Multi-organ dysfunction scoring in neonatal encephalopathy (MODE Score) and neurodevelopmental outcomes

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Abstract

Aim: Neonatal encephalopathy (NE) is associated with an increased risk of multi-organ injury. The lack of standardised definitions for multi-organ dysfunction in NE hinders accurate quantification of these complications.

Methods: A simple multi-organ dysfunction in neonatal encephalopathy scoring (MODE) system was created to include the cardiovascular, respiratory, gastrointestinal, haematological and neurological systems with a maximum score of 15. The MODE score was then compared with the grade of NE, Bayley Scales of Infant Development (Bayley-III) at 2 years of age and mortality. The Bayley score was used as it gave an objective score making it easier to compare the MODE score. Bayley score of <90 and/or abnormal MRI as an adverse outcome.

Results: Infants with perinatal asphyxia (PA: n = 85) were prospectively enrolled (PA only n = 9; NE I = 23; NE II = 42; NE III = 11). Infants with higher MODE scores were significantly more likely to have moderate/severe NE (NE II/III: median scores (IQR) 7(5–10) versus mild NE 2 (1–3); p-value < 0.001) The MODE score was highly predictive of mortality (AUC 0.96, p-value = 0.002). Infants who had an abnormal neurological examination at discharge or abnormal Bayley-III scores had significantly higher MODE scores (p-value = 0.001).

Conclusion: Quantifying multi-organ injury is important to plan optimal early management and long-term follow-up. Additional use of clinical biomarkers may be useful as surrogate endpoints in future clinical trials and link to multi-organ longer-term developmental follow-up.
1 | INTRODUCTION

Neonatal encephalopathy (NE) refers to a complex syndrome characterised by altered consciousness, seizures and/or difficulty in initiating or maintaining respiration\(^1,2\) and affects 1–3 per 1000 births worldwide.\(^3\) Perinatal asphyxia and NE are associated with increased risk of multi-organ injury.\(^4,8\) Although much of the published literature has concentrated on brain injury and its manifestations, NE commonly also involves multiple organs, including the heart, kidney and liver.\(^7\) Each organ system of the body is at risk of cell injury and death when subjected to global hypoxia secondary to interruption of the placental vascular supply. The underlying cause of cell damage is likely to be secondary to a mixture of reperfusion, direct reactive oxidative stress and cytokine injury.\(^10,11\) In addition, the multiple aetiologies involved in NE such as metabolic, infection, genetic, placental dysfunction may also have variable multi-organ effects.\(^12,13\) Although multi-organ dysfunction syndrome (MODS) is described in NE there are no standardised consensus definitions of individual organ dysfunction.\(^8\)

Therapeutic hypothermia (TH) is a standard of care for the treatment of moderate to severe neonatal encephalopathy\(^14,15,\) but there is a paucity of information on the exact degree of multi-organ dysfunction exhibited by infants receiving TH. The rates of individual organ dysfunction vary across the literature\(^4-7\) possibly as a result of the non-uniformity of definitions making accurate quantification of the extent of these complications difficult.\(^16,17\) We hypothesised that a rapid but comprehensive scoring system, which quantifies the degree of multi-organ dysfunction in infants with neonatal encephalopathy may help with outcome prediction. We aimed to create a scoring system for multi-organ dysfunction in NE that accurately represents the degree of organ injury and whether such a scoring system of multi-organ dysfunction in NE correlated with outcomes.

