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CLINICAL RESEARCH ARTICLE

Early postnatal echocardiographic characteristics impact survival and extracorporeal life support in congenital diaphragmatic hernia

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BACKGROUND: Early echocardiographic characteristics (EC) of congenital diaphragmatic hernia (CDH) neonates and their associations with outcomes, especially differences by laterality and size, are unknown.
METHODS: Congenital Diaphragmatic Hernia Study Group data between 2015 and 2020 were used. Early postnatal EC, including atrial and ductal shunt direction, pulmonary hypertension (PH) severity, and ventricular size and function, were assessed based on defect laterality and size. Outcomes included mortality and extracoporeal life support (ECLS) use.
RESULTS: The study population included 1777 infants. Severe PH, right-to-left shunt, left ventricular (LV) hypoplasia, right ventricular dilation, and ventricular dysfunction were more prevalent in larger defects. Independent of defect size, neonates with R-CDH had more severe PH, more bidirectional and right-to-left atrial shunt, and more biventricular (BV) dysfunction. In contrast, L-CDH neonates had more LV hypoplasia and left-to-right atrial shunt. After adjusting for defect side, larger defects were associated with LV hypoplasia and right-to-left and bidirectional atrial shunt. In multivariate analysis, right-to-left atrial shunt and BV dysfunction were associated with increased mortality, whereas bidirectional atrial shunt and BV dysfunction were associated with ECLS use.
CONCLUSIONS: CDH neonates are at increased risk for early cardiac dysfunction. EC differ by laterality and size. Management of cardiac dysfunction in CDH may improve outcomes.

Pediatric Research (2026) 99:166–173; https://doi.org/10.1038/s41390-025-04443-w

IMPACT:

- Cardiac dysfunction has emerged as a factor contributing to adverse outcomes in congenital diaphragmatic hernia (CDH). However, there are limited data on the impact of defect size, laterality, and severity of postnatal cardiac dysfunction on outcomes.
- Echocardiographic characteristics in the first two days of life differ by defect laterality and size. Right-to-left atrial shunt and biventricular dysfunction are associated with increased mortality. Bidirectional atrial shunt and biventricular dysfunction were associated with extracorporeal life support use.
- Our results support the need for standardized cardiac function assessment in critically ill neonates with CDH. Future strategies to identify and manage these diverse hemodynamic profiles are needed to improve outcomes.

INTRODUCTION

Congenital diaphragmatic hernia (CDH) is a common birth defect occurring in approximately 1 in 3000 live births.[1] Impaired fetal lung development and pulmonary vascular remodeling play central roles in CDH pathophysiology.[2] Postnatally, these developmental changes result in pulmonary hypoplasia and pulmonary hypertension (PH), which were thought to be responsible for the significant mortality and morbidity in CDH.[3–5] Despite advances in neonatal critical care, surgical management, extracorporeal life support (ECLS), pharmacological management of PH, and standardizations of clinical practice, survival without significant morbidity remains challenging for severely affected newborns. Recently, cardiac dysfunction has emerged as an important factor contributing to adverse outcomes in CDH.[6,7] Early postnatal

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Received: 28 May 2025 Accepted: 14 August 2025
Published online: 1 October 2025

echocardiographic assessment has been proposed as a valuable adjunct to risk stratification.[8,9] In 2015, the Congenital Diaphragmatic Hernia Study Group (CDHSG) began gathering echocardiographic data to understand the impact of cardiac dysfunction in CDH and found that left ventricular (LV) dysfunction was associated with more adverse outcomes than right ventricular (RV) dysfunction while biventricular (BV) dysfunction had the highest mortality and increased ECLS use.[10] In two single-center studies, LV dysfunction with or without LV hypoplasia[9] and RV or LV dysfunction[11] have been shown to impact the mortality and use of ECLS.

Despite these associations between ventricular function and outcomes, investigations of the impact of the size and laterality of the diaphragmatic defect and the severity of postnatal cardiac dysfunction in CDH are limited.[11] Echocardiographic measures can be utilized to understand underlying cardiac phenotypes.[12] Recognizing the cardiac phenotypes in CDH may have important implications for improving clinical management and outcomes.[12] This study aimed to compare echocardiographic characteristics seen in infants with different CDH laterality (left vs. right) and defect sizes to determine the impact of these variables on ECLS use and mortality.

