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Prediction of Early Childhood Outcome of Term Infants using Apgar Scores at 10 Minutes following Hypoxic-Ischemic Encephalopathy

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Abstract

Context—Death or severe disability is so common following an Apgar score of 0 at 10 minutes in observational studies that the Neonatal Resuscitation Program suggests considering discontinuation of resuscitation after 10 minutes of effective CPR.

Objective—To determine if Apgar scores at 10 minutes are associated with death or disability in early childhood following perinatal hypoxic-ischemic encephalopathy (HIE).

Design, Setting, and Patients—This is a secondary analysis of infants enrolled in the NICHD Neonatal Research Network hypothermia trial. Infants ≥ 36 weeks gestation had clinical and/or biochemical abnormalities at birth, and encephalopathy at < 6 hours. Logistic regression and classification and regression tree (CART) analysis was used to determine associations between Apgar scores at 10 minutes and neurodevelopmental outcome adjusting for covariates. Associations are expressed as odds ratios (OR) and 95% confidence interval (CI).

Main Outcome Measure—Death or disability (moderate or severe) at 18–22 months of age.

Results—Twenty of 208 infants were excluded (missing data). More than 90% of infants had Apgar scores of 0–2 at 1 minute and Apgars at 5 and 10 minutes shifted to progressively higher values; at 10 minutes 27% of infants had Apgar scores of 0–2. After adjustment each point decrease in Apgar score at 10 minutes was associated with a 45% increase in the odds of death or disability (OR 1.45, CI 1.22–1.72). Death or disability occurred in 76, 82 and 80% of infants with Apgar scores at 10 minutes of 0, 1 and 2, respectively. CART analysis indicated that Apgar scores at 10 minutes were discriminators of outcome.

Conclusion—Apgar scores at 10 minutes provide useful prognostic data before other evaluations are available for infants with HIE. Death or moderate/severe disability is common but not uniform

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with Apgar scores < 3; caution is needed before adopting a specific time interval to guide duration of resuscitation.

Keywords

Apgar scores; Hypoxic-Ischemic Encephalopathy; cardiopulmonary resuscitation

Apgar scores are almost universally assigned to newborns at birth in the United States and most developed countries. The original intent of the Apgar score was to provide a description of the newborn's physical condition and enable comparison of obstetric practice, maternal analgesia and resuscitative efforts.[1] The Apgar score uses readily available observations, deemed to be objective and acquired without interfering in delivery room care. Apgar and colleagues demonstrated an inverse relationship between neonatal mortality and the 1 min Apgar in 15,348 infants.[2] These observations were subsequently extended to the 5 min Apgar score in more than 17,000 infants born at 13 institutions.[3] Although the inter-observer reliability of assigning Apgar scores and equal weighting of the components of the Apgar score remains a concern,[4, 5] the predictive relationship between the 5 min Apgar score and neonatal mortality was confirmed almost 50 years after introduction of the Apgar score among a cohort of 145,627 singleton premature and term newborns in a retrospective cohort from a single institution. [6]

The Neonatal Resuscitation Program (NRP) recommends assignment of Apgar scores beyond 5 minutes of age when the Apgar score is < 7 (the extended Apgar score) in order to indicate the response to interventions/resuscitation at birth.7 The relationship between the extended Apgar score and outcome at 7 years of age (mortality and cerebral palsy, CP) has been analyzed from approximately 49,000 singleton live births during 1959–1966 as part of the National Collaborative Perinatal Project.8 Eighty percent of surviving children who had Apgar scores of 0–3 at ten minutes or later (up to 20 minutes) were free of major handicap (CP, cognitive deficits, hearing loss, speech delay) at early school age. High rates of CP among survivors (57%) were found only when extended Apgar scores of 0–3 persisted to 20 minutes. These observations were often used to justify resuscitation of infants at birth for at least 20 minutes. More recently the International Liaison Committee on Resuscitation (ILCOR) has suggested that it may be justifiable to stop resuscitation if there are no signs of life after 10 minutes of continuous and adequate resuscitation.9 The ILCOR recommendation is based on more recent observational data10 of the outcome of infants with an Apgar of 0 at 10 minutes. Ten minutes of life and 10 minutes of effective resuscitation are typically not equivalent but represent the best available data for the ILCOR statement.

