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REVIEW ARTICLE

Gastroesophageal reflux in children with neurological impairment: a systematic review and meta-analysis

Giuseppe Lauriti[1,2] · Gabriele Lisi[2] · Pierluigi Lelli Chiesa[2] · Augusto Zani[1] · Agostino Pierro[1]

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Abstract

Neurologically impaired children (NIC) suffer severe gastroesophageal reflux (GER) with poor fundoplication outcome. Aims of the study were: (1) to determine the recurrence of GER after fundoplication in NIC; (2) to compare fundoplication versus gastro-jejunal tube feeding insertion (GJ) and fundoplication versus total esophagogastric dissociation (TEGD) in primarily treating GER in NIC. Using defined search strategy, two investigators identified all comparative studies reporting the mentioned procedures to primarily treat GER in NIC. The study was conducted under PRISMA guidelines. The meta-analysis was performed using RevMan 5.3. Data are mean ± SD. Of 3840 titles/abstracts screened, 14 studies on fundoplication (2716 pts.) reported a recurrence/persistence of GER higher in NIC (14.2 ± 8.3%) than in neurologically normal (9.4 ± 5.2%; $p = 0.0001$), with an increased incidence of re-do fundoplication (12.6 ± 7.0% versus 9.1 ± 4.5%; $p < 0.01$). Three studies revealed a similar risk of undergoing subsequent fundoplication after GJ (4.9 ± 2.1%) or initial fundoplication (12.0 ± 0.6%; p = ns). Four studies showed a lower recurrence of GER following TEGD (1.4 ± 1.1%) than fundoplication (24.8 ± 1.4%; $p = 0.002$). NIC are at risk of recurrence/persistence of GER after fundoplication or GJ. TEGD seems more effective to primarily treat GER in NIC. Prospective randomized controlled trials are necessary to establish which is the ideal treatment of GER in NIC.

Keywords Gastroesophageal reflux · Neurologically impaired children · Fundoplication · Gastro-jejunal tube feeding · Total esophagogastric dissociation · Systematic review · Meta-analysis

Introduction

Neurologically impaired children (NIC) often present feeding problems because of esophageal dysmotility, reduced lower esophageal pressure, increased intra-abdominal pressure, and delayed gastric emptying [1, 2]. As a consequence, NIC have an increased risk of gastroesophageal reflux (GER): several studies have demonstrated the high incidence of GER in NIC, reporting symptoms such as vomiting, rumination and regurgitation in about 20–30% of this population [3–5]. Furthermore, these patients frequently continue to experience symptoms and complications during the medical management of GER, thus requiring a surgical procedure [6–8].

The most frequently performed surgical approach to primarily treat this disease remains fundoplication via open or laparoscopic approach [9, 10]. However, high rates of complications and recurrences after fundoplication in NIC have been reported [10–12], even if these results are not homogeneous [13]. The success rate of fundoplication varies from 95 to 98% in neurologically normal children (NNC) to 70–85% in NIC [14]. Moreover, the prevalence of re-operation following failed fundoplication was significantly higher in NIC (15.4%) compared to NNC (7.0%; $p = 0.003$) [10].

Because of these apparently limited outcomes of fundoplication, different techniques have been proposed in primarily treating GER in NIC, including gastro-jejunal tube feeding (GJ) and total esophagogastric dissociation (TEGD) [15, 16]. However, on the one hand, GJ is usually considered

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✉ Giuseppe Lauriti
giuseppe.lauriti@gmail.com

[1] Division of General and Thoracic Surgery, The Hospital for Sick Children, Toronto, ON, Canada

[2] Department of Pediatric Surgery, "G. d'Annunzio" University and "Spirito Santo" Hospital, Chieti-Pescara, Italy

as an intermediate solution before proceeding to surgery, it requires periodic replacement, and it is easily exposed to complications, such as tube displacement, kink, intussusception, clog, and possible jejunal perforation [17]. On the other hand, TEGD is uncommonly performed, with a few published data regarding long-term outcomes, and it is frequently executed as a salvage operation after failed fundoplication rather than as a primary procedure to treat GER in NIC [18].

The aims of the study were: (1) to systematically review the literature to determine whether the recurrence rate of GER after fundoplication is significantly higher in NIC in comparison with NNC; (2) to compare the outcome of fundoplication versus GJ and fundoplication versus TEGD in the treatment of GER in NIC.

Materials and methods

Both the systematic review and the meta-analysis were drafted with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [19]. Two different health librarians were involved: the Bibl@Ud'A ("d'Annunzio" University of Chieti-Pescara, Italy) and the Gerstein Science Information Centre (University of Toronto, ON, Canada).

Systematic review

The present study was registered on PROSPERO, an international prospective register of systematic reviews (registration number: CRD42017065462) [20].

A systematic review of the literature was made using a defined search strategy. Two investigators (GL and GL) independently searched scientific databases (PubMed, Medline, Cochrane Collaboration, Embase and Web of Science) using a combination of keywords (Table 1). MeSH headings and terms used are "gastroesophageal reflux AND neurological impairment AND children" and "fundoplication AND neurological impairment AND children" (Supplementary file 1). Case reports, opinion articles, and case series with less than ten patients were excluded.

All grey literature publications (i.e. reports, theses, conference proceedings, bibliographies, commercial documentations, and official documents not published commercially) were excluded.

The full text of the potentially eligible studies was retrieved and independently assessed for eligibility by the same two investigators. Any disagreement between them over the eligibility of particular studies was resolved through discussion with a third author (AZ).

