







REGULAR ARTICLE

Considerable mortality and morbidity in neonates born below 500 gram

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Abstract

Data evaluating mortality and morbidity in infants born ≤ 500 g are scarce and show wide variability. To support counselling and decision-making, we analysed neurodevelopmental outcome in all neonates ≤ 500 g birth weight.

Retrospective analysis including preterm infants with a birth weight ≤ 500 g and a gestational age >22 weeks born at a single tertiary perinatal centre between 2010 and 2017.

Of 59 live births, 88% received standard care. Birth weight ranged from 318 to 500 g and gestational age from 23 to 29 weeks. 56% of neonates were born ≤ 3 rd percentile and 42% of treated infants survived. Neurodevelopmental outcome was available in 91% of patients and was evaluated using Bayley Scales of Infant Development at two years. 50% showed a favourable mental development (normal or mild impairment), 75% a favourable motor development and 45% a favourable outcome in both outcome subcategories. When additionally considering visual and hearing disability and, or, cerebral palsy level ≥ 2 according to the Gross Motor Function Classification System 35% had a good neurodevelopmental outcome.

Survival rate was 37% for all live births and 42% for infants with standard care. More than one-third of survivors showed no significant neurodevelopmental impairment at two years.

KEYWORDS

morbidity, neonatology, neurodevelopment, outcome, survival

Abbreviations: BPD, bronchopulmonary dysplasia; BSID II/Bayley-III, Bayley Scales of Infant Development grade II or grade III; cPVL, cystic periventricular leukomalacia; GA, gestational age; GMFCS, Gross Motor Function Classification System; IVH, intraventricular haemorrhage; LISA, less invasive surfactant administration; MDI, Mental Development Index; NEC, necrotising enterocolitis; NICU, neonatal intensive care unit; PDA, persistent ductus arteriosus; PDI, Psychomotor Development Index; ROP, retinopathy of prematurity.

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1 | INTRODUCTION

With on-going advances in perinatal medicine and neonatal intensive care, marked improvements in the survival of extremely preterm infants have been well documented.^{1,2} The rate of survival and survival without disability at the border of viability increased over the last decade.³ Nevertheless, the decision whether to offer intensive care or withhold life-saving treatments to periviable patients ≤ 500 g birth weight independent of GA remains an ethical dilemma and area of controversy.^{4,5} It is challenging as the best interest of the child, the family and societal norms all play a role in the process of decision-making.⁴ Currently, the biologic viability threshold is not clearly defined, hence, clinicians base their counselling and decision-making on various clinical measures such as GA or estimated foetal weight and correlated outcomes.⁵

Data providing a systematic assessment of mortality, short-term as well as long-term morbidity in infants born ≤ 500 g is scarce and shows wide variability: early publications found survival rates of 22–37%,^{6,7} while subsequent reports revealed a wide range from 21–22%^{8,9} to 28–38%^{5,7} up to 54–80%.^{10–15} Potential explanations for such immense discrepancies in reported survival rates are most notably differences in cohort definitions¹⁶ as well as differences in local clinical practices.⁵

Our centre's approach was reformed in 2009 including a proactive obstetric management, like performing scheduled Caesarean section (C-section) for periviable neonates regardless of age and weight. Moreover, immediate postnatal care at the NICU was modified to include less invasive surfactant administration (LISA).¹⁷ In order to support counselling and decision-making with local data, we reviewed our single-centre cohort of infants born at or below 500 g birth weight between 2010–2017 and evaluated both survival and neurodevelopment outcome at two years corrected age.

2 | METHODS

2.1 | Setting

Our paediatric hospital is a 155-bed tertiary medical centre with 54 beds dedicated to neonatal care. The mean annual birth rate during the study period was 2453. On average, 92 preterm infants < 1000 g and 177 < 1500 g were treated per year with a survival rate of 82% and 90%, respectively. This study was a retrospective analysis of preterm infants born at a single tertiary perinatal centre between January 2010 and December 2017. Inborn live births with a birth weight ≤ 500 g and a GA ≥ 23 weeks were included. Below 23 weeks, no life support was offered according to national guidelines.^{18,19} Infants with major birth defects were excluded from the study population.