Present recommendations for shorter intervals of resuscitation suggest that newborn resuscitation techniques and/or obstetric surveillance during labor have changed the relationship between Apgar scores and mortality and/or morbidity. Results of the NICHD Neonatal Research Network Whole Body Cooling Trial[11] provide an opportunity to reassess early childhood outcomes of infants with low Apgar scores at 10 minutes of age. We hypothesized that the Apgar score at 10 minutes is independently associated with death or disability at 18–22 months of age for near term and term infants with encephalopathy of hypoxic-ischemic origin. This information may provide support for the ILCOR recommendation regarding resuscitation of infants with an Apgar of zero at 10 minutes.

METHODS

This was an observational study using data from the NICHD Neonatal Research Network randomized trial comparing whole body hypothermia and current usual care.11 The trial was performed in 16 centers, and infants were enrolled after informed consent was obtained. Eligibility criteria included a gestational age ≥ 36 weeks, post-natal age ≤ 6 hours, and

sequential fulfillment of specific physiological and/or clinical criteria (acute perinatal event, acidemia within an hour of birth, low Apgar scores, and need for ventilation), followed by demonstration of moderate or severe encephalopathy using a modification of the Sarnat stages. (Ref 12 should be here) Exclusion criteria included major congenital abnormality, birth weight less than 1800 grams, or extremis condition.12 (Move ref 12 to previous sentence)

Infants randomized to whole body cooling were positioned on a cooling/heating blanket attached to a Blanketrol II Hyper-hypothermia system (Cincinnati Sub-Zero). The automatic control mode was used to maintain an esophageal temperature of 33.5°C for 72 hours, followed by rewarming and subsequent temperature regulation according to the practices of each participating center. Infants randomized to usual care were treated by using a radiant warmer that was initially servo-controlled to maintain abdominal skin temperature between 36.5°C and 37.0°C and to maintain core temperature. Subsequent adjustments of the servo control set point in response to core temperatures were made according to practices of each participating center. Treatment practices concerning ventilator management, intravenous fluid therapy, volume expansion, blood pressure support, treatment of seizures and use of antibiotics were all per the discretion of the attending physician of each participating center.

Prospectively collected data regarding resuscitation at birth included Apgar scores at 1, 5, 10, and 20 minutes of age and delivery room variables (use of oxygen, bag mask ventilation, intubation, chest compressions, resuscitative medications, cord blood gases and time to initiate spontaneous respiration). Maternal and infant characteristics were as previously detailed.[11]

The primary outcome was death or moderate/severe disability at 18–22 months of age.10 (should be ref 11) Trained personnel blinded to treatment group evaluated outcome using standardized assessments. Disability was pre-defined as either severe or moderate. Severe disability included any of the following: Bayley II Mental Developmental Index (MDI) < 70, Gross Motor Functional Classification System (GMFCS) level of 3–5, blindness, or a hearing deficit with amplification. Criteria for moderate disability were an MDI of 70–84 with any of the following: GMFCS level 2, persistent seizure disorder, or hearing deficit without amplification. Infants in whom a Bayley Scale of Infant Development could not be administered due to cognitive impairment were assigned a score of 49.

Of the 208 infants enrolled in the trial, 188 were included in the current analysis. Three infants were lost to follow-up and thus were missing the primary outcome. Seventeen infants (7 out-born, 10 in-born) were missing the Apgar score at 10 minutes, one of whom was missing all Apgar scores. Apgar scores at 20 minutes were assigned to only 74 infants and therefore are not presented.

