Pediatric Surgery International (2019) 35:303–313
https://doi.org/10.1007/s00383-019-04442-z

ORIGINAL ARTICLE

Congenital diaphragmatic hernia: the good, the bad, and the tough

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Accepted: 16 January 2019 / Published online: 24 January 2019

Abstract

Objectives We aim to determine factors that are associated with better outcomes of CDH patients.

Methods A retrospective review was performed on all CDH patients admitted to our institution between 2003 and 2016. This study was performed at a single institution which has a fetal care center. Patients admitted with CDH with at least 1-year follow-up during the analysis were included in the study.

Results Twenty-six (13.8%) patients had a hernia sac, 124 (59%) patients had liver herniation, and 56 (25.1%) patients had an accompanying syndrome. Overall survival to discharge was 73.1% while overall survival to date was 69.5%. The presence of a hernia sac, liver herniation, and accompanying syndromes showed as independent predictors influencing the survival, B 1.968, $p = 0.04$, OR 7.158, 95% CI 0.907–56.485, $B - 1.178$, $p = 0.01$, OR 3.932, 95% CI 1.798–8.602 and $B - 1.032$, $p = 0.05$, OR 2.795, 95% CI 0.976–7.764, respectively.

Conclusion In our CDH cohort, the presence of a hernia sac was proven to be associated with better outcomes, while thoracic herniation of the liver was associated with worse outcomes. The accompanying syndromes although being more difficult to manage had a little effect on the outcome of the disease itself.

Keywords Congenital diaphragmatic hernia · Hernia sac · Liver herniation · Syndrome · Prognostic factors · Cardiac anomalies

Introduction

Congenital diaphragmatic hernia (CDH) has always been considered a medical and surgical challenge in pediatrics. "For the patient in whom the hernia makes its appearance at birth, little or nothing can be done from a surgical standpoint." This statement belongs to Greenwald and Steiner who thought that the surgical management of the CDH was almost impossible [1]. Only 11 years after this statement, Ladd and Gross published an article related to the first successful repair of CDH [2]. Delayed repair of the defect, selective usage of extracorporeal membrane oxygenation (ECMO), in-utero fetal intervention, improved ventilator strategies preventing barotrauma and advancements in neonatal care have increased the overall survival rates of these patients [3]. However, there is still a group of patients with severe CDH that have high morbidity and mortality. Even the criteria for selecting patients for proposed treatment and heterogeneity in the disease severity are variable in the literature; there are some commonly accepted prognostic factors which help to predict outcomes related to the disease. The presence of a hernia sac, the herniation of the liver, and accompanying syndromes or major anomalies are some of the known prognostic factors. Herein, we presented a cohort study to evaluate the effects of these factors on the outcomes of CDH patients in a large series, and to have a better understanding of the prognosis of the disease in conjunction with new improvements in patient management.

Materials and methods

After Institutional Review Board approval was obtained (IRB #2017-6361), a retrospective chart review was performed of all the congenital diaphragmatic hernia patients

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admitted to our institution for care and management between 2003 and 2016. Data, which were assembled through an institutional database and augmented with the hospital electronic medical records, were collected on demographics, preoperative characteristics, and postoperative outcomes including ECMO, oxygen need, length of hospital stay, and survival. Patients were grouped into three by the presence of a hernia sac, thoracic herniation of the liver, and presence of major anomalies such as major cardiac anomalies (tetralogy of Fallot, A–V canal, ASD, VSD, and pulmonary stenosis) or syndromes. The presence of a hernia sac was determined at the time of surgery. The location of the liver was confirmed by prenatal and postnatal imaging, and also during surgery. Prenatal and postnatal workups confirmed the presence of comorbidities. The primary outcome of the study was survival of the patients to date, and the secondary outcome was the ECMO and oxygen need, length of hospital stays, and improvements in the hernia characteristics.

Statistical analysis was performed with IBM SPSS Statistics 20.0.0 (Chicago, IL). The characteristics of the study sample were summarized by descriptive statistics, with dichotomous or ordinal data presented as percentages and continuous data as means with standard deviations. Kolmogorov–Smirnov test was used to demonstrate normal distribution. One-way ANOVA was used for homogeneity of the variables. Student's *T* test and Pearson correlation were used for parametric data. Mann–Whitney *U*, Wilcoxon, and Kruskal–Wallis tests and Spearman correlation were used for non-parametric data. Separate univariable analyses using linear regression models were performed to examine the relationship between each predictor and outcome. Residual plots of the regression models were used to assess the linear models, and scatter plots were used to examine the relationships between continuous variables and outcome variables. Histograms of each of the outcome variables per presence or absence of categorical predictors were produced to assess the relationship between categorical predictors and outcome variables. When the relationship between the continuous predictor and the outcome variable was not linear, appropriate transformations or piecewise linear regression models were pursued to better understand the relationship between variables. Multivariate logistic regression analyses were performed for each outcome of interest where only one of the correlated variables was entered the model at a time which included stepwise, forward selection, and backward elimination. Results were compared to determine if the final model includes the same predictors with all methods. Exact logistic regression was used when appropriate. Statistical associations were considered significant if the p value was < 0.05.

