Sex-Specific Differences in Congenital Diaphragmatic Hernia Mortality

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Objective To compare disease severity and mortality differences between female and male patients with congenital diaphragmatic hernia (CDH).

Study design We queried the CDH Study Group (CDHSG) database for CDH neonates managed between 2007 and 2018. Female and males were compared in statistical analyses using *t* tests, χ^2 tests, and Cox regression, as appropriate ($P \leq .05$).

Results There were 7288 CDH patients, of which 3048 (41.8%) were female. Females weighed less on average at birth than males (2.84 kg vs 2.97 kg, $P < .001$) despite comparable gestational age. Females had similar rates of extracorporeal life support (ECLS) utilization (27.8% vs 27.3%, $P = .65$). Although both cohorts had equivalent defect size and rates of patch repair, female patients had increased rates of intrathoracic liver herniation (49.2% vs 45.9%, $P = .01$) and pulmonary hypertension (PH) (86.6% vs 81.1%, $P < .001$). Females had lower survival rates at 30-days (77.3% vs 80.1%, $P = .003$) and overall lower survival to discharge (70.2% vs 74.2%, $P < .001$). Subgroup analysis revealed that increased mortality was significant among those who underwent repair but were never supported on ECLS ($P = .005$). On Cox regression analysis, female sex was independently associated with mortality (adjusted hazard ratio 1.32, $P = .02$).

Conclusion After controlling for the established prenatal and postnatal predictors of mortality, female sex remains independently associated with a higher risk of mortality in CDH. Further study into the underlying causes for sex-specific disparities in CDH outcomes is warranted. *(J Pediatr 2023;259:113481)*.

Congenital diaphragmatic hernia (CDH) is a major anatomic anomaly in which there is failed embryonic closure of the diaphragm, resulting in intrathoracic abdominal viscera herniation. Affected infants have varying degrees of pulmonary hypoplasia, pulmonary hypertension (PH), and cardiac dysfunction, leading to high morbidity and an overall neonatal mortality rate approaching 25%-30%.[1,2]

Over the last 2 decades, numerous prenatal and postnatal variables have been identified as useful predictors of clinical disease severity and hospital resource utilization.[3-5] Most notably, the observed/expected lung-to-head ratio (O/E LHR) and presence of intrathoracic liver herniation by fetal ultrasound are widely recognized prenatal factors associated with CDH severity and survival.[6,7] Prognostic variables increase in the postnatal period and include gestational age, birthweight, Apgar scores, concomitant anomalies, measures of PH, and diaphragmatic defect size.[8-16] Using many of these modifiers, prediction models and calculators including the CDH Study Group (CDHSG) prediction model and the Brindle prediction model, have been established.[3,17-19] These tools enhance the ability to estimate mortality risks, thus enabling providers to counsel families with improved accuracy.

While increased prevalence of CDH in male patients has been reported in several studies,[20,21] the impact of patient sex in CDH outcomes is not well understood, as revealed by conflicting data regarding outcomes between the sexes.[22-28] Although numerous reports found no evidence of survival differences between the sexes, most of these studies were of small size and restricted by geographic regionality, thereby limiting their external validity.[22-25] Furthermore, several investigators have shown decreased survival in female infants with CDH based on unadjusted data.[26-28]

In this study, we used a large, multicenter, international database to compare disease severity and to analyze differences in survival between female and male patients with CDH. We hypothesized that female patients would have decreased survival rates

CDH	Congenital diaphragmatic hernia
CDHSG	Congenital Diaphragmatic Hernia Study Group
CI	Confidence interval
ECLS	Extracorporeal life support
HR	Hazard ratio
O/E LHR	Observed/expected lung-to-head ratio
PH	Pulmonary hypertension

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compared with their male counterparts after adjusting for known risk factors of mortality in CDH.

