


# ORIGINAL ARTICLE

## Anti-reflux surgery for gastroesophageal reflux in neurological impaired and non-impaired children: Long term outcomes after a median follow-up of more than 10 years

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### Abstract

**Introduction:** The durability of a fundoplication (FP) in the treatment of gastroesophageal reflux disease (GERD) in children must be confirmed in the long-term. This study aimed to present the long-term outcome after a minimum of five years.

**Methods:** Perioperative data were retrospectively reviewed from clinical records, and the follow-up data were collected through a standardized questionnaire. In total, 21 neurologically impaired (NI) and nine neurologically non-impaired (NNI) children were included in this study. The statistical analysis was performed using SPSS software (version 25) through Fisher's exact test, t-test, and Kaplan-Meier analysis. A p-value less than 0.05 was considered statistically significant.

**Results:** The median follow-up period was 10.8 years (5-19.7), and the refundoplication rates ranged from 11% to 19%. Revisions were usually necessary within the first two postoperative years. Most delayed refundoplications were necessary for the NI children with a laparoscopic Nissen FP. In the long-term, symptoms and medication administration program were favorable in most cases. Most parents were highly satisfied with the postoperative outcome and would approve that FP is conducted on their child again under the same circumstances.

**Conclusions:** The FP is a safe procedure with consistent benefits in the first 10 postoperative years in NI and NNI children with documented GERD. The NI children treated with a laparoscopic Nissen FP necessitate longer postoperative surveillance since more delayed redofundoplications were required in this group.

**Key words:** Child, Fundoplication, Gastroesophageal reflux

### Introduction

Fundoplication (FP) is an established surgical procedure for the treatment of gastroesophageal reflux disease (GERD) in children. Published studies have revealed a high success rate of FP in 86% of the cases resulting in the complete relief of reflux symptoms (1). However, different studies have reported a wide range of success rates in this regard (1). This marked variance reflects differences in the length of follow-up, the author's definition of success, patient comorbidity,

and operative techniques. In particular, the postoperative success rates differed significantly considering the length of the follow up, and the rate of failure increased in children after a longer period (2). Late deterioration may occur more frequently in neurologically impaired children, compared to neurologically healthy children (3). However, current reports in children cover limited follow-up periods, and there are very few reports on the outcome of fundoplication in children with a follow up of more than five years (Table 1). Reports on longer-term outcomes are scarce and

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**Table 1: Overview of exemplary published reports on the outcome after fundoplication in children with a minimal follow-up of five years**

Author, year (Reference)	Study type	Fundoplication method	Patients n=	Age mean± SD or median (range)	Patients characteristics	Follow-up Mean±SD or median (range)	Overall success rate (%)*	Definition of success
Pimpalwar 2002 (14)	R	LNF	54	5m-16y	NI	5.2 y (0.3-8.6)	84%	S
Capito 2008 (4)	P	LNF	127	3.5y NNI, 5.4y NI (0.25-20y)	NI, NNI	5.5 y (3-9)	87-98%	S
Kristensen 2007 (20)	R	LNF, ONF	93	3.4y (0.13-14.8y)	NI, NNI, EA	6 y (2.5-12)	83%	S
Esposito 2012 (5)	R	LNF, LTF	32	x-y	NI, NNI	11-12y	87.5%	S

P: Prospective study, R: a retrospective study, LNF: laparoscopic Nissen fundoplication, LTF: laparoscopic Thal fundoplication, ONF: open Nissen fundoplication, OTF: open Thal fundoplication, NF: Nissen fundoplication (not described if open or laparoscopic), TFThal fundoplication (not described if open or laparoscopic), NI: neurologically impaired, NNI: neurologically non-impaired, EA: esophageal atresia, CDH: congenital diaphragm hernia, AWD: abdominal wall defects, CAD: Chronic airway disease, SD: standard deviation, y: years, m: months, S: symptoms, D: Diagnostics, RedoRefundoplicatio rate, NR not reported. \* Overall success rate as defined in the respective study. S: symptoms course, D: diagnostic findings, Redo Rate of repeated fundoplications.

often only describe the long-term postoperative outcomes in a few individual cases (4). Therefore, the accurate assessment of long-term FP success in children has not been determined conclusively. This study aimed to evaluate the long-term (more than five years) outcomes of FP in the cohort of neurologically impaired and non-impaired children with documented GERD. Based on the evidence, the surgical outcome in these two groups may differ significantly (2).