METHODS

Study design and population

The CDHSG prospectively collects de-identified data on infants with CDH from 89 centers in 18 countries (Supp Table 1).[13] The CDHSG registry is approved by the Institutional Review Board at the University of Texas at Houston (HSC-MS-03-223) with a waiver of informed consent. Prenatal and postnatal information is collected until discharge, transfer, or death. Missing or aberrant data were validated by direct contact with the submitting center. Infants born with left- or right-sided CDH (L-CDH or R-CDH) between January 1, 2015, and September 30, 2020, were included in the collection of postnatal echocardiographic data that began in 2015.[10,14,15] We excluded infants with bilateral, central, or unknown side of defect; infants with unknown survival or ECLS status; infants transferred to a non-CDHSG center on a ventilator, continuous positive airway pressure support, or with unknown respiratory status; infants without postnatal echocardiographic data obtained in the first 2 days of life; and infants whose first echocardiogram was obtained the day following inhaled nitric oxide (iNO) initiation, CDH repair, or ECLS cannulation. Cardiac, gastrointestinal, pulmonary, neurologic, and genetic anomalies were classified as major or minor based on a consensus review by investigators as previously described (Supp Table 2).[3] Cardiac anomalies that could alter echocardiographic characteristics and other anomalies that could affect ECLS use or survival were classified as major (e.g., Tetralogy of Fallot, hypoplastic left heart syndrome, transposition of great arteries, total anomalous pulmonary venous return, etc.). Infants with major anomalies were excluded.

Study variables

Echocardiographic variables were acquired from a postnatal echocardiogram in the first 2 days of life before ECLS and/or surgical repair. The variables collected included severity of PH, ductal and atrial shunt directions, and size and function of both ventricles. The severity of PH was reported in four categories based on pulmonary arterial pressure (PAP) in relation to systemic blood pressure (SBP): normal (PAP < 1/2 SBP), mild PH (1/2 SBP ≤ PAP < 2/3 SBP), moderate PH (2/3 SBP ≤ PAP < SBP), or severe PH (SBP ≤ PAP).[16] LV size was categorized as below normal, normal, or dilated; RV size was reported as normal or dilated. As previously described, ventricular function was classified as normal, isolated LV dysfunction, isolated RV dysfunction, or BV dysfunction.[16] As LV diastolic function information was not collected as part of the registry, we utilized shunting patterns by echocardiography as surrogates for elevated pulmonary vascular resistance (ductal shunt) and changes in ventricular compliance (atrial shunt).[17] For example, right-to-left (R-to-L) ductal and atrial shunts reflect the presence of severe PH and decreased RV compliance in relation to LV compliance. In contrast, R-to-L ductal and left-to-right (L-to-R) atrial shunts reflect decreased LV compliance with LV diastolic dysfunction and increased left-sided filling pressures in the presence of R-to-L ductal shunt consistent with severe PH.[18] Early iNO use was defined as use in the first 3 days of life and before ECLS cannulation.[15] Defect laterality and neonatal characteristics, including birth weight, estimated gestational age, delivery method (vaginal delivery vs. cesarean section), 5-minute Apgar score, and inborn status, were collected. Characteristics determined following repair included defect size and repair method (primary vs. patch repair). Defect size was graded from A to D (smallest to largest) per CDHSG consensus criteria by direct visualization during operation.[19] Infants without a reported defect size were classified as non-repair (NR) group if no surgical repair was performed. If no defect size was reported and surgical repair occurred, the defect size was classified as "unknown". The primary and secondary outcomes were death and ECLS use before discharge or transfer, respectively.

Statistical analysis

We first compared echocardiographic characteristics by defect laterality and defect size. These comparisons between categorical variables were performed using either Fisher's exact test or χ^2 test, as appropriate. To assess the association between the first postnatal echocardiographic measures and the primary and secondary outcomes, we performed univariate and multivariate regressions for mortality and ECLS use. Multivariate logistic regression models were developed to adjust for differences in early iNO use, neonatal characteristics, and anatomic factors that could affect the outcomes. Model A was adjusted for early iNO use; in Model B, neonatal characteristics and defect laterality were added to Model A; and lastly, in Model C, anatomic factors, including defect size, were added to Model B. Patients with incomplete data were excluded from the regression analyses. As defect size and repair type were unavailable for the NR group, they were not included in Model C. As larger defects were more frequently present in R-CDH than in L-CDH, a post hoc analysis of laterality stratified by size (A&B vs. C&D&NR) was performed. Analyses were conducted using R, version 4.4.1 (http://www.r-project.org).

RESULTS

Population characteristics

A total of 2935 infants from 89 CDHSG centers were identified. Following exclusions, 1777 CDH infants were included in the final analysis (Fig. 1). The baseline demographics and clinical characteristics of the left and right-sided CDH cohorts are summarized in Table 1. Fourteen percent of the patients had R-CDH. More R-CDH were postnatally diagnosed, had lower Apgar scores at 5 min, received cardiopulmonary resuscitation in the delivery room, had an intrathoracic liver position, received iNO in the first three days of life, were placed on ECLS, and underwent patch repair than L-CDH. Defect size was also more often C, D, or NR for R-CDH (63.0%) than L-CDH (45.1%). The majority of first postnatal echocardiograms for both L-CDH and R-CDH groups were performed on the day of birth (73.1% and 72.7%, respectively) or within the first 2 days (96.5% and 96.0%, respectively).