Antenatal counselling at the limit of viability is standard of care in our facility. At 23 weeks of GA, we aim for a shared decision-making process, granting more autonomy to the parents. Although it is possible to withhold, withdraw or not escalate postnatal care in the presence of severe complications at the border of viability, patients born

Key Notes

- The imminent delivery of a periviable neonate presents a multitude of difficult and complex ethical issues and represents a controversial and emotionally charged area in perinatology.
- There is a considerable risk of death or neurodevelopmental impairment in neonates below 500 g birth weight.
- 42% of treated patients survived and more than one-third of survivors showed no significant neurodevelopmental impairment at 2 years.

≥ 23 weeks typically receive proactive care.^{18,19} Neonatologists attend each high-risk delivery and neonates are admitted to the NICU immediately after birth. Our postnatal management approach for extremely preterm infants includes high flow CPAP via Benveniste valve,²⁰ use of caffeine-citrate, early prophylactic surfactant treatment via LISA protocol¹⁷ and plastic bags to prevent hypothermia.

2.2 | Descriptive data and primary outcomes

Maternal and neonatal characteristics, including growth assessment until discharge, were obtained from electronic patient charts. GA was determined by crown-rump length using ultrasonography during early pregnancy or first trimester screening.

The primary outcomes were survival and neurodevelopmental outcome at two years.

2.3 | Short-term outcome

Severe brain injury was defined as grade 3 or 4 intraventricular haemorrhage (IVH) according to Volpe et al²¹ and, or, cystic periventricular leukomalacia (cPVL).²² The rates of surgically treated persistent ductus arteriosus (PDA), necrotising enterocolitis (NEC) above Bell's stage 2²³ and intestinal perforation with surgical intervention were analysed. Bronchopulmonary dysplasia (BPD) was defined as oxygen requirement at 36 weeks of postmenstrual age. Severe retinopathy of prematurity (ROP) was defined as stage 3 and above according to the International Classification²⁴ requiring intervention. Severe morbidity was defined as either of the following: IVH grade 3 or 4, cPVL, BPD and ROP.

2.4 | Long-term outcome at two years corrected age

Neurodevelopmental outcome was measured using Bayley Scales of Infant Development, BSID II or Bayley-III. Mental Development

Index (MDI) and Psychomotor Development Index (PDI) were obtained using BSID II; Cognitive, Language and Motor Composite Score using Bayley-III. For comparison, the following conversions were applied: $MDI = (Cognitive + Language Composite Score)/2$ and $PDI = Motor Composite Score$. For Bayley-III, both German and American norms were calculated. Based on German norms, outcomes were classified into four groups: normal ≥ 85 , mild impairment 84–70, moderate impairment 69–55 and severe impairment < 55 . Normal outcome and mild impairment were categorised as favourable outcome.

Furthermore, growth assessment and functional assessment of visual and hearing ability were included. In the presence of cerebral palsy, a level according to the Gross Motor Function Classification System (GMFCS) was assigned.²⁵

Finally, the combined outcome of significant neurodevelopmental impairment was defined as any of the following: MDI or PDI < 70 , visual or hearing impairment with need of visual or hearing aid and, or, cerebral palsy with a GMFCS level 2–5. Profound neurodevelopmental impairment was defined as any of the following: MDI or PDI < 55 and, or, profound cerebral palsy with a GMFCS level 4–5.

2.5 | Statistical analysis and ethics

Statistical analysis was performed using SPSS Statistics 23.0 (IBM Corporation, New York, USA) and GraphPad Prism 6 (GraphPad software, California, USA). $p < 0.05$ was considered statistically significant. Quantitative data are shown as means \pm SD or medians (IQR) as appropriate and qualitative data as counts and percentages. Differences between groups were calculated using Mann–Whitney *U* test and chi-square test.

