Predictive performance of multiple organ dysfunction in asphyxiated newborns treated with therapeutic hypothermia on 24-month outcome: a cohort study

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ABSTRACT

Background Perinatal asphyxia may be followed by multiple organ dysfunction (MOD) and is often included in prognostication of the individual patient, but evidence of discriminating accuracy is lacking. The aim of this study was to assess whether MOD in asphyxiated neonates during therapeutic hypothermia (TH) predicts mortality or neurodevelopmental impairment (NDI) at 24 months of age and which peripartum variables are associated with the onset of MOD.

Methods A retrospective analysis of a prospective cohort study of asphyxiated newborns undergoing TH was performed. MOD was defined as dysfunction of the brain (encephalopathy) combined with two or more organ systems. Outcome was routinely assessed by standardised developmental testing at the age of 24 months. The predictive accuracy of MOD on the combined outcome and its components (death and NDI) was expressed as areas under the receiver operating characteristic curves (AUROCs). The associations of peripartum variables and development of MOD were expressed as ORs and their CIs.

Results 189 infants (median gestation 40 (range 36–42 weeks) with moderate to severe hypoxic ischaemic encephalopathy were included. 47% developed MOD. The prediction of the combined 24-month outcome or its components showed AUROCs <0.70. Associated with MOD were pH at birth (OR 0.97, CI 0.95 to 0.99), lactate at birth (OR 1.09, CI 1.04 to 1.15), Base Excess (BE) at birth (OR 0.94, CI 0.90 to 0.99) and epinephrine administration during resuscitation (OR 2.09, CI 1.02 to 4.40).

Conclusion MOD has a low discriminating accuracy in predicting mortality or NDI at 24 months age and might not be useful for prognostication. Signs of acid–base disturbance and adrenalin use at birth are associated with the development of MOD.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Multiple organ dysfunction (MOD) frequently occurs following neonatal resuscitation.
⇒ MOD is often seen as a clinical sign of disease severity in cooled newborns suffering perinatal asphyxia.
⇒ The presence of MOD is often taken into account during prognostication, but evidence is lacking.

WHAT THIS STUDY ADDS

⇒ Based on the current literature, MOD is defined for neonatal patients.
⇒ Severe acid-base disturbance after birth, Lactate value and the use of adrenalin during neonatal resuscitation are associated with the development of MOD.
⇒ The presence of MOD does not predict neurodevelopmental impairment, death or combined outcome at 24 months.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ To prevent further heterogeneity in the literature, consensus is needed for the definition of MOD.
⇒ Clinical variables are associated with development of MOD, but MOD does not predict outcome.
⇒ MOD should not be considered in discussions on redirection of care.

INTRODUCTION

Multiple organ dysfunction (MOD) in newborns treated with controlled therapeutic hypothermia (TH) for hypoxic–ischaemic encephalopathy (HIE) after perinatal asphyxia is a well-known clinical phenomenon. It is commonly defined as a dysfunction of the central nervous system combined with two or more other organ systems.[1 2] Although clear evidence is lacking, MOD is often seen as a clinical sign of disease severity and taken into account in the long-term prognostication of the patient.

Several studies have investigated the association between MOD and outcomes in newborns treated with TH after perinatal asphyxia.[3–6] However, these studies are hampered by the fact that the definition of MOD is not well described or that they only reported an association between MOD and clinical outcome, which is not equivalent to accurate prediction of the outcome of interest. Other studies did not investigate long-term neurodevelopmental outcome but investigated only the relation between MOD and short-term and/or surrogate outcomes such as severe brain injury on MRI.[3–6] Therefore, it is uncertain whether the presence of MOD is a predictor for long-term outcome.

The association between peripartum clinical and laboratory variables and MOD has only been investigated in one small study which demonstrated

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an association between the Apgar scores and MOD, but large cohort studies are lacking.[7]

Therefore, the primary objective of our study was to assess the predictive value of MOD for mortality and neurodevelopmental impairment (NDI) at 24 months of age in newborns with HIE treated with TH after perinatal asphyxia. The secondary objective was to assess whether peripartum variables were associated with the development of MOD.