Echocardiographic measures by defect laterality

Pulmonary hypertension (Fig. 2a). Eighty-seven percent of all CDH patients had some degree of PH, and 73% had at least moderate or severe PH. Severe PH was more frequently present in infants with R-CDH than those with L-CDH (L 28.2% vs. R 35.0%, $P = 0.044$). The proportion with normal PAP or mild PH was similar.

Ductal and atrial shunt direction (Fig. 2b, c). While the ductal shunt pattern was overall similar between left and right CDH, the atrial shunt direction differed. There were more bidirectional (L 25.9% vs. R 38.1%, $P < 0.001$) and R-to-L (L 8.5% vs. R 15.3%, $P = 0.004$) atrial shunts in R-CDH and more L-to-R atrial shunts (L 53.6% vs. R 35.6%, $P < 0.001$) in L-CDH.

Ventricular size and function (Fig. 2d, e, f). LV hypoplasia and RV dilation were present in 11.9% and 52.0% of all infants with CDH in this study cohort, respectively. LV and RV sizes were not significantly different in L-CDH vs. R-CDH; however, there was more frequent LV hypoplasia in L-CDH without statistical significance (L 12.5% vs. R 7.8%, $P = 0.062$). Ventricular function was normal in 66.5% of all infants with CDH, and RV dysfunction was more frequent than LV

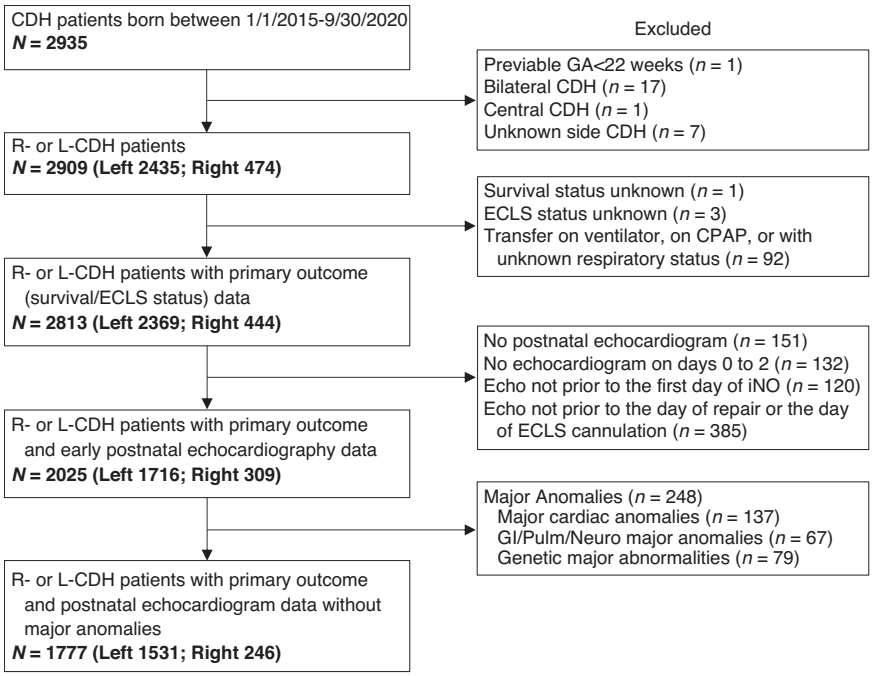

Fig. 1 Flow diagram of the study cohort.

dysfunction (30.2% vs. 17.9%, $P < 0.001$) overall. There was more BV dysfunction in R-CDH than in L-CDH (L 13.8% vs. R 19.5%, $P = 0.042$). LV dilation (OR 14.84, 95% CI 7.17–33.03) and LV hypoplasia (OR 3.38, 95% CI 2.36–4.81) were associated with LV dysfunction. LV dilation had a much higher association with LV dysfunction than RV dilation and RV dysfunction (OR 5.84, 95% CI 4.50–7.63).

Echocardiographic measures by defect size

Pulmonary hypertension (Fig. 3a). Defect size was associated with PH of any severity (A 74.5%, B 82.1%, C 92.8%, D 94.3%, and NR 97%). Severe PH occurred more frequently as defect size increased (A 14.0%, B 20.1%, C 34.9%, D 42.6%, and NR 58.6%), while fewer had mild PH (A 21.0%, B 18.4%, C 11.0%, D 8.5%, and NR 5.3%).

Ductal and atrial shunt direction (Fig. 3b, c). With larger defect sizes, there were stepwise decreases in L-to-R and increases in R-to-L shunts at both ductal and atrial levels. The bidirectional atrial shunt increased with a larger defect size, while the bidirectional ductal shunt did not vary significantly.

Ventricular size and function (Fig. 3d, e, f). Infants with a larger defect had more LV hypoplasia, ranging from 5.5% in A to 23.8% in NR. RV dilation occurred more commonly and increased with larger defect sizes, ranging from 41.5% to 71.1%. The prevalence of isolated LV, isolated RV, and BV dysfunction in all CDH patients was 3.7%, 15.4%, and 14.6%, respectively. BV dysfunction was more commonly seen than isolated LV or RV dysfunction and increased with larger defect sizes, ranging from 3.6% to 23.6% in the A through D groups and 42.4% in the NR group.

