Ultrasound Obstet Gynecol 2023; **62**: 788–795
Published online in Wiley Online Library (wileyonlinelibrary.com). **DOI:** 10.1002/uog.26290

Mortality and severe neurological morbidity in extremely preterm growth-restricted fetuses

E. MAZARICO[1,2,3], E. MELER[4], M. MENDOZA[5], I. HERRAIZ[6,7,8], E. LLURBA[3,9], R. DE DIEGO[10], M. COMAS[11], D. BOADA[4], A. GONZÁLEZ[1], E. BONACINA[5], M. ARMENGOL-ALSINA[5], E. MOLINE[3,9], I. HURTADO[10], N. TORRE[11], M. D. GOMEZ-ROIG[1,2,3], A. GALINDO[6,7,8] and F. FIGUERAS[4]

[1]*Hospital Sant Joan de Déu, BCNatal, Barcelona, Spain;* [2]*Departament de Ciències Clíniques, Facultat de Medicina i Ciències de la Salut, Universitat de Barcelona, Barcelona, Spain;* [3]*Primary Care Interventions to Prevent Maternal and Child Chronic Diseases of Perinatal and Developmental Origin Network (RICORS), RD21/0012/0003, Instituto de Salud Carlos III, Madrid, Spain;* [4]*Hospital Clínic de Barcelona, Seu Maternitat, BCNatal, Barcelona, Spain;* [5]*Department of Obstetrics, Hospital Universitari Vall d'Hebron, Barcelona, Spain;* [6]*Fetal Medicine Unit, Department of Obstetrics and Gynaecology, Hospital Universitario 12 de Octubre, Instituto de Investigación Hospital 12 de Octubre (imas12), Madrid, Spain;* [7]*Faculty of Medicine, Universidad Complutense de Madrid, Madrid, Spain;* [8]*Primary Care Interventions to Prevent Maternal and Child Chronic Diseases of Perinatal and Developmental Origin Network (RICORS), RD21/0012/0024, Instituto de Salud Carlos III, Madrid, Spain;* [9]*Institut d'Investigació Biomèdica Sant Pau (IIB Sant Pau), Hospital de la Santa Creu i Sant Pau, Barcelona, Spain;* [10]*Hospital Hospital Germans Trias i Pujol, Badalona, Spain;* [11]*Parc Taulí Hospital Universitari, Institut d'Investigació i Innovació Parc Taulí (U3PT), Sabadell, Spain*

KEYWORDS: fetal growth restriction; FGR; neurodevelopment; perinatal mortality; prematurity

CONTRIBUTION

What are the novel findings of this work?
Prediction of intact survival (survival without major neurological morbidity) in extremely preterm growth-restricted fetuses could be better achieved by considering additional parameters, such as fetal weight, sex and Doppler status, beyond just gestational age at birth.

What are the clinical implications of this work?
Our findings could improve the prediction of mortality or severe morbidity in extremely preterm and antenatally diagnosed growth-restricted infants. This could facilitate more comprehensive patient counseling and shared decision-making in these cases.

ABSTRACT

Objective *To develop a model for the prediction of adverse perinatal outcome in growth-restricted fetuses requiring delivery before 28 weeks in order to provide individualized patient counseling.*

Methods *This was a retrospective multicenter cohort study of singleton pregnancies with antenatal suspicion of fetal growth restriction requiring delivery before 28 weeks' gestation between January 2010 and January 2020 in six tertiary public hospitals in the Barcelona area, Spain. Separate predictive models for mortality only and mortality or severe neurological morbidity were created using logistic regression from variables available antenatally. For each model, predictive performance was evaluated using receiver-operating-characteristics (ROC)-curve analysis. Predictive models were validated externally in an additional cohort of growth-restricted fetuses from another public tertiary hospital with the same inclusion and exclusion criteria.*

Results *A total of 110 cases were included. The neonatal mortality rate was 37.3% and, among the survivors, the rate of severe neurological morbidity was 21.7%. The following factors were retained in the multivariate analysis as significant predictors of mortality: magnesium sulfate neuroprotection, gestational age at birth, estimated fetal weight, male sex and Doppler stage. This model had a significantly higher area under the ROC curve (AUC) compared with a model including only gestational age at birth (0.810 (95% CI, 0.730–0.889)* vs *0.695 (95% CI, 0.594–0.795);* P = *0.016). At a 20% false-positive rate, the model showed a sensitivity, negative predictive value and positive predictive value of 66%, 80% and 66%, respectively. For the prediction of the composite adverse outcome (mortality or severe neurological morbidity), the model included: gestational age at birth, male sex and Doppler stage. This model had a significantly higher AUC compared with a model including only gestational age at birth (0.810 (95% CI, 0.731–0.892)* vs *0.689 (95% CI, 0.588–0.799);* P = *0.017). At a 20% false-positive rate,*

Correspondence to: Dr E. Mazarico, Hospital Sant Joan de Déu, BCNatal, Barcelona, Spain (e-mail: edurne.mazarico@sjd.es)

Accepted: 30 May 2023

the model showed a sensitivity, negative predictive value and positive predictive value of 55%, 63% and 74%, respectively. External validation of both models yielded similar AUCs that did not differ significantly from those obtained in the original sample.

Conclusions *Estimated fetal weight, fetal sex and Doppler stage can be combined with gestational age to improve the prediction of death or severe neurological sequelae in growth-restricted fetuses requiring delivery before 28 weeks. This approach may be useful for parental counseling and decision-making.* © *2023 International Society of Ultrasound in Obstetrics and Gynecology.*

INTRODUCTION

Fetal growth restriction (FGR) is defined as a failure of a fetus to reach its growth potential. When diagnosed in early pregnancy, it is usually secondary to placental insufficiency[1] and is a major contributor to perinatal morbidity and mortality[2].

Currently, there is no treatment for FGR during pregnancy[3–6]. Intensive monitoring and elective delivery when the intrauterine risks outweigh the risks of prematurity constitute standard management. Planned delivery is supported by several guidelines[7–10] based on the findings of observational studies, meta-analyses[11] and two randomized trials[12,13]. Nevertheless, there is no consensus on the lower limit of gestational age (GA) beyond which delivery would be justified to prevent stillbirth. Recent series showed that the probability of survival without severe sequelae (intact survival) reaches 50% in fetuses with early-onset FGR only when delivery occurs after 27 weeks, which is accepted as the limit of viability in this subgroup of growth-restricted fetuses, as opposed to 24 weeks in fetuses with normal growth[14,15].