Methods

This was a retrospective, multicenter cohort study utilizing demographic, clinical, and outcomes data from the CDHSG registry (CPHS approval HSC-MS-03-223). Institutional review board approval was also obtained at Johns Hopkins University (IRB00127299). This registry is an observational database on live-born infants with Bochdalek diaphragmatic hernias and includes numerous measurements regarding prenatal severity, birth characteristics, operative management, details of the extracorporeal life support (ECLS) clinical course, and discharge data.[29] The database was queried to include all female and male CDH patients managed from January 2007 to December 2018. The participating hospitals in the CDHSG included 105 centers from seventeen countries. Patients with missing sex data (n = 10) were excluded from analysis.

Study Outcomes and Statistical Analyses

The primary study outcomes were 30-day, 60-day, and in-hospital mortality. Secondary outcomes included weight gain during admission, as well as feeding and oxygen status at 30-days and at discharge.

The majority of data was obtained as a continuous or a categorical (yes/no) variable. The description of major vs minor cardiac anomalies was determined by the CDHSG data administrator based on reports from individual centers.[10] The data regarding repair on/off ECLS were determined on an individual basis using the day of life for ECLS cannulation, ECLS decannulation, and CDH repair.

Pearson's χ^2 tests were used to analyze categorical variables, whereas *t* tests were used to assess continuous variables after confirming normal distribution using the Shapiro-Wilk test. Survival trends of females and males with and without the use of ECLS were compared using Kaplan-Meier estimates. A Cox proportional regression analysis was used to compare the effect of multiple variables on the risk of mortality at 30-days. Variables with a known effect on mortality risk were used in the regression. Statistical analyses were performed with STATA Version 16.1. Significance was defined with a two-sided *P*-value ≤.05.

Results

Between January 2007 and December 2018, there were 7288 neonates with CDH from 105 institutions, of which 3048 (41.8%) were female and 4240 (58.2%) were male (**Table I**). There were no racial/ethnic differences between the 2 sexes. Rates of prenatal CDH diagnoses in females compared with males (female: 2258 [74.4%] vs male: 3013 [71.3%], $P = .004$). At the time of birth, females weighed significantly less than males despite comparable gestational ages (female: 2.84 kg [95% confidence interval {CI} 2.82-2.87] vs male: 2.97 kg [95% CI 2.95-2.99], $P < .001$). Females also had significantly lower Apgar scores at 5-minutes compared with males (female: 6.4 [95% CI 6.3-6.4] vs male: 6.7 [95% CI 6.7-6.8], $P < .001$).

Table I. Prenatal and birth characteristics of patient population

	Male	Female	
	n = 4240	n = 3048	*P* value
Race			.10
Unknown	2285 (53.9)	1631 (53.5)	
Hispanic	546 (12.9)	397 (13.0)	
Non-Hispanic Black	302 (7.1)	217 (7.1)	
Asian	528 (12.5)	438 (14.4)	
Native American	36 (0.9)	25 (0.8)	
Unknown	543 (12.8)	340 (11.1)	
Prenatal diagnosis	3013 (71.3)	2258 (74.4)	.004
O/E LHR	40.9 (39.3-42.6)	43.4 (41.3-45.4)	.06
Prenatal steroid use	790 (24.5)	572 (24.5)	.98
Inborn	2344 (55.4)	1801 (59.1)	.001
Birthweight (kg)	2.97 (2.95-2.99)	2.84 (2.82-2.87)	<.001
Gestational age (weeks)	37.4 (37.4-37.5)	37.4 (37.3-37.5)	.89
Vaginal delivery	2154 (51.3)	1490 (49.6)	.14
Apgar score at 5-minutes*	7 (6-8)	7 (5-8)	<.001
Surfactant	576 (14.3)	416 (14.3)	.94

O/E LHR, Observed/Expected Lung-to-Head Ratio.
Values reported in n (%) vs mean (95% CI).
*Apgar score at 5-minutes reported as median (IQR).

