

Development of an integrated risk scale for prediction of shunt placement after neonatal intraventricular hemorrhage

Michael C. Jin, BS,¹ Jonathon J. Parker, MD, PhD,¹ Adrian J. Rodrigues, BA,¹ Gabriela D. Ruiz Colón, BA,¹ Cesar A. Garcia, BA,¹ Kelly B. Mahaney, MD,^{1,2} Gerald A. Grant, MD,^{1,2} and Laura M. Prolo, MD, PhD^{1,2}

¹Department of Neurosurgery, Stanford University School of Medicine, Stanford, California; and ²Division of Pediatric Neurosurgery, Stanford Children's Health, Lucile Packard Children's Hospital, Palo Alto, California

OBJECTIVE Neonatal intraventricular hemorrhage (IVH) is a major cause of mortality and morbidity, particularly following premature birth. Even after the acute phase, posthemorrhagic hydrocephalus is a long-term complication, frequently requiring permanent ventriculoperitoneal shunt (VPS) placement. Currently, there are no risk classification methods integrating the constellation of clinical data to predict short- and long-term prognosis in neonatal IVH. To address this need, the authors developed a two-part machine learning approach for predicting short- and long-term outcomes after diagnosis of neonatal IVH. Integrating both maternal and neonatal characteristics, they developed a binary classifier to predict short-term mortality risk and a clinical scale to predict the long-term risk of VPS placement.

METHODS Neonates with IVH were identified from the Optum Clininformatics Data Mart administrative claims database. Matched maternal and childbirth characteristics were obtained for all patients. The primary endpoints of interest were short-term (30 day) mortality and long-term VPS placement. Classification of short-term mortality risk was evaluated using 5 different machine learning approaches and the best-performing method was validated using a withheld validation subset. Prediction of long-term shunt risk was performed using a multivariable Cox regression model with stepwise variable selection, which was subsequently converted to an easily applied integer risk scale.

RESULTS A total of 5926 neonates with IVH were identified. Most patients were born before 32 weeks' gestation (67.2%) and with low birth weight (81.2%). Empirical 30-day mortality risk was 10.9% across all IVH grades and highest among grade IV IVH (34.3%). Among the neonates who survived > 30 days, actuarial 12-month postdiagnosis risk of shunt placement was 5.4% across all IVH grades and 31.3% for grade IV IVH. The optimal short-term risk classifier was a random forest model achieving an area under the receiver operating characteristic curve of 0.882 with important predictors ranging from gestational age to diverse comorbid medical conditions. Selected features for long-term shunt risk stratification were IVH grade, respiratory distress syndrome, disseminated intravascular coagulation, and maternal preeclampsia or eclampsia. An integer risk scale, termed the Shunt Prediction After IVH in Neonates (SPAIN) scale, was developed from these 4 features, which, evaluated on withheld cases, demonstrated improved risk stratification compared with IVH grade alone (Harrell's concordance index 0.869 vs 0.852).

CONCLUSIONS In a large cohort of neonates with IVH, the authors developed a two-pronged, integrated, risk classification approach to anticipate short-term mortality and long-term shunt risk. The application of such approaches may improve the prognostication of outcomes and identification of higher-risk individuals who warrant careful surveillance and early intervention.

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KEYWORDS intraventricular hemorrhage; IVH; neonatal; predictive modeling; machine learning; ventriculoperitoneal shunt; hydrocephalus

ABBREVIATIONS AUC = area under the curve; AUPRC = area under the PR curve; AUROC = area under the ROC; CPT = Current Procedural Terminology; DIC = disseminated intravascular coagulation; ICD = *International Classification of Diseases*; IVH = intraventricular hemorrhage; NICU = neonatal intensive care unit; PDA = patent ductus arteriosus; PHH = posthemorrhagic hydrocephalus; PR = precision recall; RBF = radial basis function; RDS = respiratory distress syndrome; ROC = receiver operating characteristic; SPAIN = Shunt Prediction After IVH in Neonates; SVM = support vector machine; VPS = ventriculoperitoneal shunt.

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NEUONATAL germinal matrix hemorrhage into the ventricular system is a major cause of morbidity and mortality among premature infants born at 32 weeks' gestation or earlier. The incidence of intraventricular hemorrhage (IVH) in premature infants is currently 15% to 25% and, in infants who survive, is associated with long-term neurodevelopmental disability and posthemorrhagic hydrocephalus (PHH).^{1,2} IVH severity is characterized by the Papile grading scale ranging from I to IV.³ Lower grades involve germinal matrix hemorrhage without (grade I) and with (grade II) extension into the ventricle, without ventriculomegaly. Higher grades involve IVH with ventriculomegaly (grade III) and intraparenchymal extension (grade IV). The incidence of PHH is inversely related to IVH grade, with as many as 50% of patients with grades III and IV IVH developing PHH.^{1,4} Overall, approximately 15% of infants who have IVH will require permanent CSF diversion, usually in the form of a ventriculoperitoneal shunt (VPS).⁵ Furthermore, VPSs in infants with IVH have a higher rate of subsequent revisions, either due to failure or infection, compared with age-matched controls with hydrocephalus from other causes.⁶

IVH of prematurity is multifactorial, and a number of neonatal risk factors for developing IVH have been identified. The most well-characterized neonatal risk factors are low birth weight and the degree of prematurity,⁷ although other factors, including lack of antenatal steroid therapy, asphyxia, acidosis treated with NaHCO₃, and hypotension,⁸ are also important. Maternal factors that have been found to increase the risk of IVH include intrauterine infection, and factors that are correlated with decreased risk include primiparity and hypertensive disorders.^{9,10} To our knowledge, there have been no large national database studies combining maternal and neonatal risk factors into a unified risk assessment model for predicting mortality and PHH requiring shunt placement in this patient population.

