

REGULAR ARTICLE

Swiss medical centres vary significantly when it comes to outcomes of neonates with a very low gestational age

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Keywords

Neonatal morbidity, Outcome variability, Perinatal predictors, Survival, Very low-gestational-age neonates

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Received

6 January 2015; revised 6 April 2015;
accepted 19 May 2015.

DOI:10.1111/apa.13047

ABSTRACT

Aim: This study quantified the impact of perinatal predictors and medical centre on the outcome of very low-gestational-age neonates (VLGANs) born at <32 completed weeks in Switzerland.

Methods: Using prospectively collected data from a 10-year cohort of VLGANs, we developed logistic regression models for three different time points: delivery, NICU admission and seven days of age. The data predicted survival to discharge without severe neonatal morbidity, such as major brain injury, moderate or severe bronchopulmonary dysplasia, retinopathy of prematurity (\geq stage three) or necrotising enterocolitis (\geq stage three).

Results: From 2002 to 2011, 6892 VLGANs were identified: 5854 (85%) of the live-born infants survived and 84% of the survivors did not have severe neonatal complications. Predictors for adverse outcome at delivery and on NICU admission were low gestational age, low birthweight, male sex, multiple birth, birth defects and lack of antenatal corticosteroids. Proven sepsis was an additional risk factor on day seven of life. The medical centre remained a statistically significant factor at all three time points after adjusting for perinatal predictors.

Conclusion: After adjusting for perinatal factors, the survival of Swiss VLGANs without severe neonatal morbidity was strongly influenced by the medical centre that treated them.

INTRODUCTION

Survival rates and survival without morbidity increase sharply with gestational age (GA) among very low-GA neonates (VLGANs) born at <32 completed weeks, and GA has traditionally been used as the sole outcome predictor. More recently, models that have included perinatally known factors, such as estimated foetal weight, gender, single or multiple birth, antenatal corticosteroid (ANC) administration and delivery mode, have been shown to increase the accuracy of predicting survival (1–3).

Variations in the survival rates of preterm neonates have been observed between centres providing health care in

several populations and networks (4–7). Factors contributing to these differences in outcome have included the inherent risk of the patient population served, the local approach towards primary nonintervention at the border of viability and/or the effectiveness of the patient care delivered at a particular medical centre. Despite the availability of national guidelines on perinatal care at the limit of

Abbreviations

ANC, Antenatal corticosteroids; BPD, Bronchopulmonary dysplasia; CI, Confidence interval; GA, Gestational age; NICU, Neonatal intensive care unit; NEC, Necrotising enterocolitis; OR, Odds ratio; PIVH, Periventricular/intraventricular haemorrhage; PVL, Periventricular leucomalacia; ROP, Retinopathy of prematurity; VLGANs, Very low-gestational-age neonates.

Key notes

- This study quantified the impact of perinatal predictors and medical centre on the outcome of very low-gestational-age neonates (VLGANs).
- Using prospectively collected data, we identified 6892 VLGANs born in Switzerland at <32 weeks of gestation between 2002 and 2011.
- Important predictors for adverse outcomes were patient-level factors, obstetrical interventions, proven sepsis in the first week of life and the medical centre where the neonate was treated.

viability, between 22 and 26 completed weeks of gestation (8), survival rates vary widely across the nine tertiary level perinatal centres in Switzerland, even after adjusting for important patient-related factors (9,10).

The chance of survival changes rapidly throughout the first week of life in infants born at <32 weeks of gestation, due to the fact that mortality is highest during the first few days of life. Therefore, predictors for survival and short-term morbidity may vary depending on postnatal age.

Existing models that aim to predict survival or morbidity rates of VLGANs do not address the potential centre effect on outcome and do not take into account the rapidly changing chances of survival during the first few days of life. Therefore, we sought to quantify the impact of different perinatal predictors and medical centre on survival and short-term morbidity at three different time points in infants born at <32 weeks in Switzerland.

