Evolution of the Sarnat exam and association with 2-year outcomes in infants with moderate or severe hypoxic-ischaemic encephalopathy: a secondary analysis of the HEAL Trial

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ABSTRACT

Objective To study the association between the Sarnat exam (SE) performed before and after therapeutic hypothermia (TH) and outcomes at 2 years in infants with moderate or severe hypoxic-ischaemic encephalopathy (HIE).

Design Secondary analysis of the *H*igh-dose *E*rythropoietin for *A*sphyxia and Encepha*L*opathy Trial. Adjusted ORs (aORs) for death or neurodevelopmental impairment (NDI) based on SE severity category and change in category were constructed, adjusting for sedation at time of exam. Absolute SE Score and its change were compared for association with risk for death or NDI using locally estimated scatterplot smoothing curves.

Setting Randomised, double-blinded, placebo-controlled multicentre trial including 17 centres across the USA.

Patients 479/500 enrolled neonates who had both a qualifying SE (qSE) before TH and a SE after rewarming (rSE).

Interventions Standardised SE was used across sites before and after TH. All providers underwent standardised SE training.

Main outcome measures Primary outcome was defined as the composite outcome of death or any NDI at 22–36 months.

Results Both qSE and rSE were associated with the primary outcome. Notably, an aOR for primary outcome of 6.2 (95% CI 3.1 to 12.6) and 50.3 (95% CI 13.3 to 190) was seen in those with moderate and severe encephalopathy on rSE, respectively. Persistent or worsened severity on rSE was associated with higher odds for primary outcome compared with those who improved, even when qSE was severe.

Conclusion Both rSE and change between qSE and rSE were strongly associated with the odds of death/NDI at 22–36 months in infants with moderate or severe HIE.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ The Sarnat exam (SE), a tool to measure the degree of encephalopathy, is dynamic throughout the first week after birth.

WHAT THIS STUDY ADDS

⇒ Both the initial SE prior to initiation of therapeutic hypothermia and SE performed after rewarming were associated with outcome at 22–36 months.

⇒ In particular, the trajectory of the SE between the two time points shows a strong association with outcome at 22–36 months.

⇒ Therefore, routine SE performed after rewarming adds a valuable tool to clinical practice.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Incorporating standardised SEs after rewarming and comparison to the initial exam can assist clinicians and parents in assessing risk for death and neurodevelopmental impairment, facilitating resource allocation after hospital discharge.

BACKGROUND

In high-resource settings, hypoxic-ischaemic encephalopathy (HIE) affects approximately 1–4/1000 live births. Therapeutic hypothermia (TH) improves outcome after moderate or severe HIE,[1–4] though up to half of affected neonates still experience adverse outcomes such as death or neurodevelopmental impairment (NDI).[2 5] The Sarnat exam (SE) was initially developed in 1976 to describe the dynamic clinical nature of neonatal encephalopathy over time.[6 7] It has been adapted several times and is now commonly referred to as the 'modified SE'.[3 4 6 8–12] SE is widely used to assess the initial stage of encephalopathy and to determine eligibility for TH. The Thompson Encephalopathy Score (TS), developed to simplify SE, is an alternative clinical assessment.[13] The two scoring systems vary slightly and are reported differently, the TS as a numerical score, and the SE generally as a categorical result.

A

Category	Normal	Mild	Moderate	Severe
Level of Consciousness	Normal	Hyperalert or irritable	Lethargic or poorly responsive	Minimal or no responsiveness
Spontaneous Activity	Normal	Slightly decreased	Decreased	Absent
Posture	Normal	Mild distal flexion	Distal flexion, complete extension	Decerebrate
Muscle Tone	Normal	Hypertonic	Hypotonic	Flaccid
Primitive Reflexes				
1. Suck Reflex	1. Normal	1. N/A	1. Weak or bite	1. Absent
2. Moro reflex	2. Normal	2. Low threshold to elicit	2. Weak or incomplete	2. Absent
Autonomic Reflexes				
1. Pupils	1. Normal	1. N/A	1. Constricted	1. Dilated and either fixed or sluggishly reactive; asymmetric
1. Respirations	1. Normal	1. N/A	1. Periodic breathing	2. Intubated and ventilated

B

NDI	Motor Impairment	Cognitive Impairment
None	None	BSID-III ≥ 90
Mild	Hemiparesis or diparesis with GMFCS <1 or no CP with GMFCS =1	BSID-III 85-89
Moderate	Quadriparesis with GMFCS <1, hemiparesis/diparesis with GMFCS ≤ 2, or no CP with GMFCS = 2	BSID-III 70-84
Severe	Quadriparesis with GMFCS ≤ 1, hemiparesis/diparesis, or no CP with GMFCS ≥ 3	BSID-III <70
Any	GMFCS ≥1, any CP diagnosed on a standardised neurological exam or BSID-III cognitive score <90	

Figure 1 Sarnat exam and outcome definitions. (A) Modified Sarnat exam used in this study. (B) Definitions of neurodevelopmental outcome used in this study. BSID-III, Bayley Scales of Infant Toddler Development—third edition; CP, cerebral palsy; GMFCS, Gross Motor Function Classification System; NDI, neurodevelopmental impairment.

