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Surgical treatment of advanced megaesophagus: A systematic review and meta-analysis

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ABSTRACT

Introduction: Advanced megaesophagus predisposes to clinical risks of malnutrition, infections, and cancer, in addition to having a significant impact on quality of life. There is currently no consensus in the literature regarding the best surgical option for advanced megaesophagus, although there is a predilection on esophagectomy surgery, which is associated with significant morbidity and mortality. Other surgical procedures, such as esophageal mucosectomy and Heller cardiomyotomy, have been proposed with good results. Aim: To conduct a systematic review and meta-analysis of the literature on the surgical treatment of advanced megaesophagus. Methods: Databases used included PubMed, Lilacs, Embase and MedLine, as well as reference research. Two reviewers chose the articles independently. Results: In total, 14 articles were chosen, with 1,862 patients included. The studies were divided into two groups: laparoscopic cardiomyotomy with fundoplication (213 patients) and major surgeries (1,649 patients). Comparative analyses were performed between variables found on the studies. A comparative analysis between morbidity/complications and mortality versus late outcomes considered good or excellent for both groups was performed for the meta-analysis. Discussion: The studies indicate that both groups had similar results regarding late outcomes, which was considered mostly good or excellent. However, there was significant morbidity associated with the major surgeries group. The cardiomyotomy group had a significantly lower number of patients evaluated and a shorter time of follow-up. Conclusion: Laparoscopic Heller myotomy can be performed on patients with advanced megaesophagus, with lower rates of complications and mortality compared to major surgeries, with reservations to the late outcomes results.

Keywords: Meta-analysis, Systematic Review, Esophageal Achalasia, Digestive System Surgical Procedures, Treatment Outcomes.

1 INTRODUCTION

Achalasia is an inflammatory neurodegenerative disorder of the esophagus that, through the destruction of neurons of the myenteric plexus of the distal esophagus, causes an absence of relaxation of the lower esophageal sphincter (LES) and incoordination of esophageal peristalsis[32, 44, 46]. It is defined as an esophagopathy due to denervation with dysmotility, difficulty in emptying and dilatation of the sphoragus, whose clinical representation is the megaesophagus[22].

It presents in the primary form, with mainly idiopathic, immune-mediated characteristics, not yet completely elucidated, or secondary, acquired, mainly as a consequence of Chagas disease[13,14]. In both situations, it is considered an incurable and predominantly progressive chronic disease46.

The disease does not have a predilection for sex or ethnicity, with a predominant peak of involvement in individuals between 30 and 60 years of age46. The incidence of achalasia is rare: it varies from 1 to 3 cases per 100,000 inhabitants per year, with an estimated prevalence of 10 to 15 individuals per 100,000 inhabitants, in general32,46.

It has an incidence of neoplasia close to 10% in patients with achalasia, which reaches a risk 50 times higher than in the general population[23]. Squamous cell carcinoma is the most common histological type, followed by adenocarcinoma in patients undergoing therapeutic procedures on the lower esophageal sphincter32.

The interventional surgical treatment of achalasia and megaesophagus has undergone several changes over time, due to the lack of knowledge of its pathophysiology and different interpretations of the pathology by surgeons[37]. Laparoscopic Heller surgical cardiomyotomy with partial anti-reflux fundoplication is currently considered the initial treatment of choice for patients with non-advanced megaesophagus, elective for surgical treatment[6,36,46].

There is no consensus in the literature regarding the best treatment in cases of POEM failure or laparoscopic cardiomyotomy[16]. In general, when surgical cardiomyotomy fails, pneumatic dilation, revisional surgery, or POEM can be used[32, 46].

Terminal achalasia occurs in about 10-15% of all patients with the disease 30 and is characterized by advanced megaesophagus (grades III and IV – Resende/Mascarenhas classification), with dolichomegaesophagus ("sigmoid-esophagus*"), significant tortuosity, esophageal diameter above 6 cm, and failure of previous treatments16,32*. These patients present in conditions with severe symptoms, which directly impact quality of life. In addition, they commonly present life-threatening complications, such as malnutrition, immunodeficiency, repetitive bronchoaspiration, and a high risk of developing sepsis and neoplasms[16, 32, 46].

