Accepted Manuscript

Surgical Treatment and Major Complications within the First Year of Life in Newborns with Long-Gap Esophageal Atresia Gross Type a and B – a Systematic Review

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PII: S0022-3468(19)30443-9
DOI: https://doi.org/10.1016/j.jpedsurg.2019.06.017
Reference: YJPSU 59258

To appear in: *Journal of Pediatric Surgery*

Received date: 28 December 2018
Revised date: 16 April 2019
Accepted date: 21 June 2019

Please cite this article as: T. Stadil, A. Koivusalo, J.F. Svensson, et al., Surgical Treatment and Major Complications within the First Year of Life in Newborns with Long-Gap Esophageal Atresia Gross Type a and B – a Systematic Review, Journal of Pediatric Surgery, https://doi.org/10.1016/j.jpedsurg.2019.06.017

1. Title

Surgical treatment and major complications within the first year of life in newborns with long-gap esophageal atresia Gross type A and B – A systematic review.

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3. Abstract

3.1 Background

The surgical repair of long-gap esophageal atresia (LGEA) is still a challenge and there is no consensus on the preferred method of reconstruction. We performed a systematic review of the surgical treatment of LGEA Gross type A and B with the primary aim to compare the postoperative complications related to the different methods within the first postoperative year.

3.2 Methods

Systematic literature review on the surgical repair of LGEA Gross type A and B within the first year of life published from January 01, 1996 to November 01, 2016.

3.3 Results

We included 57 articles involving a total of 326 patients of whom 289 had a Gross type A LGEA. Delayed primary anastomosis (DPA) was the most applied surgical method (68.4%) in both types, followed by gastric pull-up (GPU) (8.3%). Anastomotic stricture (53.7%), gastro-esophageal reflux (GER) (32.2%) and anastomotic leakage (22.7%) were the most common postoperative complications, with stricture and GER occurring more often after DPA (61.9% and 40.8% respectively) compared to other methods (p <0.001).

3.4 Conclusion

The majority of patients in this review were managed by DPA and postoperative complications were common despite the surgical method, with anastomotic stricture and GER being most common after DPA.

4. Key words

Esophageal atresia – Long-gap – Gross type A – Gross type B – Surgical repair – Postoperative complication.

5. Level of evidence

Systematic review of case series and case reports with no comparison group (level IV).

6. Introduction

Esophageal atresia (EA) is a rare malformation with a prevalence of 1 in every 2500-4500 live births [1, 2]. Approximately 10% of children have a long-gap esophageal atresia (LGEA) [3]. The surgical repair of LGEA is challenging, and there are great controversies regarding the optimal surgical treatment.

The etiology of the malformation is unknown and the embryology not fully understood. During embryogenesis, a disruption with abnormal separation of the embryonic foregut into the trachea and the esophagus occurs, resulting in an upper and a lower esophageal segment and most of the time in a tracheo-esophageal fistula (TEF) [4, 5]. Other major anomalies are often associated with EA, a common one being the VACTERL/VATER association [6] consisting of vertebral, anal, cardiac, tracheal, esophageal, renal and limb anomalies.

The definition of LGEA is varying from the inability to obtain a primary anastomosis to a measured gap-length of not less than two centimeters or covering not less than two thoracic vertebras [7, 8]. Different classification systems to describe the different types of EA have been proposed and the Gross classification system is the most accepted [9]. We have chosen to restrict the review to Gross type A and B, which may be the most challenging to repair. The various surgical procedures described include delayed primary anastomosis (DPA) [10-12] with or without prior elongation techniques as for instance the Foker [13] or Kimura [14] technique, organ interposition with jejunum [15] or colon [16] and gastric pull-up (GPU) [15, 17] with or without the construction of a gastric tube [18, 19]. Both a retrosternal or posterior mediastinal route for organ interposition or GPU is feasible [8]. A gold standard in the surgical treatment of LGEA is lacking, and the chosen treatment often depends on surgical experience and preference. The existing literature includes many institutional small patient series and reports covering innumerable individual experiences. The

objective of this review was to perform a systematic review of the surgical treatment of LGEA Gross type A and B in newborns with the aim to compare the postoperative complications the different surgical methods reported.