To address this need, we developed a two-part machine learning approach for predicting short- and long-term outcomes following neonatal IVH. Integrating both maternal and neonatal characteristics, including IVH grade, comorbid conditions, pregnancy risk factors, and gestation details, we built a binary classifier to predict short-term mortality risk and a clinical scale to predict the long-term risk of VPS placement. Further assessment has suggested that our approach of integrating diverse clinical characteristics outperforms predictions based solely on IVH grade. The application of such methods may offer clinicians the ability to better predict post-IVH prognosis and identify opportunities for preventative intervention.

Methods

Data Source

All data used in our study were derived from the Clininformatics Data Mart (Optum, Inc.) claims database, which we have previously described and which contains the longitudinal healthcare claims of approximately 77 million patients insured by a major provider between 2003 and 2019.^{11,12} De-identified patients can be identified by an encrypted patient identifier number, and family units can be

linked by the presence of shared subscriber numbers within groups or policies. Mortality statistics were also available through back-end incorporation of internal discharge information and external data from the Social Security Death Master File and the Centers for Medicare and Medicaid Services. Diagnoses and procedures are documented using the *International Classification of Diseases Ninth and Tenth Revisions* (ICD-9 and ICD-10) and Current Procedural Terminology 4th edition (CPT-4) codes. This study was approved by the IRB.

Cohort Definition and Study Design

Neonatal patients with an inpatient IVH diagnosis between 2003 and 2019 were identified. In order to restrict our cohort to neonates, we only included patients for whom we were able to identify a matched maternal hospital admission for childbirth; for this, maternal and neonatal records were matched using both hospitalization dates and encrypted family identifiers (see *Data Source* section). A minority of patients younger than 1 year of age did not have associated maternal healthcare records or an identifiable childbirth admission; these patients were excluded from the study (see Fig. 1).

Our study focused on two primary outcomes of interest: short-term mortality and long-term risk of shunt dependence. Short-term mortality was defined as death within 1 month of the index IVH diagnosis. In patients who survived > 1 month post-IVH diagnosis, we assessed long-term risk of shunt dependence during the period of continuous follow-up. Continuous follow-up was defined by the period of uninterrupted enrollment in a qualifying healthcare plan spanning the index diagnosis date. Events were identified by a claim indicating placement of a VPS during the period of continuous follow-up. The index IVH diagnosis date was defined as the first date a qualifying IVH diagnosis code was associated with the neonate. The maternal and neonatal risk characteristics that were assessed are presented in Table 1 and Supplementary Table 1. Neonatal gestational age and birth weight were categorized according to ICD-9 and ICD-10 diagnosis codes previously validated in healthcare registries.¹³ Low body weight was defined as < 2500 g while very low body weight was defined as < 1500 g. The estimated ages at the index IVH diagnosis and hospital discharge were computed based on service dates related to maternal childbirth. The duration of the neonatal intensive care unit (NICU) stay was determined based on the number of hospitalized days with ≥ 1 NICU-associated service code. Other maternal risk factors, such as a history of infertility and history of preterm labor, were derived from longitudinal maternal healthcare records during the prenatal period. For a comprehensive list of the ICD-9, ICD-10, and CPT-4 codes used, see Supplementary Table 1.

Statistical Analysis and Model Development

Predictive modeling of our primary outcomes of interest (short-term mortality risk and long-term risk of shunt dependence) used binary classifier and time-to-event models, respectively. For model development, our cohort was randomly split into a 70% training cohort and a 30% vali-

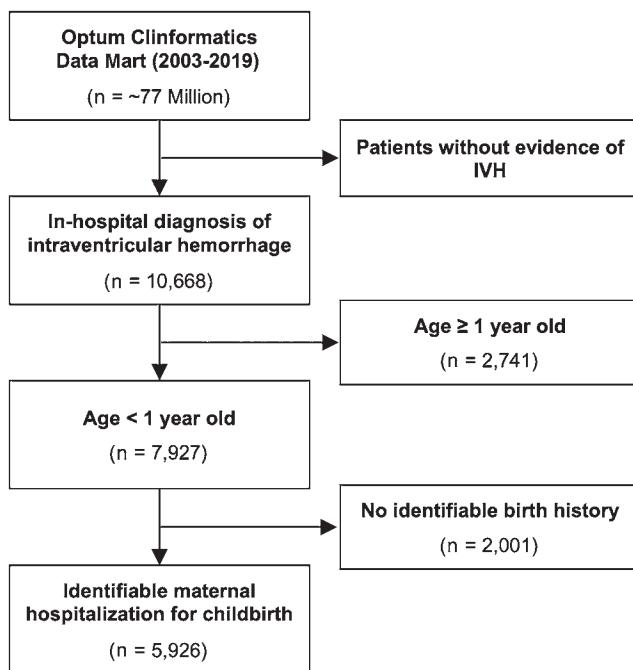


FIG. 1. CONSORT diagram of study inclusion and exclusion criteria.