However, other factors aside from GA can influence the likelihood of intact survival. Estimated fetal weight (EFW) modifies the risk of mortality and major morbidity, and work has shown that only when 600–700 g is reached does the probability of intact survival exceed the viability threshold[16]. It also has been shown that low-weight, extremely preterm female fetuses have a better prognosis than do males at equal weight and GA[14]. Regarding corticosteroids for lung maturation, observational evidence does not consistently indicate a benefit in FGR fetuses similar to that in preterm infants without placental insufficiency[17]. However, all international guidelines recommend corticosteroid use[7–10]. Similarly, there is no good evidence of the benefit of neuroprophylaxis with magnesium sulfate in growth-restricted infants. However, since hypoxia–ischemia is a contributor to cerebral palsy independently of GA, the same guidelines recommend this treatment[7–10]. Finally, hemodynamic status as reflected by fetal Doppler parameters may also modify the neonatal prognosis, but the largest observational series to date indicates that, at < 28 weeks, it does not have value independent of GA[16].

This study aimed to develop a model for the prediction of perinatal mortality and severe neurological morbidity in pregnancies with FGR requiring delivery at < 28 weeks, in order to provide individualized parental counseling.

METHODS

Subjects

This was a retrospective multicenter cohort study of pregnancies delivered between January 2010 and January 2020 in any of the public hospitals within the Barcelona area, Spain: Hospital Sant Joan de Déu, Hospital Clínic, Hospital Vall d'Hebron and Hospital de la Santa Creu i Sant Pau (Barcelona); Hospital Germans Trias i Pujol (Badalona); and Hospital Parc Taulí (Sabadell).

The inclusion criteria were: (i) singleton pregnancy; (ii) absence of major congenital anomalies, genetic abnormalities with clinical significance (pathogenic or likely pathogenic according to the American College of Medical Genetics and Genomics) and congenital infection; (iii) known pregnancy outcome; (iv) extremely preterm pregnancy, defined according to the World Health Organization classification as delivering between 24 + 0 and 27 + 6 weeks' gestation (dated by first-trimester crown–rump length[18]); (v) suspected FGR with confirmed birth weight < 10th centile, according to international standards[19]; (v) live birth. The study was approved by the local ethics committee (PIC-131-21).

Measurements

In all cases, accurate anatomical examination, fetal biometry and prenatal Doppler ultrasound examination were performed by experienced operators at the time of diagnosis. EFW was calculated from the biparietal diameter, head and abdominal circumference and femur length, using the Hadlock formula[20]. Doppler measurements of the umbilical artery (UA), middle cerebral artery (MCA), uterine artery (UtA) and ductus venosus (DV) were performed according to standardized recommendations[21]. The cerebroplacental ratio (CPR) was calculated as the ratio of pulsatility index (PI) of the MCA to that of the UA.

In those pregnancies with EFW < 3rd centile before 24 weeks' gestation, microcephaly (head circumference more than 3 SD below the mean) and/or short femur length (more than 3 SD below the mean), invasive testing was offered for chromosomal microarray analysis and study of cytomegalovirus infection by amniotic fluid polymerase chain reaction, unless there was serological evidence of negative IgG and IgM.

Pre-eclampsia and severe pre-eclampsia were defined according to the criteria of the International Society for the Study of Hypertension in Pregnancy[22].

Management

UA and MCA Doppler evaluation was performed at each visit, according to standard protocol[23]. DV Doppler

evaluation was carried out only when Doppler signs of placental insufficiency/hypoxia were present (abnormal UA or MCA Doppler). Cardiotocography (CTG) was performed between 26 and 28 weeks in those pregnancies with placental insufficiency/hypoxia. Abnormal CTG was defined as reduced/absent fetal heart-rate variability, recurrent decelerations or persistent bradycardia[24].

Before 28 + 0 weeks, abnormal CTG or reversed DV end-diastolic velocity (EDV) were the only fetal indications for delivery (Cesarean section). Severe pre-eclampsia with maternal complications or progressive maternal deterioration was also an indication for delivery.

Magnesium sulfate (4 g given intravenously for 15 min followed by 1 g/h for a maximum of 24 h and minimum of 4 h) for neuroprotection and a single course of antenatal corticosteroids (two doses of 12-mg betamethasone administered intramuscularly within 24 h) for accelerating fetal lung maturation were administered, if possible and not previously given, as soon as the decision to deliver was made.

Outcome definitions

Composite adverse outcome was defined as mortality or severe neurological morbidity. Mortality was defined as neonatal death or infant death during follow-up (at least 2 years). Severe neurological morbidity was defined as any of the following: cognitive impairment (Bayley Scales of Infant and Toddler Development third edition score < 85); cerebral palsy; hearing loss, evaluated by evoked otoacoustic emissions (< 2 years of age), play audiometry (2–4 years of age) or conventional audiometry (> 4 years of age); or vision loss, defined at 6 months to 2 years of age as failure to fix and follow, at 3 to 4 years of age as visual acuity < 0.4, at > 4 to 5 years of age as visual acuity < 0.5, and at > 5 years of age as visual acuity < 0.66[25].

Neonatal complications were defined as follows: neonatal sepsis (presence of positive blood or cerebrospinal fluid cultures); abnormal cranial ultrasound (cystic periventricular leukomalacia and/or intraventricular hemorrhage > Grade II); necrotizing enterocolitis (requiring surgery); acute renal failure (serum creatinine > 1.5 mg/dL); cardiac failure (requiring ionotropic agents); respiratory distress syndrome (clinical signs of breathing difficulties, such as grunting sounds, rapid and shallow breathing, sharp pulling inward of the muscles between the ribs when breathing, or widening or flaring of the nostrils with each breath, and X-ray signs of atelectasis or lung collapse); and severe bronchopulmonary dysplasia requiring oxygen > 30% beyond 36 weeks of corrected GA or at discharge.

Statistical analysis

Separate models were constructed for mortality only and mortality or severe neurological morbidity. Using logistic regression, an automatic selection of variables was made (backward p-in, 0.05 and p-out, 0.1) to define parsimonious models, i.e. providing the maximum explanation of the uncertainty (measured with Nagelkerke's R^2) for the minimum possible number of variables included in the model. Candidate predictors were: pre-eclampsia, GA at delivery, fetal sex, EFW within 1 week before delivery, magnesium sulfate (more than 1 h before birth), corticosteroids for lung maturation (0, 1 or 2 doses) and Doppler stage within 48 h before delivery: (i) positive UA-EDV and DV-PI ≤ 95th centile; (ii) absent UA-EDV; (iii) reversed UA-EDV or DV-PI > 95th centile; and (iv) absent or reversed DV-EDV. The uncertainty explained by the models was quantified by Nagelkerke's R^2.

