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# Antenatal prediction of neonatal mortality in very premature infants

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ABSTRACT

*Objective:* To develop a prognostic model for antenatal prediction of neonatal mortality in infants threatening to be born very preterm (<32 weeks).
*Study design:* Nationwide cohort study in The Netherlands between 1999 and 2007. We studied 8500 singletons born between $25^{+0}$ and $31^{+6}$ weeks of gestation where fetus was alive at birth without congenital anomalies. We developed a multiple logistic regression model to estimate the risk of neonatal mortality within 28 days after birth, based on characteristics that are known before birth. We used bootstrapping techniques for internal validation. Discrimination (AUC), accuracy (Brier score) and calibration (graph, *c*-statistics) were used to assess the model's predictive performance.
*Results:* Neonatal mortality occurred in 766 (90 per 1000) live births. The final model consisted of seven variables. Predictors were low gestational age, no antental corticosteroids, male gender, maternal age ≥35 years, Caucasian ethnicity, non-cephalic presentation and non-3rd level of hospital. The predicted probabilities ranged from 0.003 to 0.697 (IQR 0.02–0.11). The model had an AUC of 0.83, the Brier score was 0.065. The calibration graph showed good calibration, and the test for the Hosmer Lemeshow *c*-statistic showed no lack of fit ($p = 0.43$).
*Conclusions:* Neonatal mortality can be predicted for very preterm births based on the antenatal factors gestational age, antental corticosteroids, fetal gender, maternal age, ethnicity, presentation and level of hospital. This model can be helpful in antenatal counseling.


## 1. Introduction

Preterm birth is the leading cause of neonatal morbidity and mortality in high income countries [1], and is estimated to be responsible for a million neonatal deaths world-wide each year [2]. The consequences of preterm birth arise from the fact that the immature organ systems of the neonate are not yet prepared to support extrauterine life. This is expressed in respiratory insufficiency, intracranial hemorrhage and infections.

The impact of very preterm birth, defined as birth before 32 completed weeks of gestation, on neonatal morbidity and mortality risk is dependent on the actual length of gestation, as the risk decreases when pregnancy progresses [3–5]. The risk of neonatal complications in very preterm birth influences antenatal clinical decision-making concerning the administration of tocolytics/corticosteroids and/or referral to a 3rd level perinatal centre [6,7].

Prediction models can be a helpful tool for clinicians working in perinatal care [8–10]. To assess the risk of neonatal mortality in infants born very preterm there are around 40 prediction models available to clinicians [11]. Medlock et al. systematically reviewed all these prediction models and found that besides gestational age and birth weight, several other variables were recurrently found to be independent predictors for neonatal mortality after very preterm birth. These predictors were: being small for gestational age (SGA), male gender, white ethnicity, congenital anomalies, no use of antenatal corticosteroids, lower Apgar score, neonatal hypo- or hyper-thermia at time of admission and clinical or biochemical signs of respiratory insufficiency [11]. The majority of these prediction models were only applicable after birth as they included predictors that are not known antenatally, like birth weight, SGA

*Abbreviations:* SGA, small for gestational age; PRN, The Netherlands Perinatal Registry; SES, socio-economic status; AUC, the area under the receiver operating characteristic curve; IQR, inter quartile range; PROM, prelabour rupture of the membranes; PPV, positive predictive value; NPV, negative predicted value.

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and Apgar score. Prediction models for neonatal mortality after very preterm birth based solely on antenatal factors are rare: only two models have been developed for infants threatening to be born before 26 weeks of gestation [12,13].

The lack of antenatal prediction models for very preterm births after the threshold of viability hinders counseling of patients who are confronted with this threat. Therefore, the aim of this study was to develop a prognostic model for obstetricians/midwives to be used during gestation predicting neonatal mortality after very preterm birth, based on only information known before birth.

## 2. Materials and methods

### 2.1. Dataset

This study was performed in a prospective nationwide cohort using The Netherlands Perinatal Registry (PRN). The PRN consists of population-based data containing information on pregnancies, deliveries and (re)admissions until 28 days after birth. The PRN database is obtained by a validated linkage of three different registries: the midwifery registry (LVR1), the obstetrics registry (LVR2) and the neonatology registry (LNR) of hospital admissions of newborns [14,15]. The midwifery and obstetrics data collection starts at the booking visit and contains perinatal data from 20 gestational weeks onwards. The neonatal registry contains data on hospital (re)admissions of newborns within 28 days after birth. The coverage of the PRN registry is about 96% of all deliveries in The Netherlands. The incompleteness is due to non-registering general practitioners (1–2%) and non-registering midwifery practices (2–3%).

