National cohort of infants born before 24 gestational weeks showed increased survival rates but no improvement in neonatal morbidity

Downloaded from: https://research.chalmers.se, 2022-08-25 09:13 UTC

Citation for the original published paper (version of record):
Lundgren, P., Morsing, E., Hård, A. et al (2022). National cohort of infants born before 24 gestational weeks showed increased survival rates but no improvement in neonatal morbidity. Acta Paediatrica, International Journal of Paediatrics, In Press. http://dx.doi.org/10.1111/apa.16354

N.B. When citing this work, cite the original published paper.
National cohort of infants born before 24 gestational weeks showed increased survival rates but no improvement in neonatal morbidity

Pia Lundgren1 | Eva Morsing2 | Anna-Lena Hård1 | Alexander Rakow3 | Lena Hellström-Westas4 | Lena Jacobson1,5 | Mats Johnson6 | Gerd Holmström7 | Staffan Nilsson8,9 | Lois E. Smith10 | Karin Sävman11,12 | Ann Hellström1

1The Sahlgrenska Centre for Pediatric Ophthalmology Research, Department of Clinical Neuroscience, Institute of Neuroscience and Physiology, Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden
2Department of Pediatrics, Clinical Sciences Lund, Lund University, Lund, Sweden
3Department of Women’s and Children’s Health, Karolinska Institutet and Karolinska University Hospital, Stockholm, Sweden
4Department of Women’s and Children’s Health, Uppsala University, Uppsala, Sweden
5Division of Eye and Vision, Department of Clinical Neuroscience, Karolinska Institutet and Karolinska University Hospital, Stockholm, Sweden
6Gillberg Neuropsychiatry Centre, Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden
7Department of Surgical Sciences/Opthalmology, Uppsala University, Uppsala, Sweden
8Mathematical Sciences, Chalmers University of Technology, Gothenburg, Sweden
9Institute of Biomedicine, Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden
10Department of Ophthalmology, Boston Children’s Hospital, Harvard Medical School, Boston, Massachusetts, USA
11Region Västra Götaland, Department of Neonatology, The Queen Silvia Children’s Hospital, Sahlgrenska University Hospital, Gothenburg, Sweden
12Institute of Neuroscience and Physiology, Department of Psychiatry and Neurochemistry, Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden

Correspondence
Pia Lundgren, Department of Ophthalmology, Institute of Neuroscience and Physiology, Sahlgrenska Academy, University of Gothenburg, S-416 85 Gothenburg, Sweden.
Email: pia.lundgren@gu.se

Funding information
This study was supported by the Swedish Medical Research Council #2020-01092#, The Gothenburg Medical Society and Government grants under the ALF agreement ALFGBG-717971, De Blindas Vänner, Knut and Alice Wallenberg Clinical Scholars, NIH EY017017, EY020904 and BCH IDSRC (1U54HD090255 Massachusetts Lions Eye Foundation). The funders played no role in any aspect of the study.

Abstract
Aim: To describe survival and neonatal morbidities in infants born before 24 weeks of gestation during a 12-year period.
Methods: Data were retrieved from national registries and validated in medical files of infants born before 24 weeks of gestation 2007–2018 in Sweden. Temporal changes were evaluated.
Results: In 2007–2018, 282 live births were recorded at 22 weeks and 460 at 23 weeks of gestation. Survival to discharge from hospital of infants born alive at 22 and 23 weeks increased from 20% to 38% (p = 0.006) and from 45% to 67% (p < 0.001) respectively. Caesarean section increased from 12% to 22% (p = 0.038) for infants born at 22 weeks. Neonatal morbidity rates in infants alive at 40 weeks of postmenstrual age (n = 399) were unchanged except for an increase in necrotising enterocolitis from 0 to 33% (p = 0.017) in infants born at 22 weeks of gestation.