Table 1 Inclusion criteria of systematic review

Publication	
Language	Any
Date	After 1950
Subject	Human studies
Study type	Retrospective
	Prospective
	Case–control
	Cohort
Excluded	Case reports
	Case series
	Letters
	Editorials
	Grey literature
Keywords	Gastroesophageal reflux
	Neurologically impaired children
	Fundoplication
	Gastro-jejunal tube feeding
	Total esophagogastric dissociation

Meta-analysis

Only studies comparing fundoplication in NIC versus NNC and fundoplication versus GJ or fundoplication versus TEGD to primarily treat GER in NIC were included. The primary outcome was the success rate of the surgical procedure (or the recurrence/persistence of GER). The secondary outcomes included the incidence of complications, the operative time, the length of post-operative intensive care unit (ICU) stay, the time to reach full enteral feeding, and the risk of further surgical procedures.

Meta-analysis was conducted with RevMan 5.3 [21], using the fixed-effects model to produce the risk ratio (RR) for categorical variables and the mean differences (MD) for continuous variables, along with 95% confidence intervals (CI). We produced I^2 values to assess homogeneity. Publication biases were assessed using the funnel plot method.

Data were compared using Fisher's exact test and are expressed as mean ± SD and range.

Quality assessment

Two investigators (GL and GL) independently assessed the quality and then came to a consensus of all papers that met our inclusion criteria using the Cochrane 'Risk of bias' tool for comparative studies [22]. Two senior authors (PLC and AP) independently evaluated the present systematic reviews and the meta-analysis using A Measurement Toll to Assess Systematic Reviews (AMSTAR) [23]. The PRISMA checklist of the study was subsequently completed [19].

Results

Outcome of fundoplication in NIC versus NNC

Of 3840 titles screened, 2153 abstracts were analyzed, 142 full-text articles were examined, and 21 studies met our inclusion criteria and were included in the meta-analysis (Fig. 1). Of these, 14 papers (2716 children) compared fundoplication in NIC versus NNC (Table 2) [24–37]. Eleven studies were retrospective [24–29, 31–34, 37] and only three were prospective but not randomized [30, 35, 36]. Moreover, a classical 360° Nissen fundoplication was performed in 9 studies [24, 27, 29–34, 36], a partial anterior Thal fundoplication was executed in 2 [25, 35], and either a Nissen or a Thal fundoplication was carried out in 3 [26, 28, 37].

The recurrence or persistence of GER symptoms was significantly higher in NIC (14.2 ± 8.3%, range 0–33.3%) than in NNC [9.4 ± 5.2%, range 0–21.0%; RR 1.55 (95% CI 1.24, 1.93); $p = 0.0001$, Fig. 2a]. Heterogeneity was not significant between the studies included ($I^2 = 38\%$, p = ns). The funnel plot of published studies demonstrated a convincing symmetry, thus indicating not potential publication bias (Fig. 2b). Consequently, the incidence of re-do fundoplication was significantly increased in NIC in comparison with NNC [12.6 ± 7.0 versus 9.1 ± 4.5%, respectively; RR 1.46 (95% CI 1.11, 1.91); $p < 0.01$, Fig. 2c]. Furthermore, two different studies [14, 29] reported a relevant albeit not significant risk of failure of the re-do fundoplication in NIC [39.4 ± 8.9 versus 29.7 ± 3.9%, respectively; RR 1.41 [95% CI 0.80, 2.48); p = ns, Fig. 2d].

Outcome of fundoplication versus GJ in NIC

Only three studies compared fundoplication (431 infants) versus GJ (123 infants) to primarily treat GER in NIC (Table 3) [38–40]. Two studies were retrospective [38, 40] and one was prospective but not randomized [39].

There was no difference in the recurrence or persistence of GER symptoms following fundoplication (35.2 ± 7.4%) versus GJ [30.5 ± 11.8%; RR 1.16 (95% CI 0.79, 1.70); p = ns, Fig. 3a]. Similarly, the risk of a subsequent fundoplication was similar after fundoplication (12.0 ± 0.6%) in comparison with GJ [4.9 ± 2.1%; RR 2.28 (95% CI 0.81, 6.41); p = ns, Fig. 3b]. The incidence of complications was significantly