dation cohort. The binary classification approaches that were evaluated included regularized logistic regression (lasso and elastic net penalization), random forest, support vector machine (SVM; radial basis function [RBF] kernel), and gradient-boosted decision tree. Classifier discrimination was evaluated using receiver operating characteristic (ROC) and precision-recall (PR) curves. Quantification of model performance was determined based on the area under the ROC (AUROC) curve and area under the PR curve (AUPRC). The confidence interval of the area under the curve (AUC) estimate was estimated from 1000 bootstrap resamplings. Accuracy of the predicted risk probabilities was assessed using the Brier score and the Spiegelhalter z-test. Robust model calibration was verified by the assessment of calibration plot slope and intercept. Additional performance metrics, including positive predictive value, negative predictive value, sensitivity, and specificity, were computed using the withheld validation data set.

Long-term risk of shunt dependence was modeled using a parsimonious time-to-event framework. In the training cohort, a multivariable Cox regression was trained using a subset of variables identified by backward feature elimination. Computed hazard ratios were converted to a points system using the method described by Sullivan et al.¹⁴ The derived scale, termed the Shunt Prediction After IVH in Neonates (SPAIN) scale, was applied to the withheld validation cohort to assess risk stratification. Model performance was evaluated using both the comparison of cumulative incidence curves and Harrell's concordance index.¹⁵

Across our study, comparisons of continuous and categorical data were performed using the Mann-Whitney U-test and chi-square test of independence. All hypothesis testing was two-tailed and statistical significance was

TABLE 1. Cohort characteristics

Characteristic	Value (n = 5926)
Sex	
F	2654 (44.8)
M	3272 (55.2)
Race	
Asian	245 (4.1)
Black	412 (7.0)
Hispanic	411 (6.9)
Unknown	2679 (45.2)
White	2179 (36.8)
Median age at discharge, days (IQR)	46 (22–84)
IVH grade	
I	2477 (41.8)
II	840 (14.2)
III	575 (9.7)
IV	757 (12.8)
Unspecified	1277 (21.5)
Gestational age, wks	
<24	301 (5.1)
24	418 (7.1)
25–26	772 (13.0)
27–28	751 (12.7)
29–30	800 (13.5)
31–32	941 (15.9)
33–34	483 (8.2)
35–36	254 (4.3)
Btwn 28 & 37, NOS	18 (0.3)
Before 37, NOS	82 (1.4)
Term	551 (9.3)
Unspecified	555 (9.4)
Birth weight, g	
<500	188 (3.2)
500–749	878 (14.8)
750–999	875 (14.8)
1000–1249	746 (12.6)
1250–1499	733 (12.4)
1500–1749	563 (9.5)
1750–1999	413 (7.0)
2000–2499	417 (7.0)
>2500	197 (3.3)
Unspecified	916 (15.5)
Median mother's age, yrs (IQR)	31 (28–35)
Neonatal risk factors	
Birth trauma	552 (9.3)
RDS	4409 (74.4)
PDA	2497 (42.1)
Pulmonary hemorrhage	223 (3.8)
Pneumothorax/interstitial emphysema	729 (12.3)
Coarctation of the aorta	81 (1.4)

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TABLE 1. Cohort characteristics

Characteristic	Value (n = 5926)
Neonatal risk factors (continued)	
Neonatal DIC	194 (3.3)
Other coagulopathy/hemorrhage	1356 (22.9)
Maternal risk factors	
Cesarean section	3037 (51.2)
Fetal malposition	2041 (34.4)
Chorioamnionitis	862 (14.5)
Preeclampsia/eclampsia	1170 (19.7)
Oligohydramnios	621 (10.5)
Premature membrane rupture	1561 (26.3)
Gestational diabetes mellitus	311 (5.2)
Multiple gestation	1326 (22.4)
Pregnancy risk factors	
Grand multiparity	57 (1.0)
Elderly primigravida	392 (6.6)
Elderly multigravida	1023 (17.3)
History of infertility	637 (10.7)
History of preterm labor	307 (5.2)

NOS = not otherwise specified.

Values represent the number of patients (%) unless stated otherwise.

established using a p value threshold of 0.05. All analyses and graphical representations were performed using R version 4.0.0 (The R Project for Statistical Computing) and Prism version 8 (GraphPad Software). Analyses were performed using the glmnet, survival, MASS, e1071, randomForest, PRROC, and rms packages.

Results

Cohort Characteristics

A total of 5926 neonates were included in the study (Fig. 1). IVH severity was explicitly noted for the majority of patients (n = 4649, 79.5%), with most patients diagnosed with a grade I (n = 2477, 41.8%) or grade II (n = 840, 14.2%) hemorrhage. Most patients were either extremely preterm (\leq 28 weeks' gestation; n = 2242, 37.8%) or very preterm (29–32 weeks' gestation; n = 1741, 29.4%), and most patients had low birth weight (n = 4813, 81.2%). Gestational age and birth weight were not available for 9.4% and 15.5% of the cohort, respectively (Table 1). Common neonatal risk factors included respiratory distress syndrome (RDS; n = 4409, 74.4%), patent ductus arteriosus (PDA; n = 2497, 42.1%), and either disseminated intravascular coagulation (DIC) or another coagulopathy (n = 1550, 26.2%). Approximately half of the neonates were born by cesarean section (n = 3037, 51.2%). The median neonate age at discharge was 46 days (IQR 22–84 days) and the median maternal age was 31 years (IQR 28–35 years), while the median follow-up duration for discharged patients was 8.1 months (IQR 2.1–20.7 months).