Echocardiographic measures by both laterality and size

Considering larger defects were more frequently present in R-CDH than in L-CDH, a post hoc analysis of laterality stratified by defect size (A&B vs. C&D&NR) was performed, which suggested that in L-CDH compared to R-CDH: the difference in the severity of PH and biventricular dysfunction were no longer significant; however, the difference in the atrial shunt direction and LV hypoplasia remained significantly more prevalent in the subgroup with larger defects (Supp Table 3).

Echocardiographic measures associated with death and ECLS use

A series of multivariate logistic regression models using echocardiographic parameters and different sets of covariates to predict mortality and ECLS use were developed as sensitivity analyses. Figure 4 shows a select group of echocardiographic measures associated with death and/or ECLS use based on different tested models. The complete results of all models are shown in Supp Table 4. R-to-L ductal shunt, bidirectional or R-to-L atrial shunt, LV hypoplasia, and BV dysfunction were associated with mortality based on Model B adjusted for defect side, neonatal characteristics, and early iNO use, all of which are readily available in the first few days after birth, with an area under the receiver operating characteristic curve (AUROC) of 0.87 (Supp Fig. 1). In contrast, Model C incorporates information obtained after repair (i.e., defect size and repair type) in addition to variables included in Model B. Bidirectional atrial shunt and BV dysfunction were associated with ECLS use, and R-to-L atrial shunt and BV dysfunction were associated with increased mortality in all models.

DISCUSSION

We assessed the early echocardiographic findings of a large cohort of infants with CDH followed in the CDHSG multicenter registry. Our results demonstrated novel associations between the postnatal echocardiogram and defect laterality (L-CDH vs. R-CDH) and size based on the CDHSG staging system.[19,20] The atrial shunt patterns differed by defect side. There were more L-to-R shunts in L-CDH and more bidirectional or R-to-L shunts in R-CDH, independent of defect size. There were strong associations between echocardiographic measures and defect size: larger defects were associated with more severe PH, R-to-L ductal and atrial shunt, bidirectional atrial shunt, LV hypoplasia, RV dilation, LV dysfunction, RV dysfunction, and BV dysfunction. As larger defects are present more commonly in R-CDH, an analysis of laterality by size was performed and showed that only the differences in atrial shunt direction and the prevalence of LV hypoplasia remained significant. Looking at primary outcomes using multivariate logistic regression models, biventricular dys-

Table 1. Cohort characteristics

Characteristics	L-CDH (n = 1531)	R-CDH (n = 246)
Neonatal Characteristics		
Male sex, *n* (%)	883/1528 (57.8%)	137/245 (55.9%)
Estimated gestational age (EGA), weeks, median [IQR]	38 [37–39]	38 [36–39]
Preterm (EGA < 34wk), *n* (%)	61/1528 (4.0%)	14/245 (5.7%)
Birth weight, kg, mean ± SD	3.0 ± 0.6	3.0 ± 0.6
Cesarean delivery, *n* (%)	742/1511 (49.1%)	122/243 (50.2%)
Apgar at 1-minute, median [IQR]	5 [3, 8]	5 [3, 7]
Apgar at 5-minute, median [IQR]	7 [6, 9]	7 [5, 8]
Apgar at 5-minute ≤ 5, *n* (%)	305/1434 (21.3%)	65/228 (28.5%)
CPR in the delivery room, *n* (%)	98/1269 (7.7%)	26/208 (12.5%)
Inborn, *n* (%)	940/1531 (61.4%)	139/246 (56.5%)
Prenatal diagnosis, *n* (%)	1189/1530 (77.7%)	161/245 (65.7%)
Liver in chest, *n* (%)	482/1384 (34.8%)	197/215 (91.6%)
Early iNO use[a], *n* (%)	725/1531 (47.4%)	138/246 (56.1%)
Repair Characteristics		
Timing of repair, days, median [IQR]	4 [2, 6]	5 [3, 8]
Defect size[b], *n* (%)		
A	218/1531 (14.2%)	13/246 (5.3%)
B	608/1531 (39.7%)	76/246 (30.9%)
C	434/1531 (28.3%)	96/246 (39.0%)
D	136/1531 (8.9%)	32/246 (13.0%)
Non-repair	121/1531 (7.9%)	27/246 (11.0%)
Unknown	14/1531 (0.9%)	2/246 (0.8%)
Patch repair, *n* (%)	659/1406 (46.9%)	143/216 (66.2%)
Outcomes		
Death, *n* (%)	254/1531 (16.6%)	49/246 (19.9%)
Age at death, days, median [IQR]	11.5 [1, 31]	4 [1, 19]
ECLS use, *n* (%)	264/1531 (17.2%)	66/246 (26.8%)
Days on ventilator[c], days, median [IQR]	10 [6, 19]	14 [8, 26.5]
Days in hospital[c], days, median [IQR]	35 [22, 63]	53 [30, 86]
Oxygen at discharge[c], *n* (%)	222/1276 (17.4%)	63 /195 (32.3%)