Results

Between 2003 and 2016, 223 patients were admitted to our institution for CDH care and management (Fig. 1). Among these patients, 184 (82.5%) were formerly evaluated at our fetal center, while the rest were admitted postnatally. Overall survival to discharge was 73.1% (163/223), while overall survival to date was 69.5% (155/223). Twenty-six (13.8%) patients had a hernia sac, 124 (59%) patients had liver herniated into the thorax, and 56 (25.1%) patients had an accompanying syndrome. Eighty-one (36.3%) patients required ECMO support. Operative repair was performed in 188 (84.3%) patients, of which 24.5% (46/188) were repaired on ECMO. Of the 35 (15.7%) patients who were not repaired and died, four had associated syndromes, 13 had major cardiac anomalies, and 18 did not achieve cardiac stability despite maximal support. Patients' characteristics are summarized in Table 1.

The good: presence of hernia sac

The presence of a hernia sac could not be determined in the 35 patients that were not repaired. Twenty-six (13.8%) of the 188 patients proved to have a hernia sac during operative repair. Of these patients, 69.2% (18/26) had liver herniation into the thorax, and 23.1% (6/26) had accompanying syndromes. Of these 26 patients, one patient whom the liver herniated into the thorax expired, while all syndromic patients were alive to date. Although the difference of means was very small, CDH patients with a hernia sac delivered later in pregnancy compared to their counterparts without a hernia sac (37.94 ± 1.42 vs. 37.66 ± 1.72), which was statistically significant ($p = 0.00$). These patients also had higher birth weights (3111.81 ± 514.91 g vs. 2890.10 ± 565.16 g, $p = 0.00$). CDH patients with a hernia sac had better lung-to-head ratio (LHR), observed-to-expected (O/E) LHR, and O/E total lung volume (TLV) throughout the pregnancy. The presence of the hernia sac demonstrated that there is a decrease in need of a diaphragmatic replacement with a synthetic patch or muscle flap by 50% (95% CI 0.213–1.209). Thoracostomy tube need was also significantly lower in patients with a hernia sac (23.1% vs. 34.6%). Survival was higher in the CDH patients who had a hernia sac with a shorter hospital stay compared to their counterparts without a hernia sac ($p = 0.00$).

The bad: thoracic herniation of the liver

The liver position could not be stated in 13 (5.8%) of the 223 patients. All of these 13 patients were diagnosed with CDH postnatally, and their liver positions were not determined in their charts, imaging studies, or operative reports. Therefore, they were excluded from the analysis. Of the remaining

