Longitudinal B-Type Natriuretic Peptide Levels Predict Outcome in Infants with Congenital Diaphragmatic Hernia

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Objective To evaluate B-type natriuretic peptide (BNP) as a longitudinal biomarker of clinical outcome in infants with congenital diaphragmatic hernia (CDH).

Study design We conducted a retrospective study of 49 infants with CDH, classifying the cohort by respiratory status at 56 days, based on a proposed definition of bronchopulmonary dysplasia for infants ≥32 weeks' gestation: good outcome (alive with no respiratory support) and poor outcome (ongoing respiratory support or death). BNP levels were available at age 1-5 weeks. Longitudinal BNP trends were assessed using mixed-effects modeling. Receiver operating characteristic curves were generated to identify BNP cutoffs maximizing correct outcome classification at each time point. The time to reach BNP cutoff by outcome was assessed using Kaplan-Meier curves for weeks 3-5.

Results Twenty-nine infants (59%) had a poor outcome. Infants with a poor outcome were more likely than those with a good outcome to have liver herniated into the thorax (90% vs 50%; $P = .002$) and to undergo nonprimary repair (93% vs 35%; $P < .001$). Mixed-effects modeling demonstrated a differing decline in BNP over time by outcome group ($P = .003$ for interaction). BNP accurately predicted outcome at 3-5 weeks (area under the curve, 0.81-0.82). BNP cutoffs that maximized correct outcome classification decreased over time from 285 pg/mL at 3 weeks to 100 pg/mL at 4 weeks and 48 pg/mL at 5 weeks. Time to reach the cutoffs of 100 pg/mL and 48 pg/mL were longer in the poor outcome group (log-rank $P = .006$ and <.0001, respectively).

Conclusions Elevated BNP accurately predicts poor outcome in infants with CDH at age 3-5 weeks, with declining cutoffs over 3-5 weeks of age. *(J Pediatr 2021;229:191-8)*.

Pulmonary vascular disease in congenital diaphragmatic hernia (CDH) is a consequence of pulmonary hypoplasia, disruption of vascular development, and altered vasoreactivity.[1,2] Both fixed and dynamic vascular components contribute to ascertainment of pulmonary hypertension in infants with CDH, making the approach to treatment challenging.[1-3] Persistence of pulmonary hypertension in infants with CDH, as assessed by echocardiography, is common and associated with morbidity and mortality.[3-5] Echocardiography provides noninvasive hemodynamic measurements, with right-sided pressure estimates, but its utility for pulmonary hypertension diagnosis in infants with lung disease is variable, even with use of multiple echocardiographic parameters.[5-8] Preservation of right ventricular (RV) function is likely to be at least as important as estimates of right-sided pressure in infants with chronic elevation in pulmonary vascular resistance (PVR). Despite recognition that echocardiographic measurements of RV function in infants with CDH are generally abnormal, the relationship of RV performance to clinical outcomes is less consistent, although these studies have been limited to the first 48 hours of life.[9-12] Thus, additional biomarkers are needed to longitudinally assess illness severity owing to pulmonary vascular disease and RV function in infants with CDH.

B-type natriuretic peptide (BNP) is a biomarker of cardiovascular disease produced in response to ventricular stress.[13,14] BNP is produced from cleavage of pro-BNP (synthesized in ventricular cardiomyocytes) into BNP and an inert amino-terminal fragment, N-terminal-proBNP (NT-BNP).[13,14] Physiological effects of BNP include natriuresis, diuresis, and systemic vasodilation.[13-15] Similar to echocardiography, natriuretic peptide levels are often used as noninvasive markers of illness severity due to pulmonary hypertension. In pediatric populations, BNP level has been correlated with both direct and echocardiographic measurements of RV and pulmonary artery pressures.[9,16-21]

AUC	Area under the receiver operating characteristic curve
BNP	B-type natriuretic peptide
CDH	Congenital diaphragmatic hernia
CPAP	Continuous positive airway pressure
ECLS	Extracorporeal life support
NT-BNP	N-terminal pro–B-type natriuretic peptide
PVR	Pulmonary vascular resistance
RV	Right ventricular

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BNP and NT-BNP levels are often measured at diagnosis in children with pulmonary hypertension, and they are associated with clinical outcomes initially and over time.[20,22-25] In infants with CDH, elevations in BNP and NT-BNP in the first day of life are associated with adverse clinical outcomes.[9,26,27] There are limited data evaluating changes in BNP levels during the neonatal hospitalization in infants with CDH. BNP interpretation is influenced by abnormal hemodynamics in CDH, which affects the anticipated BNP decrease in healthy infants in the weeks after birth.[3,21,26,28,29] In addition, although prognostic cutoffs for BNP have been proposed in older children with pulmonary hypertension, similar cutoffs have not been established in infants with CDH.[19,30]

The primary objective of this study was to evaluate BNP as a longitudinal biomarker for clinical outcome in CDH. We hypothesized that persistent elevation of BNP is associated with the adverse clinical outcome of death or need for prolonged respiratory support at age 56 days. We also aimed to establish serial threshold BNP values predictive of clinical outcome in CDH.