In general, patients with terminal achalasia or advanced megaesophagus and patients with previous treatment failures are indicated for subtotal esophagectomy, however, several considerations should be made in this situation[6, 11, 32, 46]. It is a major abdominal surgery, therefore, it should be indicated for patients with adequate cardiopulmonary and nutritional conditions, in addition to the consideration of other comorbidities, preferably performed in patients classified by the American Society of Anesthesiology (ASA) type I or II15.

Subtotal esophagectomy surgery involves significant risks in the perioperative period and is more challenging in achalasia surgery when compared to cancer surgery[26]. The main factors that add

greater morbidity and mortality in this form of treatment include the risks of pneumonia, anastomotic fistula, and bleeding47.

In the literature, there is still no consensus regarding the best surgical option for the definitive treatment of advanced megaesophagus. Subtotal esophagectomy is still suggested as the main treatment option for advanced megaesophagus in elective cases, however, it has significant rates of morbidity (19 to 69%) and mortality (0 to 9%)[1, 31, 43].

Alternative techniques such as esophageal mucosectomy, developed by Aquino et al.[3], presents significantly better results when compared to esophagectomy in the treatment of terminal achalasia. On the other hand, it involves the performance of a major abdominal surgery, with digestive anastomosis and other risks inherent to such 5,[7].

With the intention of achieving a less morbid treatment for these patients, who may already be weakened by this pathology, some authors propose laparoscopic Heller cardiomyotomy, with results generally considered satisfactory. However, the accumulated risk of long-term neoplasia, regurgitation and bronchoaspiration is questioned when the esophagus is kept *in situ*, an inert sac with impaired emptying19,29.

The present study is justified by the need for a better understanding of the different types of surgical treatment of advanced megaesophagus, given the risks, complications, morbidity and mortality involved. There is also a need for a better understanding of its results and effectiveness, as well as late outcomes. The purpose of this study is to guide more incisively the choice of surgical treatment of advanced megaesophagus by the surgeon.

The aim of this study is to carry out a systematic review with meta-analysis on the surgical treatment of advanced megaesophagus, in order to expose the main modalities currently performed, and whose scope involves the comparative evaluation of their morbidity, mortality, complications, outcomes and late results.

2 METHODS

The systematic review was conducted according to the recommendations and *checklist* of the PRISMA33 method. The PICO (*Patient or Problem, Intervention, Control or Comparison, Outcomes*) strategy was used, after a question was elaborated, in order to identify the outcomes of the surgical treatment of advanced megaesophagus.

The eligibility criteria were as follows:

Types of participants (P): patients with a diagnosis of advanced megaesophagus

Types of intervention (I and C): esophagectomy, esophageal mucosectomy, Serra-Doria surgery, Heller cardiomyotomy. It does not apply to control patients. The study included the analysis of non-comparative studies.

Types of outcomes (O): surgical outcomes related to morbidity, mortality, complications, length of hospital stay, late outcomes, effectiveness, quality of life.

The aim of this study was to search for the most current forms of surgical treatment of advanced megaesophagus, and for this reason, it was decided to include articles published in the last 10 years. In addition, because it is a rare pathology, it was decided to include articles with a sample of patients greater than or equal to 8 cases, whether or not they had undergone previous treatments.

2.1 INCLUSION CRITERIA

- Studies that include patients with advanced achalasia and/or advanced megaesophagus of any etiology (grades III and IV, sigmoid esophagus, terminal achalasia), undergoing any type of definitive surgical treatment.
- Studies with patients ≥ 18 years of age.
- Studies with a sample of patients greater than or equal to 8 cases.
- Cohort studies, cross-sectional studies, case series, randomized or non-randomized controlled trials.
- Studies evaluated and selected by two reviewers.
- Studies in the following languages: English, Portuguese or Spanish.
- Articles published from 2012 onwards.