MATERIALS AND METHODS

Data sources

The Swiss Neonatal Network and Follow-Up Group maintains a database, the Minimal Neonatal Data Set (MNDS), to prospectively collect anonymised information about the demographics and outcome to the point of hospital discharge of all live-born infants weighing between 400 and 1500 g at birth and with a GA of between 23 0/7 and 31 6/7 weeks. It covers infants born at, or transferred to, one of the nine level III neonatal intensive care units (NICUs) caring for VLGANs in Switzerland. Data collection and evaluation were approved by the institutional ethical review boards and by the Swiss Federal Commission for Privacy Protection in Medical Research. In this study, data from the Swiss MNDS were used to analyse information on all VLGANs of 23–31 completed weeks born alive between January 1, 2002, and December 32, 2011.

Definition of neonatal variables

Gestational age was calculated based on ultrasound examinations during the first trimester of pregnancy and defined as the postmenstrual age in weeks and days. Birthweight standard deviation scores (z-scores) for GA were calculated based on the growth curves published by Voigt et al. (11).

Antenatal corticosteroids administration was considered to have occurred if at least one dose was given prenatally. Major congenital malformation was defined as any type of malformation that had a severe impact on prognosis, such as complex congenital heart disease or malformation syndromes. Neonatal sepsis was assumed if positive blood cultures were present. We defined major brain injury as periventricular/intraventricular haemorrhage (PIVH) \geq grade 3 (12) and/or cystic periventricular leucomalacia (PVL) (13). Diagnosis of moderate or severe bronchopulmonary dysplasia (BPD) was based on the National Institute of Child Health and Human Development consensus definition as a requirement for supplemental oxygen and/or mechanical respiratory support at 36 weeks of postmenstrual age (14). Severe retinopathy of prematurity (ROP)

was defined as \geq stage 3 as suggested by the International Committee for the Classification of Retinopathy of Prematurity (15). Necrotising enterocolitis (NEC) was diagnosed in the presence of at least intestinal pneumatosis and/or portal venous gas (Bell's stage ≥ 2) (16).

Outcome definition

The main outcome assessed was survival to discharge without severe neonatal morbidity, in other words without major brain injury, moderate or severe BPD, ROP \geq stage 3 or NEC \geq stage 2.

Time points of risk assessment

Outcome predictors were evaluated at delivery, on NICU admission and on the seventh day of life. Infants who had already died at a previous assessment time point were excluded from the following assessments.

Statistical analysis

Missing data and multiple imputation

Missing data were more frequent in nonsurvivors than in survivors, raising concerns about overestimating survival and other bias. To prevent casewise deletion of infants from analyses, we imputed missing predictor values using the multivariate normal model and generated 10 completed data sets, resulting in imputed variables of binary variables taking on noninteger values, which were then carried forward without performing rounding (17,18). Data were imputed for survivors and nonsurvivors. All nonmissing predictors and outcomes were included in the imputation model.

Predictors

Predefined predictors with high *a priori* plausibility were evaluated. The following prenatal predictors were tested at all time points: GA, z-score for birthweight, gender, singleton/multiple birth, ANC, mode of delivery, major congenital malformation and the medical centre where the infants were cared for. In addition, sepsis within the first seven days of life was evaluated at the seventh day of life.

Model assessment and selection

The following candidate logistic regression models for the binary outcomes of survival to discharge without severe neonatal morbidity were evaluated for each time point:

- A GA as the only predictor
- B All considered predictors except medical centre
- C Applying backward elimination to model B
- D Model B including medical centre
- E Applying backward elimination to model D.

Backward elimination was performed by dropping non-significant predictors (p value >0.05) one at a time until all the predictors had a p value of <0.05 .

The continuous predictors GA and z-score for birthweight were tested for departure from linearity. Nonlinearity was addressed by including GA as a categorical variable,

by weeks, and birthweight by categorising the z-score. Following the usual convention, z-score for birthweight was split into ten 0.5-range categories from <-2 to more than +2.

We chose one primary model from A to E for each time point using the following procedure: the cross-validated c-statistic was calculated across the 10 multiple imputed data sets. This resulted in 10 c-statistics for each model, which were combined using Rubin's rule to provide the final cross-validated c-statistic and confidence interval (CI) for each model (19). For each time point, the model with the highest cross-validated c-statistic was chosen as the final prediction model. Calibration of the models was assessed with plots.