There was a higher rate of overall cardiac anomalies in females (687 [22.6%]) when compared with males (843 [19.9%], $P = .03$) but comparable rates of major anomalies requiring cardiac surgical intervention (female: 266 [8.7%] vs male: 331 [7.8%], $P = .16$) (**Table II**). Females had significantly higher rates of PH compared with males (female: 1856 [86.6%] vs male: 2983 [81.1%], $P < .001$). There were no differences in ECLS cannulation rates, day of ECLS cannulation, and oxygenation/ventilation parameters within 24 hours of birth, based on sex.

Fewer females underwent surgical repair than males (female: 2543 [83.5%] vs male: 3613 85.3%], $P = .03$) (**Table III**). Of those who were repaired, there was a significantly higher rate of intrathoracic liver herniation in females (female: 1233 [49.2%] vs male: 1633 [45.9%], $P = .01$) but comparable defect size, side of defect, and patch repair rates. Among those receiving ECLS, there were no differences in repair rates on ECLS (female: 385 [45.3%] vs male: 497 [42.8%], $P = .27$).

In patients who survived until discharge, the majority did not require supplemental oxygen (female: 1616 [76.2%] vs male: 2345 [75.3%], $P = .45$) and tolerated enteral feeds (female: 1330 [63.9%] vs male: 2011 [65.8%], $P = .15$). Females gained less weight during their admission compared with males (female: 1.05 kg [95% CI 1.03-1.08] vs male: 1.11 kg [95% CI 1.09-1.13], $P = .002$).

Females had significantly lower survival rates at 30 days (female: 2355 [77.3%] vs male: 3397 [80.1%], $P = .003$), 60 days (female: 2241 [73.5%] vs male: 3274 [77.2%], $P < .001$), and at discharge (female: 2140 [70.2%] vs male: 3144 [74.2%], $P < .001$). (**Table IV**). Females and males

Table II. Comorbidities and in-hospital data

	Male n = 4240	Female n = 3048	*P* value
Cardiac anomalies	843 (19.9)	687 (22.6)	.03
Major anomalies	331 (7.8)	266 (8.7)	.16
Minor anomalies	512 (12.1)	423 (13.9)	.02
Chromosomal anomalies	271 (6.4)	227 (7.5)	.08
Pulmonary hypertension	2983 (81.1)	1856 (86.6)	<.001
Medication utilization			.55
Inhaled nitric oxide	2691 (41.5)	1979 (40.8)	
Dopamine	232 (3.6)	186 (3.8)	
Prostaglandin analogs	420 (6.5)	297 (6.1)	
IV/oral sildenafil	1123 (17.3)	850 (17.5)	
Milrinone	1072 (16.5)	800 (16.5)	
Prostacyclin analogs	373 (5.7)	279 (5.7)	
IV corticosteroids	51 (0.8)	33 (0.7)	
Endothelial receptor antagonists	125 (1.9)	97 (2.0)	
Epinephrine	229 (3.5)	168 (3.5)	
Diuretics	36 (0.6)	48 (1.0)	
Dobutamine	51 (0.8)	37 (0.8)	
Antihypertensives	11 (0.2)	12 (0.3)	
Other	71 (1.1)	63 (1.3)	
ECLS	1157 (27.3)	846 (27.8)	.65
DOL at ECLS cannulation	2.5 (2.1-3.0)	3.2 (2.5-3.9)	.11
DOL at ECLS decannulation	13.7 (13.0-14.3)	14.8 (13.9-15.7)	.04
Prior to ECLS			
Preductal saturation	94.6 (93.6-95.6)	94.2 (93.1-95.4)	.60
Postductal saturation	91.3 (90.2-92.4)	90.9 (89.6-92.2)	.66
PaCO2 peak	75.7 (73.7-77.7)	76.3 (73.9-78.6)	.72
Patients not requiring ECLS			
Preductal saturation	95.5 (95.0-96.0)	95.5 (95.0-96.1)	.83
Postductal saturation	91.7 (91.1-92.4)	92.2 (91.4-93.0)	.39
PaCO2 peak	76.2 (74.9-77.4)	74.8 (73.3-76.3)	.18

DOL, day of life; *ECLS*, extracorporeal life support; *PaCO2*, PCO2; *IV*, intravenous.
Values reported in n (%) vs mean (95% CI).

who received ECLS cannulation had similar 30-day trajectories on Kaplan-Meier survival estimates (Wilcoxon test $P = .71$) (**Figure**). However, females who did not receive ECLS had lower survival than males who were not on ECLS (Wilcoxon test $P = .005$).

