The Impact of Neurobehavior on Feeding Outcomes in Neonates with Congenital Heart Disease

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Objective To evaluate the association between neonatal neurobehavioral state and oral feeding outcomes following congenital heart disease (CHD) surgery.

Study design This single center retrospective cohort study described neonates undergoing cardiac surgery evaluated perioperatively with the Neonatal Intensive Care Unit Network Neurobehavioral Scale (NNNS). We compared NNNS attention scores, which evaluates neonates' ability to orient and fixate on stimuli, with the feeding outcomes percentage of feeds taken orally at discharge and time to reach full oral feeds using regression analyses. Models were constructed for both preoperative and postoperative NNNS evaluations.

Results Between August 2015 and October 2017, 124 neonates underwent 89 preoperative and 97 postoperative NNNS evaluations. In multivariable Cox regression, higher preoperative NNNS attention scores were associated with a shorter time to achieve full oral feeds (hazard ratio 1.4; 95% CI 1.0–2.0; P = .047). This relationship was not seen for post-operative NNNS attention scores or percentage of oral feeds at discharge. Depending on the model, younger age at surgery, increased ventilator days, increased length of stay, and single or 2-ventricle anatomy with aortic arch obstruction were associated with lower percentage of oral feeds at discharge and/or delay in full oral feeds.

Conclusions Higher neonatal attention before cardiac surgery is associated with improved feeding outcomes. Prospective assessment of neonatal neurobehavioral state may be a novel approach to predict and target interventions to improve feeding outcomes in CHD. Future studies should examine the impact of intrinsic neurodevelopmental delay vs environmental adaptation on the neurobehavioral state of neonates with CHD. *(J Pediatr 2019;214:71-8)*.

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Delay in achieving full oral feeds following neonatal cardiac surgery is associated with increased hospital length of stay (LOS), poor weight gain, and parental stress.[1-4] Neurodevelopmental delay in neonates with congenital heart disease (CHD) is one of many factors contributing to their difficulty achieving full oral feeds.[5,6] In premature infants, abnormalities in neonatal neurobehavior are associated with worse long-term feeding outcomes.[7] Neonates undergoing CHD surgery also have abnormal neurobehavior.[8,9] Although individual neurobehavior varies significantly among neonates, poor attention has emerged as a hallmark of neurobehavioral state in neonates with CHD.[8,10] The impact of neonatal attention on feeding outcomes among infants undergoing CHD surgery has not been studied.

The Neonatal Intensive Care Unit Network Neurobehavioral Scale (NNNS) is a standardized assessment that evaluates neonatal neurobehavior across 12 subdomains, including attention.[11] The NNNS assessment evaluates neonates' neurologic function, behavior, and level of stress.[11] Our study focused on neonatal attention, which is the ability for a neonate to alert, fixate, and focus on an object.[12] There is a significant relationship between the regulation and organization associated with neonatal neurobehavior and successful oral feeding.[13] Thus, we hypothesized that neonates undergoing cardiac surgery who have difficulty achieving full

CHD	Congenital heart disease
HR	Hazard ratio
LOS	Length of stay
MI	Multiple imputation
NNNS	Neonatal Intensive Care Unit Network Neurobehavioral Scale

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oral feeds will also have abnormal NNNS scores, particularly in the area of attention. The objective of this study was to determine the association between preoperative and postoperative NNNS attention scores and 2 feeding outcomes—the percent oral feeds at hospital discharge and time to achieve full oral feeds after cardiac surgery.

Methods

This was a single-center, retrospective cohort study. Neonates were included if they required cardiac surgery before 30 days of age with cardiopulmonary bypass or a staged surgery off bypass for single-ventricle palliation and received at least 1 perioperative (preoperative or postoperative) NNNS evaluation between August 2015 and October 2017. Neonates who died before discharge or had a congenital upper airway or neurologic anomaly were excluded. Individuals lost to follow-up after hospital discharge were excluded from analyses regarding time to full oral feeds. This study was approved by the University of Utah Institutional Review Board (IRB_00099252).

The NNNS development and methods have been previously described.[12,14] The NNNS uses a standardized behavioral evaluation to determine 12 subdomain scores plus a stress scale that describe an infant's situational neurobehavior. Attention scores evaluate neonates' ability to alert, fixate on visual and auditory stimuli, and maintain attention to these stimuli. A lower score equates to a lower and abnormal level of attention. Infants who cannot maintain a calm and awake state cannot be scored.[12] We have previously described our clinical utilization of the NNNS.[8] Briefly, licensed physical, speech, and occupational therapists certified in the NNNS assessment formally evaluate almost all (~90%) neonates undergoing CHD surgery at our institution. The assessment is performed on all clinically stable neonates before cardiac surgery and just prior to hospital discharge. Primary drivers for missing NNNS assessments were not objectively collected, but, anecdotally, most often included lack of therapists' availability (ie, because of holiday and weekend breaks) or clinical instability of the patient preoperatively.

CHD diagnoses were grouped into 4 categories: (1) single ventricle with aortic arch obstruction; (2) single ventricle without aortic arch obstruction; (3) 2 ventricles with aortic arch obstruction; and (4) 2 ventricles without aortic arch obstruction. Prematurity was defined as <37 weeks of gestational age. Genetic syndromes were determined through genetic testing or required a clinical diagnosis by a geneticist. Gastrointestinal complications included documentation of necrotizing enterocolitis, intestinal obstruction, or volvulus during the neonatal hospitalization. Neurologic complications included perioperative stroke or seizure during the neonatal hospitalization. Ventilator days included the number of days intubated postoperatively. Extubation failure was defined as re-intubation ≥24 hours after extubation. The percentage of oral feeds taken at hospital discharge and time to achieve 100% oral feeds were identified through retrospective chart review. When calculating time to achieve 100% oral feeds, day zero was the date of sternal closure. If a subject reached 100% oral feeds (with goal feeds predetermined by a dietician) after hospital discharge, the date documented in any clinic note or the date of the first clinic visit confirming full oral feeds was used. Infants who were not taking full oral feeds by the end of the chart review were censored from the date of the last clinic note.

At our institution, neonates admitted perioperatively for cardiac surgery are assigned to 1 of 2 feeding protocols, depending on if they have single ventricle or 2-ventricle cardiac anatomy, that determine their pre- and postoperative feeding plans. These protocols have previously been published.[15,16] Notable components of the protocols include mandatory feeding evaluations by licensed therapists and swallow studies on all neonates undergoing aortic arch reconstruction.