The study protocol was approved by the Institutional Review Board of the Medical University Vienna (EK 1093/2019).

3 | RESULTS

3.1 | Participants

A total of 59 live-born infants ≤ 500 g birth weight were included in this 8-year study period, which corresponds to one-third of all cases nationwide. The majority of 52 neonates (88%) received proactive care according to institutional guidelines and were immediately admitted to the NICU. Of those infants, 26 (50%) were born at 23 weeks of GA, nine (17%) at 24, seven (14%) at 25, five (10%) at 26, two (4%) at 27, one (2%) at 28 and two (4%) at 29 weeks. The decision to offer primary palliative care in the remaining seven patients, all born at 23 weeks, was based on a shared decision-making process with the parents. Considering the entire cohort, 29 neonates (56%) were born ≤ 3 rd percentile, 13 (25%) 4–10th percentile and 10 (19%) > 10 th percentile. Additional demographic characteristics are shown in Table 1. Except for administration of surfactant via LISA,

no significant differences were seen between survivors and neonates who died.

Overall, 37% (22/59) of live-born infants survived. Excluding patients who received primary palliative care, this corresponds to an overall survival rate of 42% (22/52). Survival rate was 20% (2/10) ≤ 400 g birth weight and 48% (20/42) in infants 401–500 g ($p = 0.107$).

The median time to death among treated infants was two (IQR 0.5–4.2) days. The majority of 24 patients (80%) died despite maximum intensive care. In four patients (13%), therapy was withdrawn due to severe complications including high-grade IVH (2x death day of life 1, 1x day 2 and 1x day 37), and two (7%) died on day of life 1 and were not submitted to full respiratory resuscitation based on initial presentation, thus, the full potential of intensive care was not offered.

Regarding obstetric data, 49 infants (94%) received antenatal steroids, and 39 (75%) were delivered by C-section, only three (6%) by emergency C-section. Regarding neonatal data, all surviving infants received surfactant via LISA immediately after birth, which was significantly more often than in non-survivors (Table 1).

3.2 | Short-term outcome

Short-term morbidities in survivors and details on discharge are shown in Table 2. At least one severe morbidity was present in 17 survivors (77%). Thus, only five patients (23%) showed no severe morbidity, while 11 (50%) showed one, four (18%) two and two (9%) three severe morbidities. The most common severe morbidity seen in 62% of surviving neonates was BPD.

Median weight, length and head circumference were below the 10th percentile at discharge.

3.3 | Long-term outcome at two years corrected age

Neurodevelopmental follow-up was available for 20 survivors (91%) (Table 3). The remaining two were lost to follow-up as they moved to another country. The majority of 27 patients (68%) was tested using Bayley-III, the remaining 13 (33%) using BSID II. Mental development was normal or mildly abnormal in 10 infants (50%) and moderately or severely abnormal in 10 (50%); the median score was 72. Motor development was normal or mildly abnormal in 15 infants (75%) and moderately or severely abnormal in five (25%); the median score was 80. Regarding both outcome subcategories, 9 neonates (45%) showed a favourable outcome. Median subscores obtained using Bayley-III were generally higher when using American compared to German norms: cognitive 90 versus 70, language 86 versus 75 and motor 85 versus 76.

Growth assessment from birth until 2 years is provided in Figure 1. As shown, poor growth until discharge can be observed. However, the percentage of patients in the lowest percentile groups

TABLE 1 Maternal and neonatal data.