Methods

This retrospective cohort study included infants admitted to the intensive care nursery at University of California's Benioff Children's Hospital San Francisco between July 2012 and December 2018 with either a fetal diagnosis of CDH or a radiographic postnatal diagnosis of CDH, prompted by respiratory distress at birth. Infants were required to have a BNP level measured within 21 days of life. Infants with only atrial septal defect, ventricular septal defect, or patent ductus arteriosus were included, whereas those with more complex structural congenital heart disease were excluded.

Primary Outcome

We performed chart review to collect anatomic characteristics of the CDH and repair, longitudinal respiratory support, inhaled nitric oxide and other pulmonary vasodilator therapy, use of extracorporeal life support (ECLS), and BNP measurements.

We classified eligible infants for the primary outcome, based on survival and respiratory status at 56 days of age. Poor outcome was defined as death or need for ongoing respiratory support at 56 days or at earlier discharge. Good outcome was defined as infants who were alive and off respiratory support at 56 days of life. This outcome is based on the proposed classification of moderate-to-severe bronchopulmonary dysplasia for infants born at or after 32 weeks gestational age, and we have used it in previous studies in the CDH population.[3,26,31] This study was approved by the University of California San Francisco's Institutional Review Board.

Clinical Management

As described previously, infants with CDH underwent routine echocardiogram within 48 hours of life, followed by weekly echocardiograms for pulmonary hypertension surveillance, until resolution of pulmonary hypertension off respiratory support, discharge, or death.[3,5] Evaluations focused on estimated degree of right-sided pressure elevation and assessment of cardiac function.[5] BNP measurements were performed by the clinical laboratory from blood collected on the anticipated day of the echocardiogram but were not used in a protocolized manner for clinical management. Additional echocardiograms and BNP levels were obtained if clinically indicated.

Generally, infants were managed by a gentle ventilation strategy with attention to the restrictive physiology of lung hypoplasia. Pressure delivery was limited with high ventilation rates and permissive hypercapnia strategies to prevent barotrauma, and hyperoxia exposure was aggressively minimized. Pulmonary hypertension identified by surveillance echocardiogram was managed with a standard approach including inhaled nitric oxide, prostaglandin E1 to maintain ductal patency if right-sided pressure estimates were suprasystemic, and milrinone for biventricular afterload reduction in the first weeks of life. ECLS was used as a rescue therapy for infants with inadequate gas exchange or impending inadequate oxygen delivery; veno-venous ECLS was the preferred approach. Surgical repair was performed after clinical stabilization. Therapies were weaned as indicated by clinical and echocardiographic improvement. Generally, supplemental oxygen was administered to maintain preductal oxygen saturation by pulse oximetry 95%, although parameters were lowered if infants were difficult to wean from high levels of supplemental oxygen, to limit exposure to hyperoxia. Infants with persistent hypoxemia were discharged on supplemental oxygen.

Infants with evidence of persistent elevation in right-sided heart pressure after 6-8 weeks of age were evaluated by cardiac catheterization to diagnose and assess the severity of pulmonary hypertension before the initiation of chronic therapy, usually consisting of some combination of bosentan, sildenafil, and parenteral (subcutaneous or intravenous) treprostinil.[32]

BNP Measurements

As clinical BNP samples were collected in coordination with echocardiograms, we focused analysis on data collected on a weekly basis. We used data from 1 to 5 weeks of age. Near birth, only 9 infants (18%) had BNP measurements, and beyond 5 weeks, available BNP data became increasingly skewed by outcome group as this approached the 56-day outcome.

Statistical Analyses

Descriptive statistics were performed with nonparametric methods for continuous variables and the Pearson χ^2 test for categorical variables, as appropriate. A mixed-effects model was used to assess the longitudinal trend between BNP and our primary clinical outcome. The dependent variable in the mixed-effects model was BNP, with predictors of time point (week of age) and outcome group, clustered by infant due to repeated measures of BNP. The interaction of

time point by outcome was evaluated. We calculated area under the receiver operating characteristic curve (AUC) for BNP as a predictor of clinical outcome at each weekly time point. For this analysis, we log-transformed BNP. We defined the BNP threshold as the value that maximized correct classification at that time point. The time to decline to each BNP threshold by outcome group was assessed with Kaplan-Meier curves. All statistical analyses were performed using Stata 15.0 (StataCorp, College Station, Texas). P values < .05 were considered significant. Data are presented as percentage, median and IQR, or mean ± SD.

