 (0.9)
Other	17,048 (23.2)	-	577 (3.4)	688 (4.0)	232 (1.4)
Isolated anomalies	44,991 (61.3)	44,991 (100)	611 (1.35)	721 (1.60)	276 (0.61)
CNS	5,288 (7.2)	2,303 (5.1)	236 (10.2)	172 (7.5)	32 (1.4)[#]
Neural tube defects	1,234 (1.7)	747 (1.7)	160 (21.4)	132 (17.7)	12 (1.6)[#]
Spina bifida	782 (1.1)	435 (1.0)	26 (6.0)	15 (3.4)	6 (1.4)[#]
Anencephaly	287 (0.4)	240 (0.5)	123 (51.2)	112 (46.7)	4 (1.7)[#]

Anomaly group	Total number excluding TOPFA (n, % of total)	Number isolated (n, % of total)	Stillbirth (n,% of group)	Early neonatal mortality (n, % of group)	Late neonatal mortality (n, % of group)
Encephalocele	165 (0.2)	72 (0.2)	11 (15.3)	5 (6.9)	2 (2.8)#
Hydrocephaly	1,063 (1.4)	435 (1.0)	37 (8.5)	16 (3.7)	5 (1.1)#
Arhinencephaly/holoprosencephaly	175 (0.2)	43 (0.1)	5 (11.6)	8 (18.6)	2 (4.7)#
Eye anomalies	2180 (3.0)	913 (2.0)	2 (0.2)	3 (0.3)	1 (0.1)#
Congenital cataract	630 (0.9)	392 (0.9)	0	0	0##
Ear, face, neck	1,082 (1.5)	221 (0.5)	3 (1.4)	1 (0.5)	0
Anotia	67 (0.1)	29 (0.1)	1 (3.4)	1 (3.4)	0
Congenital heart defects	26,835 (36.6)	14,932 (33.2)	101 (0.7)	235 (1.6)	168 (1.1)#
Severe CHD**	6,446 (8.8)	2,768 (6.2)	50 (1.8)	170 (6.1)	132 (4.8)#
Transposition great vessels	1,059 (1.4)	563 (1.3)	2 (0.4)	35 (6.2)	25 (4.4)#
Coarctation aorta	1,405 (1.9)	526 (1.2)	6 (1.1)	6 (1.1)	10 (1.9)##
Fallot’s tetralogy	960 (1.3)	475 (1.0)	8 (1.7)	8 (1.7)	2 (0.4)
Hypoplastic left/right heart	640 (0.8)	352 (0.8)	17 (4.8)	92 (26.1)	63 (17.9)#
Single ventricle	164 (0.2)	59 (0.1)	5 (8.5)	7 (11.9)	1 (1.7)#
Common arterial truncus	194 (0.3)	72 (0.2)	3 (4.2)	8 (11.1)	9 (12.5)#
Atrioventricular septal defect	1,259 (1.7)	243 (0.5)	8 (3.3)	3 (1.2)	8 (3.3)#
Tricuspid atresia/stenosis	202 (0.3)	46 (0.1)	1 (2.2)	1 (2.2)	2 (4.3)^
Ebstein’s anomaly	152 (0.2)	52 (0.1)	0	0	5 (9.6)#
Aortic valve atresia/stenosis	586 (0.8)	299 (0.7)	1 (0.3)	5 (1.7)	3 (1.0)
Pulmonary valve atresia	295 (0.4)	73 (0.2)	0	1 (1.4)	4 (5.5)#