	Entire study group n = 52	Survived n = 22	Died n = 30	p-value
Age at birth (years)*	30.6 (26.3–34.7)	29.2 (22.4–34.8)	31.2 (27.2–35.0)	ns
Hypertensive disorders of pregnancy	13 (25%)	5 (23%)	8 (27%)	ns
Preterm labour	28 (54%)	11 (50%)	17 (57%)	ns
Cervical insufficiency	18 (35%)	8 (36%)	10 (33%)	ns
Placental insufficiency	20 (38%)	7 (32%)	13 (43%)	ns
Placental abruption	2 (4%)	2 (9%)	0 (0%)	ns
Foetal distress	14 (27%)	6 (27%)	8 (27%)	ns
Preterm premature rupture of the membranes	16 (31%)	7 (32%)	9 (30%)	ns
Days before birth*	6 (2–17)	3 (1–15)	9 (3–24)	
GA at pPROM (weeks)*	23 ^{0/7} (21 ^{5/7} -23 ^{2/7})	23 ^{0/7} (22 ^{6/7} -23 ^{4/7})	22 ^{6/7} (20 ^{6/7} -23 ^{2/7})	
Antenatal steroids				ns
Yes	49 (94%)	22 (100%)	27 (90%)	
No	3 (6%)	0 (0%)	3 (10%)	
Type of delivery				ns
Vaginal delivery	13 (25%)	3 (14%)	10 (33%)	
C-section	39 (75%)	19 (86%)	20 (67%)	
GA at birth (weeks) [#]	24 ^{0/7} (23 ^{0/7} -29 ^{3/7})	24 ^{3/7} (23 ^{0/7} -29 ^{3/7})	23 ^{6/7} (23 ^{0/7} -29 ^{2/7})	ns
Birth weight (grams) [#]	453 (318–500)	475 (380–500)	443 (318–500)	ns
≤400 g	10 (19%)	2 (9%)	8 (27%)	
401–500 g	42 (81%)	20 (91%)	22 (73%)	
Birth weight percentile*	2 (1–8)	4 (1–14)	2 (1–7)	ns
Birth length percentile*	10 (1–47)	16 (1–37)	7 (1–48)	ns
Head circumference percentile*	9 (4–28)	17 (8–30)	9 (2–28)	ns
Male	19 (37%)	7 (32%)	12 (40%)	ns
Multiples	14 (27%)	4 (18%)	10 (33%)	ns
Twin to twin transfusion syndrome	4 (29%)	2 (50%)	2 (20%)	
APGAR score at 1 min*	6 (4–7)	7 (6–8)	6 (4–7)	ns
APGAR score at 5 min*	8 (7–9)	8 (8–9)	8 (6–9)	ns
APGAR score at 10 min*	9 (8–9)	9 (9–9)	9 (8–9)	ns
Umbilical artery pH*	7.29 (7.20–7.38)	7.32 (7.22–7.38)	7.28 (7.17–7.33)	ns
Surfactant received	51 (98%)	22 (100%)	29 (97%)	ns
Surfactant via LISA ¹⁷	45 (87%)	22 (100%)	23 (77%)	0.015

Data are shown as n (%), as median (IQR)* or median (range)[#]; p-values were calculated using Mann–Whitney U test and chi-square test; surfactant received refers to time immediately after birth.

Abbreviations: GA, gestational age; LISA, less invasive surfactant administration; pPROM, preterm premature rupture of the membranes.

decreases up to two years corresponding to a compensatory growth especially for weight and length. Assessing visual ability, 17 survivors (85%) showed no impairment while 3 (15%) had myopia requiring corrective lenses. Hearing ability was normal in all survivors. Cerebral palsy was present in six patients (30%), with a median GMFCS level of 1 (IQR 1–2). Only two neonates (10%) were classified as GMFCS level 2, none as level 3 or above. Finally, significant neurodevelopmental impairment was present in 13 survivors (65%) and profound impairment in 5 (25%).

4 | DISCUSSION

Infants born at or below 500 g are rare, even in high volume tertiary perinatal centres, making outcome prediction difficult.⁸ In our study, the survival rate for preterm infants born ≤500 g and ≥23 weeks receiving standardised institutional care after birth was 37% for all live births and 42% for all NICU admissions. In the literature, reported survival rates in this high-risk population range from 21 to 80%.^{5–15}

TABLE 2 Short-term outcome in survivors.