Prediction of Short-Term Mortality

Overall risk of mortality during the first 30 days following IVH diagnosis was 10.9% (n = 581/5324 neonates; 602 patients with < 30 days of continuous follow-up who did not die prior to censoring were excluded). Risk correlated with IVH severity (34.3% grade IV, 15.1% grade III, 9.4% grade II, and 4.0% grade I) and with extremely premature compared with very premature birth (26.6% vs 5.5%). Among all neonates, the comorbid conditions that were most strongly associated with mortality risk were pulmonary hemorrhage (39% with vs 9.8% without) and DIC (37.5% with vs 10.0% without).

To determine an optimal approach for predicting short-term mortality, 5 competing models (lasso logistic regression, elastic net logistic regression, RBF-kernel SVM, gradient-boosting decision tree, and random forest) were trained on a randomly sampled training data set (70% of the entire cohort). Evaluating model performance based on both discriminative ability and overall prediction performance, the random forest approach performed best among assessed models (AUC 0.882 and Brier score 0.067; Fig. 2A and Supplementary Fig. 1A and B). Comparison of predicted and empirical probabilities verified model calibration (slope 1.07 and intercept 0.08; Fig. 2B). The AUPRC of the random forest model was 0.581 (Supplementary Fig. 1C), outperforming other approaches (Supplementary Fig. 1D). The top 6 contributing features are shown in Fig. 3A; notably, diverse features beyond IVH grade were important for model predictions, including comorbid conditions and hospitalization characteristics. Importantly, the random forest model demonstrated high specificity (98.2%) and high negative predictive value (91.7%) while retaining good positive predictive value (65.8%) (Fig. 3B). Although the mortality model was intended to be applied dynamically, with variables such as NICU stay duration, which frequently change over the course of hospitalization, omitting such variables did not significantly affect performance (AUROC 0.865, 95% CI 0.830–0.895). The random forest model, with dynamic variables omitted, significantly outperformed mortality prediction using IVH grade alone, even when only considering IVH cases with a known grade (AUC 0.865 vs 0.757, Brier score 0.076 vs 0.087; Supplementary Fig. 2A). When a more liberal cutoff of 0.1 was established (vs 0.5, shown in Fig. 3B), the false-negative rate was only 2.4% for our model (without NICU duration included) compared with 5.8% using IVH grade alone. When restricting model prediction (excluding NICU stay duration) to only neonates born prematurely (\leq 32 weeks' estimated gestational age), the model retained high performance with an AUROC of 0.869 (95% CI 0.837–0.897; Supplementary Fig. 2B).

Long-Term Risk of Hydrocephalus and VPS Placement

In patients surviving \geq 30 days, the overall actuarial risk of VPS placement was 3.8% (95% CI 3.2%–4.4%), 4.9% (95% CI 4.2%–5.5%), and 5.4% (95% CI 4.7%–6.1%) at 3, 6, and 12 months post-IVH diagnosis, respectively. The risk of shunt dependence at 12 months was 31.3% (95% CI 26.4%–35.9%) for grade IV IVH, 13.9% (95% CI 10.3%–17.4%) for grade III IVH, and 0.6% (95% CI 0.3%–0.9%) for grade I and II IVH. Few patients received

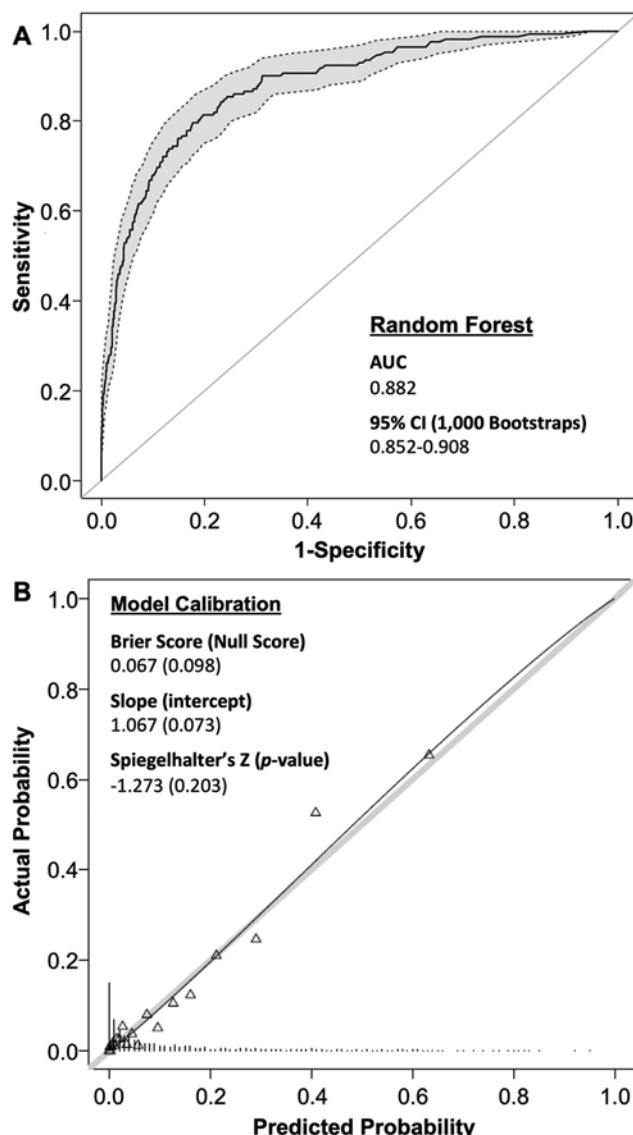


FIG. 2. Risk classifier performance for short-term mortality risk. **A:** The random forest approach achieved optimal discriminative performance with an AUC of 0.882. **B:** Model calibration was confirmed by comparing predicted and empirical risk estimates. All performance evaluations were performed on the withheld validation subset.