2.2 EXCLUSION CRITERIA

- Studies covering patients without a diagnosis of advanced achalasia/advanced megaoesophagus.
- Studies covering patients diagnosed with advanced achalasia/megaesophagus undergoing definitive non-surgical treatments.
- Case reports, charts, animal models, literature reviews, systematic reviews, or meta-analyses.
- Studies without full text.

2.3 SELECTION OF ARTICLES

A search was carried out with a pre-defined strategy in electronic databases, by two reviewers, independently. Any disagreement among the reviewers was resolved by consensus, after discussion with a third researcher. The articles were screened according to the previously established inclusion/exclusion criteria. In case of screening of similar articles from the same institution, the article with the largest sample of patients was selected.

Two distinct analyses were performed, one qualitative and one quantitative, the meta-analysis. The latter compared the following outcomes: morbidity/complications, mortality, and late outcomes considered good or excellent.

2.4 DATABASE

The databases searched electronically were PubMed, MedLine, Lilacs and Embase.

The review also considered the search for references of pertinent articles and abstracts published in conference proceedings. The last survey was conducted in June 2022. The search strategy is characterized in Table 1, shown below.

Table 1 – Search strategy.

Database	Search Strategy	Number of Articles Found	Number of Selected Articles
PubMed	(esophageal achalasia) OR (achalasia) OR (end-stage achalasia) OR (megaesophagus) OR (advanced megaesophagus) OR (sigmoid-esophagus) AND (surgery) OR (minimally invasive surgery) OR (laparoscopic myotomy) OR (laparoscopic heller myotomy) OR (laparoscopic cardiomyotomy) OR (serra-doria surgery) OR (esophagectomy) OR (esophageal resection) OR (mucosectomy) OR (esophageal mucosectomy) AND (groups) OR (trial) OR (surgery) OR (randomly) OR (randomized) OR (clinical trial) OR (comparative study) OR (controlled clinical trial) OR (randomized controlled trial) AND (sugery outcomes) OR (outcomes) OR (morbidity) OR (mortality) OR (follow-up) OR (quality of life)	127	2
MedLine		260	2
Lilacs		247	3
Embase		324	1
Other	Search for references of articles and abstracts of publications in conferences	11	6
Total		969	14

Note: Lilacs: Latin American and Caribbean Literature in Health Sciences; MedLine: *Medical Literature Analysis and Retrieval System Online.*

Source: Prepared by the author (2022).

2.5 METHODOLOGY FOR RISK OF BIAS ANALYSIS IN NON-RANDOMIZED STUDIES

The non-randomized studies were submitted to risk of bias analysis using the ROBINS-I platform (Risk of Bias in Non-Randomized Intervention Studies), together with this same methodology for judging the risk of bias of a randomized study41.

2.6 STATISTICAL ANALYSIS

The statistical analysis was carried out through the development of a meta-analysis using the Review Manager (RevMan) software produced by Cochrane (https://training.cochrane.org/online-learning/core-software/revman), organized in *fore-plot* and *funnel plots.* Statistical significance was

set at $p < 0.05$ and a 95% confidence interval21. The heterogeneity of the studies was assessed using the I^2 test.

3 RESULTS

The total number of articles evaluated was 969 and the total number of articles selected for the study, which met the pre-established inclusion/exclusion criteria, was 14 articles. The total number of patients included in the study was 1862.

The screening of the database involved 958 articles. Of these, after excluding duplicate articles and articles that were not pertinent to the study, 84 articles were selected for full-text reading. Of these, 8 articles were selected for the study. The remaining articles were excluded because they did not present a pertinent scope for the study or because data were missing from the objective of this study.