The models were screened for statistically significant interactions, using the p value of the Wald test for the interaction term <0.05. This showed that including any of the interaction terms did not improve the cross-validated c-statistics. However, to examine centre-to-centre difference based on GA groups, we fitted the final models to include an interaction term for GA groups (<25 weeks, 25–27 weeks or >27 weeks) and medical centre.

Prediction

We calculated predicted survival probabilities and their 95% CIs from the combined estimates of the multiple imputed data sets by applying Rubin's rule (19). All statistical analyses were performed using Stata 13 (*Stata Statistical Software: Release 13*; StataCorp LP, College Station, TX, USA).

RESULTS

Between January 1, 2002, and December 31, 2011, 6892 infants with a GA of between 23 and 31 completed weeks were cared for at the nine level III perinatal centres in Switzerland, and 5854 (85%) infants survived. Of all the deaths, 394 (38%) occurred in the delivery room and 644 (62%) occurred in the NICU: 405 (63%) of the NICU deaths occurred early, within seven days of admission, and 239 (37%) occurred after the seventh day of life. Of the 5854 survivors, 4905 (84%) survived the neonatal period without any severe neonatal complications. Table 1 summarises the characteristics of the patient population.

The cross-validated c-statistics of the five models for each time point are listed in Table S1. The models were used for predictions after applying backward elimination for prenatal and postnatal predictors, including the medical centre. Figure S1 shows the calibration plots.

Table 2 lists the logistic regression models with the effects of the various predictors on survival without severe neonatal morbidity.

The medical centre where care was provided was statistically a highly significant predictor of outcome after adjustment for prenatal and postnatal predictors. For example, at delivery, an infant born at medical centre nine, which had the highest overall survival rate, had an odds ratio (OR) for survival without severe neonatal morbidity of 4.5 (95% CI 3.4–6.0), compared to reference centre one, which had the lowest overall survival rate. This exceeded the effect of being born at 25 weeks vs 24 weeks (OR 3.2,

Table 1 Characteristics of study population

	Survivors		Nonsurvivors	
	5854	Missing % (n)	1038	Missing % (n)
Predictors				
Gestational age in weeks and days, Mean ± SD	29 2/7 ± 14	0 (0)	26 0/7 ± 16	0 (0)
Birthweight in grams, Mean ± SD	1240 ± 370	0 (0)	840 ± 410	1 (10)
Female, % (n)	46 (2707)	0 (0)	45 (464)	0.1 (1)
ANC, % (n)	82 (4823)	4 (234)	52 (537)	13 (138)
Caesarean section, % (n)	78 (4595)	0.14 (8)	54 (565)	6 (62)
Major congenital malformation, % (n)	3 (201)	0 (0)	16 (164)	0 (0)
Multiples, % (n)	34 (1966)	0 (0)	25 (263)	0 (0)
Inborn, % (n)	94 (5479)	0 (0)	95 (982)	1 (12)
Sepsis within first seven days of life*, % (n)	3 (166)	2 (117)	6 (58)	23 (236)
Any missing predictor, % (n)		6 (353)		29 (300)
Outcomes, % (n)				
Died in delivery room	NA	NA	38 (394)	0 (0)
Died after admission to NICU but before day of life seven	NA	NA	39 (405)	0 (0)
Died after day of life seven but before discharge	NA	NA	23 (239)	0 (0)
Moderate or severe BPD	9 (548)	0.2 (9)	NA	NA
PIVH ≥ III and/or cPVL	6 (323)	0.1 (7)	NA	NA
ROP ≥ stage 3	1.8 (103)	0 (0)	NA	NA
NEC	1.8 (108)	0 (0)	NA	NA
Any severe neonatal morbidity†	16 (949)	0.3 (16)	NA	NA

ANC = Antenatal corticosteroids; BPD = Bronchopulmonary dysplasia; cPVL = Cystic periventricular leucomalacia; NEC = Necrotising enterocolitis; NICU = Neonatal intensive care unit; PIVH = Periventricular/intraventricular haemorrhage; ROP = Retinopathy of prematurity.