METHODS

Study design and participants

This study is a retrospective analysis of prospectively collected data of the PharmaCool study.[8] This observational study investigated the pharmacokinetics and dynamics of commonly administered drugs during TH in newborns suffering from HIE following perinatal asphyxia.[8] This study was performed between November 2010 and October 2014 in 11 neonatal intensive care units (NICUs) in The Netherlands and Belgium. All participants of the original PharmaCool study were included in the current study. The primary outcome was mortality and NDI at 24 months of age in a cohort of newborns with HIE treated with TH after perinatal asphyxia.

Multiorgan dysfunction definition

There is currently no consensus on the definition of MOD in patients suffering from HIE after perinatal asphyxia.[1] Therefore, following the majority of the published definitions and taking into account the standardised measurements as described by the study protocol,[1 5 8 9] MOD in the current study was defined as a dysfunction of two or more of the following organs/systems in the first 5 days of life (in addition to HIE): (1) cardiovascular: the need for ≥2 inotropic drugs to maintain a normal blood pressure; (2) pulmonary: the need for invasive mechanical ventilation or treatment with a surfactant, a diagnosis of persistent pulmonary hypertension treated with inhaled nitric oxide, meconium aspiration syndrome or neonatal pneumonia; (3) hepatic: ≥2 of the following abnormal laboratory tests: aspartate aminotransferase >100 IU/L, alanine aminotransferase >100 IU/L or lactate dehydrogenase >2085 U/L; (4) renal: urine output <1 mL/kg/hour combined with creatinine level >100 µmol/L; and (5) haematological: thrombocyte count $<100\times10^9$/L, and coagulopathy or disseminated intravascular coagulation as defined by the attending physicians. Laboratory investigation was performed at a standardised time point every day for the TH and rewarming period.

In our study, HIE and its severity were not part of the diagnosis of MOD. Following our national protocol, all included infants were at least moderately encephalopathic (Thompson Score (TS)>7) and thus had a clinical indication for hypothermia treatment. For descriptive purposes, moderate HIE was defined as a TS between 7 and 11, and severe HIE as a TS of >11.[10]

On each day the patient was treated with TH, the presence or absence of MOD was assessed. A single abnormal organ parameter or laboratory value was not taken into account for the diagnosis MOD.

Outcome

All infants underwent a standardised follow-up visit at 24 months of age. The 24-month neurodevelopmental outcome was assessed with the Bayley Scales of Infant and Toddler Development (Third Edition, Dutch Language (BSID-III-NL)).[11] In the presence of cerebral palsy (CP), the level of CP was classified using the Gross Motor Function Classification System (GMFCS).[12] NDI was defined as a test score of ≥1 SD below the reference mean BSID-III-NL composite cognitive score or composite motor score (eg, a score <85 points), a GMFCS score of ≥2 and a hearing loss requiring aids or cerebral visual impairment (blind or abnormal vision). For statistical analyses, the binary outcomes of interest at 24 months were the combined outcome of death or NDI and its separate components. Although most participating centres used the BSID-III-NL for assessing neurodevelopmental outcome, in case another version of the BSID was used, a correction as previously described was performed to compensate for discrepancies between these scales.[13 14]

Statistical analyses

Data were analysed using R statistical software V.3.6.3 for Windows and R Studio (integrated development for R, Boston, 2015) (R Studio Desktop V.1.2.5033). Descriptive statistics summarised patient characteristics and outcome parameters, depending on their distribution (mean (±SD) or median (IQR)). To minimise missing data, the principal investigator of each centre was contacted to provide the NICU discharge letter from which additional data were extracted. When outcome data could not be retrieved and were randomly missing, multiple imputation was performed.[15] To assess selection bias due to lost to follow-up at 24 months of age, the clinical characteristics between survivors and those who were lost to follow-up were compared. The predictive accuracy of MOD (dichotomous) for the combined outcome of death or NDI and the separate outcome domains were calculated with an area under the receiver operating curve (AUROC). The association between the clinical peripartum variables and the presence of MOD was investigated using ORs with 95% CIs. The selection of variables was based on a combination of known risk factors reported in literature and expert opinion.[7] Given the existing variability of MOD definitions in literature, sensitivity analyses were performed using a modified (stricter) definition of MOD. In this definition, at least three affected domains were needed to fulfil the definition of MOD: hepatic, renal and one of the other organ systems as described previously.

