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

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ORIGINAL ARTICLE

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

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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.

Bronchopulmonary dysplasia was more common in boys than girls, 90% versus 82% ($p = 0.044$). The number of infants surviving to 40 weeks doubled over time.

Conclusion: Increased survival of infants born before 24 weeks of gestation resulted in increasing numbers of very immature infants with severe neonatal morbidities likely to have a negative impact on long-term outcome.

KEYWORDS
extremely preterm, necrotising enterocolitis, neonatal morbidities, proactive approach, survival rates

1 | INTRODUCTION

The survival of extremely preterm infants has changed remarkably during the last two decades.[1,2] Infants born at 22 weeks of gestation can now survive due to medical advances.[3] Whether or not to initiate intensive care for the most immature infants is controversial.[4] Guidelines for active interventions and resuscitation vary among centres and countries, reflected in survival rates and outcomes.[5,6] 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.[7,8] 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.[7] 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.[2] 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.[9]

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).[3] 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.[10–14]

This retrospective register and medical file-based study aimed to report survival rates and neonatal morbidities in a national cohort of extremely preterm infants born before 24 gestational weeks in 2007–2018 who were alive at 40 weeks of postmenstrual age in Sweden.

Key Notes

- Survival of extremely preterm infants born before 24 weeks of gestation has increased with unknown effects on morbidity.
- The number of infants born before 24 weeks who survived to 40 weeks of postmenstrual age doubled from 2007 to 2018 while neonatal morbidity rates were unchanged.
- An increasing number of infants born before 24 weeks of gestation will suffer from severe neonatal morbidities with anticipated impact on long-term outcome.

2 | METHODS

2.1 | Study population and data retrieval

Birth outcomes of infants born before 24 weeks of gestation in 2007–2018 were retrieved from The Swedish Medical Birth Register. This register comprises mandatory reported data of all births, live or stillborn from 22 weeks starting in 2008. Infants who survived until 40 weeks of postmenstrual age were identified through the Swedish national registry for ROP, (SWEDROP), with a coverage rate of 98%.[15] Infants were stratified into two gestational age groups: infants born at 21+0–22+6 (weeks+days) and 23+0–23+6. Data on maternal and pregnancy characteristics and diagnoses were retrieved from the National Board of Health and Welfare and from SWEDROP. All infants' medical charts were scrutinised to verify the diagnoses. The Swedish Ethical Review Authority approved the study, DNR 2019-05265.

2.2 | Survival rates

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.[16] 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.[17,18] For IVH, Papile's grading system had been used.[19] 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.[20] 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