Anomaly group	Total number excluding TOPFA (n, % of total)	Number isolated (n, % of total)	Stillbirth (n,% of group)	Early neonatal mortality (n, % of group)	Late neonatal mortality (n, % of group)
Total anomalous pulmonary venous return	231 (0.3)	109 (0.2)	0	6 (5.5)	7 (6.4)[#]
VSD (no severe CHD)	9,268 (12.6)	6,882 (15.3)	15 (0.22)	15 (0.22)	11 (0.16)[#]
ASD (no severe CHD)	4,512 (6.2)	1,963 (4.4)	10 (0.5)	1-4 (0.2)	6 (0.3)
VSD + ASD (no severe CHD)	1,724 (2.4)	245 (0.5)	0	1 (0.4)	1 (0.4)
Pulmonary valve stenosis (no severe CHD)***	1,708 (2.3)	976 (2.2)	1 (0.1)	3 (0.3)	1 (0.1)[#]
Respiratory	1,834 (2.5)	664 (1.5)	29 (4.4)	51 (7.7)	6 (0.9)[#]
Choanal atresia	300 (0.4)	103 (0.2)	0	0	0
Digestive	5,620 (7.7)	2,823 (6.3)	40 (1.4)	129 (4.6)	36 (1.3)[#]
Diaphragmatic hernia	758 (1.0)	443 (1.0)	15 (3.4)	98 (22.1)	12 (2.7)[#]
Orofacial clefts	4,576 (6.2)	2,925 (6.5)	29 (1.0)	16 (0.5)	0[#]
Cleft lip with or without cleft palate	2,622 (3.6)	1,919 (4.3)	21 (1.1)	10 (0.5)	0[#]
Abdominal wall defects	1,375 (1.9)	828 (1.8)	47 (5.7)	24 (2.9)	11 (1.3)[#]
Gastroschisis	830 (1.1)	653 (1.5)	37 (5.7)	12 (1.8)	10 (1.5)[#]
Omphalocele	493 (0.7)	164 (0.4)	9 (5.5)	10 (6.1)	1 (0.6)[#]
Urinary	9,781 (13.3)	5,111 (11.4)	61 (1.2)	60 (1.2)	14 (0.3)[#]
Bilateral renal agenesis	213 (0.3)	4 (0.01)	0	1 (25.0)	0[##]
Renal dysplasia	1254 (1.7)	705 (1.6)	13 (1.8)	16 (2.3)	4 (0.6)
Congenital hydronephrosis	3,906 (5.3)	2,050 (4.6)	11 (0.5)	10 (0.5)	0[#]
Genital	6,513 (8.9)	4,577 (10.2)	2 (0.04)	8 (0.2)	0[#]

Anomaly group	Total number excluding TOPFA (n, % of total)	Number isolated (n, % of total)	Stillbirth (n,% of group)	Early neonatal mortality (n, % of group)	Late neonatal mortality (n, % of group)
Hypospadias	5,466 (7.5)	4,126 (9.2)	1 (0.02)	2 (0.04)	0 (0)#
Limb defects	13,565 (18.5)	8,682 (19.3)	41 (0.5)	20 (0.2)	5 (0.04)#
Limb reduction	1,426 (1.9)	497 (1.1)	9 (1.8)	5 (1.0)	0
Clubfoot/talipes equinovarus	2,917 (4.0)	2,018 (4.5)	22 (1.1)	7 (0.3)	3 (0.1)#
Hip dislocation/dysplasia	4,006 (5.5)	3,077 (6.8)	0	0	1 (0.03)#
Polydactyly	2,468 (3.4)	1,663 (3.7)	5 (0.3)	4 (0.24)	1 (0.06)#
Syndactyly	1,443 (2.0)	659 (1.5)	1 (0.1)	1 (0.1)	0 (0)#
Other anomalies	4,833 (6.6)	1,354 (3.0)	34 (2.5)	29 (2.1)	6 (0.4)##

TOPFA: termination of pregnancy for fetal anomaly; ASD: atrial septal defect; VSD: ventricular septal defect; CHD: congenital heart disease; CNS: central nervous system

* Overlap of main group less than 1%

** More than one component present in 627 cases

*** Overlap with VSD or ASD without severe CHD in 555 (32.5%) of total cases and 109 isolated cases (11.2%)

# P< 0.001; ## P< 0.01; ^ P<0.05 for comparison to overall mortality in all other CA.

Table 3. Stillbirth by gestational age for chromosomal anomalies, syndromes, and isolated anomalies