## Methods

An over 20-year retrospective cohort study (January 1, 1990 to December 31, 2011) was performed on children undergoing an FP for GERD at our single tertiary referral center for pediatric surgery. The study protocol was approved by the institutional Ethics Committee of the University of Heidelberg, Germany. Moreover, all procedures were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the updated Helsinki Declaration. It should be mentioned that it was not necessary to obtain patients' participation consent in accordance with the local Ethical Committee due to the retrospective study design.

In total, 188 consecutive patients underwent surgery throughout the study period. Preoperative diagnosis of GERD was made if at least two of the following GERD-diagnostic criteria were pathological. These criteria included: 1) prolonged multilevel pH-metry, 2) barium swallow or

esophagogastrosopy, and 3) histological assessed esophagitis. All patients were contacted by mail and phone; however, 58 cases could not be reached and a further 33 individuals refused to participate in the study. Afterward, informed consent was obtained from all the participants. In the following, demographic and pre-and postoperative data were extracted through retrospective chart review. Furthermore, the follow-up data were collected using a standardized questionnaire during a semi-structured telephone interview performed by a single examiner who was not blinded but had not been involved in the clinical care of the patients.

Postoperative symptoms and medication course along with the need for reintervention, subjective overall burden, and parent's satisfaction with postoperative outcome were evaluated during the follow-up interview. It should be mentioned that the data of 97 patients were complete, and out of these 97 patients with available data, the cases with a follow-up of more than five years following an FP were included in this study to investigate the long-term outcomes.

Therefore, the cohort presented in this study includes 30 children, who were subdivided into neurologically impaired (NI) (n=21) and neurologically non-impaired (NNI) (n=9) groups. On the other hand, the cases with a shorter follow-up period, esophageal atresia, and deceased patients (n=67) were excluded from the study. In total, eight children who underwent the operation were already deceased by the follow-up time-point, and all of whom were among NI children. These deaths occurred within 18-30 months following the

FP with non-surgery related causes, such as ruptured brain aneurysms and multi-organ failure due to sepsis.

The FP procedures were performed exclusively through open surgery until 1996, followed by laparoscopy at our institution. A supraumbilical median laparotomy was used to access the intra-abdominal cavity in the open procedure. In the laparoscopic approach, a 5-mm trochar was introduced periumbilically for the camera, and another one was placed in the epigastrium for the liver retractor. Moreover, a 5-mm trochar was placed in both the right and left upper quadrant for the instruments. Pneumoperitoneum pressure ranged from 8 to 15 mm Hg of CO<sub>2</sub>.

After dissection and mobilization of esophageal hiatus, hiatoplasty was performed by suturing the crural pillars posteriorly of the esophagus with nonabsorbable 3-0 Ethibond sutures (Ethicon, Johnson and Johnson Medical GmbH, Norderstedt, Germany). The FP was created using two different techniques. Nissen FP was performed by wrapping a 3-4 cm long 360° posterior fundus around the lower oesophagus, while for the modified Thal FP, the fundus was folded 180° anteriorly to the oesophagus. The Nissen FP was performed as a circumferential tension-free floppy wrap; therefore, there was an occasional need for dividing the short gastric vessels. The patency of the wrap and the diameter of the hiatus were controlled intraoperatively with a 10-12 mm orogastric tube. Esophageal dilatations were performed by pressure-controlled balloon-

dilatation to treat dysphagia and/or recurrent boluses. After guiding the balloon-catheter at the level of stenosis under gastroscopic and fluoroscopic control, the balloon was filled with contrast medium intermittently up to three times, each time the procedure took 1-3 min with a manometric-controlled pressure of 1-3 atm. Dilatation results were controlled by gastroscopy.

The obtained data were analyzed in SPSS software (version 25). Moreover, the categorical data were presented by the frequency distributions and compared using Fisher's exact test. In addition, the continuous variables were presented by medians (range) and mean±standard error of the mean (SEM) and were compared using a paired or unpaired t-test as appropriate. Kaplan-Meier analysis was also used to evaluate the long-term need for redofundoplication (reFP). A p-value less than 0.05 was considered statistically significant.

