Improved survival of very preterm born infants from 2000 to 2013 in Denmark

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ABSTRACT

INTRODUCTION: Survival have improved among very preterm born infants, but improved treatment strategies might be associated with increasing rates of neonatal morbidity. The aim of this study was to assess survival and major morbidities among very and extremely preterm born infants treated in a Danish neonatal intensive care unit.

METHODS: This was an observational cohort study including very preterm infants (gestational age (GA) < 32 weeks) born between year 2000 and 2013. Because of changes in three standard treatments from 2008, we aimed to compare survival and major neonatal morbidity between two birth-year periods: 2000-2007 and 2008-2013.

RESULTS: The overall survival rate increased from 81.6% to 85.0%. In GA group 26-27 weeks, survival increased from 65% to 89% (p = 0.02). A total of 31/412 (7.5%) in the first time period and 30/280 (10.7%) in the second time period were diagnosed with bronchopulmonary dysplasia. No difference was found for necrotising entrocolitis or intraventricular haemorhage. Antibiotic treatment was similar in the two time periods, though antibiotic treatment for suspected clinical infection increased in the second time period (35.1% versus 44.1%).

CONCLUSIONS: We found a significant increase in the survival rate in GA group 26-27 weeks, but no significant increase in any major morbidity when comparing the two time periods.

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Preterm birth complications remain the leading cause of morbidity and mortality in children under the age of five years [1]. Though significant advances have been achieved in prenatal care in recent decades, the preterm birth rate has continued to rise in many industrialised countries during the past two decades [2]. Since the establishment of neonatal intensive care units (NICU) and the introduction of antenatal steroids in the 1970s and surfactant in the 1980s, the mortality of preterm born infants has decreased significantly. Improved treatment strategies in postnatal care has increased the survival of preterm born infants and at the same time lowered the gestational age limit of viability [3]. However, the risk of neonatal mortality and prematurity-related morbidities, such as bronchopulmonal dysplasia (BPD), necrotising enterocolitis (NEC), intraventricular haemorrhage (IVH), periventricular leukomalacia (PVL) and retinopathy of prematurity (ROP), increases with decreasing gestational age and/or birth weight [4, 5].

Our primary objective was to evaluate changes in the survival and morbidity among very and extremely preterm infants born at a level III NICU in Denmark from 2000 to 2013. Our aim was to compare survival and prematurity-related morbidity between two periods. We hypothesised an increase in survival rate and an increase in prematurity-related morbidity possibly correlated with survival at a lower gestational age. We also hypothesised a higher risk of morbidity among extremely preterm and low-birth-weight infants.

METHODS

Study population

This was an observational cohort study of very preterm born infants. Data were extracted from a local clinical neonatal database (NeoBase) at Odense University Hospital, Denmark. We included infants (with an address on the island of Funen), born between year 2000 and 2013, delivered prior to a gestational age (GA) of 32 weeks, born at Odense University Hospital and admitted to the level III NICU immediately after birth. We divided the infants into two groups; infants born before and after 1 January 2008. From 2008 onwards, prophylactic treatment with indomethacin to close a persistent ductus arteriosus was no longer used as standard treatment. Two new standard treatments were implemented: i) Only donor milk if mother's milk was not available for all infants with a GA < 32 weeks and ii) Nasal continuous positive airway pressure (nCPAP) at birth for all infants with a GA < 30 weeks. The study was approved by the Danish Data Protection Agency (15/7518 - 06.02.15) and the Danish Health and Medicines Authority (3- 3013-955/1 - 12.06.15).

Data were extracted from the NeoBase database and subsequently validated through individual-level comparison with data from the medical file. The following data were used in the analysis: GA, birth weight, mode of delivery, source of nutrition at discharge (breast milk/infant formula), systemic antibiotic therapy, incidence and average length of nCPAP and