*For infants alive on day of life seven (n = 5705).

†Any severe neonatal morbidity: moderate/severe BPD and/or PIVH ≥ grade III and/or cPVL and/or proven NEC and/or ROP ≥ stage III.

Table 2 Logistic models of the multiple imputed data for different time points

Outcome	Survival without severe neonatal morbidity*		
	At delivery OR (95% CI)	On NICU admission OR (95% CI)	On day of life seven OR (95% CI)
Time point			
Gestational age			
23 weeks	Reference	Reference	Reference
24 vs 23 weeks	13.7 (3.3–57.4)	2.2 (0.61–8.0)	2.6 (0.64–10.3)
25 vs 24 weeks	3.2 (2.2–4.6)	2.3 (1.54–3.3)	1.93 (1.27–2.9)
26 vs 25 weeks	2.3 (1.71–2.97)	2.2 (1.71–3.0)	2.0 (1.48–2.7)
27 vs 26 weeks	1.69 (1.32–2.2)	1.65 (1.30–2.1)	1.55 (1.19–2.0)
28 vs 27 weeks	1.74 (1.36–2.2)	1.70 (1.34–2.2)	1.61 (1.25–2.1)
29 vs 28 weeks	1.29 (1.01–1.66)	1.31 (1.03–1.67)	1.24 (0.96–1.60)
30 vs 29 weeks	1.67 (1.3–2.14)	1.63 (1.28–2.1)	1.66 (1.28–2.16)
31 vs 30 weeks	1.79 (1.37–2.3)	1.68 (1.30–2.2)	1.67 (1.26–2.2)
BW (z-score)			
<–2	0.16 (0.10–0.24)	0.17 (0.11–0.25)	0.22 (0.14–0.35)
–2 to –1.5	0.37 (0.27–0.51)	0.39 (0.28–0.53)	0.46 (0.33–0.66)
–1.5 to 1	0.51 (0.39–0.65)	0.52 (0.40–0.67)	0.57 (0.43–0.76)
–1 to –0.5	0.69 (0.55–0.86)	0.70 (0.56–0.86)	0.76 (0.60–0.96)
–0.5 to 0	0.94 (0.77–1.15)	0.94 (0.77–1.14)	0.92 (0.74–1.15)
0 to 0.5	Reference	Reference	Reference
0.5 to 1	1.11 (0.88–1.39)	1.08 (0.86–1.34)	1.04 (0.82–1.33)
1 to 1.5	1.27 (0.91–1.77)	1.29 (0.94–1.77)	1.34 (0.93–1.93)
1.5 to 2	0.84 (0.50–1.41)	0.96 (0.57–1.61)	1.06 (0.57–1.96)
>2	0.14 (0.07–2.63)	0.22 (0.11–0.45)	0.69 (0.22–2.2)
Prenatal steroids	1.60 (1.32–1.94)	1.4 (1.17–1.70)	–
Female	1.39 (1.21–1.59)	1.44 (1.26–1.65)	1.47 (1.27–1.69)
Caesarean section	–	–	–
Multiples	1.17 (1.01–1.36)	1.22 (1.06–1.41)	1.27 (1.08–1.49)
Birth defect	0.19 (0.15–0.25)	0.24 (0.18–0.31)	0.43 (0.31–0.60)
Sepsis first seven days of life	NA	NA	0.49 (0.35–0.70)
Centre			
1	Reference	Reference	Reference
2	1.68 (1.32–2.1)	1.54 (1.22–1.93)	1.34 (1.05–1.72)
3	2.0 (1.50–2.7)	1.89 (1.42–2.51)	1.66 (1.21–2.3)
4	1.26 (0.87–1.83)	1.14 (0.80–1.63)	1.02 (0.71–1.51)
5	1.67 (1.33–2.1)	1.38 (1.11–1.71)	1.17 (0.92–1.48)
6	2.1 (1.55–2.8)	1.89 (1.43–2.5)	1.45 (1.08–1.94)
7	2.1 (1.68–2.55)	1.89 (1.53–2.3)	1.48 (1.12–1.86)
8	2.8 (2.1–3.6)	2.6 (2.0–3.5)	2.1 (1.58–2.9)
9	4.5 (3.4–6.0)	3.9 (3.0–5.3)	3.4 (2.5–4.6)

ANC = Antenatal corticosteroids; BPD = Bronchopulmonary dysplasia; cPVL = Cystic periventricular leucomalacia; NEC = Necrotising enterocolitis; NICU = Neonatal intensive care unit; PIVH = Periventricular/intraventricular haemorrhage; ROP = Retinopathy of prematurity.