IQR interquartile range, SD standard deviation, CPR cardiopulmonary resuscitation, iNO inhaled nitric oxide, ECLS extracorporeal life support.
[a]iNO use in the first 3 days of life before ECLS cannulation.
[b]Percentages may not add up to 100% due to rounding.
[c]Among survivors.

function was universally associated with increased risk of ECLS use and mortality. R-to-L atrial shunt was associated with mortality, and bidirectional atrial shunt with ECLS use in all models. Mortality and ECLS use were predicted with AUROC of 0.87 and 0.82, respectively, based on a model that included only demographic characteristics and initial postnatal echocardiogram measurements, all known early in the clinical course.

Our results provide new insights into the complexity of cardiac dysfunction in neonates with CDH. Early recognition of these pathophysiological patterns may allow the identification of individual patient phenotypes and the development of patient-specific physiology-based therapy approaches, such as timely initiation of cardiotropic and pulmonary vasodilating or modulating treatment. The echocardiographic findings may guide ECLS utilization or help define the optimal timing of surgical repair. Lastly, incorporating early echocardiographic assessment may help to improve mortality and morbidity in the critically ill CDH population.[7,8,12]

Changes in cardiac development and their impact on postnatal outcomes in CDH have recently gained attention.[6,8,10,11,21–25] There is increasing evidence that early cardiac dysfunction is an equally important component of CDH-associated pathophysiology and is associated with adverse outcomes.[7,12] The lack of detailed understanding of how cardiac dysfunction impacts outcomes may at least in part explain the only modest change observed in mortality and morbidity in neonates with CDH when past treatment mainly focused on lung-protective ventilation strategies and optimizing pulmonary vascular resistance. Our investigation supports and extends previous single-center reports on early postnatal echocardiographic measures and their association with outcomes in the last decade. These studies found that diastolic RV function on tissue Doppler imaging was predictive of length of hospitalization and respiratory support among survivors[22]; that both left and right ventricular function on speckle tracking echocardiogram were associated with ECLS use[9]; that a three-dimensional left to right ventricle volume ratio imbalance is associated with mortality[25]; and that impaired LV systolic function correlated with lung hypoplasia measured by observed/expected total lung volume and a composite outcome of death or ECLS.[8] More recently, Fraga et al.[24] described the severity of LV