**Results**

In total, 30 children fulfilled the inclusion criteria and were included in this study. Table 2 tabulates the characteristics of the patients. Out of these 30 children, 21 cases with a mean age of 6.6±1.4 years were included in the NI group (microcephaly/encephalopathy of hypoxic [n=3], genetic [n=2], mitochondrial [n=1], infectious [n=1], prematurity [n=1], unclear [n=10], or other reasons [n=3]). In addition, 9 children with a mean age of 6.9±1.4 years were included in the NNI group. Both groups were matched in terms

**Table 2: Patient's characteristics (NI=neurologically impaired, NNI=neurologically non-impaired)**

	NI	NNI	p-value
<b>Demographic characteristics</b>			
Patients	21	9	
Age at funduplications (years)	6.6±1.4	6.9±1.4	0.907
<b>Main symptoms</b>			
Gastrointestinal	21 (100%)	9 (100%)	0.506
Respiratory	15 (71.4%)	4 (44.4%)	0.690
Failure to thrive	15 (71.4%)	5 (55.6%)	0.766
<b>Pathological diagnostic</b>			
pH-metry	14.16 (87.5%)	6.6 (100%)	0.364
Barium swallow	18.18 (100%)	8.9 (88.9%)	0.150
Esophagogastroscopy	9.13 (69.2%)	4.4 (100%)	0.215
<b>Fundoplication type</b>			
Thal	11 (53.4%)	7 (77.8%)	
Nissen	10 (47.6%)	2 (22.2%)	
<b>Operative access</b>			
Laparoscopic	11 (53.4%)	6 (66.7%)	0.469
Open	10 (47.6%)	3 (33.3%)	
Conversion	1 (4.8%)		

of demographic characteristics, pre-operative symptoms, and diagnostic findings following the surgical approaches. A conversion to open surgery was necessary for an NI child due to a laparoscopically non-manageable diffuse bleeding from fatty tissue between the liver and stomach, which was controlled by an open ligation (conversion rates of 4.8% and 3.3% in the NI and collective groups, respectively).

A postoperative abdominal revision was necessary only in the NI group (n=3; 14.3%), on average, after  $7.6 \pm 0.7$  months (median 3.1 months, range 0.25-24) (Table 3). Moreover, one revision was necessary six months after open Nissen FP due to intestinal obstruction. The FP was found to be intact after adhesiolysis. A further revision was necessary due to an acute abdomen together with elevated sepsis parameters six days following the laparoscopic Thal FP. No defined cause was detected by laparotomy, and the FP was found to be intact.

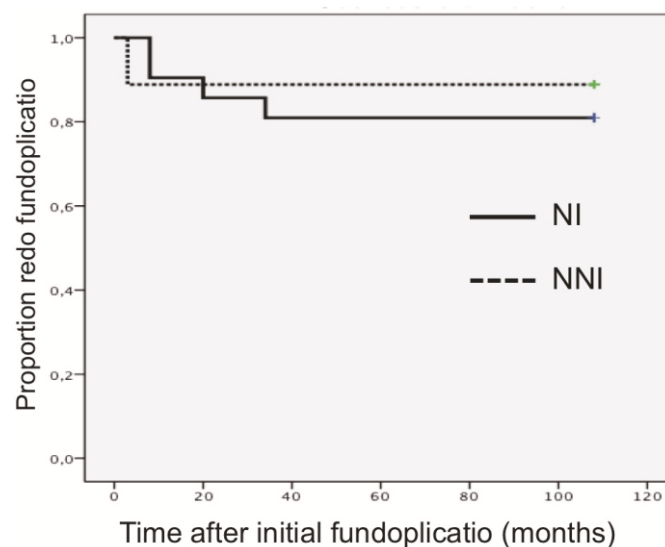
On the assumption of post-operative migratory peritonitis, antibiotic regime change led to the full recovery. Another child developed a chronic cough, followed by convulsive vomiting two years after

laparoscopic Nissen-FP. A hiatal hernia was diagnosed by computed tomography scan that required open surgery (simple reduction) and hiatoplasty, while the FP was found intact. After one more year, this child developed new gastroesophageal symptoms and underwent a further laparotomy. This time, the Nissen-FP was found disrupted, followed by performing an open reFP.