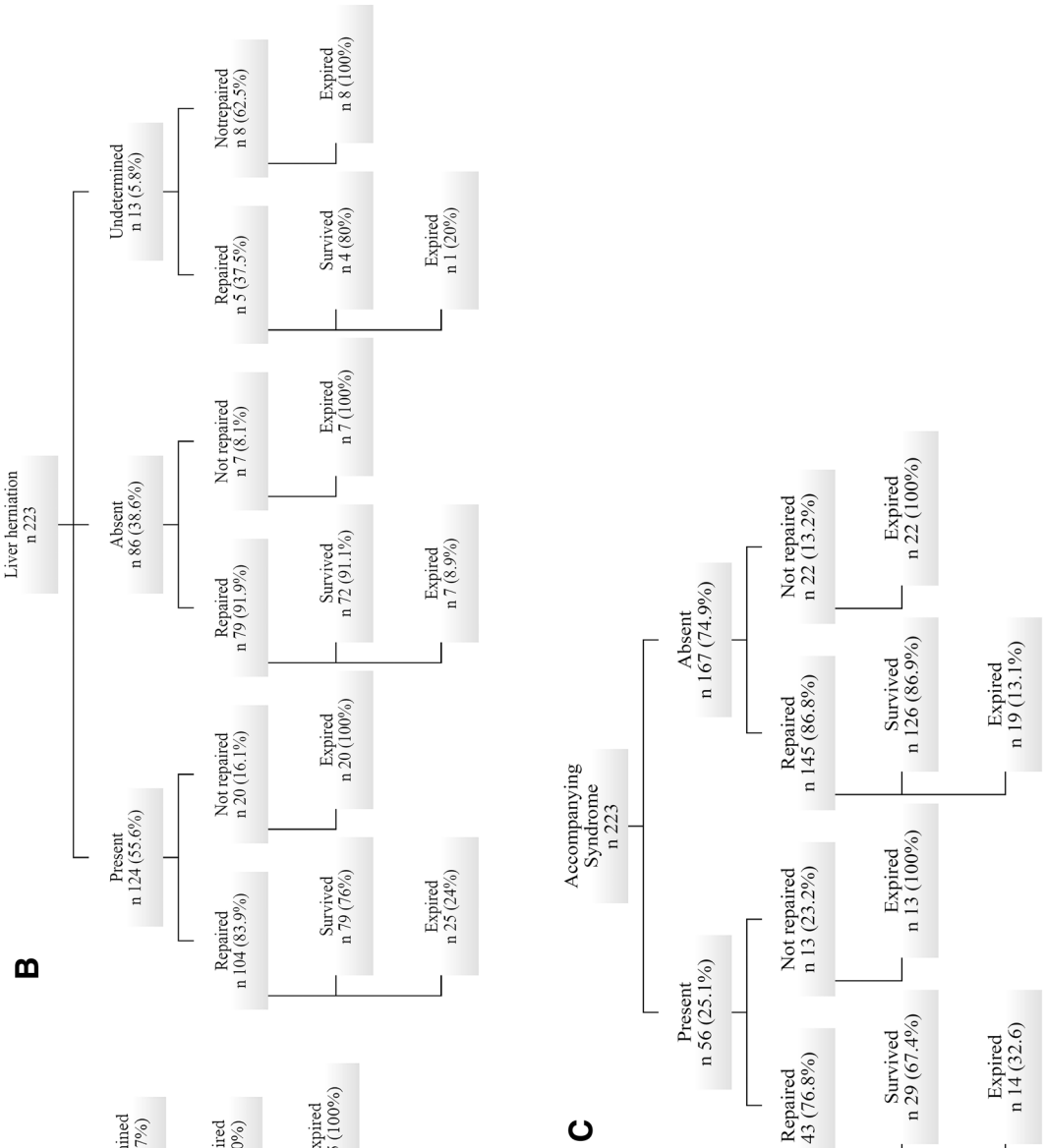

Fig. 1 Classification of congenital diaphragmatic hernia (CDH) patients per the presence of a hernia sac (**a**), location of the liver (**b**), and accompanying syndromes (**c**)

Table 1 Patient and hernia characteristics, and operative and outcome data distributed in groups

	Hernia sac			Liver herniation			Accompanying syndrome		
	Present	Absent	*p*	Present	Absent	*p*	Present	Absent	*p*
	26 (13.8%)	162 (86.2%)		124 (59%)	86 (41%)		56 (25.1%)	167 (74.9%)	
	Mean ± SD/*n* (%)	Mean ± SD/*n* (%)		Mean ± SD/*n* (%)	Mean ± SD/*n* (%)		Mean ± SD/*n* (%)	Mean ± SD/*n* (%)	
Patient characteristics									
Maternal age (years)	26.69 ± 5.71	27.96 ± 6.47	0.64	26.68 ± 6.15	28.94 ± 6.41	**0.01**	28.05 ± 6.67	27.6 ± 6.24	0.65
Gestational age at delivery (weeks)	37.94 ± 1.42	37.66 ± 1.72	**0.00**	37.41 ± 1.75	37.68 ± 2.36	0.33	37.47 ± 1.88	37.5 ± 2.12	0.93
Male (%)	16 (61.5)	94 (58)	0.93	74 (59.7)	50 (58.1)	0.82	37 (66.1)	93 (55.7)	0.17
Weight (g)	3111.81 ± 514.91	2890.10 ± 565.16	**0.00**	2807.72 ± 574.49	2924.28 ± 658.65	0.18	2720.43 ± 676.16	2895.68 ± 591.08	0.07
Type of delivery			**0.01**			**0.00**			0.11
Vaginal (%)	12 (46.2)	72 (44.4)	0.32	33 (26.6)	56 (65.1)	**0.00**	18 (32.1)	75 (44.9)	0.09
Cesarean section (%)	13 (50.0)	87 (53.7)	0.94	84 (67.7)	28 (32.6)	**0.00**	37 (66.1)	84 (50.3)	**0.04**
EXIT (%)	1 (3.8)	3 (1.9)	**0.00**	7 (5.6)	2 (2.3)	0.24	1 (1.8)	8 (4.8)	0.32
APGAR									
1	5.48 ± 2.37	4.69 ± 2.65	0.09	4.45 ± 2.63	5.11 ± 2.59	0.08	3.89 ± 2.74	4.9 ± 2.57	**0.02**
5	7.45 ± 2.22	6.80 ± 2.22	**0.04**	6.46 ± 2.48	7.26 ± 1.95	**0.02**	5.98 ± 2.55	6.99 ± 2.15	**0.01**
10	7.17 ± 1.77	6.71 ± 2.02	0.25	6.49 ± 2.10	6.83 ± 2.33	0.55	6.29 ± 2.1	6.75 ± 2.13	0.41
Prenatal diagnosis (%)	22 (84.6)	131 (80.9)	0.24	111 (89.5)	68 (79.1)	0.04	48 (85.7)	136 (81.4)	0.47
Hernia characteristics									
Side (left) (%)	18 (69.2)	137 (84.6)	**0.04**	93 (75)	84 (97.7)	**0.00**	48 (85.7)	139 (83.2)	0.59
CDH study group staging system defect size			**0.00**			**0.00**			0.26
A (%)	3 (11.5)	16 (9.9)	0.18	1 (0.8)	18 (20.9)	**0.00**	3 (5.4)	16 (9.6)	0.33
B (%)	7 (26.9)	47 (29)	**0.00**	14 (11.3)	38 (44.2)	**0.00**	11 (19.6)	43 (25.7)	0.36
C (%)	10 (38.5)	60 (37)	**0.00**	50 (40.3)	19 (22.1)	**0.01**	15 (26.8)	55 (32.9)	0.39
D (%)	6 (23.1)	39 (24.1)	**0.04**	40 (32.3)	4 (4.7)	**0.00**	15 (26.8)	31 (18.6)	0.19
LHR 1	1.49 ± 0.77	1.26 ± 0.54	**0.05**	1.05 ± 0.39	1.58 ± 0.63	**0.00**	1.1 ± 0.52	1.31 ± 0.56	**0.04**
O/E LHR 1	33.11 ± 13.471	29.38 ± 10.26	0.26	25.61 ± 9.16	35.61 ± 10.39	**0.00**	26.06 ± 10.87	30.67 ± 10.58	**0.02**
O/E TLV 1	24.32 ± 11.79	15.88 ± 11.10	**0.01**	12.32 ± 7.00	20.96 ± 13.75	**0.00**	12.87 ± 9.4	16.33 ± 11.1	0.08
LHR 2	1.82 ± 0.51	1.56 ± 0.69	0.13	1.42 ± 0.58	1.85 ± 0.77	**0.00**	1.32 ± 0.49	1.63 ± 0.7	0.05
O/E LHR 2	33.10 ± 9.17	30.19 ± 12.34	0.17	27.63 ± 10.61	35.35 ± 13.58	**0.01**	25.59 ± 9.27	31.22 ± 12.47	0.06
O/E TLV 2	35.49 ± 12.50	26.28 ± 10.30	**0.00**	24.29 ± 9.99	33.66 ± 11.13	**0.00**	25.99 ± 12.45	26.93 ± 10.46	0.70