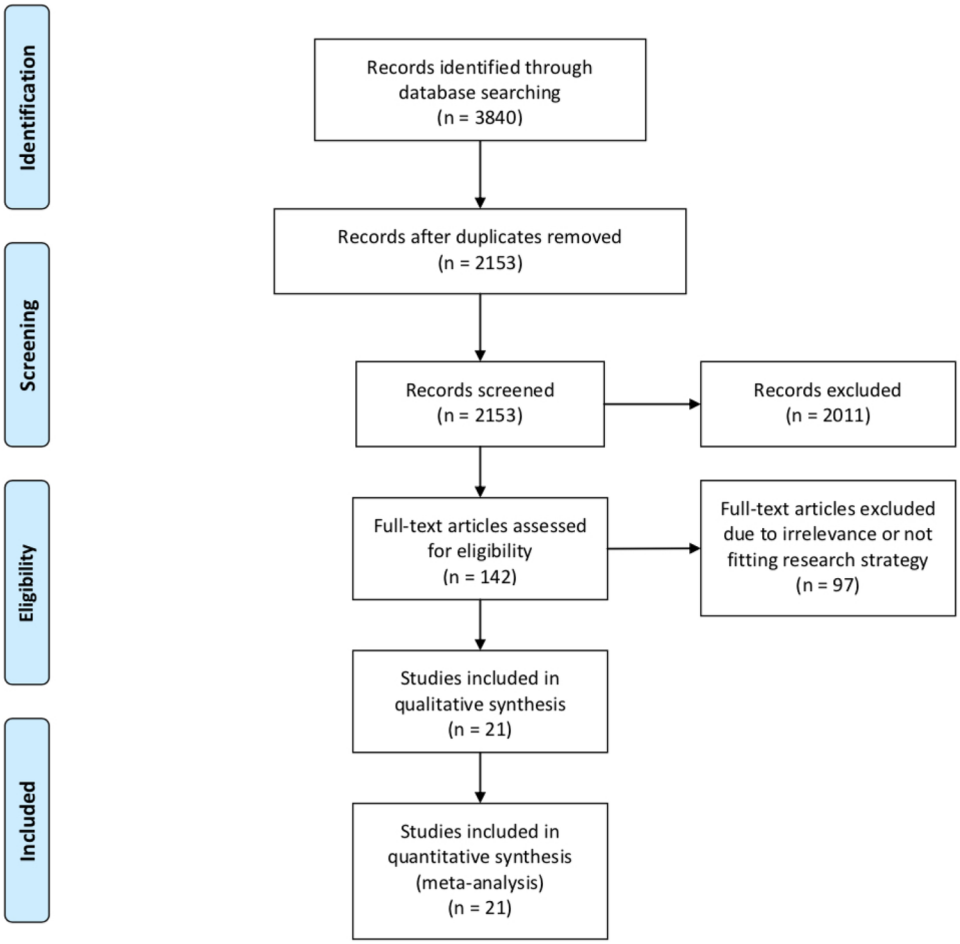


Fig. 1 Diagram of workflow in the systematic review and meta-analysis

Table 2 Studies comparing outcomes of fundoplication to treat GER in NIC versus NNC

References	Year	Type of study	Type of fundo	Recurrence of GER		Re-do fundoplication	
				NIC (%)	NNC (%)	NIC (%)	NNC (%)
Dedinsky et al. [24]	1987	R	ON	29/297 (9.8)	9/132 (6.8)	29/297 (9.8)	9/132 (6.8)
Tuggle et al. [25]	1988	R	OT	8/48 (16.7)	2/68 (2.9)	nr	nr
Pearl et al. [26]	1990	R	ON, OT	43/153 (28.1)	5/81 (6.2)	29/153 (18.9)	4/81 (4.9)
Rice et al. [27]	1991	R	ON	3/52 (5.8)	2/25 (8.0)	3/52 (5.8)	2/25 (8.0)
Kazerooni et al. [28]	1994	R	ON, OT	7/74 (9.5)	4/86 (4.6)	7/74 (9.5)	4/86 (4.6)
Subramanian et al. [29]	2000	R	ON	2/38 (5.3)	0/18 (0)	2/38 (5.3)	0/18 (0)
Capito et al. [30]	2007	P	LN	9/49 (18.4)	1/54 (1.8)	nr	nr
Mathei et al. [31]	2008	R	LN	0/49 (0)	3/57 (5.3)	nr	nr
Shariff et al. [32]	2010	R	LN	11/48 (22.9)	3/31 (9.7)	11/48 (22.9)	3/31 (9.7)
Baerg et al. [33]	2013	R	LN	49/395 (12.4)	51/428 (11.9)	49/395 (12.4)	51/428 (11.9)
Lopez-Fernandez et al. [34]	2014	R	ON, LN	13/100 (13.0)	29/260 (11.1)	nr	nr
Mauritz [35]	2014	P	LT	6/26 (23.1)	5/28 (17.9)	nr	nr
Knatten et al. [36]	2016	P	ON, LN	12/44 (27.3)	7/41 (17.1)	7/44 (15.9)	2/41(4.9)
Heinrich et al. [37]	2016	R	ON, LN, OT, LT	5/15 (33.3)	4/19 (21.0)	4/15 (26.7)	3/19 (15.8)

Fundo fundoplication, *GER* gastroesophageal reflux, *NIC* neurologically impaired children, *NNC* neurologically normal children, *R* retrospective, *P* prospective not randomized, *ON* open Nissen, *OT* open Thal, *LN* laparoscopic Nissen, *LT* laparoscopic Thal, *nr* not reported

higher in the fundoplication group (51.8 ± 7.9%) versus GJ cases [32.9 ± 9.0%; RR 1.58 (95% CI 1.12, 2.21); $p < 0.01$], even if there was a relevant albeit not significant heterogeneity between the studies ($I^2 = 46\%$, p = ns, Fig. 3c). However, the incidence of pneumonia was not statistically different between NIC treated by fundoplication or by GJ [16.9 ± 8.0 versus 21.6 ± 6.3%; RR 0.89 (95% CI 0.60, 1.31), respectively; p = ns, Fig. 3d].

When reported [39], the most common complications other than pneumonia were retching, esophagitis, and recurrence of reflux after fundoplication (36.5, 19.0, and 14.3%, respectively) and tube dislodgment, intussusception or small bowel obstruction, and esophagitis following GJ insertion (66.7, 20.8, and 14.6%, respectively).

Outcome of fundoplication versus TEGD in NIC

Four studies compared fundoplication (105 children) versus TEGD (71 patients) to primarily treat GER in NIC (Table 4) [41–44]. Two studies were retrospective [42, 43], one was a retrospective analysis from a prospectively collected database [44], and one paper was prospective but not randomized [41].

As expected, operative time was significantly shorter in fundoplication (143 ± 47.5 min) in comparison with TEGD [255 ± 90.0 min, MD − 113.34 (95% CI − 141.84, − 84.83); $p < 0.00001$, Fig. 4a], with a relevant yet not significant heterogeneity between the studies ($I^2 = 58\%$, p = ns). However, the length of post-operative ICU stay was not statistically different between fundoplication (2.1 ± 4.5 days) and TEGD [2.1 ± 4.2 days, MD − 0.02 (95% CI − 1.42, 1.37); p = ns, Fig. 4b]. Similarly, the time to reach full feeds was similar after fundoplication (6.6 ± 11.7 days) and TEGD [8.4 ± 9.0 days, MD − 2.25 (95% CI − 5.42, 0.93); p = ns, Fig. 4c].

