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Congenital diaphragmatic hernias

Severe defect grade predicts the need for fundoplication

Laura C. Guglielmetti, MD[a], Arturo E. Estrada, MD[b], Ryan Phillips, MD[b], Ralph F. Staerkle, MD[c], Jason Gien, MD[d], John P. Kinsella, MD[d], Kenneth W. Liechty, MD[b], Ahmed I. Marwan, MD[b], Raphael N. Vuille-dit-Bille, MD, PhD[b,e,*]

Abstract

Over one-third of infants with congenital diaphragmatic hernia (CDH) eventually require a Nissen fundoplication (NF). We examined pre- and intraoperative predictors for need of a NF in children undergoing CDH repair to elucidate, which patients will need a later NF.

A retrospective analysis of all consecutive patients undergoing CDH repair at our institution from 2008 to 2018 was performed. Patients who underwent a NF were compared to those who did not (noNissen). Logistic regression analysis was performed to find independent predictors for NF in patients undergoing CDH repair. *Severe Defect Grade* was defined as defect >50% of the hemidiaphragm and intrathoracic liver.

One hundred twenty-six patients were included, 42 (33%) underwent NF at a median of 61 days after CDH repair. Intrathoracic liver was more frequent in the NF (71%) versus noNissen (45%) group ($P = .008$). Absence of >50% of the hemidiaphragm was more frequent in the NF group (76% vs 31%, $P < .001$). *Severe Defect Grade* emerged as independent predictor for NF (odds ratio 7, 95% confidence interval 3–16, $P < .001$).

Severe Defect Grade emerged as independent predictor for NF after CDH repair.

Abbreviations: AUC = area under the curve, CDH = congenital diaphragmatic hernia, CI = confidence interval, ECMO = extracorporeal membrane oxygenation, GERD = Gastroesophageal reflux disease, LHR = lung-to-head ratio using MRI or fetal ultrasound, LOS at ICU = length of stay at the intensive care, LV RV disproportion = Left ventricle-to-right ventricle disproportion, NF = Nissen fundoplication, NICU = neonatal intensive care unit, PPHN = persistent pulmonary hypertension, PPLV = percentage predicted lung volume, PTFE = polytetrafluoroethylene, SD = standard deviation, TLV = total lung volume.

Keywords: congenital diaphragmatic hernia, Nissen fundoplication, predictors, gastroesophageal reflux

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[a] Department of Visceral- and Thoracic Surgery, Cantonal Hospital Winterthur, Winterthur, Switzerland, [b] Department of Pediatric Surgery, Children's Hospital Colorado, University of Colorado School of Medicine, Denver, CO, [c] Clarunis, University Center for Gastrointestinal and Liver Diseases, Basel, Switzerland, [d] Department of Pediatrics, Section of Neonatology, University of Colorado School of Medicine and Children's Hospital Colorado, Aurora, CO, [e] University Children's Hospital of Basel, Switzerland.

[*] Correspondence: Raphael N. Vuille-dit-Bille, Department of Pediatric Surgery, University Children's Hospital of Basel, Spitalstrasse 33, 4056 Basel, Switzerland (e-mail: rnvuille@gmail.com).

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1. Introduction

Congenital diaphragmatic hernia (CDH) is a rare disease with approximately 3 cases per 10,000 live births.[1] Gastroesophageal reflux disease (GERD) frequently complicates the course in CDH, leading to failure to thrive, apparent life-threatening events, and aspiration. GERD occurs in 1.6% to 83.3% among CDH survivors,[2–9] depending on the cohort analyzed and about one-third of CDH survivors require surgical intervention with Nissen fundoplication (NF) later in the course.[2,10]

NF dates back to 1956 when Nissen et al[11] reported the first two cases undergoing the fundoplication with great success. NF remains one of the common procedures for GERD up to today. NF after CDH repair can be difficult due to postoperative scarring and distorted anatomy. If patients needing subsequent NF following CDH repair could be identified before or during CDH repair, contemporaneous fundoplication could be offered. We aimed to examine pre- and intraoperative predictors of need for NF in children with CDH to determine whether a subset of CDH patients exists, who might benefit from a NF at the time of diaphragmatic hernia surgery.