Table 1 (continued)

	Hernia sac			Liver thoracic herniation			Accompanying syndrome		
	+	−	*p*	+	−	*p*	+	−	*p*
	26 (13.8%)	162 (86.2%)		124 (59%)	86 (41%)		56 (25.1%)	167 (74.9%)	
	Mean ± SD/*n* (%)	Mean ± SD/*n* (%)		Mean ± SD/*n* (%)	Mean ± SD/*n* (%)		Mean ± SD/*n* (%)	Mean ± SD/*n* (%)	
Operative characteristics									
Surgery (%)	26 (100)	162 (100)		105 (84.7)	79 (91.9)	0.12	44 (78.6)	145 (86.8)	0.14
Operation date (day-of-life)	12.88 ± 12.44	14.01 ± 11.95	0.66	14.86 ± 12.38	12.32 ± 11.31	0.16	15.84 ± 13.89	13.27 ± 11.35	0.22
Surgery time (min)	237.30 ± 87.71	234.68 ± 87.50	0.90	257.81 ± 80.59	210.68 ± 87.71	**0.00**	240.78 ± 92.98	233.33 ± 85.42	0.65
Blood loss (ml)	12.52 ± 11.65	23.48 ± 66.77	0.48	30.00 ± 87.13	12.38 ± 13.85	0.09	18.67 ± 23.9	23.05 ± 72.87	0.72
Thoracostomy tube (%)	6 (23.1)	56 (34.6)	**0.00**	48 (38.7)	13 (15.1)	**0.00**	14 (25.5)	48 (29.3)	0.78
Concurrent appendectomy (%)	5 (21.7)	43 (28.9)	**0.00**	29 (25.7)	19 (23.2)	0.13	11 (22)	37 (24.2)	0.61
Repair type			**0.00**			**0.00**			0.36
Primary (%)	10 (38.5)	39 (24.1)	**0.00**	8 (6.5)	41 (47.7)	**0.00**	11 (19.6)	38 (22.8)	0.63
Patch (%)	7 (26.9)	58 (35.8)	**0.00**	45 (36.3)	15 (17.4)	**0.00**	15 (26.8)	50 (29.9)	0.65
Flap (%)	9 (34.6)	64 (39.5)	**0.00**	50 (40.3)	23 (26.7)	**0.04**	17 (30.4)	56 (33.5)	0.66
Outcome									
ECMO (%)	4 (15.4)	57 (35.2)	**0.00**	65 (52.4)	13 (15.1)	**0.00**	23 (41.1)	58 (34.7)	0.14
Repair on ECMO (%)	2 (7.7)	43 (26.5)	**0.00**	39 (31.5)	6 (7)	**0.00**	17 (30.4)	29 (17.4)	**0.02**
ECMO starting time (days)	1.00 ± 0.00	3.36 ± 9.06	0.84	3.02 ± 8.56	3.33 ± 5.43	0.90	2.83 ± 7.47	3.1 ± 8.11	0.89
ECMO lasting (days)	9.50 ± 4.20	14.02 ± 12.05	0.73	14.97 ± 11.86	8.50 ± 4.44	0.07	15.23 ± 16.78	13.02 ± 7.78	0.43
Survival (%)	25 (96.2)	130 (80.2)	**0.00**	79 (63.7)	72 (83.7)	**0.00**	29 (51.8)	126 (75.4)	**0.00**
Intubated time (days)	30.50 ± 42.17	47.36 ± 81.39	0.16	57.45 ± 95.28	24.07 ± 20.05	**0.00**	45.19 ± 64.68	39.24 ± 74.46	0.62
Length of stay (days)	69.12 ± 53.05	82.01 ± 69.70	**0.00**	84.65 ± 74.05	57.87 ± 53.98	**0.01**	88.41 ± 85.81	64.29 ± 58.44	**0.03**

Statistically significance values are in bold

Values expressed as means ± standard deviations or counts (percentage of the group). EXIT shows ex utero intrapartum treatment procedure

CDH congenital diaphragmatic hernia, *LHR 1* indicates lung-to-head ratio before 30th gestational week, *O/E LHR 1* observed-to-expected lung-to-head ratio before 30th gestational week, *O/E TLV 1* observed-to-expected total lung volume before 30th gestational week, *LHR 2* indicates lung-to-head ratio after 30th gestational week, *O/E LHR 2* observed-to-expected lung-to-head ratio after 30th gestational week, *O/E TLV 2*, observed-to-expected total lung volume after 30th gestational week, *ECMO* extracorporeal membrane oxygenation

