BMJ Open

Morbidity and trends in length of hospitalisation of very and extremely preterm infants born between 2008 and 2021 in the Netherlands: a cohort study

Karen de Bijl-Marcus ,[1] Manon J N L Benders,[1] Jeroen Dudink,[1] Kees Ahaus ,[2] Marijn Kahlmann,[1] Floris Groenendaal[1]

To cite: de Bijl-Marcus K, Benders MJNL, Dudink J, *et al*. Morbidity and trends in length of hospitalisation of very and extremely preterm infants born between 2008 and 2021 in the Netherlands: a cohort study. *BMJ Open* 2024;**14**:e078842. doi:10.1136/bmjopen-2023-078842

► Prepublication history and additional supplemental material for this paper are available online. To view these files, please visit the journal online (https://doi.org/10.1136/bmjopen-2023-078842).

Received 14 August 2023
Accepted 14 May 2024

[1]Department of Neonatology, Universitair Medisch Centrum Utrecht-Locatie Wilhelmina Kinderziekenhuis, Utrecht, The Netherlands
[2]Erasmus School of Health Policy & Management, Erasmus Universiteit Rotterdam, Rotterdam, The Netherlands

Correspondence to
Dr Karen de Bijl-Marcus; k.a.marcus@umcutrecht.nl

ABSTRACT

Objectives This study investigated changes in the length of stay (LoS) at a level III/IV neonatal intensive care unit (NICU) and level II neonatology departments until discharge home for very preterm infants and identified factors influencing these trends.

Design Retrospective cohort study based on data recorded in the Netherlands Perinatal Registry between 2008 and 2021.

Setting A single level III/IV NICU and multiple level II neonatology departments in the Netherlands.

Participants NICU-admitted infants (n=2646) with a gestational age (GA) <32 weeks.

Main outcome measures LoS at the NICU and overall LoS until discharge home.

Results The results showed an increase of 5.1 days (95% CI 2.2 to 8, p<0.001) in overall LoS in period 3 after accounting for confounding variables. This increase was primarily driven by extended LoS at level II hospitals, while LoS at the NICU remained stable. The study also indicated a strong association between severe complications of preterm birth and LoS. Treatment of infants with a lower GA and more (severe) complications (such as severe retinopathy of prematurity) during the more recent periods may have increased LoS.

Conclusion The findings of this study highlight the increasing overall LoS for very preterm infants. LoS of very preterm infants is presumably influenced by the occurrence of complications of preterm birth, which are more frequent in infants at a lower gestational age.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ One of the first studies to provide information regarding the total duration of hospital stays for very preterm infants until discharge home, encompassing both the length of stay (LoS) at the level III neonatal intensive care department and LoS at the level II departments.
⇒ Examines LoS in a single, relatively large neonatal intensive care unit over a relatively long period of time.
⇒ Organisational factors such as bed capacity were not included or accounted for in the analysis. It provides no data regarding maternal or pregnancy-related factors, foetal death, death before admission or infants for whom intensive care treatment was not initiated in the delivery room.

INTRODUCTION

Length of stay (LoS) at the neonatal intensive care unit (NICU) is an important indicator of clinical outcomes and (economic) performance of the healthcare system.[1 2] Predicting LoS is crucial for resource planning, decision-making and parental counselling. Many factors influence LoS, including infant characteristics, quality and complexity of care, management and the availability of postdischarge healthcare facilities.[1 3 4] Trends towards shorter hospital stays have been observed for many hospital populations within developed countries, attributed to enhanced patient outcomes and the delivery of more efficient care.[5–7] During the final decade of the previous century, the Vermont–Oxford Network and others reported similar trends of decreasing LoS at the NICU.[8 9] In more recent years, NICUs have implemented multiple interventions to facilitate the safe and earlier discharge of (very) preterm infants.[10–14] However, despite the implementation of these interventions, recent studies conducted in multiple developed countries have shown a consistent or even increased LoS at the NICU.[8 15 16] Extended hospital stays put significant pressure on healthcare resources, which may jeopardise patient safety and escalate healthcare expenses. Such prolonged periods of hospitalisation not only heighten the risk of infants encountering healthcare-associated infections but also place substantial emotional and financial strain on their families. Moreover, an increase in LoS, when combined with restricted bed availability,

may necessitate more frequent patient transfers to facilities outside the region, further complicating care continuity and accessibility.

The cause of the stabilisation or increase in LoS is unknown. It is speculated that improvements in survival may have led to higher LoS since more infants at extremely low gestational age (GA) and/or with more severe health conditions survive to discharge.[8 15 16] If and how these changing population characteristics are related to the LoS at the NICU has not been elucidated. Furthermore, in several neonatal healthcare systems (including the Netherlands), infants are being transferred to a level II hospital to receive convalescent care (online supplemental file 1). Limited information is available regarding the overall duration of hospitalisation for preterm infants until they are discharged home after being transferred.

With the present study, we aim to investigate changes in the overall length of hospitalisation until discharge home, encompassing both the LoS at the NICU and the level II departments, for surviving preterm infants (GA <32 weeks) between 2008 and 2021. In addition, we aim to identify key variables that influence trends in LoS. These data could facilitate predicting LoS and possibly provide deeper knowledge of developments regarding the care demands of preterm infants.

METHODS

Study design

This study is a retrospective cohort study based on data from the Netherlands Perinatal Registry (www.perined.nl), which were completed by manual medical record review of all individual records. Patients or the public were not involved in the design, or conduct, or reporting, or dissemination plans of our research.

Study subjects

All infants born alive below 32 weeks gestation between 1 January 2008 and 31 December 2021, admitted to the level III/IV NICU of the Wilhelmina Children's Hospital of Utrecht, were eligible for inclusion. The exclusion criteria consisted of (1) major congenital anomalies (defined as chromosomal anomalies, congenital anomalies requiring surgery within the neonatal period and/or congenital anomalies incompatible with life) and (2) infants transferred from/to another level III/IV NICU.

Study period

The study period was divided into three subgroups:

1. 2008–2010: period in which infants with a GA <25 weeks were admitted to the NICU only by exception.
2. 2011–2015: first period after the revision of the Dutch perinatal guideline, lowering the threshold to offer active treatment from 25 to 24 weeks of gestation.
3. 2016–2021: for trend analyses, a third period was studied.

Setting

The NICU of the Wilhelmina Children's Hospital is part of a Dutch university hospital with 24 level III/IV NICU beds and many paediatric medical subspecialists, including (neuro/cardiac) surgeons, ophthalmic and anesthesiologic subspecialists. The NICU is located in a highly regionalised area with four regional post-NICU/high care (HC) departments and three non-post-IC/HC units. A high percentage (>90%) of infants are transferred to level II hospitals for convalescent care. Infants are transferred when all of the following criteria are met: corrected GA ≥30 weeks, weight ≥1000 g, respiratory support consisting of nasal continuous positive airway pressure (nCPAP), humidified high-flow nasal cannula (HHFNC), or low flow, and no need for specialised intensive care treatment.

Patient and public involvement

Patients or the public were not involved in the design, or conduct, or reporting, or dissemination plans of our research.