From the data search carried out, some abstracts published in conference proceedings were analyzed. Also, a search for references of pertinent articles was conducted. A total of 11 pertinent articles were found in this way, and after applying exclusion criteria, 6 articles were finally selected.

The articles were separated into two similar groups: patients undergoing cardiomyotomy (6 articles; N = 213) and patients undergoing major surgeries (9 articles; N = 1,649; this group included the following surgical modalities: esophagectomy, subtotal esophagectomy, transhiatal esophagectomy, minimally invasive esophagectomy, esophageal mucosectomy, Serra-Doria esophagocardioplasty). The major surgeries mentioned above were considered as such because they necessarily encompass a digestive anastomosis.

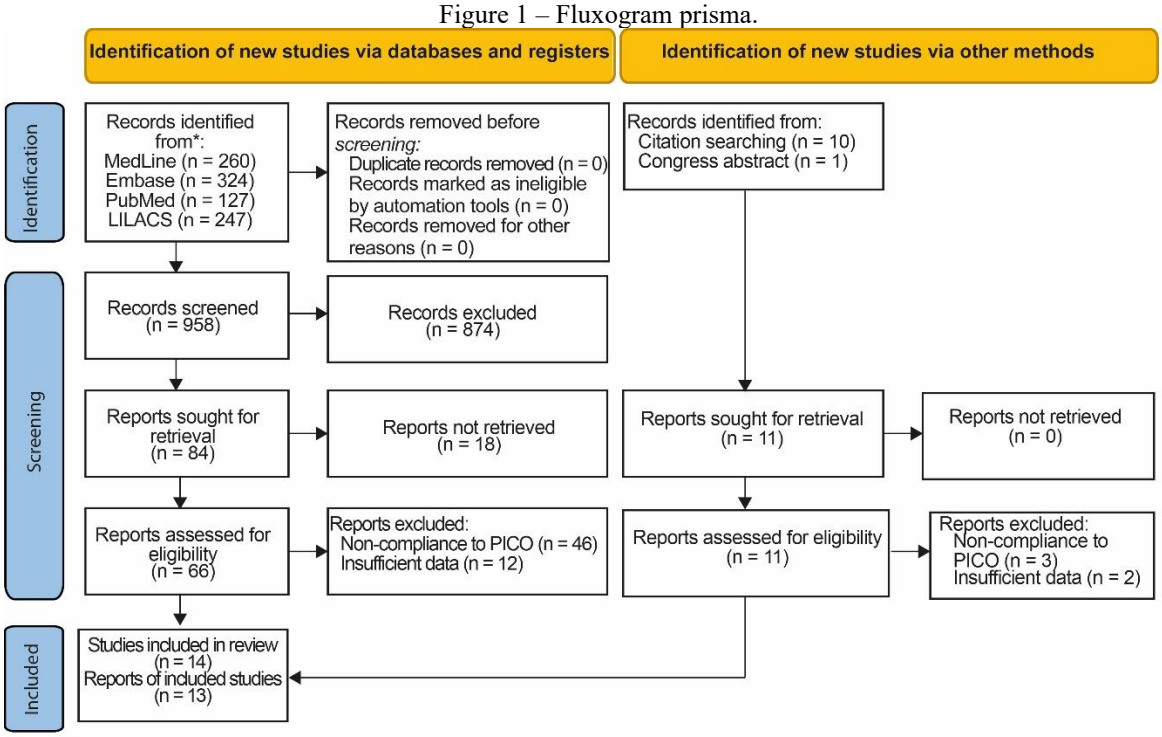
One of the articles by Tassi et al.[42] was allocated to both groups because it included patients studied by these two surgical modalities. Some studies within the group of major surgeries have presented results involving more than one surgical technique2,18,28.

Of the 14 studies selected for the study, one of them25 was not eligible for meta-analysis due to missing data. The meta-analysis then encompassed 13 articles and 686 patients in total.

3.1 FLUXOGRAM PRISMA

The selection and inclusion of articles was represented in the PRISMA flowchart, shown below (Figure 1).