In total, a reFP was necessary in five children in the NI (n=4; 19.0%) and NNI group (n=1; 11.1%) (Table 3). The principal reasons for reFP were recurrent gastroesophageal reflux as indicated by recurrent postoperative symptoms and pathological postoperative findings in prolonged pH-metry and barium swallow. In the NI group, the reFP rate was higher and operations were performed later, compared to the NNI-group. Following Nissen-FP, the reFP rate was higher and the reFP was performed later, compared to Thal-FP. The reFP rate was also higher after an initial laparoscopic FP, and the reFP was performed later, compared to an initial open-FP (Figures 1-3). In total, 80% of reFP were performed within the first 20 postoperative months after initial FP.

**Table 3: Secondary surgery (NI=neurologically impaired, NNI=neurologically non-impaired)**

	NI	NNI	p-value
<b>Postoperative abdominal revision</b>	3 (14.3%)	0	0.073
Time to abdominal revision (months)	$7.6 \pm 0.7$	-	-
Intestinal obstruction	1 (4.8%)	-	-
Axial hernia	1 (4.8%)	-	-
Acute abdomen (migratory peritonitis)	1 (4.8%)	-	-
<b>Refundoplication</b>	4 (19.0%)	1 (11.1%)	0.593
Mean p.o. time to refundoplication (months)	$17.5 \pm 6.2$	$3 \pm 0$	0.371



**Figure 1: Kaplan-Meier curves for refundoplication necessity during follow-up period depending on neurologic impairment (NI: neurologically impaired group, NNI: neurologically non-impaired group)**

The median follow-up period for the entire study group was 10.8 years (5-19.7 years). There was no significant difference between the NI and NNI groups in terms of the follow-up time (mean=11.1±1.1 vs. 9.2±1.3 years, P>0.05). In addition, there was no statistically significant difference between both groups regarding the course of symptoms at follow up (Table 4).

At follow-up, gastroesophageal symptoms were either completely absent or significantly improved in the NI (95.2% of the cases) and NNI groups (100% of the cases). Moreover, respiratory symptoms were completely absent or significantly

improved in 66.7% of the cases in the NI and 75% of the cases in the NNI group.

Thrive for improvement after preoperative failures and difficulties were observed in 73.3% and 80% of the cases in the NI and NNI groups, respectively. There was no statistically significant difference between both groups regarding medication administration at the follow-up period (Table 4). Gastrointestinal medication, including proton pump inhibitors, was postoperatively discontinued or reduced in 50% and 100% of the cases in the NI and NNI groups, respectively. Regarding the respiratory medication,

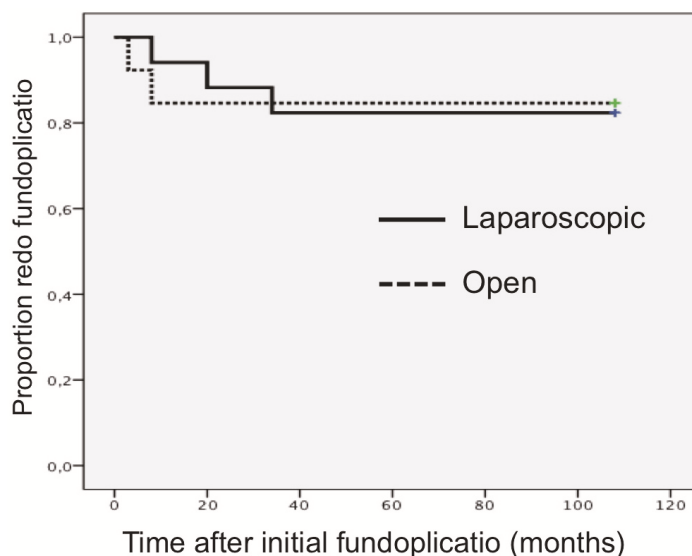


Figure 2: Kaplan-Meier curves for refundoplication necessity during follow-up period depending on surgical access (laparoscopic or open surgery).