For each model, predictive performance was evaluated using receiver-operating-characteristics (ROC)-curve analysis of the predicted values, from which the sensitivity, specificity, predictive values and likelihood ratios were extracted. Paired ROC curves were compared using the DeLong method[26]. Models were validated internally by a *k*-fold cross-validation procedure, which averages the areas under the curve (AUCs) corresponding to each fold ($n = 20$) and applies a bootstrap procedure to obtain statistical inference and bias-corrected 95% CIs. Models were calibrated by the construction of plots showing observed against expected probabilities (with 95% CI), smoothed by Lowess regression.

The external validity of the model for death or severe neurological morbidity was assessed in a cohort of cases delivered at Hospital Universitario 12 de Octubre, Madrid, Spain, during the same time period and meeting the same inclusion and exclusion criteria. Model validity was assessed by calculating R^2 shrinkage, and a cut-off of < 10% was considered to indicate validity[27].

The statistical software STATA version 17 (StataCorp., College Station, TX, USA) (packages 'pmcalplot' and 'cvauroc') and R version 3.1.2 (R Foundation for Statistical Computing Platform, Vienna, Austria) (package 'pROC') were used to conduct the statistical analysis.

RESULTS

A total of 110 cases were included, of which seven were delivered between 24 + 0 and 24 + 6 weeks, 15 between 25 + 0 and 25 + 6 weeks, 37 between 26 + 0 and 26 + 6 weeks and 51 between 27 + 0 and 27 + 6 weeks. Antenatal characteristics and perinatal outcome are shown in Table 1. Almost 82% (90/110) of fetuses received magnesium sulfate and almost 72% (79/110) of fetuses received a full course of corticosteroids for lung maturation.

Neonatal outcomes are detailed in Table 2. Birth weight ranged from 360 g to 815 g. There were 41/110 (37.3%) cases of neonatal mortality and, among the survivors, 15/69 (21.7%) cases of severe neurological morbidity. The mortality rate decreased with advancing GA, reaching 23.5% at 27 + 0 to 27 + 6 weeks. Likewise, survival without severe neurological morbidity reached 58.8% at 27 + 0 to 27 + 6 weeks.

The following factors were retained in the multivariate analysis as significant predictors of mortality: magnesium sulfate neuroprotection (odds ratio (OR), 0.37 (95% CI, 0.12–1.12)), GA at birth (per 1-week increase) (OR, 0.49

(95% CI, 0.29–0.84)), EFW (per 100-g increase) (OR, 0.57 (95% CI, 0.35–0.94)), male sex (OR, 2.48 (95% CI, 0.91–6.78)) and Doppler stage (positive UA-EDV (reference)); absent UA-EDV (OR, 1.12 (95% CI, 0.14–9.01)); reversed UA-EDV or DV-PI > 95th centile (OR, 3.09 (95% CI, 0.84–11.27)); and absent or reversed DV-EDV (OR, 5.52 (95% CI, 1.33–22.85))) (Table 3). The uncertainty explained by this model was significantly higher than that explained by the model including only GA at birth (Nagelkerke's R^2, 23.0% *vs* 7.1%; $P < 0.001$).

Table 1 Antenatal characteristics of pregnancies with fetal growth restriction requiring delivery at < 28 weeks, according to gestational age at delivery

Characteristic	*Total (n = 110)*	*24 + 0 to 24 + 6 weeks (n = 7)*	*25 + 0 to 25 + 6 weeks (n = 15)*	*26 + 0 to 26 + 6 weeks (n = 37)*	*27 + 0 to 27 + 6 weeks (n = 51)*
Maternal age (years)	32.4 (17–48)	27.4 (20–36)	35.8 (20–46)	32.1 (20–48)	32.3 (17–44)
Nulliparous	63 (57.3)	1 (14.3)	9 (60.0)	24 (64.9)	29 (56.9)
EFW (g)	588 (378–857)	516 (450–612)	509 (390–665)	581 (378–755)	626 (392–857)
Pre-eclampsia	64 (58.2)	2 (28.6)	11 (73.3)	24 (64.9)	27 (52.9)
UA-PI > 95th centile	110 (100)	7 (100)	15 (100)	37 (100)	51 (100)
MCA-PI < 5th centile	84 (76.4)	3 (42.9)	11 (73.3)	32 (86.5)	38 (74.5)
Absent UA-EDV	32 (29.1)	1 (14.3)	4 (26.7)	12 (32.4)	15 (29.4)
Reversed UA-EDV	39 (35.5)	0 (0)	4 (26.7)	15 (40.5)	20 (39.2)
DV-PI > 95th centile	62 (56.4)	2 (28.6)	7 (46.7)	24 (64.9)	29 (56.9)
DV-AREDV	25 (22.7)	0 (0)	2 (13.3)	9 (24.3)	14 (27.5)
Corticosteroids					
None	8 (7.3)	0 (0)	1 (6.7)	5 (13.5)	2 (3.9)
1 dose	23 (20.9)	1 (14.3)	4 (26.7)	3 (8.1)	15 (29.4)
2 doses	79 (71.8)	6 (85.7)	10 (66.7)	29 (78.4)	34 (66.7)
Magnesium sulfate	90 (81.8)	5 (71.4)	12 (80.0)	30 (81.1)	43 (84.3)
Cesarean section	105 (95.5)	6 (85.7)	14 (93.3)	35 (94.6)	50 (98.0)

Data are given as mean (range) or *n* (%). AREDV, absent or reversed end-diastolic velocity; DV, ductus venosus; EDV, end-diastolic velocity; EFW, estimated fetal weight; MCA, middle cerebral artery; PI, pulsatility index; UA, umbilical artery.