7. Materials and Methods

7.1 Identification of studies

We conducted a systematic review of the existing literature on the surgical treatment of LGEA Gross type A and B published between January 01, 1996 and November 01, 2016. PubMed, Embase and the Cochrane Databases were searched for relevant literature. In PubMed and the Cochrane Databases the following search query was used: “esophageal atresia OR esophageal atresias” and “long-gap OR long gap” or “LGEA”. Embase was searched using the subject heading “esophagus atresia” and the keywords “esophageal atresia*”, “long-gap”, “long gap” and “LGEA”. The latest search was made on the 31th October 2016.

Literature search results were uploaded to the Covidence online software [20] and used as screening tool during the study selection process. Abstracts and full text articles were uploaded at which duplicates were sorted out automatically. Titles and abstracts were examined against the inclusion criteria and full texts of potentially eligible studies were obtained. The full text reports were then screened by two of the authors (TS and NQ) for inclusion or exclusion. Any discrepancies were reviewed and solved in agreement. To ensure literature saturation we also screened references of the relevant studies. The study was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) [21] and guided by The Cochrane Handbook for Systematic Reviews of Interventions [22].

Our methods are available in a review protocol previously registered with the International Prospective Register of Systematic Reviews (PROSPERO) [23].

7.2 Eligibility criteria

The criteria for eligibility and evidence were as follows: Surgical treatment of LGEA Gross type A and B to establish continuity of the gastrointestinal tract within the first year of life and associated postoperative complications within one year postoperatively. Information on preoperative gasless abdomen by plain abdominal X-ray was a prerequisite. Associated major anomalies were no reason for exclusion, given that these are common in this patient group. Studies on newborns with LGEA Gross type C, D or E as well as on animal models were excluded from this study to gain a more homogeneous group of patients. There were no language limits, although only studies that could be translated adequately were included.

7.3 Data collection and quality assessment

Exposure variables of interest were the applied surgical interventions for reconstruction of the LGEA, such as an attempted primary anastomosis, a DPA, an active elongation technique, an organ interposition procedure and any other technique to obtain continuity of the gastrointestinal tract. The main outcome parameters were reporting of any postoperative complications, such as anastomotic leakage, gastro-esophageal reflux (GER) and mortality within the first postoperative year. Secondary outcome parameters were hospital stay, duration of parenteral nutrition and the total number of thoracotomies, fundoplications and re-operations due to stricture or leakage during the first year of life as well as body weight and length at 1-year follow-up. Other parameters were gestational age (GA), birth weight and length, type of delivery and associated congenital anomalies.

Risk of bias of the individual studies was evaluated systematically using critical appraisal tools provided by the Joanna Briggs Institute (JBI) [24]. Data from eligible studies were extracted by means of a standardized data extraction form.

7.4 Statistical analysis

We conducted descriptive statistics to summarize and display the collected data. Categorical variables were analyzed by cross-tabulations and the relationships between those variables were presented as frequencies and percentages. Means and standard deviations (SDs) were used to present numerical, continuous variables. The χ^2 test or the Fisher exact test was applied on categorical, binary outcome variables to test for differences. The association between these outcomes and the exposure variables were displayed by a logistic regression model. A Student's t-test was used to test for differences in means of the numerical variables. Missing values were excluded from the analyses of outcome variables. A *p*-value <0.05 was considered statistically significant. Stata version 14.2. was used.

Conducting a meta-analysis was assessed as impossible due to the expected diversity of the study interventions.

8. Results

The literature search resulted in a total of 438 articles of which 212 were retrieved for full text screening. Finally, 57 articles were included in this review, involving a total of 326 patients (Figure 1). All included studies were retrospective, either case report (*n* = 25) or case series (*n* = 32) and the majority of patients had Gross type A LGEA (*n* = 289). Details of the included studies are shown in Table 1.

Due to missing reported data in most of the articles patient characteristics such as GA, birth weight and associated anomalies could not be assessed statistically.

Table 5 summarizes the risk of bias assessed by the JBI critical appraisal checklist and shows, that the included articles varied considerably in the quality of reporting.

8.1 Surgical methods

Regarding the definitive repair of LGEA 223 (68.4%) patients were managed by DPA, 27 (8.3%) by GPU, 26 (8,0%) by a gastric tube, 25 (7.7%) received colonic interposition and in 24 (7.4%) other methods such as partial gastric pull-up and magnetic compression anastomosis were applied. Only one (0.3%) patient received jejunal interposition. In 125 (38.3%) patients an active elongation technique was applied prior to the definitive reconstruction and the most common elongation method was the Foker technique. A primary anastomosis of the two esophageal pouches was attempted in 42 (14.5%) patients with Gross type A compared to only one (2.7%) patient with Gross type B. Otherwise there were no significant difference in the preferred surgical method for repair between the two type of LGEA. More details on the distribution of the applied surgical methods are shown in Table 2.