RESULTS

Patient flow and characteristics

In total, 189 newborns were enrolled in the original PharmaCool study. Of these newborns, 10 patients were excluded: 3 had a delayed diagnosis of congenital malformations, and in 7 newborns, it was not possible to determine if they had MOD (missing data). The remaining 179 newborns were included in the analysis. The outcome assessment was incomplete for 26 infants (18%), and 9 infants (6%) were lost to follow-up (figure 1). These outcome data were imputed. In 27% of the infants, the BSID scores were converted to the (currently used) third Dutch edition of the BSID. Analyses of the patient characteristics of the survivors assessed at follow-up versus those lost to follow-up showed no significant differences except for gender (online supplemental table 1). The patient characteristics and the incidence of MOD are shown in table 1. A total of 84 (47%) infants developed MOD. When using the modified (stricter) MOD definition, the incidence decreased to 8% in this study cohort. During admission, 38 infants died (21%) and NDI was present in 28 (26%) of the 141 survivors.

MOD as predictor of outcome

The AUROC of the predicted probabilities showed a low predictive power of MOD for the combined outcome of death or NDI (AUROC 0.62, 95% CI 0.54 to 0.70), mortality (AUROC 0.67,

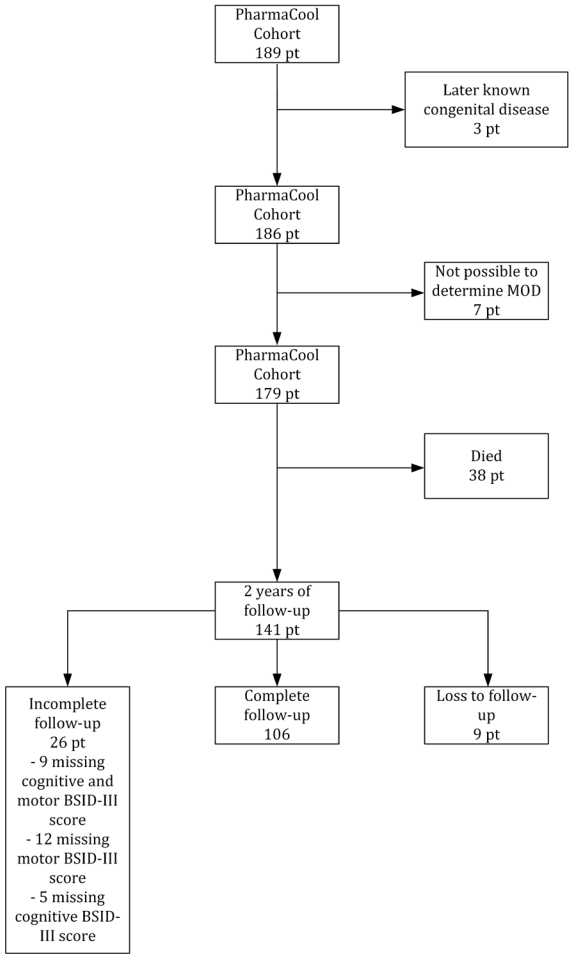

Figure 1 Pt flowchart. BSID-III, Bayley Scales of Infant and Toddler Development; MOD, multiple organ dysfunction, pt, patient.

Table 1 Patient characteristics

	Patients with MOD (n=84)	Patients without MOD (n=95)
Clinical characteristics		
Male	50 (60)	59 (62)
Gestational age (weeks)	40 (36–42)	40 (36–42)
Birth weight (kg)	3.4 (2.2–4.5)	3.5 (2.1–5.1)
Apgar at 1 min	1 (0–9)	1 (0–9)
Apgar at 5 min	3 (0–10)	3 (0–10)
Apgar at 10 min	5 (0–10)	5 (0–9)
pH (at admittance)	6.89 (6.53–7.38)	7.04 (6.56–7.38)
TS	10 (4–19)	9 (3–16)
TS 7–11 (moderate HIE)	46 (55)	62 (65)
TS >11 (severe HIE)	24 (29)	19 (20)
aEEG-proven seizures, days 1–3	30/81 (37)	28/86 (33)
MRI Weeke score	6 (0–42)	4 (0–37)
Organ dysfunction*		
Circulatory dysfunction	52/80 (65)	7/67 (10)
Respiratory dysfunction	44/83 (53)	4/88 (5)
Hepatic dysfunction	42/67 (63)	5/53 (9)
Renal dysfunction	29/77 (38)	3/82 (4)
Haematological dysfunction	75/84 (89)	34/58 (59)
Outcome at 24 months*		
Combined outcome (death or NDI)	43/76 (57)	23/69 (33)
Death	28/84 (33)	10/95 (11)
NDI in survivors	15/48 (31)	13/59 (22)
GMFCS >grade 2 in survivors	5/52 (10)	9/79 (11)
Visual impairment in survivors	3/52 (6)	1/79 (1)
Hearing loss in survivors	2/51 (4)	1/78 (1)
Composite cognitive score in survivors (n=93)	96 (54–140)	101 (70–143)
Composite motor score in survivors (n=114)	104 (52–132)	107 (58–131)