Correlations were explored between the Apgar score at 10 minutes and earlier assigned Apgar scores and acid base status at birth. Logistic regression analysis and classification and regression tree (CART) analysis were used to determine associations between the Apgar score at 10 minutes and the primary outcome. Logistic regression analysis was performed with and without adjustment for birth weight, gestational age, gender, out-born and treatment assignment (hypothermia vs usual care). Similar analyses were performed for the individual components of the primary outcome (death, moderate or severe disability). Associations between Apgar scores and outcomes are expressed as odds ratios (OR) and 95% confidence intervals (CI). Classification and Regression Trees (CART) methodology[13] was implemented using CART software14 and used to identify the groups that were most likely to be at risk of death or neurodevelopmental impairment. The CART procedure seeks hidden structures in data by constructing a series of binary splits, called recursive partitioning. Splits are made to identify the most homogeneous subgroups with respect to the outcome. As in logistic regression, independent variables are entered that are thought to be associated with the

outcome; the variables entered into the CART analysis were identical to the logistic regression analysis. The CART software selects variables in order of magnitude of improvement in prediction of the outcome and the variables which contribute the most to the outcome are listed first at the top of the tree. Cross validation is used to test the results of the model once the tree is grown. Only those branches of the nodes of the tree that improve the correct classification of the tree survive the test. The area under the curve for CART analysis is analogous to area under the curve for logistic regression with higher values indicating better prediction.

Results are expressed as a mean ± standard deviation where appropriate.

RESULTS

The frequency distribution of Apgar scores at 1, 5 and 10 minutes for the 188 subjects included in this observational cohort are plotted (Figure I). Eighty nine percent of the infants had Apgar scores of 0–2 at 1 minute of age and Apgar scores at 5 and 10 minutes were shifted to progressively higher values. Although not shown, there were no significant differences in the frequency distribution of Apgar scores between hypothermic and usual care groups. The birth weight and gestational age of this cohort was 3.4±.6 kg and 39±2 weeks and delivery room interventions consisted of the following: 100% of infants received oxygen, 97% received bag and mask ventilation, 96% of infants were intubated, 63% had chest compressions and 57% of infants received resuscitative medications. Consistent with the need for resuscitation was acidemia (blood gas from umbilical cord or within the first post-natal hour) with a pH of 6.8 ±0.2 and a base deficit of 19.5±7.8mEq/L.

The incidence of the primary outcome and its components (death, survival with moderate or severe disability) for each corresponding 10 minute Apgar score are listed in Table I. In general, the incidence of the primary outcome increases with decreases in the 10 minute Apgar score; however, there appears to be a plateau at the lower end of Apgar scores with similar rates of the primary outcome for 10 minute Apgar scores of 0, 1 and 2. Results of the logistic regression to determine associations between the Apgar score at 10 minutes and the primary outcome and its components are listed in Table II. An Apgar score at 10 minutes was associated with the primary outcome with and without adjustments for birth-weight, gestational age, gender, out-born and treatment group; each point decrease in the Apgar score is associated with a 45% increase in the odds of death or disability. Similar associations were present for each of the components of the primary outcome. The covariate treatment group (hypothermia) lowered the odds of the primary outcome (odds ratio, 0.44) and death alone (odds ratio, 0.5). A reduction in death was not found in the NICHD trial[11] and presumably reflects the exclusion of 20 infants with missing 10 minute Apgar scores. The logistic regression was also performed with inclusion of the 1 and 5 minute Apgar score in addition to the 10 minute Apgar score; when all three Apgar scores are included only the 10 minute Apgar score and treatment group was associated with the primary outcome.

The CART model for prediction of death or moderate/severe disability is depicted in Figure II. Apgar scores at 10 minutes determined the initial discrimination of the presence or absence of the primary outcome. Specifically a 10 minute Apgar of ≥ 5 is the first cut-point with 65% of infants with Apgar ≤ 4 having the primary outcome compared to 30% for those with higher Apgars. The next cut-point is the treatment intervention (hypothermia) where 54% of infants had the primary outcome compared to 75% for infants with usual care. Of infants that received hypothermia, a 10 minute Apgar of 3 or 4 was associated with the primary outcome in 44% compared to 71% for infants with a 10 minute Apgar ≤ 2. An Apgar score of 0 is not a cut-point to provide further discrimination of the primary outcome. Of infants with an Apgar at 10 minutes of 3 or 4, the primary outcome is further discriminated by a birth weight of 3.2kg (primary outcome present in 29% of those with a higher birth weight compared to 67% in those

with a lower birth weight). The area under the curve for the CART analysis was 0.72 and was similar to the regression analysis.