Abbreviations: BPD, bronchopulmonary dysplasia; CI, confidence interval; EXPRESS, Extremely Preterm Infants in Sweden study; IVH, intraventricular haemorrhage; NEC, necrotising enterocolitis; OR, odds ratio; PDA, patent ductus arteriosus; ROP, retinopathy of prematurity; SDS, standard deviation score; SWEDROP, Swedish National Registry for ROP.
The survival of extremely preterm infants has changed remarkably during the last two decades. Infants born at 22 weeks of gestation can now survive due to medical advances. Whether or not to initiate intensive care for the most immature infants is controversial. Guidelines for active interventions and resuscitation vary among centres and countries, reflected in survival rates and outcomes. Sweden has a tradition of an active approach when managing extremely preterm births, although regionally different management policies have existed reflected in differences in increased survival rates. The more proactive approach at extremely preterm birth in the north of Sweden included a higher degree of centralised management, liberal use of antenatal corticosteroids, higher Caesarean section rates and active resuscitation of infants with very low birth weight or very short gestational length. The Extremely Preterm Infants in Sweden study (EXPRESS) in 2004–2007 confirmed higher survival rates for infants born before 25 weeks of gestation in centres with proactive obstetric and neonatal interventions. And a follow-up EXPRESS study reported 1-year survival rates of 30% and 61%, respectively, for live-born infants born at 22 and 23 weeks in 2012–2016. Based on these findings, Swedish obstetricians and gynaecologists agreed on national guidelines in 2016 which suggested that neonatal resuscitation should be considered from 22 weeks and recommended from 23 weeks. Extremely preterm infants are at high risk of neonatal morbidities such as bronchopulmonary dysplasia (BPD), intraventricular haemorrhage (IVH), necrotising enterocolitis (NEC) and retinopathy of prematurity (ROP). It is not clear whether medical advances in neonatal care reduced morbidity in infants born before 24 weeks of gestation. Even in large cohort studies, the number of included infants born so early is often low, which may have affected reported outcomes. 

Survival rates at birth, at 24 h of age and at the time of discharge from hospital were reported. In addition, the number of infants alive at 40 weeks of postmenstrual age was reported.
2.3 | Maternal, pregnancy and birth characteristic

Data on maternal and pregnancy characteristics were retrieved, including maternal age, parity, assisted fertilisation, multiple births, at least one dose of antenatal steroids and mode of delivery. Gestational age had been determined by ultrasound at 17–18 weeks of gestation. Infant birth weight and gender were retrieved, and birth weight standard deviation scores (SDS) were calculated. Being small for gestational age was defined as having a birth weight SDS < -2.

2.4 | Severe neonatal morbidities

The evaluated morbidities included ROP, which was classified and treated according to current guidelines. For IVH, Papile's grading system had been used. Periventricular leukomalacia and hydrocephalus requiring a reservoir and/or shunt had been diagnosed using cranial ultrasound. For a diagnosis of septicaemia, clinical symptoms, a positive blood culture and a C-reactive protein level > 5 mg/L were required. NEC was defined according to Bell et al. Persistent pulmonary hypertension and patent ductus arteriosus (PDA) were diagnosed by a cardiologist using echocardiography and surgical treatments for PDA were recorded. BPD had been diagnosed if the infant required supplemental oxygen at 36 weeks of postmenstrual age. Days of oxygen treatment, including days with mechanical ventilation or continuous positive airway pressure, were recorded as well as days of hospital care before discharge.

2.5 | Statistical analysis

Numbers and percentages are given for categorical variables, and mean and standard deviations for continuous variables. Data are presented in periods of 3 years: 2007–2009, 2010–2012, 2013–2015 and 2016–2018. Logistic regression was used for dichotomous outcomes and linear regression for continuous outcomes to investigate temporal trends.

**FIGURE 1** Flowchart of the study population
with the calendar year as the predictor. For linear regression, residuals were examined to justify the model assumptions. The logistic model fit was tested with the Hosmer–Lemeshow test, and when the model fit was accepted, odds ratios (ORs) for the whole 12-year period were presented. If the model was rejected, the four 3-year periods were used as a categorical predictor and OR presented between 2016–2018 and 2007–2009. The change for the whole study period was presented for the linear regression. We used Pearson's Chi-square test or Fisher's exact test for categorical variables, Mann–Whitney U test or Students T-test for continuous variables to compare the two gestational age groups. We excluded 2007–2009 in statistical trend analyses of live-born infants since it was not mandatory to report stillbirths born at less than 28 weeks until 2008. The significance level was set to 0.05. Statistical analysis was performed using SPSS version 27 (IBM corp.).

3 | RESULTS

3.1 | Survival rates

We identified 1206 infants born before 24 weeks of gestation in Sweden in 2007–2018: 282 were born alive at 22 weeks, and 460 at 23 weeks. A flowchart of the study population is presented in Figure 1. An increasing percentage of infants born at 22 weeks was registered as live-born over time. Survival as live-born discharged from hospital to home increased from 20% to 38% ($p = 0.006$) in infants born at 22 weeks and from 45% to 67% ($p < 0.001$) in infants born at 23 weeks. Survival to discharge for infants born at 22 weeks almost doubled from 20% in 2013–2015 to 38% in 2016–2018 (Table 1, Table S1). The number of infants born before 24 weeks who were alive at 40 weeks of postmenstrual age increased by 51% from 2007–2009 to 2016–2018 (Figure 2a).

