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Mortality and morbidity of preterm neonates weighing less than 750 g: a 2-year retrospective cohort study

Short title: Outcome of preterm neonates weighing less than 750 g

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Abstract

Background: The rate of premature births in France is 6% and is increasing, as is the rate of extremely premature births. Morbidity and mortality rates in this population remain high despite significant medical progress. We aimed to evaluate the morbidity and mortality rate in preterm neonates weighing < 750 g and to evaluate their outcome at 2 years' corrected age (CA).

Methods: This was a retrospective monocentric study including babies born between May 2011 and April 2013 who were preterm and weighed < 750 g. We evaluated mortality and morbidity in the neonatal period. At 2 years' CA, we focused on developmental quotient (DQ) with the Brunet–Lézine test, on neurosensory assessment (sleeping/ behavior), and growth evaluation.

Results: Among the 107 infants included, 29 (27%) died in the neonatal period. Mean gestational age was 25.6 weeks' gestation. Female sex and higher birth weight were independent predictors of survival. A total of 61 (78.2%) infants showed extrauterine growth retardation at 36 weeks' postmenstrual age. At 2 years' CA, 57 children were followed up; 38 were evaluated using the Brunet–Lézine test, 20 (52.6%) had a DQc < 85, and none had a severe developmental delay (DQc< 50). Six (10%) children had cerebral palsy and 22 of 56 (39.2%) showed language delay. Growth retardation persisted in 15 of 52 (28.8%) children.

Conclusion: Our results confirm the acute fragility of extremely low-birth-weight babies with a high rate of morbidity and mortality. At 2 years' CA, this population still shows a considerable rate of mild difficulties, whose long-term evolution needs to be followed.

Keywords: Low birthweight, Preterm, Mortality, Retrospective study, Premature/growth and development

1. Introduction

Preterm birth is a major public health problem. Each year, 15 million infants are born prematurely, 3 million of whom die during the neonatal period. Iterative French National Perinatal surveys revealed an increasing rate of prematurity: from 5.4% to 6.6% from 1995 to 2010, respectively, and 8.3% in 2016 [1,2]. Significant advances in perinatal and neonatal care (antenatal steroids, regionalization, surfactants, etc.) have improved survival rates among preterm infants. In the national French cohorts EPIPAGE and EPIPAGE 2, survival without severe morbidity between 25 and 29 weeks' gestation (WG) increased by 14.4% from 1997 to 2011 [3].

Several studies reported mortality rates in preterm infants, but few of them specifically focused on babies weighing < 750 g. Because of advances in medical care, survival without severe morbidity has significantly increased in extremely preterm infants (< 28 WG) or extremely low-birth-weight (ELBW) infants (< 1000 g). However, these infants remain at high risk of neurodevelopmental and growth disorders [1,3–6]. In a cohort of 101 preterm infants born weighing < 750 g during 1996–2000 and 200102005, 74.3% showed normal neurodevelopmental outcome at 2 years' corrected age (CA). Poor catch-up growth (between birth and 5.5 years) was associated with poor neurodevelopmental outcome [7,8]. In the latter study, 38% of infants weighed < -2 SD at 2 years' CA [7,8].

Increased survival may come at the cost of later neurodevelopmental disabilities among survivors. The aims of this study were to describe in a monocentric cohort of preterm neonates weighing < 750 g at birth the following characteristics: (i) neonatal mortality and morbidity; (ii) growth characteristics at birth, at 36 weeks' postmenstrual age (PMA), and at 2

years' CA; (iii) neurodevelopmental outcomes at 2 years' CA including Brunet–Lézine test results, neurosensory evaluation (cerebral palsy, deafness, ophthalmologic disorder), and parental report on behavior / feeding and sleeping habits of their child.

2. Materials and Methods

2.1 Study population and data collection: This retrospective study involved a monocentric cohort. The population comprised newborns with birth weight < 750 g admitted (inborn and outborn) to the level-three Port Royal Hospital neonatal intensive care unit (NICU) in Paris, France, between May 2011 and April 2013. Exclusion criteria were congenital malformations.