An Apgar score of 0 at 10 minutes occurred in 25 infants of whom 12 died. Of the 13 survivors, 6 infants were without moderate or severe disability at follow-up. The MDI of these 6 surviving infants was 87±9 (range 73–100). In contrast, the MDI of surviving infants with a moderate or severe disability that could be tested (n=3) was 53±6 (range 49–59); 4 infants could not be tested and were assigned a score of 49.

DISCUSSION

The principal findings of this report are 1) Apgar scores assigned at 10 minutes of age for infants participating in the NICHD Neonatal Research Network hypothermia trial provide useful prognostic information, 2) death or moderate/severe disability is common with persistently low Apgar scores (< 7) at 10 minutes of age and 3) outcome of infants with an Apgar of 0 at 10 minutes do not appear distinctly different from infants with an Apgar of 1 or 2. Seventeen infants were excluded due to missing 10 minute Apgar scores. Of these infants, 62% had Apgar scores at 5 minutes ≥ 6, only one infant had an Apgar score < 3 (Apgars score of 1), and may account for failure to assign Apgars scores at 10 minutes. Analyses to examine the relationship between Apgar scores at 10 minutes and death or disability at 18–22 months were adjusted for demographic characteristics (birth weight, gestational age, and gender), out-born status and the treatment intervention. Analyses were performed in this manner to assess whether Apgar scores are helpful to clinicians prior to a neurological examination, determination of extent of encephalopathy, brain electrophysiological and imaging studies, and other clinical or laboratory parameter which may indicate prognosis.

The relationship between Apgar scores and early childhood outcome has been the subject of intense interest. Both the American Academy of Pediatrics and the American College of Obstetrics and Gynecology have cautioned against prediction of later neurological dysfunction based solely on low Apgars scores at 5 minutes.[15] This reflects the low prevalence of extremely low Apgar scores (0–3) in spite of the high relative risk for death or CP with such low Apgar scores. These observations are based on population cohort studies using national registries to link Apgar scores with outcome in Scandinavia.[16–18] Very low Apgar scores of 0–3 at 5 minutes of age have greater prognostic value when combined with peri-partum complications, fetal acidemia and signs of neonatal encephalopathy.[19–21]

Between 1959–1966 infants with a birth weight more than 2.5kg and Apgar scores of 0–3 at 10 minutes (latest Apgar score in this range) had rates of mortality at one year and CP at 7 years of 18% and 4.7%, respectively.[8] Since that era there is limited data on early childhood outcome of infants with Apgar scores assigned at 10 minutes of age. The long term outcome of infants with an Apgar score of 0 at 10 minutes and successfully resuscitated to be admitted to a Neonatal Intensive Care Unit has been summarized by Harrington et al.10 This is a retrospective experience that yielded 94 infants based on either population data or cohort studies spanning 35 years with the earliest report using infants born between 1965–1975 and the most recent based on infants born between 1991–2004;[10, 22–28] Four of the eight reports are based on infants born in the 1980s and 1990s and only the data from Harrington10 includes infants born beyond 2000. Of the 94 infants identified with an Apgar of 0 at 10 minutes, 78 died, 12 survived with severe or moderate disability, one had a mild disability and 3 were lost to follow-up. Thus, death or disability (moderate or severe in extent) occurred in 95% of infants with an Apgar score of 0 at 10 minutes. The earlier observational studies within Harrington et al(9) (should be ref 10) form the basis for the ILCOR recommendation regarding discontinuation of resuscitation after 10 min of adequate resuscitation.7(change to ref 9) None of the previous reports included infants subjected to hypothermia which is being increasingly

used in these infants. Important limitations to the outcome data for infants with an Apgar of 0 at 10 minutes includes retrospective data collection, inclusion of preterm and term infants, unclear exclusion criteria, variable duration of outcome, lack of consistency in outcome measures, and difficulty in determining the adequacy of resuscitation.