3.2 | Perinatal characteristics and infants characteristics

Maternal, pregnancy and infant characteristics in 399 infants who survived to approximately 40 weeks of postmenstrual age presented in Table 2 and Table S2. Two infants born at 21 weeks survived to 40 weeks of postmenstrual age. Caesarean section rate increased over the study period ($p = 0.029$) and infants born at 22 weeks of gestation were less often delivered by Caesarean section than infants born at 23 weeks (12% vs. 27%; $p = 0.003$).

3.3 | Neonatal diagnoses

Of the whole cohort, 90% had PDA, 50% had PDA ligation and 86% had BPD. Persistent pulmonary hypertension of the newborn

TABLE 1 Survival among infants born at 22–23 weeks of gestation 2007–2018 in Sweden and trends for calendar years stratified in gestational age groups

| Infants born at 22 weeks of gestation | 2007–2009 | 2010–2012 | 2013–2015 | 2016–2018 | Change (95% CI) | p-value |
|-------------------------------------|-----------|-----------|-----------|-----------|----------------|---------|
| All deliveries | | | | | | |
| Live-born infants of total births, No (%) | 49/89 (55%) | 57/130 (44%) | 94/150 (63%) | 82/143 (57%) | 2.85 (1.21–6.73) | 0.017 |
| Live-born | | | | | | |
| Survival of live-born infants to 24 h, No (%) | 19/49 (39%) | 19/57 (33%) | 40/94 (43%) | 50/82 (61%) | 4.10 (1.73–9.70) | 0.001 |
| Survival of live-born infants to discharge home, No (%) | 10/49 (20%) | 11/57 (19%) | 19/94 (20%) | 31/82 (38%) | 4.11 (1.49–11.36) | 0.006 |

| Infants born at 23 weeks of gestation | 2007–2009 | 2010–2012 | 2013–2015 | 2016–2018 | OR (95% CI) | p-value |
|-------------------------------------|-----------|-----------|-----------|-----------|-------------|---------|
| All deliveries | | | | | | |
| Live-born infants of total births, No (%) | 108/141 (77%) | 100/165 (61%) | 133/200 (66%) | 119/188 (63%) | 0.99 (0.46–2.12) | 0.98 |
| Live-born | | | | | | |
| Survival of live-born infants to 24 h, No (%) | 82/108 (76%) | 82/100 (82%) | 117/133 (88%) | 102/119 (86%) | 2.65 (1.20–5.88) | 0.016 |
| Survival of live-born infants to discharge home, No (%) | 49/108 (45%) | 45/100 (45%) | 73/133 (55%) | 80/119 (67%) | 3.03 (1.66–5.55) | <0.001 |

Note: ORs are presented for the whole study period.
Abbreviations: CI, confidence interval; OR, odds ratio.
*Not included in trend analysis.
Bold values are significant values (<.05).
was diagnosed in 18%. Details of ROP development and treatment modality have been previously published. NEC had been diagnosed in 21% and 14% had undergone surgery for NEC. IVH occurred in 51% and severe IVH grades 3–4 in 17% (Table S3). BPD was more common, and IVH grades 3–4 was less frequent in infants born at 22 weeks than in infants born at 23 weeks (Table 3, Figure 2b). BPD was more common in boys than in girls (90% vs. 82%; p = 0.044).

For most neonatal morbidities, there were no changes over time. However, NEC, conservatively and surgically treated, increased from 0% to 33% (p = 0.017) in infants born at 22 weeks. PDA ligation decreased over time (p < 0.001). Days of inpatient care before discharge from hospital increased from a mean of 142 to 164 days (p = 0.032). Neonatal morbidities in all infants and stratified by gestational age groups, and over time are presented in Table 3, Table S3, and Figure S1. In Table S4, we present results of neonatal morbidities.
TABLE 2 Maternal and infant characteristics of infants born before 24 weeks of gestation and surviving to 40 weeks postmenstrual age 2007-2018 in Sweden and temporal trends for calendar year stratified by gestational age groups