8.2 Postoperative course

The postoperative complications after the different surgical methods are shown in Table 3. The most common postoperative complications were anastomotic stricture which occurred in 175 (53.7%) out of the 326 patients, GER which was reported in 105 (32.2%) patients and anastomotic leakage which occurred in 74 (22.7%) patients. The reported mortality within the first postoperative year was 15 (4.6%). Significant differences between the surgical methods were found in the occurrence of postoperative anastomotic stricture (p <0.001), postoperative GER (p <0.001), the need of fundoplication (p = 0.001) and the total number of thoracotomies (p <0.001),

which all were higher after DPA as opposed to the mortality rate which was lower after DPA compared to gastric tube formation and colonic interposition (p <0.001).

Due to heterogeneity of the different treatment groups a regression analysis was performed, which showed a significant difference in the risk of anastomotic stricture, which was lower after GPU (p = 0.028) and colonic interposition (p <0.001) compared to DPA (Table 5). Compared to DPA, the risk of GER was significantly lower after colonic interposition (p = 0.021). Other associations between the different surgical methods and the postoperative course were not significant. Adjustment for potential confounding factors such as associated anomalies could not be performed due to missing reported data.

9. Discussion

Our study showed a great variety in the surgical procedures, with several different modifications used for the reconstruction of LGEA Gross type A and B and it confirms that there is no gold standard in the surgical treatment of LGEA [3]. We found that the most common method in both type A and B atresia was DPA [7, 25]. A recent survey of European pediatric surgeons [25] and a review by Von Allmen et al. [7] showed that in cases where an esophageal replacement was needed, GPU was the preferred procedure. This, however, does not emanate from our results, as GPU, gastric tube formation, colonic interposition and other methods, such as partial gastric pull-up, were equally applied. In a recently conducted retrospective multi-center study comparing the management of long-gap esophageal atresia Gross type A and B in the Nordic countries from 2000 to 2014 [26] a similar distribution of DPA and esophageal replacement procedure was found, and GPU was the most frequent replacement procedure. Due to relative few cases in our Nordic multi-center study and the long review period of the present study, eventual changes in treatment

modality could not be assessed. We excluded patients with Gross type C atresia, which is a more heterogeneous group with a much more different surgical approach, and the inclusion of these patients would have made the definition of LGEA more inconsistent.

The total rate of postoperative complications was high and regardless of the surgical approach major complications such as anastomotic leakage, anastomotic stricture and GER were inevitable. The incidence of an anastomotic leak after DPA, GPU and gastric tube formation was 22.4%, 25.9% and 26.9% respectively, which is comparable to the reported 28.7% in a meta-analysis on long-term outcome in patients with LGEA managed by DPA [12] and similar to the results from the Nordic multi-center study with an incidence of 32.4% [26]. Some institutions may perform routine postoperative contrast studies of the esophagus and include clinical as well as subclinical leaks. The risk of an anastomotic leak was lowest after colonic interposition. The reported frequency of re-operation due to a leak was low (2.5%) indicating that most leaks can be treated conservatively or may be subclinical and resolve spontaneously without the need for further therapy [11, 12].
Anastomotic stricture was the most common postoperative complication with the highest incidence after DPA (61.9%), which was similar to the 62,2% incidence in our Nordic multi-center study [26] and the incidence on 57% reported by Friedmacher et al. [12]. The lowest incidence was after colonic interposition (8.0%) and may be explained by a tension free anastomosis compared to the other procedures.

Friedmacher et al. [12] found an association between symptomatic reflux and recurrent stricture formation and they reported that the development of GER after DPA required a more aggressive treatment compared to other reconstruction methods, since up to 30.0% of the patients had anti-reflux surgery within the first postoperative year, which is similar to the results from the Nordic multi-center study

with an incidence on 27.0% [26]. One reason for GER after DPA may be the mobilization of the distal esophagus and the displacement of the gastroesophageal junction upward to the thoracic cavity [27]. Thus one would have expected a higher incidence of GER after GPU than the reported 3.7% [28, 29]. The different incidences of GER in the different treatment groups may be hampered by a significant difference and inconsistence in the definition of GER.

The relative low mortality rate in this review (4.6%) can be attributed to the continuous advances in pediatric surgery and anesthesia, neonatal intensive care and parenteral nutrition throughout the review period, which have improved the survival rate of children with EA to approximately 95% [12]. However, some kind of selection could have occurred. The mortality in our Nordic multi-center study was similarly low (1.4%), as only one of the included patients died, supporting the advances in medicine over the years [26].