Statistical Analyses

Descriptive statistics included median with interquartile range (IQR) and count (%). Standardized NNNS were constructed by subtracting the means of published normative scores and dividing by the normative standard deviation (SD), with the exception of hypertonia because of a lack of normative values.[17]

Because the proportion of oral feeds at discharge included zero, with many patients not taking any oral feeds at discharge, zero-inflated beta-regression models were applied.[18] Values of one (indicating 100% oral feed) were also present but rare. Because of our limited sample size, we chose to transform the non-zero values for analysis by (y[n-1]+0.5)/n, where y is the proportion of oral feeds at discharge and n is the number of non-zeros.[19] The first part of the model included only patients who were feeding orally at discharge, and their outcomes were modeled by a beta distribution with a logit link function. The exponentiated results were the odds ratio (OR) of converting to oral feeds at discharge for each one point increase in NNNS attention score. The second part modeled oral feeds at discharge being 0%, as opposed to >0%, for all patients in our cohort using logistic regression with a logit link function. The exponentiated coefficients of this model were interpreted as the odds of not taking any oral feeds at discharge for each one point increase in NNNS attention score. We implemented both univariable and multivariable models using the GAMLSS package in R (The R Foundation, Vienna, Austria),[20] where the latter compared NNNS attention scores with proportion of oral feeds at discharge adjusting for sex, genetic syndrome, age at surgery, cardiac anatomy, and ventilator days. The variables prematurity, hospital length of stay (LOS), extubation failure, preoperative feeds, development of a gastrointestinal complication, and development of a neurologic complication were assessed in univariable analysis but were not included in the multivariable models due to the total number of variables that could be included with this sample size, their very low occurrence in our cohort, and/or their lack of significance in the univariable analyses. These covariates were selected because they have previously been found to correlate with neurodevelopment and/or neonates' ability to orally feed.[1,21-24]

For the second feeding outcome, Cox proportional hazard regression models were used to evaluate the association between attention scores and time (days) to achieve full oral feeds. Hazard ratios (HRs) and 95% CIs for achieving full oral feeds were reported from these models, where HRs >1 indicated improved feeding outcomes. Alternatively, HRs can be interpreted as an increase (HR <1) or decrease (HR >1) in time to achieving full oral feeds. For example, a HR = 0.75 corresponds to a 25% reduced risk of achieving full oral feeds or a 1/0.75 = 33% increase in time to achieving full oral feeds.[25] Again, univariable and multivariable models were constructed, including the same variables used for the previous feeding outcome.

One difficulty with the outcome modeling described above was a high rate (30%) of nonrecordable preoperative NNNS attention scores. Most of the other NNNS subdomain scores were available in these cases (≤1% missing data), and some were correlated with NNNS attention scores (Pearson correlations up to −0.85, **Table I**; available at www.jpeds.com). As a result, our primary analysis used multiple imputation (MI) to address the high missing data in NNNS attention scores. As supportive data, we excluded those without an attention score (**Table II**; available at www.jpeds.com), and we used a dichotomized variable for attention, where absent attention scores and standardized attention score <-2.5 were combined into 1 variable indicating low attention scores (**Table III**; available at www.jpeds.com).

Under the MI approach, we simulated 10 complete observation data sets. Missing attention scores and missing values from other variables were simulated based on other NNNS subdomain scores, patient characteristics, covariates in our outcome models, use of bypass, bypass time, and preoperative intubation category. Models were fit to each simulated data set, and results of estimates, 95% CIs, and *P* values were pooled using the Rubin method.[26] Generalized R-squared values were averaged across the 10 simulated data sets and reported as the overall measure of goodness-of-fit for each model.

Statistical analyses were conducted in R v 3.2.4 (The R Foundation, Vienna, Austria).[20] All tests were 2-tailed, and significance was assessed at $P < .05$.

Results

Between August 2015 and October 2017, 173 neonates with CHD were admitted to the cardiac intensive care unit. A total of 49 patients were excluded due to not undergoing surgery before 30 days of life (n = 28), death prior to discharge (n = 12), neurologic or airway anomaly (n = 8), or missing feeding data (n = 1). Of the 124 remaining patients in the analytic cohort, 89 underwent preoperative and 97 underwent postoperative NNNS evaluations. About 30% (27 of 89) of the neonates with preoperative NNNS assessments and 9% (9 of 97) with postoperative assessments were insufficiently attentive to achieve a recordable attention score, thereby requiring MI for attention scores. The percent of oral feed at discharge was not documented in 5 patients with postoperative NNNS assessments. Two patients with preoperative NNNS assessments and 9 with postoperative assessments were lost to follow-up after hospital discharge. These patients with missing feeding data were excluded from the survival analyses pertaining to the respective feeding outcomes. Of the 124 subjects, 49 were male (40%). Our cohort racially identified as (not mutually exclusive) 97% Caucasian, 17% Hispanic/Latino/Spanish origin, 2% American Indian or Alaska Native, and 2% Asian. Nearly 70% of the patients had 2-ventricle anatomy; 36% had 2 ventricles without aortic arch obstruction, and 32% had 2 ventricles with arch obstruction. Eight percent of the 124 patients had single ventricle without aortic arch obstruction, and 23% had single ventricle with aortic arch obstruction. The median age at surgery was 7.0 (IQR 5-10, total range 0-29) days, with a median of 130 (IQR 104-148) minutes on bypass. The median postoperative ventilator time was 4.9 (IQR 3.7-6.3, total range 0.6-24) days, and the median total LOS was 23 (IQR 18-32, total range 7-104) days. Nearly one-half of the subjects were fed by mouth preoperatively (preoperative cohort: 39%, postoperative cohort: 48%).

Most infants were taking fewer than 50% of their feeds orally at discharge, with nearly 40% of infants taking no oral feeds at hospital discharge (**Figure 1**, A). The median and range of time to achieve full oral feeds was 32 (0-540) and 36 (1-540) days for the cohorts with pre- and postoperative NNNS assessments, respectively. Approximately 70% of the cohort was taking all feeds orally within 100 days. Six neonates were potential outliers requiring ≥365 days to achieve full oral feeds (**Figure 1**, B). Five of the 6 outliers had nonrecordable or consistently low pre- and postoperative attention scores (z score <-2, data not shown). In addition, 33% of these outliers had a genetic syndrome.

Feeding outcomes ranged widely among neonates, with some patterns based on cardiac anatomies (**Table IV**; available at www.jpeds.com). Although the ranges appeared to include outliers in all anatomic groups, the IQR for percent oral feeds at discharge was generally lower in the setting of arch obstruction, and the time to achieve full oral feeds was generally higher in the single ventricle groups.