<i>Morbidities</i>	
Severe brain injury	3 (14%)
Severe IVH	2 (9%)
Cystic PVL	1 (5%)
PDA with surgical intervention	7 (32%)
NEC with surgical intervention	1 (5%)
Intestinal perforation	2 (9%)
BPD	13 (62%)
ROP with intervention	8 (36%)
<i>Discharge in detail</i>	
Day of life*	116 (99–134)
GA (weeks)*	40 ^{3/7} (38 ^{5/7} –44 ^{0/7})
Weight (grams)*	2673 (2200–3210)
Length (cm)*	45 (42–48)
Head circumference (cm)*	32 (30–33)
Weight percentile*	4 (0–10)
Length percentile*	0 (0–2)
Head circumference percentile*	1 (0–3)

Data are shown as n (%) or median (IQR)*; for morbidity definitions see section *Methods, Short-term outcome*.

Abbreviations: BPD, bronchopulmonary dysplasia; GA, gestational age; IVH, intraventricular haemorrhage; NEC, necrotising enterocolitis; PDA, persistent ductus arteriosus; PVL, periventricular leukomalacia; ROP, retinopathy of prematurity.

Our general approach for this high-risk cohort of fragile neonates is proactive starting at 23 weeks. This attitude is reflected by our obstetric management with a 94% rate of antenatal steroids and a 75% rate of C sections in the presented group. Data derived from the California Perinatal Quality Care Collaborative indicated lower rates of 42–44% both for antenatal steroids and C-section.⁸ The authors still stated a positive association of survival with antenatal steroids and C-section in these profoundly low birth weight infants without proof of causality.⁸ Many centres with high survival rates believe that proactive care of infants close to viability thresholds starting already before birth leads to improvements in prognosis.¹² Our rate of proactive postnatal treatment and hence the rate of NICU admission was high with 88% of all live-born infants. Apart from Japanese reports with treatment rates up to 100%,^{11,12} all other reports revealed considerably lower rates ranging from 12 to 78%.^{5–7,9,13,15} This might in part explain the pronounced difference in reported survival rates.¹⁵ A critical discussion about the denominator bias seems reasonable since selection bias may limit the comparability of different study results. Even more, it remains unclear in most reports whether parental decision after prenatal counselling, socio-cultural norms or local clinical practices was responsible for the decision not to offer treatment in individual patients.

TABLE 3 Neurodevelopmental outcome at 2 years corrected age in survivors.

Corrected age (months)*	24.1 (23.8–24.3)
Mental outcome*	72 (53–91)
≥85	6 (30%)
84–70	4 (20%)
69–55	5 (25%)
<55	5 (25%)
Motor outcome*	80 (68–92)
≥85	8 (40%)
84–70	7 (35%)
69–55	3 (15%)
<55	2 (10%)
Visual impairment	3 (15%)
Hearing impairment	0 (0%)
Cerebral palsy	6 (30%)
GMFCS level 1	4 (20%)
GMFCS level 2	2 (10%)
GMFCS level ≥3	0 (0%)

Data are shown as n (%) or median (IQR)*; mental and motor development were evaluated using Bayley Scales of Infant Development.

Abbreviation: GMFCS, Gross Motor Function Classification System.²⁵

Furthermore, the definition of death in delivery room needs clarification. Some centres choose to initially stabilise and treat patients in the delivery room and only admit them to the NICU if further care is indicated. Therefore, differences in local infrastructure may cause a bias by neglecting live births with insufficient stabilisation in the delivery room.¹⁶

Our centre admits all patients to the NICU, including those who could not successfully be resuscitated, thus, survival data will reflect a higher mortality rate. Only seven patients all born at 23 weeks of GA received palliative care in the delivery room based on the declared parental request. This seems to be a relevant factor determining survival rate, as a meta-analysis of 65 studies regarding survival in extremely preterm infants delineates separate survival rates for all births, live births and NICU admissions.⁴ Data from a large cohort of profoundly small for GA and extremely low birth weight neonates revealed >50% mortality for infants born <500 g in the delivery room prior to NICU admission, and the highest mortality during the first 12 hours of life.⁸ Also, thresholds for initiation, continuation or discontinuation of life support vary between studies, epochs and countries.⁴ Future studies should take into account and report the outcome of all pregnancies by including terminations, miscarriages, stillbirths and all live births, separately for each gestational week.¹⁶