Anomaly group	All stillbirth (n,% of total/isolated)	Extreme preterm <28 wks (n, % of group)	Very preterm 28 - <32 wks (n, % of group)	Moderate-late preterm 32 - <37 wks (n, % of group)	Term ≥37 wks (n, % of group)
All anomalies	1,955 (100)	740 (37.9)	315 (16.1)	480 (24.6)	420 (21.5)
Chromosomal anomalies	595 (30.4)	224 (37.6)	88 (14.8)	135 (22.7)	148 (24.9)
Trisomy 21	179 (9.2)	52 (29.1)	19 (10.6)	56 (31.3)	52 (29.1)##
Trisomy 18	176 (9.0)	35 (19.9)	39 (22.2)	39 (22.2)	63 (35.8)##
Trisomy 13	45 (2.3)	21 (46.7)	7 (15.6)	11 (24.4)	6 (13.3)
Other	195 (10.0)	116 (59.5)	23 (11.8)	29 (14.9)	27 (13.8)##
Syndromes	749 (38.3)	299 (39.9)	134 (17.9)	188 (25.1)	128 (17.1)##
Genetic syndromes/microdeletions	53 (3.9)	25 (47.2)	9 (17.0)	13 (24.5)	6 (11.3)
Monogenic anomalies	15 (0.2)	5 (33.3)	4 (26.7)	5 (33.3)	1 (6.7)
Sequences	65 (4.8)	36 (55.4)	5 (7.7)	16 (24.6)	8 (12.3)
Teratogenic anomalies	19 (1.4)	6 (31.6)	6 (31.6)	4 (21.1)	3 (15.8)
Skeletal dysplasias	22 (1.6)	2 (9.1)	4 (18.2)	12 (54.5)	4 (18.2)
Other	575 (42.3)	225 (39.1)	106 (18.4)	138 (24.0)	106 (18.4)
Isolated anomalies	611 (31.3)	221 (35.9)	93 (15.1)	157 (25.5)	145 (23.5)
CNS	236 (38.6)	60 (25.4)	31 (13.1)	76 (32.2)	69 (29.2)##
Neural tube defects	160 (26.2)	29 (18.1)	22 (13.8)	53 (33.1)	56 (35.0)##
Spina bifida	26 (4.3)	10 (38.5)	1 (3.8)	5 (19.2)	10 (38.5)
Anencephaly	123 (20.1)	16 (13.0)	21 (17.1)	45 (36.6)	41 (33.3)##

Anomaly group	All stillbirth (n,% of total/isolated)	Extreme preterm <28 wks (n, % of group)	Very preterm 28 - <32 wks (n, % of group)	Moderate-late preterm 32 - <37 wks (n, % of group)	Term ≥37 wks (n, % of group)
Encephalocele	11 (1.8)	3 (27.3)	0	3 (27.3)	5 (45.6)
Hydrocephaly	37 (6.1)	14 (37.8)	3 (8.1)	11 (29.7)	9 (24.3)
Arhinencephaly/holoprosencephaly	5 (0.8)	0	1 (20.0)	2 (40.0)	2 (40.0)
Eye anomalies	2 (0.3)	0	0	1 (50.0)	1 (50.0)
Congenital cataract	0	-	-	-	-
Ear, face, neck	3 (0.5)	0	2 (66.7)	1 (33.3)	0
Anotia	1 (0.2)	0	0	1 (100.0)	0
Congenital heart defects	101 (16.5)	40 (39.6)	21 (20.8)	23 (22.8)	17 (16.8)
Severe CHD*	50 (8.2)	17 (34.0)	10 (20.0)	13 (26.0)	10 (20.0)
Transposition great vessels	2 (0.3)	0	1 (50.0)	1 (50.0)	0
Coarctation aorta	6 (1.0)	3 (50.0)	2 (33.3)	1 (16.7)	0
Fallot’s tetralogy	8 (1.3)	4 (50.0)	3 (37.5)	1 (12.5)	0
Hypoplastic left/right heart	17 (2.8)	6 (35.3)	2 (11.8)	5 (29.4)	4 (23.5)
Single ventricle	5 (0.8)	2 (40.0)	1 (20.0)	1 (20.0)	1 (20.0)
Common arterial truncus	3 (0.5)	0	1 (33.3)	0	2 (66.7)
Atrioventricular septal defect	8 (1.3)	2 (25.0)	0	4 (50.0)	2 (25.0)
Tricuspid atresia/stenosis	1 (0.2)	0	0	0	1 (100.0)
Ebstein’s anomaly	0	-	-	-	-
Aortic valve atresia/stenosis	1 (0.2)	0	0	1 (100.0)	0