Outcomes (of each period)

- Primary outcomes
  - Median LoS (days) at the NICU.
  - Median LoS (days) until discharge home (LoS NICU+LoS level II hospital).
- Secondary outcomes
  - In-hospital mortality rate, which was compared with the expected mortality rate calculated using a previously published prognostic model.[17 18]
  - The morbidity rate of each period is defined as a composite variable of at least one of the following complications: chronic lung disease (CLD, defined as at least 28 cumulative days of oxygen therapy), intraventricular haemorrhage grade 3 (IVH-III), cerebral venous infarction (VI), posthaemorrhagic ventricular dilatation (PHVD) needing intervention, cystic periventricular leukomalacia (cPVL grade II/III), laser coagulation for retinopathy of prematurity (ROP) and necrotising enterocolitis with indication for surgery (NEC_s).[19 20]
  - Type of respiratory support at the time of transfer since changing policies regarding (maximum) respiratory support at the time of transfer could affect LoS.
  - Readmission rate.
  - The association between LoS and variables such as period of birth, GA, birth weight less than the third percentile (small for GA (SGA), sex, antenatal corticosteroids, multiple pregnancies, Apgar score, outborn, caesarean section, CLD, duration of mechanical ventilation, IVH-III, VI, PHVD, cPVL, persistent ductus arteriosus (PDA) with treatment, ROP, NEC_s, late-onset sepsis, type of receiving level II department).

Efforts were made to retrieve the missing data. Hospital admission records were compared with local department

Table 1 Patient characteristics at the time of admission

Patient characteristics	Period 1: 2008–2010	Period 2: 2011–2015	Period 3: 2016–2021	
All included infants, including deceased	**n=594**	**n=1034**	**n=1018**	**P value***
GA (weeks) at birth (median IQR)	30.0†‡ (28.3–31.0)	29.4† (27.4–30.9)	29.6‡ (27.7–30.9)	<0.001
Number of infants with a GA at birth <25 weeks	10	45	54	
Sex (% male)	50.8%‡	50.8%§	55.8%‡§	0.043
Birth weight in g (median IQR)	1265† (1000–1555)	1215§ (920–1475)	1263§ (970–1545)	0.001
Survivors	**n=563 (94.8%)**	**n=969 (93.7%)**	**n=946 (92.9%)**	**P value***
GA (weeks) at birth (median IQR)	30.1†‡ (28.4–31.1)	29.7† (27.7–30.9)	29.7‡ (28.0–31.0)	0.001
Sex (% male)	51.2%	50.4%	55.3%	0.077
Birth weight in g (median IQR)	1300 (1035–1570)	1235§ (960–1498)	1285§ (1005–1573)	0.001
Birth weight percentile (median IQR)	−0.61‡ (-1.55–0.33)	−0.60§ (-1.59–0.14)	−0.43‡§ (-1.45–0.38)	0.004
Small for GA (% < 3rd percentile)	17.6%	17.5%	15.2%	0.317
Small for GA (% <10th percentile)	36.8%	37.5%	32.5%	0.054
Multiple pregnancy (%)	32.7%‡	27.9%	25.1%‡	0.006
Antenatal corticosteroids (% optimal)	53.6%‡	51.7%§	60.8%‡§	<0.001
Caesarean section (%)	54.7%	58.6%	53.9%	0.253
Inborn (%)	87.6%	86.6%	89.8%	0.081
Apgar score at 5 min (median IQR)	9†‡ (8–9)	8†§ (7–9)	8§‡ (7–9)	<0.001

*Kruskal-Wallis.
†Statistically significant difference between period 0 and period 1.
‡Statistically significant difference between period 0 and period 2.
§Statistically significant difference between period 1 and period 2.
GA, gestational age.

databases. Missing data from level II units were corrected by letters and phone calls.

Statistical analysis

Patient characteristics and outcome variables were summarised as proportions, means and medians, where appropriate. We estimated changes in medians of primary and secondary outcomes during the study period using univariate analyses with 95% CIs. Generalised linear models were used to examine differences in LoS as a dependent variable across the three study periods, with GA, SGA, multiplicity and several neonatal complications (NEC, ROP, CLD and late-onset sepsis) as independent variables due to their well-known effect on length of hospital stay (see online supplemental appendix 2 for a complete list of tested variables based on textbook knowledge). Interactions between periods and complications were also tested. After step-by-step backwards removal of the variables that were not significant, that is, those with a p value greater than 0.05, the results of the final model, including the interactions, are presented. Statistical analyses were performed using Statistical Package for Social Sciences for Windows V.29 (SPSS, Chicago, Illinois, USA) and R statistical software (http://www.r-project.org).

RESULTS

Overall, 2646 infants were included in the study. Of the 2776 live births below 32 weeks, 90 infants were excluded due to major congenital anomalies and 40 due to transfer from/to another NICU. Patient characteristics (potentially) affecting the LoS of the included infants during the three study periods are presented in tables 1–3. There were significant differences between study periods regarding median GA, sex, birth weight, duration of mechanical ventilation and treatment of PDA. Furthermore, the incidence of late-onset sepsis and severe ROP varied between study periods. In period 3, infants were more often transferred to a level II department while receiving intensive forms of non-invasive respiratory support, such as HHFNC or nCPAP (table 4). LoS at the NICU was available for all 2646 infants. The total duration of LoS until discharge home was available for 2256 of 2478 surviving infants (91%). Patient characteristics at

Table 2 Morbidity and mortality

Patient characteristics	Period 1: 2008–2010	Period 2: 2011–2015	Period 3: 2016–2021	
All included infants, including deceased	**n=594**	**n=1034**	**n=1018**	**P value***
In-hospital mortality number (%)	31 (5.2%)	65 (6.3%)	72 (7.1%)	0.336
Survival rate (%)	94.8%	93.7%	92.9%	0.336
Expected survival rate (mean survival prediction)†	92.5% @#	89.6% ‡	90.2% §	<0.001
Survivors	**n=563 (94.8%)**	**n=969 (93.7%)**	**n=946 (92.9%)**	**P value***
Intraventricular haemorrhage grade 3 and/or cerebral venous infarction (%)	5.7%	4.5%	3.7%	0.196
Posthaemorrhagic ventricular dilatation (%)	1.2%	1.0%	1.7%	0.443
Cystic periventricular leukomalacia (%)	0.5%	0.5%	0.5%	0.999
Necrotising enterocolitis (%)	5.7%	7.4%	5.8%	0.255
Necrotising enterocolitis with laparotomy (%)	2.5%	3.2%	3.4%	0.611
Mechanical ventilation (% receiving mechanical ventilation)	42.6%§	45.1%¶	35.3%§¶	<0.001
Chronic lung disease (%)	31.6%	37.0%	32.8%	0.059
Medication for persistent ductus arteriosus (%)	15.1%	19.6%¶	14.5%¶	0.006
Surgical ligation persistent ductus arteriosus (%)	3.0%	4.4%¶	1.9%¶	0.006
Late-onset sepsis (%)	23.1%§	19.1%¶	14.6%§¶	<0.001
Retinopathy of prematurity with laser coagulation (%)	0.2%‡§	1.3%‡	2.1%§	0.007
At least one major morbidity** (%)	34.1%	38.4%	35.4%	0.189
No major morbidities (%)	65.1%	61.6%	64.6%	
1 major morbidity (%)	27.7%	30.3%	28.9%	
2 major morbidities (%)	3.9%	5.6%	4.1%	
>2 major morbidities (%)	2.5%	2.5%	2.4%	

*Kruskal-Wallis.
†Survival prediction calculated using model described by van Beek *et al*.
‡Statistically significant difference between period 0 and period 1.
§Statistically significant difference between period 0 and period 2.
¶Statistically significant difference between period 1 and period 2.
**At least one of the following neonatal complications: chronic lung disease (defined as at least 28 cumulative days of oxygen therapy), intraventricular haemorrhage grade III and IV (defined by Papile's classification), posthaemorrhagic ventricle dilatation requiring intervention, cystic periventricular leukomalacia grade II and III (defined by de Vries' classification), laser coagulation for retinopathy of prematurity and necrotising enterocolitis with indication for surgery.
GA, gestational age.

the time of discharge and the effect of severe complications on LoS are presented in tables 3 and 4. LoS at the NICU and corrected GA at the time of transfer did not change significantly during the study period. However, the results approached statistical significance, indicating a trend towards longer durations of hospitalisation. Total LoS increased 5.1 days between period 1 and period 3 after accounting for confounding variables (95% CI 2.2 to 8.0, p<0.001) (table 5). LoS at the NICU, depending on GA and the occurrence of severe complications are shown in figure 1. LoS, depending on the presence or absence of various variables during the different time periods, is illustrated using boxplots (see online supplemental appendix 3). In table 5, the results of the multivariable analysis of LoS at the NICU and overall LoS are presented. Most infants with NEC were also diagnosed with CLD. In survivors, there was a difference in overall LoS per period, adjusted for SGA, NEC, PHVD, CLD, late-onset sepsis and ROP. In the final model, some interactions were significant: the variables SGA, NEC and CLD had significantly different effects on LoS during the three time periods. In the final model of total LoS, the variables GA, mode of delivery, sex and multiple births were no longer significant. Exclusion of infants with a GA <25 weeks at the time of birth did not alter the observed results regarding trends in LoS (see online supplemental appendix 4).

