Dysmorphism and major anomalies are a main predictor of survival in newborns admitted to the neonatal Intensive Care unit in the Democratic Republic of Congo.

Running tittle: Dysmorphism predicts survival in NICU

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ABSTRACT

In Central-Africa, neonatal infections, asphyxia and prematurity are main reasons for admission to the neonatal intensive care unit and major determinants of newborn survival. Also, the outcome of newborns with congenital anomalies is expected to be poor, due to a lack of state-of-the art care. We conducted a study of 102 newborns recruited in the Neonatal Intensive Care Unit (NICU) at the University Hospitals of Kinshasa, DR Congo, to assess the impact of congenital anomalies. The presence of a major anomaly was associated with a hazard ratio of death of 13.2 (95%CI: 3.7 – 46.7, $p<0.001$). In addition, the presence of three or more minor anomalies was associated with a 4.5-fold increased risk of death (95%CI: 1.1 – 18.6, $p=0.04$). We conclude that like major anomalies, the presence of three or more minor anomalies should also be given particular attention and that the evaluation of dysmorphism should be promoted in NICU.

Key words: newborns, congenital anomalies, survival, NICU

Introduction

In Central Africa, an estimated 1 in 7 children dies before the age of 5 years (Forae et al., 2014; Fotso et al., 2007). For children with a congenital anomaly, life expectancy is even lower (Modell et al., 2012). Reliable epidemiological data on the incidence of congenital malformations are scarce, despite the presence of risk factors such as the lack of screening programs, exposure to chemical and infectious agents, malnutrition, and also high rates of consanguinity in certain regions, advanced parental age, and large family size (Christianson et al., 2006; WHO, 2011). To address this question, the World Health Organization (WHO) has emphasized the need to conduct epidemiological studies and needs assessments in low- and middle-income countries to determine the most prevalent congenital and genetic disorders and the burden they impose on health (WHO, 2011).

In low-income countries such as the Democratic Republic of Congo (DRC), the care for children with congenital anomalies currently has a low priority, mainly due to a poor prognosis and high cost of treatment, if available at all. In the Neonatal Intensive Care Unit (NICU) of the University Hospital of Kinshasa, congenital malformations are the fourth most frequent cause of mortality, after infections, neonatal asphyxia and jaundice (Biselele et al., 2013). However, access to treatment for congenital anomalies such as cleft lip/palate, club feet and congenital heart disease is becoming increasingly available, either through local specialized physicians or through international charity organizations. These interventions improve survival and will thus increase the prevalence of such malformations in the population. At the same time, improved living conditions is being achieved by reducing the burden of environmental factors such as malnutrition and infectious diseases. Therefore, the relative contribution of congenital malformations to child mortality and morbidity will increase in comparison to other causes. This is in line with recent findings by Liu et al. (Liu et al., 2015), who showed that decreased child mortality is mainly due to a reduction in infectious disease, whereas the decrease of the contribution of congenital malformations is limited. This transition is well illustrated in Europe, where congenital malformations account now for 25% of neonatal death, compared to 8% worldwide (WHO, 2004).

This increased importance of congenital malformations on neonatal mortality in low- and middle-income countries underscores the need to build up expertise in the evaluation of dysmorphological features in newborns and in the management of major congenital anomalies. In a previous study of unselected newborns born in two maternity hospitals in Kinshasa, DR Congo, we detected a prevalence of major anomalies of at least 2.2% and dysmorphism in 4.3%

(Mubungu et al., 2020). However, we were not able to evaluate the known association of multiple minor anomalies with an increased risk of a major malformation (Hennekam, 2011) nor their contribution to the mortality. Further insight in the association between major and minor anomalies and their impact on mortality would, however, provide valuable information for the clinical assessment of newborns in Central African countries. We therefore conducted a prospective study in a cohort of newborns admitted to a single academic NICU in Kinshasa, DRC, a population in which we expected a higher prevalence of both minor anomalies and major malformations.

Material and methods

Patients' selection and recruitment

This study was conducted in the Neonatal Intensive Care Unit (NICU), at the University Hospitals of Kinshasa, DR Congo. This is a tertiary institution that provides care to ill newborns from across the city.