210 patients, 124 (59%) had liver herniated into the thorax. Patient characteristics were similar between the group with liver herniation and without liver herniation with the only exception in the maternal age, which was slightly lower in patients with liver herniation ($p=0.01$). Cesarean section rate was higher in the liver herniation group. In addition, patients with liver herniation had a larger size of CDH defect and decreased lung measurements (LHR, O/E LHR, O/E TLV) ($p=0.00$). Although the herniation of the liver into the thorax did not affect the operability of the patients and the timing of the surgery, it did significantly increase the duration of surgical repair ($p=0.00$). More patients with liver herniation needed ECMO as well as CDH repair while on ECMO ($p=0.00$). However, it did not predict ECMO cannulation time and how long the patient was on ECMO. Patients with liver herniation had a higher mortality rate, increased need for a thoracostomy tube, longer oxygen requirements, and hospital stays ($p=0.00$).

The degree of liver herniation was also analyzed in detail per percentage of the liver mass that herniated into the thorax. Twenty percent was determined as the cut-off point, i.e., if less than 20% of the liver mass was in the thoracic cavity, it was considered as a mild herniation (*n* 44, 37.3%), while over 20% is classified as a severe herniation (*n* 74, 62.7%). As the percentage of the liver herniation increases, the need for ECMO increases ($p=0.00$), while the survival decreases ($p=0.04$) (Fig. 2). The prenatal lung measurements also decreased as more portion of the liver is herniated ($p=0.00$).

The tough: accompanying syndromes or major malformations

Fifty-six (25.1%) patients had accompanying associated major fetal defects, of which 14 (6.3%) patients had syndromes and 42 (18.8%) patients had major cardiac anomalies. Patient and hernia characteristics were mostly similar between isolated and non-isolated CDH except in Apgar scores on first and fifth minutes, and LHR measurements before the 30th week of gestation. The surgical data, however, were not affected by the presence of any anomalies. Although the need for oxygen was similar between groups, the length of the hospital stay was higher in the CDH patients with anomalies ($p=0.03$). The survival was significantly lower in complex CDH patients compared to isolated ones ($p=0.00$). However, 5/56 (8.9%) patients in the syndromic group and 6 (10.7%) patients in the isolated group expired due to non-CDH pathology ($p=0.12$).

Mortality analysis

Univariate analysis showed that the presence of a hernia sac, liver position, and accompanying syndromes were the

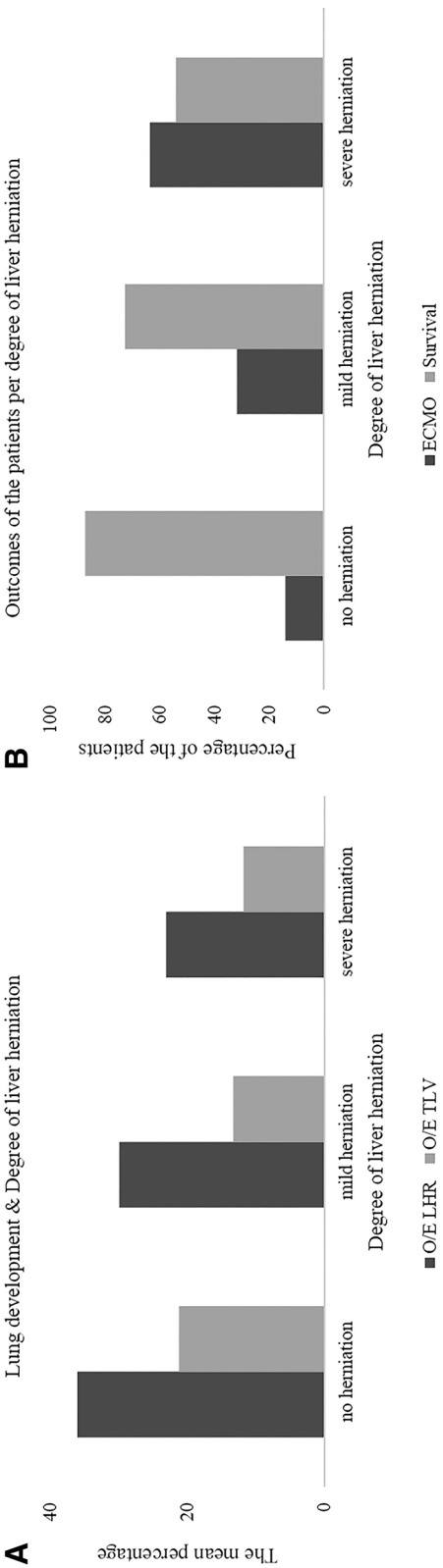

Fig. 2 **a** Comparison of the lung development per degree of the liver herniation. As the degree of the liver herniation increases, the mean percentage of O/E LHR and O/E TLV decreases. **b** Comparison of the outcomes of the patients in means of ECMO need and survival per degree of the liver herniation. As the degree of the liver herniation increases, the number of patients that necessitates ECMO cannulation increases, while the number of patients who survive decreases (O/E LHR, observed-to-expected lung-to-head ratio after 30th gestational week; O/E TLV, observed-to-expected total lung volume after 30th gestational week; ECMO, extracorporeal membrane oxygenation.)