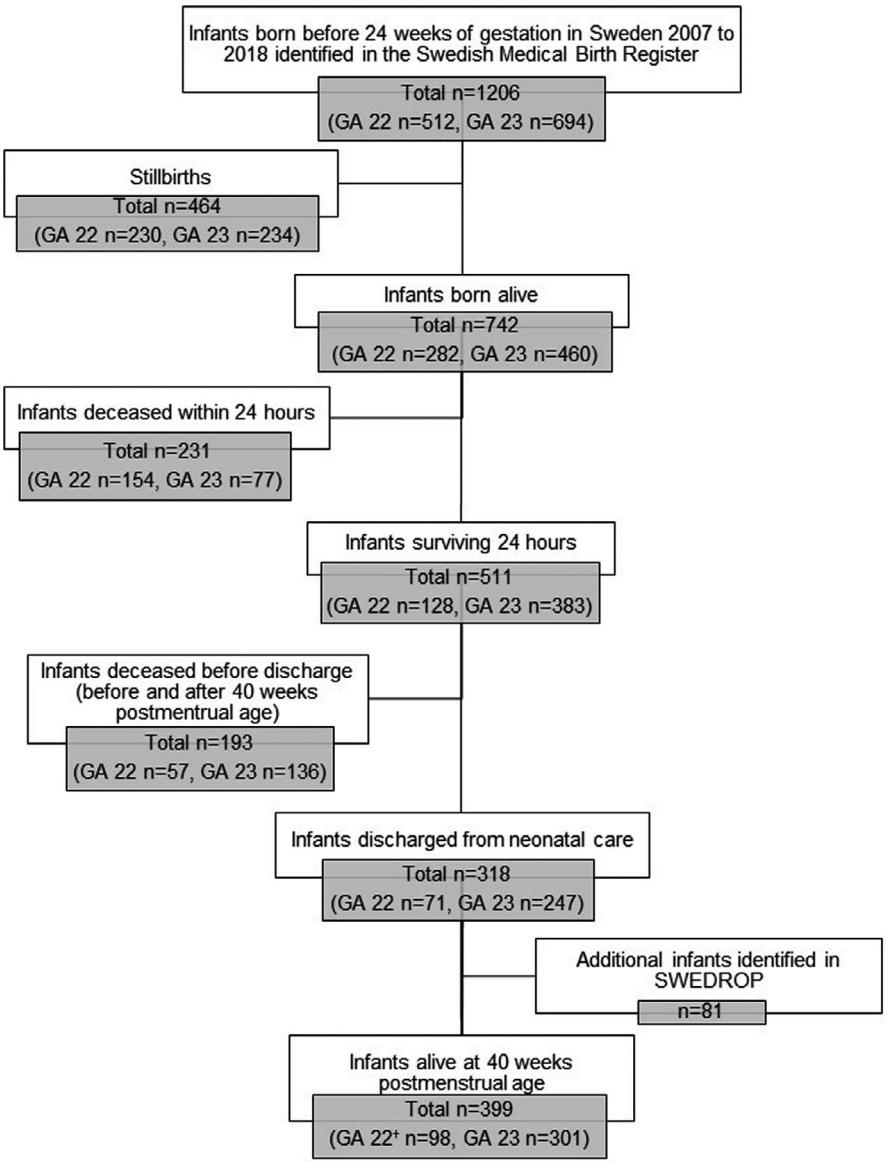

FIGURE 1 Flowchart of the study population

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[a] (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[a] (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.

[a]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.[21] 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