The initial SE and TS when performed shortly after birth are poorly correlated with outcome.[14 15] However, evolution of the TS over the first week better predicts outcomes.[16] In studies of SE performed on days of life 3, 4 or after rewarming, varying relations to short-term outcome are described; associations with long-term outcomes are promising but remain unclear due to confounding factors such as sedative medications and variable study populations.[17–19] Numerical assessments of SE have shown superior performance compared with categorical interpretation with respect to predicting MRI injury, but it is not known whether numerical SE or change in SE over time is associated with long-term outcome.[20 21]

We hypothesised that the change in Sarnat category, the individual components of the modified SE, as well as its numerical equivalent, before and after TH, would be associated with the risk of death or NDI at 22–36 months of age in a large contemporary cohort of neonates with moderate or severe HIE.

METHODS

This is a secondary analysis of the multicentre, double-blinded, randomised, placebo-controlled *H*igh-Dose *E*rythropoietin for *A*sphyxia and Encepha*L*opathy (HEAL) Trial which included 500 infants born ≥36 weeks gestational age and treated for 72 hours with TH for moderate or severe HIE based on qualifying SE (qSE) on day 0, between 1 hour and 6 hours after birth.[5] All participating sites agreed to use the same modified SE for the trial (figure 1A) and every enrolling provider received standardised training. Only trained providers performed or verified SEs. After enrolment, infants were randomised to either five doses of erythropoietin (1000 IU/kg/dose) or placebo. Infants were reassessed with the same standardised SE after rewarming (rSE) on day of life 5. The use of sedating medications within 4 hours of the assessment was recorded. Infants with both a qSE and rSE were included in this analysis. SE findings were categorised as normal (no abnormalities), mild (<3 moderate or severe subcategories), moderate (≥3 moderate or severe subcategories, but <3 in severe category) or severe (≥3 severe subcategories) encephalopathy. A score of 0 was assigned to normal findings, 1 to mild findings, 2 to moderate findings and 3 to severe findings. To generate a total Sarnat Score, the assigned scores of each Sarnat category (figure 1A) were summed (possible range 0–18). For categories with two subscores, the worst of the two scores was counted. Primary outcome was defined as the composite outcome of death or any NDI at 22–36 months (figure 1B). Details of the trial protocol were published previously.[5 22]

Statistical analysis

Demographics, illness severity and outcome variables were compared between infants whose SE improved versus those whose score remained stable or worsened. Adjusted ORs (aORs) for death/NDI based on qSE and rSE severity categories, change in category, and the individual components (as dummy variables) at both time points were constructed using logistic regression, adjusting for extracorporeal membrane oxygenation and sedation at time of exam. The few missing Sarnat components were imputed using multiple imputation with chained equations (n=5 imputations), using information from the available Sarnat components given the high level of correlation between items. Absolute rSE Score and change in score as continuous variables were visually compared against risk of death and level of NDI

Table 1 Patient characteristics comparing those neonates who improved in their Sarnat exam from birth to rewarming versus those who worsened or did not change