### Infants born at 22 weeks of gestation

|                         | 2007–2018 (n = 98) | 2007–2009 (n = 13) | 2010–2012 (n = 19) | 2013–2015 (n = 27) | 2016–2018 (n = 39) | OR (95% CI) | Change (95% CI) | p-value |
|-------------------------|--------------------|--------------------|--------------------|--------------------|--------------------|-------------|-----------------|---------|
| **Maternal characteristics** |                    |                    |                    |                    |                    |             |                 |         |
| Maternal age, years, mean (SD) | 31 (6)            | 30 (7)             | 31 (7)             | 30 (6)             | 31 (6)             | 2.20 (−2.45–6.84) | 0.35               |         |
| Primipara, No (%) | 52/90 (58%)      | 7/11 (64%)         | 14/18 (78%)        | 17/26 (65%)        | 14/35 (40%)        | 0.19 (0.04–0.97) | 0.045              |         |
| Assisted fertilisation, No (%) | 11/61 (18%) | 0/11 (0%)      | 3/14 (21%)         | 5/15 (33%)         | 3/23 (13%)         | 1.12 (0.12–0.68) | 0.045              |         |
| Antenatal steroids, No (%) | 56/64 (88%) | 8/8 (100%)      | 7/10 (70%)         | 21/24 (88%)        | 20/22 (91%)        | 1.49 (0.10–23) | 0.77               |         |
| Caesarean section, No (%) | 11/93 (12%)** | 0/11 (0%)      | 2/18 (11%)         | 1/27 (4%)          | 8/37 (22%)         | 35 (1.23–1009) | 0.038              |         |

### Infant characteristics

| Birth weight, mean (SD) | 500*** (61) | 565 (78) | 508 (76) | 498 (64) | 497 (57) | −67 (−114–20) | 0.005          |         |
| Gestational age weeks, mean (SDS) | 22.6*** (0.3) | 22.6 (0.2) | 22.6 (0.3) | 22.6 (0.2) | 22.6 (0.2) | −0.17 (−0.19–0.15) | 0.84            |         |
| SDS birth weight, mean (SD) | −0.35 (0.94) | 0.43 (1.50) | −0.25 (1.05) | −0.37 (0.91) | −0.40 (0.86) | −0.85 (−1.57–0.13) | 0.021          |         |
| Small for gestational age, No (%) | 2/97 (2%) | 1/13 (8%) | 1/19 (5%) | 0/27 (0%) | 1/39 (3%) | 0.01 (0–3.86) | 0.14            |         |
| Gender (female), No (%) | 46/98 (47%) | 5/13 (38%) | 10/19 (53%) | 14/27 (52%) | 17/39 (44%) | 0.78 (0.20–3.07) | 0.72            |         |
| Twins, No (%) | 17/98 (17%) | 1/13 (8%) | 3/19 (16%) | 6/27 (22%) | 7/39 (18%) | 1.45 (0.23–9.24) | 0.69            |         |

### Infants born at 23 weeks of gestation

|                         | 2007–2018 (n = 301) | 2007–2009 (n = 69) | 2010–2012 (n = 58) | 2013–2015 (n = 89) | 2016–2018 (n = 85) | OR (95% CI) | Change (95% CI) | p-value |
|-------------------------|--------------------|--------------------|--------------------|--------------------|--------------------|-------------|-----------------|---------|
| **Maternal characteristics** |                    |                    |                    |                    |                    |             |                 |         |
| Maternal age, years, mean (SD) | 31 (6)            | 32 (6)             | 32 (6)             | 30 (6)             | 30 (6)             | −2.72 (−4.90–0.54) | 0.015              |         |
| Primipara, No (%) | 176/277 (64%)      | 46/64 (72%)        | 34/49 (69%)        | 49/83 (59%)        | 47/81 (58%)        | 0.34 (0.15–0.77) | 0.009              |         |
| Assisted fertilisation, No (%) | 33/204 (16%) | 6/63 (10%)      | 6/45 (13%)         | 9/48 (19%)         | 12/47 (25%)        | 3.62 (1.09–12) | 0.036              |         |
| Antenatal steroids, No (%) | 171/182 (94%) | 46/48 (96%)      | 24/27 (89%)        | 47/51 (92%)        | 54/56 (96%)        | 1.52 (0.25–9.41) | 0.65               |         |
| Caesarean section, No (%) | 77/288** (27%) | 17/67 (25%) | 12/55 (22%)        | 28/84 (33%)        | 20/82 (24%)        | 2.37 (1.00–5.58) | 0.049              |         |

### Infant characteristics

| Birth weight, mean (SD) | 585*** (87) | 585 (74) | 589 (100) | 585 (71) | 583 (73) | −7.96 (−36–20) | 0.58            |         |
| Gestational age weeks, mean (SDS) | 23.5*** (0.3) | 23.5 (0.3) | 23.5 (0.3) | 23.5 (0.3) | 23.5 (0.3) | 0 (−0.10–0.10) | 0.99            |         |
DISCUSSION

4.1 Main findings

This study found increased survival with no improvement in severe neonatal morbidity for extremely preterm infants born before 24 gestational weeks in Sweden, 2007–2018. The absolute number of infants surviving to 40 weeks of postmenstrual age doubled over time.