*Severe neonatal morbidity: moderate/severe BPD and/or PIVH \geq grade III/IV intracranial haemorrhage and/or cPVL and/or proven NEC and/or ROP \geq stage III.

95% CI 2.2–4.6) or even being born at 27 weeks vs 25 weeks (OR 3.8, 95% CI 2.9–5.0). This association with the centre where the infants were treated persisted on NICU admission (OR 3.9, 95% CI 3.0–5.3) and on the seventh day of life after an additional adjustment for proven sepsis during the first week of life (OR 3.4, 95% CI 2.5–4.6).

When we used the model that allowed interactions between GA groups and centres, the OR for survival without severe morbidity at delivery for an infant born <25 weeks in centre nine compared to centre one was 4.5 (CI 2.5–8.1). The OR for an infant born between 25 and 27 weeks was 5.3 (CI 3.0–9.3), and for an infant born

>28 weeks, it was 3.3 (CI 2.2–4.9). The corresponding ORs for an infant on admission to the NICU were 3.4 (CI 1.89–6.5), 4.6 (CI 2.6–7.9) and 3.0 (CI 2.1–4.4), respectively.

Gestational age-specific prediction estimates and CIs for all time points were calculated for singleton infants without severe malformations with *favourable* perinatal predictors, namely z-score for birthweight of +0.5 to 1, female gender, ANC, and, for the model on day of life seven, no sepsis during first week of life and compared to singleton infants without severe malformations and *unfavourable* perinatal predictors, namely z-score for birthweight of –1 to –0.5,

male gender, no ANC, and, for the model on the seventh day of life, proven sepsis during first week of life.

Figure 1a–c and the corresponding Table S2a–c illustrate the above-mentioned predictions for the entire country, using the model without the centre as a predictor, and the centres with the highest and lowest predicted rates of survival without severe neonatal morbidity – centres one and nine – for the three time points. Findings were similar if only survival to discharge was examined (Fig. 2a–c, Table S3a–c).

As GA increased, the impact of perinatal risk factors, as well as medical centre on survival and survival without severe neonatal morbidity, became less pronounced, although differences persisted up to 31 weeks of gestation.

DISCUSSION

Our study quantifies the impact of different prenatal and postnatal risk factors and medical centre on the probability of survival to discharge without any severe neonatal morbidity in a large national cohort of VLGANs in Switzerland.

Our three prediction models illustrate how prognosis changed rapidly throughout the first week of life. At the lowest GAs – 23 and 24 completed weeks – the chances of survival without severe neonatal morbidity increased substantially for those infants who were admitted to a NICU (Fig. 1a,b). This is not surprising, as delivery room deaths in borderline viable infants are usually the result of primary nonintervention rather than failed resuscitation. At the limit of viability, such an approach invariably leads to death (20–22). Despite the availability of national guidelines or legal definitions of human viability, considerable centre-to-centre differences in the initiation of life-sustaining therapies at the limit of viability were documented in many countries and are likely to reflect a particular NICU's culture (23).

In the present study, chances for survival without severe neonatal morbidity were substantially reduced for all VLGANs who sustained an episode of sepsis during the first week of life (Table 2, Fig. 1c).