2 | MATERIALS & METHODS

Ethics approval was received from the National Maternity Hospital, Ireland and written informed consent was obtained in all cases. The study included infants prospectively recruited for the MODE (multi-organ dysfunction in neonatal encephalopathy) study and the inclusion criteria and methods were previously described.\(^18,19\) Briefly, the MODE study included infants >36 weeks’ gestation at risk of neonatal brain injury who were admitted to the NICU between 2011 and 2013 and fulfilled the Huang criteria for perinatal asphyxia\(^20\) requiring resuscitation at birth. These criteria were as follows: abnormal neurological signs, such as hypotonia or seizures in the immediate postnatal period, and/or other organ dysfunction (kidneys, liver, lung, heart, haematological and at least two of the following three criteria: (a) evidence or suspicion of hypoxic-ischaemic injury based on a history of foetal distress ie type II decelerations, loss of beat-to-beat variability on cardiotocograph and/or abnormal scalp pH; (b) need for resuscitation after birth ie bag valve mask ventilation; (c) base deficit of >14 mmol/L or pH <7.2 in cord blood or admission arterial blood gas. Clinical groups were retrospectively designated on completion of the study using the classification of Sarnat & Sarnat\(^20\) as follows: (a) resuscitation only group: Infants requiring resuscitation only with no neurological signs of encephalopathy (NE 0); (b) mild encephalopathy (NE I); (c) moderate (NE II) and (d) severe (NE III).\(^5\)

Neonates with normal Apgar scores and clinical outcomes were also recruited on the postnatal wards in the same institution contemporaneously and designated the control group. Baseline clinical demographics were collected for each infant in the control group. This included gestational age, antenatal complications, maternal history, time of birth, birth weight, type of delivery, delivery complications, Apgar scores and feeding status.

All infants with NE had cranial ultrasound scans (CrUSS) twice over the first week of life on day 1 and 5–7 which were performed by a consultant paediatric radiologist (VD) using a broadband transducer (5–8.5 MHz). CrUSS was used to confirm normal cerebral anatomy, quantify cerebral oedema and echogenicity of the basal ganglia, and in addition, haemorrhage was graded according to the Papile classification system\(^10\) and scored using Robertson et al (2012).\(^21\) Magnetic resonance imaging (MRI) of the brain was performed between day 5 and 10 using a 1.5 Tesla GE scanner and the following sequences were employed: T\(_1\) & T\(_2\) weighted, T1 flair, spectroscopy and diffusion-weighted imaging. MRI scans were scored and reported independently (VD) who was blinded to outcome, using the Barkovich scoring system\(^22\) which employs a combination score including components of both basal ganglia and watershed patterns of injury.

aEEG was commenced in infants with NE following admission to NICU, and continuous multichannel EEG was recorded after birth and for 72 h when trained staff available and analysed later by an expert in electrophysiology (GB) who was blinded to clinical information and outcome.\(^12\) All seizures on EEG were annotated and were included as part of the MODE score.\(^23\) Study infants underwent a detailed neurological examination serially over the first week of life. Each infant was examined on postnatal day 1,2,3 and 7 using a combined neurobehavioural scoring system that incorporates the Sarnat\(^23,24\) scoring systems. Overall, the neurological examination that was performed assessed each infant’s level of consciousness, central and peripheral tone, reaction to stimulus, primitive reflexes and deep tendon reflexes. Each infant was assigned a Sarnat grade for the day of examination and their overall assigned Sarnat grade
equated to the worst Sarnat grade they reached over the course of their admission. Infants were divided by grade of encephalopathy using the Sarnat criteria and the highest grade over the first week used.22,24,25

### 2.1 Serum troponin-T sampling & analysis

Serum samples were collected from infants at risk of NE serially on day 1, 2, 3 and day 7. At each time point, 1.2 ml of blood was collected from either a peripheral venous or an arterial catheter sample and was analysed and performed on the Elecsys 2010 system, Cobas 8000 analyzers from Roche Diagnostics.26