In this ICU during this period, infants were reanimated after discussion with the parents. At 22 and 23 WG, no reanimation was performed in France during this period [3].

The primary objective was to describe and analyze hospital mortality before discharge. The secondary objective was to describe neonatal morbidities in this population and the outcome at 2 years' CA. For the follow-up at 2 years' CA, infants discharged alive took part in a standardized follow-up program after the NICU, which consisted of growth and neurosensory (sleeping/ behavior/ feeding/ language/ deafness/ ophthalmologic disorder) evaluation and a neurodevelopmental test (Brunet–Lézine test). This evaluation was planned for all children born before 27 WG. Data were extracted from medical charts by the main investigator. To check for accuracy, data were double-checked.

For the neonatal period, GA was based on the early ultrasonography examination or if not available, the last menstrual period. The perinatal characteristics included pregnancy variables (type of maternal complications, antenatal steroids) and per partum variables (multiple births, delivery, GA, birth weight, sex, Apgar score and inborn/outborn status). Newborns were

classified as small for GA (SGA) if their birth weight was less than the 10th percentile (Audipog charts) and appropriate for GA (AGA) if this was not the case.

Neonatal variables analyzed were in-hospital mortality, bronchopulmonary dysplasia (BPD; defined by the need of oxygen therapy at 28 days of life and severity evaluated at 36 weeks' PMA: no oxygen supplementation at 36 weeks' PMA [light BPD], less than 30% oxygen [moderate BPD], or more than 30% oxygen or invasive or noninvasive ventilation [severe BPD]) [9], necrotizing enterocolitis (NEC), neurological morbidity (grade III/IV intraventricular hemorrhage [IVH] [10] and periventricular leukomalacia [PVL]) diagnosed with cranial ultrasonography or magnetic resonance imaging (MRI), postnatal systemic steroids (used for respiratory disorders), retinopathy of prematurity (ROP), pulmonary hemorrhage and extrauterine growth retardation (EUGR) at 36 weeks' PMA (weight less than the 10th percentile [Audipog charts]).

At 2 years' CA, variables analyzed were growth (height, occipital frontal circumference [OFC], and weight), nutrition, behavior, and neurological examination: walking, cerebral palsy (CP), motor disabilities, Brunet–Lézine test (by a trained psychologist), language, deafness, and ophthalmological disorder. CP was defined according to Bax et al. and characterized as hemiplegic, tetraplegic, diplegic, or dyskinetic [11]. For growth, we used the Audipog curves in the neonatal period and the Leroy and Lefort curve for the follow-up [12].

The Brunet–Lézine test is a psychomotor developmental scale that evaluates four domains (developmental quotient [DQ]): gross and fine motor skills, language, and social interaction. We calculated a global DQ based on the results for each domain. The test is calibrated so that the average for the overall quotient in the French population is 100 (SD = 15). The DQ was corrected for prematurity: adjusted on corrected age (DQc). Mild developmental delay was defined as a DQc score < 85; moderate delay, < 70; and severe mental developmental delay,

< 50. The DQ was revised in 1994 and 1996 and adjusted on the basis of French children born at term; it is routinely used in studies conducted in French-speaking countries [13].

2.2 Statistical analysis: To analyze the main objective of the study, characteristics of infants who died and those discharged home were compared. Quantitative variables are described with medians and their interquartile range (IQR) and were compared by unpaired Wilcoxon tests. Qualitative variables are described with percentages and were compared by chi-square or Fisher exact tests. We estimated odds ratios (ORs) and 95% confidence intervals (CIs). All statistical tests were two-tailed and a *p*-value < .05 was considered statistically significant. We performed a multivariable logistic regression with a stepwise selection with in-hospital death as outcome. Adjustment variables were selected on the basis of the literature or when the *p*-value was <.10 on univariate analysis. Missing data were not imputed ("complete-case analysis"). To analyze the secondary outcomes, we described quantitative variables using median and IQR, qualitative variables with number and proportions, respectively. We compared qualitative variables among children regarding their weight at birth using a chi-square test or a Fisher test (as necessary). Data analysis involved use of SAS 9.4 (SAS® Inst., Cary, NC, USA).