Table 2 Neonatal outcomes of pregnancies with fetal growth restriction requiring delivery at < 28 weeks, according to gestational age at delivery

Characteristic	*Total (n = 110)*	*24 + 0 to 24 + 6 weeks (n = 7)*	*25 + 0 to 25 + 6 weeks (n = 15)*	*26 + 0 to 26 + 6 weeks (n = 37)*	*27 + 0 to 27 + 6 weeks (n = 51)*
Male sex	53 (48.2)	4 (57.1)	8 (53.3)	19 (51.4)	22 (43.1)
Birth weight (g)	572 (360–815)	460 (420–550)	495 (383–590)	554 (360–666)	619 (396–815)
Birth weight < 3rd centile	69 (62.7)	3 (42.9)	10 (66.7)	24 (64.9)	32 (62.7)
Umbilical artery pH < 7.10*	15/92 (16.3)	1/6 (16.7)	1/10 (10)	7/33 (21.2)	6/43 (14.0)
5-min Apgar score < 7†	36/109 (33.0)	6/7 (85.7)	8/14 (57.1)	12/37 (32.4)	10/51 (19.6)
Neonatal resuscitation					
Bag-mask ventilation	43 (39.1)	1 (14.3)	7 (46.7)	11 (29.7)	24 (47.1)
Intubation	65 (59.1)	6 (85.7)	8 (53.3)	25 (67.6)	26 (51.0)
None	2 (1.8)	0 (0)	0 (0)	1 (2.7)	1 (2.0)
Neonatal mortality	41 (37.3)	5 (71.4)	8 (53.3)	16 (43.2)	12 (23.5)
Severe neurological morbidity‡	15/69 (21.7)	1/2 (50.0)	2/7 (28.6)	3/21 (14.3)	9/39 (23.1)
Cognitive impairment	12/69 (17.4)	1/2 (50.0)	1/7 (14.3)	1/21 (4.8)	9/39 (23.1)
Cerebral palsy	1/69 (1.4)	0/2 (0)	0/7 (0)	0/21 (0)	1/39 (2.6)
Hearing loss	4/69 (5.8)	0/2 (0)	1/7 (14.3)	2/21 (9.5)	1/39 (2.6)
Visual loss	1/69 (1.4)	0/2 (0)	0/7 (0)	0/21 (0)	1/39 (2.6)
Intact survival	54 (49.1)	1 (14.3)	5 (33.3)	18 (48.6)	30 (58.8)
Days in NICU§	45 [10–95]	22 [8–106]	18 [3–147]	28 [4–84]	80 [26–106]
Neonatal complication	89 (80.9)	5 (71.4)	12 (80.0)	31 (83.8)	41 (80.4)
Respiratory distress syndrome	77 (70.0)	4 (57.1)	8 (53.3)	29 (78.4)	36 (70.6)
Sepsis	38 (34.5)	1 (14.3)	5 (33.3)	15 (40.5)	17 (33.3)
Necrotizing enterocolitis	9 (8.2)	1 (14.3)	1 (6.7)	2 (5.4)	5 (9.8)
Cardiac insufficiency	9 (8.2)	1 (14.3)	3 (20.0)	3 (8.1)	2 (3.9)
Renal insufficiency	13 (11.8)	2 (28.6)	2 (13.3)	8 (21.6)	1 (2.0)
Abnormal CNS on ultrasound	46 (41.8)	1 (14.3)	8 (53.3)	15 (40.5)	22 (43.1)
Severe bronchopulmonary dysplasia‡	35/69 (50.1)	0/2 (0)	4/7 (57.1)	8/21 (38.1)	23/39 (59.0)

Data are given as *n* (%), mean (range), *n*/*N* (%) or median [interquartile range]. *Data missing for 18 patients. †Data missing for one patient. ‡Only survivors included in denominator. §Until death or discharge. CNS, central nervous system; NICU, neonatal intensive care unit.

The full model had a significantly higher AUC compared with the model including only GA at birth (0.810 (95% CI, 0.730–0.889) *vs* 0.695 (95% CI, 0.594–0.795); $P = 0.016$) (Table 4, Figure 1). The validation procedure yielded an AUC of 0.78 (95% CI, 0.56–0.79), which did not differ statistically from that obtained in the whole sample ($P = 0.215$) (Figure S1). Table 4 shows the sensitivity and positive and negative predictive values for both models for mortality at fixed false-positive rates of 10%, 20% and 30%. At a 20% false-positive rate, the full model showed a sensitivity, negative predictive value and positive predictive value of 66%, 80% and 66%, respectively.

Table 3 Logistic regression analysis of included predictors of neonatal mortality only and neonatal mortality or severe neurological morbidity

Predictor	*OR (95% CI)*	P
Mortality		
Magnesium sulfate	0.37 (0.12–1.12)	0.080
GA at birth*	0.49 (0.29–0.84)	0.009
EFW†	0.57 (0.35–0.94)	0.027
Male sex	2.48 (0.91–6.78)	0.076
Doppler stage		
Stage II *vs* Stage I	1.12 (0.14–9.01)	0.912
Stage III *vs* Stage I	3.09 (0.84–11.27)	0.087
Stage IV *vs* Stage I	5.52 (1.33–22.85)	0.018
Mortality or severe neurological morbidity		
GA at birth*	0.38 (0.21–0.68)	0.001
Male sex	2.79 (1.12–6.92)	0.027
Doppler stage		
Stage II *vs* Stage I	1.12 (0.14–9.01)	0.901
Stage III *vs* Stage I	4.40 (1.46–12.24)	0.008
Stage IV *vs* Stage I	5.52 (1.33–22.85)	0.001

*Per 1-week increase. †Per 100-g increase. EFW, estimated fetal weight; GA, gestational age; OR, odds ratio; Stage I, positive umbilical artery (UA) end-diastolic velocity (EDV) and ductus venosus pulsatility index (DV-PI) ≤ 95th centile; Stage II, absent UA-EDV; Stage III, reversed UA-EDV or DV-PI > 95th centile; Stage IV, absent or reversed DV-EDV.

For the composite adverse outcome (mortality or neurological morbidity), the predictive model included: GA at birth (OR, 0.38 (95% CI, 0.21–0.68)), male sex (OR, 2.79 (95% CI, 1.12–6.92)) and Doppler stage (positive UA-EDV (reference)); absent UA-EDV (OR, 1.12 (95% CI, 0.14–9.01)); reversed UA-EDV or DV-PI > 95th centile (OR, 4.40 (95% CI, 1.46–12.24)); and absent or reversed DV-EDV (OR, 5.52 (95% CI, 1.33–22.85))) (Table 3). The uncertainty explained by this model was significantly higher than that explained by the model including only GA (Nagelkerke's R^2, 20.0% *vs* 6.1%; $P < 0.001$). The full model had a significantly higher AUC compared with the model including only GA at birth (0.810 (95% CI, 0.731–0.892) *vs* 0.689 (95% CI, 0.588–0.799); $P = 0.017$) (Table 4, Figure 2). The validation procedure yielded a similar AUC of 0.77 (95% CI, 0.65–0.83), which did not differ statistically from that