	All infants, n (%)	Improved, n (%)	No change/worsened, n (%)
Total Included, n (% of total)	479	360 (75.2)	119 (24.8)
Maternal age, mean (SD)	29.7 (6.4)	29.8 (6.5)	29.4 (6.0)
Maternal education			
High school or less	181 (37.8)	132 (36.7)	49 (41.2)
Some college	102 (21.3)	79 (21.9)	23 (19.3)
College graduate or higher	173 (36.1)	139 (38.6)	34 (28.6)
Not reported	23 (4.8)	10 (2.8)	23 (19.3)
Maternal parity			
1	276 (57.6)	213 (59.2)	63 (52.9)
2	104 (21.7)	76 (21.1)	28 (23.5)
≥3	99 (20.7)	71 (19.7)	28 (23.5)
Maternal SSRI use	28 (5.8)	26 (7.2)	2 (1.7)
Pregnancy complications			
Pregnancy-induced hypertension	56 (11.7)	42 (11.7)	14 (11.8)
Pre-eclampsia or eclampsia	45 (9.4)	34 (9.4)	11 (9.2)
Gestational diabetes/insulin-dependent diabetes mellitus	57 (11.9)	40 (11.1)	17 (14.3)
Thyroid disease	40 (8.4)	31 (8.6)	9 (7.6)
Maternal chorioamnionitis or fever	75 (15.7)	57 (15.8)	18 (15.1)
Labour and delivery complications and sentinel events			
Placenta abruption	67 (14.0)	44 (12.2)	23 (19.3)
Cord prolapse	22 (4.6)	22 (6.1)	0 (0.0)
Uterine rupture	23 (4.8)	12 (3.3)	11 (9.2)
Shoulder dystocia	31 (6.5)	25 (6.9)	6 (5.0)
Chorioamnionitis	63 (13.2)	50 (13.9)	13 (10.9)
Any sentinel event	136 (28.4)	99 (27.5)	37 (31.1)
Delivery mode			
Spontaneous vaginal delivery	116 (24.2)	92 (25.6)	24 (20.2)
Instrumented vaginal delivery	48 (10.0)	38 (10.6)	10 (8.4)
Elective caesarean delivery	12 (2.5)	9 (2.5)	3 (2.5)
Emergent/urgent caesarean delivery	303 (63.3)	221 (61.4)	82 (68.9)
Male sex	265 (55.3)	203 (56.4)	62 (52.1)
Apgar (median, IQR)			
5 min	3 (2–5)	4 (2–5)	3 (1–5)
10 min	5 (4–7)	5 (4–7)	4 (3–6)
Worst blood gas parameters			
pH, mean (SD)	6.93 (0.17)	6.96 (0.16)	6.85 (0.20)
Base deficit, mean (SD)	−18.3 (6.1)	−17.6 (5.8)	−20.5 (6.7)
Resuscitation measures:			
Intubation	330 (68.9)	235 (65.3)	95 (79.8)
Cardiac compressions	148 (30.9)	95 (26.4)	53 (44.5)
Epinephrine	84 (17.5)	47 (31.1)	37 (31.1)
Placenta pathology			
Chorioamnionitis	122 (25.5)	102 (28.3)	20 (16.8)
Any abnormality	264 (55.1)	213 (59.2)	51 (42.9)
Any acute abnormality	197 (41.1)	158 (43.9)	39 (32.8)
Any chronic abnormality	200 (41.8)	161 (44.7)	39 (32.8)
Sarnat stage at randomisation (qSE)			
Moderate	377 (78.7)	291 (80.8)	86 (72.3)
Severe	102 (21.3)	69 (19.2)	33 (27.7)
Total Sarnat Score, median (IQR)	12 (10–14)	12 (10–13)	13 (11–15)
Sedative medications around time of exam	53 (11.1)	37 (10.3)	16 (13.4)
Sarnat stage after rewarming (rSE)			
Normal	99 (20.7)	99 (27.5)	0 (0.0)
Mild	230 (48.0)	230 (63.9)	0 (0.0)
Moderate	97 (20.3)	31 (8.6)	66 (55.5)

Continued

Table 1 Continued

	All infants, n (%)	Improved, n (%)	No change/worsened, n (%)
Severe	53 (11.1)	0 (0.0)	53 (44.5)
Total Sarnat Score, Median (IQR)	3 (1–9)	2 (0–5)	13 (10–16)
Sedative medications around time of exam	146 (30.5)	69 (19.2)	77 (64.7)
End-organ injury			
Liver injury (AST>100 IU/L)	184 (38.4)	115 (31.9)	69 (58.0)
Disseminated intravascular coagulopathy (INR >2.0)	141 (29.4)	84 (23.3)	57 (47.9)
Anuria/oliguria/acute kidney injury (creatinine >1.5 mg/dL)	50 (10.4)	24 (6.7)	26 (21.8)
Thrombocytopenia	13 (2.7)	6 (1.7)	7 (5.9)
Respiratory support			
Intubation	330 (68.9)	235 (65.3)	95 (79.8)
iNO	88 (18.4)	45 (12.5)	43 (36.1)
Extracorporeal membrane oxygenation	19 (4.0)	9 (2.5)	10 (8.4)
Hypotension treatment by day 5			
Inotropic support	172 (35.9)	98 (27.2)	74 (62.2)
Hydrocortisone	89 (18.6)	41 (11.4)	48 (40.3)
Seizures	174 (36.3)	87 (24.2)	87 (73.1)
Erythropoietin treatment	244 (50.9)	188 (52.2)	56 (47.1)
Discharge			
All oral feedings at discharge	370 (77.2)	319 (88.6)	51 (42.9)
Outcomes			
Death	45 (9.4)	9 (2.5)	36 (30.3)
Day of death, median (IQR)	11 (7–29)	12 (6–30)	10 (7–26)
Any neurodevelopmental impairment	174 (36.3)	121 (33.6)	53 (44.5)
Not known	19 (4.0)	15 (4.2)	4 (3.4)

AST, Aspartate Aminotransferase; iNO, Inhaled nitric oxide; INR, International normalised ratio; IQR, Interquartile range; qSE, qualifying SE ; rSE, SE after rewarming; SD, Standard deviation; SSRI, Selective serotonin reuptake inhibitor.