The lethargy scores were informative for imputing attention scores, with a correlation of $r = -0.85$ ($P < .001$) between preoperative NNNS attention scores and preoperative NNNS lethargy scores (and $r = -0.67$, $P < .001$ among the same postoperative scores), (**Table I**). NNNS nonoptimal reflexes and hypotonic scores also correlated with preoperative attention scores (**Table I**). The relationship between NNNS attention and NNNS lethargy are shown in **Figure 2** (available at www.jpeds.com), where the imputed values for NNNS attention scores (for 2 randomly selected data sets among the 10 that were imputed) were well aligned with the observed lethargy scores. NNNS subdomains that were predictive of nonobtainable NNNS attention included habituation, regulation, nonoptimal reflexes, and excitability. NNNS

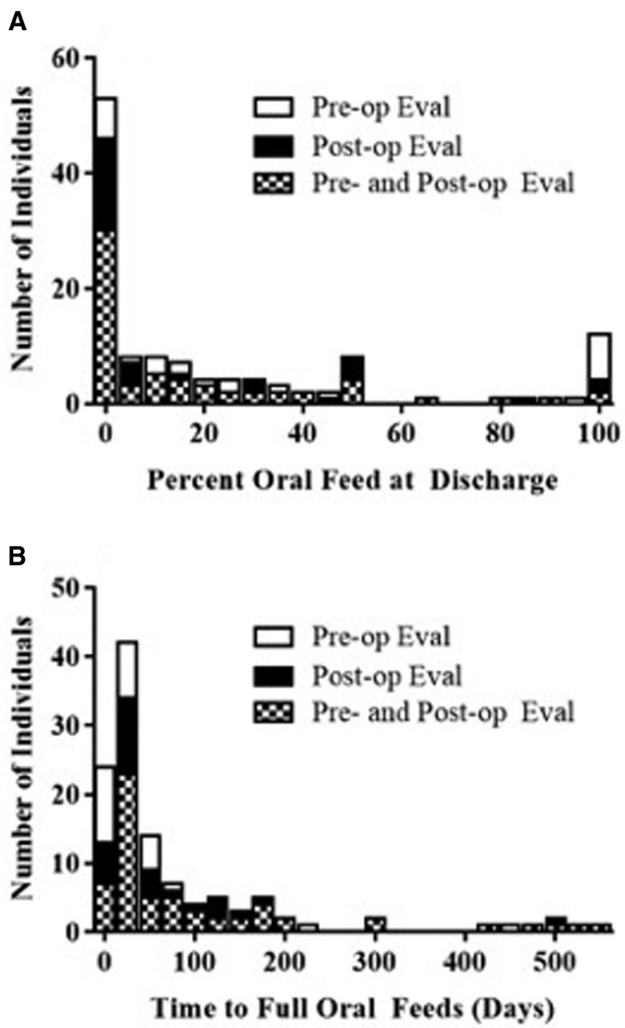

Figure 1. Feeding outcomes. Distribution of outcomes is shown, with delineation based on whether NNNS assessment was done preoperatively (*open*), postoperatively (*closed*), or at both time points (*checkered*). Histograms show the distribution of percent oral feeds taken at **A,** the time of discharge and **B,** the time to reach 100% oral feeds in days. The majority of patients with nonrecordable NNNS attention scores took 50% or fewer feeds at discharge. Most neonates achieved full oral feeds within 100 days of chest closure, but 6 patients took >365 days to achieve full oral feeds.

habituation was lower among neonates with nonobtainable attention scores in the preoperative assessments (P = .006) but higher among these infants in the postoperative assessments (P = .029). NNNS regulation was lower among infants with missing attention scores in both the pre- and postoperative assessments (both P < .05). NNNS nonoptimal reflexes scores were higher among infants with nonobtainable attention scores in both the pre- and postoperative assessments (both P < .05). Finally, the excitability scores were higher in patients with nonobtainable attention scores in the postoperative (P < .001) but not the preoperative assessments. Because both correlation with NNNS attention and prediction of NNNS attention missing data were available from the other NNNS subdomains, which had minimal missing data, MI was the primary analysis strategy. Results from alternative approaches, including complete case analysis and a dichotomization strategy for nonobtainable NNNS attention, are shown in Tables II and III.

The NNNS score distribution of our study sample appeared different from scores of healthy term infants, particularly in the areas of attention, nonoptimal reflexes, and response to stress (Figure 3). Standardized scores were comparable in pre- and postoperative NNNS assessments.

In the zero-inflated beta-regression model using preoperative NNNS assessments, attention scores were not associated with percent of oral feeds at discharge (Table V). In the multivariable logistic regression portion of this model, the odds of not orally feeding at discharge among those who had single ventricle with arch obstruction was 9.30 times the odds for patients with 2 ventricles without arch obstruction. Similarly, the odds of not orally feeding at discharge among those who had 2 ventricles with arch obstruction was 5.82 times the odds for patients with 2 ventricles without arch obstruction. In the univariable analysis of the beta-regression portion of the model, for every 1 ventilator day increase, infants had a 17% decrease (OR = 0.83, 95% CI 0.73, 0.95, P value = .008) in the odds of achieving full oral feeds by discharge. This finding was retained in the multivariable model, where the odds of achieving full oral feeds by discharge decreased 15% (OR = 0.85, 95% CI 0.73, 0.98; P value = .028) for each 1 ventilator day increase.

The results of the zero-inflated beta-regression model for the postoperative NNNS assessments were similar to results with the preoperative evaluations (Table V). Postoperative attention scores were not associated with achieving oral feeds by discharge. In the univariable beta-regression portion of the model, every 1 ventilator day increase was associated with 16% decreased odds (OR = 0.84, 95% CI 0.73, 0.97, P value = .02) of achieving full oral feeds by discharge. This association was not significant in the multivariable analysis. In the logistic part of the zero-inflated beta model, ventilator days was significant in both univariable and multivariable models, where every 1 ventilator day increase was associated with higher odds of 0% oral feeds (OR = 1.38, 95% CI 1.09, 1.73, P value = .01). In both univariable and multivariable analyses, the cardiac anatomy of single ventricle with aortic arch obstruction was associated with higher odds of not taking oral feeds at discharge compared with the odds of 2 ventricles without aortic arch obstruction (OR = 5.75, 95% CI 1.79, 18.52, P value = .004).