Median (minimum–maximum), number (percentage).
*n=dependent on available data.
aEEG, amplitude integrated electroencephalography; GMFCS, Gross Motor Function Classification System (at 24 months); HIE, hypoxic–ischaemic encephalopathy; MOD, multiorgan dysfunction; NDI, neurodevelopmental impairment; TS, Thompson Score.

95% CI 0.58 to 0.75) and NDI (AUROC 0.51, 95% CI 0.42 to 0.61). Analyses of the predictive power of MOD regarding the individual organ systems for the combined outcome of death or NDI and its components all showed a low AUROC of <0.70 (table 2).

Association between perinatal variables and MOD

The analyses investigating associations between peripartum variables and the development of MOD showed an increased risk of MOD in case of a higher TS (OR 1.13, 95% CI 1.02 to 1.25), the use of adrenalin medication during resuscitation (OR 2.09, 95% CI 1.02 to 4.40), a lower pH at birth (OR 0.97, 95% CI 0.95 to 0.99), a higher lactate at birth (OR 1.09, 95% CI 1.04 to 1.15), a lower base excess at birth (OR 0.94, 95% CI 0.90 to 0.99) and the presence of meconium-stained amniotic fluid during labour (OR 3.30, 95% CI 1.72 to 6.50). No association was found for the other peripartum variables and clinical characteristics (table 3).

Sensitivity analyses

The sensitivity analyses with the modified (stricter) definition for MOD as a predictor for the combined outcome, mortality and NDI showed no different results regarding the discriminating performance (AUROC 0.56, 95% CI 0.51 to 0.62; AUROC 0.62, 95% CI 0.53 to 0.71; and AUROC 0.51, 95% CI 0.47 to 0.55, respectively), compared with the MOD definition used in the primary analysis.

Using the modified (stricter) MOD definition showed a similar association between MOD and lactate (OR 1.17, 95% CI 1.06 to 1.31), pH measured at birth (OR 0.95, 95% CI 0.90 to 0.98) and base excess (OR 0.88, 95% CI 0.80 to 0.97). The use of adrenalin during resuscitation remained significant (OR 4.11, 95% CI 1.20 to 14.08). However, the clinical characteristics TS and meconium-stained amniotic fluid were no longer significantly associated with the presence of MOD (online supplemental table 2).

DISCUSSION

This is the first study primarily investigating the discriminating performance MOD as a predictor for the outcome death or NDI at 24 months of age after TH for newborns suffering from HIE after perinatal asphyxia. Analyses showed that the presence of MOD had a low predictive value for this combined outcome or its components. Given these results, taking the presence or absence of MOD into account for individual prognostication and possible redirection of care might not increase discriminating accuracy for outcome.

No other studies investigating the predictive value of MOD for death and NDI (eg, at 24 months) were identified in the literature in this high-risk population. One study showed a high sensitivity (100%) and low positive predictive value (64%) of the diagnosis

Table 2 Prediction of the outcomes

Outcome	MOD AUROC (95% CI)	Circulatory AUROC (95% CI)	Respiratory AUROC (95% CI)	Hepatic AUROC (95% CI)	Renal AUROC (95% CI)	Haematological AUROC (95% CI)
Combined	0.62 (0.54 to 0.70)	0.55 (0.47 to 0.64)	0.52 (0.44 to 0.59)	0.62 (0.53 to 0.70)	0.64 (0.57 to 0.70)	0.62 (0.54 to 0.69)
Death	0.67 (0.58 to 0.75)	0.65 (0.55 to 0.74)	0.54 (0.46 to 0.63)	0.67 (0.56 to 0.76)	0.69 (0.59 to 0.77)	0.63 (0.56 to 0.71)
NDI	0.51 (0.42 to 0.61)	0.55 (0.45 to 0.65)	0.54 (0.45 to 0.62)	0.51 (0.41 to 0.61)	0.55 (0.48 to 0.62)	0.52 (0.43 to 0.62)

AUROC, area under the receiver operating characteristic curve; CI, Confidence interval; MOD, multiple organ dysfunction; NDI, neurodevelopmental impairment.