All (n=102) newborns admitted to the NICU between April 2017 and July 2019 were eligible for inclusion, but actual recruitment depended on the presence of the principal investigator (GM) at the time of admission. Parents were informed about the aims and design of the study and provided a signed informed consent. None of the parents declined to participate. The study was approved by the Ethical Committee of the Public Health School of the University of Kinshasa (ESP/CE/015/2018).

Data acquisition

All children were examined by the same clinician (GM). This included biometry, neurological examination, evaluation of dysmorphism and clinical photography, as described previously (Mubungu et al., 2020). A congenital physical anomaly was defined as an anatomic phenotype that deviates substantially from an appropriate reference population (Hennekam et al., 2013). Major anomalies were defined as congenital anomalies that have a significant impact on the health of the child, whereas minor anomalies, are those with little or no functional or esthetic impact. Morphological features that occur in 4% or more of children in a population are considered as common variants, while those that occur less frequently are considered dysmorphic or minor anomalies.

Morphologic features were defined according to the Elements of Dysmorphology (Allanson, Cunniff, et al., 2009) and designated using the Human Phenotype Ontology (HPO) nomenclature. Additional information was extracted from the medical records. This included

the reason(s) for admission and gestational age. Reasons for admission were classified as: prematurity, infection, asphyxia, or major malformation. Gestational age was determined using the Finnström score, as routinely done in each newborn admitted to the NICU (Finnstrom, 1971). Children born between 37 and 42 weeks of amenorrhea were considered term, whereas those born before 37 weeks or after 42 weeks were preterm or after post-term, respectively.

Weight, length and head circumference at birth were converted to z-scores using the reference curves for size at birth of the INTERGROWTH -21st PROJECT (Villar et al., 2014). Small for gestational age was defined as birth weight below the percentile 10, adjusted for gestational age.

Follow-up data on mortality of the newborns after discharge from the NICU were collected from the parents by phone one month, four months, six months and one year after discharge.

Data management and statistical analysis

Data were recorded in an excel file and further analyzed with IBM SPSS Statistics version 22.0 and R version 4.0 (R foundation for Statistical Computing, Vienna, Austria). Continuous variables were summarized as means and standard deviations, and categorical variables as proportions with exact binomial 95% confidence intervals. The presence of dysmorphism according to child and parental characteristics, mortality according to premature birth, and the proportion of newborns with a major anomaly or other condition that impacts health according to the number of minor malformations was estimated with logistic regression. Results are expressed as odds ratio's (OR) with a 95% confidence interval. Survival up to one year after discharge of newborns admitted to the NICU was estimated with Kaplan-Meier curves. Survival according to the presence of a major malformation or minor anomalies was compared with a log-rank test, and Cox regression was used to estimate the hazard ratio in children with vs without anomalies adjusted for birth weight and gestational age. A *p*-value less than 0.05 was considered as statistically significant.

Results

General characteristics

Over a period of 2 years, a total of 102 newborns were recruited in the NICU. Sixty newborns were male (60%) and forty females (40%), and a conjoined pair of twins presented ambiguous external genitalia.

The newborns were admitted for infections (n=82, 80.4%), prematurity (n=29, 28.4%), asphyxia (n=23, 22.5%), hemolytic disease (n=19; 18.8%), congenital anomalies (n=16,

15.7%), intraventricular hemorrhage (n = 13, 12.7%) or other (n=32, 31.4%). There was more than one reason for admission for 77 (75.5%) children in the study. As for the mothers, there were 43 primipara, 56 multipara and 3 with unknown parity. Eighty-five newborns were singletons, 17 multiples (8 twin pairs, and one single child part of a twin). The mean gestational age was 37.3 ± 2.8 weeks (n=86), and 41 out of 102 children were born premature and 2 post term. The mean z-score of weight at birth was -0.71 ± 1.24 (n=85) and 28 newborns (32.9%) were small for gestational age.

Minor anomalies

Table 1 presents the spectrum and prevalence of 62 different minor variants and anomalies that were observed in this study, along with their prevalence in a reference population of unselected newborns in Kinshasa (Mubungu et al., 2020). In total, 13 morphological anomalies were observed in the NICU but not in the reference population. Three of these did not have a HPO reference (table1).