The ethics committee of the French National Society of Neonatology (SFN) approved this study (no. 1747084). During the child's hospitalization, parents were informed that their infant's medical information could be recorded for clinical studies. This study complies with STROBE statements for reporting of observational studies[14] .

3. Results

3.1 Clinical characteristics

A total of 112 patients were eligible but five were excluded (congenital malformation, *n*=2, and missing data, *n*=3); thus 107 patients were included in the study (Figure 1). The mean GA was 25.6 (IQR: 24.8–27.1) WG and mean birth weight 660 g. Altogether, 44 (41.1%) children were SGA at birth. The characteristics of the population and the major morbidities are described in Table I.

For the 2-year CA evaluation, follow-up was planned for all children born before 27 WG, but some of them did not come to their appointment (*n*=17), and some did not participate in all tests. Thirty-eight passed the Brunet–Lézine psychometric test. We had data for growth from 52 patients, and for language from 56.

3.2 Neonatal outcomes

3.2.1 Mortality

Seventy-eight infants were discharged alive; the mortality rate in the NICU was 27% (*n*=29). The median age of death was 5.5 (IQR: 3.0–15) days. The rate of death was similar between SGA and AGA infants (22.7%, *n*=10, and 30.1%, *n*=19; *p*=.38). The causes of death were infectious disease (20.6 %), neurologic (27.5%), pulmonary (27.5%), cardiologic (20.6%), and other (3.8%). In the multivariate analysis, factors associated with mortality before discharge were male sex, no antenatal steroids, and birth weight (Table II).

3.2.2 Growth characteristics

At 36 weeks' PMA, 61 (78.2%) children had EUGR (Table I). At 2 years' CA, the weight of 15 of 52 (28.8%) children was below the 10th percentile. Height and OFC were < -2 SD for one (1.8%) and five (9.3%) children. Table III presents the evolution of weight at birth, discharge, and 2 years' CA for AGA and SGA infants.

3.3 Neurodevelopmental outcomes at 2 years' CA

At 2 years' CA, 57 of 78 (73%) children were followed up (Figure 1). Children lost to follow-up did not differ from those analyzed regarding neonatal characteristics (supplemental data); for 52 children there were data on growth at 2 years' CA, and for 38 the Brunet-Lézine psychometric test results were available.

A total of 96.5% children achieved walking; two were not able to walk at 2 years' CA. Median age at walking was 18 months (IQR: 13–29).

Neurological examination results were normal for 44 (81.5%) children; six (10%) had CP: three with hemiparesis (5.6%), two with diplegia (3.6%), and one with (1.8%) tetraplegia. In all, 22 of 56 (39.2%) children had poor language skills with less than 10 words; 13 (23.2%) were only able to associate two words and 14 (25%) were able to speak with full sentences. One (1.7%) had no language at all.

Strabismus was present in five (11.9%) children; seven (15%) needed glasses. No infant was deaf (many missing data and invalid test results).

Behavior was calm in 38 (60%) children. Attention was evaluated by studying playing behavior, and 33 (68.7%) children could sustain play. Contact was easy and normal in 46 (86.8%) children.

Feeding was normal in 36 (68%) children; nine (17%) had few difficulties. One patient had a gastrostomy.