MOD in infants treated with TH for HIE for the outcome of death, but did not report the definition of MOD nor the timing of outcome. This makes it impossible to compare the results and assess the quality of this study.[4] A large randomised trial investigating TH reported that the presence of organ dysfunction, in addition to HIE, was related to the primary outcome of death or NDI at 18–22 months. Although pulmonary or renal dysfunction was found to be associated with this primary outcome, these complications were not tested as predictors.[16]

We can only speculate on possible explanations for the lack of performance of MOD to predict long-term outcome. First, it might be explained by the fact that the pathophysiological mechanism of (post)resuscitation shock is multifactorial and complicated. The sequence of the perinatal ischaemia–reperfusion process after asphyxia resulting in myocardial dysfunction and sepsis-like features such as vasoplegia, hypovolaemia and endothelial dysfunction might be too complex to accurately predict long-term outcome using a single predictor.[17 18] Future research should therefore focus on a multivariable prediction model using multiple parameters instead of a single predictor to increase accuracy of the prediction.[19] Second, a validated internationally accepted MOD definition is currently not available. Different definitions, heterogeneous in the number of affected organ systems and cut-offs for laboratory measurements, have been published in the literature.[1 5 8 9] We based our MOD definition on criteria used in the majority of the published definitions and included those routinely available in daily clinical care.[1 5 8 9] However, we cannot rule out that this, or any other published MOD definitions for that matter, does not sufficiently reflect (severe) organ dysfunction in asphyxiated newborns. This might impact the predictive performance of MOD for the outcome. Using a stricter MOD definition, requiring more organs to be dysfunctional, did not change these findings. Future studies in this specific population should establish if more specific parameters of (severe) organ damage, such as echocardiographic assessments of left and right ventricular functions, troponin or creatine kinase myoglobin binding fraction measurement, might be needed to define MOD and improve its predictive power for long-term outcome.[17 18] The results of these studies should lead to an internationally accepted consensus definition of MOD.

The second objective of this study was to investigate the association between peripartum variables and MOD. One other study investigating this association was published, but it included patients in the era before implementation of TH with a different MOD

Table 3 Association of perinatal variables with MOD

Peripartum variable	MOD			P value
	Yes (T=84*)	No (T=95*)	OR (CI 95%)	
Vaginal labour	26 (30%)	38/95 (40%)	0.67 (0.36 to 1.24)	0.21
Vacuum or forceps assisted vaginal labour	15 (17%)	17/95 (18%)	0.99 (0.46 to 2.15)	0.99
Secondary or emergency caesarean section	43 (51%)	40/95 (42%)	1.44 (0.80 to 2.61)	0.22
Breech position during birth	9 (11%)	6 (6%)	1.78 (0.61 to 5.52)	0.29
Meconium-stained amniotic fluid	**38 (45%)**	**19 (20%)**	**3.30 (1.72 to 6.50)**	**<0.01**
Sex (male)	50 (60%)	59 (62%)	1.11 (0.61 to 2.04)	0.72
Gestational age (weeks)	40 (36–42)†	40 (36–42)†	1.12 (0.93 to 1.36)	0.24
Birth weight (kg)	3.4 (2.2–4.5)†	3.5 (2.1–5.1)†	0.62 (0.37 to 1.01)	0.06
Apgar 1 min	1 (0–9)†	1 (0–9)†	1.05 (0.90 to 1.23)	0.53
Apgar 5 min	3 (0–10)†	3 (0–10)†	1.02 (0.88 to 1.17)	0.82
Apgar 10 min	5 (0–10)†	5 (0–10)†	0.98 (0.83 to 1.15)	0.77
Mask and balloon ventilation	2/83 (2%)	3/92 (3%)	1.37 (0.22 to 10.56)	0.73
Chest compressions	42/79 (53%)	48/89 (54%)	1.03 (0.56 to 1.90)	0.92
Administration of bicarbonate during resuscitation	59/79 (75%)	74 (83%)	1.92 (0.72 to 5.48)	0.20
Administration of (nor)adrenalin during resuscitation	**59/83 (71%)**	**77/92 (84%)**	**2.09 (1.02 to 4.40)**	**0.05**
Duration of reanimation (min)	10 (0–30)†	10 (0–35)†	1.02 (0.98 to 1.06)	0.30
Duration before first gap (min)	5 (0–45)†	5 (0–60)†	1.00 (0.97 to 1.03)	0.99
Required intubation	21 (25.0%)	29 (30.5%)	1.32 (0.68 to 2.57)	0.41
Thompson score	**10 (4–19)†**	**9 (3-16)†**	**1.13 (1.02 to 1.25)**	**0.02**
pH at admission	**6.89 (6.53–7.38)†**	**7.04 (6.56–7.38)†**	**0.97 (0.95 to 0.99)**	**<0.01**
Lactate	**14.0 (2.6–30.4)†**	**10.5 (1.2–24.7)†**	**1.09 (1.04 to 1.15)**	**<0.01**
Base excess	**−19 (-37–2)†**	**−16 (-30–0.0)†**	**0.94 (0.90 to 0.99)**	**<0.01**