### 2.2 Multi-Organ dysfunction (MODE) scoring

The multi-organ dysfunction (MODE) scoring was developed by assigning a score to abnormalities in each organ system (Table 1). Dysfunction in each organ system (cardiovascular, respiratory, gastrointestinal and renal including fluid management, neurological, endocrine, haematological and hepatic systems) were quantified (Figure 1).22 Laboratory data on multi-organ dysfunction outcome were taken from the hospital laboratory system and inputted into an encrypted Excel database for analysis. Variables in each organ system were investigated for their ability to predict the outcomes of death, MRI brain scan result, and neurological examination at discharge and 2-year neurodevelopmental outcome using logistic regression. The simplified scoring system was created as follows with 1 point for any of the following: cardiovascular system: troponin-T > 0.1 ng/mL,17 heart rate of <80 bpm; respiratory: need for ventilation for >72 h, oxygen requirement >72 h26; gastrointestinal/liver: aspartate aminotransferase (AST) or alanine aminotransferase (ALT) to >100 IU/L;24 time to full oral feeds ≥6 days; haematological: platelet count of <150×10⁹/L, prothrombin time (PT) >20s or fibrinogen level <1.0g/L;19 renal: oliguria <1 ml/kg/h and serum creatinine >100 umol/L27 (the standardised fluid intake during therapeutic hypothermia was 40 ml/kg/day, in addition, each baby had individualised treatment as some had SIADH or significant renal impairment).8 Scoring of the neurological system was more complicated as not all infants had MRIs or cEEG. If an infant had any abnormal cranial imaging (cranial ultrasound scan or MRI brain scan), they were awarded a score of 1 and then if they also had an abnormal MRI brain scan, then they were awarded an extra 1 point making the maximum number of points that an infant could score for abnormal cranial imaging equal to 2. This facilitated inclusion of infants without an MRI as not all infants had MRI brain scans (n = 68 MRI scans) and not all infants had continuous multichannel EEG monitoring (n = 55). Finally, if an infant was diagnosed with clinical seizures, they were awarded a score of 1.

Table 1: MODE scoring system for term infants with neonatal encephalopathy

| Organ System | No | Yes | Total score |
|--------------|----|-----|-------------|
| CVS HR <80 bpm | 0 | 1 | 1 |
| Trop-T > 0.1 ng/ml | 0 | 1 | 1 |
| Resp MV >72 h | 0 | 1 | 1 |
| FiO₂ Req >72 h | 0 | 1 | 1 |
| GIT AST >100 IU/L | 0 | 1 | 1 |
| ALT >100 IU/L | 0 | 1 | 1 |
| Time to FOF≥6 days | 0 | 1 | 1 |
| Haem Platelets <60×10⁹/L | 0 | 1 | 1 |
| PT >20 s | 0 | 1 | 1 |
| Fibrinogen <1 g/L | 0 | 1 | 1 |
| Neuro Abnormal cranial imaging | 0 | 1 | 1 |
| Abnormal MRI imaging | 0 | 1 | 1 |
| Total imaging score* | 1 or 2 | 1 or 2 | 1 or 2 |
| Clinical seizures | 0 | 1 | 1 |
| Renal Oliguria <1 ml/kg/h | 0 | 1 | 1 |
| sCr >100 μmol/L | 0 | 1 | 1 |
| cEEG Seizures | 0 | 1 | 1 |

Note: Total imaging score: an infant who only had a cranial ultrasound carried out can score 1 if abnormal, an infant who had an abnormal CUS and abnormal MRI brain scan can score 2, an additional score of 1 was added to those infants who had abnormal MRI brain scans. Modified MODE score includes cEEG.

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; cEEG, continuous electroencephalogram; CVS, cardiovascular system; FOF, full oral feed; GIT, gastrointestinal system; Haem, haematological; HR, heart rate; MV, mechanical ventilation; NE, neonatal encephalopathy; PT, prothrombin time; Req, requirement; Resp, system; respiratory system; sCr, serum creatinine.

Within this final group of 80 infants, a subgroup of infants who had cEEG performed and Troponin-T results was also created. The maximum score with this modified MODE score was 16 (as seizures only counted once) and the total score for each infant was compared with the outcome of grade of NE (normal/mild [NE 0/I] versus abnormal [NE II/III]). Infants without troponin-T results were excluded from the scoring system database bringing the total number of infants included to 80.

Compared with the outcome of grade of NE (normal/mild [NE 0/I] versus abnormal [NE II/III]), infants without troponin-T results were excluded from the scoring system database bringing the total number of infants included to 80.