In univariable and multivariable analyses, higher preoperative NNNS attention score was associated with a shorter time to achieve full oral feeds (Table VI, HR = 1.4, 95% CI 1.0, 2.0, P value = .045). Similarly, in both univariable and

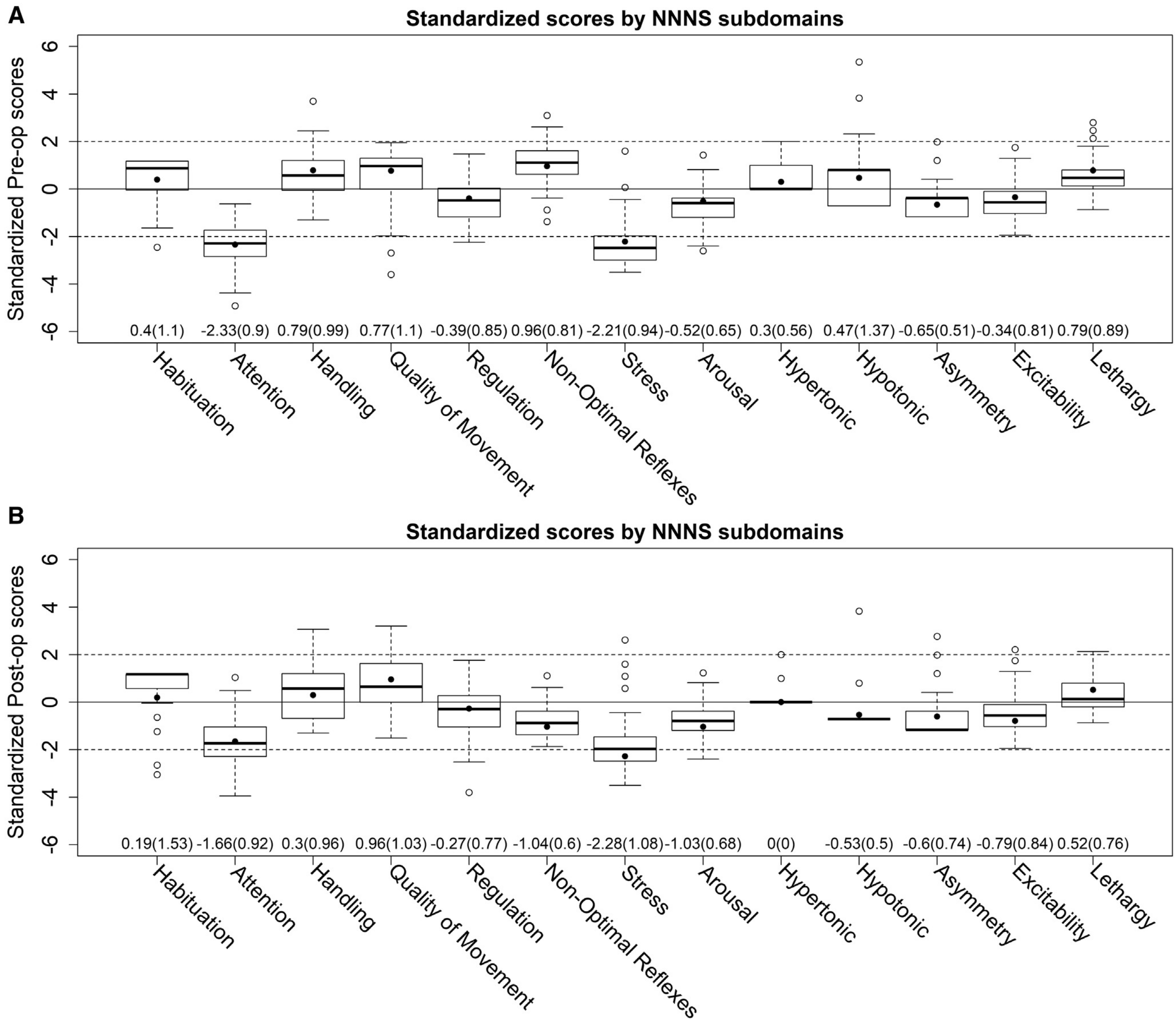

Figure 3. Normalized NNNS subdomain scores. Boxplots demonstrate the median values and interquartile ranges of the differences of our cohorts' **A,** preoperative and **B,** postoperative NNNS subdomain scores. The attention, nonoptimal reflexes, and stress scores are noticeably distributed away from the standardized normative range. (Hypertonic score was not standardized because normative summaries were not available.)

multivariable analyses, older age at surgery was associated with shorter time to achieve full oral feeds (HR = 1.8, 95% CI 1.3, 2.6, *P* value = .001). Infants with increased ventilator days took longer to achieve full oral feeds (HR = 0.8, 95% CI 0.7, 0.9, *P* value = .003).

Postoperative NNNS attention scores were not associated with time to achieve full oral feeds (Table VI). Each 1 day increase in LOS was associated with a 20% reduction in achieving full oral feeds (HR = 0.8, 95% CI 0.7, 0.9, *P* value = .024). Relative to 2 ventricles without arch obstruction, 2 ventricles with arch obstruction was associated with a 50% decrease in achieving full oral feeds (HR = 0.5, 95% CI 0.3, 0.99, *P* value = .045) in the univariable but not the multivariable analysis.

Discussion

Multiple factors contribute to a neonate's ability to orally feed. Oral motor strength, coordination, perioperative complications, medical comorbidities, and neurobehavioral state are among the potential determinants of feeding success.[27] Similar to our previous study, we found relatively low attention scores in neonates before and after cardiothoracic surgery.[8] A low NNNS attention score may be seen in individuals who are physiologically less stable.[28] However, it may be indicative of intrinsic pathology. For example, low NNNS attention scores identified in presumed healthy term neonates were associated with abnormal social and communicative behavior at 5 years of age.[29] Similarly, the