their first shunt placement > 6 months after the initial IVH diagnosis (14/3389 [0.4%] with ≥ 6 months of continuous follow-up), as 94.1% of shunts were placed within the first 6 months after IVH diagnosis.

Using a backward variable selection paradigm, we identified 4 maternal and neonatal features that were associated with shunt placement (among neonates surviving ≥ 30 days after the initial IVH diagnosis): IVH grade, RDS, neonatal DIC, and maternal preeclampsia/eclampsia. Intriguingly, while an increased IVH grade and the presence of DIC portended higher risk of long-term shunt placement, the presence of RDS and preeclampsia/eclampsia were negatively associated with shunt risk. The SPAIN score was derived from these 4 features. (Table 2). Across

all patients, a higher SPAIN score was associated with significant increases in the risk of long-term shunt placement (Fig. 4). Actuarial 3-, 6-, and 12-month postdiagnosis cumulative risks are presented in Table 3. Compared with the IVH grade, the SPAIN score improved on risk stratification granularity (grade I vs IV, HR 56.31, 95% CI 31.12–101.9; SPAIN score < 0 vs ≥ 8 , HR 104.6, 95% CI 48.88–223.7). Furthermore, the SPAIN score demonstrated the ability to stratify shunt risk within IVH grades (grade IV, grade III, and grades I and II in Fig. 5A, B, and C, respectively). Harrell's concordance index was also improved using the SPAIN score compared with the IVH grade alone (0.869 vs 0.852).

To further evaluate the performance of the SPAIN score for prediction of long-term shunt placement risk versus using IVH grade alone, we compared model performance anticipating shunt risk by 6 months postdiagnosis. When evaluating patients with a known IVH grade, we demonstrated superior performance using the SPAIN score (AUROC 0.912 vs 0.868; Supplementary Fig. 2C). This performance was retained when restricting the validation cohort to only neonates born prematurely (< 32 weeks' estimated gestational age) (AUROC 0.921, 95% CI 0.894–0.944; Supplementary Fig. 2D).

Discussion

In this study, we evaluated short- and long-term outcomes in neonates with IVH and developed a two-part predictive modeling scheme: a binary classification model for short-term mortality risk and a time-to-event model of shunt placement risk condensed into an easily applied numerical score, the SPAIN score. In addition to a number of neonatal comorbidities and hospitalization characteristics, maternal characteristics such as the presence of preeclampsia, age at childbirth, and delivery by cesarean section were also available and, thus, incorporated in model training and optimization. These models may offer simple, readily applied approaches for prognosticating outcomes after neonatal IVH diagnosis by consolidating individual characteristics into integrated risk predictions.

Predicting Short-Term Mortality Risk in Neonates With IVH

The majority of prior studies evaluating mortality as an endpoint after neonatal IVH diagnosis have described diverse risk factors that influence outcomes. For example, Han et al.¹⁶ described clinical and demographic features ranging from race to IVH grade that are independently associated with differential mortality risk. Others, such as Trifan et al.,¹⁷ have evaluated volumetric IVH severity according to the Graeb scale and demonstrated significant association between radiological features with patient outcomes. While these studies reveal and establish important associations potentiating future investigations, a key element missing is the personalized prediction of risk based on an individual's assembly of risk factors. In the current study, we aimed to incorporate contributing features into a unified risk model that can be applied rapidly in a personalized setting. While other studies have conducted analogous investigations,^{18,19} our study leverages both maternal and neonatal characteristics, while eval-