Table 1. Prevalence (%) of morphological variants (left) and dysmorphic features according to the Human Phenotype Ontology (HPO) and Elements of Dysmorphology in the general population (9) and in a NICU in Kinshasa, DRC.

Common variants (≥ 4% in the population) *				Dysmorphism (< 4% in the population) *			
HPO	Phenotype	REF	NICU	HPO	Phenotype	REF	NICU
HP:0000278	Retrognathia	10.5	19.6	HP:0009909	Uplifted earlobe	3.9	9.8
HP:0011260	Darwin notch of helix	8.2	8.8	HP:0004467	Preauricular pit	3.7	2.0
HP:0000377	Abnormality of the pinna	8.2	26.5	HP:0000957	Cafe-au-lait spot	3.3	2.0
HP:0000322	Short philtrum	7.8	7.8	HP:0008577	Underfolded helix	3.3	5.9
HP:0000463	Anteverted nares	7.6	8.8	HP:0002558	Supernumerary nipple	3.3	2.0
HP:0009890	High anterior hairline	7.5	8.8	HP:0000378	Cupped ear	2.8	2.0
HP:0000337	Broad forehead	7.1	7.8	HP:0000286	Epicanthus	2.4	2.9
HP:0000582	Upslanted palpebral fissure	6.5	6.9	HP:0000343	Long philtrum	2.4	6.9
HP:0000316	Hypertelorism	5.5	11.8	HP:0000219	Thin upper lip vermilion	2.2	6.9
HP:0006610	Wide intermammillary distance	5.5	10.8	HP:0000276	Long face	2.2	6.9
HP:0000396	Overfolded helix	5.1	3.9	HP:0011232	Infra-orbital fold	1.9	3.9
HP:0000347	Micrognathia	4.3	2.0	HP:0011262	Crimped helix	1.9	2.9
HP:0002007	Frontal bossing	4.0	7.8	HP:0001162	Postaxial hand polydactyly	1.8	1.0
				HP:0030084	Clinodactyly	1.8	7.8
				HP:0011263	Forward facing earlobe	1.5	2.0
				HP:0000331	Short / small chin	1.5	8.8
				HP:0000400	Large ears / Macrotia	1.4	1.0
				HP:0009748	Large earlobe	1.4	2.0
				HP:0002562	Low-set nipples	1.2	1.0
				HP:0000293	Full cheeks	1.1	2.0

HP:0100015	Stahl ear	1.1	1.0
HP:0000325	Triangular face	1.0	3.9
HP:0000369	Low-set ears	0.8	2.0
HP:0012812	Fullness of paranasal tissue	0.7	3.9
HP:0005590	Spotty skin hypopigmentation	0.6	1.0
HP:0000154	Wide mouth	0.6	1.0
HP:0001159	Syndactyly	0.6	3.9
HP:0400004	Long ear	0.4	2.0
HP:0000054	Micropenis	0.4	1.0
HP:0000470	Short neck	0.4	2.9
HP:0002002	Deep philtrum	0.4	2.0
HP:0005585	Spotty hyperpigmentation	0.4	4.9
HP:0000954	Single transverse palmar crease	0.3	1.0
HP:0000387	Absent earlobe	0.3	1.0
HP:0000506	Telecanthus	0.3	2.0
HP:0000411	Protruding ear	0.1	1.0
HP:0011233	Antihelical shelf	-	1.0
HP:0000893	Bulging chest	-	1.0
HP:0000494	Downslanted palpebral fissure	-	1.0
HP:0000520	Exophthalmos	-	1.0
HP:0000324	Facial asymmetry	-	1.0
HP:0001380	Ligamentous laxity	-	1.0
HP:0000485	Megalocornea	-	1.0
HP:0001059	Neck Pterygium	-	1.0
HP:0030676	Satyr ear	-	3.9
HP:0006665	Short chest (Coat hanger sign of ribs)	-	1.0
	Flattened base of the nose	-	1.0
	Short eyes	-	1.0
	Tubercle in the breast	-	1.0

* REF: prevalence (%) in the reference population (Mubungu et al., 2020); NICU: prevalence (%) in the NICU group

