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Right versus left congenital diaphragmatic hernia – What's the difference?☆

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ABSTRACT

Background: Right-sided congenital diaphragmatic hernias (CDH) and bigger defect sizes have been associated with poorer outcomes.
Aim: The aim of this study was to evaluate right- and left-sided CDH in terms of size, survival, associated anomalies, and morbidity.
Material and methods: We used information from a multicenter, multinational database including patients with CDH born between 2007 and 2015. All infants with data on defect side were included for this analysis. We compared differences in outcomes between right- and left-sided CDH. Further analysis on the association between side, size of the defect, and outcome was performed.
Results: A total of 3754 cases of CDH were entered in the registry between January 2007 and September 2015, with an overall survival of 71%. Of those, 598 (16%) were right-sided and 3156 left-sided, with a survival rate of 67% and 72%, respectively. Right-sided CDH had a larger proportion of C and D defects ($p < 0.001$ and 0.04, respectively). Survival rates for the same size defect were similar, independent of the side of the defect. Multivariable logistic regression analysis with survival as dependent variable identified a significant correlation with defect size, but not side.
Conclusions: The higher proportion of large defects (C & D) in right-sided CDH, not the side itself, accounts for the reported poorer survival in right-sided CDH.
Level of evidence: Level I for a prognosis study – This is a high-quality, prospective cohort study with 99% of patients followed to the study end point (death or discharge).

Right-sided congenital diaphragmatic hernias (CDH) have been associated with higher morbidity and mortality compared to left-sided defects [1–3]. Whether the side of the defect has any prognostic value remains controversial, since other groups have reported no differences [3] or better survival [4] for prenatally diagnosed right-sided CDH. It is clear that the size of the defect is inversely correlated with survival and the most powerful predictor of outcome, both in terms of survival and morbidity [5,6]. Whether or not there is a relationship between defect size and the side of the hernia has not been studied.

The aim of the current study was to evaluate and compare outcomes between right- and left-sided CDH in terms of size, survival, associated anomalies, and morbidity.

1. Methods

The Congenital Diaphragmatic Hernia Study Group (CDHSG) was formed in 1995 to collect prospective data on live-born infants with CDH. In 2007 the CDH Study Group Staging System for diaphragm defect size was introduced [5] (Fig. 1).

The CDHSG is a voluntary international collaboration of centers providing care for CDH patients. Data on all infants with CDH born or transferred to a participating center is entered to a central registry. The number of participating centers has increased during the years, with a total of 72 currently participating centers (specified in the Appendix A).

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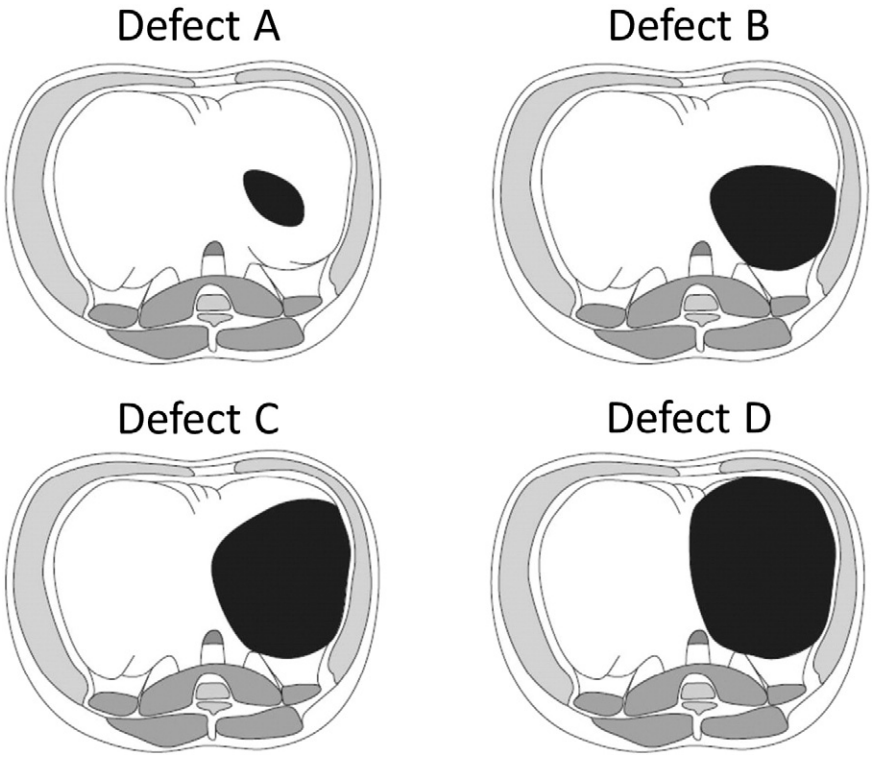