Fundoplication showed a significantly higher recurrence of vomiting (24.8 ± 1.4%) than TEGD in NIC [1.4 ± 1.1%, RR 7.40 (95% CI 2.02, 27.05); $p = 0.001$, Fig. 4d]. The incidence of complications was reduced after fundoplication (8.2 ± 8.3%) in comparison with TEGD (21.6 ± 2.8%), albeit no statistical significance was found [RR 0.57 (95% CI 0.27, 1.20); p = ns, Fig. 4e].

Discussion

Fundoplication in NIC versus NNC

There continues to be considerable uncertainty regarding the optimal treatment option when faced with the primary treatment of GER in NIC. As reported in a recent meta-analysis, surgeons and patients should be aware that in NIC both open and laparoscopic Nissen fundoplication are associated with high rates of recurrence and mortality [12]. In NIC, medical treatment and fundoplication should be well considered, given the risks and benefits of each treatment. Furthermore, the lack of high-quality evidence regarding the relative merits and drawbacks of each option should be shared with families [45].

As described by Pearl et al. [25] the success ratio of the fundoplication is dependent on the neurologic status of the patient and the major cause of fundoplication failure is the herniation of the wrap into the chest. Because of

concomitant spasticity, convulsions, or scoliosis, the risk of herniation is high in NIC. One of the possible risk factors that induced failure of fundoplication was epilepsy. Repeatedly, the increased abdominal pressure and the prolonged relaxations of the lower esophageal sphincter due to a direct vagal effect are the principle causes of the herniation or disruption of the wrap [11]. Furthermore, because of their neurologic impairment, these children are also susceptible to early postoperative complications, especially recurrent pulmonary infections. This is mostly the result of poor oropharyngeal clearance of saliva with subsequent aspiration [31].

Moreover, the right crus and muscles of the diaphragm are weak in NIC because of malnutrition and distorted anatomy. Hence, it has been reported that if the crural muscles are weak, there is a significant chance for reflux to recur because the angle of His is not maintained after the fundoplication and the whole wrap is liable to prolapse through the hiatus [29].

The studies reported in Table 2 seem to be homogeneous, demonstrating an overall significant increased risk of recurrence or persistence of GER in NIC versus NNC (Fig. 2a), as well as an increased rate of re-do fundoplication (Fig. 2c). However, it is noticeable that a case-control study by Ngerncham et al. failed to confirm the above findings most likely because the study had rigorously controlled for obvious confounding variables, such as surgeon, operative technique, and duration of follow-up [46]. This result was also confirmed in a more recent prospective cohort study with a meticulous follow-up, a well-defined classification of NIC, and a scoring of complications according to a standardized classification system [36].

These results lead us to the principal limitation of the present study: the lack of a validated tool to assess GER symptoms and outcome after fundoplication for the pediatric patient population [36]. As reported, there is no a uniform definition of failure after antireflux surgery, especially in pediatric syndromic patients [11].

Criteria for evaluation of outcome after treatment for GER includes subjective assessment of symptoms, including the recurrence of reflux, and subjective assessment of overall respiratory or feeding difficulties. An international panel of experts created guidelines in 2009 [7]; however, most studies were published before 2009. Moreover, these guidelines have yet to be universally adopted. Still, few comparative studies provided a lack of clear outcomes and standardized follow-up protocols. Hence, many complications were likely not detected, not reported or both. Moreover, observer bias and lack of objective measures of outcome has led to inconsistency in the literature. Furthermore, the length of follow-up varies greatly among the studies analyzed. A possible factor causing the wide range of recurrences is that most studies on long-term efficacy of pediatric fundoplication were retrospective and introduced selection bias by including only alive and available patients into the analysis [35]. To overcome the difficulties in assessing symptoms of recurrent GER in NIC, objective evaluations of all these patients, including 24-h pH monitoring, are required. Moreover, long-term follow-up studies are required as reduction of respiratory symptoms after fundoplication seemed to be limited to the first post-operative year. A number of reasons can account for the persistence of respiratory symptoms after fundoplication in NIC, including discoordinated swallowing, gastroesophageal dysmotility, spasticity, aerophagy, chronic constipation, scoliosis, or a predominantly supine position [37].

Outcome of fundoplication versus GJ in NIC

Because of the high complication rate of fundoplication and the significant comorbid disease in NIC, many investigators have favored GJ as an alternative to fundoplication. As know, GJ could be preferred because of a high successful insertion rate and the requirement of sedation and local anesthesia; therefore, this procedure can also be tolerated to some weak NIC unfit to receive general anesthesia for fundoplication [39].

However, NIC treated with GJ are at continued risk for vomiting and aspiration pneumonia of gastric fluid because GJ does not treat GER, necessitating that patients continue medical management [38]. NIC treated with GJ are fed continuously via an infusion pump increasing the complexity and the cost of treatment in the community. In addition, there are complications associated with GJ such as dislodgement of the GJ tube, intussusception, and leakage that necessitate readmission to the hospital and anesthesia. The quality of life of these children treated with GJ has not been prospectively evaluated [8, 47, 48]. Moreover, none of the included comparative studies reported quality of life or patient-reported outcomes using validated measures.

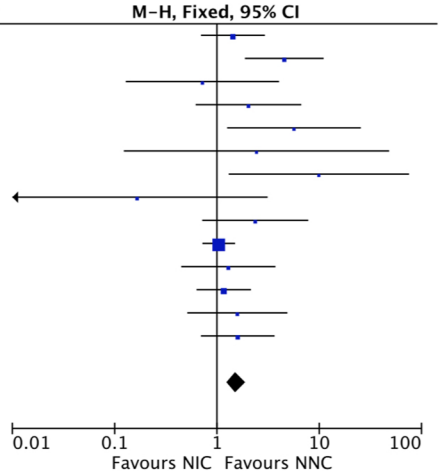
As an expected consequence, in our meta-analysis the persistence of GER symptoms were similar following both fundoplication and GJ (Fig. 3a), with a relevant incidence of pneumonia following both these primary procedures (Fig. 3d).