Table 2 Multiple logistic regression of factors influencing survival in CDH patients

	B	*p*	OR	95% CI
Presence of hernia sac	1.968	0.04	7.158	0.907–56.485
Liver herniated into thorax	−1.178	0.01	3.932	1.798–8.602
Patients with accompanying syndromes and CHD	−1.032	0.05	2.795	0.976–7.764

B coefficient, *p* probability value, *OR* odds ratio, *CI* confidence interval, *CHD* congenital heart disease e.g. tetralogy of Fallot, A–V canal, ASD, VSD, and pulmoner stenosis

most crucial factors that determine the survival of the CDH patients. Variables from Table 1 with statistical significance were then entered into a stepwise logistic regression model to assess their multivariate validity in predicting survival. Multinomial regression analysis identified the presence of a hernia sac, liver herniation, and accompanying syndromes as independent predictors influencing the survival (Table 2).

The Kaplan–Meier analysis demonstrated significant differences in survival of the CDH patients depending on the factors which we looked at ($p=0.00$). Hence, the majority of the death occurred early in life; 1 year, 5 year, and 10 year life tables were composed (Fig. 3). All patients with a hernia sac were discharged alive in contrast to 38/124 (30.6%) patients with liver herniation, and 24/56 (42.9%) patients with an accompanying syndrome expired before discharge. After discharge of the patients, only 1/26 (3.8%) patient with a hernia sac expired, while 7/86 (8.1%) patients with liver herniation and 3/32 (9.4%) patients with an accompanying syndrome expired.

Morbidity analysis

In multinomial regression analysis for comorbidity, the presence of a hernia sac and thoracic herniation of the liver was independent risk factors. The presence of a hernia sac decreased the likelihood of ECMO cannulation (*B*: 1.443, $p=0.02$, OR 4.234 95% CI 1.314–13.646), while liver herniation increased the need for ECMO cannulation (*B*: 1.778, $p=0.00$, OR 5.919 95% CI 2.728–12.841). There was only one patient with a hernia sac and without liver herniation that needed ECMO support. The presence of the hernia sac also decreased the need for a diaphragmatic replacement (*B*: 2.028, $p=0.00$, OR 7.603 95% CI 2.160–26.762) in contrast to liver herniation that increased its need (*B*: 3.231, $p=0.00$, OR 25.300 95% CI 8.475–75.527). There were only two patients with a hernia sac and without liver herniation that required diaphragmatic replacement. In correlation analysis, the highest correlations were found between the presence of a sac and operability of the patients (0.951, $p=0.00$); the presence of a sac and need for thoracostomy tube (0.837, $p=0.00$); absence of liver herniation and primary repair of the diaphragmatic defect (0.679, $p=0.00$). The absence of a sac was associated with four times higher probability of intubation time longer than 30 days (*B* 1.474, $p=0.01$, OR 4.365 95% CI 1.415–13.465). On the other hand, the absence of liver herniation was associated with 1.5 times higher probability of extubation within the first 30 days of life (*B* 1.606, $p=0.00$, OR 4.982 95% CI 2.390–10.383).

Discussion

There has been a great improvement in the management of CDH patients in the past years with a selective usage of ECMO and advancements in neonatal care. However, pulmonary hypertension is still the main challenging issue in these patients. Although the severity of pulmonary hypertension varies in patients, it is not the only factor that determines the disease outcome. While there are some factors, such as the timing of ECMO, timing, and type of surgery, which could be decided by the surgeon, there are some factors those cannot be manipulated but should be aware of such as liver herniation, the presence of a sac and accompanying syndromes. Traditionally, the sac is a good prognostic factor that protects the lungs from being compressed, and herniation of the liver into the thorax, on the other hand, is a bad prognostic factor that causes compression of the lungs and contributes to pulmonary hypoplasia. Accompanying syndromes, although affect the survival, do not directly affect the disease itself.

Hernia sac, reported in 20% of cases in the literature, is formed by parietal peritoneum and lung pleura [4]. However, the studies focused on the impact of the sac are scarce, although all of them refer the presence of sac as associated with a higher pulmonary volume and a better overall prognosis [5–7]. In our study, the incidence of a sac was 13.8%, and the presence of a sac does not seem to be affected by the age of mother or gender of the baby. It is speculated in the literature that the presence of a sac in CDH is evidence of late herniation [8]. The mean gestational age at diagnosis was higher in the presence of a hernia sac. Fetal lung development parameters were also higher throughout the pregnancy in patients with a hernia sac. In the presence of the sac, it was the principal factor that determines the need for ECMO cannulation and survival of the patients. The length of stay in the hospital is positively affected by the presence of the sac, which was statistically significant.