Fig. 1. CDH Study Group Staging System. A left diaphragmatic defect is shown as viewed from the peritoneal cavity looking toward the hemi-thorax. Defects are classified as "A" (smallest, usually "intramuscular" defect with >90% of the hemi-diaphragm present; this defect involves <10% of the circumference of the chest wall), "B" (50–75% hemi-diaphragm present; this defect involves <50% of the chest wall), "C" (~25% hemi-diaphragm present; this defect involves >50% of the chest wall), or "D" (largest defect – previously known as "agenesis" with <10% hemi-diaphragm present; this defect involves >90% of the chest wall.

The registry includes information on newborns with CDH until death or discharge, including infants who died in the delivery room or survived only a few hours in the participating centers. Data from January 2007 to September 2015 were analyzed. Data fields concerning patient demographics, birth weight, gestational age, prenatal diagnosis, associated malformations, need for extra-corporeal membrane oxygenation (ECMO), defect size, need of patch, survival, age at death, length of hospital stay, length of intubation, and need for oxygen at 30 days were evaluated.

Infants with data on defect side were included in this analysis, and comparisons were made between right- and left-sided CDH. Survival rates of right- versus left-sided CDH in patients with records on defect size according to the CDHSG Staging System [5] were further analyzed.

Data are presented as means ± SD, median, absolute values (n) and percentages (%), odds ratios (OR) and 95% confident intervals (CI). Survival to discharge, need for ECMO, survival without ECMO, and need of oxygen at 30 days were used as end points in the analysis. For numerical data, multiple comparisons between groups were performed with the non-parametric Mann–Whitney *U* test, and for categorical data, Fisher's Exact test was performed to investigate differences between groups. Multivariable logistic regression methods were used when appropriate to investigate association between risk variables and outcomes.

Significance was defined as $p \leq 0.05$. Analyses were performed using PRISM 6 (Graphpad Software Inc., La Jolla, CA) and SPSS® version 23.

2. Results

A total of 3754 cases of CDH were entered in the registry between January 2007 and September 2015, with an overall survival of 71%. In 3211 of all the cases and in 99.5% of the cases who underwent surgical repair, the size of the defect was recorded, an indicator of completeness of the data. The side was designated in all recorded cases, showing completeness of side data as well. Right-sided defects accounted for 16% (598) of the total, with a 67% survival rate, and 3156 were left-sided, with significantly better survival rates of 72% ($p = 0.01$). The rates of inborn cases and prenatal diagnosis was significantly higher in left-CDH, with significantly better outcomes for postnatally diagnosed CDH in both groups.

There were no differences in gender rates (60% males in both groups), birth weight (Bw), gestational age (GA) at birth, delivery mode or the rates of associated major cardiac or chromosomal anomalies between groups. There were no differences in survival, side or size between genders.

Right-sided hernias had a higher incidence of non-repair (21% vs. 16%, $p = 0.006$), and a significantly higher proportion of larger defects (C and D) compared to left-CDH (43% vs 31, $p < 0.0001$ respectively 17% vs 13%, $p = 0.04$). The larger defect size was also reflected in the significantly higher rates of patch repair for right-sided hernias (66% vs. 50%, $p < 0.0001$).

Right-sided defects were associated with higher morbidity, reflected in the significantly higher need for ECMO, longer hospital stay, and greater need for O_2 at 30 DOL. There were no differences in the rates of patients that were discharged home or transferred to other institutions, or the length of intubation (Table 1).

2.1. Defect side, size and staging

The rate of associated major heart malformations categorized as A+, B+, C+ and D+ stages, was similar between right- and left-sided defects (Table 2). Survival rates within the same stage were similar between right and left hernias (Table 2, Fig. 2).

Table 1
Patients characteristics and outcome data for Right vs Left sided CDH. Fisher's Exact test for categorical variables, Mann–Whitney *U* for numerical *p < 0.05. For OR calculation left sided CDH serve as reference.