In contrast, the results from the NICHD Neonatal Research Network hypothermia trial differ for the outcome of infants with an Apgar of 0 at 10 minutes. Although death or disability is very high (76%, Table I) similar to retrospective reports, the outcome of survivors were more heterogeneous; 6 of the 13 survivors either had a mild or absent disability at an 18–22 month assessment. The unadjusted outcome of infants with an Apgar of 0, 1 or 2 at 10 minutes appears similar (Table I) although an Apgar of ≤ 2 in the CART analysis is a cut point for death or disability only in the infants undergoing hypothermia. These observations are based upon a large contemporary cohort of infants with a uniform gestational age (≥ 36 weeks), prospective data collection, and a standardized, rigorous follow-up program with examiners trained to reliability, uniform assessment tools and a low attrition rate at follow-up.

The decision of when to terminate resuscitative efforts for newborn infants after birth is difficult. The outcome of infants with an Apgar score of 0 at 10 minutes derived from reports over the past 20 years appears to have been the best available data to guide resuscitative efforts. The results of this analysis adds new observations to the outcome of infants with an Apgar of 0 at 10 minutes and raises concern regarding the ILCOR/NRP recommendation to consider discontinuation of resuscitation if there are no signs of life. These new observations are based on infants that qualified for the NICHD Neonatal Research Network randomized trial of therapeutic hypothermia and may not be applicable to all infants with an Apgar score of 0 at 10 minutes. Data are not available on the adequacy of resuscitative efforts or the number of infants admitted to neonatal intensive care units that were deemed too sick to approach for study entry or died prior to enrollment. These factors may result in an over-estimate of the rate of intact survival among infants with an Apgar score of 0 at 10 minutes. In addition the assessment of neurodevelopmental outcome may change later in childhood.[29] Nevertheless, caution is warranted before adopting a defined time interval to guide the duration of resuscitation.

Abbreviations

HIE	Hypoxic-Ischemic Encephalopathy
CPR	cardiopulmonary resuscitation
NRP	Neonatal Resuscitation Program
CART	Classification and Regression Trees
OR	odds ratios
CI	confidence intervals