Table V. Percent oral feeds at discharge

	Univariable OR (95% CI)				Multivariable OR (95% CI) (Generalized R^2 0.32-0.33)			
	Odds of oral feed when oral feed >0		Odds of 0% oral feeds		Odds of oral feed when oral feed >0		Odds of 0% oral feeds	
Predictors	Pre	Post	Pre	Post	Pre	Post	Pre	Post
Female	1.24 (0.65, 2.36)	0.97 (0.51, 1.83)	0.68 (0.27, 1.75)	0.70 (0.30, 1.67)	1.47 (0.74, 2.91)	1.28 (0.63, 2.58)	0.77 (0.25, 2.34)	0.52 (0.19, 1.45)
Genetic syndrome	0.55 (0.25, 1.24)	0.66 (0.31, 1.42)	1.52 (0.52, 4.44)	1.32 (0.49, 3.50)	0.49 (0.18, 1.35)	0.73 (0.30, 1.77)	1.38 (0.38, 5.04)	0.95 (0.27, 3.30)
Age at surgery (d)	1.04 (0.98, 1.10)	1.01 (0.93, 1.09)	***0.86***[*] ***(0.74, 0.99)***	0.98 (0.88, 1.08)	1.04 (0.98, 1.11)	1.04 (0.95, 1.14)	0.90 (0.77, 1.05)	0.97 (0.85, 1.11)
Single ventricle with arch obstruction	1.23 (0.47, 3.20)	0.81 (0.32, 2.06)	***12.96***[†] ***(3.01, 55.89)***	***5.75***[†] ***(1.79, 18.52)***	1.75 (0.66, 4.63)	1.28 (0.41, 3.99)	***9.30***[†] ***(1.97, 43.99)***	***5.95***[†] ***(1.60, 22.16)***
Single ventricle without arch obstruction	0.80 (0.26, 2.40)	1.01 (0.33, 3.12)	1.39 (0.12, 15.81)	1.72 (0.33, 8.91)	0.82 (0.27, 2.52)	0.77 (0.22, 2.64)	0.98 (0.07, 13.16)	2.29 (0.34, 15.62)
Two ventricles with arch obstruction	1.36 (0.66, 2.82)	1.04 (0.50, 2.16)	3.97 (0.96, 16.33)	2.03 (0.68, 6.05)	1.08 (0.52, 2.27)	0.92 (0.41, 2.02)	***5.82***[*] ***(1.25, 26.99)***	2.81 (0.79, 10.00)
Two ventricles without arch obstruction	reference	reference	reference	reference	reference	reference	reference	reference
NNNS attention score	1.18 (0.80, 1.72)	1.26 (0.85, 1.88)	0.75 (0.44, 1.26)	0.91 (0.58, 1.42)	1.13 (0.76, 1.69)	1.25 (0.80, 1.97)	0.75 (0.36, 1.56)	1.03 (0.60, 1.74)
Ventilator d	***0.83***[†] ***(0.73, 0.95)***	***0.84***[*] ***(0.73, 0.97)***	1.19 (0.97, 1.46)	***1.31***[*] ***(1.07, 1.60)***	***0.85***[*] ***(0.73, 0.98)***	0.85 (0.71, 1.02)	1.25 (0.94, 1.66)	***1.38***[†] ***(1.09, 1.73)***
Length of stay (d)	1.00 (0.98, 1.02)	0.98 (0.95, 1.01)	1.00 (0.97, 1.03)	1.03 (0.99, 1.06)	-	-	-	-
Extubation failure	1.07 (0.30, 3.84)	0.59 (0.20, 1.69)	1.71 (0.36, 8.21)	1.41 (0.38, 5.26)	-	-	-	-
Gastrointestinal complication	0.50 (0.18, 1.42)	0.61 (0.23, 1.62)	0.34 (0.04, 2.96)	0.42 (0.08, 2.22)	-	-	-	-
Neurologic Complication	0.44 (0.13, 1.50)	0.61 (0.16, 2.32)	0.53 (0.06, 4.95)	0.44 (0.04, 4.38)	-	-	-	-
Premature	0.53 (0.20, 1.40)	0.50 (0.17, 1.44)	0.93 (0.22, 3.88)	1.75 (0.49, 6.20)	-	-	-	-
Preoperative oral feeds	1.05 (0.34, 3.19)	1.26 (0.66, 2.39)	0.45 (0.12, 1.71)	***0.41***[*] ***(0.18, 0.94)***	-	-	-	-

Univariable and multivariable zero-inflated beta regression models for percentage of oral feeds at discharge among patients with preoperative ("Pre," n = 89) and postoperative ("Post," n = 97) NNNS assessments.
*$P < .05$.
†$P < .01$.
Values in bold and italics are statistically significant.

association between preoperative NNNS attention scores and time to full oral feeds in our cohort highlights the impact of neonates' intrinsic abnormal neurobehavior on feeding outcomes. We suspected that preoperative NNNS assessments were more indicative of neonates' intrinsic neurobehavioral state because they were obtained only in clinically stable neonates prior to surgery and subsequent medical complications. The intra- and postoperative extrinsic factors and their effects on neonatal neurobehavior likely have greater impact on the postoperative NNNS assessments and may be why postoperative attention was not associated with oral feeding outcomes.

Although the number of nonobtainable attention scores increased the complexity of our analyses, the association of the missing scores with other risk factors and subdomain scores provides insight into what impacts neurobehavioral state in patients with CHD. During the NNNS evaluation, infants must be sufficiently alert to achieve an attention score.[12] We suspected that neonates with nonobtainable attention scores were more sedate; thus, not being able to assess attention was a marker of extremely low attention. Contrary to our hypothesis, however, most of the imputed attention scores were near the median NNNS attention score (Figure 2). Thus, missing attention scores may not indicate simply low attention.

To better understand the distribution of and ability to measure attention, we compared the measured and imputed NNNS attention scores as well as inability to measure attention with the other subdomain scores. Both the measured and imputed attention scores were well aligned with the observed lethargy scores (Figure 2). However, lethargy scores were not predictive of the nonobtainable NNNS attention scores, further supporting the conclusion that nonobtainable attention was not simply very low attention. NNNS subdomain scores that were predictive of nonobtainable attention scores included lower regulation and higher nonoptimal reflexes in both the preoperative and postoperative cohorts.