4.2 Survival

This study confirms increased survival rates for infants born before 24 weeks during the last decade in Sweden. In 2016–2018, 38% of infants born alive at 22 weeks and 67% of those born alive at 23 weeks survived to discharge compared to 20% and 45%, respectively, in 2007–2009. Since 2016, Swedish national guidelines have suggested that neonatal resuscitation should be considered from 22 weeks and recommended from 23 weeks of gestation. Increased survival of infants born at 22 weeks was especially pronounced from 2016 when new Swedish recommendations were implemented. The increased Caesarean section rates may also reflect these new guidelines.

Several studies have reported increased survival in hospitals with an active life-saving approach compared with comfort care after birth in infants born before 24 weeks of gestation.

4.3 Comparison with survival rates in other studies

Comparisons with survival rates in other studies were problematic as birth registration practices, definitions of stillborns and clinicians’ willingness to give active care influenced the results. Population-based studies in Sweden, England and France have reported wide variations in survival during labour and the first hours and days of life. Survival to 112 days for infants born at 22–23 weeks of gestation was 28%, 11% and 0.5% in each respective country. In a review from 2020, Franzcal et al. reported survival rates for infants receiving intensive care from 0% to 36% in infants born at 22 weeks and from 1% to 63% in infants born at 23 weeks of gestation. The authors concluded that different methodologies limit comparisons of results. However, problematic, studies of survival and morbidity rates are crucial to correctly inform parents and clinicians, guide decisions and develop policies to promote survival with an acceptable outcome.

4.4 Neonatal morbidity rates

Comparisons of neonatal morbidity rates were hampered by a limited number of infants in comparable studies and varying policies for different gestational ages from the present study and previous Swedish national studies.
TABLE 3 Neonatal morbidities among infants born before 24 weeks of gestation and surviving to 40 weeks postmenstrual age 2007–2018 in Sweden and temporal trends for calendar year stratified by gestational age

| Infants born at 22 weeks of gestation | 2007–2018 (n = 98) | 2007–2009 (n = 13) | 2010–2012 (n = 19) | 2013–2015 (n = 27) | 2016–2018 (n = 39) | OR (95% CI) | Change (95% CI) | p-value |
|--------------------------------------|------------------|------------------|------------------|------------------|------------------|-------------|----------------|---------|
| PDA                                  | 86/98 (88%)      | 13/13 (100%)     | 19/19 (100%)     | 26/27 (96%)      | 28/39 (72%)      | 0.00 (0.00–1.04) | <0.001        |         |
| PDA ligation, No (%)                 | 44/96 (46%)      | 15/12 (42%)      | 13/19 (68%)      | 16/27 (59%)      | 10/38 (26%)      | 0.50 (0.13–1.94) | 0.11           |         |
| BPD, No (%)                          | 88/95 (93%)      | 11/11 (100%)     | 16/18 (89%)      | 26/27 (96%)      | 35/39 (90%)      | 0.21 (0.01–5.12) | 0.34           |         |
| Persistent pulmonary hypertension of | 22/92 (24%)      | 2/11 (18%)       | 5/19 (26%)       | 7/25 (28%)       | 8/37 (22%)       | 1.24 (0.22–6.94) | 0.90           |         |
| the newborn, No (%)                  |                  |                  |                  |                  |                  |             |                |         |
| Severe ROP ≥stage 3 and/or treated ROP, No (%) | 62/98 (63%) | 10/13 (77%) | 7/19 (37%) | 19/27 (70%) | 26/39 (67%) | 1.56 (0.38–6.40) | 0.54           |         |
| ROP treatment, No (%)                | 48/98 (49%)      | 9/13 (69%)       | 6/19 (32%)       | 12/27 (44%)      | 21/39 (54%)      | 1.30 (0.33–5.13) | 0.71           |         |
| NEC No (%)                           | 18/98 (18%)      | 0/13 (0%)        | 2/19 (10%)       | 3/27 (11%)       | 13/39 (33%)      | 17.79 (1.69–188) | 0.017         |         |
| NEC surgery, No (%)                  | 12/98 (12%)      | 0/13 (0%)        | 2/19 (10%)       | 3/27 (11%)       | 7/39 (18%)       | 1.08 (0.38–43)  | 0.24           |         |
| Septicaemia, No (%)                  | 62/98 (63%)      | 9/13 (69%)       | 12/19 (63%)      | 16/27 (59%)      | 25/39 (64%)      | 0.84 (0.20–3.50) | 0.81           |         |
| IVH, No (%)                          | 46/98 (47%)      | 5/13 (38%)       | 9/19 (47%)       | 15/27 (56%)      | 17/39 (44%)      | 1.18 (0.30–4.66) | 0.81           |         |
| IVH grades 3–4, No %                 | 9/98* (9%)       | 1/13 (8%)        | 1/19 (5%)        | 3/27 (11%)       | 4/39 (10%)       | 1.99 (0.16–24.28) | 0.59           |         |
| Periventricular leukomalacia, No (%) | 10/98 (10%)      | 0/13 (0%)        | 6/19 (32%)       | 1/27 (4%)        | 3/39 (8%)        | 0.44 (0.05–3.95) | 0.47           |         |
| Hydrocephalus, No %                  | 5/98 (5%)        | 0/13 (0%)        | 0/19 (0%)        | 2/27 (7%)        | 3/39 (8%)        | 29 (0.27–3184)  | 0.16           |         |
| Oxygen dependency, days, mean (SD)   | 145 (51)         | 133 (30)         | 138 (51)         | 142 (47)         | 154 (59)         | 22 (–15–60)     | 0.24           |         |
| Length of care, days, mean (SD)      | 161 (60)         | 158 (35)         | 157 (42)         | 162 (61)         | 164 (70)         | 12 (–30–55)     | 0.57           |         |
| Age at discharge home, days, mean (SD)| 319 (59)        | 317 (34)         | 315 (44)         | 319 (64)         | 322 (70)         | 13 (–31–57)     | 0.56           |         |