using locally estimated scatterplot smoothing curves. For these visualisations only, the median of imputed scores was used to determine total and change in score. For all other analyses, estimates from models using all five imputations were pooled using the 'with' function from the mice package in R. Analyses were conducted in RStudio using the R statistical package (V.4.1.2, Foundation for Statistical Computing, Vienna, Austria).[23]

RESULTS

Patients

Of the 500 neonates enrolled in HEAL, 479 had both a qSE and rSE and were included. On the qSE, 377 (79%) neonates had moderate and 102 (21%) had severe encephalopathy. The rSE was conducted at a median (IQR) age of 5 (5,5) days after birth; 381 (80%) were assessed on day 5 and 467 (98%) on days 4–6 after birth. The rSE was normal in 99 (21%) neonates, whereas 230 (48%) had mild, 97 (20%) moderate and 53 (11%) severe encephalopathy. Based on their rSE, neonates were grouped into two categories—improved exam or same/worsened exam (table 1). The primary outcome was available for 460/479 (96%); neonates with missing outcome data were excluded from the outcome analyses.

Initial qSE and outcome

Fifty-seven per cent of infants with moderate encephalopathy on qSE experienced a normal outcome compared with 24% with severe qSE ($p<0.001$, figure 2A). At 22–36 months, infants with severe qSE had an aOR of 4.2 (95% CI 2.6 to 6.8) for primary outcome compared with those with moderate qSE. Death also occurred more commonly in neonates with severe qSE (35%) compared with those with moderate qSE (3%, $p<0.001$). Among survivors, NDI was less severe in the infants with moderate compared with severe qSE (no NDI 60% vs 39%, mild NDI 12% vs 9%, moderate NDI 13% vs 17%, severe NDI 11% vs 30%; $p<0.001$).

rSE and outcome

rSE was strongly associated with primary outcome (figure 2B). A normal outcome was seen in 73% of infants with a normal rSE, and in 62% with mild, 22% with moderate, and 6% with severe encephalopathy on rSE, respectively. Severe encephalopathy was most associated with death, and surviving infants experienced worse NDI with increasing degree of encephalopathy on rSE: Mild encephalopathy on rSE showed a trend towards an abnormal outcome (aOR 1.7, 95%CI 0.98 to 2.8), whereas a significant association with primary outcome was seen for moderate (aOR 6.2, 95%CI 3.1 to 12.6) and severe encephalopathy (aOR 50.3, 95%CI 13.3 to 190).

Change in SE and outcome at 22–36 months

Improvement was seen between qSE and rSE in 360 (75.2%) infants and 119 (24.8%) remained the same or worsened (table 1). Change in SE was associated with primary outcome (figure 3). Infants whose SE improved to normal or mild, even when initially severe, were most likely to experience no or mild NDI, whereas an unchanged or worsened exam was associated with moderate–severe NDI or death. Among infants who started severe and remained severe, the aOR for primary outcome was 53.4 (95%CI 7.1 to 410) and most infants in this group died. If an initial severe exam improved to moderate, the aOR for primary outcome decreased to 7.6 (95%CI 2.9 to 20.1). Infants who started moderate and became severely encephalopathic had