Table 1: 2007–2015	Right CDH	Left CDH	p < 0.05 (Fisher's Exact test categorical variables, Mann–Whitney *U* for numerical)	OR 95% CI
n	598	3156		
%	16	84		
Survival (%)	67	72	0.013	0.8 (0.6–0.9)
Inborn (%)	40	49	< 0.0001	0.7 (0.6–0.8)
Prenatal diagnosis (%)	50	71	< 0.0001	0.4 (0.3–0.5)
Survival prenatal diagnosis (%)	57	66	0.001	0.7 (0.5–0.8)
Survival postnatal diagnosis (%)	77	86	0.0005	0.5 (0.4–0.8)
Male	60	59	ns	
Bw Kg (mean ± SD)	2.9 ± 0.6	3.0 ± 0.6	ns	
GA weeks (mean ± SD)	37.3 ± 2.6	37.6 ± 2.3	ns	
Major heart anomalies(%)	9	8	ns	
Chromosomal anomalies (%)	7	6	ns	
Defect size (n)	501	2710		
A frequency (%)	9	15	0.0003	0.5 (0.3–0.7)
B frequency (%)	31	41	< 0.0001	0.6 (0.5–0.8)
C frequency (%)	43	31	< 0.0001	1.7 (1.4–2.0)
D frequency (%)	17	13	0.04	1.3 (1.0–1.7)
ECMO (%)	36	28	0.0002	1.4 (1.2–1.7)
Survival w/o ECMO (%)	71	81	< 0.0001	0.4 (0.2–0.5)
Patch repair (%)	66	50	< 0.0001	1.9 (1.5–2.3)
No repair (%)	21	16	0.006	1.4 (1.1–1.7)
Length of intubation days (median)	8	8	ns	
LOS days (median)	50	35	< 0.0001	
O2 @ 30 DOL (%)	54	38	< 0.0001	1.9 (1.6–2.4)

Overall survival rates were similar to those previously reported by this group [5].

2.2. Multiple logistic regression analysis

To adjust for possible confounders, multivariable logistic regression analysis was performed with survival as dependent variable and the independent variables defect size as continuous variable (A as reference), side as categorical variable (left as reference) and associated major cardiac anomaly also categorical variable (no association of major cardiac anomaly as reference). We found a significant correlation between size (OR 3.5) and survival, along with associated major anomaly (OR 2.7) and survival. Side of defect did not have a significant correlation with survival (Table 3).

3. Discussion

Previous studies have shown that patients with right-sided CDH have worse outcomes. This CDH Study Group registry investigation confirms that patients with right-sided CDH have poorer outcomes, but this result can be explained by the higher proportion of larger defects size in this group compared to left-sided hernias. It therefore seems to be the size but not the side that is important for the outcome of babies born with CDH. There seems to be developmental timing differences, as seen in the nitrofen rat model, with larger proportion of right-sided defects when the rats are exposed to the teratogenic insult later on in gestation [7]. We speculate that the right lobe of the liver impairing diaphragmatic development may explain the propensity to develop larger defects on the right side. Another possible explanation is the presence of the liver in the defect, with possible contributions from the liver precursors to the post-hepatic mesenchymal plate (also referred as to the pleuroeritoneal fold, the second most important component of the developing diaphragm) [8], is part of the reason why defects are less frequent on the right than the left side.

Proportionally more right-sided CDH are diagnosed after birth compared to left-sided ones (Table 1), suggesting that right-sided CDH would be more likely to be missed prenatally, probably because the liver resembles pulmonary parenchyma by ultrasound and there is less bowel in thorax and less shift of the mediastinum.

Prenatal factors such as O/E LHR, are known predictors of outcome [9,10], and seem also to correlate to postnatal mortality risk stratification [11].

When comparing survival rates for left versus right-sided prenatally diagnosed CDH, it seems clear that right-sided have worse outcomes at similar observed to expected lung to head ratio (O/E-LHR) [9]. With less shifting of the mediastinum in the right-sided, larger lung areas are

Table 2
Outcomes in relation to the international CDH staging system. Fisher's Exact test to explore differences between right and left CDH, *p < 0.05.

Stage	Defect	n	Right CDH (%)	Left CDH (%)	Survival Right CDH (%)	Survival Left CDH (%)	Overall survival (%)	Survival by Lally et al., CDHSG 2013
I	**A**	422	8	***14****	100	99	99	99
II	**A+**	23	1	1	83	86	83	88
II	**B**	1224	27	***40****	95	96	96	96
III	**B+**	54	2	2	72	70	68	67
III	**C**	981	41	***29****	78	78	79	78
IV	**C+**	68	3	2	63	55	54	56
IV	**D**	395	16	***12****	62	56	58	58
V	**D+**	44	1	1	33	34	31	39