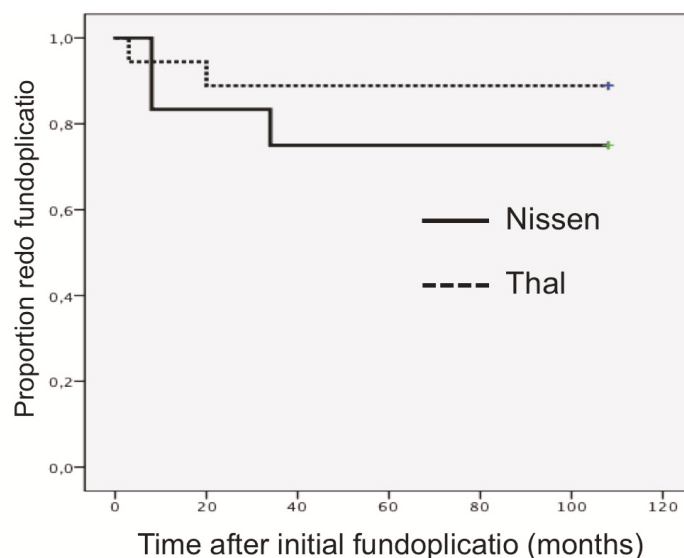


Figure 3: Kaplan-Meier curves for refundoplication necessity during follow-up period depending on fundoplication-type (Nissen and Thal).

**Table 4: Postoperative long-term outcome (NI=neurologically impaired, NNI=neurologically non-impaired)**

	NI	NNI	p-value
<b>Clinic Course</b>			
<b>Gastrointestinal symptoms</b>	21	9	
Complete regression	12 (57.1%)	4 (44.4%)	0.694
Significant improvement	8 (38.1%)	5 (55.6%)	0.443
Unchanged/unclear	1 (4.8%)	0	1.000
<b>Respiratory symptoms</b>	15	4	
Complete regression p.o.	8 (53.3%)	2 (50%)	0.800
Significant improvement p.o.	2 (13.4%)	1 (25%)	0.570
Unchanged/unclear	5 (33.3%)	1 (25%)	0.750
<b>Failure to thrive</b>	15	5	
Improved	11 (73.3%)	4 (80%)	0.946
Persisting	4 (26.7%)	1 (20%)	0.946
<b>Medication Course</b>			
<b>Gastrointestinal medication</b>	14	4	
Discontinued p.o.	3 (21.4%)	3 (75%)	0.083
Reduced p.o.	4 (28.6%)	1 (25%)	1.000
Unchanged p.o.	5 (35.7%)	0	0.278
Increased p.o.	2 (14.3%)	0	1.000
<b>Respiratory medication</b>	9	1	
Discontinued p.o.	1 (11.1%)	0	1.000
Reduced p.o.	3 (33.3%)	1 (100%)	0.400
Unchanged p.o.	5 (55.6%)	0	1.000
Increased p.o.	0	0	-
<b>Parent's outcome estimation</b>			
<b>Estimated overall patient's burden*</b>			
Before surgery	9.2±0.2	6.9±0.6	0.004
After surgery	2.9±0.8	4.9±1.2	0.158
<b>Parents overall satisfaction with the outcome</b>			
Very satisfied	17 (80.9%)	4 (44.4%)	0.082
Satisfied	4 (19.1%)	4 (44.4%)	0.195
Dissatisfied	0	1 (11.1%)	0.300

discontinuation or reduction was reported in 44.4% and 100% of the cases in NI and NNI groups, respectively. The preoperative overall burden related to GERD symptoms as perceived by the parents was significantly higher in the NI group, compared to the NNI group (Table 4).

For both groups, the perceived burden decreased after the FP. This improvement was significant in the NI group (9.2±0.2 to 2.9±0.8; P<0.001), compared to the NNI group (6.9±0.6 to 4.9±1.2; P=0.108).

Postoperatively, both groups were comparable in terms of the perceived burden. More parents were "very satisfied" with the results of the surgery in the NI group, compared to those in the NNI group (Table 4). Additionally, they were more eager to have an FP performed on their child again under the same circumstances, compared to the NNI group ("Yes" 20 cases=95.2% vs. 6 cases=66.7%, P=0.069), ("Possibly yes" 1 case=4.8% vs. 2 cases=22.2%, P=0.207), ("No" no case in the NI group vs. 1 case=11.1% in the NNI group, P=0.300).