Table III. Surgical data of patient population

	Male n = 4240	Female n = 3048	*P* value
Diaphragmatic repair	3613 (85.3)	2543 (83.5)	.03
Side of defect			.44
Right	654 (15.5)	489 (16.1)	
Left	3554 (84.0)	2527 (83.1)	
Bilateral	25 (0.6)	24 (0.8)	
Day of life at repair	7.2 (6.9-7.5)	7.3 (7.0-7.7)	.58
Defect size			.95
A	478 (13.5)	327 (13.2)	
B	1396 (39.5)	972 (39.1)	
C	1158 (32.7)	827 (33.3)	
D	505 (14.3)	360 (14.5)	
Patch repair	1947 (54.1)	1361 (53.6)	.71
Intrathoracic liver herniation	1633 (45.9)	1233 (49.2)	.01
Repair on ECLS	497 (42.8)	385 (45.3)	.27
Repair after ECLS	368 (31.7)	245 (28.2)	.17
Repair prior to ECLS	101 (8.7)	81 (9.5)	.52

ECLS, extracorporeal life support.
Values reported in n (%) vs mean (95% CI).

A Cox regression analysis was utilized to assess the independent variables associated with CDH mortality (**Table V**). In adjusted analyses, increasing birthweight (hazard ratio [HR] = 0.68, $P = .002$) and CDH repair (HR = 0.01, $P < .001$) were significantly associated with reduced mortality at 30 days, whereas female sex (HR = 1.32, $P = .02$), prenatal diagnosis (HR = 1.47, $P = .02$), ECLS utilization (HR = 5.05, $P < .001$), and intrathoracic liver herniation (HR = 2.05, $P < .001$) were significantly associated with increased 30-day mortality.

Discussion

Using a large, multicenter prospective database containing over 7000 patients, we found a 30-day survival rate of 77.3% in females, which was significantly lower when compared with 80.1% survival in males. This disparity remained significant at 60-days and when assessing in-hospital survival, as demonstrated by a 70.2% survival rate in females compared with 74.2% in males. Our findings from this large, prospective, international registry suggest that sex is an underappreciated and underutilized variable that adds important prognostic information on disease mortality for CDH.

Another interesting finding from our study was that the survival differences based on sex primarily affected CDH

Table IV. Outcomes and discharge data

	Male	Female	
	n = 4240	n = 3048	*P* value
30-day survival	3397 (80.1)	2355 (77.3)	.003
60-day survival	3274 (77.2)	2241 (73.5)	<.001
In-hospital survival	3144 (74.2)	2140 (70.2)	<.001
Length of stay (days)	51.1 (48.7-53.4)	48.6 (46.5-50.7)	.14
Day of life at death	29.4 (24.1-34.6)	25.4 (22.5-28.2)	.22
Oxygen status at discharge			.45
Room air	2345 (75.3)	1616 (76.2)	
Supplemental oxygen	770 (24.7)	505 (23.8)	
Type of oxygen at discharge			.18
Nasal cannula	558 (72.7)	372 (75.0)	
CPAP	43 (5.6)	22 (4.4)	
Ventilator	161 (21.0)	102 (20.6)	
Unknown	6 (0.8)	0 (0.0)	
Oxygen status at 30 days			.51
Room air	1707 (52.8)	1157 (51.9)	
Supplemental oxygen	1527 (47.2)	1073 (48.1)	
Type of oxygen at 30 days			.32
Nasal cannula	527 (12.4)	340 (11.2)	
CPAP	200 (4.7)	125 (4.1)	
Ventilator	643 (15.2)	472 (15.5)	
ECLS	61 (1.4)	44 (1.4)	
Unknown	2808 (66.2)	2067 (67.8)	
Enteral feeding at discharge	2011 (65.8)	1330 (63.9)	.15
Weight gain during admission (kg)	1.11 (1.09-1.13)	1.05 (1.03-1.08)	.002