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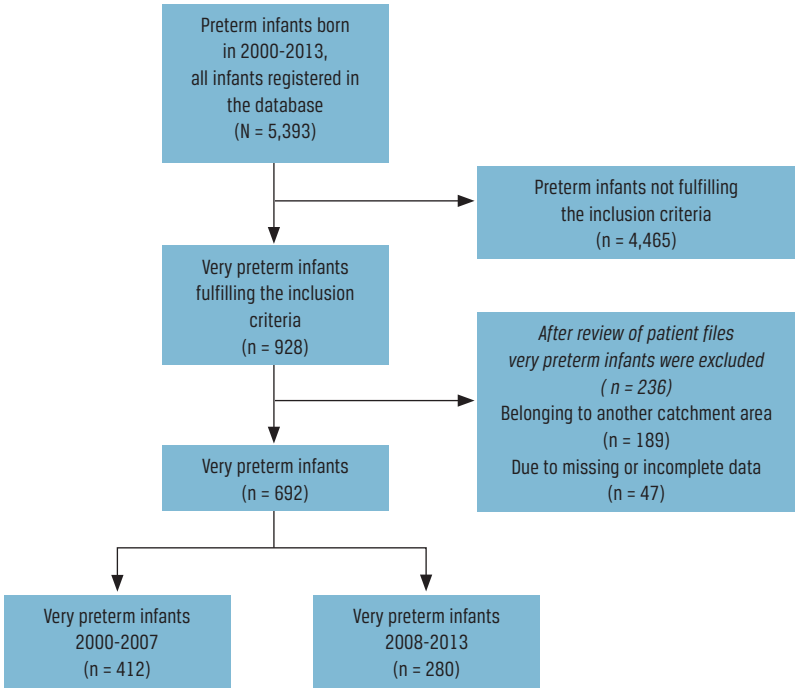
FIGURE 1 / Flow chart of the study population.



mechanical ventilation therapy (MVT) (including non-invasive ventilation therapy), length of hospitalisation and diagnostic codes at discharge (i.e., ROP, BPD, IVH, PVL and NEC). Only infants with less than three missing variables were included. We defined severe morbidity as follows: i) BPD on the basis of the P27.1 code from the International Classification of Diseases, tenth revision (ICD10) and/or as "infants in need of continuous oxygen therapy at gestational age 36 + 0 weeks", ii) IVH according to the Papile LA et al. Classification System [6], iii) PVL as non-cystic PVL or cystic PVL diagnosed using cranial ultrasound, and iv) NEC as "treated with surgery". Prematurity was divided into being born extremely preterm with a GA < 28 weeks and very preterm GA ≥ 28 weeks. Likewise, birth weight was divided into extremely low birth weight < 1,000 g and birth weight ≥ 1,000 g.

Statistical analyses

Characteristics of the study population and neonatal outcomes were compared between the two birth-year periods 2000-2007 and 2008-2013. Continuous variables were summarised as mean and standard deviation or median and interquartile range (25th-75th percentile) if the distribution was asymmetrical. Categorical variables were summarised as numbers and percentages. Two independent samples t-tests, the Wilcoxon rank sum and the chi-squared tests were conducted to compare the two birth-year periods. A multiple regression model was used to investigate the impact of GA group (23-25, 26-27 and 28-31 weeks), gender, multiple births and time periods (2000-2007 and 2008-2013) on survival. The selection of variables included was based on the construction of a directed acyclic graph. The Mantel-Haenszel method was used to stratify the risk of mortality, NEC, BPD and IVH by GA and birth weight. The significance level was set at $p < 0.05$. Because there were differences in the numbers of missing data, we excluded missing values when calculating the significance level to avoid a false positive test of the association between exposure and outcome.

Trial registration: not relevant.

RESULTS

A total of 5,393 preterm infants were born at Odense University Hospital between 1 January 2000 and 31 December 2013 and included in the NeoBase database. Overall, 4,465 infants did not meet the inclusion criteria (mainly due to a gestational age > 31 weeks) and 236 very preterm infants were subsequently excluded during the manual review. A total of 189 infants belonged to another catchment area and 47 infants had incomplete or missing data: 34 in the first and 13 in the second time period, with a mortality of two in each time period with GA 28 weeks and 30 weeks in the first and GA 27 weeks and 30 weeks in the second time period. A total of 692 very preterm infants born within the two time periods were included: 2000-2007 (n = 412 infants) and 2008-2013 (n = 280 infants) (**Figure 1**). The characteristics of the study population are shown in **Table 1**. The average number of infants admitted annually was 49.4 (min.: 30, max: 67), with a decrease from 51.5 infants per year in the first time period to 46.7 infants per year in the second time period. The number of boys was 206 (50.0%) in the first and 177 (63.2%) in the second time period ($p = 0.001$). In the first time period, the lowest GA was 24 weeks (24 + 0 days), whereas five infants in the second time period had a GA of 23 weeks (lowest GA 23 weeks + 3 days with two surviving to discharge).

Multiple births were more frequent in the second birth year period with 116 twins (41.5%), and four triplets (1.4%) compared with 119 twins (28.9%) and four triplets (1.0%) in the first period. The proportion of infants with a GA < 28 weeks treated with antibiotic for suspected clinical infection and clinical infection verified by blood culture were 28.1% and 35.9%, respectively, in the first time period and 39.0% and 35.4%, respectively, in the second time period.