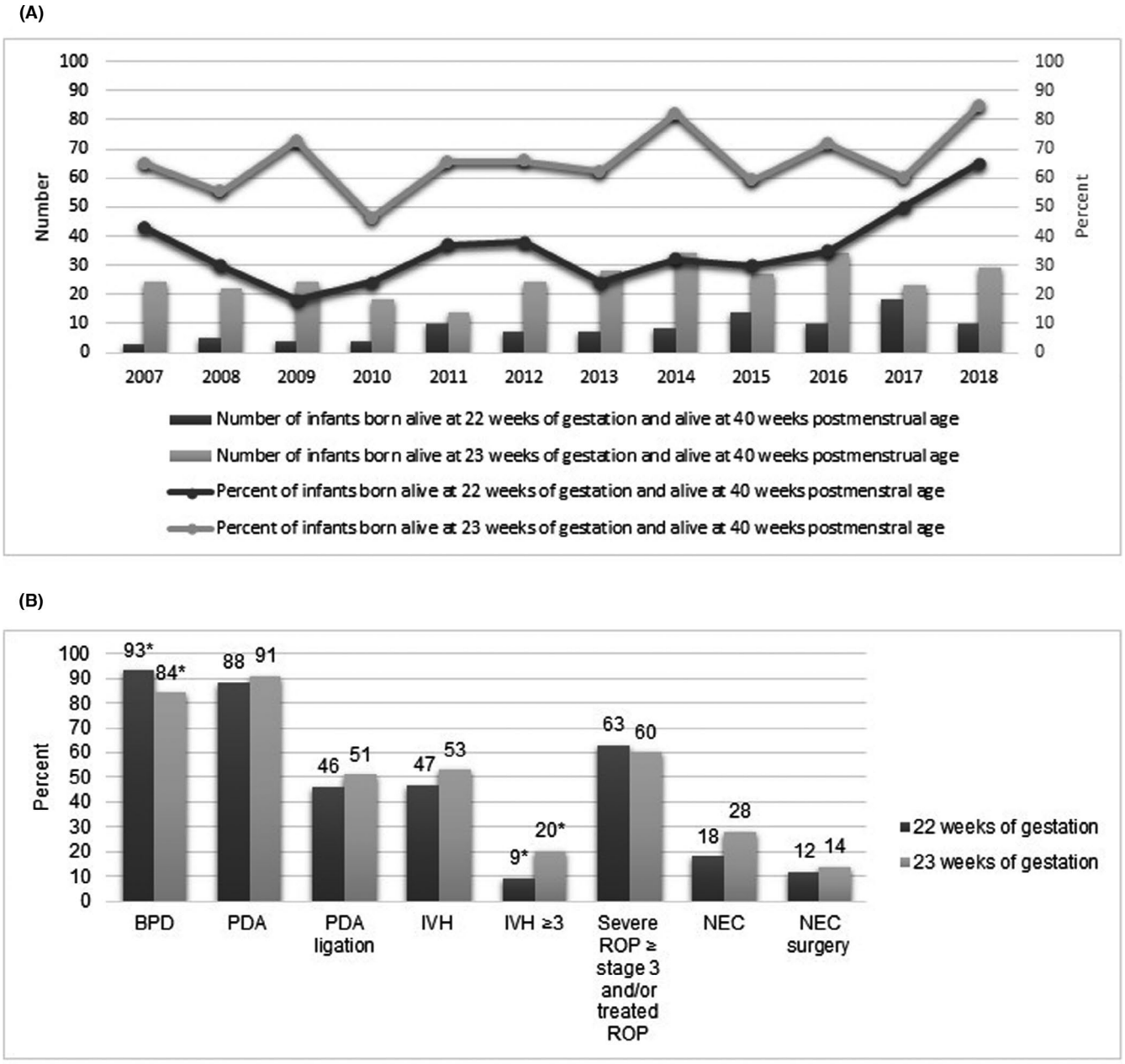

FIGURE 2 (A) Numbers and percentages of live-born infants surviving to 40 weeks of postmenstrual age during the study period, number and percent of infants are stratified by gestational age group, 22 and 23 weeks ($n = 399$). Two infants born at 21 weeks of gestation, in 2015 and 2016, were included in the 22 weeks group. (B). Percent of infants in the cohort developing neonatal morbidities in 2007–2018 stratified by gestational age group, 22 and 23 weeks ($n = 399$). Significant differences between infants born at 22 and 23 weeks of gestation are indicated as $^*p < 0.05$

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)[a]	2016–2018 (*n* = 39)[a]	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)		0.92
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

TABLE 2 (Continued)

	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
SDS birth weight, mean (SD)	−0.45 (0.92)	−0.46 (0.90)	−0.42 (1.18)	−0.48 (0.85)	−0.42 (0.89)		−0.03 (−0.37–0.30)	0.84
Small for gestational age, No (%)	14/301 (5%)	3/69 (4%)	3/58 (5%)	3/89 (3%)	5/85 (6%)	1.46 (0.26–8.29)		0.67
Gender (female), No (%)	143/301 (48%)	35/69 (51%)	29/58 (50%)	39/89 (44%)	40/85 (47%)	1.08 (0.52–2.22)		0.84
Twins, No (%)	47/300 (16%)	13/69 (19%)	12/58 (21%)	13/88 (15%)	9/85 (11%)	0.47 (0.18–1.28)		0.14

Note: Significant differences between infants born at 22 and 23 weeks of gestation are indicated as $^{**}p < 0.01$ and $^{***}p < 0.001$.

ORs and changes are presented for the whole study period.

Abbreviations: CI, confidence interval; OR, odds ratio; SD, standard deviation; SDS, standard deviation scores.

[a]One infant born at 21 weeks of gestation.

Bold values are significant values (<.05).

for different gestational ages from the present study and previous Swedish national studies.

4 | 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.[2,7] 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.[9] 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.[7,8,10,14,22–24]

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.[10,14,25] 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.[23] 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.[3] 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.[26]

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

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)[a]	2016–2018 (*n* = 39)[a]	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)[b]		**<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)[b]		**0.011**
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 the newborn, No (%)	22/92 (24%)	2/11 (18%)	5/19 (26%)	7/25 (28%)	8/37 (22%)	1.24 (0.22–6.94)[b]		0.90
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)**	**ß (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)[b]		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)[b]		**<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 the newborn, No (%)	47/281 (17%)	4/67 (6%)	14/57 (25%)	18/81 (22%)	11/75 (15%)	2.71 (0.82–8.95)[b]		**0.03**
Severe ROP ≥stage 3 and/or treated ROP, No (%)	182/301 (60%)	42/69 (61%)	33/58 (57%)	55/89 (62%)	52/85 (61%)	1.14 (0.55–2.39)		0.13
ROP treatment, No (%)	126/301 (42%)	28/69 (41%)	21/58 (36%)	40/89 (45%)	37/85 (44%)	1.56 (0.75–3.26)		0.23
NEC, 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 Surgery, No (%)	42/298 (14%)	2/68 (3%)	11/58 (19%)	16/88 (18%)	12/85 (14%)	2.89 (0.96–8.68)		0.06
Septicaemia, No (%)	192/300 (64%)	53/69 (77%)	33/58 (57%)	53/88 (60%)	53/85 (62%)	0.81 (0.38–1.72)		0.58

TABLE 3 (Continued)