In bold the statistically significant associations
*If not otherwise specified
†Median (minimum–maximum).
MOD, multiple organ dysfunction.

definition (the central nervous system was used as one of the two dysfunctioning organs).[7] In contrast to this study, we did not find an association with the Apgar scores at 1 and 5 min. Our analyses showed that the presence of meconium-stained amniotic fluid, the TS at admission, the use of adrenalin medication during resuscitation and blood gas measurements reflecting a disturbed acid–base balance (ie, lactate, pH and base excess) at admission in the NICU were associated with MOD in our cohort.

The possible impact of the MOD definition used on the robustness of the reported association between perinatal variables and MOD is also illustrated by our finding that the variables meconium-stained amniotic fluid and TS were no longer associated with MOD when using a stricter MOD definition. However, the blood gas variables lactate, pH and base excess and adrenalin use during resuscitation did remain significant when using different MOD definitions in this study, suggesting that signs of the severity of perinatal hypoxia ischaemia predispose for the risk of developing MOD.

There are strengths but also limitations in this study. A strength of this study is the prospectively collected dataset from a large multicentre cohort with a high follow-up rate using a national standardised neurodevelopmental assessment at 24 months. However, a limitation of this study was the need to convert the BSID scores in a part of the infants. Although studies assessing the impact of these conversion methods are reassuring,[13 14] we cannot rule out that overestimation or underestimation of the assessment of NDI has occurred. Furthermore, not all infants completed the follow-up assessment at 24 months of age. Although the comparison of patients' characteristics between those survivors assessed and those lost to follow-up showed no major differences, imputation of missing data may have produced overestimation. Finally, a longitudinal data analysis investigating the development of MOD over time was not possible within this cohort. The original research question of the PharmaCool cohort was investigating drug pharmacokinetics administered during TH, and therefore the study focused on the kidney function such as oliguria and creatinine during first 3–5 days of postnatal life. Although liver function was measured as a standard of care in the first days following local treatment protocols, the exact timing of that measurement could differ between hospitals.

In conclusion, this study showed that in a high-risk population of infants treated with TH for HIE after perinatal asphyxia, MOD as currently defined has no predictive value for the combined outcomes of mortality or NDI at 24 months or its individual components. Severe acid–base disturbances after birth due to perinatal asphyxia and the use of adrenalin medication during resuscitation are all associated with MOD.

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Contributors JL prepared the database, performed the statistical analyses, prepared the data tables, drafted the initial manuscript and revised the manuscript. LdV and FG made substantial contributions to the interpretation of data, and reviewed and revised the manuscript for important intellectual content. TRdH, WO, DV and AHvK are local investigators, made substantial contributions to the concept and design of the study, had full access to all of the data in the study, take responsibility for the integrity of the data and the accuracy of the data analysis, and critically reviewed the manuscript for important intellectual content. TRdH acts as guarantor.All authors approved the final manuscript as submitted and agreed to be accountable for all aspects of the work.

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Competing interests TRdH reports grants from The Netherlands Organization for Health Research and Development ZonMW during the conduct of the study.