Our cohort included neonates between 23^{0/7} and 29^{3/7} weeks of GA. Most other published reports of preterm infants <500 g include infants born at 22 weeks. Systematic survival of infants at 22 weeks is well documented in neonatal networks with survival rates of up

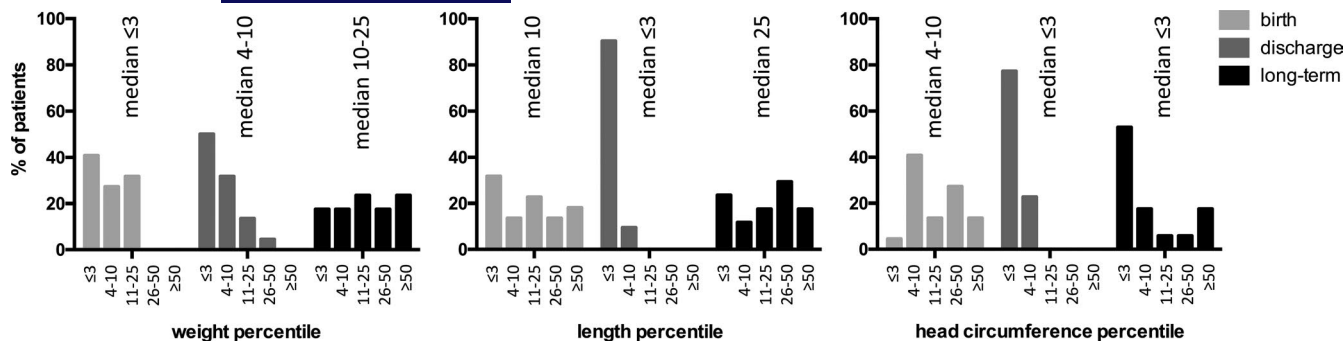


FIGURE 1 Growth assessment from birth until two years corrected age. Percentage given shows % of patients for the respective percentile group; values at the top of the figure represent median percentile at given age.

to 30–36% among live births.^{1,26} Hence, the cut-off for offering treatment in our cohort is arbitrary and under on-going discussion in Austria, and since 2020 resuscitation was initiated also below 23 weeks of GA in some cases.

With regard to GA, a meta-analysis of 65 studies revealed a increase in mean survival rates as well as mean chance of survival without impairment with increasing GA.⁴ This study was published by Myrhaug et al in 2019 and evaluated neonates between 22^{0/7} and 27^{6/7} weeks of GA. Similarly, Nagara et al showed a 2.8-fold increased risk of mortality per 1-week decrease in GA¹² which was confirmed by increasing survival for more mature babies in another study.⁹ Due to low numbers of patients born above 25 week, we were not able to confirm a decreased risk of mortality with increasing GA in our cohort.

Advances in perinatal and neonatal medicine led to higher survival rates of infants born ≤500 g in Japan (from 40% in 2003 to 68% in 2012), but did not decrease the high rate of major morbidities, in survivors (81–89%).¹¹ Similarly, 77% of survivors in our study experienced at least one severe short-term morbidity. Therefore, the collection of data on long-term neurodevelopment outcome of these high-risk infants is essential. Half of studied neonates had a favourable mental and three-quarter a favourable motor outcome. In the literature, normal development is reported in a quarter to one-third of survivors,^{5,12,15} and survival without severe neurodevelopmental disability ranges from 27 to 71%.^{5,12,13,15,27} Another factor possibly contributing to developmental delay might be the missing compensatory growth of head circumference until two years corrected age.