About 30% (n = 31) of newborns in the NICU had no minor anomalies, while another 30% (n = 31) had one, 22.5% (n=23) two and 16.7% (n = 17) three or more minor anomalies (nine newborns with 3, four with 4, three with 5 and one with 8 minor anomalies). Dysmorphism (three or more minor anomalies) was not related to the sex (OR in boys 0.94; 95%CI 0.33 – 2.83; p=0.9), maternal age (OR 0.99; 95%CI 0.90 -1.08; p=0.8), paternal age (OR 1.00; 95%CI 0.93 – 1.07; p=0.9), exposure to alcohol (OR 0.36; 95%CI 0.02 – 2.06; p=0.3) or maternal infections during pregnancy (OR 1.12; 0.33 – 3.40; p=0.9).

Major anomalies.

A total of 19 major anomalies were observed in 16 newborns (15.7%), including clubfoot (n=4), spina bifida (n=1), duodenal stenosis (n=1), gastroschisis (n=2), agenesis of lacrimal puncti

(n=1), congenital heart defect (n=6), anorectal malformation (n=1), anencephaly (n=1), myelomeningocele (n=1), hydrocephaly (n=1). Three children presented with 2 major anomalies (clubfoot + spina bifida, hydrocephaly + heart defect and heart defect + clubfoot), and two children with 3 major anomalies (Siamese with clubfoot). The risk of having a major anomaly increased significantly with the number of minor anomalies in this sample, even though the number of children is relatively small (fig 1) (OR: 1.43; 95%CI: 1.02 – 2.05 p=0.04). Adjustment for the birthweight z-score, gestational age and age of the mother had little impact on this result, and neither factor was significantly associated with the presence of a major malformation.

The number of minor anomalies was not significantly associated with any of the other common reasons for admittance: infection (OR 0.94; 95%CI: 0.68 – 1.35), asphyxia (OR 0.78; 95%CI: 0.51 – 1.11), haemolytic disease (OR 1.00; 95%CI: 0.68 – 1.40), intraventricular hemorrhage (OR 0.95; 95%CI: 0.58-1.39) and other (OR 1.03; 95%CI: 0.76 – 1.37).

Of the 16 newborns with major anomalies, 11 had an isolated major anomaly. Of the five newborns with a major anomaly with dysmorphism (i.e., three or more minor anomalies), none represented a recognizable syndrome. Of the 12 newborns with dysmorphism, one child had the characteristics of Down syndrome.