Finally, our study quantifies centre-to-centre outcome variability in this vulnerable population in Switzerland (Figs 1a–c and 2a–c, Tables S2a–c and S3a–c). The fact that centre-to-centre differences existed for both survival to discharge without severe neonatal morbidity and survival to discharge suggests that more proactive treatment approaches resulted in higher survival rates without increasing short-term morbidity rates. Over the last decade, several publications have addressed centre-to-centre differences in multiple populations and networks (4,5,7,24,25). Three factors provide possible explanations for centre differences: first, the inherent risk of the patient population served by a centre; second, the approach of any given centre towards primary nonintervention in infants born at the border of viability; and third, the effectiveness of the patient care delivered at a particular centre. In our study, the association between medical centre and survival without

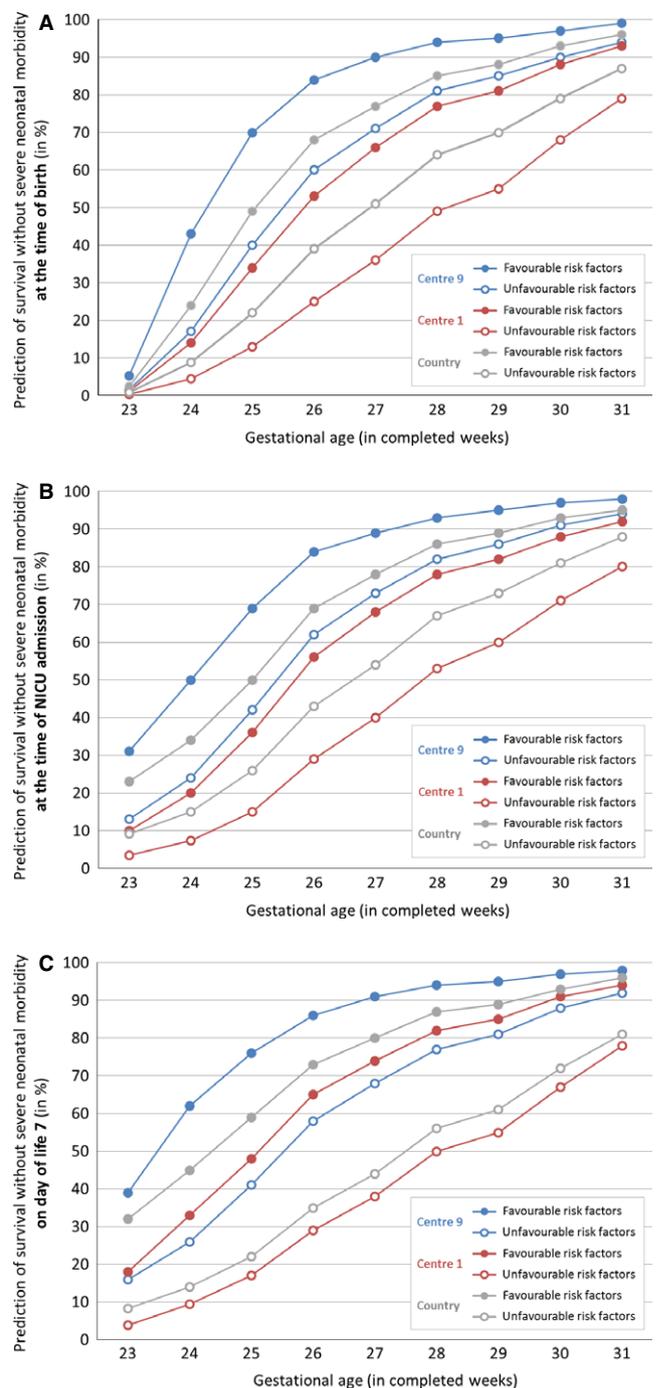


Figure 1 Prediction of survival without severe neonatal morbidity at the time of birth (a), at the time of NICU admission (b) and on day of life seven (c) (favourable risk factors: z-score for BW +0.5 to 1, female, antenatal corticosteroids (ANC), and, for the model on day of life seven, no proven sepsis during first week of life; unfavourable risk factors: z-score for BW –0.5 to –1, male, no ANC, and, for the model on day of life seven, proven sepsis during first week of life).

severe neonatal morbidity remained substantial after adjusting for important patient-level factors (Table 2). This is consistent with centre-to-centre outcome differences reported by other networks that could not be explained by