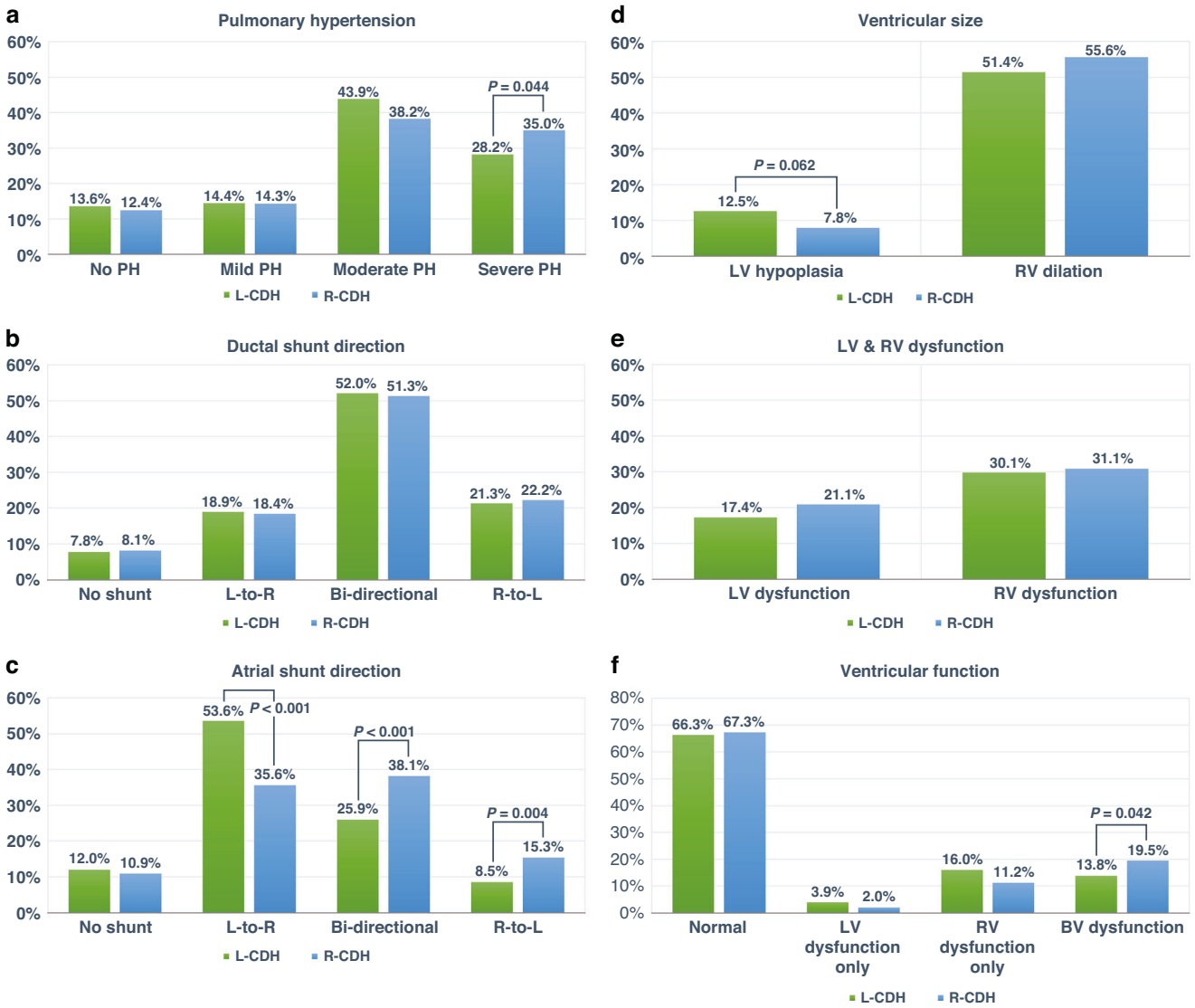

Fig. 2 The first postnatal echocardiographic characteristics by defect side. (PH pulmonary hypertension, LV left ventricle, RV right ventricle, BV bi-ventricular).

dysfunction and left heart hypoplasia in neonates with CDH and demonstrated that only 20% of patients had normal cardiac anatomy and function. They further showed that patients with both LV dysfunction and hypoplasia had nearly two times higher odds of ECLS use and almost three times higher odds of death.[24]

Our study also expanded on the previous multicenter work from the CDHSG that found that ventricular dysfunction was associated with increased ECLS, higher risk of death (hazard ratio for isolated LV dysfunction of 1.96 with 95% CI 1.29–2.98 and for BV dysfunction of 2.27 with 95% CI 1.77–2.92),[10] and increased adverse outcomes in even low-risk infants.[11] In the current study, a wide range of echocardiographic parameters, including PH severity, shunt directions at both ductal and atrial levels, and ventricular size and function, were systematically explored and stratified by defect side and size to determine the impact on outcomes. We confirmed that echocardiographic measures were correlated with defect size. Although larger defects are known to be associated with higher mortality,[19,20] the defect size can only be determined if and when the infant is surgically repaired. The accessibility of early postnatal echocardiograms and the strong association between size and outcomes allow for individualized counseling before repair, and early recognition of echocardiographic patterns may help improve the treatment and outcomes of these infants.

Identifying CDH neonates at the highest risk for cardiac dysfunction and altered hemodynamics may allow for preventive or anticipatory therapy approaches. There is increasing evidence that cardiac dysfunction in CDH begins in utero.[26–28] Direct compression from the herniated abdominal organs might be responsible for the observed smaller left heart structures and the distortion of other cardiac structures, affecting flow patterns.[29,30] These anatomical changes lead to decreased left cardiac output, higher LV strain, and diastolic dysfunction.[31–33] Correlating fetal and early postnatal echocardiographic findings may aid in identifying cardiac phenotypes, developing individually targeted therapy, and enhancing outcomes in CDH.

Investigations of the cellular, metabolic, and genetic determinants of cardiac development and function abnormalities,[34–36] as well as how an individualized pathophysiologic-targeted multimodal approach, including pulmonary vasodilators, cardiotropes, and vasopressors combined with optimal ventilatory strategies mitigates cardiac dysfunction in this critically ill patient population are important areas of ongoing research.[7,12,37,38] Finally, in addition to a more standardized approach to evaluating cardiac