Results

Of 114 infants meeting the inclusion criteria, 9 were excluded for complex congenital heart disease and 1 was excluded for diaphragmatic eventration; 49 infants had BNP measurements within 21 days of life (**Figure 1**; available at www.jpeds.com). Of these 49 infants, 29 (59%) had a poor outcome and 20 (41%) had a good outcome. Infants were of term gestation with predominantly left-sided hernias (**Table I**). As expected, liver herniation into the thorax was more common in poor outcome group (90% vs 50%; P = .002), and all infants with ECLS support had poor outcome (7 of 29; 24%). Infants in the poor outcome group also underwent CDH repair at an older age (median, 4 days [IQR, 3-6 days] vs 2 days [IQR, 2-3 days]; P = .002), were more likely to have nonprimary repair (93% vs 35%; P < .001), and were successfully extubated at an older age (median, 19 days [IQR, 14-23 days] vs 8 days [IQR 4-11]; P < .001). The median age of death (n = 7) was 24 days, with 4 infants dying before 4 weeks of life (16-24 days of age) and 3 dying later (140-177 days of age).

Respiratory support, pulmonary hypertension therapy, and BNP values available for analysis at each weekly time point are shown in **Table II**. Notably, no BNP samples included this analysis were obtained while infants were supported with ECLS. All 4 infants with mortality before 56 days died from pulmonary hypertension and respiratory failure. One of these infants also had an aortic thrombosis with bowel ischemia following ECLS and a second had culture negative sepsis. Of the 25 surviving infants with poor outcome, 16 (64%) were receiving noninvasive positive-pressure ventilation as nasal continuous positive airway pressure (CPAP), and 9 (36%) had a nasal cannula at 56 days of age; no infants were intubated at that time. Two of the 3 infants with mortality after 56 days died from progression of pulmonary hypertension and respiratory failure, and the other one deteriorated with infectious pneumonia. Both of the infants with progression of pulmonary hypertension had been receiving chronic therapy for pulmonary hypertension before death. Fourteen of the 22 surviving infants (64%) were subsequently discharged on respiratory support, including 3 infants receiving nasal CPAP overnight with nasal cannula during the day and 1 infant with tracheostomy and mechanical ventilation (following venrtricular septal defect repair on bypass). Seven of the 22 infants (32%) were discharged on chronic pulmonary vasodilator therapy; all but 1 were also discharged on home respiratory support, although that infant was placed back on home nasal cannula support after discharge due to chronic desaturation. The 3 infants who died late and those discharged with chronic pulmonary hypertension therapy were all receiving nasal CPAP at 56 days of age; no infants in the good outcome group were discharged on pulmonary vasodilator therapy.

Compared with the good outcome group, BNP levels were lower in the poor outcome group at week 1, similar at week 2, and higher at weeks 3-5 (**Figure 2**). The pattern of decline in BNP levels over time appeared to differ by outcome group. This was demonstrated in a mixed-effects model evaluating the longitudinal changes in BNP. In this model, there was a significant interaction between time point and outcome (P = .003), confirming that the pattern of change in BNP differs between the good outcome and poor outcome groups over the first 5 weeks of life (**Figure 3**; available at www.jpeds.com).

BNP was not informative for clinical outcome at weeks 1 and 2 (**Table III**). Although AUC was initially 0.73 at week 1, specificity was low at 60%. At week 2, sensitivity and AUC decreased; however, the AUC subsequently increased and plateaued over weeks 3-5 (0.82, 0.82, and 0.81, respectively), showing good discrimination of BNP for outcome at these time points. The highest percentage of correct classification for a given BNP value was seen at week 3; a BNP level of 285 pg/mL classified 87.5% of the infants correctly. By Kaplan-Meier analysis, the poor outcome group demonstrated a significantly slower decline to the BNP cutoffs in only weeks 4 and 5 (by log-rank; **Figure 4**; available at www.jpeds.com). These trajectories can be further understood as 50% of each group reaching the week 3-5 BNP cutoffs (week 3, 285 pg/mL; week 4, 100

Table I. Selected characteristics of the study cohort (N = 49)