Bayley-III data were analysed both with German and American norms to emphasise the differences. We were previously able to show that German norms using Bayley-III do not overestimate performance and underestimate developmental delay to the same extent as American norms and therefore, data obtained using German Bayley-III is comparable to German BSID II.²⁸ The present data confirm these findings and show a difference with median scores 9–20 points higher when using American compared to German norms. This has to be taken into account when comparing reported long-term testing from different countries.

The strengths of our study were the comparably high follow-up rate of 91% including growth assessment and the comparison

between German and American norms regarding outcome. The number of treated neonates can be regarded as a limitation of our study but is due to this rare condition even in high volume centres. An additional limitation was the age at neurodevelopmental testing. The evaluation of long-term follow-up shortly before school age might give more meaningful results regarding the long-term performance of those infants.

5 | CONCLUSION

The imminent delivery of a periviable neonate presents a multitude of difficult and complex ethical issues and represents a controversial and emotionally charged area in perinatology.⁵ In the grey zone of viability, evidence-based data are required to guide prenatal counselling and allow for informed shared decision-making processes with parents. To avoid bias of data interpretation, examination of the entire data set including at least all live births regardless of proactive or palliative care as well as those dying in the delivery room after insufficient stabilisation is essential.

In our study population, there was a considerable risk of death or impairment in this cohort of high-risk infants. Nevertheless, 37% of all live births and 42% of patients with treatment survived, and more than one-third of survivors showed no major impairment at 2 years corrected age.

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CONFLICTS OF INTEREST

The authors have no conflicts of interest relevant to this article to disclose.

