**PREDICTING HIE: CONVENTIONAL RISK FACTORES COMPARED TO AGNOSTIC MACHINE LEARNING ALGORITHMS.**

**INTRODUCTION**

While mothers report that the well-being of their unborn infant is the single biggest priority for them1 there is little evidence to guide them or the professionals looking after their baby2. The prediction of which infants will become compromised around birth is poorly understood3, and has been identified as a priority for the RCOG4 and the UK Department of Health5. We have presented some work that shows that modelling of risk is feasible6 and we know that simple interventions can improve neonatal and maternal7,8 outcomes.

One significant cause of perinatal brain injury is perinatal asphyxia, leading to hypoxic-ischaemic encephalopathy (HIE). HIE if often devastating, with life-long impacts for the infant13 and their family, as well as costing society millions of pounds in medical compensation, lost earnings and welfare support14. As well as the direct impact on infants and families, obstetric practice represents the biggest proportion of legal claims against the NHS15 and even small improvements in outcomes would yield substantial health benefits for individuals and economic benefits for health care services. Indeed, perinatal asphyxia is the 12th biggest cause of disability life years worldwide16 (i.e. a bigger impact than diabetes mellitus or tuberculosis), and even those infants with mild asphyxia have worse measures in cognition, movement and social metrics when compared to their peers17–19 and the true impact of this and other post-term related pathologies, and the economic implications, are unclear20. However interventions, such as induction of labour or operative delivery, can be employed if the risks of continuing the pregnancy are higher than delivery: for either the mother or the infant21. This lack of clear data on the perinatal risks and long term outcomes of these infants likely contributes to the variation in management of mothers with post-term babies11 and current NICE guidelines recognise this, and suggest that a research priority is to “identify babies at particularly high risk of morbidity and mortality who will benefit from induction and therefore avoid induction for babies who do not need it”22.

Risk factors for perinatal asphyxia and encephalopathy have been derived by a number of papers; although one of the most cited remains the work by Badawi *et al*10,26. This work identifies 35 potential risk factors for encephalopathy in an Australian population (Figure 1) and together have been cited over 700 times (Data extracted Web of Science 17/12/2019). In contrast the use of Machine Learning (ML) and Artificial Intelligence algorithms to predict health outcomes is currently of great interest. However often these models require cleaned data, preparatory work and advanced training and expertise to develop, before they are able to meet, or exceed, clinical prediction. Recently more automated techniques have become available, collectively known as Auto Machine Learning (AutoML). While computationally expensive they are now available as both standalone packages and cloud platforms.

This work is based on the Collaborative Perinatal Project24. Collection of Data was from 14 units across the United States and showed little evidence of selection bias25. The dataset collected data on approximately 60,000 pregnancies, and 58,000 live born infants born between 1959 and 1965. Data was collected throughout the prenatal period, labour and delivery, postpartum and as the child grew.

**AIMS**

1. The aim of this work is to identify if an agnostic ML model can predict, from historic data, as well, or better than established risk factors, to predict a poor outcome at the onset of labour.
2. To test if measures of infant growth can improve the prediction of hypoxic-ischaemic encephalopathy.
3. Estimate the amount of hypoxic brain injury potentially preventable using the above models.

**METHODS**

**Cohort Development**

The dataset is based on the full CPP variable file dataset; containing data in 58,760 infants. A total of 12,005 infants were born preterm (<37 weeks of completed gestation), 5476 were born after 42 weeks, and 964 were born to a mother of less than 16 years age; leaving a total of 40,315 for the analyses. 19,487 infants were born between 1959 and 1962 (and were placed in the first cohort), while 20,828 were born between 1963 and 1966 (and were placed in the second).

Primary outcome is hypoxic-ischaemic encephalopathy (HIE) defined as having definite seizures, hypertonia, jitteriness, hypotonia, abnormal reflexes, or abnormal cry; after having a low 5 minute Apgar score (<7)27. Analyses were repeated for perinatal death [the need for resuscitation after birth and the presence of a low Apgar score (<7 at 5 minutes)].