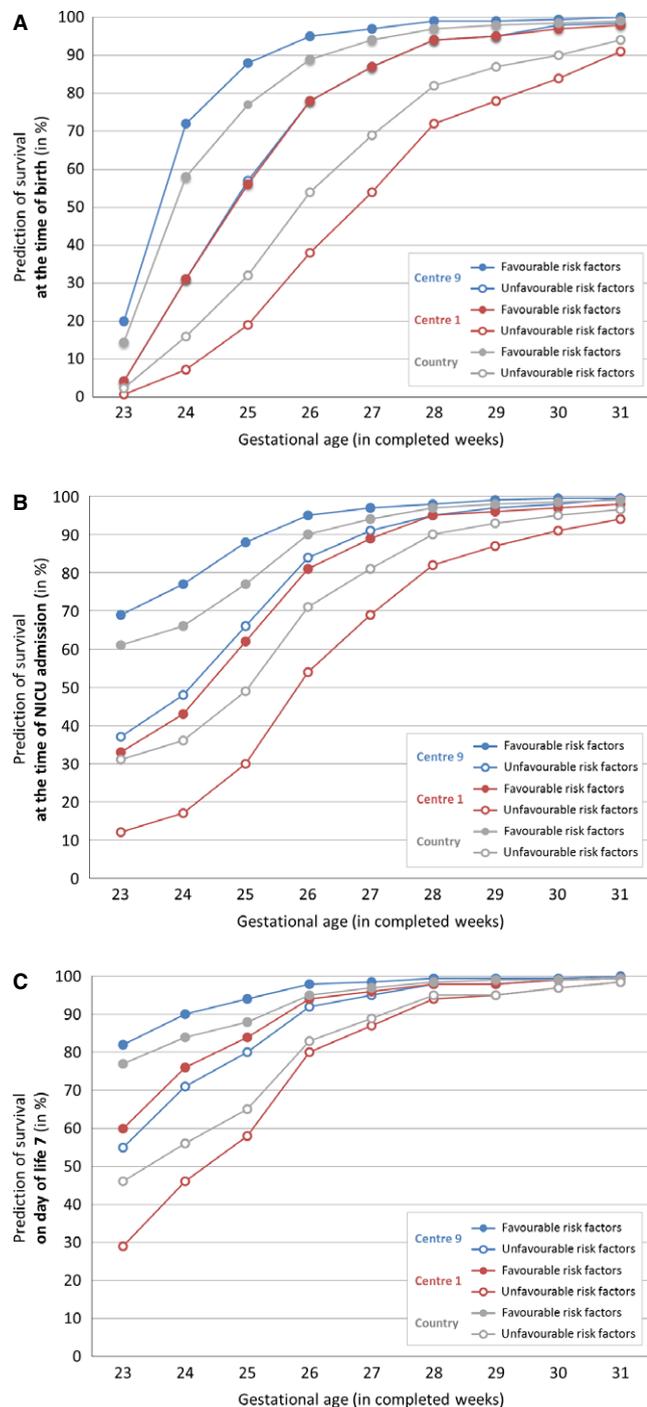


Figure 2 Prediction of survival to discharge at the time of birth (a), at the time of NICU admission (b) and on day of life seven (c) (favourable risk factors: z-score for BW +0.5 to 1, female, antenatal corticosteroids (ANC), and, for the model on day of life seven, no proven sepsis during first week of life; unfavourable risk factors: z-score for BW -0.5 to -1, male, no ANC, and, for the model on day of life seven, proven sepsis during first week of life).

differences in patient demographics (5), health insurance coverage (4) or hospital case load (26,27). These findings suggest that differences in centre-specific neonatal practices strongly influence outcome (24,27,28).