DISCUSSION

Trends regarding overall LoS until discharge home

This study aimed to investigate changes in overall LoS, encompassing both the duration of stay at the NICU and the level II departments. After accounting for

Table 3 Patient characteristics at the time of discharge during three time periods

Discharge characteristics	Period 1: 2008–2010	Period 2: 2011–2015	Period 3: 2016–2021	P value*
All survivors	n=563	n=969	n=946	
Corrected GA (weeks) at the time of first discharge from the NICU (median IQR)	32.6 (31.9–33.9)	32.4 (31.6–34.1)	32.7 (31.9–34.6)	0.051
LoS of first admission at the NICU (days) (median IQR)	18 (10–36)	17 (10–44)	20 (11–43)	0.060
Respiratory support at the time of first discharge from the NICU	None: 56%†¶ Low flow: 43% HHFNC: 0% nCPAP: 1%	None: 42%¶§ Low flow: 55% HHFNC: 1% nCPAP: 2%	None: 44%†§ Low flow: 20% HHFNC: 24% nCPAP: 12%	<0.001
Readmission rate (%)	8.0%	7.6%	5.5%	0.092
Infants transferred to level II department (%)	98%†	96%	94%†	0.002
Infants transferred home from level II hospital (%)	95%	94%	92%	0.070
Corrected GA (weeks) at the time of discharge home (from NICU or level II hospital) (median IQR)	37.4†¶ (36.6–39.0)	37.9¶ (36.7–39.9)	38.0† (36.9–40.0)	<0.001
Total duration hospitalisation NICU (days) (median IQR)	18 (11–39)	18 (10–45)	21 (11–44)	0.070
Total duration hospitalisation level II hospital (days) (median IQR)	32*¶ (27–40)	36¶ (28–45)	35†(28–45)	<0.001
Total duration hospitalisation: NICU+level II hospital (days) (median IQR)	55*¶ (44–72)	60¶ (45–84)	61† (46–82)	<0.001
Survivors without major morbidities‡	n=371	n=597	n=611	
Corrected GA (weeks) at the time of first discharge from the NICU (median IQR)	32.3¶	32.0¶§	32.1§	<0.001
LoS of first admission at the NICU (median IQR)	13¶ (8–18)	11§¶ (8–15)	13§ (8–20)	<0.001
Corrected GA (weeks) at the time of discharge home (from NICU or level II hospital) (median IQR)	37.0 (36.3–38.3)	37.1§ (36.3–38.3)	37.3§ (36.6–38.6)	0.017
Total duration hospitalisation: NICU+level II hospital (days) (median IQR)	48† (40–58)	49§ (41–59)	51†§ (42–63)	0.020
Survivors with at least one major morbidity ‡	n=192	n=372	n=335	
Corrected GA (weeks) at the time of first discharge from the NICU (median IQR)	34.1§¶ (32.7–36.2)	35.0¶ (33.0–37.6)	35.1† (33.3–37.6)	0.003
LoS of first admission at the NICU (median IQR)	45†¶ (33–60)	53¶ (38–76)	52† (38–76)	0.001
Corrected GA (weeks) at the time of discharge home (from NICU or level II hospital) (median IQR)	38.6†¶ (37.4–40.9)	39.9¶ (38.1–42.1)	40.0† (38.3–42.1)	<0.001
Total duration hospitalisation: NICU+level II hospital (days) (median IQR)	77†¶ (64–94)	90¶ (74–110)	88† (71–109)	<0.001

*Kruskal-Wallis test
†Statistically significant difference between period 0 and period 2.
‡At least one of the following neonatal complications: chronic lung disease (defined as at least 28 cumulative days of oxygen therapy), intraventricular haemorrhage grade III and IV (defined by Papile's classification), posthemorrhagic ventricle dilatation requiring intervention, cystic periventricular leukomalacia grade II and III (defined by de Vries' classification), laser coagulation for retinopathy of prematurity and necrotising enterocolitis with indication for surgery.
§Statistically significant difference between period 1 and period 2.
¶Statistically significant difference between period 0 and period 1.
GA, gestational age; HHFNC, humidified high-flow nasal cannula; LoS, length of stay; nCPAP, nasal continuous positive airway pressure; NICU, neonatal intensive care unit.

confounding variables, we found a median increase of 6 days in the overall LoS for surviving preterm infants born below 32 weeks of gestation between 2008 and 2021. This increase was primarily driven by extended stays at level II hospitals. Similar trends of increased LoS have been reported in other recent studies.[8 15 16] However, these studies did not differentiate between or include the LoS at the NICU and the level II hospitals.

Variables influencing LoS

We observed a strong association between severe complications of preterm birth and LoS at the NICU, as well as

Table 4 Patient characteristics at the time of discharge depending on type of receiving level II department

Discharge characteristics	Non-postintensive care/high care level II department n=699 (31%)	Postintensive care/high care level II department n=1606 (69%)	P value*
GA at birth (weeks) (median IQR)	30.3 (28.6–31.1)	29.7 (28.0–30.9)	<0.001
At least one major morbidity† (%)	33.5%	33.7%	0.899
Corrected GA at the time of first discharge from the NICU (weeks) (median IQR)	32.9 (32.1–34.6)	32.3 (31.4–33.6)	<0.001
Respiratory support at the time of first discharge from the NICU (%)	None: 55% Low flow: 38% HHFNC: 6% nCPAP: 1%	None: 38% Low flow: 43% HHFNC: 12% nCPAP: 7%	<0.001
Corrected GA at the time of discharge home (weeks) (median IQR)	38.0 (37.0–39.7)	37.6 (36.6–39.4)	0.001

*Mann-Whitney U test.
†At least one of the following neonatal complications: chronic lung disease (defined as at least 28 cumulative days of oxygen therapy), intraventricular haemorrhage grade III and IV (defined by Papile's classification), posthemorrhagic ventricle dilatation requiring intervention, cystic periventricular leukomalacia grade II and III (defined by de Vries' classification), laser coagulation for retinopathy of prematurity and necrotising enterocolitis with indication for surgery.
GA, gestational age; HHFNC, humidified high-flow nasal cannula; nCPAP, nasal continuous positive airway pressure; NICU, neonatal intensive care unit.

overall LoS. Infants *without severe complications* exhibited a consistent LoS at the NICU, with a modest increase of 3 days in the overall hospitalisation during the study period. In contrast, infants experiencing *at least one severe complication* showed a substantial prolongation of 7 days in NICU stays and an overall hospitalisation increase of 11 days. We hypothesise that (the treatment of) severe ROP may have contributed to this extended hospitalisation, considering the observed rise in the incidence of this complication during the study period. These findings underscore and confirm the significant impact of complications on the LoS of very preterm infants.[21] This emphasises the importance of comprehensive care and tailored interventions to address the complexities associated with these medical illnesses.