Characteristics	Good outcome (N = 20)	Poor outcome (N = 29)	*P* value
Male sex, n (%)	12 (60)	15 (52)	.57
Gestational age, wk, median (range)	39.0 (38.3-39.3)	39.1 (38.1-39.3)	.81
Birth weight, kg, median (range)	3.3 (3.0-3.5)	3.0 (3.0-3.5)	.68
Left-sided CDH, n (%)	17 (85)	22 (76)	.44
Liver herniated into the chest, n (%)	10 (50)	26 (90)	.002
Age at surgery, d, median (range)	2 (2-3)	4 (3-6)	.002
Nonprimary repair, n (%)	7 (35)	27 (93)	<.001
VSD, n, median (range)	3	1	.51
Inhaled nitric oxide, n (%)	8 (40)	29 (100)	<.001
Extracorporeal life support, n (%)	0	7 (24)	.02
Age at extubation, d, median (range)	8 (4-11)	19 (14-23)	<.001
Death, n (%)		7 (24)	
Age at death, d, median (range)		24 (17-147)	

VSD, ventricular septal defect.

Table II. BNP, medical interventions, and clinical status for study cohort

	Week 1		Week 2		Week 3		Week 4		Week 5	
	Good	Poor	Good	Poor	Good	Poor	Good	Poor	Good	Poor
Clinical outcomes	**(N = 13)**	**(N = 15)**	**(N = 17)**	**(N = 23)**	**(N = 14)**	**(N = 26)**	**(N = 12)**	**(N = 24)**	**(N = 10)**	**(N = 25)**
BNP										
BNP, pg/mL, median (IQR)	1310 (551-1540)	348 (181-1020)	446 (247-916)	645 (390-1180)	93 (76-191)	644 (466-1040)	38 (33-76)	275 (121-446)	28 (17-41)	77 (70-264)
Respiratory support, n (%)										
None	3 (23.1)	0	2 (11.8)	0	2 (14.3)	0	3 (25	0	3 (30)	1 (4)
High-flow nasal cannula/nasal cannula	0	0	5 (29.4)	0	4 (28.6)	0	5 (41.7)	0	4 (40)	2 (8)
Nasal CPAP/NIPPV	3 (23.1)	0	7 (41.2)	7 (30.4)	7 (50)	14 (53.8)	3 (25)	21 (87.5)	3 (30)	21 (84)
Conventional ventilation	6 (46.2)	12 (80)	3 (17.6)	10 (43.5)	1 (7.1)	10 (38.5)	1 (8.3)	3 (12.5)	0	1 (4)
High-frequency oscillatory ventilation	1 (7.7)	3 (20)	0	6 (26.1)	0	2 (7.7)	0	0	0	0
ECLS	0	0	0	0	0	0	0	0	0	0
Pulmonary hypertension therapy, n (%)										
Inhaled nitric oxide	4 (30.8)	13 (86.7)	4 (23.5)	22 (95.7)	3 (21.4)	24 (92.3)	1 (8.3)	20 (83.3)	1 (10)	18 (72)
Prostaglandin 1	2 (15.4)	10 (66.7)	4 (23.5)	17 (73.9)	2 (14.3)	22 (84.6)	2 (16.7)	16 (66.7)	2 (20)	10 (40)
Milrinone	0	4 (26.7)	1 (5.9)	9 (39.1)	0	13 (50.0)	0	9 (37.5)	0	6 (24)
Available for analysis										
Infants available for analysis, n	49		49		45		38		36	
Total exiting analysis the next week, n	0		4		7		2		N/A	
Reason for exiting aAnalysis										
Discharge (n)	0	0	2 (12 d, 13 d)	0	4 (18 d, 21 d, 22 d, 24 d)	0	2 (28 d)	0	2 (35 d)	0
Transfer, n	0	0	0	0	1 (18 d)	0	0	0	1 (37 d)	0
Death, n	0	0	0	2 (16 d, 17 d)	0	2 (19 d, 24 d)	0	0	0	0

NIPPV, non-invasive positive pressure ventilation.