Anomaly group	All stillbirth (n,% of total/isolated)	Extreme preterm <28 wks (n, % of group)	Very preterm 28 - <32 wks (n, % of group)	Moderate-late preterm 32 - <37 wks (n, % of group)	Term ≥37 wks (n, % of group)
Pulmonary valve atresia	0	-	-	-	-
Total anomalous pulmonary venous return	0	-	-	-	-
VSD (no severe CHD)	15 (2.5)	10 (66.7)	4 (26.7)	1 (6.7)	0[#]
ASD (no severe CHD)	10 (1.6)	2 (20.0)	0	3 (30.0)	5 (50.0)
VSD + ASD (no severe CHD)	0	-	-	-	-
Pulmonary valve stenosis (no severe CHD)	1 (0.2)	0	1 (100.0)	0	0
Respiratory	29 (4.7)	13 (44.8)	4 (13.8)	6 (20.7)	6 (20.7)
Choanal atresia	0	-	-	-	-
Digestive	40 (6.5)	10 (25.0)	4 (10.0)	13 (32.5)	13 (32.5)
Diaphragmatic hernia	15 (2.5)	3 (20.0)	0	5 (33.3)	7 (46.7)
Orofacial clefts	29 (4.7)	15 (51.7)	4 (13.8)	5 (17.2)	5 (17.2)
Cleft lip with/without cleft palate	21 (3.4)	13 (61.9)	2 (9.5)	1 (4.8)	5 (23.8)[#]
Abdominal wall defects	47 (7.7)	19 (40.4)	9 (19.1)	11 (23.4)	8 (17.0)
Gastroschisis	37 (6.1)	15 (40.5)	7 (18.9)	8 (21.6)	7 (18.9)
Omphalocele	9 (1.5)	3 (33.3)	2 (22.2)	3 (33.3)	1 (11.1)
Urinary	61 (10.0)	21 (34.4)	12 (19.7)	10 (16.4)	18 (29.5)
Bilateral renal agenesis	0	-	-	-	-
Renal dysplasia	13 (2.1)	2 (15.4)	6 (46.2)	3 (23.1)	2 (15.4)[#]

Anomaly group	All stillbirth	Extreme preterm <28 wks	Very preterm 28 - <32 wks	Moderate-late preterm 32 - <37 wks	Term ≥37 wks
	(n,% of total/isolated)	(n, % of group)	(n, % of group)	(n, % of group)	(n, % of group)
Congenital hydronephrosis	11 (1.8)	5 (45.5)	0	2 (18.2)	4 (36.4)
Genital	2 (0.3)	0	0	1 (50.0)	1 (50.0)
Hypospadias	1 (0.2)	0	0	0	1 (100.0)
Limb defects	41 (6.7)	26 (63.4)	4 (9.8)	6 (14.6)	5 (12.2)[#]
Limb reduction	9 (1.5)	4 (44.4)	2 (22.2)	1 (11.1)	2 (22.2)
Clubfoot/talipes equinovarus	22 (3.6)	15 (68.2)	1 (4.5)	4 (18.2)	2 (9.1)[#]
Hip dislocation/dysplasia	0	-	-	-	-
Polydactyly	5 (0.8)	2 (40.0)	2 (40.0)	0	1 (20.0)
Syndactyly	1 (0.2)	1 (100.0)	0	0	0
Other anomalies	34 (5.6)	21 (61.8)	4 (11.8)	5 (14.7)	4 (11.8)[#]

ASD: atrial septal defect; VSD: ventricular septal defect; CHD: congenital heart disease; CNS: central nervous system

[*] Two components in one case

[#] P<0.05, [##] P≤0.001 for comparison to overall mortality in all other CA.