CPAP, continuous positive airway pressure; *ECLS*, extracorporeal life support.
Values reported in n (%) vs mean (95% CI).

patients who did not undergo ECLS cannulation, regardless of liver position. The survival rate in females who did not receive ECLS was 77.5%, compared with 82.1% in males. These data are consistent with prior database studies that reported decreased survival in female CDH patients, including 1 that reported decreased survival in females who were not cannulated to ECLS.[26-28] However, since the aims of these previous studies did not focus on sex-specific differences, they did not control for many of the known predictors of mortality in their multivariable analyses.

Our analysis also demonstrated that female sex is a significant prognosticator of mortality, being independently associated with a 32% increased mortality risk at 30-days after controlling for several markers of disease severity. There were various prognostic metrics that differed between females and males, which were hypothesized to increase the risk of mortality in female patients. Females had a higher rate of prenatal CDH diagnosis and had lower birthweights, despite equivalent gestational age. Females also had higher rates of cardiac anomalies and PH, with a smaller percentage of patients who underwent CDH repair. Lastly, despite similar defect size and laterality, females had higher rates of intrathoracic liver herniation. Despite these differences in known predictors of CDH disease severity, the increased adjusted HR in females remained significant.

Interestingly, the association between female sex and mortality was similar in magnitude to other established risk prognosticators including birthweight, which was associated with a 32% decreased risk of 30-day mortality. The relative impact of birthweight on mortality from our data is consistent with findings from another study by the CDH Study Group demonstrating that every 1 kg increase in birthweight increased odds of survival after CDH repair by 34%.[9] Additionally, our analysis showed that female sex had a greater impact on mortality than cardiac anomalies. The patient sample in our database had higher rates of minor cardiac anomalies compared with major anomalies, potentially decreasing the overall effect of this variable.

The basis for the adjusted mortality differences between females and males with CDH cannot be easily explained from our study. Both female and male CDH patients had similar timing of ECLS cannulation, arterial blood gas parameters, pulmonary antihypertensive medication utilization, resource allocation, and surgical repair metrics. These results suggest that females and males in our study were treated similarly in terms of major treatment modalities, and it seems unlikely that differential access to care affected outcomes. Nevertheless, there has been a limited focus on pediatric disease in the healthcare equity sector and an even smaller numbers of pediatrics studies focusing on differences in sex and healthcare disparities.[30,31] Access to care and healthcare utilization have been extensively researched in distinct subsets of the population, with a focus on marginalized and vulnerable populations.[32-35] There is also a body of literature focused on societies with a known predilection toward improved care for males.[36-38] Of those studies that have examined pediatric sex disparities in high-resource, developed nations, there was evidence toward increased utilization of intensive care units in males, but overall higher mortality rates in females.[39,40] Future studies are needed to evaluate