Among the 78 children who were followed up, 27 infants were born after 27 WG and were not eligible for the Brunet–Lézine test following our protocols. However, among these 27 infants, five had the test. Finally, 38 of 56 children passed the test (18 did not come to the appointment). The median global DQ in the Brunet–Lézine test was 74 (IQR: 55–100) and median DQc was 85 (62–115) (Table IV). There was mild impairment, defined as DQc < 85,

in 20 of 38 (52.6%) infants and three of 38 (7.9%) had moderate delay (DQc< 70); none had severe delay (DQc<50)**.**

4. Discussion

Providing accurate data on both mortality and long-term neurodevelopmental outcomes is important for families and professionals in order to offer appropriate neonatal care. Therefore, we focused on the smallest preterm children in this recent cohort of preterm infants weighing < 750 g at birth and admitted to the NICU. The mortality rate was 27% in the NICU. At 36 weeks' PMA, 78% of children had EUGR and this delay persisted in 28.8% of them at 2 years' CA. Median DQc at 2 years' CA was 85.

The rate of mortality and neonatal morbidities seems to have improved over the years with medical progress. In 2004, Locatelli et al. reported a mortality rate of 49%, a median birth weight that was lower than in our study (567 g), and that 54% of infants were SGA. Antenatal steroid administration was different significantly (p=0.02) between infants who died (59%) and those who survived (87%) [15]. Claas et al., studying infants (between 1996 and 2005) with median birthweight of 675 g and 86.2% of antennal steroid administration, reported a 24% mortality rate [8]. In the EPIPAGE-2 cohort (2011), when focusing on infants born earlier than 26 WG (median weight 748 g), the mortality rate was 23% and antenatal steroids were administered in 65% [3]. In the EXPRESS cohort, a national population-based prospective study of all infants born before 27 WG between 2004 and 2007 in Sweden, 30% of preterm infants died. The results of these cohorts seem to be similar to ours, even if our cohort was smaller (median weight 660 g) but with a high level of antenatal steroid administration: 79%.

We identified factors associated with neonatal death. These predictors may be important for discussions with parents for the most immature babies (< 26 WG). Tyson et al. identified three factors associated with survival: birth weight, female sex, and antenatal steroids [16]. Our results are in agreement with those. In our cohort, after adjustment for prenatal and early postnatal factors, higher birth weight and female sex were associated with a higher probability of survival.

One of the biases in the evaluation of the mortality rate is that some of the deaths in our cohort were secondary to palliative care. Indeed, our population is at risk of severe cerebral hemorrhage and multiorgan failure in the first days of life. In these cases of unreasonable obstinacy, we proposed palliative care to the family.

Beyond survival, one of the major problems is the rate of EUGR: 78.2% on discharge from the hospital in our cohort. Claas et al. studied postnatal growth in infants weighing less than 750 g at 2 years' CA: weight, OFC, and height were < -2 SD, respectively, for 38%, 19%, and 37% of infants. At 2 years' CA, the weight of SGA children was still < -2 SD for 66% of infants (33% caught up) as compared with 31% of the AGA children [7]. Persistent growth retardation was also found in the cohort of de Jesus et al., in the same proportion: 60% SGA and 37.4% AGA infants [17]. The rate of EUGR was also more frequent in SGA babies in our cohort. In our study, at 2 years' CA, the weight for 28.8% of the children was still below the 10th percentile, and height and OFC were < -2 SD for 1.8% and 9.3% of the children. These data are lower than those reported in the literature. EUGR is a problem in ELBW infants because of the consequences on motor and cognitive developmental outcome at 2 years [7,18,19]. In particular, poor head growth has been associated with poor outcomes at school age. However, the studies differ in methods and results, and some found no effect or worse effect of weight gain after birth on neurological outcome [20–22].

In the context of increased survival, evaluation of the global outcome is necessary. In the EXPRESS study, at age 2.5 years, 42% of infants had no disability, and most disabilities were mild (31%). Moderate and severe disabilities increased with decreasing WG. The mean score was 94 (93–96) for cognitive evaluation, 98 (97–100) for language, and 95 (92–96) for motor evaluation using the Bayley III scale. The prevalence of CP was 7%, and only 1.3% of children had severe CP. Few children were blind (0.9%) and/or deaf (0.2%) [23]. Comparison between studies for the neurodevelopmental outcome is difficult because of different populations, different psychometric tests, and different exclusion criteria at 2 years.