The herniation of the liver into the thorax was associated within earlier gestation time at diagnosis, increased need for ECMO, and attenuated development of the fetal lung which has already been demonstrated in the literature [8–13]. The necessity of ECMO in patients with liver-up was lower (52.4%) than reported in the literature (80%) [13]. The presence of the liver in the chest in left-sided CDH

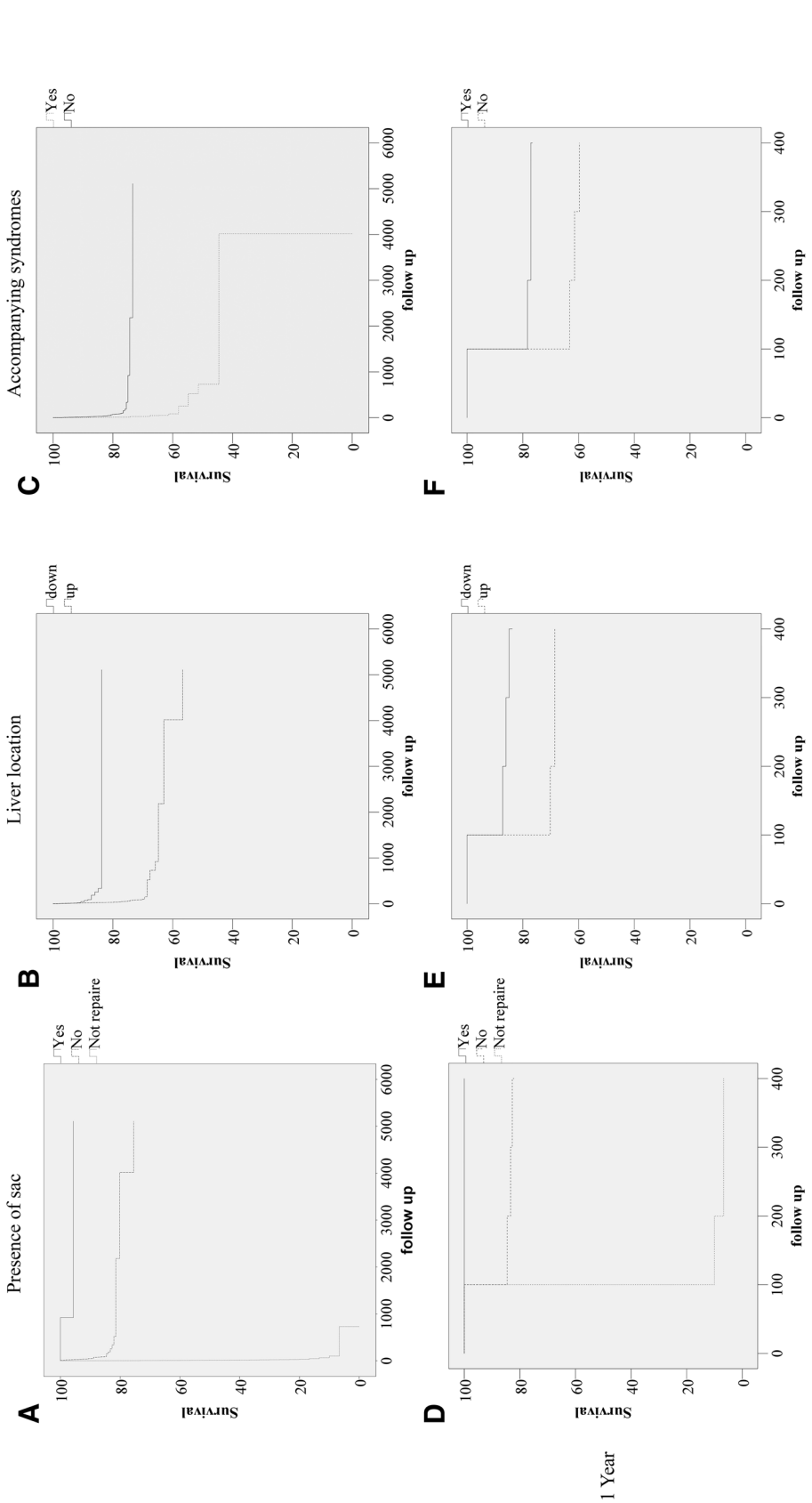

Fig. 3 Survival analysis per **a** presence of sac, **b** liver position, and **c** presence of accompanying syndromes with Kaplan–Meier Analysis curve throughout the study period demonstrated significant differences in time to death between groups in each parameter ($p = 0.00$). Life table analysis of survival rate, comparing the cumulative survival between groups in one (**d–f**), five (**g–i**), and ten (**j–l**) years' time demonstrated that the majority of the deaths occurred early in life