In this review and in our Nordic multi-center study [26] we focused on complications within the first postoperative year but long-term complications such as persistent GER, dysphagia and respiratory problems [30, 31] should also be investigated to identify the most favorable surgical treatment for children born with LGEA. As this review demonstrates, the research in this field is complicated by many barriers such as the rarity of the condition and possibly a difference in surgical routine.

There is still a continuous development of new surgical modifications and techniques and one of the most recent is tissue engineering of functional esophageal grafts in which vascularization and innervation still constitutes an obstacle [7], and the applicability of these methods has yet to be proven in a clinical setting. A working group of the International Network of Esophageal Atresia (INoEA) [3], has been set up to initiate consensus on guidelines on the treatment of EA including LGEA.

9.1 Methodological considerations

The results in the present review may be influenced by the long study period of 20 years due to continuous advances in surgery, nutrition, pediatric anesthesia and neonatal intensive care [12]. Our literature review has been systematic and thorough, why we are confident that we included all the relevant literature in the study period. Given the nature of retrospective data collection, with the hurdle of missing values and the diversity of the various interventions described in the literature, a descriptive analysis of the collected data was performed. A meta-analysis would have been more valuable but was considered as impossible given the rather small single-center studies that constitutes the literature in this field. Due to missing values we were not able to analyze some variables with regard to confounding and interactions. All included studies were either case reports or small case series with a risk of bias and hence a low level of evidence. However, when estimating the risk of bias using the JBI critical appraisal checklists for the two study designs [24] we found that most studies scored a low risk of bias on the questions of the corresponding checklist (Table 5).

Another limitation was that the analyzed data originated from different countries with different health care systems and traditions, making the comparison of the individual data nearly unfeasible. This demonstrates the need for international registries of standardized follow-up data, which would facilitate prospective research in this area and consequently increase the level of evidence in the field.

To our knowledge, only one larger study including 21 patients (15 with type A and 6 with type B LGEA has been published since our latest literature search and the completion of data collection [32]. However, this study does not add further information to our results.

10. Conclusion

Throughout the 20-year study period the majority of patients were managed by DPA. Postoperative anastomotic stricture, GER and fundoplication were more common after DPA compared to the other surgical methods.

11. Funding sources

This study was supported by the University of Southern Denmark – Faculty of Health and Science; Surgical Department A, Odense University Hospital; the Research Foundation of Odense University Hospital, Denmark.

12. Declarations of interest

None.

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14.1 Table 1

14.1.1 Title: Articles and patients included in the present systematic review

Author	**Study design**	**Definitive treatment**	**Patient no.** (*n* = 326)	**LGEA Gross type A** (*n* = 289)	**LGEA Gross type B** (*n* = 37)
Paul Charlesworth et al. 2009 [33]	Case report	DPA	1	1	0
Hossein Allal et al. 2005 [34]	Case report	DPA	1	1	0
M.A. Giacomoni et al. 2001 [35]	Case series	DPA	1	1	0
Holger Till et al. 2008 [36]	Case report	DPA	1	1	0
Michael W.L. Gauderer 2003 [37]	Case report	DPA	1	1	0
Erik D. Skarsgard 2004 [38]	Case report	DPA	2	1	1
Sigrid Bairdain et al. 2013 [39]	Case series	DPA	7	5	2
M. Ruiz de Temiño et al. 2006 [40]	Case series	DPA	4	4	0
Valentina Buonuomo et al. 2007 [41]	Case series	DPA	3	3	0
Jin-Yao Lai et al. 1996 [42]	Case series	DPA	2	2	0
Steven S. Rothenberg and Alan W. Flake 2015 [43]	Case series	DPA	15	14	1
Iuliana Dit Bobanga and Edward Metz Barksdale 2016 [44]	Case series	DPA	5	5	0
Adam M. Vogel et al. 2006 [45]	Case report	DPA	1	1	0
Kyoko Mochizuki et al. 2015 [46]	Case series	DPA	11	11	0
Kurosh Paya et al. 2007 [47]	Case report	DPA	1	1	0
Hanmin Lee et al. 2001 [48]	Case report	DPA	1	1	0
Aayed R. Al-Qahtani et al. 2003 [49]	Case report	DPA	1	0	1
Ahmed T. Hadidi et al. 2007 [50]	Case series	DPA	2	2	0
Pietro Bagolan et al. 2004 [51]	Case series	DPA	8	8	0
Pietro Bagolan et al. 2013 [52]	Case series	DPA	32	26	6
Hui Qing Lee HQ et al. 2014 [53]	Case series	DPA/GT	20/13	15/10	5/3
T. Sri Paran et al. 2007 [54]	Case series	DPA	21	21	0
Hemanshoo S. Thakkar et al. 2014 [55]	Case series	DPA	4	4	0
Felipe Donoso et al. 2016 [56]	Case series	DPA/GPU/CI	9/1/3	9/1/0	0/0/3