2. Methods

2.1. Study cohort and clinical outcomes

A retrospective analysis of all patients managed at Children's Hospital Colorado with CDH from 2008 to 2018 ($n = 143$) was conducted. Exclusion criteria were patients who died before

surgical CDH repair ($n=6$), patients who died within 30 days after CDH repair ($n=9$) or who underwent NF at the time of the hernia repair ($n=2$).

Patients' medical records were retrospectively reviewed and data extracted including the following prenatal variables: Abnormal karyotype, presence of a syndrome, left ventricle-to-right ventricle disproportion using fetal echocardiography (LV RV disproportion), Mc Goon index, lung-to-head ratio using magnetic resonance imaging or fetal ultrasound (LHR), observed to expected LHR, total lung volume (TLV), percentage predicted lung volume (PPLV), liver position, prenatal steroids, and amniotic fluid index. Postnatal variables included gestational age, congenital heart disease, persistent pulmonary hypertension, sex, cesarean section (c-section), Apgar score at one1 and 5 minutes, and side of the hernia. Age at CDH repair, presence of a hernia sac, type of diaphragmatic defect A-D (as defined by the CDH study group),[12] type of CDH repair, surgical approach for CDH repair, location of the CDH repair, intraoperative thoracic content, time to Nissen repair, postoperative survival, length of stay at the intensive care unit (LOS at intensive care unit [ICU]), need of mechanical ventilation, ECMO use, including days on ECMO and postoperative reflux diagnosis, were also included. In cases where <95% of the data were available, a note regarding data completeness (in %) was added to the retrospective results in the tables.

2.2. Definitions of GERD and CHD defect size

Diagnosis of GERD was based on clinical diagnosis (including refusal to eat, retching, gagging, and aspiration of food) and upper gastrointestinal contrast studies (excluding other upper gastrointestinal pathologies and possibly detecting reflux). PH probe analysis was rarely performed (only in $n=4$ [5.7%] of patients diagnosed with reflux).

The diaphragmatic defects were defined as proposed by Lally et al in 2013[12]: type A defects are completely surrounded by muscle, in type B defects <50%, and in type C defects >50% of the chest wall has no diaphragmatic tissue. In type D defects, there is no or almost no diaphragm.[12] In cases where direct suture of the diaphragm was performed, a defect size <50% of the hemidiaphragm was assumed. *Severe Defect Grade* was defined as defect >50% of the hemidiaphragm and intrathoracic liver.

2.3. CDH repair

The surgical procedure was according to the surgeon's choice. Laparotomy was performed in 72% of cases. Hereby, a transverse subcostal skin incision was made. If the defect was closed primarily, interrupted nonabsorbable sutures were used. If the defect could not be closed primarily, either a transversus abdominis muscle flap or a PTFE (Gore- Tex [W.L. Gore and Associates, Flagstaff, AZ]) patch was used. Transverse abdominis muscle flap repair was performed by separating the transversus abdominis muscle from the remaining abdominal wall. Then the transversus muscle was medially divided along the rectus fascia. The muscle flap was attached to the posterior diaphragmatic rim using interrupted nonabsorbable sutures (see supplementary Figure 1A, http://links.lww.com/MD/F291). PTFE meshes were attached to the diaphragmatic rim with interrupted or running nonabsorbable sutures (see supplementary Figure 1B, http://links.lww.com/MD/F291).[13]

2.4. NF

NF was done laparoscopically versus open depending on the surgeons' preference.

2.4.1. Open NF. After transverse laparotomy, the fascia was incised, and the peritoneum was entered under direct visualization. Adhesions were taken down. The short gastric vessels were taken down with electrocautery. The hiatus was identified as well as the right and left crura and the vagal nerves. The crura were reapproximated over a nasogastric tube with interrupted sutures with care to not be too tight. The fundus was brought around the posterior stomach and an NF performed with nonabsorbable sutures.

2.4.2. Laparoscopic NF. A Verres needle was used gain access to the abdominal cavity just below the umbilicus, and a 5-mm camera port was inserted. The abdominal cavity was inflated to a pressure of 12 mmHg. Two additional 3-mm ports and 1 additional 5-mm port were placed all under direct vision. A liver retractor was positioned for visualization through an epigastric stab incision. The remaining procedure was performed as stated above for open NF.