Initially the characteristics of the population (as used by Badawi10,26) will be described, split by the presence or not, of HIE. Two sets of prediction models will then be develop.

1. One will be based on established risk factors for HIE, based on *a-priori* proposed risk factors (Figure 1)10,26(‘Conventional Analysis’).
2. The second model is based around an agnostic ML algorithm using all data available in the cohort (‘ML analysis’).

**Conventional** **Analysis**

Data was cleaned and harmonised where possible with the measures previously proposed. A logistic regression model will be developed on the first half of the data (infants born 1959-1962) and then tested on the second half (infants born 1963 to 1965). The primary model includes only variables measurable at, or before 37 weeks of gestation (Figure 1). The initial model was then repeated with antenatal measures and the identified measure of fetal growth (birthweight centile (>90th, 10-90th, 3rd-9th, <3rd)). A third model was developed using the antenatal variables and additional variables available to clinicians at the onset, or duration labour, but before the birth of the infant. The model was independently repeated for the other outcome measures of interest.  
For all models, a prediction of the outcome of interest will be derived and infants allocated to one of 10 risk deciles, ROC curves will be derived alongside AUC measures. We will calculate the number of infants with HIE in the highest decile to estimate the possible number of infants where HIE may be avoidable by targeted interventions prior to birth.

Comparisons between the three models will be performed to test if addition of growth, or intrapartum measures, improve the prediction of the model.

**ML** **analysis**

An agnostic ML model was developed using the same testing-validating cohorts from the previous component. 28 out of 518 variables were discarded as they contained >5% of missing data values; leaving a potential 490 exposure data fields for the prediction models. All variables have been identified as either antenatal (measurable before 37 weeks gestation), growth (birth measures of growth), and intrapartum (measures only available at or after 37 weeks, up to the point to delivery), and classified as either categorical or numerical. 4 different data-adaptive methods were used;

1) The first cohort was uploaded to the Google AutoML platform. The outcome of interest was identified but no further modification or classification of the data was performed. A binary classification model was then derived and limited to one node hour of computational time. Results were then applied to the second cohort to derive a risk decile score of 1-10 as above.

2) The local analysis was also trained using the first cohort and evaluated using the second cohort. All analyses were performed using a dockerised implementation of Jupyter notebook (jupyter/tensorflow-notebook:7a0c7325e470) with additional packages installed as specified. Each variable set-indication were individually processed prior to training as follows. First, unordered categorical variables were recoded as dummy variables. Second, the training data minority (disease) class was resampled using SMOTE (Synthetic Minority Over-sampling Technique [imbalanced-learn v0.5.0]) to improve class balance between affected/unaffected observations. Third, predictors with high Pearson correlation (>80%) in the training dataset were eliminated by randomly selecting a single predictor from each pair. Fourth, a random forest was applied to the training data to select features with a conservative feature importance threshold (>0.01). Finally, continuous predictors were standardised to Z-score in both training and testing data by using the mean and standard deviation of the training data estimated prior to pre-processing. Following data processing, ML models were trained using predictors identified by the random forest and evaluated using the testing dataset with the following algorithms using default parameters unless otherwise indicated.

2A) Logistic regression (sci-kit learn). The maximum number of iterations taken for convergence was increased to 100,000.

2B) Random Forest (sci-kit learn)

2C) Neural Network (TensorFlow). One hidden layer with number of nodes equal to number of predictors. Rectified linear unit activation function.

2D) Adanet ([v0.8.0]). An Ensembl/AutoML binary classifier was prepared using the following models: linear model, neural network (hidden layers/nodes 20, 50, 100, 20 & 10, 50 & 20, 100 & 40, 100 & 40 & 20), gradient boosted trees.

For all methods, the three models will be derived as above, and then repeated for the other outcomes of interest. Infants were allocated a risk decile as in the conventional model; and comparisons made between models as above, and the top 50 measures identified from the ML model as most predictive reported/defined. Finally we will then test if the corresponding ML derived model differs from the conventional model’s predictive value.