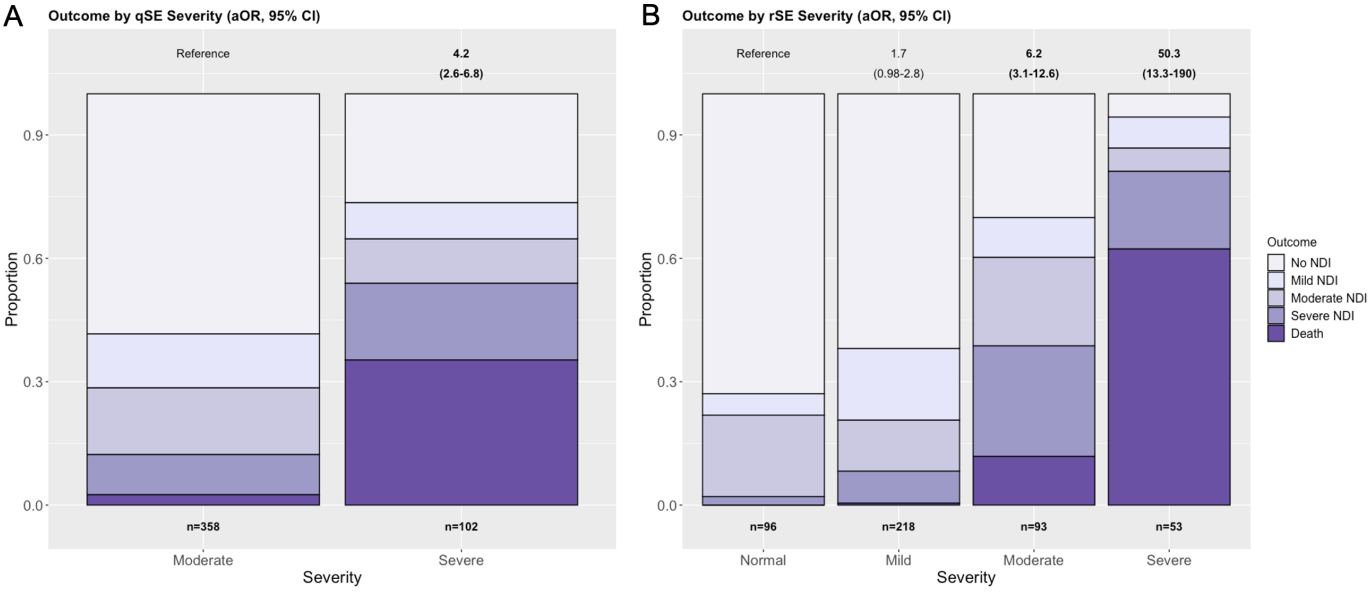

Figure 2 (A) Qualifying Sarnat exam (qSE) and association with primary outcome. Only neonates with moderate or severe encephalopathy were included. In the moderate group, n=209 (58%) experienced disability-free survival, n=47 (13%) mild NDI, n=58 (16%) moderate NDI, n=35 (10%) severe NDI, and n=9 (3%) died. In the severe group, n=27 (27%) experienced disability-free survival, n=9 (9%) mild NDI, n=11 (11%) moderate NDI, n=19 (19%) severe NDI, and n=36 (35%) died. (B) Sarnat exam after rewarming (rSE) and association with primary outcome. In the normal group, n=70 (73%) experienced disability-free survival, n=5 (5%) mild NDI, n=19 (20%) moderate NDI, n=2 (2%) severe NDI, and n=0 (0%) died. In the mild group, n=135 (62%) experienced disability-free survival, n=38 (17%) mild NDI, n=27 (12%) moderate NDI, n=17 (8%) severe NDI, and n=1 (0%) died. In the moderate group, n=28 (30%) experienced disability-free survival, n=9 (10%) mild NDI, n=20 (22%) moderate NDI, n=25 (27%) severe NDI, and n=11 (12%) died. In the severe group, n=3 (6%) experienced disability-free survival, n=4 (8%) mild NDI, n=3 (6%) moderate NDI, n=10 (19%) severe NDI, and n=33 (62%) died. aORs with 95% CI for the HEAL primary outcome (death/NDI) are shown above the plot for each group compared with infants with a moderate (qSE, A) or normal (rSE, B) Sarnat exam. Bold values display when the 95% CIs do not cross 1. Models are adjusted for sedative medications prior to assessment and ECMO. aOR, adjusted OR; CI, confidence interval; ECMO, extracorporeal membrane oxygenation; HEAL, *H*igh-Dose *E*rythropoietin for *A*sphyxia and Encepha*L*opathy; NDI, neurodevelopmental impairment.

an aOR of 22.0 (95%CI 4.2 to 115) for death/NDI, whereas infants who had an initial moderate encephalopathy and stayed moderate after rewarming had an aOR of 3.2 (95%CI 1.7 to 6.0) for the primary outcome and most infants in this group survived.

Total score and change in total score of the SE

The total numerical score on rSE was associated with primary outcome (figure 4A), with an aOR 1.22 (95% CI 1.16 to 1.29) per unit increase in total score ($p<0.001$). Each unit decrease in total Sarnat Score from qSE to rSE was associated with an aOR of 0.85 (95% CI 0.81 to 0.90; $p<0.001$, figure 4B) for primary outcome.

Association of the qSE and rSE subcategories with outcome

Of the six exam categories, a mildly abnormal level of consciousness on qSE was associated with a decreased aOR of 0.40 (95% CI 0.23 to 0.71) for primary outcome, whereas most other categories were associated with either a trend or an increased odds for primary outcome (figure 4C). Severe findings in any category were associated with an increased odds for primary outcome. Moderate findings in the categories of spontaneous activity, Moro reflex, and pupillary exam were associated with an increased odds for abnormal outcome, while respirations, suck reflex, level of consciousness and posture were not. Both increased and decreased tone on qSE were similarly associated with higher odds of primary outcome even after adjusting for sedative medications. In contrast, on rSE, all categories, except mildly abnormal Moro reflex and mildly abnormal level of consciousness, were associated with higher odds of primary outcome with increasing severity (figure 4D).

DISCUSSION

We present a large cohort of neonates treated with TH for moderate or severe HIE who were assessed with a standardised SE prior to cooling, and again after rewarming on day 5 after birth. We show that the stage of encephalopathy on rSE and the change from qSE to rSE were strongly associated with death or NDI.