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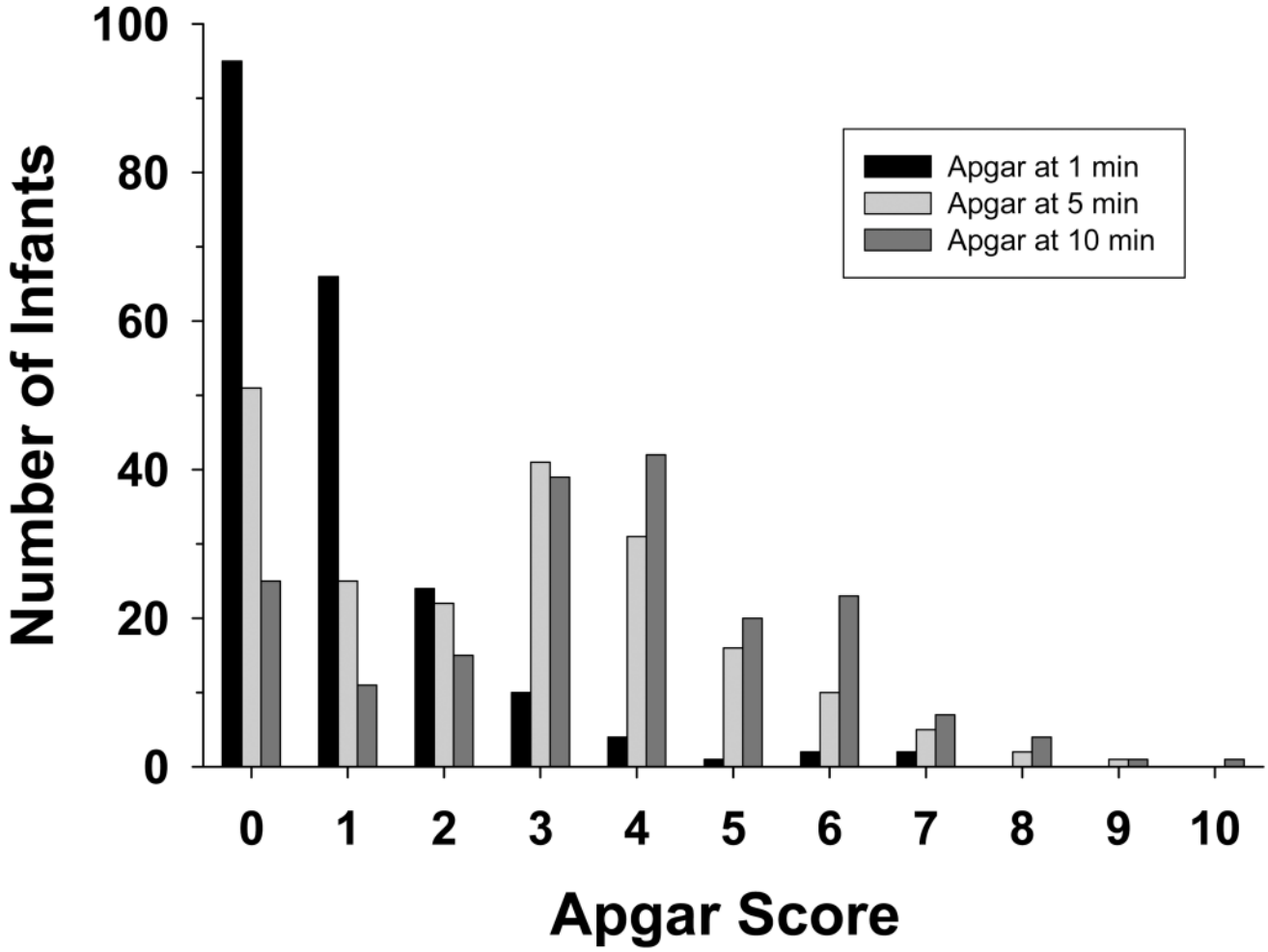

Figure 1. Distribution of Apgar Scores at 1, 5 and 10 Minutes

The distribution of Apgar scores at 1, 5 and 10 minutes among infants in the trial. Apgars at 1, 5 and 10 minutes are represented by the black, light gray and dark gray columns, respectively.