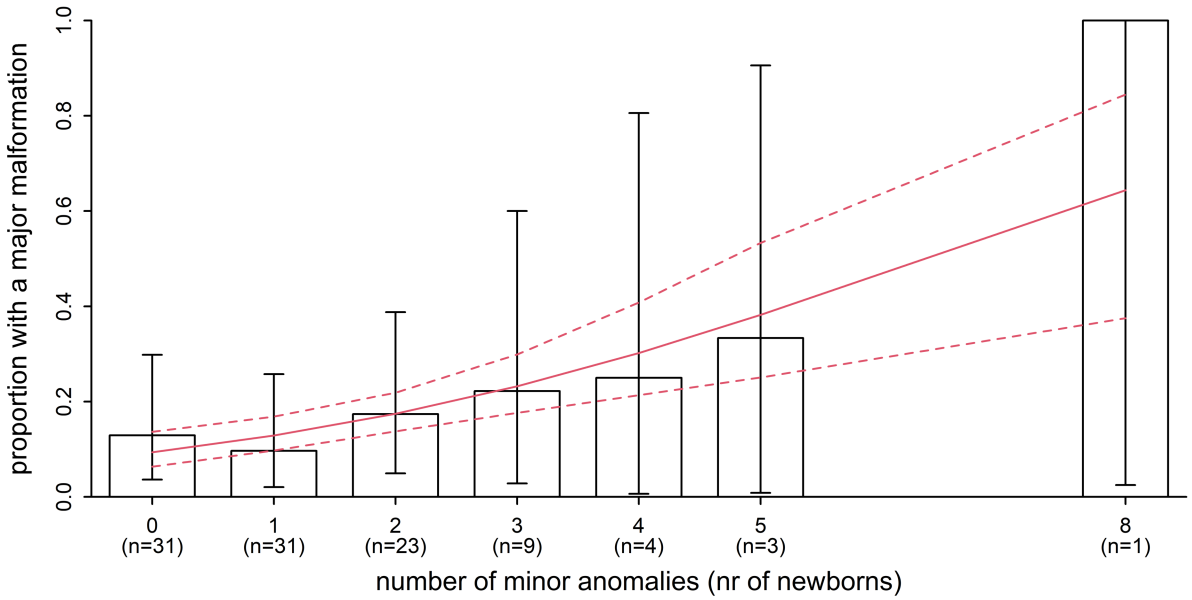

Fig 1. Proportion of newborns with a major malformation according to the number of minor anomalies. Error bars indicate the 95% Confidence Interval of the observed proportion. The number of newborns in each class is given between brackets below the axis. The curve shows the proportion predicted with logistic regression (full line) ± the standard error (broken line); OR = 1.43 (95%CI: 1.02 – 2.05), p = 0.04.

Survival

Of the 102 newborns recruited, 30 (29.4%) died during the hospitalization (n = 29) or follow-up after discharge (n = 1), and 6 were lost to follow-up. Among these were 17 males (28.6% of males), 11 females (27.5% of females) and the conjoined pair of twins with ambiguous external genitalia, and 10 were premature (34.5% of premature) and 20 term (27.4% of term) newborns (OR in premature 1.39; 95%CI 0.54 – 3.48). The reason for admission in the 30 children who died was a major anomaly (n = 13, 43.3%), neonatal infection (n = 26, 86.6%), intraventricular hemorrhage (n = 8, 26.6%) or asphyxia (n = 5, 16.6%), hemolytic disease (n = 5, 16.6%) or other (n = 9, 30%)). Of these, 26 (86.7%) had more than one reason for admission.

Death occurred during the first 7 days after birth in 16 newborns (53.3%) and another 6 (20%) died during the second week (figure 2). Of the newborns discharged (n = 72), follow-up data at 1 year after discharge were available on 66. Of these, another one died before the age of one year.

In newborns without dysmorphism (i.e. less than 3 minor anomalies) and no major anomaly (n =74), survival at the end of follow-up was 80.8%. For those with three or more minor anomalies but no major anomalies (n=12) survival was 58.3%. For newborns with at least one major anomaly (n = 16), survival was 25% at 1 months and 18.7% at 1 year. Those who survived had a clubfoot or duodenum stenosis as major anomaly.