The modified SE is routinely used to determine eligibility for TH, and this early stage SE has shown an association with long-term outcome. The TS and the standardised Amiel-Tison Neurological Assessment at Term, when applied after rewarming, result in a stronger association with short-term and long-term outcomes.[16 24 25] This has not consistently been demonstrated for the SE, and studies comparing the early SE with SE performed at 72–96 hours were done prior to the TH era and have not routinely accounted for sedative medications or the trajectory of the SE over time.[17 18] In our study, while the qSE was associated with long-term outcome, this association appeared even more robust for the rSE performed on day 5, after rewarming. Additionally, the temporary evolution between qSE and rSE was highly predictive of long-term outcome. This emphasises that while the qSE prior to TH provides important information, it may be confounded by dynamic factors from the initial insult, and that the rSE and the trajectory of the SE may be more reflective of permanent sequelae. Incorporating rSE in routine clinical

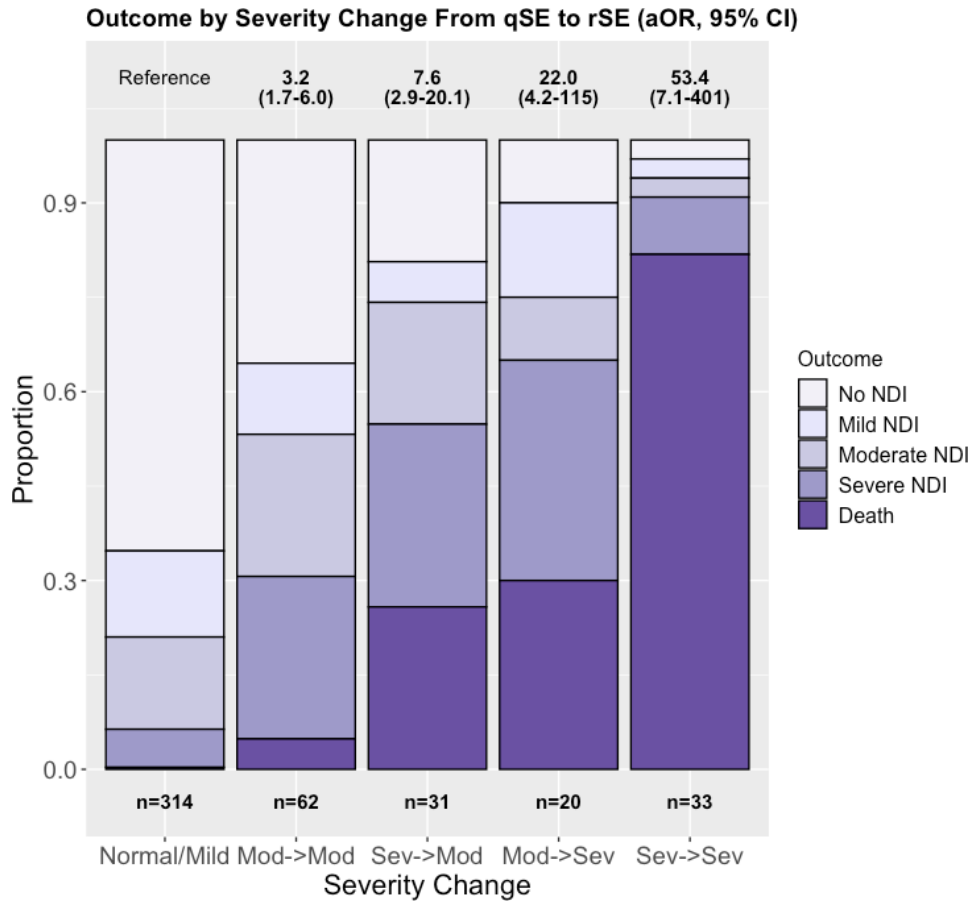

Figure 3 Primary outcome by change in encephalopathy from qualifying Sarnat exam (qSE) to exam after rewarming (rSE). In the Normal/Mild group, n=205 (65%) experienced disability-free survival, n=43 (14%) mild NDI, n=46 (15%) moderate NDI, n=19 (6%) severe NDI, and n=1 (0%) died. In the Moderate–>Moderate group, n=22 (36%) experienced disability-free survival, n=7 (11%) mild NDI, n=14 (23%) moderate NDI, n=16 (26%) severe NDI, and n=3 (5%) died. In the Severe–>Moderate group, n=6 (19%) experienced disability-free survival, n=2 (6%) mild NDI, n=6 (19%) moderate NDI, n=9 (29%) severe NDI, and n=8 (26%) died. In the Moderate–>Severe group, n=2 (10%) experienced disability-free survival, n=3 (15%) mild NDI, n=2 (10%) moderate NDI, n=7 (35%) severe NDI, and n=6 (30%) died. In the Severe–>Severe group, n=1 (3%) each experienced no NDI, mild NDI, and moderate NDI, with n=3 (9%) experiencing severe NDI and n=27 (82%) died. aORs with 95% CI for the HEAL primary outcome (death/NDI) are shown above the plot for each group compared with infants who improved from moderate or severe on qSE to mild or normal on rSE. Models are adjusted for medications prior to assessment and ECMO. aOR, adjusted OR; ECMO, extracorporeal membrane oxygenation; HEAL, *H*igh-dose *E*rythropietin for *A*sphyxia and Encepha*L*opathy; NDI, neurodevelopmental impairment.