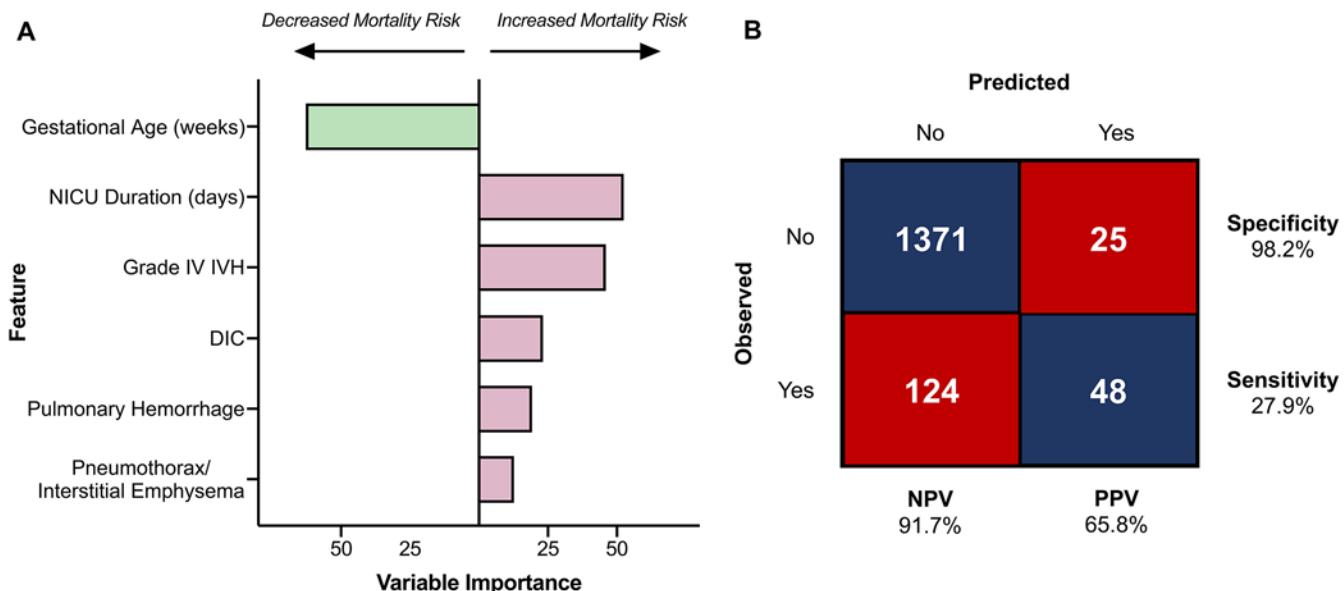


FIG. 3. Feature importance and empirical performance of mortality risk model. **A:** The top 6 features contributing to model classification were diverse, ranging from gestational duration to comorbid conditions. **B:** In the withheld subset, using an *a priori* defined risk threshold of 0.5 for classification, our model achieved high specificity, negative predictive value (NPV), and positive predictive value (PPV). Figure is available in color online only.

ating multiple approaches ranging from regression-based strategies to decision-tree models. The important predictors of short-term mortality identified in our study were multifactorial. As anticipated, grade IV IVH was a top 3 contributor to our final classifier's performance; empirically, neonates with grade IV IVH had a two-, four-, and eightfold higher short-term mortality risk than those with

grades III, II, and I IVH, respectively. Pregnancy and hospitalization characteristics, namely, the gestational age and NICU stay duration, were also major contributors to predicted risk. Neonatal comorbidities such as DIC, pulmonary hemorrhage, and pulmonary interstitial emphysema were also significant contributors to the risk of short-term mortality in neonates with IVH. This integrated model is able to more accurately predict mortality compared with predictions based solely on IVH grade and retains high performance when restricted to patients with a known IVH grade and those born prematurely. Furthermore, prediction is robust to missing variables, as omission of the NICU duration (which frequently changes over the course of hospitalization) does not significantly depress the model discrimination ability. Pending further external validation, real-time application of a predictive modeling approach toward short-term mortality may provide valuable insight for caregivers and family members.

Anticipating PHH and Shunt Placement

IVH with ventriculomegaly often leads to PHH, necessitating permanent CSF diversion. Temporary CSF diversion using ventriculosubgaleal shunts and ventricular reservoirs offer transient intracranial pressure relief while the infant gains weight and the hemorrhage clears; however, there is no clear evidence that they protect against future VPS placement.²⁰ Across prior studies, the IVH grade is well recognized as the predominant risk factor for PHH. However, identification of additional risk factors definitively associated with PHH has proven difficult. In a study of 42 neonates with IVH, late gestational age, but not RDS or birth weight, was associated with increased PHH risk.²¹ In another study, both late gestational age and

TABLE 2. SPAIN score for predicting post-IVH hydrocephalus

Characteristic	SPAIN Score Contribution
Neonatal	
IVH grade	
I	0
II	0
III	8
IV	10
Unspecified	4
RDS	
No	0
Yes	-1.5
DIC	
No	0
Yes	2
Maternal	
Preeclampsia/eclampsia	
No	0
Yes	-2