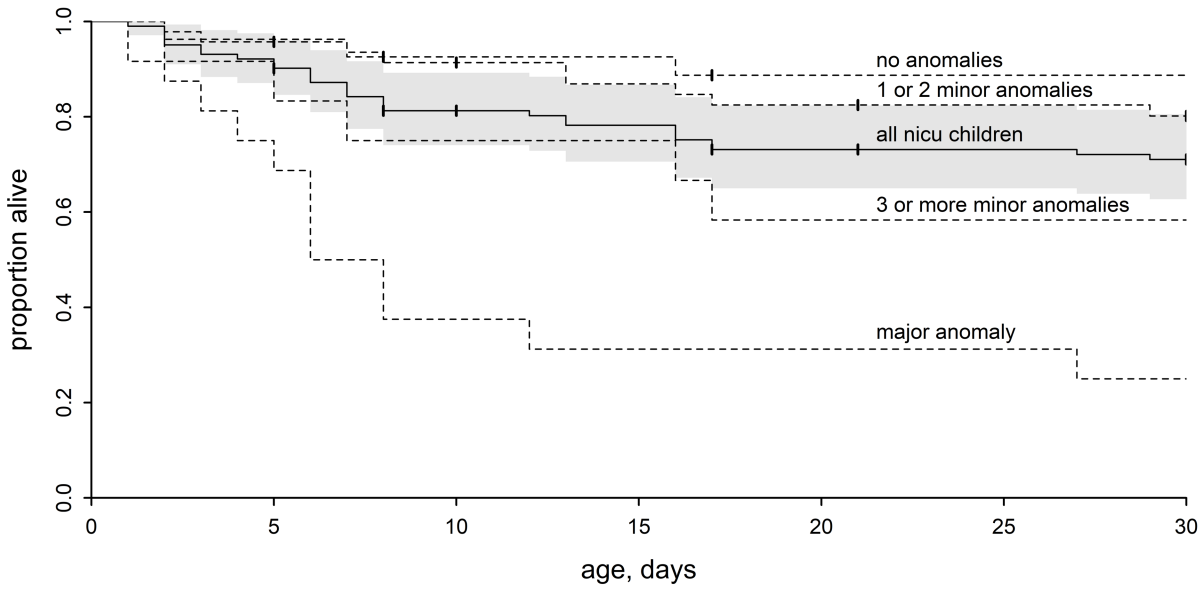

Fig. 2. Kaplan-Meier curves of overall survival and survival according to the presence of minor anomalies (no, 1-2, 3 or more) or major malformations in a NICU during the first month. The shaded area indicates the 95% confidence interval of survival in all children. Vertical markers indicate the last age of observation of censored (lost to follow-up) observations.

The presence of a major anomaly was associated with a hazard ratio of death of 13.2 (95%CI 3.7 – 46.7 p<0.001) (figure 2, table 2). The presence of three or more minor anomalies was associated with a 4.5-fold increased risk of death (95%CI 1.1 – 18.6 p=0.04). The hazard ratios are only slightly affected when adjusting for birth weight and gestational age, and the level of significance remains.

Table 2. Survival at the end of follow-up (one year after discharge) and hazard ratio's (Cox regression) according to the number of minor anomalies in newborns admitted to the NICU

	Survival (95%CI)	Hazard ratio (95%CI)	p
No anomalies	88.7% (77.5 – 100%)	reference	-
1 -2 minor anomalies	80.2% (69.4 – 92.7%)	1.8 (0.5 – 6.5)	0.4
3 or more anomalies	58.3% (36.2 – 94.1%)	4.5 (1.1 – 18.6)	0.04
Malformation	18.8% (6.8 – 52.0%)	13.2 (3.7 – 46.7)	< 0.001
all	70.0% (61.5 – 79.6%)	-	-

Discussion

Limited knowledge exists on the outcome of newborns with major anomalies and/or multiple minor anomalies in low- and middle-income countries. The obvious reason is that emphasis is still on infectious diseases or asphyxia as major causes of perinatal morbidity and mortality. According to the Health Newborn Network, worldwide, 80% of newborn mortality is related to prematurity, birth-related complications and infections, and 11% due to congenital anomalies. In the DR Congo, congenital anomalies are estimated to explain 7% of newborn mortality (https://www.healthynewbornnetwork.org/). However, advances in perinatal care are expected to result in a proportionately larger impact of congenital anomalies. The decline in neonatal mortality seen worldwide due to of infections and neonatal intrapartum-related events is not paralleled by a decline in congenital anomaly–related mortality (Liu et al., 2016). We therefore prospectively studied a cohort of newborns admitted to the NICU of a reference hospital in Kinshasa, capital of the DR Congo in Central Africa. This cohort was specifically studied since it was more likely to be enriched in major anomalies and thus being more informative. Indeed, in this cohort the incidence of major anomalies was 15.6%, which is higher compared to the incidence of 2.2% in an unselected population of newborns in the same city (Mubungu et al., 2020). This figure may underestimate the true prevalence of major anomalies, since access to imaging of the internal organs is highly restricted in The DR Congo and only performed when there are clinical indications for specific malformations. Moreover, as in many low-income countries, no social security exists, and patients have to pay themselves for each diagnostic intervention.

Less than 1 in 5 newborns admitted to the NICU with a major anomaly did survive beyond one year. The probability of survival after one year in newborns with a major anomaly is approximately one fifth of that in newborns without major anomaly and no dysmorphism. This confirms previous observations that newborns with congenital anomalies constitute a highly vulnerable population, with a poor prognosis, in this setting. The present cohort of newborns is not representative of all newborns with a major anomaly born in Kinshasa. Newborns admitted to the NICU often present additional problems including as asphyxia or infections (observed in 23 and 82 cases respectively). In contrast, the majority of newborns with congenital anomalies transferred to the University Hospitals are admitted to the pediatric surgery unit when they do not present such additional complications. Further research in that group can therefore complement the present study. Also, newborns presenting severe or multiple congenital

anomalies are underrepresented in this study, because often they are already deceased before transfer to the NICU.