### 2.3 Neurodevelopmental outcomes

Infants were assessed using Bayley Score of Infant and Toddler Development III at 2 years by a neurodevelopmental psychologist (MS) blinded to the MODE score.16,19 A composite score of the 3 domains (cognitive, language and motor) was calculated and divided into normal and abnormal scores of >90 and <90 respectively.20
2.4 | Statistical analysis

Continuous normally distributed data were displayed as means and standard deviations (SDs) and comparisons were made using the independent student t-test. For continuous non-normally distributed data, medians and interquartile ranges were used and comparisons were made using the Mann-Whitney U test or the Kruskal-Wallis test with Monte Carlo significance whether small numbers were present. Statistical tests of repeated measures for the variables were not employed, as data points for every patient at every time point were not present and therefore the Mann-Whitney U test and Kruskal-Wallis test were used. Spearman’s rank correlation was employed to assess correlation between different variables. Categorical data were compared using the chi-squared test. Receiver operator characteristic curve analysis was employed to assess the ability of particular variables to predict outcomes of interest such as developmental scores. Logistic regression was used to identify possible variables for inclusion in a multi-organ dysfunction score. Simple logistic regression was used to assess whether a relationship existed between MODE scoring and Bayley-III. The distribution of the scoring data was skewed on histogram analysis and therefore, nonparametric testing was used, the Mann-Whitney U test.

3 | RESULTS

Ninety-five infants were recruited in total, 85 with perinatal asphyxia and 10 controls. The NE grades I-III were as follows: NE I = 23; NE II = 42; NE III = 11,16,19,24,31 Four infants died. Thirty-nine infants were received TH, and sixty-eight infants had MRI brain imaging [normal (n = 57) and abnormal (n = 31)]. Infants without troponin-T results26 were excluded from the scoring system database bringing the total number of infants included to 80. Healthy control infants in this study (n = 10) were allocated a score of zero in each case. The median IQR score at the time of Bayley III was 24(21–26) months.

A significant relationship was found between the mean rank of total MODE score and grade of encephalopathy. Infants with higher MODE scores were significantly more likely to have moderate/severe NE (Grade II/III) p-value (<0.001). The median MODE scores (IQR) were 2.0 (1–3) for mild NE versus 7.0(5–10) in moderate/severe NE (p-value < 0.001).

Scoring of the neurological system was more complicated as not all infants had MRI (n = 68) or cEEG (n = 55). Infants who had an abnormal neurological examination at discharge had significantly higher MODE scores compared with infants with a normal neurological examination at discharge [8.0(5.3–10.0) versus 4.0(2.0–6.8); p-value = 0.001]. Mortality was also compared with total MODE score but the number of infants who died were small (n = 4). Infants who died had a higher MODE score compared with infants who survived [median (IQR) 12.0 (11.0–14.5) in infants who died versus 4.5 (2.0–7.0) in survivors; p < 0.001]. The MODE score was highly predictive of mortality with an AUC 0.96 (p-value = 0.002) and cut-off value of the score for prediction of mortality of 10.5.

Fifty-four infants had cEEG performed and Troponin-T measured. Infants who had grade II/III NE had significantly higher total MODE scores compared with infants with NE grade 0/1 [9(7–12) versus 3(1–4); p-value < 0.001]. Furthermore, in this subgroup, infants who died had significantly higher MODE scores compared with infants who survived [13(12–15) versus 7(4–11), p-value = 0.003; Monte Carlo significance using Kruskal-Wallis test, p = 0.001]. The infants who had an abnormal neurological examination at discharge also had significantly higher MODE scores compared with infants with a normal neurological examination at discharge in this subgroup [9.5(7–11.25) versus 6.5(3.25–8), p-value = 0.018].