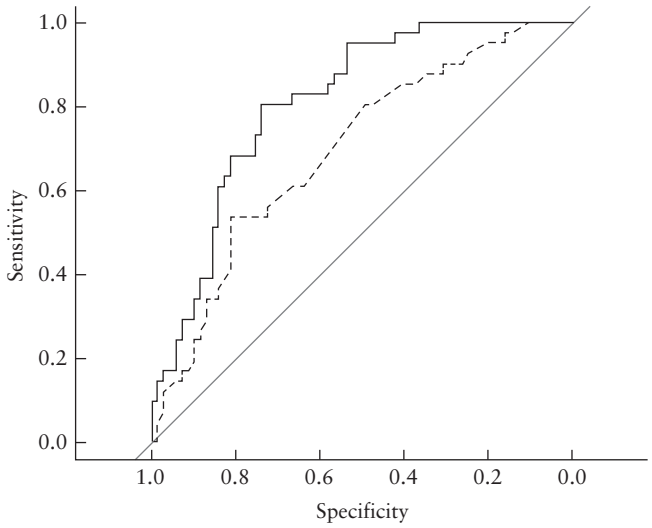

Figure 1 Receiver-operating-characteristics curves for prediction of neonatal mortality by model including only gestational age at delivery (– –) and full model (——).

Table 4 Predictive performance for neonatal mortality only and neonatal mortality or severe neurological morbidity of full model and model including only gestational age (GA) at delivery

Model	*AUC (%)*	*FPR (%)*	*Sensitivity (%)*	*NPV (%)*	*PPV (%)*
Mortality					
GA-only model	69.5 (59.4–79.5)	10	22.0 (7.3–48.4)	66.0 (62.0–74.6)	56.6 (30.3–74.2)
		20	46.3 (19.5–68.3)	71.5 (62.6–80.9)	57.9 (36.7–67.0)
		30	58.2 (39.7–75.6)	73.8 (66.1–82.9)	53.6 (44.0–60.0)
Full model	81.0 (73.0–88.9)	10	31.7 (12.2–63.4)	68.9 (63.3–80.5)	65.3 (42.0–79.0)
		20	65.9 (31.7–85.4)	79.8 (66.4–90.2)	66.2 (48.5–71.7)
		30	80.5 (58.5–92.7)	85.8 (74.0–94.2)	61.5 (53.7–64.7)
Mortality or severe neurological morbidity					
GA-only model	68.9 (58.8–79.9)	10	21.7 (7.3–46.3)	65.9 (62.0–73.8)	56.3 (30.3–73.4)
		20	47.8 (22.6–66.4)	72.1 (63.5–80.0)	58.7 (40.2–66.3)
		30	58.5 (41.5–74.9)	74.0 (66.8–82.4)	53.7 (45.1–59.7)
Full model	81.0 (73.1–89.2)	10	39.3 (10.7–60.7)	58.8 (49.3–68.8)	80.3 (52.6–86.3)
		20	55.4 (35.7–78.6)	63.3 (54.6–78.3)	74.2 (64.9–80.3)
		30	73.2 (48.2–89.3)	71.6 (56.6–86.3)	71.7 (62.5–75.5)

Data in parentheses are 95% CI. AUC, area under receiver-operating-characteristics curve; FPR, false-positive rate; NPV, negative predictive value; PPV, positive predictive value.

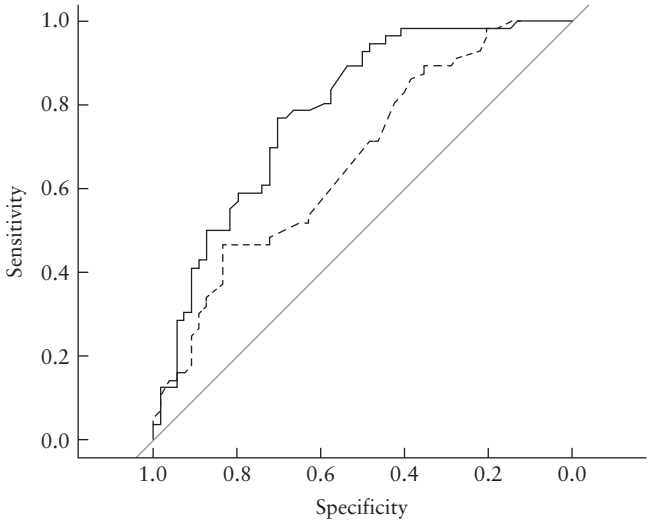

Figure 2 Receiver-operating-characteristics curves for prediction of neonatal mortality or severe neurological morbidity by model including only gestational age at delivery (– –) and full model (——).

obtained in the original sample ($P = 0.215$) (Figure S2). Table 4 shows the sensitivity and positive and negative predictive values for both models for the composite adverse outcome at fixed false-positive rates of 10%, 20% and 30%. At a 20% false-positive rate, the full model showed a sensitivity, negative predictive value and positive predictive value of 55%, 63% and 74%, respectively.

Figures S3 and S4 show the calibration plots in the construction cohort of the full models for mortality only and mortality or severe neurological morbidity, respectively, with the intercept and slope values. Both plots show little departure from the expected slope across the whole range of expected probabilities.

For the external validation cohort, 32 newborns met the inclusion criteria and their characteristics are summarized in Table S1. The full model for neonatal mortality or severe neurological morbidity had a goodness-of-fit (Nagelkerke's R^2) of 20.0% in the construction cohort and 18.9% in the validation cohort. Accordingly, the model shrinkage was 1.1%, suggesting good external validity. Figure S5 shows the ROC curves of the full model in the construction and validation cohorts for predicting mortality or severe neurological morbidity (AUC, 0.81 (95% CI, 0.73–0.89) *vs* 0.83 (95% CI, 0.69–0.98)). The calibration plot of the full model for mortality or severe neurological morbidity in the validation cohort is shown in Figure S6.

DISCUSSION

The diagnosis of extremely preterm FGR carries a great challenge for counseling and leaves parents with a considerable burden of uncertainty regarding the likelihood of survival without major sequelae if delivery occurs in the following days[28,29]. Our study shows that the prediction of intact survival could be better achieved by considering other parameters in addition to GA at birth.