### 2.2. Inclusion and exclusion criteria

All liveborns between $25^{+0}$ and $31^{+6}$ weeks of gestation and with a birth weight of 500 g or more were included in our study. Neonates were born between January 1st 2000 and December 31st 2007. Congenital abnormalities were excluded, as were multiple births. In the Netherlands 24.0 weeks is the limit of viability and active treatment of newborns was from 25.0 weeks onwards in the study period.

### 2.3. Outcome and candidate predictors

The primary outcome measure was neonatal mortality within 28 days after birth. Candidate predictors, which should be available antenatally, were specified using evidence from clinical guidelines, the literature and expert opinions. These potential predictors in the national registration were gestational age (days), fetal gender (male), use of antenatal corticosteroids (yes/no), maternal age (<25,25–34, ≥35 years), parity (primiparous/multiparous), Caucasian maternal ethnicity (yes/no), low socio-economic status (SES) (p25 yes/no), hypertension/pre-eclampsia, prelabour rupture of the membranes (PROM), history of preterm birth, bleeding in the second trimester, non-cephalic presentation and level of hospital for delivery (3rd level versus non 3rd level hospital). The SES score is based on the mean income, the percentage of people with a paid job and the percentage of household on average with a low education in a postal code area. Predictors known at or after birth, like birth weight, small for gestational age "less than the 10th percentile" (SGAp10) (Dutch reference curves for birth weight by gestational age for parity and sex) [16] and 5-min Apgar score <7 will only be presented in the baseline characteristics of the study population.

### 2.4. Model development and validation

First we measured the baseline characteristics. To inspect the individual variables that significantly contribute to the risk of neonatal mortality we performed univariate logistic regression analysis. To obtain the prediction model we performed multivariate logistic regression analysis with backward selection based on the Akaike Information Criterion. Only variables known before birth with sufficient data quality were included in the model.

We evaluated the discriminative performance of the prognostic model by the area under the receiver operating characteristic (ROC) curve, the AUC [17]. The accuracy of the prognostic model's predictions was assessed by the Brier score and Brier skill score. The Brier score (the mean squared deviation between the predicted probabilities and their respective outcomes) for a model can range from 0 for a perfect model to 0.25 for a non-informative model [17]. The Brier skill score measures the improvement of the predictions relative to a non-informative model and thus "adjusts" for the prevalence of the outcome.

We assessed the calibration of the model by plotting a smoothed calibration graph. The goodness of fit was also evaluated by the Hosmer Lemeshow *C*-statistic (a *p*-value below 0.05 indicates an overall poor fit) [18].

To provide unbiased estimates for the abovementioned performance measures we internally validated the model using the standard bootstrap method of Efron with 100 bootstrap samples [19]. To calculate the probability of neonatal mortality for clinical application a nomogram was developed.

Data were analyzed using the SAS statistical software package version 9.2 (SAS Institute Inc, Cary, NC, USA) and for the bootstrapping the R statistical software environment version 3.01 (R Foundation for Statistical Computing, Vienna, Austria) was used.

## 3. Results

Between January 1st 2000 and December 31st 2007 a total of 1,357,628 children were born, of which 12,391 were liveborn between $25^{+0}$ and $31^{+6}$ weeks of gestation without congenital abnormalities and with a birth weight of 500 g or more. Children born from multiple births ($n$ = 3938, 31.4%) were excluded. Hence the resulting study population consisted of 8500 liveborn singleton infants.

Neonatal mortality within 28 days occurred in 766 cases; 90 per 1000 (‰). Neonatal mortality was largely dependent on gestational age and ranged from 546‰ at 25 weeks to 18‰ at 31 weeks of gestation (Fig. 1). Each day gained before delivery significantly improved the survival. The mean birth weight was 1264 g. Baseline characteristics of the study population are presented in Table 1.

The univariate regression analysis (Table 2) showed that gestational age and the use of antenatal corticosteroids were the most important antenatal indicators of neonatal mortality. Furthermore, multiparity, maternal age ≥35 years, hypertensive

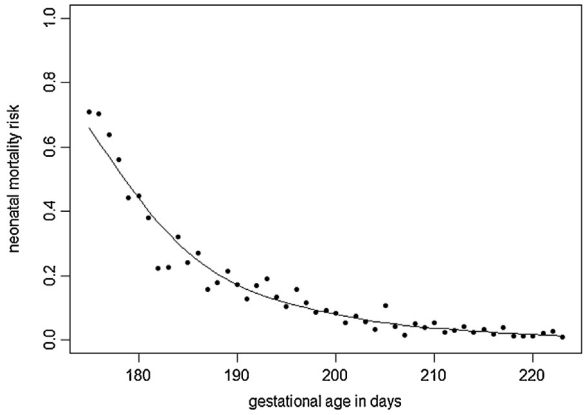


**Fig. 1.** Neonatal mortality risk by gestational age in days in live born births.