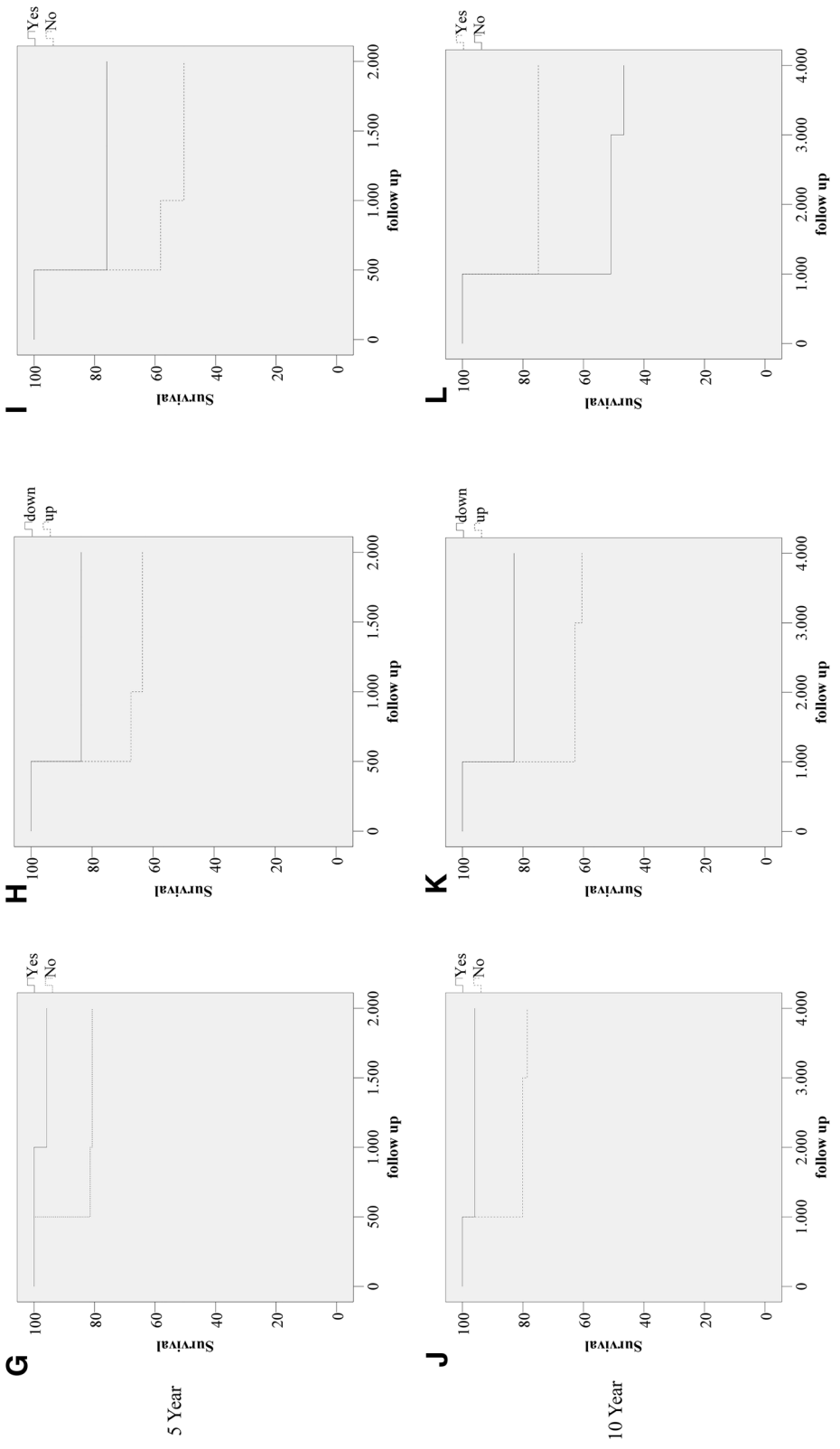

Fig. 3 (continued)

patients mostly indicates a large defect in the diaphragm with the early herniation of abdominal viscera, resulting in severe pulmonary hypoplasia and pulmonary hypertension. Even with improvements in the neonatal care management, thoracic herniation of the liver still affects the survival negatively. Even mild herniation has significant effects on both survival and ECMO need, it is very important to quantify the amount of liver herniated to estimate the prognosis, since we found significant differences in outcomes when we compare liver down, with mild herniation and significant liver-up. Some authors described that assessment of the ratio of the volume of the liver that was herniated into the thoracic cavity to the volume of the thoracic cavity was calculated (LiTR) using MRI provided prediction of postnatal survival independently from O/E TLV [14]. Mortality and the need for ECMO in neonates with isolated CDH can be best predicted using a combination of MRI and O/E TLV and percentage of liver herniation [15]. Our study correlates with the studies in the literature, which demonstrated that liver herniation also predicts the early neonatal morbidity, need for diaphragmatic replacement techniques, prolonged oxygen need, and prolonged length of hospital stay [8–13, 16].

It is well known that CDH patients with accompanying anomaly have a poor overall prognosis [17–19]. Genetic counseling and early recognition of anomalies are essential for parental counseling and postnatal management plan. The presence of cardiac anomalies in CDH patients has been reported as 10–35% in the literature [20]. Accompanying syndromes increase the burden of the disease and act as one of the poor prognostic factors, but they do not count in the nature of the disease. As it was shown in our study, the presence of accompanying syndromes did not have any direct effect on any patient or hernia characteristics. The length of hospital stay was longer in this patient population as one expects, and in the majority of the cases, the delayed discharge was because of the comorbidity related to the syndromes.

There are some limitations in our study. It is a retrospective review, which includes inherent bias. Furthermore, in different institutions and even among surgeons, there is variability in treatment protocols and operative techniques. In addition, long-term follow-up data are difficult to collect in this patient population as many of them are transitioned to other institutions or facilities that do not integrate with the electronic medical record system allowing for data collection. Anyhow, the large number of patients with CDH which we present in this series could countervail these limitations.

In our review of CDH cohort, the presence of a hernia sac, “the good”, was proven to be associated with better outcomes, while thoracic herniation of the liver, “the bad”, was associated with worse outcomes. The accompanying syndromes or associated major malformations, “The Tough”, although being more difficult to manage, had a little effect on the outcome of the disease itself. Further prospective, multicenter, randomized trials are necessary to elucidate superiority and confirm these predictors.

Author contributions All authors have made substantial contributions to the conception and design of the study, acquisition, analysis, and interpretation of data, drafting the article and revising it for important intellectual content and final approval of the version to be submitted.

Funding This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Compliance with ethical standards

Conflict of interest The authors report no proprietary or commercial interest in any product mentioned or concept discussed in this article.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee (IRB #2017-6361) and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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