Furthermore, as reported in a recent systematic review and meta-analysis on this topic, the evidence supporting the use of fundoplication versus GJ to treat refractory GER in NIC is low [8]. Only three comparative but retrospective studies have been published up to know on this focus. These observational studies indicate a lack of evidence to support one approach over the other. Hence, more studies are needed to compare the outcomes of fundoplication versus GJ to primarily treat NIC with GER. Only high-quality studies (i.e. adequately powered, multicenter randomized controlled

a

Study or Subgroup	NIC Events	NIC Total	NNC Events	NNC Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Year
Dedinsky 1987	29	297	9	132	10.7%	1.43 [0.70, 2.94]	1987
Pearl 1990	43	153	5	81	5.6%	4.55 [1.88, 11.04]	1990
Rice 1991	3	52	2	25	2.3%	0.72 [0.13, 4.05]	1991
Kazerooni 1994	7	74	4	86	3.2%	2.03 [0.62, 6.68]	1994
Tuggle 1998	8	48	2	68	1.4%	5.67 [1.26, 25.52]	1998
Subramaniam 2000	2	38	0	18	0.6%	2.44 [0.12, 48.27]	2000
Capito 2007	9	49	1	54	0.8%	9.92 [1.30, 75.48]	2007
Mathei 2008	0	49	3	57	2.8%	0.17 [0.01, 3.13]	2008
Shariff 2010	11	48	3	31	3.1%	2.37 [0.72, 7.82]	2010
Baerg 2013	49	395	51	428	42.1%	1.04 [0.72, 1.50]	2013
Mauritz 2014	6	26	5	28	4.1%	1.29 [0.45, 3.73]	2014
Lopez-Fernandez 2014	13	100	29	260	13.9%	1.17 [0.63, 2.15]	2014
Heinrich 2016	5	15	4	19	3.0%	1.58 [0.51, 4.89]	2016
Knatten 2016	12	44	7	41	6.2%	1.60 [0.70, 3.66]	2016
Total (95% CI)		**1388**		**1328**	**100.0%**	**1.55 [1.24, 1.93]**	
Total events	197		125				

Heterogeneity: $Chi^2 = 20.98$, df = 13 (P = 0.07); $I^2 = 38\%$
Test for overall effect: Z = 3.85 (P = 0.0001)



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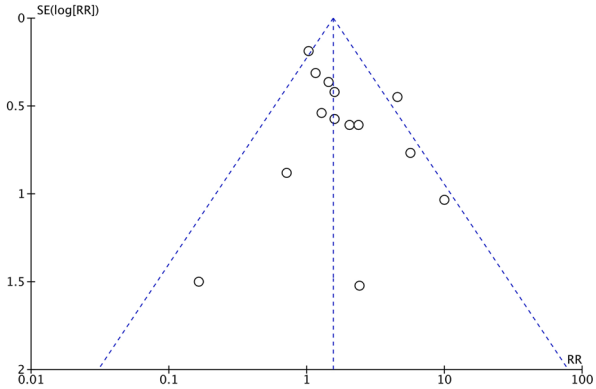
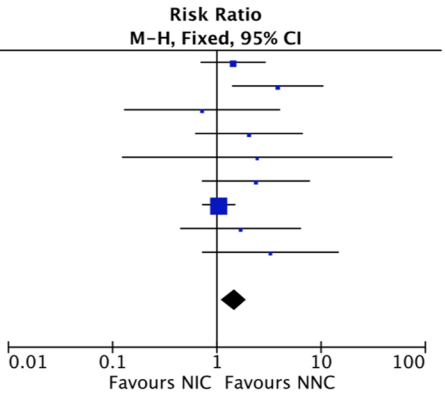


c

Study or Subgroup	NIC Events	NIC Total	NNC Events	NNC Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Year
Dedinsky 1987	29	297	9	132	15.2%	1.43 [0.70, 2.94]	1987
Pearl 1990	29	153	4	81	6.4%	3.84 [1.40, 10.54]	1990
Rice 1991	3	52	2	25	3.3%	0.72 [0.13, 4.05]	1991
Kazerooni 1994	7	74	4	86	4.5%	2.03 [0.62, 6.68]	1994
Subramaniam 2000	2	38	0	18	0.8%	2.44 [0.12, 48.27]	2000
Shariff 2010	11	48	3	31	4.4%	2.37 [0.72, 7.82]	2010
Baerg 2013	49	395	51	428	59.6%	1.04 [0.72, 1.50]	2013
Heinrich 2016	4	15	3	19	3.2%	1.69 [0.44, 6.42]	2016
Knatten 2016	7	44	2	41	2.5%	3.26 [0.72, 14.80]	2016
Total (95% CI)		**1116**		**861**	**100.0%**	**1.46 [1.11, 1.91]**	
Total events	141		78				

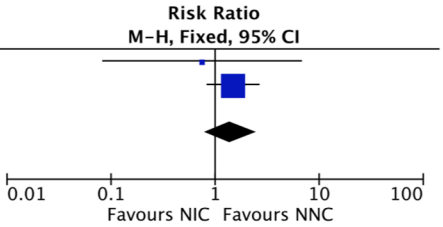
Heterogeneity: $Chi^2 = 9.59$, df = 8 (P = 0.30); $I^2 = 17\%$
Test for overall effect: Z = 2.74 (P = 0.006)



d

Study or Subgroup	NIC Events	NIC Total	NNC Events	NNC Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Year
Subramaniam 2000	2	16	1	6	10.5%	0.75 [0.08, 6.83]	2000
Pacilli 2007	24	50	10	31	89.5%	1.49 [0.83, 2.67]	2007
Total (95% CI)		**66**		**37**	**100.0%**	**1.41 [0.80, 2.48]**	
Total events	26		11				

Heterogeneity: $Chi^2 = 0.35$, df = 1 (P = 0.56); $I^2 = 0\%$
Test for overall effect: Z = 1.19 (P = 0.23)



◂**Fig. 2** **a** Forest plot comparison of recurrence or persistence of GER symptoms after fundoplication in NIC versus NNC. **b** Funnel plot of included studies comparing the recurrence or persistence of GER symptoms after fundoplication in NIC versus NNC. **c** Forest plot comparison of the incidence of re-do fundoplication in NIC versus NNC. **d** Forest plot comparison of the incidence of failure of re-do fundoplication in NIC versus NNC

trial, RCT) could determine if one approach is truthfully superior [40].