| Infants born at 23 weeks of gestation | 2007–2018 (n = 301) | 2007–2009 (n = 69) | 2010–2012 (n = 58) | 2013–2015 (n = 89) | 2016–2018 (n = 85) | OR (95% CI) | Change (95% CI) | p-value |
|--------------------------------------|-------------------|------------------|------------------|------------------|------------------|-------------|----------------|---------|
| PDA                                  | 271/299 (91%)     | 60/68 (88%)      | 53/58 (91%)      | 82/88 (93%)      | 76/85 (90%)      | 1.13 (0.41–3.09) | 0.73           |         |
| PDA ligation, No (%)                 | 148/290 (51%)     | 34/65 (52%)      | 36/56 (64%)      | 53/88 (60%)      | 25/81 (31%)      | 0.41 (0.21–0.80) | <0.001         |         |
| BPD, No (%)                          | 239/284* (84%)    | 52/62 (84%)      | 47/54 (87%)      | 74/85 (87%)      | 66/83 (80%)      | 0.89 (0.32–2.47) | 0.82           |         |
| Persistent pulmonary hypertension of | 47/281 (17%)      | 4/67 (6%)        | 14/57 (25%)      | 18/81 (22%)      | 11/75 (15%)      | 2.71 (0.82–8.95) | 0.03           |         |
| the newborn, No (%)                  | 182/301 (60%)     | 42/69 (61%)      | 33/58 (57%)      | 55/89 (62%)      | 52/85 (61%)      | 1.14 (0.55–2.39) | 0.13           |         |
| Severe ROP ≥stage 3 and/or treated ROP, No (%) | 126/301 (42%) | 28/69 (41%) | 21/58 (36%) | 40/89 (45%) | 37/85 (44%) | 1.56 (0.75–3.26) | 0.23           |         |
| ROP treatment, No (%)                | 65/300 (22%)      | 9/69 (13%)       | 14/58 (24%)      | 26/88 (30%)      | 16/85 (19%)      | 1.26 (0.52–3.03) | 0.61           |         |
| NEC, No (%)                          | 42/298 (14%)      | 2/68 (3%)        | 11/58 (19%)      | 16/88 (18%)      | 12/85 (14%)      | 2.89 (0.96–8.68) | 0.06           |         |
| NEC surgery, No (%)                  | 192/300 (64%)     | 53/69 (77%)      | 33/58 (57%)      | 53/88 (60%)      | 53/85 (62%)      | 0.81 (0.38–1.72) | 0.58           |         |
93% of infants born at 22 weeks and 84% born at 23 weeks had BPD. Costeloe et al. reported BPD rates of 100% in 3/3 infants born at 22 weeks gestation and in 86% of the 66 infants born at 23 weeks of gestation. Molsher et al. reported BPD in 24% of 25 infants born at 22 weeks and in 18% of 57 infants born at 23 weeks. Regardless of discrepancies in BPD rates between studies, infants born at 22 weeks were more affected by BPD than those born at 23 weeks in agreement with our results. Low gestational age is a significant risk factor for most prematurity-related morbidities. With respect to BPD, the EXPRESS follow-up study found that BPD affected 49% of infants born at 26 weeks compared to 79% of those born at 23 weeks. Boys compared to girls born at 23 weeks were significantly more affected by BPD. Worse respiratory outcomes in males, in addition to increased risk of IVH and ROP, have been described by others. It has also been suggested that males in general have increased vulnerability, particularly at lower gestational ages. Boys compared to girls born at 22 weeks were significantly more affected by BPD. Worse respiratory outcomes in males, in addition to increased risk of IVH and ROP, have been described by others. It has also been suggested that males in general have increased vulnerability, particularly at lower gestational ages.
5 | CONCLUSION

As survival rates of extremely preterm infants increased with no improvement in neonatal morbidity, we concluded that an increased absolute number of infants with gestational ages of less than 24 weeks suffered from severe neonatal morbidity which may impact long-term outcomes. Neonatal care faces significant challenges in reducing and possibly preventing morbidities in these vulnerable infants.