## Discussion

An FP for GERD is reported to be successful in more than 85% of the children in terms of complete relief of the symptoms (1); however, decline in symptom-free patients declined over time was described (5, 6). Therefore, a long-term follow-up evaluation is fundamental to determine whether complications develop afterward and reduce the satisfactory outcome that was initially observed. It should be noted that the length of the follow-up period is essential in the accurate evaluation of the postoperative success-rate over time. The present study aimed to assess the postoperative long-term outcomes in the cohort of children treated with an FP for GERD. The long-term outcome was defined as a minimum of five years postoperatively and only considered a closely circumscribed study population. Accordingly, out of 97 patients with complete data, only 30 children were included in this study. The excluded children (n=67) did not meet the inclusion criteria and were excluded from the

study; however, since their complete data were available, they could not be considered as lost to follow-up. Moreover, the children with possible confounding comorbidities, such as esophageal atresia and congenital diaphragm hernia were excluded from the study since they represented completely different cases with a high rate of wrap failure (7). Only children who survived the follow-up period were included in this study to eliminate the confounding effects of deterioration and comorbidities on accurate interpretation of the individual outcome after the performance of FP for the treatment of GERD. All deaths occurred 1.5-2.5 years following the FP and were therefore not directly related to the surgical intervention. The median follow-up period in the present study was 10.8 years, which was sufficient to describe the very long-term outcome after an FP accurately.

According to the results, in the long-term period, symptoms associated with GERD disappeared or improved in more than 95% of the cases, and an improvement was observed in respiratory symptoms in about 70% of the cases in the cumulative group. This indicates that in the long term, an FP might control gastroesophageal symptoms better than respiratory symptoms.

Esposito et al. observed similar results in their follow up after a similar period (4). About 50% of the NI children were still on gastrointestinal medication, including proton pump inhibitors at follow up. This might be due to the failure of FP to crucially improve gastrointestinal symptoms in the long-term, or it could indicate the necessity for the supportive medication in NI children following FP. However, these data indicate that the improved symptomatology is consistent and stable in the majority of patients within the first 10 postoperative years, even in neurologically-impaired children. Other authors have reported an 85-100% rate of symptom-free children five years after the surgery regardless of their neurological status (3). The findings in the present study are consistent with the aforementioned results and demonstrated that the reduced symptoms and ability to improve were also ensured 10 years after the intervention, even in the mentally retarded children.

These findings were also supported by a study conducted by Tovar et al. who demonstrated that the FP remained functional in approximately 90% of their patients with an individual follow-up of more than 10 years (7).

In the present study, parents of both groups observed a decrease in the overall burden following the surgery, and the majority would retrospectively agree that their child undergoes an

FP under the existing circumstances regardless of the neurological condition of their child. However, fewer parents of NNI children were "very satisfied" with the overall surgical outcome, compared to those of the NI children. This possibly reflects unrealistic expectations of postoperative results in some parents (8), or the fact that parents of NI children, who perceived a higher overall burden before the surgery, were already satisfied with their children's improved quality of life (significant improvements in feeding and handling), rather than expecting a complete loss of symptoms (7,8).

Nevertheless, the possible drawbacks of the FP as a major surgical intervention must be considered when reviewing these positive long-term effects. A conversion was reported in one patient in this study; therefore, the overall rate of conversion was obtained at 3.3%, which was lower, compared to the rate of conversion (6.2%) in other published studies (9). The rates of postoperative abdominal revisions and necessary esophageal dilatations were higher in NI, compared to NNI children. Moreover, the reinterventions were mostly performed within the first postoperative year, suggesting that NI children might be more prone to early postoperative surgery-related complications possibly due to a higher rate of associated comorbidities.