Notably, excitability scores were higher in patients with nonobtainable attention scores in the postoperative assessments only. We suspect, therefore, that high-excitability and its impact on neonatal attention is a byproduct of neonates' adaptation to the stress of surgical recovery and the disruptive, highly stimulating environment of postoperative care. Such adaptations and perioperative insults may also have a larger impact on the immediate feeding outcome of

Table VI. Time to 100% oral feeds

	Preoperative (n = 89)				Postoperative (n = 97)			
	Univariable		Multivariable (Generalized R^2 = 0.29)		Univariable		Multivariable (Generalized R^2 = 0.17)	
Predictors	HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Female	0.8 (0.5, 1.3)	36	0.7 (0.4, 1.4)	.33	0.7 (0.4, 1.1)	.14	0.8 (0.5, 1.5)	.54
Genetic syndrome	0.6 (0.3, 1.1)	.09	0.5 (0.2, 1.1)	.07	0.6 (0.3, 1.2)	.14	0.7 (0.3, 1.4)	.34
Age at surgery (wk)	***1.6 (1.1, 2.2)***	***.007***	***1.8 (1.3, 2.6)***	***.001***	1.2 (0.8, 1.7)	.37	1.2 (0.8, 1.8)	.43
Single ventricle without arch obstruction	0.8 (0.3, 1.8)	.55	1.1 (0.4, 2.9)	.92	0.7 (0.3, 1.6)	.45	0.6 (0.2, 1.4)	.22
Single ventricle with arch obstruction	0.6 (0.3, 1.1)	.08	0.9 (0.4, 1.9)	.75	0.6 (0.3, 1.1)	.09	0.6 (0.3, 1.1)	.09
Two ventricles with arch obstruction	0.8 (0.5, 1.5)	.57	0.8 (0.4, 1.6)	.58	***0.5 (0.3, 0.99)***	***.045***	0.5 (0.3, 1.0)	.054
Two ventricles without arch obstruction	reference	-	reference	-	reference	-	reference	-
NNNS attention score	***1.4 (1.0, 2.0)***	***.047***	***1.4 (1.0, 2.0)***	***.045***	1.1 (0.9, 1.5)	.40	1.0 (0.8, 1.4)	.90
Ventilator days	***0.8 (0.7, 0.9)***	***.003***	***0.8 (0.7, 0.9)***	***.002***	0.9 (0.9, 1.0)	.24	0.9 (0.9, 1.1)	.33
Length of stay (wk)	***0.8 (0.7, 1.0)***	***.035***	-	-	***0.8 (0.7, 0.9)***	***.024***	-	-
Extubation failure	0.5 (0.2, 1.3)	.17	-	-	0.5 (0.2, 1.2)	.13	-	-
Gastrointestinal complication	0.5 (0.2, 1.4)	.17	-	-	0.8 (0.3, 1.8)	.55	-	-
Neurologic complication	0.6 (0.2, 1.5)	.26	-	-	0.7 (0.2, 2.1)	.48	-	-
Premature	0.5 (0.3, 1.2)	.13	-	-	0.7 (0.3, 1.5)	.37	-	-
Preoperative oral feeds	1.6 (1.0, 2.6)	.07	-	-	1.2 (0.8, 2.0)	.40	-	-

Univariable and multivariable Cox regression models for time to achieve 100% oral feeds (days) among patients with preoperative (left) and postoperative (right) NNNS assessments. Values in bold and italics are statistically significant.

percent feeds at discharge and a smaller impact on the long-term outcome of time to achieve full oral feeds. If this is true, we speculate that the postoperative neurobehavioral state is driven more by adaptations to the environment. Conversely, the preoperative state may be driven more by intrinsic neurodevelopment and not impacted by the perioperative course, hence, its association with the longer-term feeding outcome.

Many variables in the perioperative course likely contributed to neonates' feeding difficulties. We found a significant variability in the percentage of feeds taken orally at hospital discharge and the time to achieve full oral feeds. The short-term feeding outcomes in our study are similar to what is reported in other centers in the US.[30]

Our results support previous findings that increased ventilator days, younger age at surgery, and aortic arch obstruction all negatively impact neonates' ability to take oral feeds in the perioperative period. The association with increased ventilator days is a notable finding and may be related to the disuse of oropharyngeal muscles while an oral endotracheal tube was in place. Alternative strategies, such as nasotracheal intubation, may warrant future consideration. Anecdotally, some of the very delayed oral feeders had a genetic syndrome, a characteristic that has previously been associated with poor oral feeding.[31] Our sample size prohibited us from evaluating the association of attention with feeding outcomes while adjusting for all available covariates in our heterogeneous study population. Therefore, conclusions about whether the preoperative NNNS results are driven more by innate individual factors or severity of illness and the care it requires remain speculative.

We conducted multiple statistical analyses to account for the nonrecordable attention scores. Regardless of the statistical approach that was used, the primary result, an association between higher preoperative attention and faster time to 100% oral feeds, remained unchanged. However, we cannot exclude that our results may be biased. In addition to the nonrecordable attention scores, our study was limited by the retrospective nature and small sample size. The timing of NNNS assessments and inability to evaluate critically ill neonates preoperatively may have biased our study results. Infants with longer hospital stays could have received more inpatient therapy, potentially resulting in NNNS scores that are closer to standardized norms than infants with shorter hospital stays. A recent study comparing NNNS evaluations at birth and one-month of age among healthy neonates found that attention scores may increase with age.[32] Thus, a more attentive state among infants with prolonged hospitalizations may not truly reflect normal neurobehavior and may be another explanation of why we identified an association with preoperative attention scores but not postoperative scores obtained near hospital discharge. Future studies should consider using NNNS evaluations at multiple time points during the perioperative period and/or recording a reason for missing NNNS attention scores to better understand the impact of neonatal attention on feeding outcomes.

Continued assessment of neurobehavior in neonates with CHD will likely identify neonates at risk for poor oral feeding. With early identification of these patients, we hope to improve patient prognostication and guide individualized neurobehavioral interventions to improve feeding outcomes after CHD surgery. ■