Few studies have focused on the quality of life of preterm infants during childhood or adulthood. Quality of life is difficult to evaluate because of its subjectivity. A systematic review showed that the impact of premature birth on health and quality of life seems to diminish over time, but it is still important during the first years of life, and we should improve our efforts to enhance the quality of life of these children in the growing years [24]. A meta-analysis revealed that early developmental intervention programs provided after hospital discharge could prevent motor and cognitive impairment in preterm infants [25]. Therefore, follow-up of preterm children is essential to evaluate the effects and consequences of the intensive care period.

Our study had some limitations. The first was the retrospective design and thus the important rate of missing data. However, the characteristics of patients followed up and those lost to follow-up were similar. Second, we may not have collected all the predictive factors, thereby introducing an informative bias. Third, our sample size was small.

In terms of strengths, our study included all patients in our NICU, our population was

very homogeneous and reflected the activity of a high-volume tertiary center specialized in taking care of ELBW children and their follow-up.

5. Conclusions

In this monocentric, retrospective study, our results confirm the extreme fragility of ELBW infants and the associated high rate of morbidity and mortality. Female sex and higher birth weight were independent predictors of survival. At 2 years' CA, we still found a considerable rate of mild difficulties in this population of extremely premature infants, whose longer-term evolution needs regular follow-up by specialists.

Statement of Ethics: Participants (or their parents or guardians) were informed that medical information can be used for study. Ethics Committee of the French Neonatology Society approved this study (N° 1747084).

Conflicts of interest: All the authors have no conflicts of interest to declare. No financial assistance (honorarium, sponsorship, grant, or other form of payment) was received in support of the study.

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Table I: Characteristics of the total cohort and comparison between those who died and those discharged alive.

	Total cohort (*N*=107)	**Died (*N*= 29)**	**Discharged alive (*N*= 78)**	***p***
Pregnancy variables				
Threatened preterm birth (*n*, %)	57 (53.3)	21 (72.4)	36 (46.1)	**.01**
Bleeding (*n*, %)	23 (22.4)	10 (34.5)	14 (17.9)	.07
Preeclampsia (*n*, %)	34 (31.8)	7 (24.1)	27 (34.6)	.30
Intrauterine growth restriction (*n*, %)	47 (44.3)	9 (31.0)	38 (49.3)	.09
Antenatal steroids (*n*, %)				
Complete cure	79 (73.8)	16 (55.2)	63 (80.8)	**.01**
Incomplete cure	24 (22.4)	10 (34.5)	14 (17.9)	
No steroids	4 (3.7)	3 (10.3)	1 (1.3)	
Peripartum variables				
Multiple birth (*n*, %)	28 (26.2)	11 (37.9)	17 (21.8)	.09
Caesarean delivery (*n*, %)	61 (57.0)	13 (44.8)	48 (61.5)	.12
Gestational weeks, median [IQR]	25.6 [24.8-27.1]	25.1 [24.6-25.8]	26.0 [25.1-27.4]	**0.017**
Birth weight (g) median [IQR]	660 [620-700]	635 [570-690]	670 [630-700]	**.04**
Small for gestational age (*n*, %)	44 (41.1)	10 (22.7)	19 (30.1)	.38

	Total cohort (*N*=107)	**Died (*N*= 29)**	**Discharged alive (*N*= 78)**	***p***
Sex female (*n*, %)	71 (66.4)	14 (48.3)	57 (73.1)	**.02**
5-min Apgar score median [IQR]	8 [6-9]	7 [4-9]	8 [6-10]	**.03**
Outborn (*n*, %)	9 (8.4)	6 (20.7)	3 (3.8)	**<.01**
Postpartum variables				
BPD: moderate or severe (*n*, %)	46 (57.5)	NA	NA	NA
NEC (*n*, %)	6 (6.4)	NA	6 (7.8)	.58
IVH grade III/IV (*n*, %)	9 (8.8)	6 (26.0)	3 (3.9)	**.01**
PVL (*n*, %)	9 (8.8)	3 (16.7)	6 (7.7)	.36
Systemic steroids (*n*, %)	8 (7.4)	2 (9.5)	5 (7.7)	.68
ROP stage 2/3 (*n*, %)	11 (25.6)	NA	NA	NA
Pulmonary hemorrhage (*n*, %)	20 (18.7)	11 (42.3)	9 (11.5)	**<.01**
EUGR at 36 weeks' PMA (*n*, %)	61 (78.2)	NA	61 (78.2)	NA