2.5. Statistical analysis

Descriptive statistics were used to summarize patients' characteristics. Normality was assessed graphically and with the Shapiro-Wilk Test. Continuous variables were reported as mean and standard deviation (SD) or median and interquartile range and compared between the two groups using 2-sample independent t tests or Mann–Whitney U test (non-normal data). Categorical variables were summarized as frequencies (%) and compared using Pearson χ^2 test or Fisher exact test where applicable.

Predictors of NF were determined using logistic regression analysis.[14–17] The variables included for univariate analysis in the logistic regression model were a priori determined after the literature review. A total of $n=5$ variables were tested in univariable models: *Severe Defect Grade*, gestational age, presence of a hernia sac, hernia side, and age at CDH repair. *Severe Defect Grade* was created due to a significant correlation of liver position and defect size (Spearman $r=0.252$, $P=.005$).

Variables with a P value of <.20 were retained in the multivariable model. All variables retained in the multivariable model had no more than a weak correlation (Spearman correlation coefficient $r<0.39$, as suggested by Evans et al).[18]

Results are reported as odds ratio (OR) with the corresponding 95% confidence interval (CI). Goodness of fit was tested using the Hosmer-Lemeshow test and area under the curve (AUC) is reported for predictive accuracy of the model. SPSS version 25 (IBM corp., Armonk, NY) and R Studio version 3.2.1. (RStudio, Inc., Boston, MA) were used for data analysis. P values <.05 (2-tailed) were considered statistically significant.

3. Results

One hundred twenty-six CDH neonates were included in the present study. Seventy patients (55.6% of the overall cohort) were diagnosed with GERD, and 47.6% were treated with antireflux medications. Forty-two (33%) patients underwent NF.

3.1. Prenatal characteristics

Prenatal variables for the overall cohort and for the patients undergoing a Nissen repair $n=42$ versus noNissen $n=84$ are

Table 1

Baseline demographics—prenatal.

N (%) unless otherwise stated	Overall, $n=126$	No Nissen, $n=84$	Nissen, $n=42$	*P*-value
Abnormal karyotype	1 (0.8)	0	1 (2.4)	.333
Syndrome	2 (1.6)	1 (1.2)	1 (2.4)	1.00
LV RV disproportion	12 (9.5)	7 (8.3)	5 (11.9)	.532
Mc Goon, median (IQR) (56.3% complete)	1.2 (1.03–1.3)	1.2 (1.04–1.4)	1.14 (1–1.21)	.304
McGoon ≥1.2	37 (52.1)	25 (56.8)	12 (44.4)	.338
LHR, median (IQR) (65.1% data complete)	1.3 (1.0–1.6)	1.3 (1.0–1.7)	1.24 (0.9–1.46)	.245
O/E LHR, mean (SD) (62% data complete)	43.7 (15.5)	46.5 (16.6)	39.5 (12.6)	.049
TLV, mL, median (IQR) (58.7% data complete)	26.8 (19.0–38.2)	29.8 (20.3–43.7)	24.7 (16.0–33.9)	.231
TLV ≥18 mL	59 (79.7)	38 (82.6)	21 (75)	.553
PPLV, n %, median (IQR) (60.3% data complete)	20.0 (15.0–27.0)	20.6 (18.0–28.0)	19.0 (13.3–25.5)	.176
PPLV ≥15%	58 (76.3)	38 (80.9)	20 (69)	.274
Liver intrathoracic on prenatal imaging	58 (46)	33 (39.3)	25 (59.5)	.038
Prenatal steroids	25 (19.8)	15 (17.9)	10 (23.8)	.480
Amniotic fluid				.662
Normal	71 (56.3)	49 (58.3)	22 (52.4)	
Oligohydramnion	6 (4.8)	4 (4.8)	2 (4.8)	
Polyhydramnion	20 (15.9)	11 (13.1)	9 (21.4)	
Unknown	29 (23)	20 (23.8)	9 (21.4)	

LHR = lung-to-head ratio using MRI or fetal ultrasound, LV RV disproportion = left ventricle-to-right ventricle disproportion using fetal echocardiography, Mc Goon = Mc Goon index (the combined diameter of the hilar pulmonary arteries, indexed to the ascending aorta), O/E LHR = observed to expected LHR, PPLV = percentage predicted lung volume, TLV = total lung volume using MRI or fetal ultrasound.