Complications of preterm birth were strongly associated with LoS when compared with GA. However, extremely preterm infants are more prone to experiencing severe complications associated with preterm birth, for example, all infants with a GA of 24 weeks developed CLD.[8] Our observations indicate that the treatment of infants with a lower GA at the time of birth (related to lowering the threshold for active treatment) and treating infants with severe complications of preterm birth may have contributed to an increased LoS. This supports previous research suggesting that the treatment of *extremely preterm infants* has a significant impact on LoS.[8 15 21–24] This is especially important considering the fact that the guideline is currently being evaluated in the Netherlands to determine whether the threshold should be lowered even further. The models described in this study can be used to predict the LoS of individual infants. Factors most strongly associated with LoS were severe complications of preterm birth occurring relatively late during the NICU stay (eg, CLD and ROP).

Trends regarding morbidity and mortality

Our findings did not show an improved survival rate, which suggests that the prolonged LoS cannot be directly attributed to more vulnerable infants surviving to discharge. However, the overall survival rate is a crude measure that might not capture all dynamic changes. A small number of vulnerable infants surviving could drive a change in LoS without changing overall survival rates. It is possible that the sample size was not large enough to investigate this aspect in more detail. Our study did reveal several improvements in outcome and care. We observed a decrease in the frequency and median duration of mechanical ventilation, as well as a decline in the incidence of late-onset sepsis. These positive changes, along with a stable mortality rate and a lower median GA at birth, are encouraging. They suggest advancements in preventive strategies and the overall care provided to these vulnerable infants. Furthermore, in all three periods, the observed mortality was lower than the mortality predicted by the model of van Beek *et al*.[18] The increased incidence of severe ROP was expected due to the revision of guidelines regarding saturation thresholds during the study period.[25]

Changing patterns of transfer

Traditionally, level II hospitals primarily received infants who were considered 'feeders' and 'growers' requiring minimal respiratory support after being transferred from a NICU.[26] In contrast, our study revealed a shifting trend, with more infants requiring intensive forms of

Table 5 Model most accurately describing the association between LoS and perinatal variables of surviving infants

	Model dependent variable LoS at the NICU (days)		Model: dependent variable verall LoS (days) hospital (NICU+level II)	
	Coefficient of the model with 95% CI		Coefficient of the model with 95% CI	
Constant	14.9	12.9 to 16.9	48.2	45.9 to 50.5
Factors	Additional days of admission on top of '*constant*'		Additional days of admission on top of '*constant*'	
SGA	2.3	0.6 to 3.9	7.4	2.8 to 12.1
Multiplet	2.0	0.6 to 3.5		
Period 2	−1.2	−3.1 to −0.8	2.0	−0.9 to 4.9
Period 3	1.9	−0.1 to 3.9	5.1	2.2 to 8.0
CLD	35.2	32.4 to 38.1	30.5	26.6 to 34.4
NECs	−2.2	−11.7 to 7.8	−4.2	−15.6 to 7.3
PHVD intervention	18.4	11.7 to 25.0	14.3	7.1 to 21.6
ROP intervention	38.1	31.1 to 45.1	29.6	22.0 to 37.3
Late-onset sepsis	5.2	3.5 to 6.9	5.9	3.6 to 8.1
Discharge to post-IC/HC department	−3.2	−4.6 to −1.7		
Extra days CLD period 2	4.4	0.9 to 7.9	9.1	4.3 to 13.9
Extra days CLD period 3	5.5	1.9 to 9.1	8.2	3.3 to 13.1
Extra days NECs period 2	16.5	4.4 to 28.6	34.1	20.4 to 47.7
Extra days NECs period 3	5.8	−5.9 to 17.5	−0.9	−14.8 to 12.9
Extra days SGA period 2			−6.3	−12.0 to −0.5
Extra days SGA period 3			−7.9	−13.9–−1.9

Model LoS at the NICU.
LoS (days)=14.9+(2.3*SGA)+(2.0*Multiplet)+(−1.2*Period 2)+(1.9*Period 3)+(5.2*late-onset sepsis)+(−2.2*necrotising encerocolitis with laparotomy)+(16.5*Period 2*necrotising encerocolitis with laparotomy)+(5.8*Period 3*necrotising encerocolitis with laparotomy)+(18.4*PHVD with intervention)+(35.2*CLD)+(4.4*Period 2*CLD)+(5.5*Period 3*CLD)+(38.1*ROP with intervention)+(−3.2*discharge to post-IC/HC).
Model overall LoS.
LoS (days)=48.2+(7.4*SGA)+(−6.3*Period 2*SGA)+(−7.9*Period 3*SGA)+(2.0*Period 2)+(5.1*Period 3)+(5.9*late-onset sepsis)+(−4.2*necrotising encerocolitis with laparotomy)+(34.0*Period 2*necrotising encerocolitis with laparotomy)+(−0.9*Period 3*necrotising encerocolitis with laparotomy)+(14.3*PHVD with intervention)+(30.5*CLD)+(9.1*Period 2*CLD)+(8.2*Period 3*CLD)+(29.6*ROP with intervention).
CLD, chronic lung disease; IC/HC, intensive care/high care; LoS, length of stay; NEC, necrotising enterocolitis with indication for surgery; NICU, neonatal intensive care unit; PHVD, posthaemorrhagic ventricle dilatation; ROP, retinopathy of prematurity; SGA, small for gestational age.

non-invasive respiratory support (HHFNC or CPAP) being transferred. This change can be attributed to the increasing demands on our NICU, operating at full capacity, due to a growing population of (extremely premature) infants with higher care needs and staffing issues.[27] Transferring stable, yet still vulnerable, infants who require intensive non-invasive respiratory support is necessary to optimise resource utilisation and maintain access to care.[28–30] However, the transfer of these complex infants necessitates close coordination and communication among healthcare providers to ensure patient safety. Despite the increasing complexity and higher care needs, our study did not observe an increase in readmission rates during the study period. This finding suggests that healthcare providers at level II hospitals have adapted to the changing needs of these infants and are providing effective treatment. Furthermore, our results revealed that infants transferred to post-IC/HC level II departments more frequently were on intensive respiratory support and had a lower corrected GA at the time of transfer compared with non-post-IC/HC facilities. It is intriguing to note that despite these factors, infants transferred to post-HC departments were discharged home at a lower corrected GA. Exploring these differences in future research may help optimise care pathways and provide insights into ways to reduce LoS.