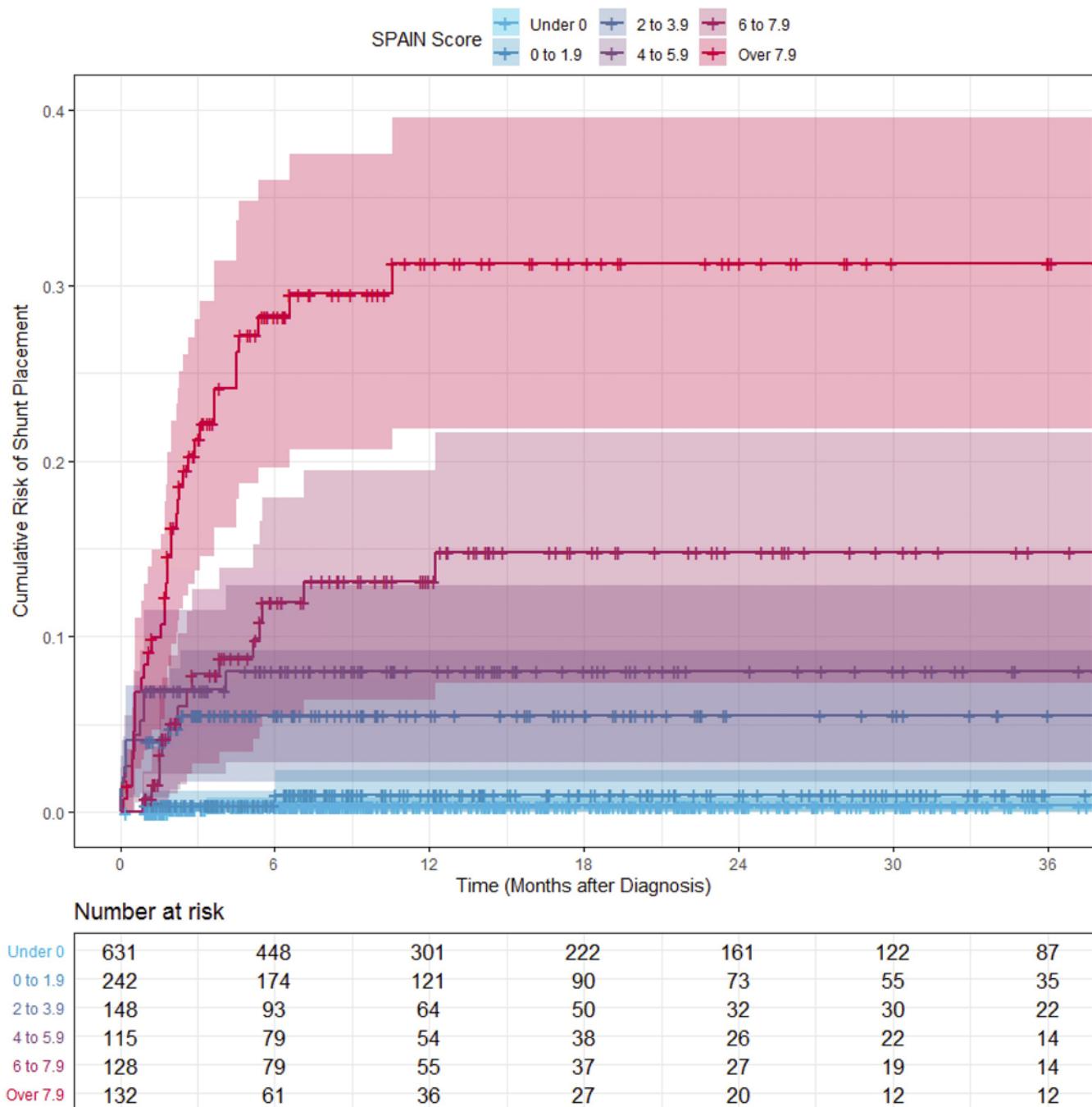


FIG. 4. Long-term risk of shunt placement stratified by the SPAIN score. Cumulative incidence curves showing the risk of shunt placement during the 3 years after an initial neonatal IVH diagnosis. The data shown are based on the withheld validation cohort that was not used to develop the SPAIN score. Figure is available in color online only.

higher birth weight were independently associated with PHH.²² Other investigations, such as that of Behjati et al., have found that gestational age and birth weight did not contribute to the need for shunt placement after adjusting for IVH grade.²³ In addition to the IVH grade, we identified concomitant DIC as a risk factor for shunt placement. As well as contributing to hemorrhage risk,²⁴ the presence of microthrombi may exacerbate CSF outlet ob-

struction, leading to hydrocephalus progression.^{25,26} Notably, our study did not identify either gestational age or birth weight as contributors to shunt placement risk after adjusting for IVH severity. While these prior studies have provided insight into factors that affect the risk of PHH, none of these studies unified diverse clinical characteristics for long-term prediction of VPS risk. We found increasing numbers of shunt placements throughout the first

TABLE 3. Predicted postdiagnosis shunt risk based on SPAIN score

SPAIN Score	3 Mos (%)	6 Mos (%)	12 Mos (%)
<0	0.19	0.31	0.40
0–1.9	0.90	1.05	1.22
2–3.9	2.07	2.30	2.30
4–5.9	5.86	6.32	6.76
6–7.9	8.27	10.66	13.30
>7.9	21.67	29.64	31.92

3 to 4 months of life for infants with low SPAIN scores and throughout the 1st year of life for infants with higher SPAIN scores. However, if a shunt was not placed by 1 year of age, it was highly unlikely the child would ever require a shunt.

Interestingly, previous reports have suggested that being born to a mother with preeclampsia may reduce the risk of long-term shunt dependence.^{27,28} While the mechanisms of this relationship remain unclear, it is possible that increased placental cortisol availability²⁹ may suppress cerebrovascular angiogenesis and contribute to improved germinal matrix vascular integrity, an effect that has been observed following prenatal glucocorticoid administration.³⁰ Another possibility is that the decreased prostacyclin levels observed in preeclampsia may emulate the physiological effects of indomethacin administration, which has been postulated to blunt IVH severity by reducing cerebral blood flow and promoting germinal matrix maturation.^{31,32} However, it is also possible that the perinatal care of mothers with preeclampsia, which includes administration of glucocorticoids³³ and magnesium sulfate,³⁴ may directly reduce the risk of severe IVH and PHH requiring shunt placement.^{35,36} Similarly, the seemingly protective effect of RDS on PHH may be a secondary effect of pre- and perinatal care (e.g., administration of corticosteroids).