Figure 1 – Fluxogram prisma.



Source: Page et al.[Article 33].

3.2 QUALITATIVE RESULTS: SYSTEMATIC REVIEW

The results were summarized in tables, as explained below. The surgeries were divided into two large groups, named "cardiomyotomy" and "major surgeries" (Tables 2 and 3). The study and comparison items in this study were as follows: study design, type of surgical treatment performed, N of patients, mean age, gender, definition and classification of advanced achalasia/megaesophagus, general complications and morbidity, mortality, length of hospital stay, mean follow-up time, and late results.

Table 2 – Systematic review of cardiomyotomy studies with fundoplication for advanced megaesophagus.

Author (year)	Study design	Treatment carried out	N patients	Average age (years)	Gender (H/M)	Classification of achalasia	Complications /morbidity	Mortality	Length of hospital stay (days)	Average follow-up time	Delayed Results
Rosemurgy et al.[38] (2018)	Retrospective cohort	Laparoscopic Heller cardiomyotomy + anterior fundoplication	10 III: 3 IV: 7	III: 61 IV 56	III: H0M3 IV: H4M3	III: > 6 cm, IV: > 3 esophageal curves and > 6 cm (diameter)	Intraoperative: 0 Postoperative: 1 (atelectasis)	There was no	III: 4 IV: 3	27 months	III: 33% Excellent 66% Good IV: 25% Excellent 75% Good
Pantanali et al.[35] 56 years old (2013)	Retrospective cohort	Laparoscopic Heller cardiomyotomy + Pain fundoplication	11	56	H6 M5	>10 cm (diameter)	Morbidity 0%	There was no	1	31.5 months	72.8% Excellent or Good
Panchanatheeswaran et al.[34] (2013)	Retrospective cohort	Laparoscopic Heller cardiomyotomy + anti-	8	39.5	H50% M50%	"*Sigmoid esophagus*"	Morbidity 0% 1 iatrogenic intraoperative complication	There was no	4.25	19.5 months	100% Excellent or Good

		reflux procedure									(50-50%)
Simic et al.[40] (2015)	Retrospective cohort	Laparoscopic Heller-Pain Cardiomyotomy	10	51	-	"*Sigmoid esophagus*"	Morbidity 0% 1 mucosal perforation 1 trocar bleeding 1 wound infection	There was no	2	28 months	94.4% dysphagia resolution
Costantini et al.[10] (2019)	Retrospective cohort	Laparoscopic Heller-Pain Cardiomyotomy	142 III: 87 IV: 55	46	-	Grade III: >6cm (diameter) grau IV: "*sigmoid-shaped esophagus*"	Morbidity 4.7% 22 mucosal perforations 1 splenic lesion 2 Trocar bleeding	0.1% (IAM)	-	62 months	89.5% Good outcome III: 90.8% IV 76.4% Fault: III 9.2% IV 23.6%
Tassi et al.[42 years old] (2022)	Retrospective cohort	Laparoscopic Heller-Pain Cardiomyotomy (CLH) vs. Esophagectomy (E)	CLH: 32	CLH: 57	CLH: H34.37% M65.62%	"*End-stage achalasia*"	CLH: 12.5% 1 mucous membrane fistula 1 mucosal desicence 1 Hyperdysphagia 1 Hypercompetent Fundoplication	There was none in both groups	CLH: 6	CLH: 68 months	CLH: 46.87% Excellent 34.37% Good

Table 3 – Systematic review of studies of major surgeries for advanced megaesophagus.