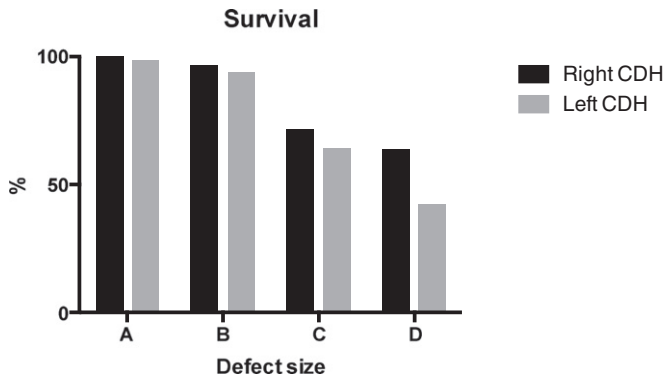

Fig. 2. Survival rates for right and left sided CDH in relation to the defect size.

Table 3
Multivariate logistic regression analysis: p-values, odds ratios and 95% CI for defect size (continuous variable, A as reference), side (categorical variable, left as reference) and associated major cardiac anomaly (categorical variable, no association of major cardiac anomaly as reference) with respect to survival.

	OR	95% CI	p value
Defect size	3.49	2.97–4.10	<0.0001
Side: Left	0.93	.658–1.31	ns
Major heart anomaly	2.71	1.81–4.07	<0.0001

measured in the contralateral side, resulting in higher O/E-LHR for right-sided CDH compared to left-sided. Consequently, right-sided CDH have shown worse survival based on the prenatal measurements and are currently being offered prenatal treatment outside of the ongoing randomized study [12,13]. Despite higher prenatal measured O/E-LHR, right-sided CDH have larger postnatal defect sizes. Thus, in right-sides cases, the measured prenatal O/E-LHR does not seem to correlate to defect size. A more detailed correlation between survival and prenatal O/E LHR for right-sided CDH is warranted, since the currently used divide the cases mainly in > or <45% O/E LHR [12].

For postnatal variables, there is an emerging evidence strengthening the association between defect size and outcome, both for in terms of survival [5] but also morbidity [6]. Defect size seems to be one of the most robust variables that can predict outcome based on postnatal data. Thus, in right-sides cases, the defect size may be more relevant to outcome that the prenatal O/E-LHR.

Other postnatal variables, as low birth weight, absent or low 5-min Apgar score, presence of chromosomal or major cardiac anomaly, and suprasystemic pulmonary hypertension, have also been proposed by this group [14]. We found similar overall survival rates at the different stages in both sides, which are similar to the previously published in 2013 [5]. The differences in survival between both groups cannot be explained by the additional complexity of the malformation, since the rate of associated major heart and chromosomal anomalies was similar for both right and left-sided CDH. We found similar survival rates with similar stages (defect size +/− major cardiac and or chromosomal anomalies).

Even though right-sided CDH has often been reported that have worse outcome [1,2,12], others have found no differences in survival [3,15], but increased pulmonary morbidity with increased need for pulmonary vasodilators and tracheostomy [3]. Other single institution reports have shown excellent survival rates for prenatally diagnosed right-sided CDH compared to both prenatally diagnosed left-sided and postnatal diagnosed right-sided CDH [4]. These differences could be explained by the highly selective nature of the cases that continued pregnancy after the prenatal diagnosis. As in many other congenital malformations, CDH seems to be more common in boys, as in previous reports [16,17], with survival rates and the distribution of side or size similar between genders.

There are a few limitations to large registries such as the CDH Study Group. The major limitation of the study is the inability to determine defect size in infants who did not undergo repair. Another limitation is the inability to account for the "hidden mortality", since centers only report infants either liveborn at their institution or infants successfully transported live to their center. In the years to come, it will be of high interest to compare how prenatal predictors such as O/E LHR correlates to postnatal defect size and outcomes, and it will potentially allow for the optimization of counseling and care in the antenatal, perinatal and immediate postnatal phase.

In summary, this study confirms that right-sided defects have worse outcome than left-sided ones. A possible explanation for this is the significantly higher proportion of large defects in right-sided CDH. We also found that survival rates correlate with the severity of the defect in terms of size, with similar survival rates for similar defects sizes independent of the side of the defect.