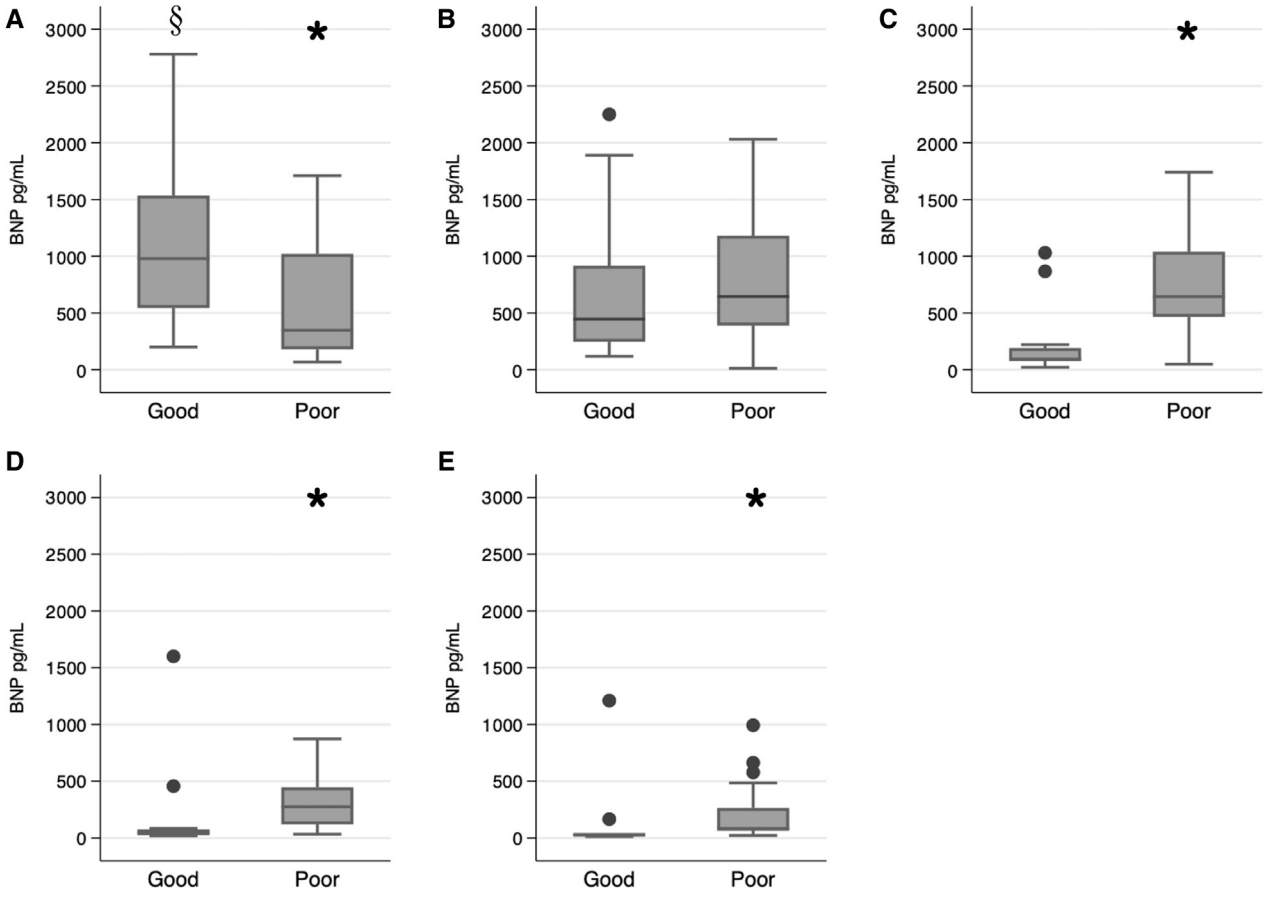

Figure 2. BNP level by clinical outcome at 1-5 weeks of age, with *P* value for comparison by outcome. **A,** Week 1; *P* = .04. **B,** Week 2; *P* = .28. **C,** Week 3; *P* = .001. **D,** Week 4; *P* = .002. **E,** Week 5; *P* = .005. *P* < .05 designated by *. Single outlier value not shown to allow for standardized scaling of the *y*-axis, designated by §.

pg/mL; week 5, 48 pg/mL) at 26, 38, and 43 days, respectively, in the poor outcome group and at 19, 22, and 28 days in the good outcome group.

Discussion

In this single-center retrospective cohort of infants with CDH, we demonstrate that serial BNP measurements follow distinct patterns with respect to clinical outcomes. Infants without respiratory support and alive at 56 days (good outcome group) had higher BNP levels at 1 week of age, followed by a steeper decline compared with infants receiving any respiratory support or not alive at 56 days (poor outcome group). Consistent with this finding, we identified declining thresholds for clinical outcome prediction over weeks 3-5 of life. Similarly, we demonstrated divergent decrease to these declining thresholds by outcome group after week 3, which may further inform the interpretation of individual BNP measurements in this population.