This observation corroborates the poor outcome of congenital anomalies in Central Africa, especially when associated with other risk factors. Studies from other African countries reported a variable outcome for congenital anomalies, with mortality ranging from 10% in Eritrea and Nigeria (Ajao & Adeoye, 2019; Andegiorgish et al., 2020; Shah et al., 2012) to around 50% in Cameroon (Mah Mungyeh et al., 2014). However, differences in the characteristics of admitted neonates makes a comparison difficult.

We also noted that the presence of three or more minor anomalies is associated with a significant 4-fold increased risk of death during the first month, compared to newborns without minor or major anomalies. Minor anomalies have no functional consequences, but, since they are errors of morphogenesis, they indicate a disturbance of embryonic or fetal development. It is likely that some of the newborns with multiple minor anomalies in this study have an underlying syndrome, which was not yet clinically recognized. In the present cohort, the incidence of multiple (3 or more) minor anomalies was 16.7%, which is significantly higher ($p<0.001$) than the 4.3% observed in a reference population by the same investigator (G.M.) (Mubungu et al., 2020). This indicates that children with dysmorphism equally represent a vulnerable population, with an increased risk of being admitted to the NICU. Previous studies have shown that the presence of minor anomalies is associated with a higher risk of a major anomaly (Hennekam, 2011). In the present study, we equally observed such a relationship, with each additional minor anomaly representing a 40% increased chance of having a major anomaly.

In this cohort of 102 newborns, we observed 13 minor anomalies that were not present in a reference cohort of 722 newborns. This is not unexpected, given the large number of possible minor anomalies. On the other hand, certain minor anomalies might be more prevalent in certain syndromes, and thus enriched in a NICU population. Of these 13 minor anomalies not observed in the general population, 7 were observed in newborns with 3 or more minor anomalies, of whom 2 also had a major anomaly.

The impact of congenital anomalies may also be related to the etiology of the disorder. In this cohort, only one of the newborns with dysmorphism or with multiple major anomalies presented a recognizable disorder, i.e., Down syndrome. For the other children, reaching an etiological diagnosis was hampered by the limited access to technical investigations such as ultrasound or radiological imaging, biochemical analyses and lack of genetic testing.

Long term follow-up of patients is challenging in the DR Congo. In our previous study of newborns examined in maternity hospitals, most newborns with anomalies were lost to follow-up. In contrast, in the present study, only 6/72 newborns were lost to follow-up at the age of one year (8.3%). This is likely due to the highly selected group of patients, with a high interest by the parents in medical follow-up.

A limitation of this study is the small sample size. Over a period of 2 years, we recruited only 102 newborns in the NICU. This limited number is due to the low number of children born in the University Hospitals, of which only few need admissions to the NICU. Moreover, given the distant location of the University Hospital from the City Center, only few external referrals occur.

In conclusion, major anomalies and multiple minor anomalies are important predictors of outcome in newborns admitted to a NICU in a low-income country. This underscores the need for training clinicians to recognize and interpret minor and major anomalies.

DATA AVAILABILITY

The data that support the findings of this study are available from the corresponding author upon reasonable request.

CONFLICTS OF INTEREST

The authors declare having no conflict of interest.

THE AUTHOR CONTRIBUTION STATEMENT

Gerrye Mubungu contributed to the protocol design, data collection, data interpretation, writing and revision of the report.

Nono Mvuama contributed to data analysis and revision of the report.

Dahlie Tshika and Prince Makay contributed to the data collection.

Tady Bruno and Thérèse Biselele contributed to the revision of the report.

Mathieu Roelants contributed to data analysis, writing and revision of the report.

Koenraad Devriendt, Prosper Lukusa-Tshilobo and Aimé Lumaka contributed to the protocol design, data interpretation, writing and revision of the report.

All authors have read and approved the final version.

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