Potential consequences of increasing LoS

Despite multiple interventions aimed at reducing LoS and transferring infants to intensive non-invasive respiratory support, our study revealed an increased overall LoS and longer LoS at the NICU for infants with major morbidities. This prolonged hospitalisation has significant consequences that need to be considered. From a healthcare perspective, the increased LoS places *additional strain on resources*, especially when NICUs are already

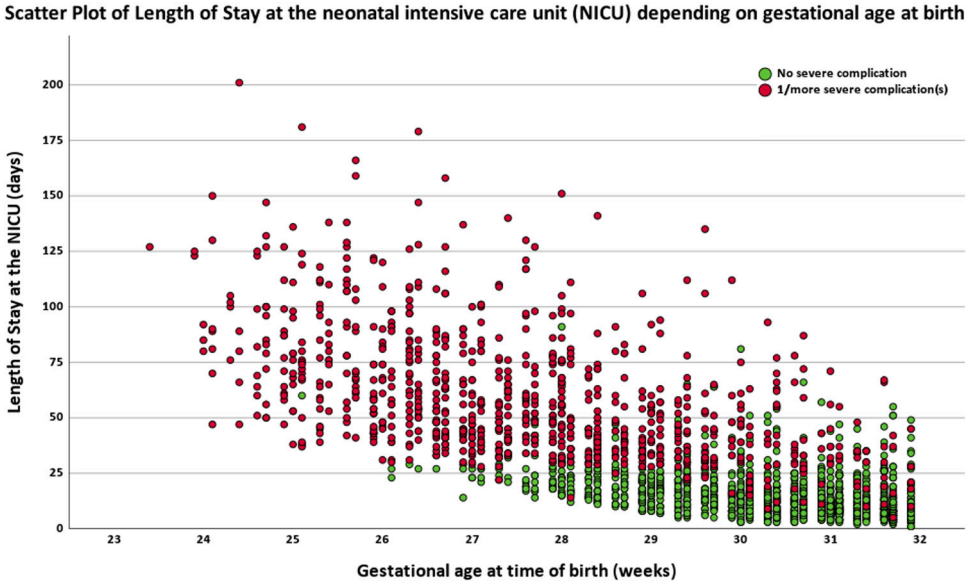


Figure 1 Scatter plot indicating the length of stay at the neonatal intensive care unit of surviving infants depending on gestational age at the time of birth and the occurrence of severe complications. The severe complication was defined as one/more of the following neonatal complications: chronic lung disease (defined as at least 28 cumulative days of oxygen therapy), intraventricular haemorrhage grade III and IV (defined by Papile's classification), posthaemorrhagic ventricular dilatation requiring intervention, cystic periventricular leukomalacia grade II and III (defined by de Vries' classification), laser coagulation for retinopathy of prematurity and necrotising enterocolitis with an indication for surgery. All infants born at a gestational age of 24 weeks and most of the infants born at 25 weeks gestation showed one or more complications.

operating at maximum capacity.[1 2 4 15 31–33] Reaching or exceeding the capacity can lead to compromised patient safety and place additional strain on healthcare providers. Moreover, reports have indicated a direct correlation between increased LoS and higher healthcare expenditure.[15] For the *infants themselves*, the extended hospitalisation may result in adverse outcomes since the NICU environment is associated with risks such as healthcare-associated infections.[1 34–36] Furthermore, the prolonged LoS influences the *families* of the infants in various ways. Parents may experience increased emotional and financial burdens due to the prolonged separation from their infants and the need to balance work and other responsibilities.[37] Efforts to optimise LoS are closely linked to those enhancing the quality of care and are both vital for improving patient outcomes, optimal resource utilisation and minimising healthcare costs.[15 16] Our findings indicate that focusing on reducing the occurrence of severe complications associated with preterm birth could positively impact both LoS at the NICU and overall LoS.

LIMITATIONS

This study examines LoS in a single, although relatively large, NICU. Previous research has identified variations in LoS across different healthcare systems.[7 16] Our NICU is located in a highly regionalised area, with a high percentage of infants being transferred. The generalisability of our findings may be limited in less regionalised areas. Additionally, organisational factors such as bed capacity were not included and accounted for in our study. In addition, we have no data regarding foetal deaths, deaths before admission to the NICU, or infants for whom it was decided not to initiate intensive care treatment in the delivery room. Another limitation is the fact that variables such as socioeconomic status, ethnicity and pregnancy-related complications were not included.

CONCLUSION

Our findings demonstrate a significant increase in overall LoS for infants born with a GA below 32 weeks between 2008 and 2021. This increase is primarily driven by the treatment of extremely premature infants and those experiencing severe complications. The prolonged LoS could potentially have far-reaching implications for healthcare systems, families and the infants themselves. Using this information, parents could be better informed about the expected LoS of their preterm born infant. In addition, knowledge of the influence of complications on LoS could guide the benchmarking of NICUs in order to reduce these complications.

Acknowledgements We gratefully acknowledge the efforts of J Hoften (Elizabeth Hospital), M Kleinhout (St. Antonius Hospital), S Hoeks (Diakonessen Hospital) and C Meijssen (Meander Hospital).

Contributors KdB-M is the principal investigator, conducted the manual medical record review of all individual records, wrote the first draft of the manuscript and acted as guarantor. MK assisted in data collection. FG was responsible for data analyses and interpretation. All authors (KdB-M, MJNLB, JD, KA, MK and FG) contributed to the conception and design of this study. All authors (KdB-M, MJNLB, JD, KA, MK and FG) approved the final version of the manuscript for accuracy, completeness and publication.

Funding Publication of the manuscript was funded by ZonMw Den Hague, grant number 10130022010008.

Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Ethics approval The data of patients were pseudonymizsed before analysis, and stored according to European requirements. The Medical Research Ethics Committee of Utrecht granted exemption from formal approval under the Dutch Medical Research Involving Human Subjects Act for the study, using pseudonymizsed data (NedMec; number 22/588). Due to the utilisation of pseudonymizsed data, the size of the cohort and the retrospective design of the study, informed consent was noteither sought nor required from participants.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request.

ORCID iDs
Karen de Bijl-Marcus http://orcid.org/0000-0001-5116-6092
Kees Ahaus http://orcid.org/0000-0001-9973-3746