**Sensitivity Analyses**

**RESULTS**

Table 1 shows the demographics of the population, split by HIE status. Overall 209 (0.5%) had evidence of HIE, 549 (1.4%) died in perinatal period, 1228 (3.1%) had a low Apgar score at 5 minutes and 2013 (5.1%) required resuscitation after birth. With regard to antenatal factors, infants with HIE were more likely to have older but primiparous mothers, without private health insurance. Mothers were also more likely to have placenta previa and infants more likely to be male and from multiple births; but otherwise antenatal risk factors did not appear to difference substantially. With regard to growth measures, infants with HIE were more likely to be poorly grown. Infants with, and without HIE, differed for most of the intrapartum factors except the recording of a nuchal cord.

Table 2 shows the area under the curve (AUC) for the prediction models, when applied to the testing (later) pregnancies. The antenatal model reported an AUC of 0.70 (0.64-0.77), which improved to 0.73 (0.67-0.80) (p=0.0263) with the addition of infant birth weight to the model, but not when intrapartum measures were included (p=0.5320). Addition of growth factors increased the number of infants in the highest risk decile with HIE from 17 (28.8%) to 22 (37.3%).

The AutoML model produced similar AUC measures to the conventional analysis for antenatal (p=0.987) and the antenatal and growth measures (p=0.5697). However, the antenatal and intrapartum ML model appeared to predict better than the corresponding conventional model (0.82 (0.78-0.86) vs 0.70 (0.63-0.76), p<0.001); and was able to identify a further 13 infants (44 (49.0%) vs 31 (34.4%)) than the antenatal along model. Factors identified from the ML HIE model as most predictive are shown in table 3. ROC curves for the 6 HIE models are shown in Figure 2.

Other ML results shown in Table 2….

**DISCUSSION**

**Conclusion**

In this work, on a historical cohort, a machine learning model with minimum data preparation was able to match and in some examples exceed the prediction of conventional analysis in predicting which infants would develop HIE after birth. The prediction was substantially improved when measures of growth were included; supporting the role for routine antenatal measures of growth during pregnancies using modern imaging techniques. Routine growth measures, and automated ML models on other routinely collected health data may provide an additional tool to obstetric services to help identify infants at high risk of brain injury around birth, and help target additional observation or interventions.

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**Figure 1. Established risk factors**

|  |  |  |
| --- | --- | --- |
| Antenatal Factors | Growth Measures | Intrapartum Factors |
| Maternal age (<20, 20-24, 25-29, 30-34, >35)  Parity 0, 1,>1  Maternal Employment  Health Insurance  Maternal race  FHx of seizures (recurrent non-febrile seizures)  FHx of neurological disorder (excludes seizures)  Infertility Treatment  Maternal Hypertension  Maternal height (<160, 160-164, >164)  Maternal Thyroid Disease  Pre-eclampsia  Antenatal bleeding (mod or severe)  Viral Illness  Alcohol (some, none, unknown)  Birthweight centile (>90th, 10-90th, 3rd-9th, <3rd)  Sex  Abnormal placenta  Late or no antenatal care  Multiple births | Birth weight centile (>90th, 10-90th, 3rd-9th, <3rd) | Gestation (37-42)  OP presentation  Maternal Pyrexia  Maternal Intrapartum Event (Haemorrhage, convulsions, uterine rupture, snapped cord, out of hospital birth)  Membrane rupture >12 hours  Blood Pressure abnormalities – Captured above  Nuchal cord  Cord prolapse  Onset of labour (spontaneous, induced, none)  Mode of delivery (Spontaneous, induced vaginal, elective CS, emergency CS, breech manoeuvre)  Shoulder dystocia  Epidural Anaesthetic  Breech Presentation  ROM>12 hours |