Outcome of fundoplication versus TEGD in NIC

TEGD is commonly considered a "rescue" procedure for recurrent GER because of the extent of the procedure and the potential for serious operative complications (i.e. bleeding, anastomotic leakage, necrosis of the Roux loop, perforation, wound dehiscence, diaphragmatic hernia, and adhesive obstruction) [42].

A systematic review on this procedure reported a 16% early complication rate and a 15.5% late complications rate following TEGD procedure. Moreover, the overall mortality related to TEGD was 3.3%, though some of these losses occurred months or even years after the procedure [49].

However, in recent years TEGD has revealed an acceptable complication rate, which was lower than some operation rates after fundoplication [43]. Hence, few authors have adopted TEGD as a useful procedure to primarily treat severe NIC affected by GER.

Predictably, operative time was significantly longer in TEGD in comparison with fundoplication (Fig. 4a). Conversely, no differences were found with regards to the length of post-operative ICU stay and the time to reach full feeds (Fig. 4b, c).

As reported in our meta-analysis, patients who underwent TEGD presented a higher albeit not significant incidence of complications compared to NIC who underwent fundoplication (Fig. 4e) and no deaths related to TEGD were reported.

As expected, TEGD showed a significantly lower recurrence of GER in comparison with fundoplication in NIC (Fig. 4d). As a matter of fact, after fundoplication hospitalization became less frequent, although a substantial decrease with a significant improvement in quality of life has been reported only after TEGD [41]. However, a carer questionnaire survey of symptoms and quality of life across previously validated domains was not significantly different between TEGD and fundoplication, even if carers reported those who had a TEGD had significantly better enjoyment of life [44].

In the end, concerns remain over the magnitude of the procedure and the potential for serious operative complications [42]. Thus, it seems appropriate to still consider TEGD as a significantly more 'invasive' procedure requiring longer periods of rehabilitation [44]. Consequently, to the best of our knowledge, further studies are necessary to demonstrate the true efficacy of TEGD as a primary procedure to treat GER in NIC and not only as a "salvage" procedure for those recurrent cases. Hence, a RCT to compare these operations is warranted [41]. Up to now, TEGD should only be offered to families of severe NIC as part of comprehensive preoperative counseling [44].

Limitations of the study

We acknowledge the limitations of the present study, which as any other meta-analysis, relies on the quality of the studies and the data available in the literature. Some of the limitations of our current meta-analysis are due to the retrospective nature of most of the studies included (Tables 2, 3, 4) as well as to the variability in the definition of GER and its recurrence. As already mentioned above, uncertainty around the diagnosis of GER based on ICD-9-CM coding or in clinical practice is widely recognized [50]. As recently reported, ESPGHAN recommends use of objective measures for the diagnosis of GER in NIC (i.e. oesophageal pH- or pH/multichannel intraluminal impedance monitoring, and/or upper gastrointestinal

Table 3 Studies comparing outcomes of fundoplication versus GJ in treating GER in NIC

References	Year	Type of study	Type of fundo	Recurrence or persistence of GER		Subsequent fundoplication		Major complications		Pneumonia	
				Fundo (%)	GJ (%)	Fundo (%)	GJ (%)	Fundo (%)	GJ (%)	Fundo (%)	GJ (%)
Albanese et al. [38]	1993	R	ON	8/45 (17.8)	1/34 (2.9)	6/45 (13.3)	0/34 (0)	15/45 (33.3)	4/34 (11.8)	2/45 (4.4)	2/34 (4.9)
Wales et al. [39]	2002	R	ON	30/63 (47.6)	24/48 (50.0)	7/63 (11.1)	4/48 (8.3)	41/63 (65.1)	23/48 (47.9)	23/63 (36.5)	15/48 (31.3)
Srivastava et al. [40]	2009	P	ON	nr	nr	nr	nr	nr	nr	48/323 (14.9)	10/43 (23.2)

GJ gastro-jejunal tube feeding, *GER* gastroesophageal reflux, *NIC* neurologically impaired children, *Fundo* fundoplication, *R* retrospective, *P* prospective not randomized, *ON* open Nissen, *nr* not reported