Table 4. Early and late neonatal mortality by gestational age for chromosomal anomalies, syndromes, and isolated anomalies

Anomaly group	Early neonatal mortality					Late neonatal mortality				
	All early neonatal mortality (n, % of mortality)	Extreme preterm <28 wks (n, % of group)	Very preterm 28-<32 wks (n, % of group)	Moderate-late preterm 32-<37 wks (n, % of group)	Term ≥37 wks (n, % of group)	All late neonatal mortality (n, % of mortality)	Extreme preterm <28 wks (n, % of group)	Very preterm 28-<32 wks (n, % of group)	Moderate-late preterm 32-<37 wks (n, % of group)	Term ≥37 wks (n, % of group)
All anomalies	1990 (100)	174 (8.7)	297 (14.9)	630 (31.7)	889 (44.7)	703 (100)	31 (4.4)	63 (9.0)	151 (21.5)	458 (65.1)
Chromosomal anomalies	345 (17.3)	28 (8.1)	59 (17.1)	117 (33.9)	141 (40.9)	130 (18.5)	2 (1.5)	12 (9.2)	38 (29.2)	78 (60.0)
Trisomy 21	50 (2.5)	7 (14.0)	3 (6.0)	17 (34.0)	23 (46.0)	26 (3.7)	1 (3.8)	3 (11.5)	10 (38.5)	12 (46.2)
Trisomy 18	147 (7.4)	4 (2.7)	26 (17.7)	53 (36.1)	64(43.5)[#]	48 (6.8)	1 (2.1)	2 (4.2)	14 (29.2)	31 (64.6)
Trisomy 13	84 (4.2)	5 (6.0)	14 (16.7)	26 (31.0)	39 (46.4)	28 (4.0)	0	4 (14.3)	5 (17.9)	19 (67.9)
Other	64 (3.2)	12 (18.8)	16 (25.0)	21 (32.8)	15 (23.4)[###]	28 (4.0)	0	3 (10.7)	9 (32.1)	16 (57.1)
Syndromes	931 (46.7)	78 (8.4)	139 (14.9)	356 (38.2)	358 (38.5)	301 (42.)	8 (2.7)	34 (11.3)	72 (23.9)	187 (62.1)[##]
Genetic syndromes/ microdeletions	67 (3.4)	8 (9.5)	9 (13.4)	23 (34.3)	27 (40.3)[###]	42 (6.0)	0	6 (12.2)	15 (30.6)	28 (57.1)
Monogenic anomalies	25 (1.3)	2 (8.0)	1 (4.0)	9 (36.0)	13 (52.0)	7 (1.0)	0	1 (14.3)	2 (28.6)	4 (57.1)
Sequences	111 (5.6)	9 (8.1)	16 (14.4)	54 (48.6)	32 (28.8)	5 (0.7)	1 (20.0)	0	2 (40.0)	2 (40.0)
Teratogenic anomalies	6 (0.3)	1 (16.7)	2 (33.3)	1 (16.7)	2 (33.3)	6 (0.9)	0	0	4 (66.7)	2 (33.3)
Skeletal dysplasias	46 (2.3)	2 (4.3)	9 (19.6)	24 (52.2)	11 (23.9)	1-4	0	0	1 (33.3)	2 (66.7)
Other	676 (34.0)	56 (8.3)	102 (15.1)	245 (36.2)	273 (40.4)	231 (32.9)	7 (3.0)	27 (11.7)	48 (20.8)	149 (64.5)
Isolated anomalies	714 (35.9)	68 (9.5)	99 (13.9)	157 (22.0)	390 (54.6)	272 (38.7)	21 (7.7)	17 (6.3)	41 (15.1)	193 (71.0)
CNS	172 (24.1)	13 (7.6)	29 (16.9)	55 (32.0)	75 (43.6)[##]	32 (11.8)	0	3 (9.4)	7 (21.9)	22 (68.8)