In-hospital survival varied between birth years, with the lowest survival rate being observed in 2004 (69.0%) and the highest rate in 2010 and 2011 (90.0%) with no statistical difference between the two birth-year periods. In a multiple regression model,

survival improved among GA group 26-27 weeks from 65% in the first to 89% the second period (p = 0.02), but no improvement among either 23-25 or 28-31 weeks. No significant difference was found in the risk of any major morbidity between time periods (**Table 2**).

Infants surgically treated for NEC had an increased mortality risk corresponding to a 60.9% risk in the first and 50.0% in the second time period. In total, 40.0% (n = 26/65, four with missing data on morbidities) of the extremely preterm infants that survived until discharge were diagnosed with at least one major morbidity (NEC, IVH grade III or IV, PVL or BPD) during their hospitalisation in the first time period. This number increased to 51.0% (n = 25/49, one with missing data on morbidities) in the second time period.

The proportion of infants treated with MVT or nCPAP was similar in the two time periods, though the median number of days with MVT or nCPAP increased in the second time period (Table 1). The maximum number of days with MVT was 35 in the first and 149 in the second period. Eight infants were treated with MTV for more than 35 days in the second time period. When excluding infants who died during hospitalisation, 14 infants (7.8%) in the first and five (4.7%) in the second time period (GA 30-31 weeks) were not in need of nCPAP. Two infants (2.3%) in the first and one (1.2%) in the second (GA 28-29 weeks) period were not in need of nCPAP. All infants with GA < 28 weeks were in need of nCPAP, and 50.8% were treated with MVT in the first and 60.2% in the second time period.

Retinopathy of prematurity is not reported as a major morbidity in Table 2 because 158 (38.4%) and 88 (31.4%) infants had missing data on ROP in the first and second time period, respectively. However, 30/254 (11.8%) versus 25/192 (13.0%) were diagnosed with ROP. Further, IVH grade I + II was reported for 40/363 (11.0%) and 30/261 (11.5%) in the first and second time period, respectively.

Infants with a gestational age < 28 weeks and infants with a birth weight < 1,000 g had higher odds of mortality and any major morbidity than infants with a gestational age ≥ 28 weeks or a birth weight ≥ 1,000 g, respectively (**Table 3**).

TABLE 1 / Characteristics of the study population.

	2000-2007 (N = 412)	2008-2013 (N = 280)	p-value
Gestational age			
Median (IQR), wks + days,	29 + 4 (27 + 2 – 31 + 0)	29 + 2 (27 + 3 – 30 + 5)	0.263
< 28 wks, n (%)	128 (31.1)	83 (29.6)	
28-32 wks, n (%)	284 (68.9)	197 (70.4)	0.689
Birth weight			
Mean ± SD, g	1,208.3 ± 414.2	1,200.5 ± 391.7	0.804
< 1000 g, n (%)	140 (34.0)	85 (30.4)	
≥ 1,000 g, n (%)	270 (65.5)	195 (69.6)	0.297
Missing, n (%)	2 (0.5)	0	
Singleton birth, n (%)	289 (70.1)	160 (57.1)	< 0.001
Method of delivery, n (%)			0.009
Vaginal	101 (24.5)	94 (33.6)	
Caesarean section	311 (75.5)	186 (66.4)	
Elective caesarean section	24 (7.7)	7 (3.8)	
Emergency caesarean section	287 (92.3)	179 (96.2)	
Antibiotic treatment,			
n_t (n_t/N, %)	242 (58.7)	176 (62.9)	0.248
Prophylactic, n_p (n_p/n_t, %)[a]	87 (36.0)	45 (25.4)	
Clinical infection, n_c (n_c/n_t, %)	85 (35.1)	78 (44.1)	
Clinical infection verified by blood culture, n_{cb} (n_{cb}/n_t, %)	70 (28.9)	53 (29.9)	
Missing, n	0	1 (0.6)	
MVT			
Infants in MVT, n (%)	99 (24.0)	77 (27.5)	0.303
Length of MVT, days, median (IQR)	3 (2-6)	5 (2-11)	0.078
nCPAP			
Infants in nCPAP, n (%)	383 (93.0)	264 (94.3)	0.784
Time in nCPAP, days, median (IQR)	9 (3-31)	14 (5-36)	0.028
Hospitalisation, days, median (IQR)[b]	53 (39-69)	50 (37-68)	0.513
Nutrition when discharged, n (%)			
Breast milk	162 (39.3)	123 (43.9)	
Infant formula	106 (25.7)	75 (26.8)	0.283
Breast milk and infant formula	62 (15.1)	37 (13.2)	
Other type of feeding	0	2 (0.7)	
Missing	82 (19.9)	43 (15.4)	

IQR = interquartile range; MTV = mechanical ventilation therapy; nCPAP = nasal continuous positive airway pressure SD = standard deviation.
a) E.g. antibiotics given right after birth if premature ruptures of membranes.
b) Excluding infants who died during hospitalisation.