	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)	ß (95% CI)	*p*-value
IVH, No (%)	158/300 (53%)	40/69 (58%)	27/58 (47%)	48/88 (54%)	43/85 (51%)	1.05 (0.51–2.16)		0.72
IVH grades 3–4, No %	59/300* (20%)	15/69 (22%)	10/58 (17%)	17/88 (19%)	18/85 (21%)	0.70 (0.29–1.74)		0,45
Periventricular leukomalacia, No (%)	28/300 (9%)	7/69 (10%)	8/58 (14%)	4/88 (4%)	9/85 (11%)	0.74 (0.22–2.55)		0.64
Hydrocephalus, No (%)	27/300 (9%)	5/69 (7%)	7/58 (12%)	6/88 (7%)	9/85 (11%)	0.95 (0.27–3.35)		0.94
Oxygen dependency days, mean (SD)	135 (52)	144 (51)	133 (42)	130 (47)	138 (64)		−11 (−32–10)	0.32
Length of inpatient care, days, mean (SD)	152 (73)	139 (44)	153 (51)	149 (57)	164 (84)		23.41 (−0.1–47)	0.05
Age at discharge home, days, mean (SD)	316 (63)	304 (44)	318 (52)	313 (56)	329 (84)		23 (−0.4–47)	0.05

Note: Significant differences between infants born at 22 and 23 weeks of gestation are indicated as $^*p < 0.05$.

ORs and changes are presented for the whole study period.

Abbreviations: BPD, bronchopulmonary dysplasia; CI, confidence interval; IVH, intraventricular haemorrhage; NEC, necrotising enterocolitis; OR, odds ratio; PDA, patent ductus arteriosus; ROP, retinopathy of prematurity; SD, standard deviation; SDS, standard deviation scores.

[a]One infant born at 21 weeks of gestation.

[b]Analysis with time as a four-level categorical predictor. OR between 2016–2018 and 2007–2009.

Bold values are significant values (<.05).

active care. In our study, 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.[27] Mehler et al. reported BPD in 24% of 25 infants born at 22 weeks and in 18% of 57 infants born at 23 weeks.[14] 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.[2]

In the present study, IVH had been diagnosed in 51% of the infants, and 17% had severe IVH grades 3–4. Infants born at 23 weeks were more affected by severe IVH than those born at 22 weeks, which may partly reflect more proactive care and higher survival rates in infants born at 23 weeks of gestation.

4.5 | Gender

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.[28] It has also been suggested that males in general have increased vulnerability, particularly at lower gestational ages.[29]

4.6 | Trends

Whether neonatal morbidities increase or decrease with more active neonatal care and with increased survival of the most immature infants has been debated. Results may differ based on intervention policies and inclusion criteria as neonatal morbidity is closely related to gestational age.[10,12] Our study found that the rate of severe morbidities remained largely unaltered over time. However, NEC diagnoses increased for infants born at 22 weeks of gestation and surgically treated NEC increased over time in all infants, which agrees with other studies.[30] We also found unaltered rates of PDA but decreasing rates of ligation for PDA, especially between the last two study periods, likely reflecting changed clinical practices towards more medical treatment.

All infants had one or more of the recorded neonatal morbidities (Table 3 and Table S3). Three infants were recorded as having only one morbidity, ROP, however, the data for the other morbidities were incomplete.

4.7 | Strengths and limitations

A limitation of this study was the retrieval of data from registers. However, registration in the Swedish Medical Birth Registry is mandatory and the rate of missing data is low regarding live births

(1%–3%) and birth characteristics (1%–2%) (https://www.socialstyrelsen.se/globalassets/sharepoint-dokument/artikelkatalog/statistik/2021-9-7547.pdf). The rate of live births in this study may have been affected by the change in recommendations in 2008, before which it was only mandatory to report stillbirths from 28 weeks of gestation. The retrospective design of the study was another limitation.

A strength of this study was that two registries, the Birth Registry and SWEDROP, were used to identify infants who fulfilled the inclusion criteria. SWEDROP has a 98% national coverage and identified infants who survived to 40 weeks of postmenstrual age.[15] Swedish personal identification numbers also enabled infant identification and accuracy when infants were transferred between hospitals. In addition, medical files of all infants were scrutinised to verify neonatal diagnoses and data retrieved from the two registries. To our knowledge, this was the most extensive cohort study of infants with gestational age below 24 weeks describing changes in survival and neonatal morbidities over time.

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.

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CONFLICT OF INTEREST

The authors have no conflicts of interest to declare.

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SUPPORTING INFORMATION

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