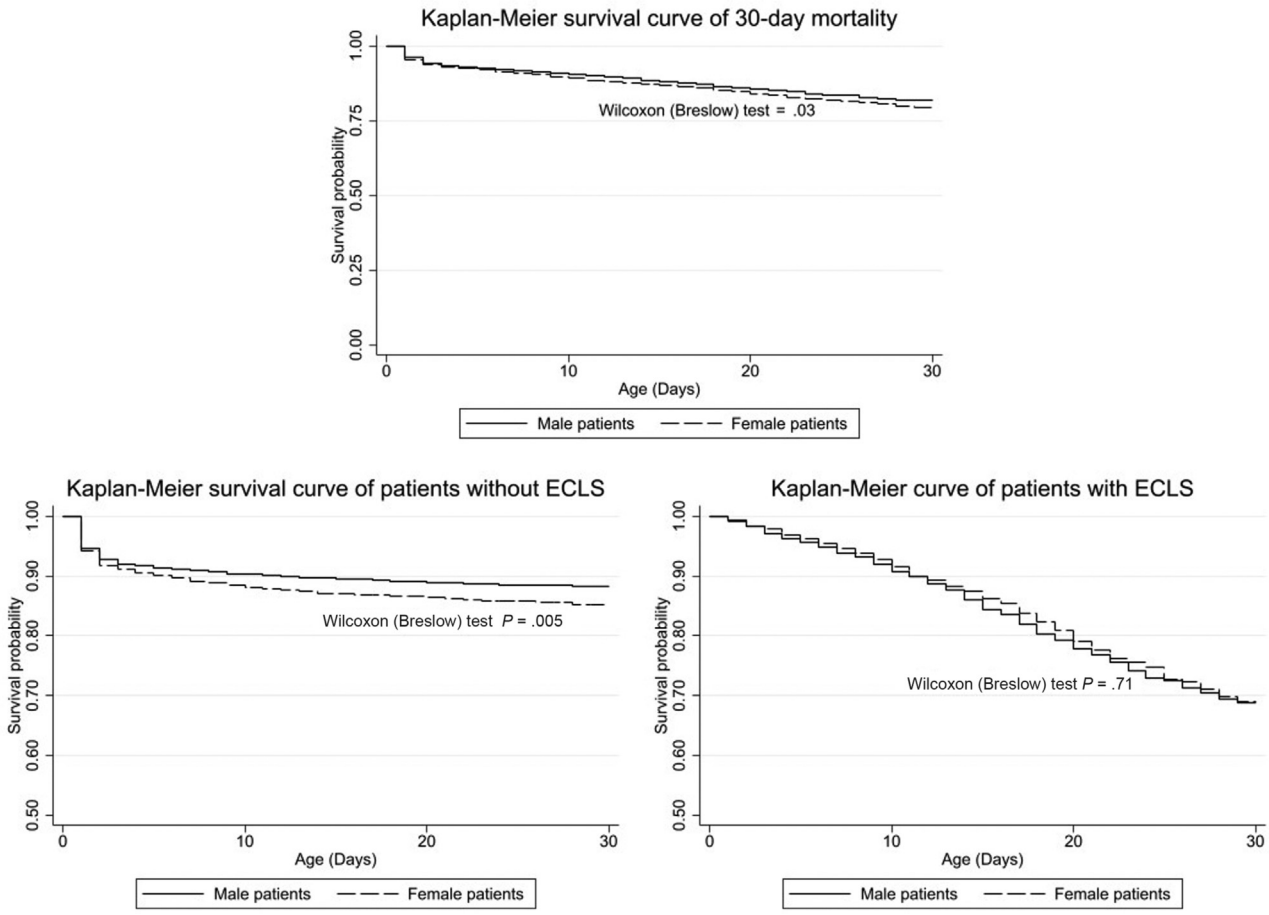

Figure. Kaplan-Meier survival estimates of 30-day mortality in males and females with congenital diaphragmatic hernia, overall and stratified by extracorporeal life support (ECLS) use.

whether sex-specific treatment strategies, such as sex-based criteria for ECLS cannulation, might eliminate the excess mortality in female CDH patients.