Bayley III neurodevelopmental assessment was available in 45 infants at 12–24 months of age, as only infants with NE II/III or TH were routinely assessed at this age. In addition, 4 infants died and 4 were lost to follow-up, the other diagnosis were: 7 patients were diagnosed with disability (including 1 patient diagnosed with cerebral palsy and 2 with autism). Overall, the distribution of abnormities in cognitive, language and motor function were 21%, 30% and 12%, respectively. Bayley score <90 was detected in 17 patients as follows: language (14), cognitive (7) and motor domain (6). Infant with disability had abnormal MRI and neurological examination on discharge and had
longer hospital stay \( (p < 0.001) \). A significant negative correlation was observed between MODE score and composite Bayley language score at 2 years \( (R = -0.3012; CI = -0.5191–0.04653; p = 0.02199 \) (Figure 1). A significant negative correlation was also noted between MODE score and BSID-III motor score \( (R = -0.3291; CI = -0.5414 -0.7739; p = 0.0117) \). In addition, a one-way ANOVA was used to assess whether there were differences between MODE scores for infants who had a normal versus an abnormal Bayley-III score at 2 years in any of the three categories (cognitive, language and motor scores). MODE scores from infants with normal and abnormal Bayley III were also compared with the group of infants who died before neurodevelopmental assessment. MODE scores were significantly lower in infants with normal versus abnormal Bayley III \( (p = 0.0302, p = 0.0104 \) and \( p = 0.0207 \) respectively), and in infants with normal Bayley III scores versus infants who died \( (p = 0.0001, p < 0.0001 \) and \( p = 0.0001 \) respectively) for all three Bayley scoring categories (Figure 1).

**4 | DISCUSSION**

We found a highly significant relationship between total multi-organ dysfunction score and grade of NE and neurological examination at discharge, mortality and Bayley-III assessment. In a subgroup analysis for 54 infants with NE who had both cEEG and Troponin-T levels, we found that a modified MODE score was also significantly associated with abnormal grade of NE, mortality and abnormal neurological examination at discharge.  

The MODE score unsurprisingly correlated with the severity of NE and mortality, although this is the first study to correlate with 2-year neurodevelopmental outcome. Several groups have described multi-organ involvement in NE but have not included outcomes other than severity of NE or mortality. All multi-organ reporting systems in NE studies included cardiovascular, respiratory and renal but there was variation in the inclusion of neurological, GI, haematological and liver function. Most recently, Alsina et al. retrospectively studied 79 infants with mild, moderate and severe neonatal encephalopathy examining 6 organ systems and 23 clinical and laboratory parameters in the first 3 days of life and found a high correlation between the severity of organ dysfunction and the degree of encephalopathy.

In the cardiovascular system, troponin was included in both the MODE and the Alsina scores. Troponin is more readily available in most healthcare settings as used in adult assessments compared with daily functional echocardiography requiring skilled personnel. Troponin also correlates with abnormal MRI and severity of NE as well as with cardiac dysfunction. In addition, coagulation abnormalities and haematological treatment parameters are well-described and therefore included in the MODE score as in Hankins and Alsina. Time to full-feeds and abnormalities of liver function test are commonly described and correlate with early outcomes, but feeding and GI issues such as NEC and gastric residuals were only mentioned in Martin-Ancel and Perlman's papers.

The concept of tertiary brain injury and persistent inflammation has been suggested in neonatal brain injury with changes evolving over months or years. Persistent deregulated immune responses have been demonstrated both in school-age children post-NE and in children with cerebral palsy at 7 years of age. Neurological follow-up is standard for infants with NE but multi-organ follow-up may be indicated. For example, renal dysfunction persists in children following neonatal acute kidney injury and requires further monitoring, although this is not currently routine.

We acknowledge that this scoring system considerably simplifies the degree of multi-organ dysfunction that occurs in neonatal encephalopathy and requires further validation. However, we suggest that such a scoring system needs to be simple in order to be applicable to all infants and also the investigations employed in the scoring system need to be accessible and feasible for the majority of NICUs. Only infants with NE II/III or requiring TH had follow-up with Bayley's III, and further validation with another cohort would be valuable. This score may be a valuable tool to quantify the degree of organ injury in infants with NE to allow multi-organ dysfunction management. We aimed to use this score to quantify and standardise these measurements to allow comparison across international centres and to use them in outcomes of future clinical trials. The MODE score is simple and may guide long-term follow-up of organ dysfunction.

There were several limitations to this study including the lack of neurodevelopmental assessment for all the patients. In addition, the outcome measures were MRI findings and Bayley's scores but did not include other specific diagnoses such as hearing or visual assessment. These initial findings need to be validated in a larger cohort of patients and combined with multi-organ function in later childhood.

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**CONFLICT OF INTEREST**

The authors declare no conflict of interest.

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