Shaun X.J.M. Chan et al. 2011 [57]	Case report	DPA	2	2	0
Augusto Zani et al. 2016 [58]	Case series	DPA/Other[a]	10/1	10/1	0/0
M.S. Lessin et al. 1999 [59]	Case series	DPA/GPU	2/1	2/1	0/0
Robert M. Dorman et al. 2016 [60]	Case report	DPA	1	0	1
Catherine J. Hunter et al. 2009 [61]	Case series	DPA/GPU/GT/CI	10/2/3/9	10/2/3/9	0/0/0/0
Holger Till et al. 2008 [62]	Case report	DPA	1	0	1
Yujiro Tanaka et al. 2013 [63]	Case report	DPA	1	1	0
Mariusz Sroka et al. 2013 [64]	Case series	DPA	6	5	1
Emmanuelle Séguier-Lipszyc et al. 2005 [65]	Case series	DPA/CI	6/4	6/4	0/0
David C. van der Zee et al. 2007 [66]	Case report	DPA	1	0	1
David C. van der Zee, 2011 [67]	Case series	DPA/JI	2/1	1/1	1/0
Linus Jönsson et al. 2016 [68]	Case series	DPA/CI/Other[a]	11/2/3	9/1/1	2/1/2
Sathyaprasad Burjonrappa et al. 2010 [69]	Case series	DPA/Other[a]	13	13	0
S.H. Yeh et al. 2010 [70]	Case series	DPA/CI	4/1	4/1	0/0
Maria Francelina Lopes et al. 2004 [71]	Case report	DPA	1	1	0
D.K. Gupta et al. 1997 [72]	Case series	GPU	3	3	0
Ronald B. Hirschl et al. 2002 [73]	Case series	GPU	8	7	1
Tadashi Iwanaka et al. 2011 [74]	Case report	GPU	1	1	0
Shawn D. St. Peter et al. 2010 [75]	Case report	GPU	1	1	0
Ryan M. Juza et al. 2010 [76]	Case report	GPU	1	0	1
Benno M. Ure et al. 2003 [77]	Case report	GPU	1	1	0
Joanna Stanwell et al. 2010 [78]	Case report	GPU	2	2	0
Shilpa Sharma and Devendra K. Gupta 2011 [79]	Case series	GPU	6	6	0
John C. Pedersen et al. 1996 [80]	Case report	GT	3	3	0
M.O. McCollum et al. 2003 [18]	Case series	GT	7	7	0
Gerald S. Lipshutz et al. 1999 [81]	Case report	CI	1	1	0
Ahmed T. Hadidi 2006 [82]	Case series	CI	3	3	0

Hanmin Lee et al. 2002 [83]	Case report	CI/Other[a]	1/1	1/1	0/0
Caroline C.P. Ong et al. 2001 [84]	Case series	CI/Other[a]	1/1	0/1	1/0
V. Varjavandi and E. Shi 2000 [85]	Case report	Other[a]	1	1	0
Anne Schneider et al. 2011 [86]	Case series	Other[a]	4	4	0
Marc Reismann et al. 2015 [27]	Case series	Other[a]	9	7	2
Harold N. Lovvorn III et al. 2014 [87]	Case report	Other[a]	2	2	0

14.1.2 Table legend: [a]Other interventions were autoanastomosis by traction-elongation device (*n* = 1), VATER operation (partial gastric transformation, Thal fundoplication and end-to-end anastomosis) (*n* = 1), Collis gastroplasty (*n* = 2), Collis gastroplasty and Dor-fundoplication (*n* = 2), Collis-Dor procedure and Heineke-Mikulicz pyloroplasty (*n* = 4), partial gastric pull-up (*n* = 9), Schärli's procedure (elongation of the lesser gastric curvature) (*n* = 1), magnetic compression anastomosis (*n* = 2) and Schärli/Rao gastroplasty (*n* = 2).