Patient consent for publication Not applicable.

Ethics approval This study involves human participants and was approved by medical ethics review committee of Amsterdam UMC Location AMC (W20_533). The participants gave informed consent to participate in the study before taking part. The institutional review board of each participating centre approved the study.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request. Data generated or analysed during the study are available from the corresponding author by request.

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REFERENCES

1 O'Dea M, Sweetman D, Bonifacio SL, *et al*. Management of multi organ dysfunction in neonatal encephalopathy. *Front Pediatr* 2020;8:239.
2 Bhagat I, Sarkar S. Multiple organ dysfunction during therapeutic cooling of asphyxiated infants. *Neoreviews* 2019;20:e653–60.
3 Hernán MA, Hsu J, Healy B. A second chance to get causal inference right: a classification of data science tasks. *CHANCE* 2019;32:42–9.
4 Kanik E, Ozer EA, Bakiler AR, *et al*. Assessment of myocardial dysfunction in neonates with hypoxic-ischemic encephalopathy: is it a significant predictor of mortality. *J Matern Fetal Neonatal Med* 2009;22:239–42.
5 Sweetman DU, Murphy JFA, Donoghue V, *et al*. Multi-organ dysfunction scoring in neonatal encephalopathy. *Arch Dis Child* 2014;99:A403.
6 Yan ES, Chock VY, Bonifacio SL, *et al*. Association between multi-organ dysfunction and adverse outcome in infants with hypoxic ischemic encephalopathy. *J Perinatol* 2022;42:907–13.
7 Martín-Ancel A, García-Alix A, Gayá F, *et al*. Multiple organ involvement in perinatal asphyxia. *J Pediatr* 1995;127:786–93.
8 de Haan TR, Bijleveld YA, van der Lee JH, *et al*. Pharmacokinetics and pharmacodynamics of medication in asphyxiated newborns during controlled hypothermia. The Pharmacool multicenter study. *BMC Pediatr* 2012;12:45.
9 Alsina M, Martín-Ancel A, Alarcon-Allen A, *et al*. The severity of hypoxic-ischemic encephalopathy correlates with multiple organ dysfunction in the hypothermia era. *Pediatr Crit Care Med* 2017;18:234–40.
10 Thorsen P, Jansen-van der Weide MC, Groenendaal F, *et al*. The Thompson encephalopathy score and short-term outcomes in asphyxiated newborns treated with therapeutic hypothermia. *Pediatr Neurol* 2016;60:49–53.
11 Bayley N, Infant S. *Bayley scales of infant and toddler development*. 2006.
12 Palisano R, Rosenbaum P, Walter S, *et al*. Development and reliability of a system to classify gross motor function in children with cerebral palsy. *Dev Med Child Neurol* 1997;39:214–23.
13 Lees CC, Marlow N, van Wassenaer-Leemhuis A, *et al*. 2 year neurodevelopmental and intermediate perinatal outcomes in infants with very Preterm fetal growth restriction (TRUFFLE): a randomised trial. *Lancet* 2015;385:2162–72.
14 Langeslag JF, Groenendaal F, Roosendaal SD, *et al*. Outcome prediction and inter-rater comparison of four brain magnetic resonance imaging scoring systems of infants with perinatal asphyxia and therapeutic hypothermia. *Neonatology* 2022;119:311–9.
15 van Buuren S. *Flexible imputation of missing data*. Second edition. Boca Raton, Florida: Chapman and Hall/CRC, CRC Press, 2012.
16 Shankaran S, Pappas A, Laptook AR, *et al*. Outcomes of safety and effectiveness in a multicenter randomized, controlled trial of whole-body hypothermia for neonatal hypoxic-ischemic encephalopathy. *Pediatrics* 2008;122:e791–8.
17 Topjian AA, de Caen A, Wainwright MS, *et al*. Pediatric post-cardiac arrest care: a scientific statement from the American Heart Association. *Circulation* 2019;140:e194–233.
18 Jozwiak M, Bougouin W, Geri G, *et al*. Post-resuscitation shock: recent advances in pathophysiology and treatment. *Ann Intensive Care* 2020;10:170.
19 Steyerberg EW. Clinical prediction Models2009. 2009. 10.1007/978-0-387-77244-8 Available: http://link.springer.com/10.1007/978-0-387-77244-8