Previous studies

Several studies[15,16,30–32] have evaluated intact survival in extremely preterm small fetuses. In all, the probability of intact survival exceeded 50% only from 28 weeks' gestation onward, 1 week later than in our cohort. Baschat *et al.*[16] found GA ≥ 28 weeks to be the best predictor for overall survival and GA > 29 + 2 weeks to be the best for intact survival and for severe morbidity. Fetal weight > 800 g was found to be a predictor of intact survival, regardless of GA[16]. In contrast to Baschat *et al.*[16], Torrance *et al.*[30] and Shah *et al.*[32] confirmed the present study's finding of fetal sex as a predictor of both mortality and neonatal morbidity. Some of these studies also identified abnormal Doppler of the DV[16] and absent or reversed UA-EDV[30] as predictors of poor neonatal outcome. However, corticosteroid administration, neuroprotection with magnesium sulfate and presence of pre-eclampsia were not consistently evaluated by these studies, results were not always stratified by GA and some participants were enrolled after 26 weeks, hampering the comparison between their study findings and ours[16,30].

Pathophysiological mechanisms

The disadvantage of male sex in very preterm infants is well established[33]. The level of catecholamines produced as a defense mechanism against hypoxia is significantly higher in females[34].

We found magnesium sulfate administration before delivery to be associated independently with neonatal mortality. This is likely to be because, as a non-competitive N-methyl-D-aspartate receptor antagonist, it exerts intra- and extracellular effects to reduce the activation of apoptosis[35].

In keeping with previous series in early growth-restricted infants[16,29,31] and overall extremely preterm infants[36–38], we found fetal weight to be associated independently with neonatal mortality. It has been reported that the survival rate of children with a birth weight at the 2nd–3rd centiles was the same as that of children with a birth weight at the 50th centile who were delivered 2 weeks earlier[14].

We failed to find any predictive capacity for neonatal complications of corticosteroid administration for lung maturation, which is likely to be because more than 90% of women in our cohort received at least one dose, and more than 70% received the full two-dose course. It is a matter of controversy whether corticosteroids have the same benefit in growth-restricted infants as that in the overall group of premature neonates, due to the exclusion of these infants from previous randomized controlled trials. However, a meta-analysis of observational studies[39] and a large nationwide study conducted in Canada[40] suggest a similar beneficial effect. As reported previously[41], we did not find pre-eclampsia to be a predictor of adverse neonatal outcome. We speculate that this risk is conferred mainly by the degree of placental insufficiency, which is already captured by the Doppler parameters. Indeed,

hypertension alone could be argued to confer a protective effect by enhancing placental perfusion.

We found that fetal Doppler status was associated with both mortality and severe neurological morbidity. Reversed UA-EDV and abnormal DV Doppler could identify neonates at high risk of multiorgan failure. Baschat *et al.*[16] found that abnormal DV Doppler had predictive capacity only in infants above 600 g and with delivery at ≥ 29 weeks' gestation. Our study extends this predictive capacity into earlier GAs. This difference can be explained by the fact that the former study was conducted at 12 centers across five different countries, suggesting higher variability in Doppler evaluation and clinical management. In our study, all centers followed an almost identical protocol.

Clinical implications

Although most guidelines recommend active management after 26 weeks' gestation, there is a gray zone before 28 weeks in extremely preterm growth-restricted fetuses, in which more accurate approximation of prenatal predictive factors is needed for individual counseling on the timing of delivery. For instance, our model, for which the coefficients for risk estimation are detailed in Appendix S1, predicts a likelihood of survival without major neurological sequelae of 49% for a 27-week female fetus with an EFW of 500 g and absent or reversed DV-EDV. In contrast, a male fetus in the same clinical situation would have a predicted chance of intact survival of only 25%. Other factors are relevant in parental decision-making in periviable births, including personal beliefs, values and cultural expectations[42,43]. Comprehensive counseling should also consider these intangible factors, and clinical sense and reasonableness should always prevail in decision-making, without causing avoidable harm or preventable fetal death.

Strengths and limitations

One strength of this study is the sample size, with more than 100 liveborn growth-restricted infants delivered before 28 weeks. Second, all patients were managed per standardized protocols with low variability in care. If all predictors are available antenatally, our models could be applied for counseling before birth. Additionally, our models showed similar performance in a validation cohort recruited from a Spanish tertiary hospital with the same management protocol. Finally, all surviving cases were followed up for at least 2 years.

We also concede several limitations to our study. First, low variability in care may limit the external validity in settings with different health systems or standards of neonatal care. Moreover, as our series is retrospective, it cannot be ruled out that the awareness by clinicians of some of the predictors may have influenced clinical management. This design could also affect the representativity of our included cases. Furthermore, our series included only 22 infants born before 26 weeks, which may result in non-robust risk estimation at this extreme of the GA spectrum. Finally, other potential predictors were not available in our series, such as the time interval between abnormal Doppler recording and delivery and maternal levels of angiogenic factors, which could add to the biophysical information provided by fetal Doppler status[44,45].

Conclusions

A model including fetal weight, sex and Doppler status in addition to GA improves the prediction of mortality or severe morbidity in extremely preterm and antenatally diagnosed growth-restricted infants. This should be considered for parental counseling and decision-making.