DISCUSSION

We found no statistically significant difference in the number of infants who survived or in the risk of any major morbidity when comparing all infants in the two time periods. We found an increase in survival in GA group 26-27 weeks. Our overall survival rates are similar to those reported by other studies from the same time period [3, 7, 8].

We observed no increase in the number of infants with BPD. There was a small increase in the number of extremely preterm infants diagnosed with BPD in the second period (from 17.9 to 24.1%), though the increase was non-significant. The proportion of extremely preterm infants treated with MVT increased from 50.0 to 60.2%. In the express study [5], 38% of infants with GA < 27 weeks were treated with MVT and 25% developed BPD. In both periods, many infants were treated for only one or just a few days with MVT, whereas a few infants were treated with MVT for many days in the second period, which seemed to be associated with BPD. The long-term consequences of BPD remain poorly understood [9]; however, this increase in the incidence of BPD and MVT is worrying with regards to the future pulmonary function of these patients. One study has reported a significantly greater risk of lung function abnormalities at school age among preterm

TABLE 2 / Survival and major morbidities, overall and stratified by gestational age and birth weight.

	2000-2007 (N_{tot} = 412)	2008-2013 (N_{tot} = 280)	p-value
Survival, n/N (%)	336/412 (81.6)	238/280 (85.0)	0.237
GA < 28 wks	69/128 (53.9)	50/83 (60.2)	0.259
GA 28-32 wks	267/284 (94.0)	188/197 (95.4)	
BW < 1,000 g	85/140 (60.7)	51/85 (60.0)	0.442
BW ≥ 1,000 g	250/270 (92.6)	187/195 (95.9)	
Missing data[a], n (%)	2 (0.5)	0	
Major morbidities, n/N (%)[b,c]	82/350 (19.9)	67/255 (23.9)	0.422
Surgical treated NEC:	23/412 (5.6)	16/280 (5.7)	0.941
GA < 28 wks	15/128 (11.7)	11/83 (13.3)	0.878
GA 28-32 wks	8/284 (2.8)	5/197 (2.5)	
BW < 1,000 g	17/140 (12.1)	10/85 (11.8)	0.792
BW ≥ 1,000 g	6/270 (2.2)	6/195 (3.1)	
IVH grade III + IV, n/N (%)[d]:	25/363 (6.9)	16/261 (6.1)	0.707
GA < 28 wks	18/115 (15.7)	12/80 (15.0)	0.749
GA 28-32 wks	7/248 (2.8)	4/181 (2.2)	
BW < 1,000 g	17/127 (13.4)	11/80 (13.8)	0.869
BW ≥ 1,000 g	8/234 (3.4)	5/181 (2.8)	
PVL, n/N (%)[e]:	18/356 (4.4)	11/249 (3.9)	0.718
GA < 28 wks	6/111 (5.4)	6/76 (7.9)	0.724
GA 28-32 wks	12/245 (4.9)	5/173 (2.9)	
BW < 1,000 g	6/120 (5.0)	5/74 (6.8)	0.734
BW ≥ 1,000 g	12/235 (5.1)	6/175 (3.4)	
BPD, n/N (%):	31/412 (7.5)	30/280 (10.7)	0.146
GA < 28 wks	23/128 (17.9)	20/83 (24.1)	0.105
GA 28-32 wks	8/284 (2.8)	10/197 (5.1)	
BW < 1,000 g	27/140 (19.3)	19/85 (22.4)	0.070
BW ≥ 1,000 g	4/270 (1.5)	11/195 (5.6)	
Infants treated with MVT, n/N (%)	19/31 (61.3)	18/30 (60.0)	0.918
Days in MVT, n, median (IQR)	6 (3-22)	24.5 (15-59)	0.006
Days with respiratory support, MVT and nCPAP, n, median (IQR)	60 (45-72)	67.5 (41-92)	0.189