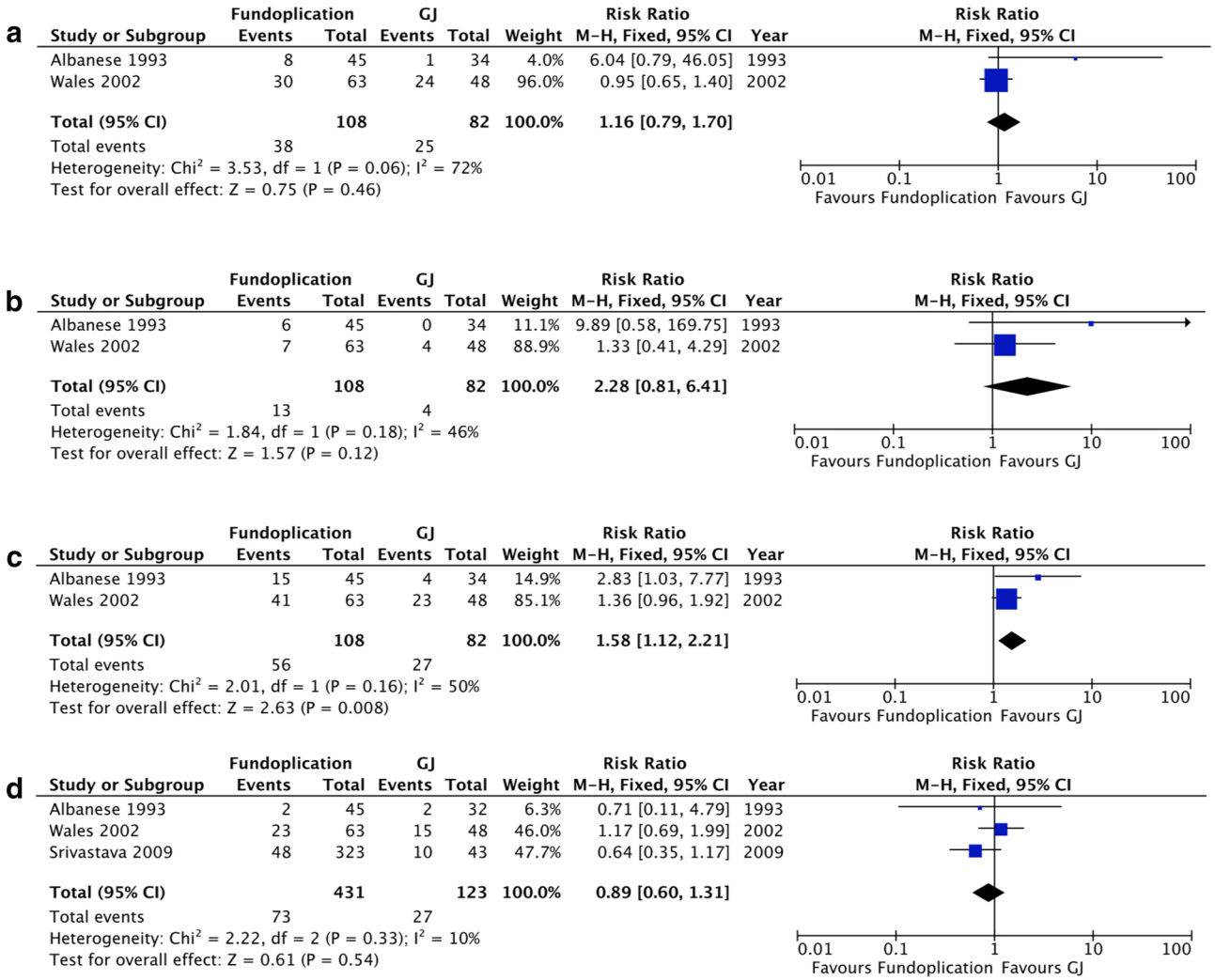


Fig. 3 **a** Forest plot comparison of recurrence or persistence of GER symptoms after fundoplication versus GJ in NIC. **b** Forest plot comparison of subsequent fundoplication after fundoplication versus GJ in NIC. **c** Forest plot comparison of the incidence of major complications after fundoplication versus GJ in NIC. **d** Forest plot comparison of the incidence of pneumonia after fundoplication versus GJ in NIC

Table 4 Studies comparing outcomes of fundoplication versus TEGD in treating GER in NIC

References	Year	Type of study	Type of fundo	Operative time		Length of post-operative ICU stay		Time to full enteral feeding		Complications		Recurrence or persistence of GER	
				Fundo (SD)	TEGD (SD)	Fundo (SD)	TEGD (SD)	Fundo (SD)	TEGD (SD)	Fundo (%)	TEGD (%)	Fundo (%)	TEGD (%)
Gatti et al. [41]	2001	P	ON	nr	nr	nr	nr	nr	nr	4/12 (33.3)	4/14 (28.6)	3/12 (25.0)	0/14 (0)
Goyal et al. [42]	2005	R	ON	150m (45.0)	238m (87.5)	4.1d (4.25)	1.6d (2.25)	9.1d (11.2)	8.4d (3.7)	nr	nr	5/20 (25.0)	0/20 (0)
Molinaro et al. [43]	2014	R	LN	nr	nr	nr	nr	nr	nr	0/49 (0)	3/14 (21.4)	13/49 (26.5)	0/14 (0)
Lansdale et al. [44]	2015	R*	LN	137m (43.7)	270m (82.5)	0.5d (2.25)	2.5d (4.0)	5.5d (4.0)	9.5 (9.0)	3/24 (12.5)	4/23 (17.4)	5/24 (20.8)	1/23 (4.3)

TEGD total esophagogastric dissociation, *GER* gastroesophageal reflux, *NIC* neurologically impaired children, *Fundo* fundoplication, *ICU* intensive care unit, *P* prospective not randomized, *R* retrospective, *R** retrospective analysis from a prospectively collected database, *ON* open Nissen, *LN* laparoscopic Nissen, *nr* not reported