REFERENCES

1. Lackman F, Capewell V, Gagnon R, Richardson B. Fetal umbilical cord oxygen values and birth to placental weight ratio in relation to size at birth. *Am J Obstet Gynecol* 2001; **185**: 674–682.
2. Figueras F, Gardosi J. Intrauterine growth restriction: new concepts in antenatal surveillance, diagnosis, and management. *Am J Obstet Gynecol* 2011; **204**: 288–300.
3. Groom KM, David AL. The role of aspirin, heparin, and other interventions in the prevention and treatment of fetal growth restriction. *Am J Obstet Gynecol* 2018; **218**: S829–840.
4. Mazarico E, Molinet-Coll C, Martinez-Portilla RJ, Figueras F. Heparin therapy in placental insufficiency: systematic review and meta-analysis. *Acta Obstet Gynecol Scand* 2020; **99**: 167–174.
5. Spencer R, Rossi C, Lees M, Peebles D, Brocklehurst P, Martin J, Hansson SR, Hecher K, Marsal K, Figueras F, Gratacos E, David AL. Achieving orphan designation for placental insufficiency: annual incidence estimations in Europe. *BJOG* 2019; **126**: 1157–1167.
6. David AL. Maternal uterine artery VEGF gene therapy for treatment of intrauterine growth restriction. *Placenta* 2017; **59**: S44–50.
7. McCowan LM, Figueras F, Anderson NH. Evidence-based national guidelines for the management of suspected fetal growth restriction: comparison, consensus, and controversy. *Am J Obstet Gynecol* 2018; **218**: S855–868.
8. Martins JG, Biggio JR, Abuhamad A. Society for Maternal–Fetal Medicine Consult Series #52: Diagnosis and management of fetal growth restriction. *Am J Obstet Gynecol* 2020; **223**: B2–17.
9. Lees CC, Stampalija T, Baschat A, da Silva Costa F, Ferrazzi E, Figueras F, Hecher K, Kingdom J, Poon LC, Salomon LJ, Unterscheider J. ISUOG Practice Guidelines: diagnosis and management of small-for-gestational-age fetus and fetal growth restriction. *Ultrasound Obstet Gynecol* 2020; **56**: 298–312.
10. Melamed N, Baschat A, Yinon Y, Athanasiadis A, Mecacci F, Figueras F, Berghella V, Nazareth A, Tahlak M, McIntyre HD, Da Silva Costa F, Kihara AB, Hadar E, McAuliffe F, Hanson M, Ma RC, Gooden R, Sheiner E, Kapur A, Divakar H, Ayres-de-Campos D, Hiersch L, Poon LC, Kingdom J, Romero R, Hod M. FIGO initiative on fetal growth: best practice advice for screening, diagnosis, and management of fetal growth restriction. *Int J Gynaecol Obstet* 2021; **152**: 3–57.
11. Caradeux J, Martinez-Portilla RJ, Basuki TR, Kiserud T, Figueras F. Risk of fetal death in growth-restricted fetuses with umbilical and/or ductus venosus absent or reversed end-diastolic velocities before 34 weeks of gestation: a systematic review and meta-analysis. *Am J Obstet Gynecol* 2018; **218**: S774–S782.e21.
12. GRIT Study Group. A randomised trial of timed delivery for the compromised preterm fetus: short term outcomes and Bayesian interpretation. *BJOG* 2003; **110**: 27–32.
13. Lees CC, Marlow N, van Wassenaer-Leemhuis A, Arabin B, Bilardo CM, Brezinka C, Calvert S, Derks JB, Diemert A, Duvekot JJ, Ferrazzi E, Frusca T, Ganzevoort W, Hecher K, Martinelli P, Ostermayer E, Papageorghiou AT, Schlembach D, Schneider KT, Thilaganathan B, Todros T, Valcamonico A, Visser GH, Wolf H; TRUFFLE study group. 2-year neurodevelopmental and intermediate perinatal outcomes in infants with very preterm fetal growth restriction (TRUFFLE): a randomised trial. *Lancet* 2015; **385**: 2162–2172.
14. Cole TJ, Hey E, Richmond S. The PREM score: a graphical tool for predicting survival in very preterm births. *Arch Dis Child Fetal Neonatal Ed* 2010; **95**: F14–19.
15. Lees C, Marlow N, Arabin B, Bilardo CM, Brezinka C, Derks JB, Duvekot J, Frusca T, Diemert A, Ferrazzi E, Ganzevoort W, Hecher K, Martinelli P, Ostermayer E, Papageorghiou AT, Schlembach D, Schneider KT, Thilaganathan B, Todros T, van Wassenaer-Leemhuis A, Valcamonico A, Visser GH, Wolf H; TRUFFLE Group. Perinatal morbidity and mortality in early-onset fetal growth restriction: cohort outcomes of the trial of randomized umbilical and fetal flow in Europe (TRUFFLE). *Ultrasound Obstet Gynecol* 2013; **42**: 400–408.
16. Baschat AA, Cosmi E, Bilardo CM, Wolf H, Berg C, Rigano S, Germer U, Moyano D, Turan S, Hartung J, Bhide A, Müller T, Bower S, Nicolaides KH, Thilaganathan B, Gembruch U, Ferrazzi E, Hecher K, Galan HL, Harman CR. Predictors of neonatal outcome in early-onset placental dysfunction. *Obstet Gynecol* 2007; **109**: 253–261.
17. Morrison JL, Botting KJ, Soo PS, McGillick E, Hiscock J, Zhang S, McMillen IC, Orgeig S. Antenatal steroids and the IUGR fetus: are exposure and physiological