REFERENCES

1 DeRienzo C, Kohler JA, Lada E, *et al*. Demonstrating the relationships of length of stay, cost and clinical outcomes in a simulated NICU. *J Perinatol* 2016;36:1128–31.
2 Sharma D, Murki S. Making neonatal intensive care: cost effective. *J Matern Fetal Neonatal Med* 2021;34:2375–83.
3 Kim Y, Ganduglia-Cazaban C, Chan W, *et al*. Trends in neonatal intensive care unit admissions by race/Ethnicity in the United States, 2008–2018. *Sci Rep* 2021;11:23795.
4 Walsh E, Li S, Black L, *et al*. Incremental cost of Prematurity by week of gestational age. *AJP Rep* 2019;09:e76–83.
5 Gay JC, Hall M, Morse R, *et al*. Observation encounters and length of stay Benchmarking in children's hospitals. *Pediatrics* 2020;146.
6 Brown CM, Williams DJ, Hall M, *et al*. Trends in length of stay and Readmissions in children's hospitals. *Hosp Pediatr* 2021;11:554–62.
7 Wen SW, Liu S, Fowler D. Trends and variations in neonatal length of in-hospital stay in Canada. *Can J Public Health* 1998;89:115–9.
8 Edwards EM, Greenberg LT, Ehret DEY, *et al*. Discharge age and weight for very Preterm infants: 2005⇓2018. *Pediatrics* 2021;147:e2020016006.
9 Costeloe KL, Hennessy EM, Haider S, *et al*. 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.
10 Gonya J, Martin E, McClead R, *et al*. Empowerment programme for parents of extremely premature infants significantly reduced length of stay and readmission rates. *Acta Paediatrica* 2014;103:727–31.
11 Moody C, Callahan TJ, Aldrich H, *et al*. Early initiation of newborn individualized developmental care and assessment program (NIDCAP) reduces length of stay: A quality improvement project. *J Pediatr Nurs* 2017;32:59–63.
12 Lehtonen L, Lee SK, Kusuda S, *et al*. Family rooms in neonatal intensive care units and neonatal outcomes: an international survey and linked cohort study. *J Pediatr* 2020;226:112–7.
13 Ortenstrand A, Westrup B, Broström EB, *et al*. The Stockholm neonatal family centered care study: effects on length of stay and infant morbidity. *Pediatrics* 2010;125:e278–85.
14 Melnyk BM, Feinstein NF, Alpert-Gillis L, *et al*. Reducing premature infants' length of stay and improving parents' mental health outcomes with the creating opportunities for parent empowerment (COPE) neonatal intensive care unit program: A randomized, controlled trial. *Pediatrics* 2006;118:e1414–27.
15 Yeung T, Rios JD, Beltempo M, *et al*. The trend in costs of tertiary-level neonatal intensive care for neonates born Preterm at 220/7-286/7 weeks of gestation from 2010 to 2019 in Canada. *J Pediatr* 2022;245:72–80.
16 Maier RF, Blondel B, Piedvache A, *et al*. Duration and time trends in hospital stay for very Preterm infants differ across European regions. *Pediatr Crit Care Med* 2018;19:1153–61.
17 Manktelow BN, Seaton SE, Field DJ, *et al*. Population-based estimates of in-unit survival for very Preterm infants. *Pediatrics* 2013;131:e425–32.
18 van Beek PE, Groenendaal F, Onland W, *et al*. Prognostic model for predicting survival in very Preterm infants: an external validation study. *BJOG* 2022;129:529–38.
19 Papile LA, Burstein J, Burstein R, *et al*. Incidence and evolution of Subependymal and Intraventricular hemorrhage: A study of infants with birth weights less than 1,500 GM. *J Pediatr* 1978;92:529–34.
20 de Vries LS, Eken P, Dubowitz LM. The spectrum of leukomalacia using cranial ultrasound. *Behav Brain Res* 1992;49:1–6.
21 Seaton SE, Barker L, Jenkins D, *et al*. What factors predict length of stay in a neonatal unit: a systematic review. *BMJ Open* 2016;6:e010466.
22 Bender GJ, Koestler D, Ombao H, *et al*. Neonatal intensive care unit: predictive models for length of stay. *J Perinatol* 2013;33:147–53.
23 Zhang M, Wang Y-C, Feng J-X, *et al*. Variations in length of stay among survived very Preterm infants admitted to Chinese neonatal intensive care units. *World J Pediatr* 2022;18:126–34.
24 Seaton SE, Draper ES, Abrams KR, *et al*. Can we estimate the length of stay of very Preterm multiples *Arch Dis Child Fetal Neonatal Ed* 2019;104:F568–70.
25 Askie LM, Darlow BA, Davis PG, *et al*. Effects of targeting lower versus higher arterial oxygen saturations on death or disability in Preterm infants. *Cochrane Database Syst Rev* 2017;4:CD011190.
26 Lainwala S, Perritt R, Poole K, *et al*. Neurodevelopmental and growth outcomes of extremely low birth weight infants who are transferred from neonatal intensive care units to level I or II nurseries. *Pediatrics* 2007;119:e1079–87.
27 Capaciteitsorgaan. Capaciteitsplan 2020-2023. Utrecht, 2020. Available: https://capaciteitsorgaan.nl/app/uploads/2020/11/20200119_Capaciteitsplan-FZO-AVP-2020_DEF-WEB.pdf
28 Wise J. Neonatal units in Wales are Understaffed and under-Resourced, says report. *BMJ* 2016;i3768.
29 Rogowski JA, Staiger D, Patrick T, *et al*. Nurse staffing and Nicu infection rates. *JAMA Pediatr* 2013;167:444–50.
30 Rogowski JA, Staiger DO, Patrick TE, *et al*. Nurse staffing in neonatal intensive care units in the United States. *Res Nurs Health* 2015;38:333–41.
31 Rolnitsky A, Unger SL, Urbach DR, *et al*. Cost of neonatal intensive care for extremely Preterm infants in Canada. *Transl Pediatr* 2021;10:1630–6.
32 Perin J, Mulick A, Yeung D, *et al*. Global, regional, and national causes of Under-5 mortality in 2000–19: an updated systematic analysis with implications for the sustainable development goals. *Lancet Child Adolesc Health* 2022;6:106–15.
33 Zein H, Yusuf K, Paul R, *et al*. Elective transfers of Preterm neonates to regional centres on non-invasive respiratory support is cost effective and increases tertiary care bed capacity. *Acta Paediatrica* 2018;107:52–6.
34 Merritt TA, Pillers DA, Prows SL. Early NICU discharge of very low birth weight infants: A critical review and analysis. *Semin Neonatol* 2003;8:95–115.
35 Santos J, Pearce SE, Stroustrup A. Impact of hospital-based environmental exposures on neurodevelopmental outcomes of Preterm infants. *Curr Opin Pediatr* 2015;27:254–60.
36 Flacking R, Lehtonen L, Thomson G, *et al*. Closeness and separation in neonatal intensive care. *Acta Paediatrica* 2012;101:1032–7.
37 Caporali C, Pisoni C, Gasparini L, *et al*. A global perspective on parental stress in the neonatal intensive care unit: a meta-analytic study. *J Perinatol* 2020;40:1739–52.

APPENDIX 1: Level of neonatal care categories.

LEVEL OF CARE	CARE DELIVERED	CARE PROVIDERS
LEVEL I **Well new born** neonatology department	- Provide neonatal resuscitation at every delivery - Evaluate and provide postnatal care to stable term newborn infants - Stabilize and provide care for infants born 35–37 wk gestation who remain physiologically stable - Stabilize newborn infants who are ill and those born at <35 wk gestation until transfer to a higher level of care	Pediatricians, family physicians, nurse practitioners, and other advanced practice registered nurses
LEVEL II **Special care** neonatology department	*Level I capabilities plus:* - Provide care for infants born ≥32 wk gestation and weighing ≥1500[A] g who have physiologic immaturity or who are moderately ill with problems that are expected to resolve rapidly and are not anticipated to need subspecialty services on an urgent basis - Provide care for infants convalescing after intensive care - Provide mechanical ventilation for brief duration (<24 h) or continuous positive airway pressure or both - Stabilize infants born before 32 wk gestation and weighing less than 1500[A] g until transfer to a neonatal intensive care facility	*Level I health care providers plus* Pediatric hospitalists, neonatologist, and neonatal nurse practitioners.
Level III **NICU**	*Level II capabilities plus:* - Provide sustained life support - Provide comprehensive care for infants born <32 wks gestation and weighing <1500[A] g and infants born at all gestational ages and birth weights with critical illness - Provide prompt and readily available access to a full range of pediatric medical subspecialists, pediatric surgical specialists, pediatric anesthesiologists, and pediatric ophthalmologists - Provide a full range of respiratory support that may include conventional and/or high-frequency ventilation and inhaled nitric oxide - Perform advanced imaging, with interpretation on an urgent basis, including computed	*Level II health care providers plus:* Pediatric medical subspecialists, pediatric anesthesiologists, pediatric surgeons, and pediatric ophthalmologists.
LEVEL IV **Regional NICU**	*Level III capabilities plus:* Located within an institution with the capability to provide: - Surgical repair of complex congenital or acquired conditions - Maintain a full range of pediatric medical subspecialists, pediatric surgical subspecialists, and pediatric anesthesiologists at the site - Facilitate transport and provide outreach education	Level III health care providers plus: Pediatric surgical subspecialists