Author (year)	Study design	Treatment carried out	N patients	Average age (years)	Gender (H/M)	Classification of achalasia	Complications/morbidity	Mortality	Length of hospital stay (days)	Average follow-up time	Delayed Results
Fontan et al.[18] (2018)	Randomized clinical trial	Open transhiatal esophagectomy vs VLP	30 Opened: 15 VLP: 15	Opened: 47.2 VLP: 44.1	Open: H8 M7 VLP: H11 M14	Grades III and IV (Rezende's classification)	Morbidity 40% 13.3% open dysphonia, 20% VLP Fistula: 26.7% open, 20% VLP Pneumothorax 6.7% open, 40% VLP Hemothorax 13.3% in both groups Pleural effusion 6.7% open, 0% VLP Paralytic ileus 7% open, 0% VLP Infection/abscess 7% open, 0% VLP	6.7% in each group	Opened: 14 VLP: 17	33 months	Brandt classification 100% = mild dysphagia 0-5pts after 24 months, no moderate or severe dysphagia
Torres-Landa et al. [92] (2021)	Retrospective cohort	The Esofagectomia	209	56	H51.8% M48.2%	-	Morbidity 43.5% Readmission 2.2% Reoperation 6.7% Sepsis 9.5% Pneumonia 12.4% Hemotransfusão 20.5%	There was no	10	1 month	Not rated
Aquinas et al.[4] (2016)	Retrospective cohort	Serra-Doria esophagocardiopasty	19	63 to 78	H14 M5	Grades III and IV (Rezende Classification)	Morbidity 26.3% 4 (21%) pneumonia, 1 (5.7%) fistula	There was no	-	60 months	1 year: 94.7% no dysphagia / 5 years: 53.8% vomiting, 30.4% moderate dysphagia
Oliveira et al. [28] (2015)	Retrospective cohort	Esofagectomia transhiatal (ET) x Mucosectomia (ME)	40 ET: 23 ME: 17	-	-	Advanced megaesophagus	Morbidity: ET 65% ME 35% The Esofagectomia anastomose fistula 17% anastomose estenosis 13% bacteremia 13% sepsis 9% lymphatic fistula 9%	There was no	ET: 19 ME: 14.9	5.36 years	8.8/10 of both groups – satisfaction score after 1 year

							Mucosectomy anastomose fistula 29%				

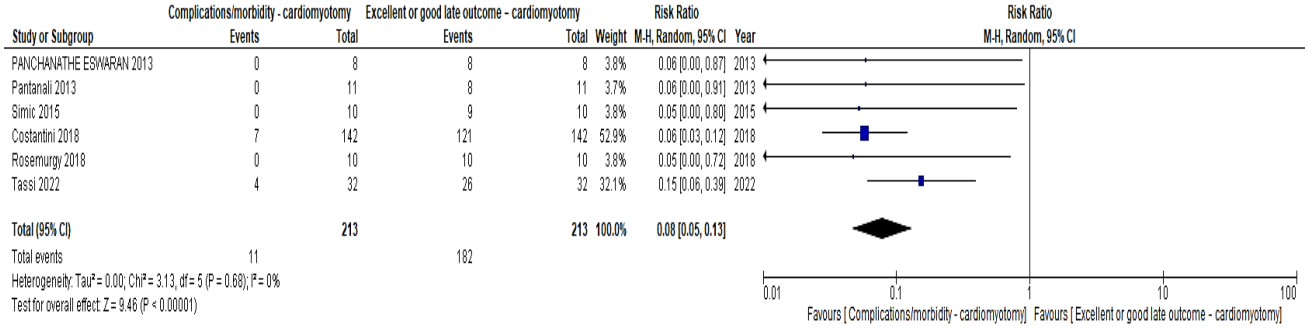
Table 3 – Systematic review of studies of major surgeries for advanced megaesophagus.