Abbreviations: No., number; LGEA, long-gap esophageal atresia; DPA, delayed primary anastomosis; GPU, gastric pull-up; GT, gastric tube; CI, colonic interposition; JI, jejunal interposition.

14.2 Table 2

14.2.1 Title: The reported surgical methods applied in the repair of long-gap

esophageal atresia (LGEA) Gross type A and B

Surgical methods[a]	**Total** (*n* = 326)	**Type A** (*n* = 289)	**Type B** (*n* = 37)
Attempted primary anastomosis[b]	43 (13.2%)	42 (14.5%)	1 (2.7%)
Active elongation technique[c]	125 (38.3%)	110 (38.1%)	15 (40.5%)
Delayed primary anastomosis	223 (68.4%)	200 (69.2%)	23 (62.2%)
Gastric pull-up	27 (8.3%)	25 (8.7%)	2 (5.4%)
Gastric tube	26 (8.0%)	23 (7.9%)	3 (8.1%)
Colonic interposition	25 (7.7%)	20 (6.9%)	5 (13.5%)
Jejunal interposition	1 (0.3%)	1 (0.3%)	0
Other methods[d]	24 (7.4%)	20 (6.9%)	4 (10.8%)

14.2.2 Table legend: [a]Presented as frequencies (n) and percentages (%). [b]There are 63 missing values. [c]There are 33 missing values. Elongation of the esophageal pouches was obtained by a traction-elongation device (*n* = 4), proximal (Livaditis technique) and distal myotomies (*n* = 18), serial bougienage/stretching (*n* = 20), combination of bougienage and myotomies (*n* = 3), Foker technique (external traction) (*n* = 23), combination of Kimura (sequential extrathoracic esophageal elongation) and Foker technique (*n* = 34), bougienage/stretching and modified Foker technique (*n* = 2), internal Foker technique and Zaritzky catheter-based magnamosis (*n* = 1), bougienage and Kimura technique (*n* = 1), Rehbein technique with string insertion to generate tension (*n* = 1), staged traction by transducing hydrostatic pressure (*n* = 8), Howard technique (*n* = 7), extensive mobilization (*n* = 2), internal traction (*n* = 1). [d]Other interventions that were applied are listed in Table 1.

Table 3
14.3.1 Title: Postoperative complications to the different surgical approaches

Surgery related complications[a]	**Total** (*n* = 326)	**DPA** (*n* = 223)	**GPU** (*n* = 27)	**GT** (*n* = 26)	**CI** (*n* = 25)	**JI** (*n* = 1)	**Other**[e] (*n* = 24)	***p*-value**
Anastomotic leakage, *n (%)*	74 (22.7%)	50 (22.4%)	7 (25.9%)	7 (26.9%)	2 (8.0%)	0	8 (33.3%)	0.491
Anastomotic stricture, *n (%)*	175 (53.7%)	138 (61.9%)	8 (29.6%)	13 (50.0%)	2 (8.0%)	0	14 (58.3%)	<0.001
GER, *n (%)*	105 (32.2%)	91 (40.8%)	1 (3.7%)	0	4 (16.0%)	-	9 (37.5%)	<0.001
Other complications[b], *n (%)*	34 (10.4%)	17 (7.6%)	6 (22.2%)	1 (3.8%)	6 (24.0%)	0	4 (16.7%)	0.179
Re-operation due to leakage, *n (%)*	8 (2.5%)	6 (2.7%)	0	-	-	-	2 (8.3%)	-
Re-operation due to stricture, *n (%)*	20 (6.1%)	17 (7.6%)	1 (3.7%)	0	0	-	2 (8.3%)	0.183
Fundoplication[c], *n (%)*	54 (16.6%)	51 (22.9%)	1 (3.7%)	-	1 (4.0%)	-	1 (4.2%)	0.001
Total number of thoracotomies, *mean ± SD*	1.1±1.1 (*n* = 125)	1.4±1.3 (*n* = 77)	0.1±0.3 (*n* = 15)	1±0 (*n* = 7)	0.3±0.5 (*n* = 6)	0 (*n* = 1)	0.9±0.6 (*n* = 19)	<0.001
Mortality[d], *n (%)*	15 (4.6%)	9 (4.0%)	1 (3.7%)	2 (7.7%)	3 (12.0%)	0	0	<0.001

14.3.2 Table legend: [a]There are missing values. [b]Other complications were mainly pneumothorax, fistulation, infection and ischemia. [c]Fundoplication due to GER: Nissen fundoplication (*n* = 41), Thal fundoplication (*n* = 3) and Toupet fundoplication (*n* = 3). [d]Mortality within the first postoperative year. [e]Other interventions that were applied are listed in Table 1. A – in the table indicates no reporting of the specific issue.