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References

1. Indramohan G, Pedigo TP, Rostoker N, Cambare M, Grogan T, Federman MD. Identification of risk factors for poor feeding in infants with congenital heart disease and a novel approach to improve oral feeding. J Pediatr Nurs 2017;35:149-54.
2. Medoff-Cooper B, Irving SY, Hanlon AL, Golfenshtein N, Radcliffe J, Stallings VA, et al. The association between feeding mode, growth and developmental outcomes in infants with complex congenital heart disease at 6 and 12 months of age. J Pediatr 2016;169:154-9.e1.
3. Mangili G, Garzoli E, Sadou Y. Feeding dysfunctions and failure to thrive in neonates with congenital heart diseases. Pediatr Med Chir 2018;40.
4. Tregay J, Brown K, Crowe S, Bull C, Knowles R, Wray J. "I was so worried about every drop of milk" – feeding problems at home are a significant concern for parents after major heart surgery in infancy. Maternal Child Nutr 2017;13:e12302.
5. Khalil A, Suff N, Thilaganathan B, Hurrell A, Cooper D, Carvalho JS. Brain abnormalities and neurodevelopmental delay in congenital heart disease: systematic review and meta-analysis. Ultrasound Obstet Gynecol 2014;43:14-24.
6. Jadcherla SR, Vijayapal AS, Leuthner S. Feeding abilities in neonates with congenital heart disease: a retrospective study. J Perinatol 2009;29:112-8.
7. Crapnell TL, Rogers CE, Neil JJ, Inder TE, Woodward LJ, Pineda RG. Factors associated with feeding difficulties in the very preterm infant. Acta Paediatrica 2013;102:e539-45.
8. Hogan WJ, Winter S, Pinto NM, Weng C, Sheng X, Conradt E, et al. Neurobehavioral evaluation of neonates with congenital heart disease: a cohort study. Dev Med Child Neurol 2018;60:1225-31.
9. Massaro AN, Glass P, Brown J, Chang T, Krishnan A, Jonas RA, et al. Neurobehavioral abnormalities in newborns with congenital heart disease requiring open-heart surgery. J Pediatr 2011;158:678-681 e2.
10. Butler SC, Sadhwani A, Stopp C, Singer J, Wypij D, Dunbar-Masterson C, et al. Neurodevelopmental assessment of infants with congenital heart disease in the early postoperative period. Congenit Heart Dis 2019;14:236-45.
11. Tronick E, Lester BM. Grandchild of the NBAS: the NICU network neurobehavioral scale (NNNS): a review of the research using the NNNS. J Child Adolesc Psychiatr Nurs 2013;26:193-203.
12. Lester BM, Tronick EZ, Brazelton TB. The Neonatal Intensive Care Unit Network Neurobehavioral Scale procedures. Pediatrics 2004;113(3 Pt 2):641-67.
13. Thoyre SM, Shaker CS, Pridham KF. The early feeding skills assessment for preterm infants. Neonatal Netw 2005;24:7-16.
14. Lester BM, Tronick EZ. History and description of the Neonatal Intensive Care Unit Network Neurobehavioral Scale. Pediatrics 2004;113(3 Pt 2):634-40.
15. Furlong-Dillard J, Neary A, Marietta J, Jones C, Jeffers G, Gakenheimer L, et al. Evaluating the Impact of a feeding protocol in neonates before and after biventricular cardiac surgery. Pediatr Qual Saf 2018;3:e080.
16. Furlong-Dillard JM, Miller BJ, Sward KA, Neary AI, Hardin-Reynolds TL, Jeffers G, et al. The association between feeding protocol compliance and weight gain following high-risk neonatal cardiac surgery. Cardiol Young 20191-8. Forthcoming.
17. Fink NS, Tronick E, Olson K, Lester B. Healthy newborns' neurobehavior: norms and relations to medical and demographic factors. J Pediatr 2012;161:1073-9.
18. Ospina R, Ferrari SLP. Inflated beta distributions. Stat Pap 2010;51:111-26.
19. Smithson M, Verkuilen J. A better lemon squeezer? Maximum-likelihood regression with beta-distributed dependent variables. Psychol Methods 2006;11:54-71.
20. Team RC, ed. R: A language and environment for statistical computing. Vienna, Austria: R Foundation for Statistical Computing; 2018.
21. McKean EB, Kasparian NA, Batra S, Sholler GF, Winlaw DS, Dalby-Payne J. Feeding difficulties in neonates following cardiac surgery: determinants of prolonged feeding-tube use. Cardiol Young 2017;27:1203-11.
22. Einarson KD, Arthur HM. Predictors of oral feeding difficulty in cardiac surgical infants. Pediatr Nurs 2003;29:315-9.
23. Kogon BE, Ramaswamy V, Todd K, Plattner C, Kirshbom PM, Kanter KR, et al. Feeding difficulty in newborns following congenital heart surgery. Congenit Heart Dis 2007;2:332-7.
24. White-Traut R, Pham T, Rankin K, Norr K, Shapiro N, Yoder J. Exploring factors related to oral feeding progression in premature infants. Adv Neonatal Care 2013;13:288-94.
25. Barraclough H, Simms L, Govindan R. Biostatistics primer: what a clinician ought to know: hazard ratios. J Thoracic Oncol 2011;6:978-82.
26. Rubin DB. Multiple imputation for nonresponse in surveys, xxix. New York: Wiley; 1987. p. 258.
27. Edwards S, Davis AM, Ernst L, Sitzmann B, Bruce A, Keeler D, et al. Interdisciplinary strategies for treating oral aversions in children. JPEN J Parenter Enteral Nutr 2015;39:899-909.
28. Boukydis CF, Bigsby R, Lester BM. Clinical use of the Neonatal Intensive Care Unit Network Neurobehavioral Scale. Pediatrics 2004;113(3 Pt 2):679-89.
29. Bowers K, Khoury J, Sucharew H, Xu Y, Chen A, Lanphear B, et al. Early infant attention as a predictor of social and communicative behavior in childhood. Int J Behav Dev 2019;43:204-11.
30. Alten JA, Rhodes LA, Tabbutt S, Cooper DS, Graham EM, Ghanayem N, et al. Perioperative feeding management of neonates with CHD: analysis of the Pediatric Cardiac Critical Care Consortium (PC4) registry. Cardiol Young 2015;25:1593-601.
31. Cooper-Brown L, Copeland S, Dailey S, Downey D, Petersen MC, Stimson C, et al. Feeding and swallowing dysfunction in genetic syndromes. Dev Disabil Res Rev 2008;14:147-57.
32. Provenzi L, Olson K, Giusti L, Montirosso R, DeSantis A, Tronick E. NICU Network Neurobehavioral Scale: 1-month normative data and variation from birth to 1 month. Pediatr Res 2018;83:1104-9.

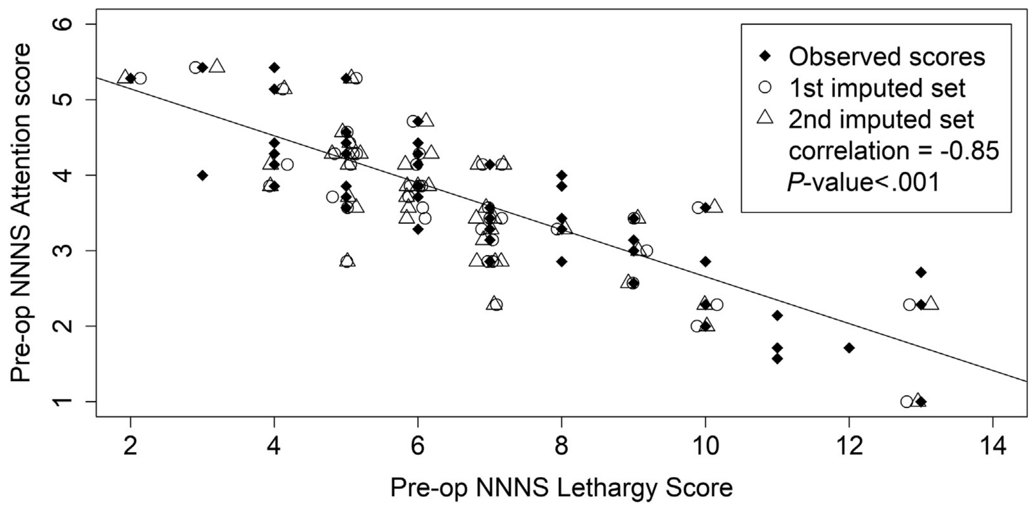

Figure 2. Attention, lethargy, and MI. Scatter plot of raw preoperative ("Pre-Op") NNNS attention scores and raw preoperative NNNS lethargy scores, including imputed attention scores from 2 randomly selected imputed data sets. Imputed attention scores were jittered on the x-axis.