Author (year)	Study design	Treatment carried out	N patients	Average age (years)	Gender (H/M)	Classification of achalasia	Complications/morbidity	Mortality	Length of hospital stay (days)	Average follow-up time	Delayed Results
Crema et al.[12] (2018)	Cohort	Transhiatal VLP esophagectomy with vagus nerve preservation	136	59.3	H59.5% M40.45%	Advanced megaesophagus	Early 13.97% Late 7.35% Hemopneumothorax 6.61%% Gastroparesis 2.2% Cervical fistula 3.67% Dysphonia 5.88%	1.47%	-	7 months to 12 years	dysphagia due to anastomotic stenosis 2.94% esophageality rose 14.7%
Aquino et al.[2] (2017)	Retrospective cohort	Esophageal Mucosectomy (EM) vs Transhiatal Esophagectomy (ET)	229 ME: 115 ETH: 114	15-76 years old	H70.3% M29.7%	Advanced megaesophagus	Intraoperative complications ME: 12.1% hydropneumotorax 11.4% Recurrent laryngeal lesion 0.8% AND: 69.2% hydropneumotorax 57.8% massive hemothorax 2.6% lymphatic fistula 2.6% tracheal injury 2.6% Recurrent laryngeal lesion 2.6% Postoperative complications: ME: 40.8% pneumonia 8.6% cardiovascular 2.6% Anastomose fistula 28.6% AND: 67.5% pneumonia 21.8% cardiovascular 13.1% fistula 32.4%,	ME: 1.7% AND: 7.8%	ME: 13.1 SD: 20.9	-	ME: 83% Excellent or Good (clinical score with personal satisfaction) 87% Excellent or Good (endoscopic score)
Felix et al. [17] (2015)	Case Series	Transhiatal esophagectomy	11	44	H8 M3	"*sink trap megaesophagus*"	No significant complications (0% fistula)	There was no	-	24 months	No changes in the remaining esophagus, good quality of life, no dysphagia, with significant weight gain
Molena et al.[25] (2014)	Retrospective cohort	The Esofagectomia	963	54.6	H49.01% M50.99%	-	UTI 6.23% Septic Shock 4.78% pulmonary involvement 29.08%	2.70%	13	-	-
Tassi et al. [42] (2022)	Retrospective cohort	Laparoscopic Heller-Pain Cardiomyotomy (CLH) vs. Esophagectomy (E)	E: 12	E: 59	And: H62.5% M37.5%	"End-stage achalasia"	E: 43.75% - 3 Anastomosis fistulas 1 pyloroplasty fistula 1 pleural empyema 1 acute respiratory failure	There was none in both groups	E: 23	E: 61 months	And: 37.5% Excellent 25% good

3.3 QUANTITATIVE RESULTS: META-ANALYSIS

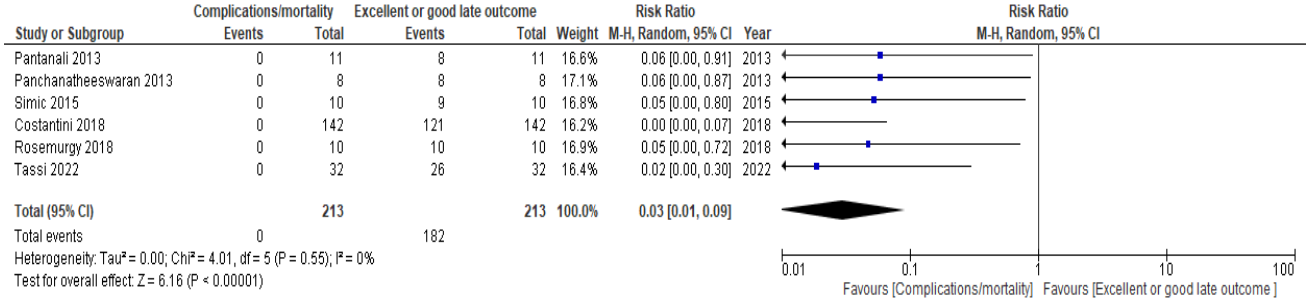
The meta-analysis was based on a systematic correlation between morbidity/complications and mortality and late outcomes considered good or excellent for both groups. Thus, 4 *forest plots* were generated, two for the cardiomyotomy group and two for the major surgery group (Graphs 1, 2, 3, 4). The risk of bias analysis of the selected studies was performed based on the ROBINS-I platform, as shown in Table 4. A correlation was made between the relative risk (RR) generated from the meta-analyses and the outcomes evaluated. Table 5 shows this comparative analysis.