Natriuretic peptides have been investigated as biomarkers in adult and pediatric populations with primary pulmonary hypertension. In these populations, both BNP and NT-BNP correlate longitudinally with catheterization-based hemodynamics as well as echocardiographic measurements of RV function.[16,30,33,34] Furthermore, elevated levels of BNP and NT-BNP are independently predictive of morbidity and mortality.[20,22,26,35] Interpretation of BNP levels during the neonatal period is more challenging, however. After birth, BNP levels peak in healthy term neonates within the first 2 days of life, then decrease to reach adult levels at approximately 1 month of age.[17,28,29,36] This pattern in healthy children is likely related to the normal transition from fetal to neonatal circulation, with a decreased PVR, increased systemic vascular resistance, and increased pulmonary blood flow, resulting in increased left ventricular volume and pressure.[29,37] In the current study, we identified the week 3 time point as that time point with optimal accuracy for prediction of clinical outcome at 56 days. The median BNP for the good outcome group is 93 pg/mL at that point in time, a level which would be reached at approximately 5 days of age in healthy newborns.[29] Thus, the current data are consistent with a delay in the usual perinatal transition in infants with CDH, as characterized by BNP.

Similarly, the circulatory transition that occurs in healthy newborns by 2-3 days of age is delayed in infants with CDH to 2-3 weeks of age, with evidence of persistent elevations in

Table III. AUC and BNP cutoff values at weekly intervals for discrimination of clinical outcome

Time point	AUC (95% CI)	BNP cutoff, pg/mL (geometric mean)	Sensitivity, %	Specificity, %	Correctly classified, %
Week 1	0.73 (0.54-0.92)	539	84.6	60.0	71.4
Week 2	0.60 (0.41-0.79)	480	69.6	58.8	65.0
Week 3	0.82 (0.67-0.97)	285	88.5	85.7	87.5
Week 4	0.82 (0.62-1)	100	87.5	83.3	86.1
Week 5	0.81 (0.59-1)	48	88.0	80.0	85.7

PVR before that time.[3] Interestingly, in a previous prospective study, we found that BNP levels at 1 day accurately predicted poor outcome at 56 days (as defined in the present study) and was superior to concurrent pulmonary hypertension severity.[26] However, BNP was increased in both outcome groups at 1 week of age and was no longer discriminatory for clinical outcome at that time. Our current retrospective data offer a similar observation, although here BNP levels have an inverse relationship at 1 week and are higher in the good outcome group compared with the poor outcome group. Consistent with the difference in later clinical outcomes, almost one-half of the good outcome group in both the current study and the previous study had been extubated by the time of the week 1 BNP measurement. Thus, this difference between groups at week 1 may reflect cardiopulmonary interactions, with increased ventricular stress related to increased respiratory demand in the good outcome group. Alternatively, fluid shifts in this group may be relevant as these infants are progressing, or if PVR has fallen considerably, a residual communication with moderate left-to-right shunt (such as patent ductus arteriosus) may result in both increased left ventricular stress and BNP. In contrast to BNP levels, in our previous study, the severity of pulmonary hypertension by echocardiography at 1 week had utility for clinical outcome. Infants with a good outcome showed improvements in extimated pulmonary pressure accompanied by decreased cardiorespiratory support, whereas improvement or resolution of RV stress may have lagged, consistent with the elevated BNP.[26] This suggests that BNP and echocardiographic assessment of right heart pressure might not be concurrently related in the perinatal physiology of CDH. In fact, the good outcome group in our previous study followed (although lagged behind) the patterns seen in the healthy perinatal transition, characterized by a transient increase of BNP in the second day of life, while estimated right heart pressures are known to be decreasing.[29,37] Of interest, Partridge et al found an increase in BNP between initial and perioperative levels only in infants who did not have pulmonary hypertension on echocardiography.[21] In the present study, the CDH repair itself is unlikely to have been a specific modifying factor, given that almost all infants in both groups had undergone surgery by 1 week of age, as shown in Table I. However, as noted, many of the infants in the good outcome group in the current cohort did have aggressive weaning off of mechanical ventilation following repair.

The steady decrease in BNP in the good outcome group after 1 week of age mirrors the resolution of pulmonary hypertension that we previously described in infants with CDH. In our previous study, the severity of pulmonary hypertension had moderate to strong accuracy for the 56-day clinical outcome, which peaked at 2 weeks of age with an AUC of 0.8 (95% CI, 0.72-0.88).[3] In the present study, the accuracy of BNP as a predictor for the 56-day clinical outcome peaks and plateaus at 3 weeks of age with an AUC curve of 0.82. Thus, the current data are consistent with our previous description of delayed transition of the pulmonary vascular bed in CDH and may reflect persistent RV stress in the setting of chronically increased RV afterload.