displayed in Table 1. Median LHR for the complete cohort was 1.3 (interquartile range [IQR] 1–1.6) and was comparable between groups (noNissen 1.3 [IQR 1.0–1.7] vs NF 1.24 (0.9–1.46], $P=.245$). Mean observed to expected LHR was significantly higher for noNissen patients (46.5%, SD 16.6) compared to 39.5 for NF patients (SD 12.6, $P=.049$), but this information was only available for 62% of the cohort. Intrathoracic liver position on prenatal imaging was present in 59.5% of the NF patients compared to 39.3% of the noNissen patients ($P=.038$). Median TLV (data available for 58.7%) was 26.8 mL (IQR 19–38.2 mL) for the overall cohort and was comparable between NF (24.7, IQR 16–33.9) and noNissen patients (29.8, IQR 20.3–43.7; $P=.231$). Median PPLV (data available for 60.3%) was 20% (IQR 15%–27%) and also comparable between NF (19%, IQR 13.3%–25.5%) and noNissen patients (20.6%, IQR 18%–28%; $P=.176$).

3.2. Postnatal baseline demographics

Baseline characteristics were comparable between NF and noNissen patients (Table 2). Extent of the diaphragm defect could be defined for $n=124$ patients (98.4%) (Table 3). As displayed in 3, 67 patients (54%) had a type A or B defect, whereas 57 patients (46%) had a defect type C or D. The NF group included significantly more type C or D defects (76.2%) than the noNissen group (30.5%), $P<.001$). *Severe Defect Grade* occurred in $n=39$ patients of the overall cohort, $n=14$ in the noNissen group (16.7%), and $n=25$ in the NF group (59.5%, $P<.001$, see also Fig. 1).

3.3. Intraoperative findings

A primary closure was conducted in 57.1% of the patients without documented NF compared to 19% in the Nissen cohort ($P<.001$).

Table 2

Baseline demographics—postnatal.

N (%) unless otherwise stated	Overall	No Nissen	Nissen	*P*
Gestational age, wk, median (IQR)	38 (36–39)	38 (36–39)	37 (35–38)	.169
Congenital Heart disease	37 (29.4)	21 (25)	16 (38.1)	.149
PPHN	56 (44.4)	41 (48.8)	15 (35.7)	.187
Male sex	75 (59.5)	51 (60.7)	24 (57.1)	.705
C-section	50 (40.3)	30 (36.1)	20 (48.8)	.243
1 min Apgar	5 (3–7)	5 (3–7)	4 (2–6)	.430
Median (IQR), 91.1% data complete				
<7	87 (69.9)	54 (64.3)	33 (78.6)	.292
7–10	29 (23.0)	23 (27.4)	6 (14.3)	
5 min Apgar	7 (5–8)	7 (6–8)	7 (5–8)	.902
Median (IQR) 91.1% data complete				
<7	45 (36.0)	27 (32.5)	18 (42.9)	.541
7–10	70 (56.0)	49 (59.0)	21 (50.0)	
Right-sided hernia	28 (22.2)	20 (23.8)	8 (19)	.652

IQR = interquartile range, PPHN = persistent pulmonary hypertension.

Table 3

Intraoperative details.