Table I. Pairwise correlation of NNNS attention scores with other NNNS subdomain scores

	Preoperative evaluated NNNS attention score		Postoperative evaluated NNNS attention score	
NNNS subdomain score	**Correlation**	***P* value**	**Correlation**	***P* value**
NNNS habituation score	−0.21	.34	−0.26	.19
NNNS attention score	1	-	1	-
NNNS handling score	−0.07	.59	−0.11	.33
NNNS quality of movement score	−0.15	.26	0.05	.65
NNNS regulation score	0.23	.08	0	.96
NNNS nonoptimal reflexes score	***−0.4***	***.001***	0	.99
NNNS stress score	−0.18	.16	0.02	.86
NNNS arousal score	0	.98	0.2	.06
NNNS hypertonic score	0.07	.61	0	.97
NNNS hypotonic score	***−0.41***	***<.001***	−0.07	.5
NNNS asymmetry score	0.01	.96	0.16	.13
NNNS excitability score	−0.06	.63	0.07	.52
NNNS lethargy score	***−0.85***	***<.001***	***−0.67***	***<.001***

Pearson correlation was used to compare the NNNS attention scores and the remaining NNNS subdomain scores. We then used these results to estimate the nonrecordable NNNS attention scores using MI for our regression models.
Values in bold and italics are statistically significant.

Table II. Excluded subjects with missing attention

Predictors	Preoperative (n = 60) (Generalized R^2 = 0.38) HR (95% CI)	*P* value	Postoperative (n = 80) (Generalized R^2 = 0.14) HR (95% CI)	*P* value
Female	0.7 (0.4, 1.5)	.43	0.9 (0.5, 1.6)	.81
Genetic syndrome	0.3 (0.1, 1.1)	.07	0.5 (0.2, 1.2)	.14
Age at surgery (weeks)	***1.8 (1.2, 2.7)***	***.004***	1.1 (0.7, 1.6)	.78
Single ventricle without arch obstruction	1.3 (0.4, 3.9)	.67	0.6 (0.2, 1.7)	.38
Single ventricle with arch obstruction	0.7 (0.3, 1.8)	.53	***0.5 (0.2, 0.9)***	***.033***
Two ventricles with arch obstruction	1.3 (0.6, 3.1)	.48	0.6 (0.3, 1.1)	.10
Two ventricles without arch obstruction	reference	-	reference	-
NNNS attention score	***1.4 (1.0, 2.0)***	***.047***	1 (0.8, 1.3)	.98
Ventilator days	***0.8 (0.7, 0.9)***	***.001***	0.9 (0.8, 1.1)	.30

Multivariable Cox regression models for time to achieve 100% oral feeds (days) among patients with pre- and postoperative NNNS assessments. This is a conventional approach where patients without attention scores were excluded from the analyses.
Values in bold and italics are statistically significant.

Table III. Dichotomized attention

Predictors	Preoperative (n = 89) (Generalized R^2 = 0.26) HR (95% CI)	*P* value	Postoperative (n = 97) (Generalized R^2 = 0.13) HR (95% CI)	*P* value
Female	0.6 (0.2, 1.5)	.25	1.0 (0.6, 1.6)	.86
Genetic syndrome	0.7 (0.2, 2.6)	.59	0.7 (0.3, 1.4)	.30
Age at surgery (weeks)	1.4 (0.6, 3.5)	.45	1.2 (0.8, 1.8)	.52
Single ventricle without arch obstruction	2.8 (0.7, 11.3)	.15	0.5 (0.2, 1.3)	.17
Single ventricle with arch obstruction	1.0 (0.3, 3.4)	.96	***0.5 (0.2, 0.9)***	***.028***
Two ventricles with obstruction	1.3 (0.4, 4.3)	.65	0.5 (0.3, 1.0)	.07
Two ventricles without arch obstruction	reference	-	reference	-
High standardized NNNS attention score	***1.6 (1.1, 2.4)***	***.023***	1.0 (0.6, 1.7)	0.97
Ventilator days	0.9 (0.7, 1.2)	.45	0.9 (0.8, 1.0)	0.16

Multivariable Cox regression for achieving 100% oral feeds (days) among patients with pre- and postoperative NNNS assessments, in which standardized NNNS attention scores were dichotomized as high and low scores. A “high score” was defined as a standardized attention score ≥−2.5, while a “low score” included scores < −2.5 plus missing attention scores.
Values in bold and italics are statistically significant.

Table IV. Feeding outcomes among the cardiac anatomy cohorts

	Preoperative (n = 89)				Postoperative (n = 97)			
	Percent oral feeds at discharge		Time to full oral feeds		Percent oral feeds at discharge		Time to full oral feeds	
Cardiac anatomy	Median [%] (IQR)	Range (%)	Median [d] (IQR)	Range (d)	Median [%] (IQR)	Range (%)	Median [d] (IQR)	Range (d)
Single ventricle without arch obstruction	25 (2-46)	0-67	37 (17-245)	14-462	15 (0-43)	0-67	79 (25-180)	16-307
Single ventricle with arch obstruction	0 (0-11)	0-100	36 (24-170)	6-540	0 (0-7)	0-80	36 (26-160)	6-540
Two ventricles without arch obstruction	15 (2-38)	0-100	30 (10-62)	0-528	6 (0-47)	0-100	23 (13-61)	1-528
Two ventricles with arch obstruction	12 (0-36)	0-100	30 (13-66)	1-501	6 (0-22)	0-100	62 (18-127)	1-501

Distribution of percent oral feeds and time to full oral feeds, in days, among the four cardiac anatomy cohorts in the pre-operative and post-operative NNNS assessments.