practice can provide significant information regarding longer-term outcomes and might be particularly useful in settings where technologies such as MRI are unavailable.

To further optimise the reliability of the SE, interest has been directed towards comparing numerical and categorical assessments.[20] When assessed within 6 hours of birth, the numerical score of the SE more accurately predicted an abnormal 2-year outcome than the categorical result in infants with mild–moderate HIE; however, in neonates with moderate or severe HIE no difference between numerical and categorical score on SE with respect to associations with MRI injury or long-term outcome were found.[20 21 24 26 27] By using a different approach, assessing the change in numerical score from qSE to rSE, we identified an association with death/NDI: for each unit increase in score, the odds for death or NDI increased whereas for each unit decrease, the odds lowered.

The contribution of the six individual SE components and their associations with long-term findings have not previously been described. We found that muscle tone was associated with poor outcome at any timepoint, a key finding considering that 'tone' has been the most adjusted category throughout SE modifications. The original Sarnat staging did not include hypertonia, whereas the Neonatal Research Network (NRN) included hypertonia as a marker of moderate encephalopathy across several trials.[6 28] The NRN modification was also adopted for studies of mild encephalopathy, which highlighted tone abnormality as the most commonly identified component of the SE associated with disability.[29] However, investigators of other large trials have opted to either not include increased tone as moderate abnormality,[3 8 9] or classified an increased tone as a symptom of mild encephalopathy instead.[10–12] Our findings show that hypertonia and hypotonia on qSE are similarly associated with death/NDI, but that on rSE hypotonia is associated with a greater odds of death/NDI than hypertonia (figure 4C,D). When interpreting these results, the timing and evolution of changes are therefore crucial. For instance, muscle tone after a hypoxic-ischaemic insult evolves from decreased to increased tone, and in the most severe cases progresses into cerebral palsy.[30 31] In contrast, irritability as sequela from an acute insult is more commonly observed in conjunction with an increased tone. Therefore, hypertonicity may represent a clinical expression of two very different origins—an older insult that is progressing in its clinical course or a very