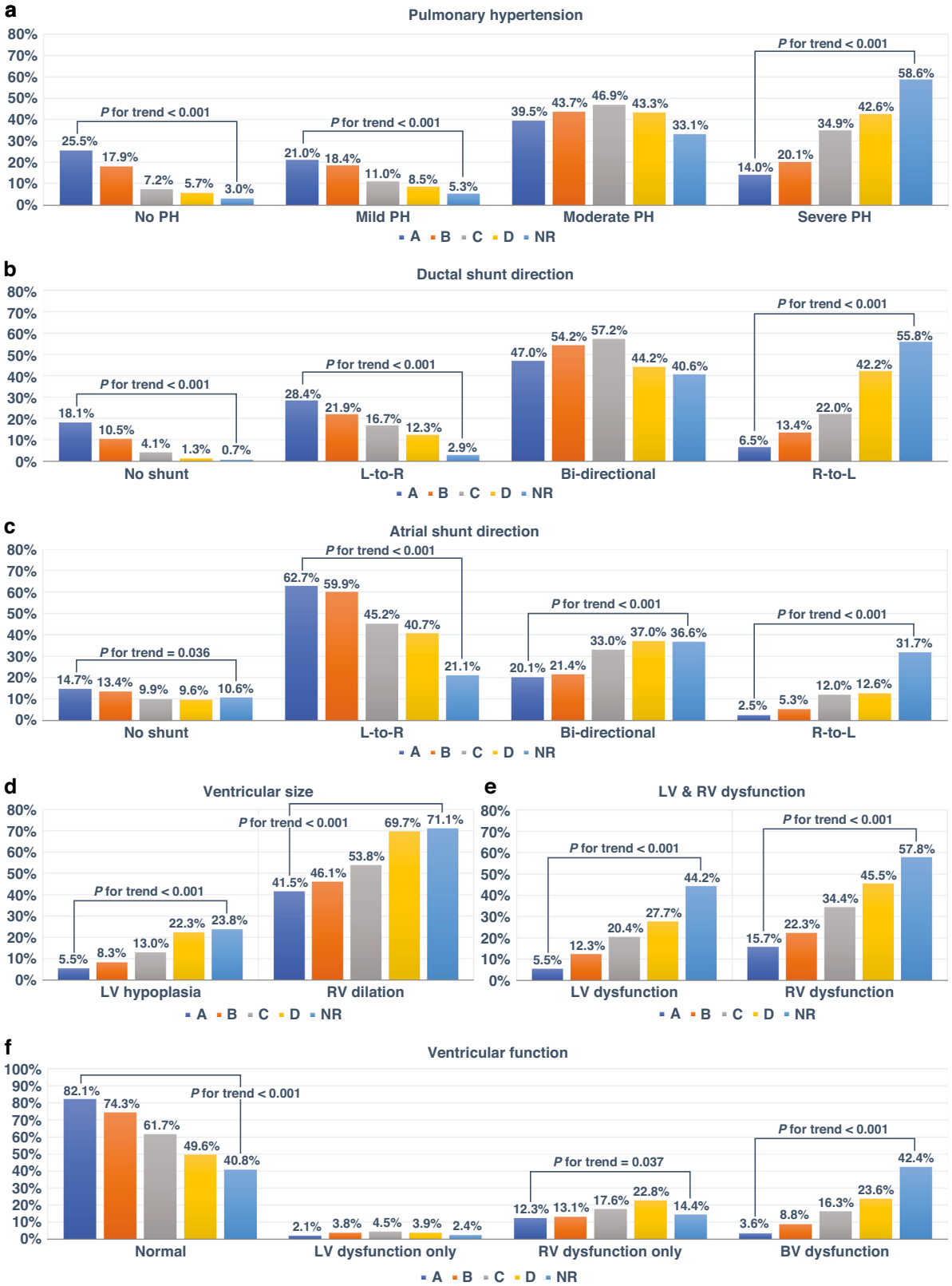

Fig. 3 The first postnatal echocardiographic characteristics by defect size. PH pulmonary hypertension, NR non-repair, LV left ventricle, RV right ventricle, BV bi-ventricular.