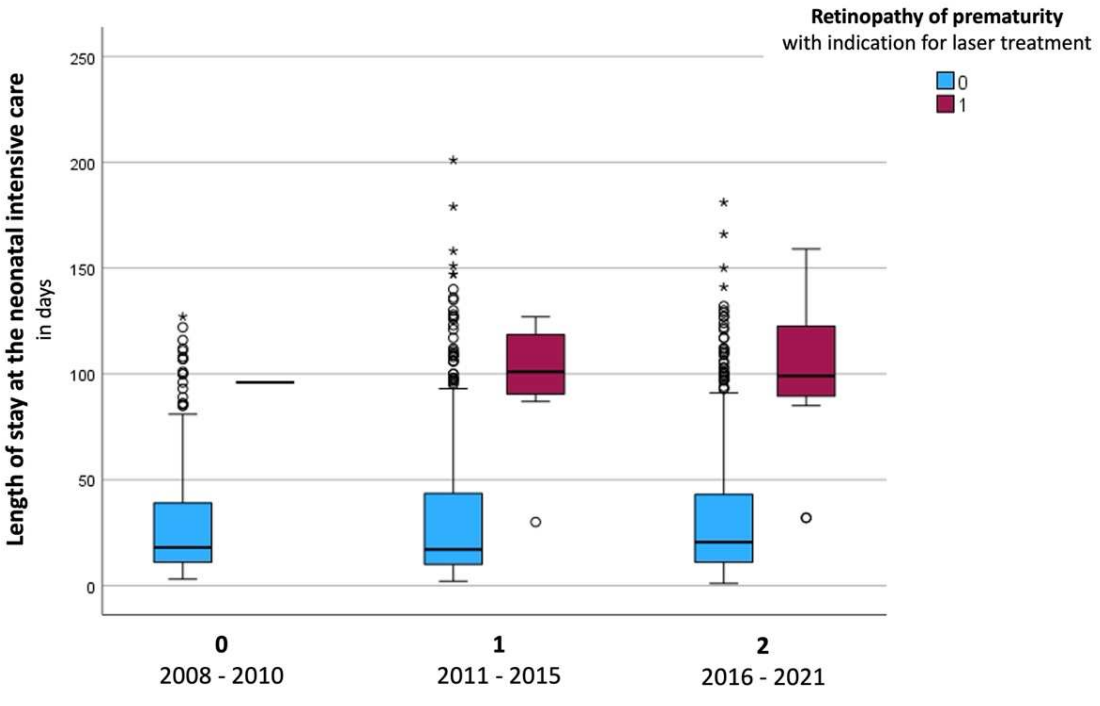
[A]: In the Netherlands, level II facilities provide care to infants born at ≥32.0 weeks gestation and weighing ≥**1200** grams. Level II post intensive care/high care department provide convalescent care to infants [39]

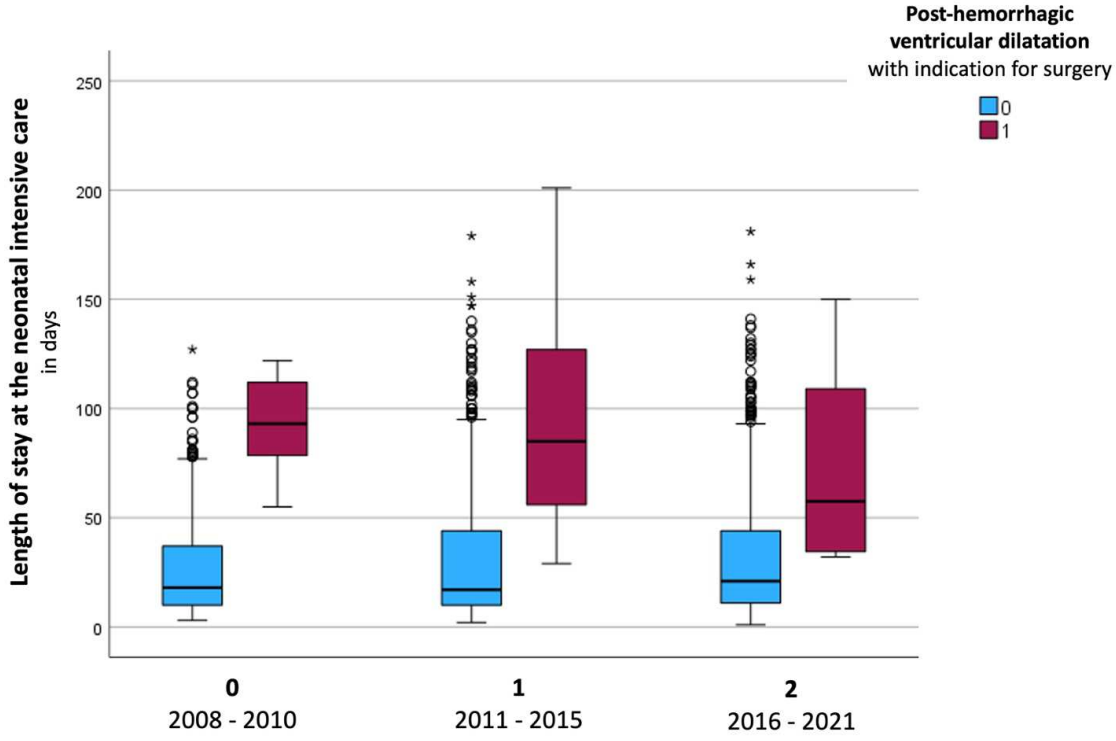
APPENDIX 2: Complete list of tested variables associated with Length of Stay at the NICU and total duration of hospitalization

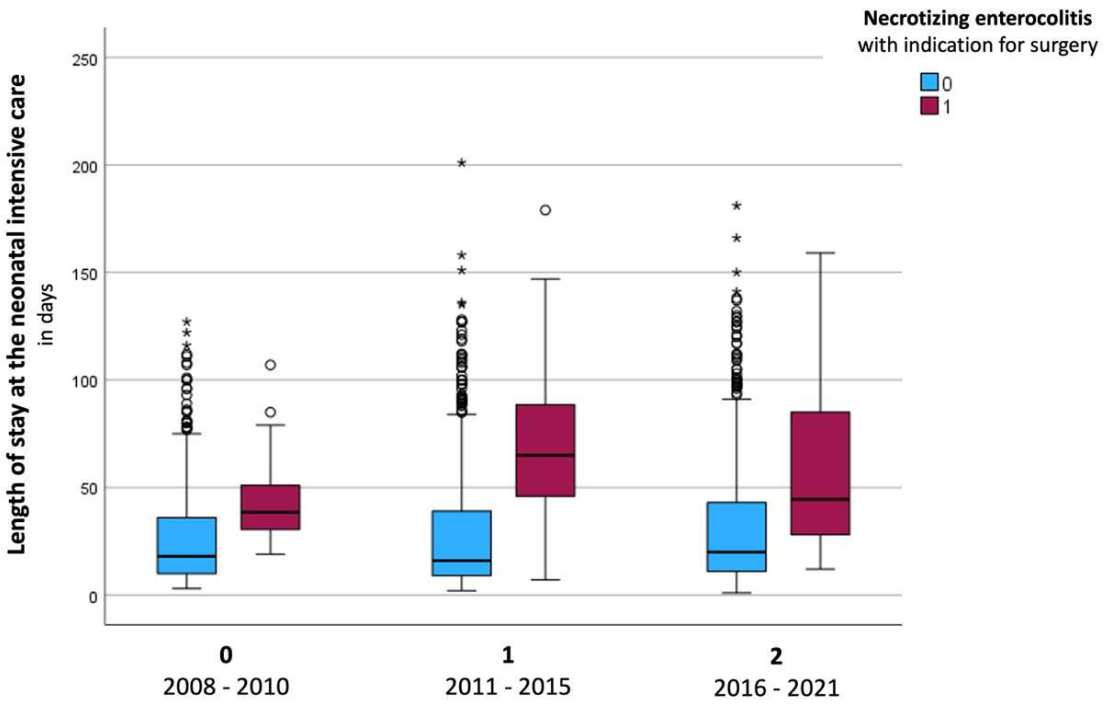
GA (days) at birth
Sex
Birthweight percentile
Small for gestational age (% < 3rd percentile)
Small for gestational age (% <10th percentile)
Multiple pregnancy
Antenatal corticosteroids
Cesarean section
Inborn
Apgar score at 5 minutes
Intraventricular hemorrhage grade III and/or cerebral venous infarction (grade IV IVH)
Posthemorrhagic ventricular dilatation
Cystic periventricular leukomalacia
Necrotizing enterocolitis with laparotomy
Mechanical ventilation
Chronic lung disease
Medication for persistent ductus arteriosus
Surgical ligation persistent ductus arteriosus
Late onset sepsis
Retinopathy of prematurity with laser coagulation
Transfer to a PostIC/High care level II department