14.4 Table 4

14.4.1 Title: Regression analyses – association between the different surgical methods and the postoperative course

Logistic regression[a]		**OR**[b]	***p*-value**	**95% Confidence interval**
Anastomotic leakage[c]	DPA vs. GPU	1.20	0.700	0.47; 3.07
	DPA vs. GT	1.08	0.877	0.43; 2.71
	DPA vs. CI	0.29	0.105	0.07; 1.29
	DPA vs. JI	1	-	-
	DPA vs. Other[f]	1.46	0.414	0.59; 3.62
Anastomotic stricture[c]	DPA vs. GPU	0.34	0.028	0.13; 0.89
	DPA vs. GT	0.47	0.073	0.21; 1.07
	DPA vs. CI	0.05	<0.001	0.01; 0.22
	DPA vs. JI	1	-	-
	DPA vs. Other[f]	0.73	0.492	0.30; 1.78
GER[c]	DPA vs. GPU	0.20	0.141	0.02; 1.70
	DPA vs. GT	1	-	-
	DPA vs. CI	0.27	0.021	0.09; 0.82
	DPA vs. Other[f]	0.73	0.470	0.30; 1.73
Other complications[c,d]	DPA vs. GPU	3.12	0.051	0.99; 9.69
	DPA vs. GT	0.58	0.611	0.07; 4.84
	DPA vs. CI	2.82	0.070	0.92; 8.67
	DPA vs. JI	1	-	-
	DPA vs. Other[f]	1.04	0.955	0.31; 3.41
Mortality[c,e]	DPA vs. GPU	0.91	0.934	0.11; 7.51
	DPA vs. GT	1.98	0.399	0.40; 9.71
	DPA vs. CI	3.24	0.094	0.82; 12.87
	DPA vs. JI	1	-	-
	DPA vs. Other[f]	1	-	-

14.4.2 Table legend: [a]With DPA as reference level. [b]Values >1 indicate an increased risk and values <1 a decreased risk. [c]There are missing values. [d]Other complications that occurred are listed in Table 4. [e]Mortality within the first postoperative year. [f]Other interventions that were applied are listed in Table 1.