N (%) unless otherwise stated	Overall	No Nissen	Nissen	*P*
Age at CDH repair, days, median (IQ)	5 (3–10)	5 (3–9)	5 (3–11)	.904
SAC	29 (23.0)	15 (17.9)	14 (33.3)	.072
Diaphragm defect* (known for *n*=124)				
A or B	67 (54)	57 (69.5)	10 (23.8)	**<.001**
C or D	57 (46)	25 (30.5)	32 (76.2)	
Severe Defect Grade†	39 (31)	14 (16.7)	25 (59.5)	**<.001**
Type of CDH repair				
-Primary closure	56 (44.4)	48 (57.1)	8 (19)	**<.001**
-Transversus abdominis muscle flap	36 (28.6)	17 (20.2)	19 (45.2)	**.006**
Patch (Goretex)	32 (25.4)	17 (20.2)	15 (35.7)	.082
other	2 (21.6)	2 (2.4)	0	.552
Surgical approach for CDH repair				
Laparoscopic	3 (2.4)	2 (2.4)	1 (2.4)	1.00
Laparotomy	91 (72.2)	61 (72.6)	30 (71.4)	1.00
Thoracotomy	7 (5.6)	4 (4.8)	3 (7.1)	.685
Thoracoscopic	4 (3.2)	3 (3.6)	1 (2.4)	1.00
Unknown	21 (16.7)	14 (16.7)	7 (16.7)	1.00
Location CDH repair				.416
NICU	99 (78.6)	63 (75.0)	36 (85.7)	
OR	23 (18.3)	18 (21.4)	5 (11.9)	
Unknown	4 (3.2)	3 (3.6)	1 (2.4)	
CDH repair on ECMO	27 (21.6)	16 (19.3)	11 (26.2)	.490
Thoracic content				
Bowel	97 (77.0)	65 (77.4)	32 (76.2)	1.00
Liver	68 (54.0)	38 (45.2)	30 (71.4)	**.008**
Spleen	76 (60.3)	49 (58.3)	27 (64.3)	.566
Stomach	65 (51.6)	41 (48.8)	24 (57.1)	.451
Unknown	23 (18.3)	15 (17.9)	8 (19)	1.00
Time to Nissen (CDH repair to Nissen; days), median (IQR)	61 (48–106.5)			

Age at OP = age at congenital diaphragmatic hernia repair, CDH = congenital diaphragmatic hernia, ECMO = extracorporeal membrane oxygenation, IQR = interquartile range, NICU = neonatal intensive care unit, SAC = presence of a hernia sac.

* For *n*=33 patients defect size was not documented. In cases where direct suture of the diaphragm was performed, a defect size <50% of the hemidiaphragm was assumed.

† *Severe Defect Grade* was defined as defect >50% of the hemidiaphragm and intrathoracic liver (see Fig. 1).

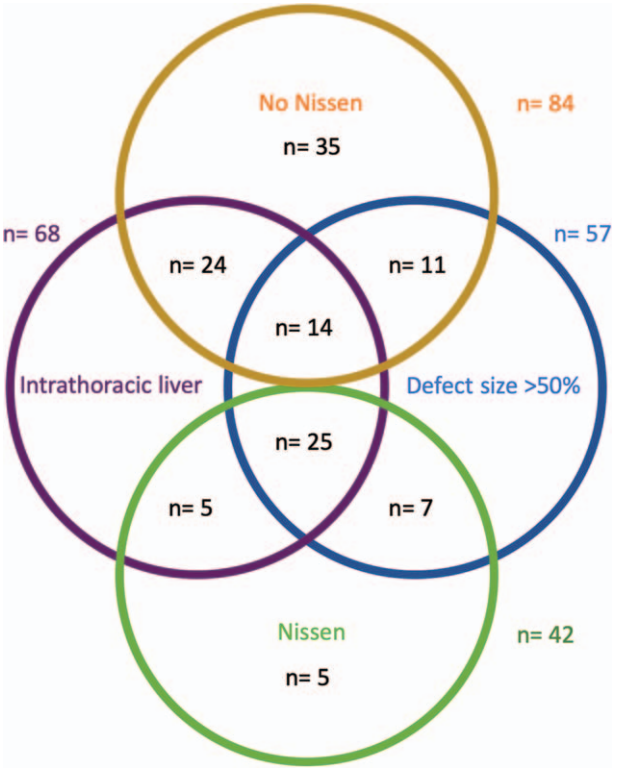

Figure 1. Illustration of the cut sets of patients undergoing a Nissen fundoplication vs no procedure, patients with an intrathoracic liver and a defect size >50%.

A herniated liver was seen in 45.2% of patients not undergoing a Nissen procedure and in 71.4% of the NF patients (*P*=.008). Other variables did not differ between groups. Median time from surgical CDH repair to NF was 61 days (IQR 48–106.5).