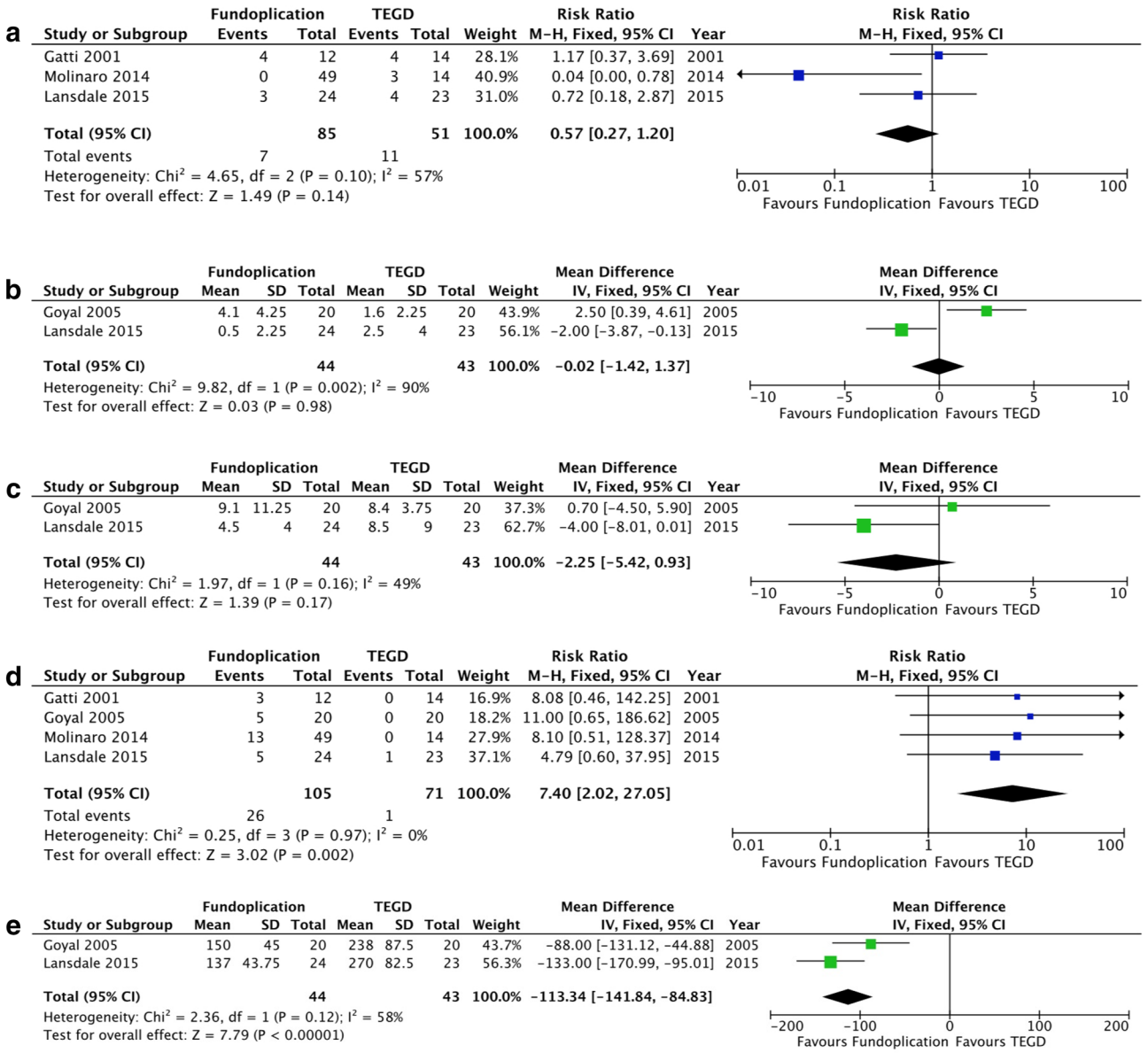


Fig. 4 **a** Forest plot comparison of operative time of fundoplication versus TEGD in NIC. **b** Forest plot comparison of the length of postoperative ICU stay after fundoplication versus TEGD in NIC. **c** Forest plot comparison of the time to full enteral feeds after fundoplication versus TEGD in NIC. **d** Forest plot comparison of recurrence or persistence of vomiting after fundoplication versus TEGD in NIC. **e** Forest plot comparison of the incidence of complications after fundoplication versus TEGD in NIC

endoscopy), with a periodical re-evaluation of long-term therapy of GER disease in these patients [51].

Moreover, the severity of the neurological impairment as well as the co-existence of other major comorbidities were not always well defined, clarified, or reported in the included studies.

Furthermore, as reported in Tables 2 and 4, there was and heterogeneity with regards to the fundoplication procedure (i.e. open or laparoscopic approach, Nissen or Thal fundoplication).

The risk of bias assessments for the individual comparing studies included in the present meta-analysis varied quite a bit (Supplementary file 2). Statistical heterogeneity of data was fairly low for all of our analyses, with a relevant yet not significant heterogeneity between the studies in three forest plots (Figs. 2a, 3c, 4a). Despite this, clinical heterogeneity does exist and it is inherent in the meta-analysis, and this must be considered when interpreting the results of this study. However, to the best of our knowledge, the present paper is the only one in the literature that attempted to analyze the outcomes of all available surgical options to treat GER in NIC. Furthermore, when independently assessed by two senior authors using AMSTAR, the present systematic reviews and meta-analysis received a

relevant score (Supplementary file 3). Lastly, the PRISMA checklist of our study was completed (Supplementary file 4).

Conclusion

In conclusion, NIC are at significantly high risk of recurrence of GER after fundoplication, with results in an increased incidence of re-do fundoplication. GJ seems not to improve the outcome of GER in NIC. TEGD seems to be effective to primarily treat GER in NIC when compared to fundoplication. However, this technique increased the risk of serious post-operative complications and it is associated to a known risk of mortality. Because of the invasiveness of this procedure, to the best of our knowledge high-quality studies (i.e. RCT) are deserved to prove the effectiveness of TEGD to primarily treat GER in NIC. Quality of life remains the primary outcome after treatment of GER in NIC and a prospective study is needed to determine which is the preferred treatment of GER in these patients.

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Compliance with ethical standards

Conflict of interest Authors have no potential conflicts of interest for this study.

Ethical approval Not applicable, since the study is a systematic review and meta-analysis.

Informed consent Not applicable, since the study is a systematic review and meta-analysis.

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