Using serial BNP assessment, we identified declining BNP cutoffs for predicting the 56-day clinical outcome: 285 pg/mL at 3 weeks, 100 pg/mL at 4 weeks, and 48 pg/mL at 5 weeks. In the original study of BNP for diagnosis of left heart failure in adults, a BNP cutoff of 100 pg/mL maximized the accuracy for diagnosis of heart failure at 83%, and a cutoff of 50 pg/mL increased the negative predictive value to 96%.[38] A proposed cutoff of 180 pg/mL in adults with pulmonary hypertension had an AUC of 0.93 for mortality when applied to children with primary pulmonary hypertension, although the AUC decreased to 0.84 when the broader array of pulmonary hypertension etiologies was included.[19] Lammers et al identified a cutoff BNP of 130 pg/mL for death or transplantation in children with pulmonary hypertension, but this threshold performed better in primary pulmonary hypertension than it did in the broader population that included pulmonary hypertension associated with congenital heart disease.[30] Finally, in the neonatal literature, Cuna et al identified a cutoff of 220 pg/mL for a peak BNP as predictor of mortality among former premature infants with bronchopulmonary dysplasia and pulmonary hypertension; there was 90% sensitivity but only 65% specificity with this threshold.[39] Thus, there is much variability in proposed BNP cutoffs in the setting of pulmonary hypertension, with some clinicians focusing on the thresholds proposed in the heart failure literature. In the present study, we identified BNP thresholds that are specific for CDH at critical time points in the neonatal course. These findings emphasize that the longitudinal trends in BNP should be prioritized in evaluation for an individual infant. However, the interpretation of individual BNP values may be facilitated by the Kaplan-Meier curves we generated. In conjunction with our previous study describing the delayed transition of the pulmonary vascular bed in infants with CDH, these trends in BNP values suggest a framework for understanding and managing pulmonary vascular disease and RV performance as they relate to clinical outcome in infants with CDH.[3]

This study has a relatively large sample size, and the data interpretation is strengthened by the standardized clinical management of the CDH population. However, this

standardization may limit the application of this single-center study to sites that have different approaches to management. Furthermore, over the study period, we had to exclude a greater number of infants than we were able to include, owing primarily to a lack of BNP measurements in the first 21 days. This may limit the generalizability of our findings. As BNP measurements were obtained for clinical care, clinicians were not blinded to BNP values. However, BNP was not used in a clinical decision algorithm, making it less likely to introduce meaningful bias, and we found important relationships 3-5 weeks before the outcome assessment. We could not validate the predictive value of early BNP that we described previously, because our retrospective data were not sufficient for this analysis.

In conclusion, our study demonstrates that BNP is a useful marker for clinical outcome in infants with CDH, particularly when BNP values are interpreted with respect to age and trends are accounted for over time. The fall in BNP in the good outcome group follows the changes in right-sided pressure estimates with resolution of pulmonary hypertension that we previously documented in this population. These patterns lend support to the interpretation that elevated BNP in CDH is an indicator of RV stress, and a decrease over time mirrors overall improved clinical status. Because both markers identify infants at high risk of morbidity, clinicians can use these markers in a complementary fashion when managing infants with CDH in the first weeks of life. ■

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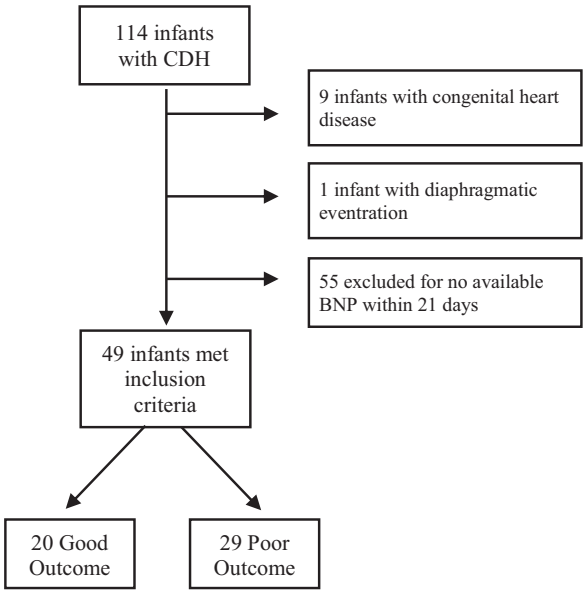

Figure 1. Study subject flow diagram.