**Table 1. Demographics of study population (split by HIE)**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Characteristic** | **Characteristic** | **Non-HIE infants** | **HIE infants** | **P** |
| **Ante-natal Measures** | | | | |
| Late Booking\*\*\* |  | 11,405 (29.1%) | 60 (28.7%) | 0.905 |
| Thyroid Disease |  | 1,028 (2.6%) | 5 (2.4%) | 0.837 |
| Maternal Age | < 20 years | 11,057 (28.2%) | 57 (27.3%) | <0.001 |
|  | 20-24 | 11,690 (29.8%) | 49 (23.4%) |  |
|  | 25-29 | 8809 (22.5%) | 36 (17.2%) |  |
|  | 30-34 | 4,644 (11.8%) | 39 (18.7%) |  |
|  | 35 or more | 3,022 (7.7%) | 28 (13.4%) |  |
| Parity | 0 | 10,434 (26.7%) | 78 (37.3%) | 0.001 |
|  | 1 | 8579 (22.0%) | 29 (13.9%) |  |
|  | 2 or more | 20,049 (51.3%) | 102 (48.8%) |  |
| Employed |  | 5,989 (15.5%) | 23 (11.2%) | 0.084 |
| Private Insurance |  | 2546 (7.0%) | 5 (2.7%) | 0.022 |
| Race | White | 19,560 (49.9%) | 63 (30.1%) | <0.001 |
|  | Black | 16,898 (43.1%) | 123 (58.9%) |  |
|  | Other | 2,764 (7.1%) | 23 (11.0%) |  |
| FHx of Seizures |  | 2560 (6.7%) | 16 (7.9%) | 0.500 |
| FHx Neurology\* |  | 1479 (3.9%) | 12 (5.9%) | 0.133 |
| Fertility Ix |  | 1008 (2.6%) | 6 (2.9%) | 0.797 |
| Hypertension |  | 167 (0.4%) | 1 (0.5%) | 0.911 |
| Preeclampsia |  | 1284 (3.3%) | 19 (9.1%) | <0.001 |
| Maternal Height | <160cm | 13,221 (36.4%) | 81 (41.3%) | 0.354 |
|  | 160-164cm | 10,961 (30.2%) | 54 (27.6%) |  |
|  | >164cm | 12,172 (33.5%) | 61 (31.1%) |  |
| Pre-labour bleeding |  | 10,792 (28.1%) | 69 (33.8%) | 0.071 |
| A/N Viral Illness |  | 2,688 (6.9%) | 15 (7.2%) | 0.846 |
| Alcoholism |  | 44 (0.11%) | 0 (0.0%) | 0.628 |
| Fever |  | 5,068 (13.0%) | 26 (12.4%) | 0.817 |
| Male |  | 19,842 (50.6%) | 134 (62.1%) | <0.001 |
| Placental Previa |  | 160 (0.41%) | 3 (1.5%) | 0.020 |
| Multiple Birth |  | 290 (0.74) | 5 (2.4%) | 0.006 |
| **Growth Measures** | | | | |
| Birth weight centile | Less than 3rd | 1208 (3.1%) | 29 (14.1%) | <0.001 |
|  | 3rd to 10th | 2898 (7.4%) | 28 (13.6%) |  |
|  | 10th to 90th | 31,265 (79.8%) | 125 (60.7%) |  |
|  | Above 90th | 3824 (9.8%) | 23 (11.7%) |  |
| **Intra-partum measures** | | | | |
| OP presentation |  | 2512 (6.6%) | 34 (16.8%) | <0.001 |
| Breech Presentation |  | 1023 (2.7%) | 31 (15.3%) | <0.001 |
| ROM>12 hours |  | 5706 (16.5%) | 50 (30.5%) | <0.001 |
| Caesarean Section |  | 2076 (5.3%) | 38 (18.2%) | <0.001 |
| MIE\*\* |  | 3000 (7.7%) | 42 (20.1%) | <0.001 |
| Nuchal cord |  | 10,225 (26.3%) | 52 (24.9%) | 0.636 |
| Prolapsed cord |  | 311 (0.8%) | 12 (5.7%) | <0.001 |
| Onset | No Labour | 1,146 (3.0%) | 12 (5.8%) | 0.019 |
|  | Spontaneous | 35,124 (90.3%) | 177 (85.1%) |  |
|  | Induced | 2636 (6.8%) | 19 (9.1%) | 0.019 |
| Shoulder Dystocia |  | 230 (0.6%) | 9 (4.3%) | <0.001 |
| Epidural |  | 617 (1.6%) | 10 (4.9%) | <0.001 |