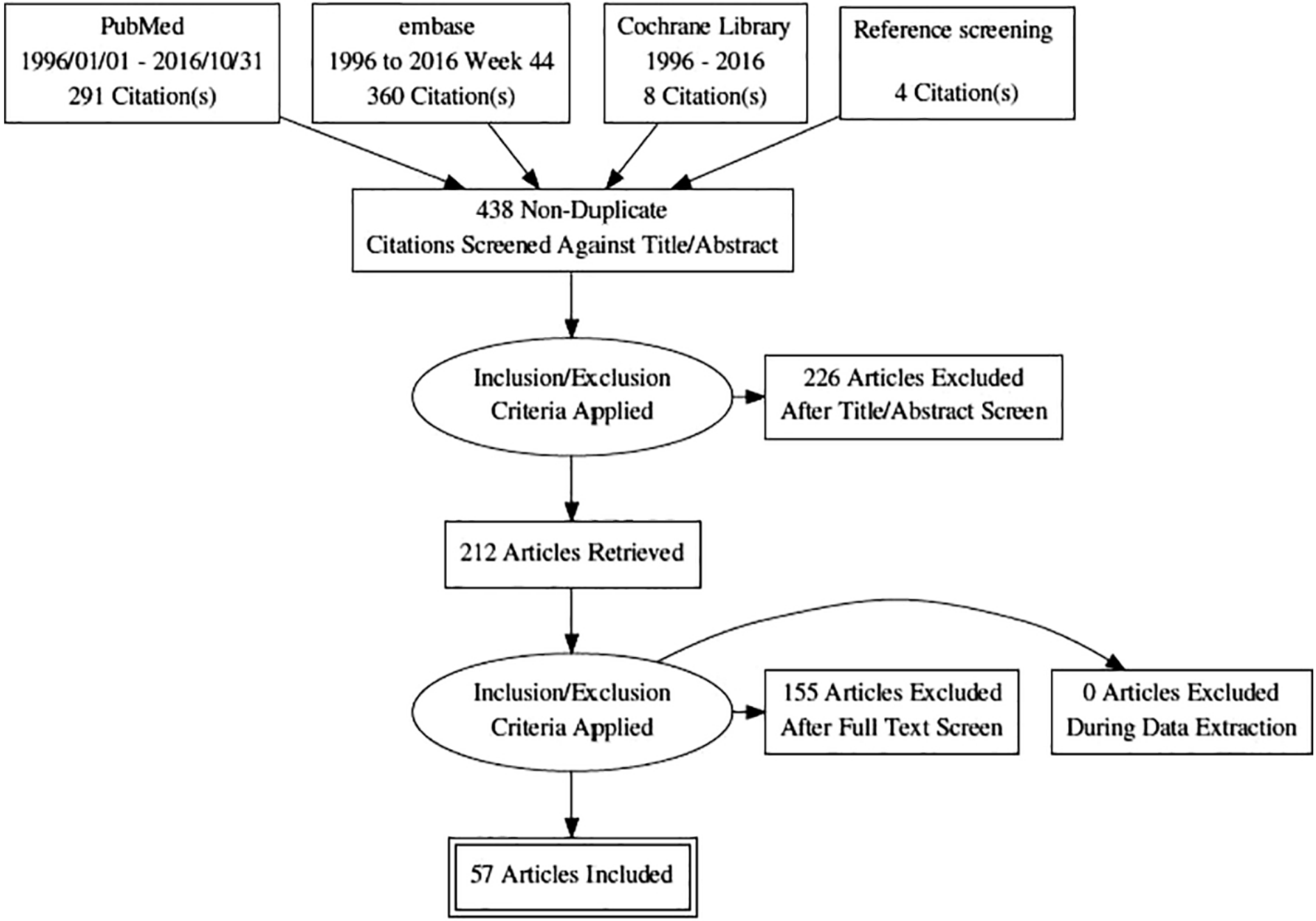
Abbreviations: OR, odds ratio; GER, gastro-esophageal atresia; DPA, delayed primary anastomosis; GPU, gastric pull-up; GT, gastric tube; CI, colonic interposition; JI, jejunal interposition.

14.5 Table 5

14.5.1 Title: Summary of the risk of bias in the 57 included studies.

Study design JBI critical appraisal checklist [24]	**Risk of bias**			
	Low *n* (%)	High *n* (%)	Unclear *n* (%)	Not applicable *n* (%)
Case reports (*n* = 25)				
Were patient's demographic characteristics clearly described?	13 (52%)	5 (20%)	7 (28%)	0
Was the patient's history clearly described and presented as a timeline?	5 (20%)	3 (12%)	2 (8%)	15 (60%)
Was the current clinical condition of the patient on presentation clearly described?	14 (56%)	3 (12%)	8 (32%)	0
Were diagnostic tests or assessment methods and the results clearly described?	14 (56%)	8 (32%)	3 (12%)	0
Was the intervention(s) or treatment procedure(s) clearly described?	24 (96%)	0	1 (4%)	0
Was the post-intervention clinical condition clearly described?	15 (60%)	3 (12%)	7 (28%)	0
Were adverse events (harms) or unanticipated events identified and described?	2 (8%)	0	10 (40%)	13 (52%)
Does the case report provide takeaway lessons?	23 (92%)	0	2 (8%)	0
Case series (*n* = 32)				
Were there clear criteria for inclusion the case series?	21 (66%)	1 (3%)	10 (31%)	0
Was the condition measured in a standard, reliable war for all participants included in the case series?	15 (47%)	14 (44%)	3 (9%)	0
Were valid methods used for identification of the condition for all participants included in the case series?	11 (34.5%)	10 (31%)	11 (34.5%)	0
Did the case series have consecutive inclusion of participants?	31 (97%)	0	1 (3%)	0
Did the case series have complete inclusion of participants?	31 (97%)	0	1 (3%)	0
Was there clear reporting of the demographics of the	23	4	5	0

participants in the study?	(72%)	(12%)	(16%)	
Was there clear reporting of clinical information of the participants?	21 (66%)	4 (12%)	7 (22%)	0
Were the outcomes or follow-up results of cases clearly reported?	18 (56%)	2 (6%)	12 (38%)	0
Was there clear reporting of the presenting site(s)/clinic(s) demographic information?	5 (16%)	1 (3%)	7 (22%)	19 (59%)
Was statistical analysis appropriate?	3 (9%)	1 (3%)	7 (22%)	21 (66%)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During Data Extraction
57 Articles Included

Figure 1