In our series, the overall reFP rates of 11-19% are similar to the reported reintervention rates of 12.2% in a multicenter study (10). Moreover, a higher reFP rate was observed in the NI group, compared to the NNI group. A reFP was more often necessary following an initial Nissen rather than after Thal-FP and following a laparoscopic rather than after an open FP. This increased reFP rate could be explained by the possibility that the FP wrap in the NI children is subjected to higher mechanical stress derived from progressive spasticity and intestinal dysmotility related to their evolving degenerative condition and multiple comorbidities (2, 3). Furthermore, this increased reFP rate can be explained by the circumferential nature of the Nissen FP, which may correlate with reduced flexibility in response to mechanical stress, compared to the semi circumferential Thal wrap. Therefore, in NI children, the higher muscle tone related to spasticity and the recurrent epileptic seizures may cause a higher burden of a less flexible circumferential Nissen wrap, which could lead to more frequent dysfunctions or disruption of the wrap and explain the reported worse outcome of NI children with a Nissen FP.

This remains controversial since Kubiak et al. observed a higher reintervention rate following Thal-FP, compared to Nissen-FP (15.9% vs. 5.9%)

(2). However, the follow-up length of these studies was limited to 4.5 (11) and 2.5 years (2). The results obtained after a longer follow-up period of about 10 years, as achieved in this study, may indicate that an initial outcome trend in the short-term might differ in the long-term which can indicate the importance of longer-term evaluations.

In the present study, 80% of the reFPs were performed within the first 20 postoperative months following other published studies (2, 3, 7). Therefore, it is necessary to continue monitoring patients at least two years after the surgery to detect any need for reintervention as soon as it is required (3). Following this period, the need for reintervention decreases which indicates that postoperative results have become stable over time. However, this and other studies (2, 3) have revealed the need for reintervention even up to eight years following the initial operation in some cases. In our series, the subgroup prone to late reFP consisted primarily of NI children with a laparoscopic NissenFP. Therefore, particular focus should be placed on this subgroup of children in the long-term after the surgery.

A prolonged pH-monitoring is suggested for the objective evaluation of this high-risk group (3). Regular clinical and diagnostic investigations are not suggested since recurrences are rare; however, such investigations should be performed upon the occurrence of symptoms (3). Furthermore, it should be considered that a delayed indication for reFP may be due to the fact that most pediatric patients cannot communicate their GERD symptoms effectively and that confusion may occur regarding the symptoms related to the underlying neurologic condition and those related to reflux disease in case of NI children (2).

Regarding the limitations of this study, one can name the restricted inclusion criteria. The study population included 30 children; accordingly, this study cannot detect significant differences between the two groups accurately. Esposito et al. included a similarly low number (n=32) of patients in their follow-up study with a similar time (4) which indicated the difficulty of such very-long-term studies. Larger long-term pediatric cohort studies may be conducted through multicenter collaborations. Another limitation of the present study was that the postoperative symptoms and medication administration program at the follow-up period were determined based on the subjective opinion of parents rather than objective parameters, such as diagnostic tests. Moreover, the anatomy and position of the FP wrap were not objectively analyzed in children over time. This could be important in addressing

the functionality of the FP as the patient grew. Although GERD was clearly documented in our cohort and indications for surgery were strict, operations were performed by different surgeons; therefore, some degree of technical disparity may exist between interventions. Another limitation of the present study was the absence of an appropriate control group to rule out factors, such as spontaneous maturation of GERD symptoms. Due to the retrospective nature of the study, various biases can affect the data quality, such as undetected confounding factors or incomplete or inaccurate data. It should be noted that a prospective, blinded, randomized, two-armed study with a control group consisting of children who did not undergo surgery might address this issue and determine procedure-related factors with more accuracy. Due to ethical limitations, such studies would likely never be conducted on children, especially considering the long follow-up period of 10 years. Therefore, retrospective studies represent the best data for future recommendations.

## Conclusions

The FP is a safe procedure with consistent benefits in the first 10 postoperative years in the NI and NNI children with documented GERD. There is a significant postoperative improvement in symptoms in the long-term, together with a reduced need for medication. Moreover, the parents were largely very satisfied with the overall outcome. It is recommended that particular focus be placed on NI children with a laparoscopic Nissen-FP during a longer postoperative observation period since late reFP were required more often in this group. As late recurrences might occur especially after Nissen-FP, the indications to Thal-FP should be favored whenever possible.

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## Conflict of Interest

The authors declare that there is no conflict of interest regarding the publication of this study.

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