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REFERENCES

- Ishii N, Kono Y, Yonemoto N, Kusuda S, Fujimura M. Neonatal research network, Japan. Outcomes of infants born at 22 and 23 weeks' gestation. *Pediatrics*. 2013;132:62-71.
- Stoll BJ, Hansen NI, Bell EF, et al. Neonatal outcomes of extremely preterm infants from the NICHD Neonatal Research Network. *Pediatrics*. 2010;126:443-456.
- Younge N, Goldstein RF, Cotten CM. Eunice Kennedy Shriver National Institute of Child Health and Human Development Neonatal Research Network. Survival and neurodevelopment of periviable infants. *N Engl J Med*. 2017;376:1890-1891.
- Myrhaug HT, Brurberg KG, Hov L, Markestad T. Survival and impairment of extremely premature infants: a meta-analysis. *Pediatrics*. 2019;143:e20180933.
- Upadhyay K, Pourcyrus M, Dhanireddy R, Talati AJ. Outcomes of neonates with birth weight \leq 500 g: a 20-year experience. *J Perinatol Off J Calif Perinat Assoc*. 2015;35:768-772.
- Lucey JF, Rowan CA, Shiono P, et al. Fetal infants: the fate of 4172 infants with birth weights of 401 to 500 grams - the Vermont Oxford Network experience (1996-2000). *Pediatrics*. 2004;113:1559-1566.
- Hsieh W, Jeng S, Hung Y, Chen P, Chou H, Tsao P. Outcome and hospital cost for infants weighing less than 500 grams: a tertiary centre experience in Taiwan. *J Paediatr Child Health*. 2007;43:627-631.
- Griffin IJ, Lee HC, Profit J, Tancedi DJ. The smallest of the small: short-term outcomes of profoundly growth restricted and profoundly low birth weight preterm infants. *J Perinatol Off J Calif Perinat Assoc*. 2015;35:503-510.
- Gillone J, Banait N, Miller N, Ward Platt M, Harigopal S. Outcomes of infants with a birthweight less than or equal to 500 g in Northern England: 15 years experience. *Acta Paediatr Oslo Nor*. 1992;2018(107):223-226.
- Jeschke E, Biermann A, Günster C, et al. Mortality and major morbidity of very-low-birth-weight infants in Germany 2008-2012: a report based on administrative data. *Front Pediatr*. 2016;4:23.
- Inoue H, Ochiai M, Yasuoka K, et al. Early mortality and morbidity in infants with birth weight of 500 grams or less in Japan. *J Pediatr*. 2017;190:112-117.e3.
- Nagara S, Kouwaki M, Togawa T, Sugiura T, Okada M, Koyama N. Neurodevelopmental outcomes at 3 years old for infants with birth weights under 500 g. *Pediatr Neonatol*. 2018;59:274-280.
- Keir A, McPhee A, Wilkinson D. Beyond the borderline: outcomes for inborn infants born at \leq 500 grams. *J Paediatr Child Health*. 2014;50:146-152.
- Pedley ML, Brown K, Scorrer TJ, Chowdhury O. Outcome of infants with birth weight less than 500 grams in a tertiary neonatal unit (PC.06). *Arch Dis Child - Fetal Neonatal Ed*. 2014;99:A38.
- Rieger-Fackeldey E, Blank C, Dinger J, Steinmacher J, Bode H, Schulze A. Growth, neurological and cognitive development in infants with a birthweight $<$ 501 g at age 5 years. *Acta Paediatr Oslo Nor*. 1992;2010(99):1350-1355.
- Evans DJ, Levene MI. Evidence of selection bias in preterm survival studies: a systematic review. *Arch Dis Child Fetal Neonatal Ed*. 2001;84:F79-84.
- Klebermass-Schrehof K, Wald M, Schwindt J, et al. Less invasive surfactant administration in extremely preterm infants: impact on mortality and morbidity. *Neonatology*. 2013;103:252-258.
- Österreichische Gesellschaft für Kinder- und Jugendheilkunde (ÖGKJ), Institut für Ethik und Recht in der Medizin der Universität Wien (IERM). Erstversorgung von Frühgeborenen an der Grenze der Lebensfähigkeit. Leitlinie der Arbeitsgruppe Neonatologie und pädiatrische Intensivmedizin und der Arbeitsgruppe Ethik. 2005;153:711-715.
- Berger A, Kiechl-Kohlendorfer U, Berger J, et al. Update: Erstversorgung von Frühgeborenen an der Grenze der Lebensfähigkeit. *Monatsschr Kinderheilkd*. 2019;167:36-45.
- Wald M, Kribs A, Jeitler V, Lirsch D, Pollak A, Kirchner L. Variety of expiratory resistance between different continuous positive airway pressure devices for preterm infants. *Artif Organs*. 2011;35:22-28.
- Volpe JJ. *Neurology of the Newborn*. Elsevier Health Sciences. 2008;1109 p.
- de Vries LS, Eken P, Dubowitz LM. The spectrum of leukomalacia using cranial ultrasound. *iBehav. Brain Res*. 1992;49(1):1-6.
- Bell M, Ternberg J, Feigin R, et al. Neonatal necrotizing enterocolitis. Therapeutic decisions based upon clinical staging. *Ann Surg*. 1978;187:1-7.
- International Committee for the Classification of Retinopathy of Prematurity. The International Classification of Retinopathy of Prematurity revisited. *Arch Ophthalmol Chic Ill* 1960. 2005;123:991-999.
- Palisano R, Rosenbaum P, Bartlett D, Livingston M. Content validity of the expanded and revised gross motor function classification system. *Dev Med Child Neurol*. 2008;50(10):744-750.
- Norman MG, O'Kusky JR. The growth and development of microvasculature in human cerebral cortex. *J Neuropathol Exp Neurol*. 1986;45:222-232.
- Bashir RA, Thomas JP, MacKay M, et al. Survival, short-term, and long-term morbidities of neonates with birth weight $<$ 500 g. *Am J Perinatol*. 2017;34:1333-1339.
- Fuiko R, Oberleitner-Leeb C, Klebermass-Schrehof K, Berger A, Brandstetter S, Giordano V. The impact of norms on the outcome of children born very-preterm when using the Bayley-III: differences between US and German norms. *Neonatology*. 2019;116:29-36.

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