3.4. Postoperative outcome

The indications for Nissen were a mutlidisciplinary clinical decision (between pediatric surgeons, gastroenterologists, and neonatologists). Twenty-eight of 42 (66.7%) patients treated with NF showed retching, and 9 of 42 (21.4%) had (recurrent) aspirations. Despite pH probe being considered as criterion standard to diagnose GERD, this test was only performed in 4 of 42 (9.5%), of Nissen patients. Likewise, upper endoscopy was only rarely (3/42 [7.1%]) performed. An upper gastrointestinal study was performed before surgery in most (31/42 [73.8]) Nissen cases to rule out malrotation; 26.2% of CDH patients were supported by ECMO for a median ECMO run of 13.5 days. Fourteen patients (11.1%) died before discharge and nine patients died within the first 30 days of life, as shown in Table 4. Median length of stay in the neonatal intensive care unit (NICU) of the surviving patients was significantly longer for NF patients (*n*=39, 91 days, IQR 58–154 days) compared to the noNissen group (*n*=73, 37 days, IQR 27–53 days, *P*<.001). Twenty-sis percent (*n*=11/42) of patients underwent a NF after being discharged from the NICU. Almost all patients depended on mechanical ventilation at some point during their NICU stay (97.6%). Duration of mechanical ventilation was significantly longer for NF patients (median 28 days) compared to noNissen patients (median 11 days, *P*<.001).

Sixty patients received anti-reflux medication during the hospitalization (47.6%), whereas only 42 (33.3%) of children were discharged with anti-reflux medication (*n*=36 children with proton pump inhibitors (17/42 [40.5] NF patients) and *n*=6 patients with H_2 receptor blocker (2/42 [4.8%] NF patients)).

One-year survival after CDH repair was 89.5% for the overall cohort and was comparable between the two groups (*P*=.216).

3.5. Predictors for Nissen after CDH repair

We grouped patients according to the combination of intrathoracic liver and a diaphragmatic defect >50% into *Severe Defect Grade* versus all others (see Figure 1: liver position and defect size in NF and noNissen patients). *Severe Defect Grade*, gestational age, and presence of a hernia sac were retained in the multivariable model. Need of ECMO support did not emerge as predictor for NF after CDH repair. Results of the univariable and multivariable logistic regression analysis are displayed in Table 5.

Severe Defect Grade emerged as independent predictor for NF after CDH repair when controlled for gestational age and presence of a hernia sac (OR 6.93, 95% CI 2.95–16.32, *P*<.001). The AUC of the model was 0.76 with a positive

Table 4

Postoperative outcome.

N (%) unless otherwise stated	Overall	No Nissen	Nissen	P
Survived up to NICU discharge	112 (88.9)	73 (86.9)	39 (92.9)	.383
ICU LOS for survivors, days, median (IQR)	47 (30–90)	37 (27–53)	91 (58–154)	**<.001**
Time to death,	46 (34–183)	39 (32–83)	193 (172–547)	**.009**
Including $n=4$ patients who died after discharge from NICU, days, median (IQR)				
NICU discharge location				
Home	95 (75.4)	64 (76.2)	31 (73.8)	.828
Other ICU	14 (11.1)	6 (7.1)	8 (19)	.069
Died	14 (11.1)	11 (13.1)	3 (7.1)	.383
-unknown	3 (2.4)	3 (3.6)	0	.550
Respiration status at NICU discharge				
Oxygen	83 (65.9)	55 (65.5)	28 (66.7)	1.00
Mechanical ventilator	9 (7.1)	2 (2.4)	7 (16.7)	**.006**
No oxygen	13 (10.3)	11 (13.1)	2 (4.8)	.217
Died	14 (11.1)	11 (13.1)	3 (7.1)	.383
-Unknown	7 (5.6)	5 (6.0)	2 (4.8)	1.00
Mechanical ventilation	123 (97.6)	82 (97.6)	41 (97.6)	1.00
Days of mechanical ventilation, days, median (IQR)	14 (8–28)	11 (7–18)	28 (18–100)	**<.001**
ECMO	33 (26.2)	19 (22.6)	14 (33.3)	.205
Days on ECMO, days, median (IQR)	13.5 (7–26)	12 (7–34)	14 (7–21)	.839
Reflux diagnosis	70 (55.6)	28 (33.3)	42 (100)	**<.001**
Retching	35 (27.8)	7 (8.3)	28 (66.7)	**<.001**
Aspirations	9 (7.1)	0	9 (21.4)	**<.001**
pH probe	4 (3.2)	0	4 (9.5)	**.011**
Upper endoscopy	4 (3.2)	1 (1.2)	3 (7.1)	.108
Upper GU study	42 (33.3)	11 (13.1)	31 (73.8)	**<.001**
Reflux medications*	60 (47.6)	27 (31.2)	33 (78.6)	**<.001**
1-year survival	111 (89.5)	71 (86.6)	40 (95.2)	.216