Table V. Cox regression analysis of 30-day mortality

	Unadjusted		Adjusted	
	Hazard ratio	*P* value	Hazard ratio	*P* value
Female sex	1.13	.03	1.32	.02
Birthweight*	0.51	<.001	0.68	.002
Gestational age	0.87	<.001	0.97	.30
Apgar at 5-minutes	1.01	.30	0.99	.81
Prenatal diagnosis	1.97	<.001	1.47	.02
ECLS utilization	2.28	<.001	5.05	<.001
Cardiac anomalies	1.59	<.001	1.05	.71
CDH repair	0.03	<.001	0.01	<.001
Intrathoracic liver herniation	4.12	<.001	2.05	<.001
Pulmonary hypertension	1.01	.46	1.06	.25
Inborn	1.54	<.001	0.84	.11
CPR in delivery room	0.89	.21	0.99	.95
Defect size				
A (Reference)	-	-	-	-
B	1.06	.52	0.99	.93
C	0.94	.57	0.78	.18
D	0.89	.32	0.73	.18

CDH, congenital diaphragmatic hernia; *CPR*, Cardiopulmonary resuscitation; *ECLS*, extracorporeal life support.
*Birthweight defined as an increase in 1 kg.

In addition to potential healthcare treatment disparities, sex as a biological modifier of disease severity in CDH is essentially unknown. Several groups have noted inherent chromosomal and hormonal differences between sexes that may have downstream implications on fetal organ development.[41] The imprinting patterns, as well as the random inactivation of X chromosomes in females, lead to sexual dimorphism and are a possible explanation for the differences seen in CDH outcomes.[41,42] Hormonally, there is a surge of testosterone during pregnancy, leading to potential differences between the sexes in their predisposition to diseases and how their cells respond to environmental/genetic stressors. In terms of fetal lung development, there is evidence that males have worse outcomes in bronchopulmonary dysplasia and respiratory distress syndrome, whereas estrogen has been associated with worse outcomes in cystic fibrosis and after congenital cardiac surgery, despite less severe anomalies.[43-50] In PH; however, the effect of estrogen is much more complex.[51-53] Estrogen has been associated with increased rates of PH and abnormal proliferation of pulmonary arterial smooth muscle cells. Conversely, estrogen is also cardioprotective and has been associated with improved markers of angiogenesis and decreased rates of arterial hyperreactivity and

vasoconstriction. To further complicate the study of PH, animal and human studies have not produced consistent and comparable results.[51-53] Finally, there is an increasing body of literature on sexual dimorphism in the fetal and neonatal lung, which suggests that there are sex differences in human lung development as early as the pseudoglandular stage.[54] When considering the chromosomal differences, multiple genetic and epigenetic factors, and existing outcomes data, it is plausible that sex-specific discrepancies occur in CDH patients as well. As espoused by the National Institutes of Health, all research endeavors should make concerted efforts to account for sex as a biological variable along the continuum of experiment research, which in the case of CDH, ranges from in vitro studies of human lung organoid development to clinical trials on fetal endoscopic tracheal occlusion.[55,56] While the mortality differences between male and female patients is likely explained through a biologic mechanism, our data do not permit us to definitively attribute associations to biologic or social etiologies, disparities of care, or a combination thereof.

We acknowledge several limitations to our study. First, we used a prospective, observational study design utilizing a large, multicenter, international registry. While it contains thousands of CDH patients, there may have been data collection challenges, including miscoding and missing data. Second, additional factors relevant to CDH outcomes, including MRI fetal lung volumes, degree of liver herniation, and emerging markers of socioeconomic status, were unavailable from the current version of the CDHSG database. Third, our outcome measures were limited to in-hospital variables and thus we are unable to assess delayed mortality and morbidity. Future goals would be to assess if there is increased mortality among females with CDH at 1-year and 5-year follow-up and to determine whether other long-term outcome measures, including pulmonary, gastrointestinal, and neurodevelopmental morbidities, are different based on sex.

In conclusion, this study of over 7000 infants born with CDH showed that females have a small but significantly decreased survival rate compared with their male counterparts, after controlling for established markers of CDH severity. Our data may be useful in both prenatal and preoperative discussions with families and should be considered in the development of future prediction models of survival. These findings also represent a call to action for investigators to better understand of the basis for these sex-specific outcome disparities in this vulnerable patient population and highlight the possibility of tailored approaches to optimize the care of female CDH neonates. ■

Declaration of Competing Interest

The authors have no conflicts of interest to disclose.

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