ACKNOWLEDGEMENTS

We thank research nurse Carola Pfeiffer-Mosesson for assistance in collecting medical files from Hospitals. We also thank hospital staff for supplying medical files from all over Sweden and the steering group members of the Swedish national registry for ROP; Lotta Gränse, Eva Larsson, Marie Saric, Birgitta Sunnqvist, Agneta Wallin and Kristina Tornqvist for collection of ROP data.

CONFLICT OF INTEREST

The authors have no conflicts of interest to declare.

ORCID

Pia Lundgren https://orcid.org/0000-0002-7731-1988
Eva Morsing https://orcid.org/0000-0001-6871-6070
Anna-Lena Hård https://orcid.org/0000-0002-2440-2851
Lena Hellström-Westas https://orcid.org/0000-0003-3498-6069
Len Jacobson https://orcid.org/0000-0001-8563-2127
Ann Hellström https://orcid.org/0000-0002-9259-1244

REFERENCES

1. Shim JW, Jin HS, Bae CW. Changes in survival rate for very-low-birth-weight infants in Korea: comparison with other countries. J Korean Med Sci. 2015;30(Suppl 1):25-34. doi:10.3346/jkms.2015.30.S1.S25

2. Norman M, Hallberg B, Abrahamsson T, et al. Association between year of birth and 1-year survival among extremely preterm infants in Sweden during 2004–2007 and 2014–2016. JAMA. 2019;321(12):1188-1199. doi:10.1001/jama.2019.2021

3. Fanczal E, Berecz B, Szijártó A, Gasparics Á, Varga P. The prognosis of preterm infants born at the threshold of viability: fog over the gray zone - population-based studies of extremely preterm infants. Med Sci Monit. 2020;26:e926947. doi:10.12659/msm.926947

4. Brunkhorst J, Weiner J, Lantos J. Infants of borderline viability: the ethics of delivery room care. Semin Fetal Neonatal Med. 2014;19(5):290-295. doi:10.1016/j.siny.2014.08.001

5. Guillén Ú, Weiss EM, Munson D, et al. Guidelines for the management of extremely premature deliveries: a systematic review. Pediatrics. 2015;136(2):343-350. doi:10.1542/peds.2015-0542

6. Serenius F, Blennow M, Maršál K, Sjörs G, Källén K. Intensity of perinatal care for extremely preterm infants: outcomes at 2.5 years. Pediatrics. 2015;135(5):e1163-e1172. doi:10.1542/peds.2014-2988

7. Serenius F, Sjörs G, Blennow M, et al. EXPRESS study shows significant regional differences in 1-year outcome of extremely preterm infants in Sweden. Acta Paediatr. 2014;103(1):27-37. doi:10.1111/apd.12421

8. Håkansson S, Farooqi A, Holmgren P-Å, Serenius F, Högberg U. Proactive management promotes outcome in extremely preterm infants: a population-based comparison of two perinatal management strategies. Pediatrics. 2004;114(1):58-64. doi:10.1542/peds.114.1.58

9. Domellöf M, Jonsson B. The Swedish approach to management of extreme prematurity at the borderline of viability: a historical and ethical perspective. Pediatrics. 2018;142(Suppl 1):553-558. doi:10.1542/peds.2018-0478C

10. Backes CH, Söderström F, Ågren J, et al. Outcomes following a comprehensive versus a selective approach for infants born at 22 weeks of gestation. J Perinatol. 2019;39(1):39-47. doi:10.1016/j.jpeds.2018.04.049

11. Ehret DEY, Edwards EM, Greenberg LT, et al. Association of antenatal steroid exposure with survival among infants receiving postnatal life support at 22 to 25 weeks’ gestation. JAMA Netw Open. 2018;1(6):e183225. doi:10.1001/jamanetworkopen.2018.3225

12. García-Muñoz Rodrigo F, Díez Recinos AL, García-Alix Pérez A, Figueras Aloy J, Vento TM. Changes in perinatal care and outcomes in newborns at the limit of viability in Spain: the EPI-SEN Study. Neonatology. 2015;107(2):120-129. doi:10.1159/000368881