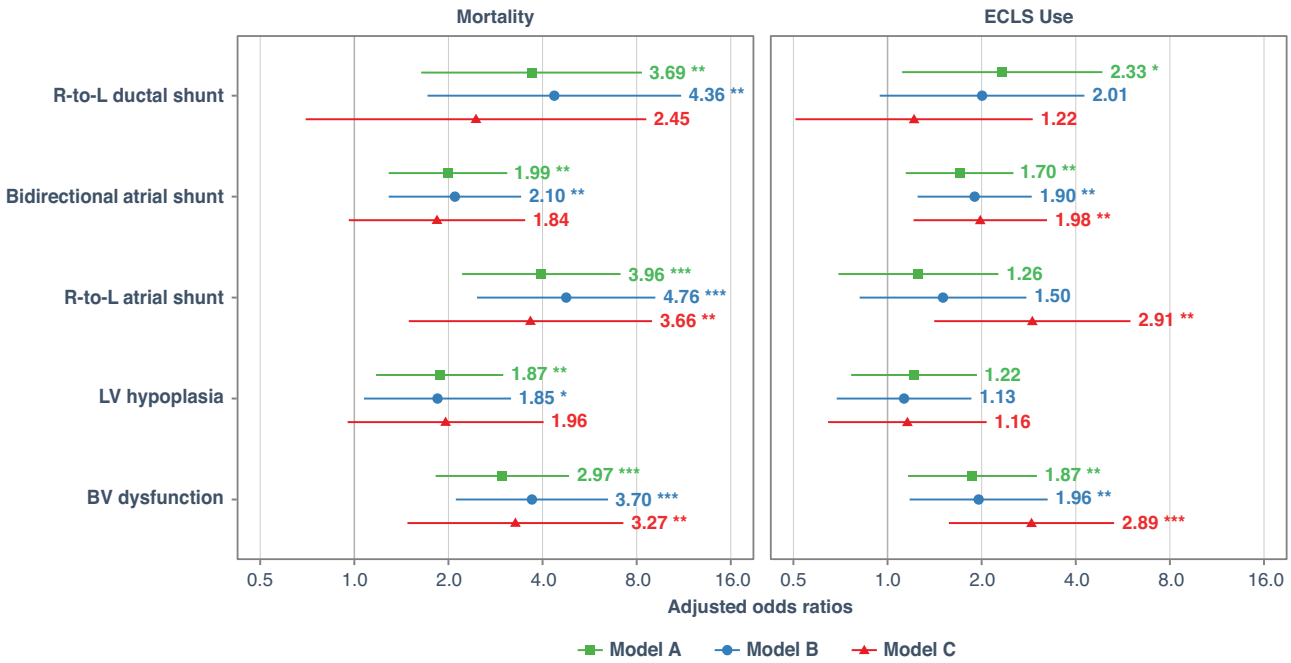

Fig. 4 Echocardiographic predictors for mortality and ECLS use based on multivariate regression models. Values are presented as "adjusted OR [95% CI]". Complete results are shown in Supp Table 4. (LV left ventricle, BV bi-ventricular, CI confidence interval). ***, P .001; **, P .01; *, P .05.

function in neonates with CDH, new management strategies need to be explored to ameliorate cardiac dysfunction either prenatally or postnatally. For example, delayed umbilical cord clamping after initiating ventilation may improve cardiorespiratory transition by maintaining circulating volumes, improving pulmonary blood flow, and optimizing LV function.[39,40] The impact of fetal tracheal occlusion on cardiac function in CDH also warrants further investigation.[41]

This report is the largest multicenter cohort study evaluating early echocardiographic characteristics in neonates with CDH, avoiding the pitfalls of single-center, low-volume studies. The large number of centers increases our sample size and allows for incorporating variations in disease presentation and practice patterns in our analysis, making our findings more generalizable. Our results should be interpreted in the context of several limitations. The observational data are collected prospectively but studied retrospectively, introducing a bias inherent to all registry studies. We also acknowledge that the definition of ventricular dysfunction remains subjective and likely varies between clinicians and centers. Despite consistent efforts to maintain a meticulous dataset, missing or incomplete data introduces a source of bias. Even though all echocardiographic evaluations were performed within 48 hours, the precise timing of scans was not recorded.

In summary, critically ill neonates with CDH are at increased risk for early cardiac dysfunction. The severity of echocardiographic abnormalities differed by defect size and laterality. Larger defects were associated with more severe PH, R-to-L ductal and atrial shunt, bidirectional atrial shunt, LV hypoplasia, RV dilation, LV, RV, and BV dysfunction. Neonates with R-CDH had more severe PH, more bidirectional and R-to-L atrial shunt, and more BV dysfunction. In contrast, L-CDH neonates had more LV hypoplasia and more L-to-R atrial shunt. In multivariate analysis, R-to-L atrial shunt and BV dysfunction were associated with increased mortality, whereas bidirectional atrial shunt and BV dysfunction were associated with ECLS use. Future strategies to prevent, identify, and manage these hemodynamic changes are urgently needed to improve outcomes.

DATA AVAILABILITY

The data supporting this study's findings are available from the CDHSG, but membership restrictions apply. Therefore, the data are not publicly available. Under unique and special circumstances, data could be made available from the authors following reasonable request, for a specific rationale, and with permission of the CDHSG.

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ACKNOWLEDGEMENTS

We acknowledge the ongoing contributions of highly committed Congenital Diaphragmatic Hernia Study Group member centers that voluntarily participate in studying congenital diaphragmatic hernia. This study was supported by a grant from the Maternal & Child Health Research Institute at Stanford awarded to C.Y.N. The sponsor had no role in the design and conduct of the study, the collection, management, analysis, and interpretation of the data, the preparation, review, or approval of the manuscript, or the decision to submit the manuscript for publication.

AUTHOR CONTRIBUTIONS

C.Y.N., E.D., S.B., V.Y.C., and K.P.V.M. contributed substantially to the study's conception and design, acquisition, analysis, and interpretation of data, and drafting and critical revision of the manuscript. N.P., A.D., M.T.H., K.P.L., and A.H.E. contributed substantially to the acquisition, analysis, and interpretation of data and critical revision of the manuscript for important intellectual content. All the authors agreed and approved this version to be submitted for publication.

COMPETING INTERESTS

The authors declare no competing interests.

CONSENT TO PARTICIPATE

The CDHSG registry is hosted by the University of Texas at Houston and approved by its Institutional Review Board (HSC-MS-03-223) with a waiver of informed consent

ADDITIONAL INFORMATION

Supplementary information The online version contains supplementary material available at https://doi.org/10.1038/s41390-025-04443-w.

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