\* Motor, sensory or developmental disorder in siblings

\*\* APH, eclampsia, uterine rupture or ruptured cord

\*\*\* >26 weeks of gestational age

**Table 2. Traditional vs ML prediction of pregnancy outcomes**

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Outcome** | **Antenatal Factors** |  | **Antenatal and Growth Factors** | |  |  | **Antenatal and Intrapartum Factors** |  |  |
|  | **AUC (95% CI)** | **Proportion in highest decile** | **AUC (95% CI)** | | **Proportion in highest decile** | **p-value\*** | **AUC (95% CI)** | **Proportion in highest decile** | **p-value\*** |
| **Hypoxic-Ischaemic Encephalopathy** | | | | | | | | | |
| Conventional Analysis | 0.70 (0.64-0.77) | 17 (28.8%) | 0.73 (0.67-0.80) | | 22 (37.3%) | 0.0263 | 0.70 (0.63-0.76) | 18 (30.5%) | 0.5320 |
| ML (Google) | 0.70 (0.63-0.77) | 31 (34.4%) | 0.75 (0.69-0.81) | | 35 (38.9%) | 0.0361 | 0.82 (0.78-0.86) | 44 (49.0%) | <0.001 |
| p-value\*\* | 0.987 |  | 0.570 | |  |  | <0.001 |  |  |
| ML (L-Regression) | 0.71 (0.65-0.77) | 18 (26.5%) | 0.73 (0.66-0.79) | | 16 (30.2%) | 0.1821 | 0.73 (0.67-0.79) | 17 (30.9%) | 0.2018 |
| p-value\*\* | 0.9471 |  | 0.7144 | |  |  | 0.2523 |  |  |
| ML (Random Forest) | 0.63 (0.57-0.69) | 16 (23.5%) | 0.59 (0.52-0.65) | | 11 (20.8%) | 0.6492 | 0.65 (0.58-0.72) | 16 (29.1%) | 0.1737 |
| p-value\*\* | 0.0144 |  | 0.0003 | |  |  | 0.1826 |  |  |
| ML (Neural Net) | 0.61 (0.5-0.68) | 12 (17.7%) | 0.62 (0.54-0.69) | | 11 (20.8%) | 0.9176 | 0.60 (0.52-0.68) | 14 (25.4%) | 0.7522 |
| p-value\*\* | 0.0108 |  | 0.0021 | |  |  | 0.0256 |  |  |
| ML (Adanet) | 0.68 (0.62-0.75) | 21 (30.9%) | 0.71 (0.64-0.78) | | 22(41.5%) | 0.1014 | 0.68 (0.60-0.76) | 17 (30.9%) | 0.9347 |
| p-value\*\* | 0.5399 |  | 0.6758 | |  |  | 0.8393 |  |  |
| **Resuscitation** | | | | | | | | | |
| Conventional Analysis | 0.64 (0.61-0.67) | 89 (22.5%) | | 0.65 (0.62-0.67) | 91 (23.1%) | 0.2503 | 0.64 (0.61-0.67) | 87 (22.1%) | 0.6889 |
| ML Model (Google) |  |  | |  |  |  |  |  |  |
| p-value\*\* |  |  | |  |  |  |  |  |  |
| ML Model (L-Regression) | 0.62 (0.64-0.66) | 182 (23.5%) | | 0.61 (0.63-0.65) | 160 (21.4%) | 0.56 | 0.63 (0.65-0.67) | 152 (23.7%) | 0.58 |
| p-value\*\* |  |  | |  |  |  |  |  |  |
| ML Model (Random Forest) | 0.56 (0.58-0.6) | 117 (15.1%) | | 0.55 (0.57-0.59) | 125 (16.7%) | 0.55 | 0.53 (0.56-0.58) | 126 (19.6%) | 0.18 |
| p-value\*\* |  |  | |  |  |  |  |  |  |