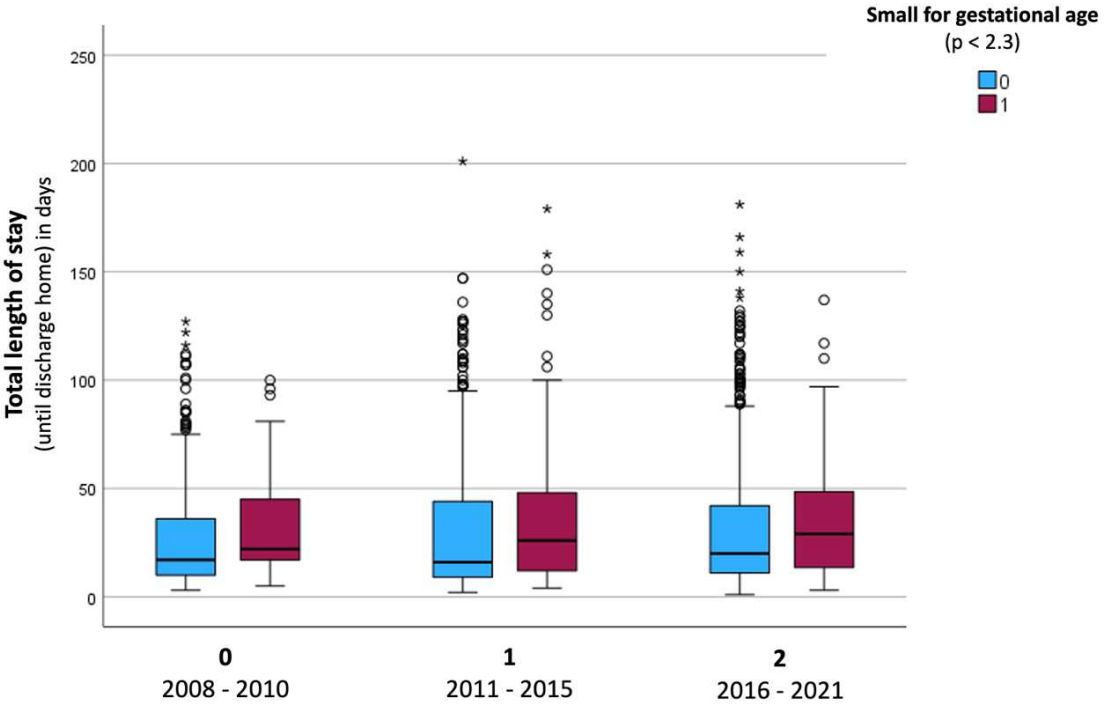
de Bijl-Marcus K, *et al*. *BMJ Open* 2024; 14:e078842. doi: 10.1136/bmjopen-2023-078842

APPENDIX 3: Boxplots regarding the relation between length of stay of surviving infants and various variables during the different time periods.






Necrotizing enterocolitis
with indication for surgery
0
1
Length of stay at the neonatal intensive care
in days
250
200
150
100
50
0
0
2008 - 2010
1
2011 - 2015
2
2016 - 2021


Small for gestational age
(p < 2.3)
0
1
Total length of stay
(until discharge home) in days
250
200
150
100
50
0
0
2008 - 2010
1
2011 - 2015
2
2016 - 2021

APPENDIX 4: Model most accurately describing the association between length of stay and perinatal variables of surviving infants excluding infants born at a gestation age below 25.0 weeks

	MODEL: dependent variable LoS at the NICU (days)		***MODEL: dependent variable overall LoS (days) hospital (NICU + level II)***	
	Coefficient of the model with 95% C.I.		**Coefficient of the model with 95% C.I.**	
Constant	**14.9**		**48.3**	
Factors	**Additional days of admission on top of '*constant*'**		**Additional days of admission on top of '*constant*'**	
SGA	2.9	1.3 – 4.5	7.7	3.2- 12.3
Multiplet	2.0	0.6 - 3.4		
Period 2	-1.2	-3.1- -0.7	1.8	-1.0 - 4.6
Period 3	1.9	-0.0 - 3.8	4.9	2.1 – 7.7
CLD	35.2	32.5 - 38.0	30.2	26.4 - 34.1
NECs**	-1.9	-11.0 - 7.3	-3.4	-14.5 - 7.7
PHVD intervention	13.5	6.8 – 20.3	9.1	1.7 – 16.6
ROP intervention	38.2	29.5 – 46.9	29.6	22.0 - 37.3
Late onset sepsis	4.8	3.1 - 6.4	4.9	2.6 – 7.2
Discharge to postIC/HC dep	-3.1	-4.5- -1.8		
Extra days CLD period 2	3.0	-0.4 – 6.5	8.1	3.4 - 12.9
Extra days CLD period 3	3.3	-0.2 – 6.8	6.2	1.3 – 11.0
Extra days NECs period 2	17.7	6.1 - 29.2	34.5	21.1 - 47.8
Extra days NECs period 3	7.6	-3.6 – 18.9	-0.3	-13.9 – 13.4
Extra days SGA period 2			-5.8	-11.4 - -0.2
Extra days SGA period 3			-7.1	-12.9 - -1.3

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	Page 1 Line 1-2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	Page 2 Line 20-44
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	Page 4 Line 76-98
Objectives	3	State specific objectives, including any prespecified hypotheses	Page 4-5 Line 99-103
Methods			
Study design	4	Present key elements of study design early in the paper	Page 5 Line 106-108
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	Page 5-7 Line 119-164
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	Page 5 Line 112-117
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	N.a.
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	Page 6-7 Line 143-164
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	Page 5 Line 107–108 Page 7 Line 163-164
Bias	9	Describe any efforts to address potential sources of bias	Page 7 Line 163-164
Study size	10	Explain how the study size was arrived at	All admitted infants were included during the study period
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	Page 5 Line 119-125
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	Page 7 Line 167-177
		(*b*) Describe any methods used to examine subgroups and interactions	Page 7 Line 173 Table 5
		(*c*) Explain how missing data were addressed	Page 7 Line 164
		(*d*) If applicable, explain how loss to follow-up was addressed	N.a.
		(*e*) Describe any sensitivity analyses	One separate analysis was performed as requested by one of the reviewers, pertaining the infants with a GA > 24+6 weeks

Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	Page 8 Line 187-188 Table 1-2
		(b) Give reasons for non-participation at each stage	N.a.
		(c) Consider use of a flow diagram	N.a.
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Table 1
		(b) Indicate number of participants with missing data for each variable of interest	Page 8 Line 194-195
		(c) Summarise follow-up time (eg, average and total amount)	Page 6 Line 143-146
Outcome data	15*	Report numbers of outcome events or summary measures over time	Table 3 + 4
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Page 8 Line 199-200 Table 5, appendix 2
		(*b*) Report category boundaries when continuous variables were categorized	Page 5, line 120-125 Page 7, line 159-160
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	N.a.
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	Appendix 4
Discussion			
Key results	18	Summarise key results with reference to study objectives	Page 9 Line 210-215 Page 12 Line 302-309
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	Page 12 Line 290-297
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	Page 12
Generalisability	21	Discuss the generalisability (external validity) of the study results	Page 12 Line 292-299
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	Page 3 Line 58-60

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

de Bijl-Marcus K, *et al. BMJ Open* 2024; 14:e078842. doi: 10.1136/bmjopen-2023-078842