	Early neonatal mortality					Late neonatal mortality				
Neural tube defects	132 (18.5)	6 (4.5)	16 (12.1)	42 (31.8)	68 (51.5)[#]	12 (4.4)	0	1 (8.3)	1 (8.3)	10 (83.3)
Spina bifida	15 (2.1)	1 (6.7)	0	5 (33.3)	9 (60.0)	6 (2.2)	0	1 (16.7)	1 (16.7)	4 (66.6)
Anencephaly	112 (15.7)	5 (4.5)	16 (14.3)	36 (32.1)	55 (49.1)[#]	4 (1.5)	0	0	0	4 (100.0)
Encephalocele	5 (0.7)	0	0	1 (20.0)	4 (80.0)	2 (0.7)	0	0	0	2 (100.0)
Hydrocephaly	16 (2.2)	5 (31.3)	6 (37.5)	5 (31.3)	0[###]	5 (1.8)	0	1 (20.0)	1 (20.0)	3 (60.0)
Arhinencephaly/ holoprosencephaly	8 (1.1)	1 (12.5)	1 (12.5)	4 (50.0)	2 (25.0)	2 (0.7)	0	0	1 (50.0)	1 (50.0)
Eye anomalies	2 (0.3)	1 (50.0)	0	0	1 (50.0)	1 (0.4)	1 (100.0)	0	0	0[#]
Congenital cataract	0	-	-	-	-	0	-	-	-	-
Ear, face, neck	1 (0.1)	0	0	1 (100.0)	0	0	-	-	-	-
Anotia	1 (0.1)	0	0	1 (100.0)	0	0	-	-	-	-
Congenital heart defects	231 (32.4)	9 (3.9)	19 (8.2)	27 (11.7)	176 (76.2)[###]	165 (60.7)	6 (3.6)	9 (5.5)	12 (7.3)	138 (83.6)[###]
Severe CHD**	166 (23.2)	4 (2.4)	9 (5.4)	16 (9.6)	137 (82.5)[###]	129 (47.4)	2 (1.6)	2 (1.6)	10 (7.8)	115 (89.1)[###]
Transposition great vessels	32 (4.5)	0	1 (3.1)	1 (3.1)	30 (93.8)[###]	24 (8.8)	0	0	3 (12.5)	21 (87.5)
Coarctation aorta	6 (0.8)	0	1 (16.7)	1 (16.7)	4 (66.6)	10 (3.7)	0	0	1 (10.0)	9 (90.0)
Fallot’s tetralogy	8 (1.1)	1 (12.5)	2 (25.0)	0	5 (62.5)	2 (0.7)	0	0	0	2 (100.0)
Hypoplastic left/right heart	92 (12.8)	3 (3.3)	2 (2.2)	11 (12.0)	76 (82.5)[###]	62 (22.7)	1 (1.6)	0	3 (4.8)	58 (93.5)[###]
Single ventricle	7 (1.0)	0	0	1 (14.3)	6 (85.7)	1 (0.4)	0	0	0	1 (100.0)
Common arterial truncus	8 (1.1)	0	1 (12.5)	2 (25.0)	5 (62.5)	9 (3.3)	0	2 (22.2)	1 (11.1)	6 (66.7)
Atrioventricular septal defect	2 (0.3)	0	0	0	2 (100.0)	8 (2.9)	1 (12.5)	0	2 (25.0)	5 (62.5)