effects on the lung and cardiovascular system the same as in normally grown fetuses? *J Pregnancy* 2012; **2012**: 839656.
18. Robinson HP, Fleming JE. A critical evaluation of sonar 'crown-rump length' measurements. *BJOG* 1975; **82**: 702–710.
19. Stirnemann J, Villar J, Salomon LJ, Ohuma E, Ruyan P, Altman DG, Nosten F, Craik R, Munim S, Cheikh Ismail L, Barros FC, Lambert A, Norris S, Carvalho M, Jaffer YA, Noble JA, Bertino E, Gravett MG, Purwar M, Victora CG, Uauy R, Bhutta Z, Kennedy S, Papageorghiou AT. International estimated fetal weight standards of the INTERGROWTH-21st Project. *Ultrasound Obstet Gynecol* 2017; **49**: 478–486.
20. Hadlock FP, Harrist RB, Sharman RS, Deter RL, Park SK. Estimation of fetal weight with the use of head, body, and femur measurements – a prospective study. *Am J Obstet Gynecol* 1985; **151**: 333–337.
21. Bhide A, Acharya G, Baschat A, Bilardo CM, Brezinka C, Cafici D, Ebbing C, Hernandez-Andrade E, Kalache K, Kingdom J, Kiserud T, Kumar S, Lee W, Lees C, Leung KY, Malinger G, Mari G, Prefumo F, Sepulveda W, Trudinger B. ISUOG Practice Guidelines (updated): use of Doppler velocimetry in obstetrics. *Ultrasound Obstet Gynecol* 2021; **58**: 331–339.
22. Tranquilli AL, Dekker G, Magee L, Roberts J, Sibai BM, Steyn W, Zeeman GG, Brown MA. The classification, diagnosis and management of the hypertensive disorders of pregnancy: a revised statement from the ISSHP. *Pregnancy Hypertens* 2014; **4**: 97–104.
23. Spanish Society of Gynaecology and Obstetrics (SEGO). Practice Guidelines: crecimiento intrauterino restringido. https://sego.es/Guias_de_Asistencia_Practica#perinatal.
24. Macones GA, Hankins GDV, Spong CY, Hauth John, Moore Thomas. The 2008 National Institute of Child Health and Human Development workshop report on electronic fetal monitoring: update on definitions, interpretation, and research guidelines. *J Obstet Gynecol Neonatal Nurs* **2008**; 37: 510–515.
25. Wallace DK, Morse CL, Melia M, Sprunger DT, Repka MX, Lee KA, Christiansen SP; American Academy of Ophthalmology Preferred Practice Pattern Pediatric Ophthalmology/Strabismus Panel. Pediatric Eye Evaluations Preferred Practice Pattern®: I. vision screening in the primary care and community setting; ii. comprehensive ophthalmic examination. *Ophthalmology* 2018; **125**: P184–227.
26. DeLong ER, DeLong DM, Clarke-Pearson DL. Comparing the areas under two or more correlated receiver operating characteristic curves: a nonparametric approach. *Biometrics* 1988; **44**: 837–845.
27. Snee RD. Validation of regression models: methods and examples. *Technometrics* 1977; **19**: 415–428.
28. Harvey ME, David AL, Dyer J, Spencer R. Pregnant women's experiences and perceptions of participating in the EVERREST prospective study; a qualitative study. *BMC Pregnancy Childbirth* 2019; **19**: 144.
29. Blakeley C, Smith DM, Johnstone ED, Wittkowski A. Women's lived experiences of a prenatal diagnosis of fetal growth restriction at the limits of viability: An interpretative phenomenological study. *Midwifery* 2019; **76**: 110–117.
30. Torrance HL, Bloemen MCT, Mulder EJH, Nikkels PGJ, Derks JB, de Vries LS, Visser GA. Predictors of outcome at 2 years of age after early intrauterine growth restriction. *Ultrasound Obstet Gynecol* 2010; **36**: 171–177.
31. Lawin-O'Brien AR, Dall'Asta A, Knight C, Sankaran S, Scala C, Khalil A, Bhide A, Heggarty S, Rakow A, Pasupathy D, Papageorghiou AT, Lees CC. Short-term outcome of periviable small-for-gestational-age babies: is our counseling up to date? *Ultrasound Obstet Gynecol* 2016; **48**: 636–641.
32. Shah PS, Ye XY, Synnes A, Rouvinez-Bouali N, Yee W, Lee SK; Canadian Neonatal Network. Prediction of survival without morbidity for infants born at under 33 weeks gestational age: a user-friendly graphical tool. *Arch Dis Child Fetal Neonatal Ed* 2012; **97**: F110–115.
33. Boghossian NS, Geraci M, Edwards EM, Horbar JD. Sex differences in mortality and morbidity of infants born at less than 30 weeks' gestation. *Pediatrics* 2018; **142**: e20182352.
34. Greenough A, Lagercrantz H, Pool J, Dahlin I. Plasma catecholamine levels in preterm infants. Effect of birth asphyxia and Apgar score. *Acta Paediatr Scand* 1987; **76**: 54–59.
35. Chollat C, Sentilhes L, Marret S. Fetal neuroprotection by magnesium sulfate: from translational research to clinical application. *Front Neurol* 2018; **9**: 247.
36. Mamopoulos A, Petousis S, Tsimpanakos J, Masouridou S, Kountourelli K, Margioula-Siarkou C, Papouli M, Rousso D. Birth weight independently affects morbidity and mortality of extremely preterm neonates. *J Clin Med Res* 2015; **7**: 511–516.
37. de Waal CG, Weisglas-Kuperus N, van Goudoever JB, Walther FJ; NeoNed Study Group, LNF Study Group. Mortality, neonatal morbidity and two year follow-up of extremely preterm infants born in The Netherlands in 2007. *PloS One* 2012; **7**: e41302.
38. Bader D, Kugelman A, Boyko V, Levitzki O, Lerner-Geva L, Riskin A, Reichman B; Israel Neonatal Network. Risk factors and estimation tool for death among extremely premature infants: a national study. *Pediatrics* 2010; **125**: 696–703.
39. Blankenship SA, Brown KE, Simon LE, Stout MJ, Tuuli MG. Antenatal corticosteroids in preterm small-for-gestational age infants: a systematic review and meta-analysis. *Am J Obstet Gynecol MFM* 2020; **2**: 100215.
40. Melamed N, Pittini A, Barrett J, Yoon EY, Lemyre B, Lee SK, Murphy KE, Shah PS; Canadian Neonatal Network Investigators. Antenatal corticosteroids and outcomes of small-for-gestational-age neonates. *Obstet Gynecol* 2016; **128**: 1001–1008.
41. Morsing E, Marsal K, Ley D. Reduced prevalence of severe intraventricular hemorrhage in very preterm infants delivered after maternal preeclampsia. *Neonatology* 2018; **114**: 205–211.
42. Kukora SK, Boss RD. Values-based shared decision-making in the antenatal period. *Semin Fetal Neonatal Med* 2018; **23**: 17–24.
43. Myers P, Andrews B, Meadow W. Opportunities and difficulties for counseling at the margins of viability. *Semin Fetal Neonatal Med* 2018; **23**: 30–34.
44. Stepan H, Galindo A, Hund M, Schlembach D, Sillman J, Surbek D, Vatish M. Clinical utility of sFlt-1 and PlGF in screening, prediction, diagnosis and monitoring of pre-eclampsia and fetal growth restriction. *Ultrasound Obstet Gynecol* 2023; **61**: 168–180.
45. Bonacina E, Mendoza M, Farràs A, Garcia-Manau P, Serrano B, Hurtado I, Ferrer-Oliveras R, Illan L, Armengol-Alsina M, Carreras E. Angiogenic factors for planning fetal surveillance in fetal growth restriction and small-for-gestational-age fetuses: A prospective observational study. *BJOG* 2022; **129**: 1870–1877.

SUPPORTING INFORMATION ON THE INTERNET

The following supporting information may be found in the online version of this article:

Figure S1 20-fold cross-validation procedure with average area under receiver-operating-characteristics curve of full model for mortality.

Figure S2 20-fold cross-validation procedure with average area under receiver-operating-characteristics curve of full model for mortality or severe neurological morbidity.

Figure S3 Calibration plot of full model for mortality in construction cohort.

Figure S4 Calibration plot of full model for mortality or severe neurological morbidity in construction cohort.

Figure S5 Receiver-operating-characteristics curves for prediction by full model of neonatal mortality or severe neurological morbidity in construction cohort (solid line) and validation cohort (dashed line).

Figure S6 Calibration plot of full model for mortality or severe neurological morbidity in validation cohort.

Table S1 Antenatal characteristics of external validation cohort ($n = 32$)

Appendix S1 Coefficients for risk estimation of neonatal death or survival with major neurological sequelae