Abbreviations: BPD: bronchopulmonary dysplasia, EUGR: extrauterine growth restriction, IQR: interquartile range, IVH: intraventricular hemorrhage, NEC: necrotizing enterocolitis, PMA: postmenstrual age, PVL: periventricular leukomalacia, ROP: retinopathy of prematurity.

Table II: Multivariable analysis of factors associated with death at 28 days.

	aOR	**95% CI**	***p***
Sex, female vs. male	0.33	0.11-0.93	**.04**
Antenatal corticosteroids			
Complete cure	Reference		
Incomplete cure	2.59	0.70-9.66	.75
No cure	11.03	2.63-50.81	**.02**
Gestational age, weeks			
≤ 26	Reference		
25–26	5.69	1.62-22.18	.36
< 25	4.26	1.09-17.72	.09
Birth weight, <660 vs. ≥ 660 g	5.58	1.94-18.14	**.002**

Footnotes: Discrimination (C-index: 0.79 (0.69–0.90); and calibration (Hosmer–Lemeshow: chi-square 3.55, *p*=0.737-, of the model.

Abbreviations: aOR: adjusted odds ratio, 95% CI: 95% confidence interval

Table III: Growth evolution from birth to 2 years' corrected age (CA) for preterm infants small for gestational age (SGA) (<10th percentile) and appropriate for gestational age (AGA) (>10th percentile).

Weight at birth (*n*= 107)	**EUGR at 36 weeks' PMA* (*n*=77)**		**Weight at 2 years' CA** (*n*=52)**	
	<10th percentile (*n*=59)	>10th percentile (*n*=18)	≤10th percentile (*n*=15)	>10th percentile (*n*=37)
SGA, *n*=44, (41%)	31/59 (52.5%)	3/18 (16.7%)	10/15 (66.7%)	11/37 (29.7%)
AGA, *n*=63, (59%)	28/59 (47.5%)	15/18 (83.3%)	5/15 (33.3%)	26/37 (70.3%)

Footnote: Weight > or < 10th percentile on Audipog curve for birth and 36 weeks' PMA, weight > or < 10th percentile on the Leroy and Lefort curve at 2 years' CA.

*p=.01, **p<.05

Abbreviations: SGA: Small for gestational age, AGA: appropriate for gestational age, CA: corrected age, EUGR: extra-uterine growth restriction, PMA: post-menstrual age

Table IV: Results of Brunet-Lézine test at 2 years' CA (*n*=38).

	Mean	**Median**	**Min**	**Max**	**IQR**
DQ global	74.3	74.0	55.0	100.0	71.0-80.0
DQc global	85.2	85.0	62.0	115.0	78.0-93.0
DQ social	79.4	84.5	54.0	96.0	73.0-88.0
DQc social	91.4	97.0	63.0	109.0	84.0-101.0
DQ language	69.4	70.0	43.0	114.0	65.0- 74.0
DQc language	79.7	80.0	49.0	131.0	73.0-85.0
DQ fine motor	75.9	74.0	56.0	99.0	68.0-85.0
DQc fine motor	87.2	88.0	65.0	115.0	78.0-97.0
DQ global motor	74.9	77.5	42.0	91.0	66.0-86.0
DQc global motor	85.4	89.0	39.0	123.0	73.0-98.0