Nonetheless, we speculate that neonates with concomitant RDS may develop IVH through distinct pathophysiological cascades compared with those born without pulmonary immaturity. The etiology of neonatal IVH has been attributed to three main pathogenic mechanisms: cerebral blood flow disruption, germinal matrix vascular fragility, and platelet/coagulation dysfunction.³⁷ Severe RDS can cause fluctuations in cerebral blood flow through impaired autoregulation, which has been linked to development of IVH during the first few hours of life but not later.^{38–40} It is possible that, in these infants, postnatal respiratory support, which has been shown to stabilize cerebral blood flow and volume,^{41–43} may protect against progressive hydrocephalus and long-term shunt dependence. On the other hand, weakness of the germinal matrix vasculature and disorders of hemostasis promote ventricular hemorrhage through distinct physiological mechanisms, potentially incurring divergent courses of disease progression.

Limitations

Limitations of this study are largely derived from its retrospective nature. Additionally, while the quantity of data available for this study was enhanced by leveraging nationally sourced administrative claims data, granularity of the data was reduced by the lack of available clinical or radiological notes. It is possible that further refinement of our models, using the aforementioned unavailable data from the Optum database, may lead to improved performance. Also, it is possible that institutional and provider-specific practice patterns and outcomes vary, which is not captured in our data set. Furthermore, while coding strategies used for this paper have been widely used in studies using administrative claims databases, the potential for underlying coding inaccuracies or inconsistencies remains. With regard to data granularity, certain clinical and laboratory measurements were unavailable; specifically, assessments of blood acidosis, arterial CO₂ content, and radiographic assessment of hemorrhage extent and presence of cytotoxic edema were not available for analysis.

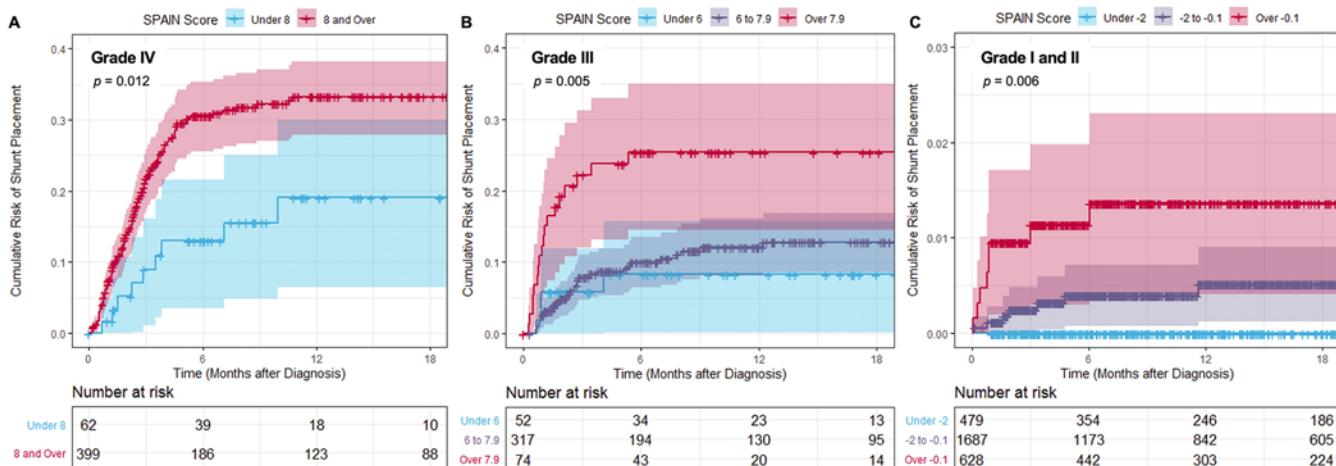


FIG. 5. SPAIN score risk stratification within IVH grade. Within subsets of patients with grades IV (A), III (B), and I or II (C) IVH, the SPAIN score allows for further stratification of long-term shunt risk. Figure is available in color online only.

Additionally, while prior studies have validated the use of diagnosis codes for categorization of prematurity based on gestational age and weight,¹³ our study did not have access to exact numerical estimates. Importantly, while we evaluated mortality and shunt placement as the endpoints of our study, other outcomes of interest, including long-term neurocognitive development, are highly important. Unfortunately, such outcomes require careful granular long-term follow-up and refined neurocognitive testing, which are not captured by large CPT/ICD code-based data sets. Lastly, only patients with qualifying healthcare plans and those with Medicare Advantage are included in the Optum Clininformatics Data Mart database; as such, uninsured patients and those covered by Medicaid were not available for inclusion in our study.

Conclusions

In our study, we developed an integrative approach leveraging diverse maternal and neonatal clinical data for prognosticating short- and long-term outcomes in neonates with IVH. Our models improved prediction of the 30-day mortality rate and long-term shunt placement compared with IVH grade alone. These models, designed to augment physician experience and institutional knowledge with empirical risk estimates, based on diverse nationally sourced data, may help guide family discussions and identify opportunities for clinical intervention in patients at high risk for mortality or long-term shunt dependence.

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Disclosures

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author Contributions

Conception and design: Prolo, Jin, Grant. Acquisition of data: Prolo, Jin. Analysis and interpretation of data: Prolo, Grant, Jin, Parker, Rodrigues. Drafting the article: Jin. Critically revising the article: all authors. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Prolo. Statistical analysis: Jin, Parker. Administrative/technical/material support: Prolo. Study supervision: Prolo.

Supplemental Information

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Correspondence

Laura M. Prolo: Stanford University School of Medicine, Stanford, CA. improlo@stanford.edu.