The magnitude of the centre-to-centre outcome differences in our study is comparable to the one described by Lee et al. (4) for Canadian NICUs and by Vohr et al. (5) for the National Institutes for Child Health and Development Neonatal Research Network (NICHD NRN) centres. Alleman et al. (24) confirmed these findings for a more recent cohort of extremely low-birthweight infants cared for by the NICHD NRN and found that centre intervention rates were statistically significant, but only when it came to predicting mortality for infants <25 weeks GA. This contrasts with the results of our study, where centre-to-centre outcome variability extended beyond the most immature infants, and primary noninterventions in infants born at the border of viability did not entirely explain the observed centre-to-centre differences. A study by Smith et al. from the NICHD NRN found similar results to our study. They reported that that centres with a more aggressive approach to care for infants born at 22–24 weeks also had reduced rates of death, death or ROP, death or NEC, death or late-onset sepsis, and death or neurodevelopmental impairment for more mature infants born at 25–27 weeks (29).

LIMITATIONS

Because data were more frequently missing in nonsurvivors, casewise deletion of infants with missing data from the prediction models would have overestimated survival probabilities. We used multiple imputation to reduce bias due to missing data, but our estimate of the associations could still be biased if missing data depended not only on the variables we used to impute missing values, but also on the unknown missing values themselves (30). A 10-fold cross-validation was used to internally validate the models and avoid overfitting, but the models were not externally validated. Furthermore, we cannot exclude the fact that some of the centre-to-centre differences were a chance finding due to multiple comparisons between the nine NICUs. Our study does not provide information on long-term neurodevelopmental impairment. However, severe neonatal morbidities, such as major brain injuries, moderate/severe BPD, proven NEC and severe ROP, are known to correlate with long-term neurodevelopmental outcomes (31,32). Finally, the study design did not allow us to analyse trends over time.

CONCLUSION

There was strong evidence for wide centre-to-centre outcome variability in rates of survival without severe neonatal morbidity among VLGANs in Switzerland over a time period of 10 years that could not be explained by patient-level factors. The observed outcome differences were not restricted to infants born at the limit of viability, but extended to more mature infants and persisted after the first week of life. Identifying and implementing potentially better practices in perinatal care may influence important outcomes.

ACKNOWLEDGEMENTS

We would like to thank the participating centres and collaborators: Aarau: Kantonsspital Aarau, Kinderklinik (Philipp Meyer-Schiffer); Basel: Universitäts-Kinderspital beider Basel, Abteilung für Neonatologie (Sven M. Schulzke); Bern: Inselspital, Abteilung für Neonatologie (Mathias Nelle), and Universitätskinderklinik, Abteilung für Intensivpflege (Bendicht Wagner); Chur: Kantonsspital Graubünden, Kinderklinik (Walter Bär); Genève: Hôpitaux Universitaires de Genève (HUG), Département de l'Enfant et de l'Adolescent, Service de Néonatalogie et des Soins Intensifs de Pédiatrie (Riccardo E. Pfister); Lausanne: CHUV, Service de Néonatalogie (Jean-François Tolsa), and CHUV, SI Pédiatriques, Médico-Chirurgicaux (Jacques Cotting); Luzern: Kinderspital Luzern, neonatologische und pädiatrische Intensivstation (Thomas M. Berger); St. Gallen: Kantonsspital St. Gallen, Klinik für Geburtshilfe und Gynäkologie (Andreas Malzacher), and Ostschweizer Kinderspital, Intensivpflege- und Frühgeburtenstation (John P. Micallef); and Zürich: USZ, Klinik für Neonatologie, Departement Frauenheilkunde (Hans-Ulrich Bucher), and Universitätskinderklinik Zürich, Abteilung für Intensivmedizin und Neonatologie (Bernhard Frey).

FUNDING

No specific funding was received for this study.

CONFLICT OF INTEREST

The authors declare no conflict of interest in relation to the manuscript.

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SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article:

Figure S1 Calibration plots for the final models for predicting survival without severe neonatal morbidity at different time points.

Table S1 10-fold cross-validated c-statistics for different time points and models using the multiple imputed data set.

Table S2 (a–c) Predictors for survival without any severe neonatal morbidity* at the time of delivery (a), at the time of NICU admission (b) and on the seventh day of life (c) for inborn singleton infants without major birth defects.

Table S3 (a–c) Predictors for survival to discharge at the time of delivery (a), at the time of NICU admission (b) and on the seventh day of life (c) for inborn singleton infants without major birth defects.