ECMO = extracorporeal membrane oxygenation, ICU LOS = length of stay at the intensive care unit, IQR = interquartile range, NICU = neonatal intensive care unit.
* Reflux medications included: proton pump inhibitors and H_2 receptor antagonists.

predictive value of 64%, a negative predictive value of 80.5%, a specificity of 83.3%, and a sensitivity of 59.5%.

4. Discussion

The present study reflects the largest cohort of CDH patients assessing predictors for later NF. We found that in our cohort of CDH neonates, *Severe Defect Grade*, defined by intrathoracic liver position and diaphragm defect size >50%, was an independent predictor for need of a NF in CDH patients. In our cohort of 126 patients with CDH, 55.6% suffered from GERD and 47.6% were treated with anti-reflux medications. NF was performed in 42 (33.3%) patients. Patients undergoing a NF had significantly lower observed to expected lung-to-head ratio (mean 39.5 ± 12.6 vs noNissen 46.5 ± 16.6, $P=.049$), were more likely to have a herniated liver into the thoracic cavity on prenatal imaging (59.5% vs 39.3% in the noNissen group, $P=.038$) and had larger diaphragmatic defects (type C/D defect in the NF group 59.5% vs 16.7% in the noNissen group, $P>.001$). Intrathoracic liver position was confirmed intraoperatively in 30 NF patients (71.4%) and in 38 noNissen patients (45.2%, $P>.008$).

Due to significant correlation of liver position and defect size (Spearman $r=0.252$, $P=.005$), the composite variable *Severe Defect Grade* defined as defect >50% of the hemidiaphragm and intrathoracic liver was created. Sixty-four per cent of patients with *Severe Defect Grade* received later fundoplication, whereas only 19.5% of patients without *Severe Defect Grade* were treated with a NF ($P<.001$).

Both, diagnosis of GERD and indication for NF was not uniform in our study. Diagnosis of GERD mainly based on clinical symptoms and upper GI study, and pH probe analysis was rarely performed. ECMO support was needed in about a quarter of our

Table 5

Univariable and multivariable logistic regression analysis of predictors of Nissen fundoplication.

	Univariable				Multivariable			
	OR	Lower CI	Upper CI	P	OR	Lower CI	Upper CI	P
Severe Defect Grade	7.35	3.17	17.07	<0.001	6.93	2.95	16.32	<.001
Gestational age, wk	0.87	0.74	1.02	.08	0.89	0.75	1.06	.20
Presence of a hernia sac	2.30	0.98	5.38	.06	1.88	0.72	4.90	.20
Hernia side (left *vs.* right)	0.75	0.30	1.89	.55				
ECMO	1.711	0.753	3.885	.20				
Age at CDH repair, days	0.99	0.96	1.03	.72				

CI = confidence interval, CDH = congenital diaphragmatic hernia, ECMO = extracorporeal membrane oxygenation, OR = odds ratio.
Hosmer Lemeshow χ^2 8.62, $P=.28$; area under the curve = 0.76.

patients and 11% died during the NICU stay. Our study cohort hence consists of severely ill patients and therefore extrapolation of our results to other, presumably healthier patients, might be limited. Additionally, keeping in mind that median time to NF in our cohort was 61 days, one has to acknowledge a natural bias for our study cohort. The sickest patients will not survive up to the time a staged NF is scheduled. This is why patients who died within 30 days after the initial CDH repair were excluded in order to examine a cohort consisting of patients who could potentially undergo a staged fundoplication.