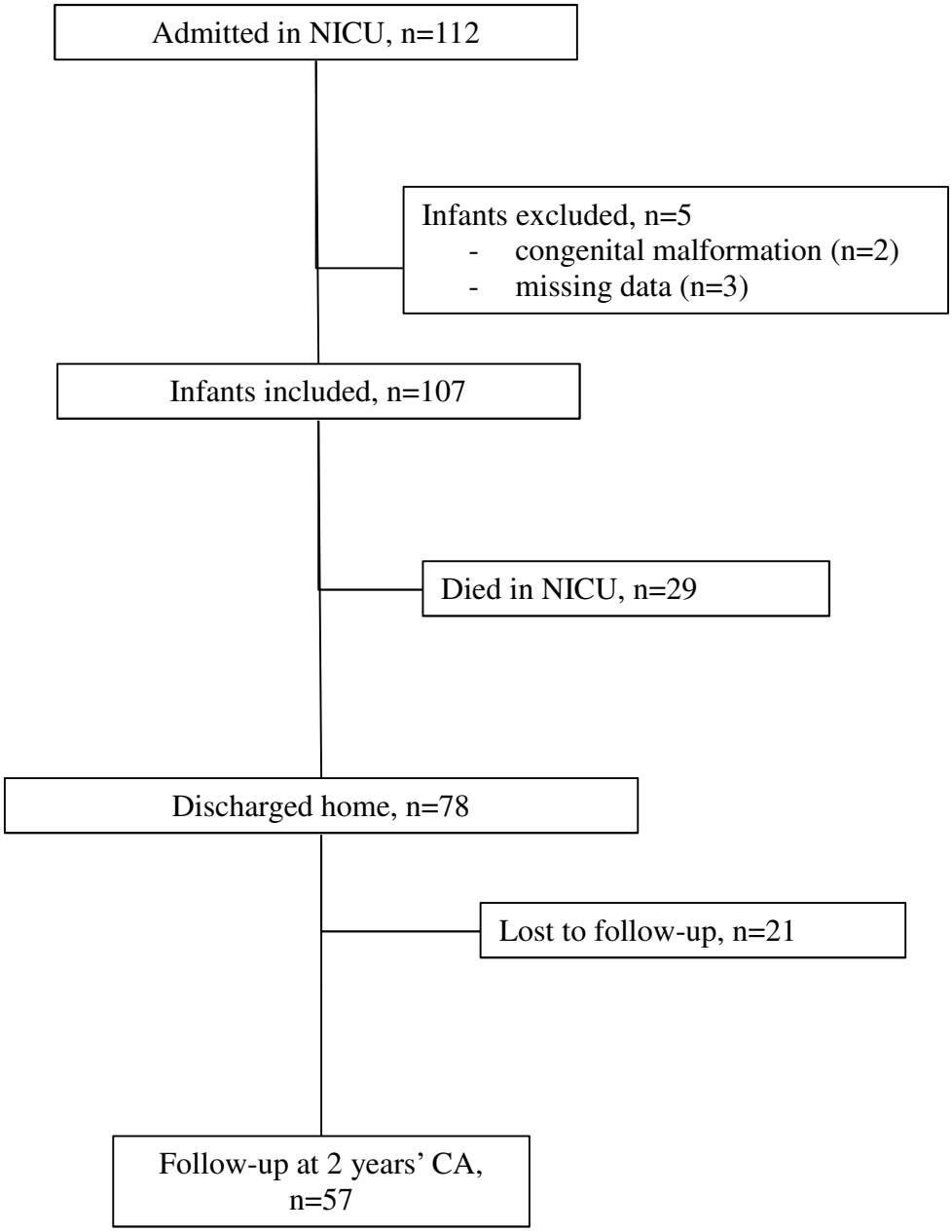
Footnote: Data were missing for 18 children. Mild developmental delay was defined as score < 85; moderate, score <70; and severe developmental delay, score <50.

Abbreviations: DQ: developmental quotient, c: corrected age (at 2 years), IQR: interval interquartile.

Figure 1: Flow chart of the study

Abbreviations: CA: corrected age, NICU: neonatal intensive care unit.

Figure 1: Flow chart of the study.



Abbreviations: CA: corrected age, NICU: neonatal intensive care unit.