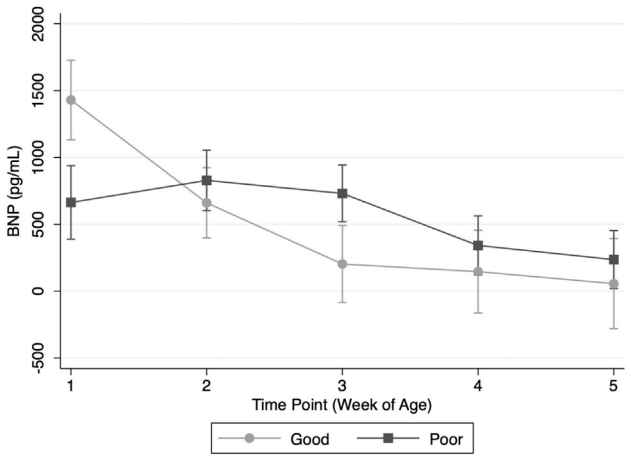

Figure 3. BNP (pg/mL) over time by clinical outcome. Predicted values from mixed linear effects model. Error bars represent standard error. *P* = .003 for interaction of outcome group and time point.

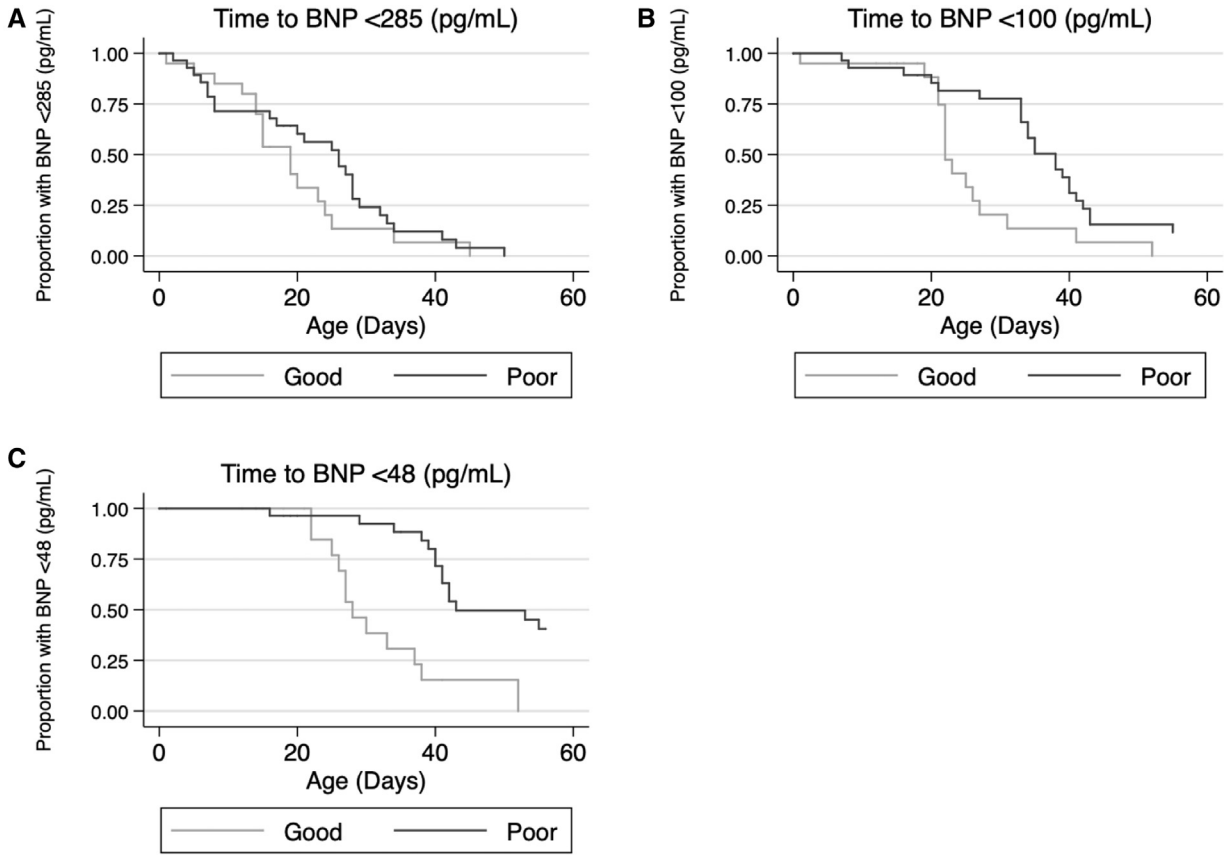

Figure 4. Time to BNP cutoff by clinical outcome at age 3-5 weeks, censored at 56 days, with log-rank *P* values for comparison by outcome. **A,** Week 3 BNP cutoff 285 pg/mL; $P = .23$. **B,** Week 4 BNP cutoff 100 pg/mL; $P = .006$. **C,** Week 5 BNP cutoff 48 pg/mL; $P < .0001$.