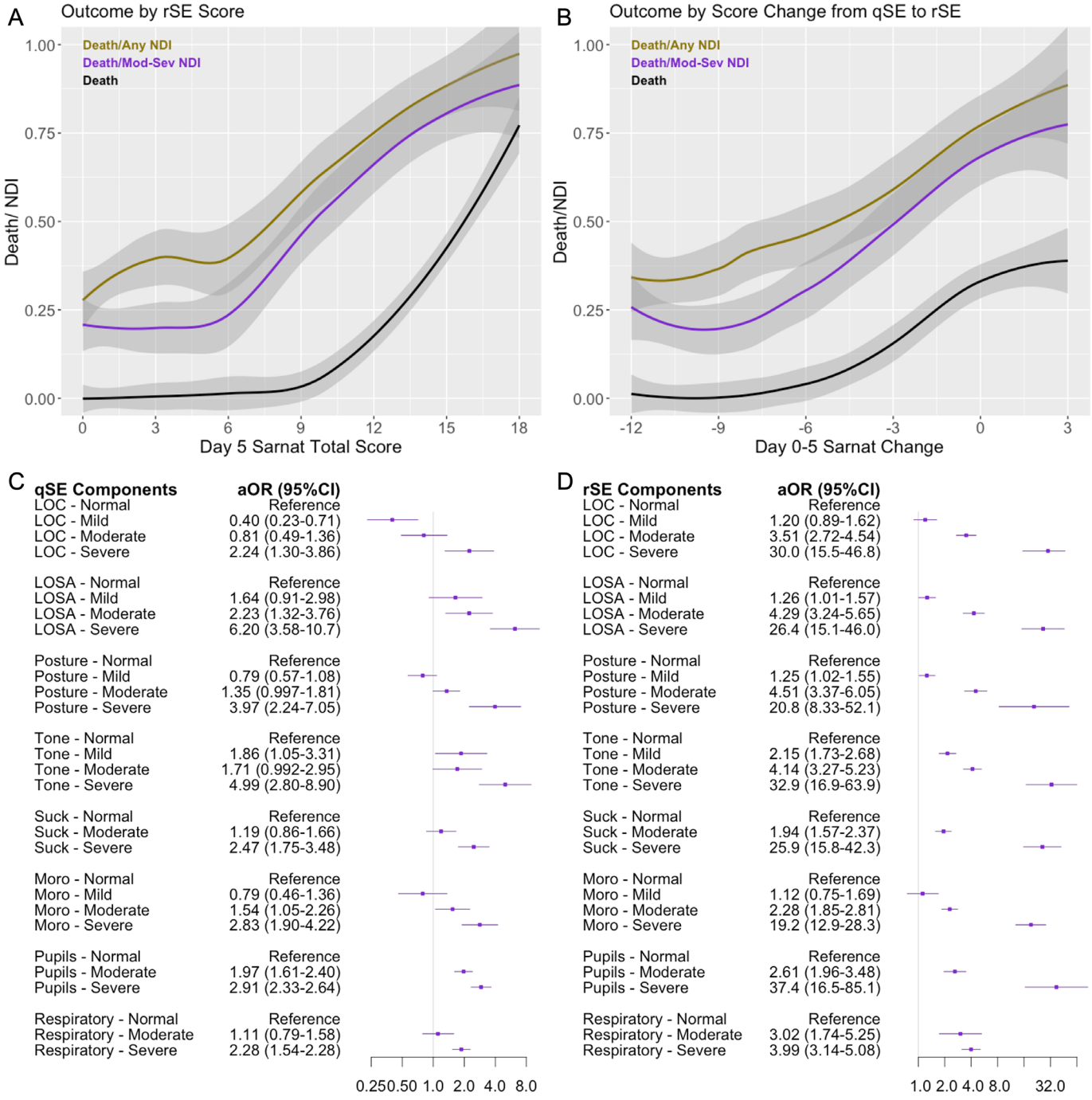

Figure 4 Unadjusted locally estimated scatterplot smoothing (LOESS) curved depicting proportion of infants experiencing death or NDI by (A) Absolute value of total rSE Score, and (B) Change in Sarnat Score from qSE to rSE. (C) Forest plot of Sarnat components and subcategories on qSE. (D) Forest plot of the Sarnat components and subcategories on rSE. Each component was included on a continuous 0–3 scale: aOR is per one unit increase in score adjusted for ECMO and medications prior to assessment. aOR, adjusted OR; ECMO, extracorporeal membrane oxygenation; LOS, level of consciousness; LOSA, level of spontaneous activity; NDI, neurodevelopmental impairment; qSE, qualifying Sarnat Exam; rSE, Sarnat exam after rewarming.

acute symptom associated with neuro-irritability following an acute insult. Correlation with timing of injury on MRI might assist with distinguishing between these two scenarios.

Dr Harvey Sarnat himself recently proposed re-evaluating the SE, advocating for studies weighing the predictive value of each component of the SE with the goal of modifying the scoring system and/or identifying specific risks based on severity and timing of component abnormality.[32] Using the rSE may enhance the prognostic ability, particularly when combined with other metrics such as blood glucose, cooling mattress temperature, MRI, MRS (magnetic resonance spectroscopy) and EEG (electroencephalogram).[33–36] Furthermore, it is plausible that the evolution of the SE and its individual components may assist in the characterisation of an individualised injury profile and facilitate tailored therapies and resource allocation.[37 38] Prospective studies examining combinations of these easily accessible yet powerful metrics to predict outcome are required.

A significant strength of this study is the standardisation across sites of the SE at two time points, the large cohort size and the high follow-up rate. In addition, the ability to adjust for medications with sedative effects in this study minimised their confounding influence on the SE. Limitations of this study are that the specific sedative medication, dose and precise timing within the 4 hours prior to the SE were not collected, and we were therefore unable to adjust or account for how the different medications may affect the SE. Furthermore, data regarding type and duration of selective serotonin uptake inhibitor exposure during pregnancy was unavailable, which limited the ability to adjust for the possible influence on SE, particularly tone. In addition, rSE and MRI occurred around the same time, and we were unable to determine how MRI findings influenced death. Due to a combination of fewer infants represented in the most severe Sarnat categories and a high percentage of those with poor outcome in those categories, high point estimates and wide CIs in the aOR reflect a degree of statistical uncertainty, however, the lower bounds of those aORs still suggest a notable increase in odds of poor outcome based on Sarnat trajectory, supporting the value of the rSE. Lastly, the aetiology and sequalae of HIE are heterogeneous, therefore confounding variables associated with multiorgan involvement may have influenced the rSE and outcome at 22–36 months. Although perinatal factors and comorbidities were assessed (table 1), the long-term impact on outcomes cannot be precisely accounted for in this study.

CONCLUSION

In this study we found that compared with the qSE, the rSE is more predictive of death or NDI, and that the change from qSE to rSE is strongly associated with outcome at 22–36 months.

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