BPD = bronchopulmonal dysplasia; BW = birth weight; GA = gestational age; IQR = interquartile range; IVH = intraventricular haemorrhage; MVT = mechanical ventilation therapy; nCPAP = nasal continuous positive airway pressure; NEC = necrotising enterocolitis; PVL = periventricular leukomalacia.
a) Missing data on BW.
b) Include ≥ 1 of the following: surgical treated NEC, IVH grade III and IV, PVL, and BPD.
c) 62 (15.1%) and 25 (8.9%) infants with missing data on ≥ 1 major morbidity in the 1st and 2nd period, respectively.
d) 49 (11.9%) and 19 (6.8%) infants with missing data on IVH in the 1st and 2nd period, respectively.
e) 56 (13.6%) and 31 (11.1%) infants with missing data on PVL in the 1st and 2nd period, respectively.

TABLE 3 / Odds ratio (95% confidence interval) of mortality and major morbidities by gestational age < 28 weeks and birth weight < 1,000 g compared with gestational age 28-32 weeks and birth weight ≥ 1,000 g, respectively.

	OR (95% CI)	
	GA < 28 wks	BW < 1,000 g
Mortality	13.56 (7.86-23.38)***	10.04 (6.02-16.72)***
NEC	5.06 (2.51-10.18)***	5.19 (2.53- 10.65)***
BPD	6.71 (3.66-12.28)***	8.12 (4.24-15.53)***
IVH 3 + 4	6.90 (3.30-14.40)***	4.80 (2.40-9.62)***

BPD = bronchopulmonal dysplasia; BW = birth weight;
CI = confidence interval; GA = gestational age;
IVH 3 + 4 = intraventricular haemorrhage grade III and grade IV;
NEC = surgically treated necrotising enterocolitis;
OR = odds ratio.
***) p < 0.001.

born children treated for BPD [10]. Another study found that BPD and/or duration of oxygen treatment predicted a lower performance IQ, lower motor and attention skills and lower school achievement at eight years of age [11]. We found no increase in the number of infants with IVH, PVL or NEC. A new standard treatment with donor milk for all very preterm infants from 2008 did not change the incidence of NEC.

An insignificant increase in use of antibiotics was seen from the first to the second time period. Clinical infection verified by blood culture was the same in the two time periods (29% and 30% respectively). In the express study [5], authors reported an incidence of 41% of septicaemia among immature infants below 27 weeks. In our study, the extremely preterm infants were more often treated with antibiotics than infants > GA 28 weeks were. We have not registered for how long each infant was treated with antibiotics or if the infants were diagnosed with septicaemia. Nor have we registered the type of bacteria found in blood cultures. In a study from Denmark (including NICU at Odense University Hospital) and Norway, the authors found that *Staphylococcus aureus* was the most frequently detected bacteria (31%) followed by Group B streptococci (26%) and *Escherichia coli* (17%) in the NICU in 2010-2013 [12]. The high rates of interventions with especially antibiotic treatment when suspecting a clinical infection and MVT for many more days in the second time period might reflect a new, more proactive approach towards resuscitation and intensive care among the extremely preterm born infants in particular. In our cohort, this has probably increased survival in the group of infants with GA 26-27 weeks. Other studies have shown that progressive developments in perinatal and postnatal intensive care have improved the rate of survival and changed the incidence rates of major prematurity-related morbidities such as NEC, BPD, IVH and ROP [13, 14]. However, questions have been raised concerning the risks of later disabilities [15, 16], adverse developmental programming and the high costs associated with intensive care treatments among infants born at the limits of viability [17, 18]. Our study showed that 40.0% of the extremely preterm infants surviving until discharge were diagnosed with one or more major morbidities in the first period. This number increased to 51.0% in the second period. In other studies utilising broadly similar definitions of major morbidities, the percentages with major morbidities ranged 21-80%, depending on the GA [19, 20].

Strengths and limitations

One strength of this study is the validation of data from

the database by comparing the data on an individual level with data from the medical file. The study also has a limitation with 47/739 infants excluded due to missing or incomplete data, which may potentially introduce selection bias. Therefore, any possible associations should be interpreted with caution.

CONCLUSIONS

In conclusion, our study found a significant increase in survival among GA 26-27-week infants comparing two time periods. We observed no increase in any major morbidity among all very preterm infants, but a non-significant increase from 40.0 to 51.0% in one or more major morbidity among the extremely preterm infants. We found a non-significant increase in days using MVT and in the incidence of BPD. Further follow-up studies are relevant in order to evaluate the consequence of these morbidities later in life.

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