			Early neonatal mortality					Late neonatal mortality		
Tricuspid atresia/stenosis	1 (0.1)	0	0	0	1 (100.0)	2 (0.7)	0	0	0	2 (100.0)
Ebstein's anomaly	0	-	-	-	-	5 (1.8)	0	0	0	5 (100.0)
Aortic valve atresia/stenosis	5 (0.7)	0	2 (40.0)	0	3 (60.0)	2 (0.7)	0	0	1 (50.0)	1 (50.0)
Pulmonary valve atresia	1 (0.1)	0	0	0	1 (100.0)	4 (1.5)	0	0	0	4 (100.0)
Total anomalous pulmonary venous return	6 (0.8)	0	0	0	6 (100.0)	7 (2.6)	0	0	0	7 (100.0)
VSD (no severe CHD)	15 (2.1)	0	4 (26.7)	4 (26.7)	7 (46.6)	11 (4.0)	1 (9.1)	2 (18.2)	2 (18.2)	6 (54.5)
ASD (no severe CHD)	4 (0.6)	2 (50.0)	0	1 (25.0)	1 (25.0)	6 (2.2)	2 (33.3)	0	0	4 (66.7)
VSD+ASD (no severe CHD)	1 (0.1)	0	0	0	1 (100.0)	1 (0.4)	0	0	0	1 (100.0)
Pulmonary valve stenosis (no severe CHD)	0	-	-	-	-	0	-	-	-	-
Respiratory	51 (7.1)	11 (21.6)	14 (27.5)	12 (23.5)	14 (27.5)$^{\#\#\#}$	6 (2.2)	2 (33.3)	0	0	4 (66.7)
Choanal atresia	0	-	-	-	-	0	-	-	-	-
Digestive	128 (17.9)	4 (3.1)	20 (15.6)	25 (19.5)	79 (61.7)$^{\#}$	35 (12.9)	4 (11.4)	1 (2.9)	12 (34.3)	18 (51.4)$^{\#}$
Diaphragmatic hernia	97 (13.6)	0	11 (11.3)	19 (19.6)	67 (69.1)$^{\#\#}$	11 (4.0)	0	0	2 (18.2)	9 (81.8)
Orofacial clefts	16 (2.2)	7 (43.8)	3 (18.8)	3 (18.8)	3 (18.8)$^{\#\#\#}$	0	-	-	-	-
Cleft lip with/without cleft palate	10 (1.4)	5 (50.0)	1 (10.0)	2 (20.0)	2 (20.0)$^{\#\#\#}$	0	-	-	-	-
Abdominal wall defects	23 (3.2)	4 (17.4)	4 (17.4)	9 (39.1)	6 (26.1)$^{\#}$	11 (4.0)	0	1 (9.1)	6 (54.5)	4 (36.4)$^{\#}$
Gastroschisis	12 (1.7)	1 (8.3)	3 (25.0)	4 (33.3)	4 (33.3)	10 (3.7)	0	1 (10.0)	5 (50.0)	4 (40.0)$^{\#}$
Omphalocele	9 (1.3)	3 (33.3)	1 (11.1)	3 (33.3)	2 (22.2)	1 (0.4)	0	0	1 (100.0)	0

	Early neonatal mortality					Late neonatal mortality				
Urinary	60 (8.4)	4 (6.7)	8 (13.3)	26 (43.3)	22 (36.7)$^{###}$	14 (5.1)	4 (28.6)	3 (21.4)	2 (14.3)	5 (35.7)$^{##}$
Bilateral renal agenesis	1 (0.1)	0	0	1 (100.0)	0	0	-	-	-	-
Renal dysplasia	16 (2.2)	1 (6.3)	3 (18.8)	8 (50.0)	4 (25.0)$^{#}$	4 (1.5)	2 (50.0)	1 (25.0)	0	1 (25.0)$^{#}$
Congenital hydronephrosis	10 (1.4)	2 (20.0)	0	5 (50.0)	3 (30.0)	0	-	-	-	-
Genital	8 (1.1)	2 (25.0)	2 (25.0)	3 (37.5)	1 (12.5)	0	-	-	-	-
Hypospadias	2 (0.3)	0	1 (50.0)	1 (50.0)	0	0	-	-	-	-
Limb defects	20 (2.8)	10 (50.0)	3 (15.0)	3 (15.0)	4 (20.0)$^{##}$	5 (1.8)	3 (60.0)	1 (20.0)	1 (20.0)	0$^{###}$
Limb reduction	5 (0.7)	3 (60.0)	0	0	2 (40.0)$^{#}$	0	-	-	-	-
Clubfoot/talipes equinovarus	7 (1.0)	4 (57.1)	2 (28.6)	0	1 (14.3)$^{###}$	3 (1.1)	2 (66.7)	0	1 (33.3)	0$^{##}$
Hip dislocation/dysplasia	0	-	-	-	-	1 (0.4)	1 (100.0)	0	0	0$^{#}$
Polydactyly	4 (0.6)	2 (50.0)	1 (25.0)	0	1 (25.0)$^{#}$	1 (0.4)	0	1 (100.0)	0	0$^{#}$
Syndactyly	1 (0.1)	0	0	1 (100.0)	0	0	-	-	-	-
Other malformations	29 (4.1)	4 (13.8)	3 (10.3)	5 (17.2)	17 (58.6)	6 (2.2)	1 (16.7)	0	1 (16.7)	4 (66.6)

ASD: atrial septal defect; VSD: ventricular septal defect; CHD: congenital heart disease; CNS: central nervous system

** Overlap of component anomalies in two cases of early mortality and 7 cases of late mortality

$^{#}$ P<0.05, $^{##}$ P ≤ 0.001, $^{###}$ P<0.0005