| ML Model (Neural Net) | 0.53 (0.55-0.57) | 105 (13.5%) | | 0.53 (0.55-0.58) | 117 (15.7%) | 0.84 | 0.56 (0.58-0.6) | 113 (17.6%) | 0.06 |
| p-value\*\* |  |  | |  |  |  |  |  |  |
| ML Model (Adanet) | 0.59 (0.61-0.63) | 155 (20%) | | 0.59 (0.61-0.63) | 155 (20.7%) | 0.95 | 0.62 (0.64-0.66) | 141 (22%) | 0.06 |
| p-value\*\* |  |  | |  |  |  |  |  |  |
| **Low Apgar Score** | | | | | | | | | |
| Conventional Analysis | 0.64 (0.61-0.67) | 89 (22.5%) | | 0.65 (0.62-0.67) | 91 (23.1%) | 0.2503 | 0.64 (0.61-0.67) | 87 (22.1%) | 0.6889 |
| ML Model (Google) |  |  | |  |  |  |  |  |  |
| p-value\*\* |  |  | |  |  |  |  |  |  |
| ML Model (L-Regression) | 0.61 (0.63-0.66) | 88 (20.6%) | | 0.58 (0.61-0.64) | 76 (19.2%) | 0.3 | 0.63 (0.66-0.69) | 101 (28.5%) | 0.13 |
| p-value\*\* |  |  | |  |  |  |  |  |  |
| ML Model (Random Forest) | 0.55 (0.57-0.6) | 68 (15.9%) | | 0.52 (0.55-0.58) | 52 (13.2%) | 0.23 | 0.51 (0.54-0.57) | 49 (13.8%) | 0.07 |
| p-value\*\* |  |  | |  |  |  |  |  |  |
| ML Model (Neural Net) | 0.53 (0.56-0.59) | 55 (12.9%) | | 0.49 (0.52-0.55) | 47 (11.9%) | 0.06 | 0.51 (0.54-0.57) | 63 (17.7%) | 0.49 |
| p-value\*\* |  |  | |  |  |  |  |  |  |
| ML Model (Adanet) | 0.57 (0.59-0.62) | 71 (16.6%) | | 0.55 (0.58-0.61) | 59 (14.9%) | 0.62 | 0.61 (0.64-0.67) | 92 (25.9%) | 0.04 |
| p-value\*\* |  |  | |  |  |  |  |  |  |
| **Perinatal Death** | | | | | | | | | |
| Conventional Analysis | 0.61 (0.57-0.65) | 30 (18.2%) | | 0.65 (0.61-0.70) | 57 (35.2%) | 0.0050 | N/A |  |  |
| ML (Google) | 0.79 (0.76-0.82) | 146 (55.9%) | | 0.87 (0.84-0.89) | 208 (79.7%) | <0.001 | N/A |  |  |
| p-value\*\* | <0.001 |  | |  | <0.001 |  | N/A |  |  |
| ML Model (L-Regression) | 0.72 (0.75-0.79) | 64 (35%) | | 0.46 (0.56-0.66) | 10 (23.3%) | 0 | N/A |  |  |
| p-value\*\* |  |  | |  |  |  | N/A |  |  |
| ML Model (Random Forest) | 0.61 (0.65-0.68) | 52 (28.4%) | | 0.52 (0.61-0.69) | 13 (30.2%) | 0.37 | N/A |  |  |
| p-value\*\* |  |  | |  |  |  | N/A |  |  |
| ML Model (Neural Net) | 0.62 (0.66-0.71) | 50 (27.3%) | | 0.46 (0.53-0.6) | 6 (14%) | 0 | N/A |  |  |
| p-value\*\* |  |  | |  |  |  | N/A |  |  |
| ML Model (Adanet) | 0.67 (0.71-0.75) | 60 (32.8%) | | 0.49 (0.57-0.65) | 5 (11.6%) | 0 | N/A |  |  |
| p-value\*\* |  |  | |  |  |  | N/A |  |  |

**\* Compared to Antenatal Factors Model**

**\*\* Comparing Conventional with ML model**

**Figure 2. Receiver operator curves for the 6 HIE models.**

**Table 3. ML derived features (HIE)**