Depending on the definition and the cohort analyzed, CDH patients suffer from gastroesophageal reflux in 1.6% to 83.3%.[2–7,9] About one-third of the CDH patients undergo a fundoplication after CDH repair.[2,10] Likewise, in our cohort, 55.6% had a diagnosis of reflux disease and one third underwent a NF. Maier et al analyzed the benefit of antireflux surgery at the time of CDH repair in a single-blinded prospective study. A total of 79 neonates were included, all with left-sided CDH. Forty-three underwent CDH repair only, whereas 36 patients had an additional fundoplication at the time of CDH repair. Allocation to regular CDH repair or additional fundoplication was random and concealed; parents remained blinded up to 2 years of age of their children. In 3 patients in the control group (6.98%), a fundoplication, a jejunostomy, or gastrostomy was required up to the age of 24months. No adverse effects of the initial antireflux surgery were recorded, whereas no remark regarding complications after a secondary fundoplication was made in the article. The authors found comparable results at the 2-year follow-up with regard to gastroesophageal reflux symptoms and comparable development of body weight and concluded that patients profit from preventive fundoplication only during the first year of life and preventive fundoplication at the time of CDH repair should not be recommended in all patients.[19]

Regarding the selectin of CDH patients who potentially benefit from a NF, only few studies have assessed risk factors for later NF after CDH repair. The so far largest published report included 86 patients.[3,10,20,21] Risk factors for later NF included (among others) liver herniation and need for patch repair, which is congruent with the findings in our cohort of 126 patients.

Verbelen et al analyzed a cohort of 77 CDH patients and reported 21% requiring antireflux surgery. The only independent predictor for antireflux surgery in their cohort was herniated liver, when controlled for type of repair, fetoscopic endoluminal tracheal occlusion, and days on high-frequency oscillatory ventilation.[3] Diamond et al reported liver herniation and patch repair as independent prognostic factors for fundoplication or gastrojejunal tube placement in a cohort of 86 children with CDH.[20]

Su et al reported a relative risk of 7.8 for fundoplication in CDH patients who required patch repair and a relative risk of 7.5 for extracorporeal life support in their retrospective analysis of 42 patients.[21]

Chamond et al stratified their 36 patients into mild, intermediate, or severe anatomical form, depending on patch repair of the CDH and liver herniation in a retrospective analysis. Seventeen patients underwent fundoplication at time of CDH repair, whereas 19 only underwent CDH repair. The decision for or against a fundoplication during the CDH repair was made by the surgeon depending on her or his assessment, and the hemodynamic stability of the patient. One patient could not undergo fundoplication during CDH repair due to hemodynamic instability and underwent a NF later on. Two patients in the group without an initial antireflux procedure were diagnosed with intermediate gastroesophageal reflux and underwent a Nissen procedure during the following 5 months. No statistically significant correlation between the anatomical form and gastroesophageal reflux during the first year of life could be found.[10]

In concordance with the literature, we found significant correlation between liver position and defect size (Spearman $r = 0.252$, $P = .005$) and defined *Severe Defect Grade* referring to the "anatomical form" reported by Chamond et al in 2008.[10] In contrary to previous publications on predictors of need for fundoplication after CDH repair,[3,20,21] we considered the correlation between our independent variables as this may lead to multicollinearity. Multicollinearity affects estimates and confidence intervals by inflating the variances of the parameter estimates. Ultimately it leads to unreliable conclusions and interpretations.[22,23] The transformation from previously reported but correlating factors into "*Severe Defect Grade*", allowed us to analyze the subgroup of patients with large diaphragmatic defects and herniated liver.

We found *Severe Defect Grade* to be an independent predictor of need for fundoplication when controlled for presence of a hernia sac and gestational age at CDH repair.

5. Conclusions

Severe Defect Grade, defined by intrathoracic liver position and diaphragm defect size >50%, emerged as independent predictor of need of a fundoplication in CDH patients. About two-thirds of patients with *Severe Defect Grade* will need later NF. While identifying a strong novel predictor for later NF, using a cohort of 126 CDH patients, there was no predictor eliminating all false-positive cases. The present evidence does hence not support the recommendation of NF solely according to factors such as *Severe Defect Grade*.

We aim to further assess *Severe Defect Grade* as possible foundation for recommendations to caregivers from CDH patients in even larger cohorts. Ultimately, further prospective studies are warranted to guide the decision for or against a simultaneous NF at time of the CDH repair.

Author contributions

All authors: Substantial contributions to the conception or design of the work; Drafting the work or revising it critically for important intellectual content; Final approval of the version to be published; Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

AEE, RP, JG and JK: acquisition, LCG and RNV: analysis, LCG, RFS, RNV, AIM and KWL: interpretation of data for the work.

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