Appendix A. Participating Centers (Online only)

Hospital	City	State	Country
Alberta Children's Hospital	Calgary	AB	Canada
Arkansas Children's Hospital	Little Rock	AR	
Astrid Lindgren Children's Hospital	Stockholm		Sweden
Azienda Ospedaliera Papa Giovanni XXIII	Bergamo		Italy
BC Children's & Women's Health Centre	Vancouver	BC	Canada
Carolinas Medical Center, Levine Children's Hospital	Charlotte	NC	
Children's Hospital & Research Center Oakland	Oakland	CA	
Children's Hospital at Skanes University Hospital	Lund		Sweden
Children's Hospital Boston	Boston	MA	
Children's Hospital of Akron	Akron	OH	
Children's Hospital of Illinois	Peoria	IL	
Children's Hospital of Los Angeles	Los Angeles	CA	
Children's Hospital of Oklahoma	Oklahoma City	OK	
Children's Hospital of San Antonio	San Antonio	TX	
Children's Hospital of Wisconsin	Milwaukee	WI	
Children's Hospital Omaha	Omaha	NE	
Childrens Hospital, University Bonn	Bonn		Germany
Children's Hospitals and Clinics (Minneapolis)	Minneapolis	MN	
Children's Memorial Hermann Hospital	Houston	TX	
Children's of Alabama	Birmingham	AL	
Cincinnati Children's Hospital Medical Center	Cincinnati	OH	
Cleveland Clinic Foundation – Children's Hospital	Cleveland	OH	
Connecticut Children's Medical Center	Hartford	CT	
Dell Children's Medical Center of Central Texas	Austin	TX	
Duke University Medical Center	Durham	NC	
Emory University	Atlanta	GA	
Georgia Health Sciences University	Augusta	GA	
Golisano Children's Hospital at Strong	Rochester	NY	
Hospital Clinico Universidad Católica de Chile	Santiago	RM	Chile
IRCCS Fondazione Ca′ Granda Ospedale Maggiore Policlinico	Milano		Italy
Juan P. Garrahan Children Hospital	Buenos Aires		Argentina
Kosair Children's Hospital	Louisville	KY	
Le Bonheur Children's Medical Center	Memphis	TN	
Legacy Emanuel Children's Hospital	Portland	OR	
Loma Linda University Children's Hospital	Loma Linda	CA	
Lucile Salter Packard Children's Hospital	Palo Alto	CA	
Mattel Children's Hospital at UCLA	Los Angeles	CA	
Miami Valley Hospital	Dayton	OH	
National Center for Child Health and Development	Setagaya-ku	Tokyo	Japan
NICU Health Sciences Centre	Winnipeg	MB	Canada
Oespedale Pediatrico Bambino Gesu	Rome		Italy
Osaka University Graduate School of Medicine	Suita	Osaka	Japan
Palmetto Health Richland	Columbia	SC	
Polish Mother's Memorial Hospital Research Institute	Lodz		Poland
Primary Children's Hospital	Salt Lake City	UT	
Radboud University Nijmegen Medical Centre	Nijmegen		The Netherlands
Research Center for Obstetrics, Gynecology and Perinatology	Moscow		Russia
Research Institute at Nationwide Children's Hospital	Columbus	OH	
Royal Children's Hospital	Parkville	Victoria	Australia
Royal Hospital for Sick Children	Glasgow		Scotland
San Diego Children's Hospital	San Diego	CA	
Shands Children's Hospital/University of Florida	Gainesville	FL	
Sophia Children's Hospital	Rotterdam		The Netherlands
St. Francis Children's Hospital	Tulsa	OK	
St. Joseph's Hospital and Medical Center	Phoenix	AZ	

Appendix A. (*continued*)

Hospital	City	State	Country
St. Louis Children's Hospital	St. Louis	MO	
Stollery Children's Hospital	Edmonton	Alberta	Canada
Sydney Children's Hospital	Randwick	NSW	Australia
Texas Children's Hospital	Houston	TX	
The Children's Hospital of Pittsburgh of UPMC	Pittsburgh	PA	
The Hospital for Sick Children	Toronto	Ontario	Canada
UNC School of Medicine	Chapel Hill	NC	
University Malaya Medical Centre	Kuala Lumpur		Malaysia
University of Michigan, C.S. Mott Children's Hospital	Ann Arbor	MI	
University of Nebraska Medical Center	Omaha	NE	
University of Padua	Padua		Italy
University of Texas Medical Branch at Galveston	Galveston	TX	
University of Virginia Medical School	Charlottesville	VA	
Vanderbilt Children's Hospital	Nashville	TN	
Vladivostok State Medical University	Vladivostok		Russia
Winnie Palmer Hospital for Women & Babies	Orlando	FL	
Yale New Haven Children's Hospital	New Haven	CT	

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