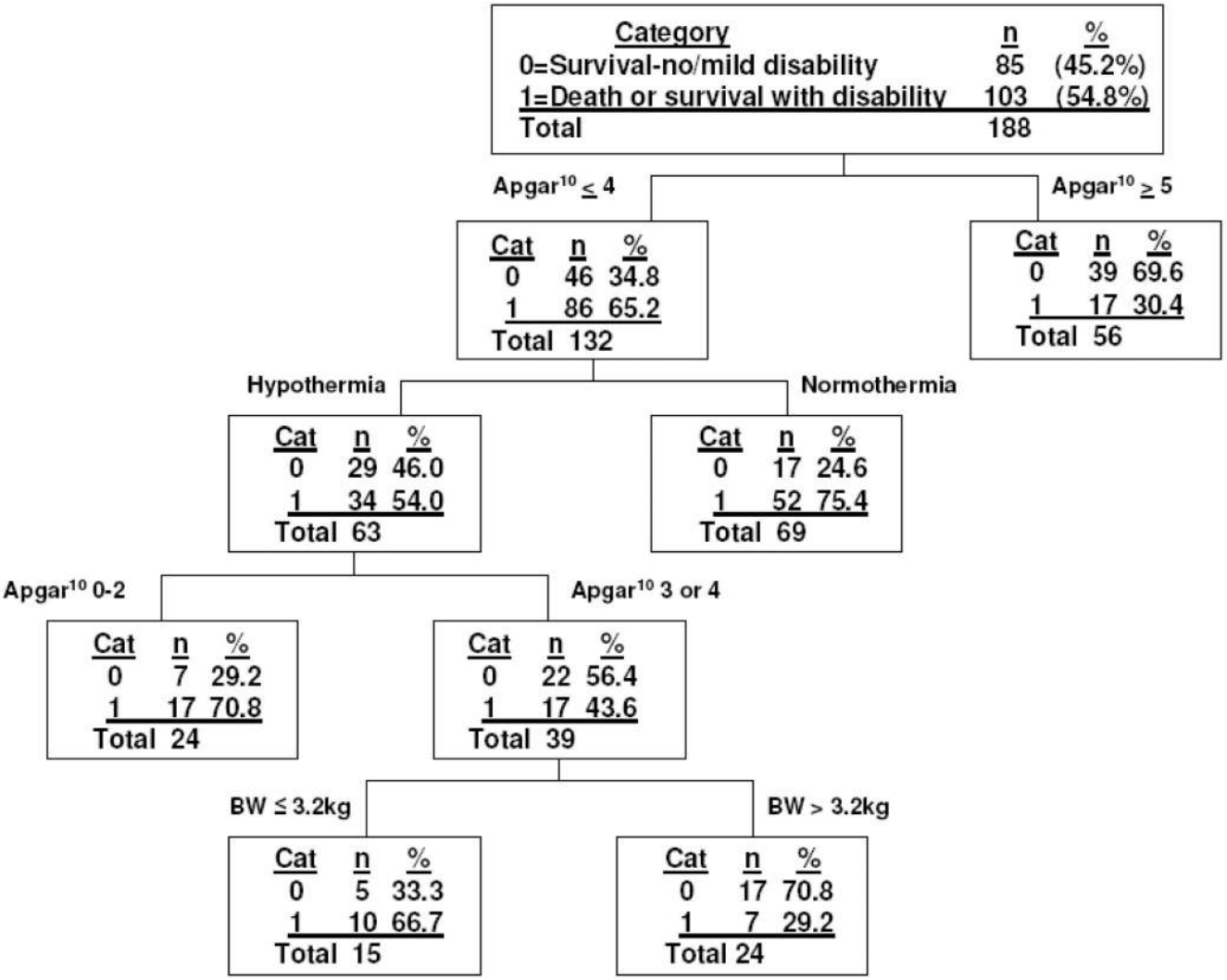

Figure 2. Classification and Regression Tree (CART) Analysis for Death or Moderate/Severe Disability

CART model for death or moderate/severe disability. The outcome of death or moderate/severe disability at 18–22 months is predicted by the decision tree. In each node (rectangle) the category 0 or 1 refers to the absence or presence of death or disability, respectively. The n and % refer to the number and percent of infants in each category. $Apgar^{10}$ is the 10 minute Apgar score and BW is birth weight.

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Table I

Outcome of Infants by Apgar Score at 10 Minutes

Apgar Score	n	Death or Moderate/Severe Disability n (%)	Death n (%)	Survivors n	Moderate/Severe Disability n (%)†
0	25	19 (76)	12 (48)	13	7 (54)
1	11	9 (82)	7 (64)	4	2 (50)
2	15	12 (80)	7 (47)	8	5 (63)
3	39	24 (62)	15 (39)	24	9 (38)
4	42	22 (52)	11 (26)	31	11 (36)
5	20	8 (40)	3 (15)	17	5 (29)
6	23	7 (30)	4 (17)	19	3 (16)
7–10*	13	2 (15)	0 (0)	13	2 (15)

*Infants with 10 minute Apgar of 7–10 are grouped due to the small number

†Represents percent of survivors

Table II

Association Between 10 Minute Apgar Score and Outcome

Outcome*	10 Min Apgar OR (95% CI) †	Covariates OR (95% CI)	Area Under the Curve
Death or Disability (moderate/severe)	1.45 (1.22–1.72)	Tx, 0.44 (.23–.83)	0.74
Death	1.42 (1.19–1.69)	Tx, 0.50 (.25–.97)	0.72
Moderate/Severe Disability	1.30 (1.06–1.58)	None	0.67

*Adjusted for birth weight, gestational age, gender, treatment group (Tx), and out-born

†OR=odds ratio CI=confidence interval