13. Ishii N, Kono Y, Yonemoto N, Kusuda S, Fujimura M. Outcomes of infants born at 22 and 23 weeks’ gestation. Pediatrics. 2013;132(1):e2-71. doi:10.1542/peds.2012-2857

14. Mehler K, Oberthuer A, Keller T, et al. Survival among infants born at 22 or 23 weeks’ gestation following active prenatal and postnatal care. JAMA Pediatr. 2016;170(7):671-677. doi:10.1001/jamapediatrics.2016.0207

15. Holmström G, Hellström A, Gränse L, et al. New modifications of Swedish ROP guidelines based on 10-year data from the SWEDROP register. Br J Ophthalmol. 2020;104(7):943-949. doi:10.1136/bjophthalmol-2019-314874

16. Maršál K, Persson P-H, Larsen T, Lilja H, Seibing A, Sultan B. Intrauterine growth curves based on ultrasonically estimated foetal weights. Acta Paediatr. 1996;85(7):843-848. doi:10.1111/j.1651-2227.1996.tb14164.x

17. Revised indications for the treatment of retinopathy of prematurity: results of the early treatment for retinopathy of prematurity randomized trial. Arch Ophthalmol. 2003;121(12):1684-1694. doi:10.1001/archophthalmology.121.12.1684

18. The International Classification of Retinopathy of Prematurity revisited. Arch Ophthalmol. 2005;123(7):991-999. doi:10.1001/archophthalmology.123.7.9991
19. Papile LA, Burstein J, Burstein R, Koffler H. Incidence and evolution of subependymal and intraventricular hemorrhage: a study of infants with birth weights less than 1,500 gm. J Pediatr. 1978;92(4):529-534. doi:10.1016/s0022-3476(78)80282-0

20. Bell MJ, Ternberg JL, Feigin RD, et al. Neonatal necrotizing enterocolitis. Therapeutic decisions based upon clinical staging. Ann Surg. 1978;187(1):1-7. doi:10.1097/00000658-197801000-00001

21. Lundgren P, Jacobson L, Hård AL, et al. High rate and large intercentre variability in retreatment of retinopathy of prematurity in infants born <24 gestational weeks. BMJ Open Ophthalmol. 2021;6(1):e000695. doi:10.1136/bmjophth-2020-000695

22. Söderström F, Normann E, Jonsson M, Ägren J. Outcomes of a uniformly active approach to infants born at 22–24 weeks of gestation. Arch Dis Child Fetal Neonatal Ed. 2021;106(4):413-417. doi:10.1136/archdischild-2020-320486

23. Morgan AS, Zeitlin J, Källén K, et al. Birth outcomes between 22 and 26 weeks’ gestation in national population-based cohorts from Sweden, England and France. Acta Paediatr. 2022;111(1):59-75. doi:10.1111/apa.16084

24. Fellman V, Hellsström-Westas L, Norman M, et al. One-year survival of extremely preterm infants after active perinatal care in Sweden. JAMA. 2009;301(21):2225-2233. doi:10.1001/jama.2009.771

25. Rysavy MA, Li L, Bell EF, et al. Between-hospital variation in treatment and outcomes in extremely preterm infants. N Engl J Med. 2015;372(19):1801-1811. doi:10.1056/NEJMoa1410689

26. Lantos JD. We know less than we think we know about perinatal outcomes. Pediatrics. 2018;142(1):e20181223. doi:10.1542/peds.2018-1223

27. Costeloe KL, Hennessy EM, Haider S, Stacey F, Marlow N, Draper ES. Short term outcomes after extreme preterm birth in England: comparison of two birth cohorts in 1995 and 2006 (the EPICure studies). BMJ. 2012;345:e7976. doi:10.1136/bmj.e7976

28. Townsel CD, Emmer SF, Campbell WA, Hussain N. Gender differences in respiratory morbidity and mortality of preterm neonates. Front Pediatr. 2017;5:6. doi:10.3389/fped.2017.00006

29. Shim SY, Cho SJ, Kong KA, Park EA. Gestational age-specific sex difference in mortality and morbidities of preterm infants: A nationwide study. Sci Rep. 2017;7(1):6161. doi:10.1038/s41598-017-06490-8

30. Sjoberg Bexelius T, Ahle M, Elfvin A, Björling O, Ludvigsson JF, Andersson RE. Intestinal failure after necrotising enterocolitis: incidence and risk factors in a Swedish population-based longitudinal study. BMJ Paediatr Open. 2018;2(1):e000316. doi:10.1136/bmjpo-2018-000316

SUPPORTING INFORMATION
Additional supporting information may be found in the online version of the article at the publisher’s website.