Graph 1 – Comparative meta-analysis between morbidity/complications vs. good or excellent late outcome in cardiomyotomy – *Forest plot.*



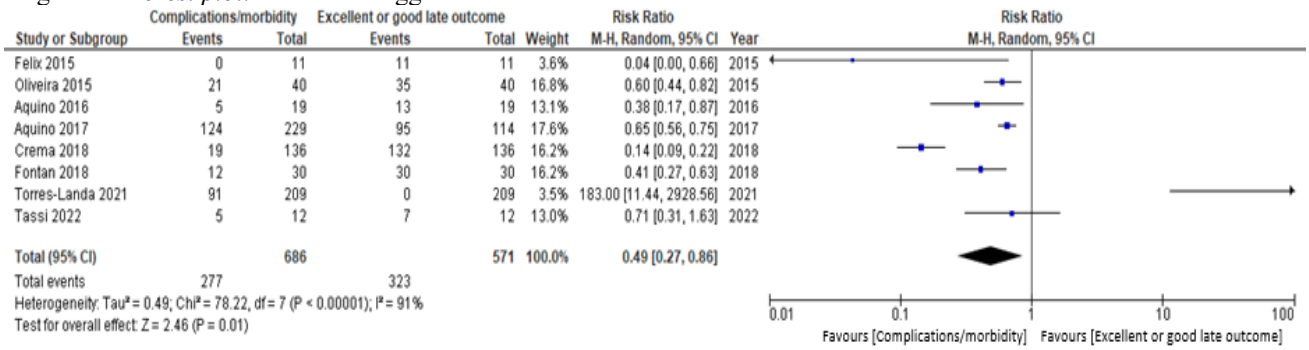
Cast iron: Higgins et al.[Article 21.]

Graph 2 – Comparative meta-analysis between mortality and good or excellent late outcome in cardiomyotomy – *Forest plot.*



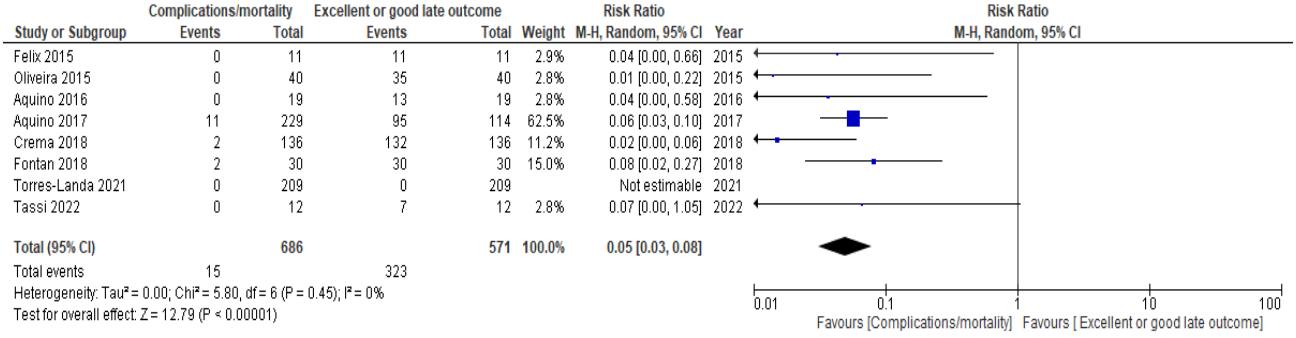
Cast iron: Higgins et al.[Article 21.]

Graph 3 – Comparative meta-analysis between morbidity/complications vs. good or excellent late outcome in major surgeries – *Forest plot.* Cast iron: Higgins et al.[Article 21].



Cast iron: Higgins et al.[Article 21].

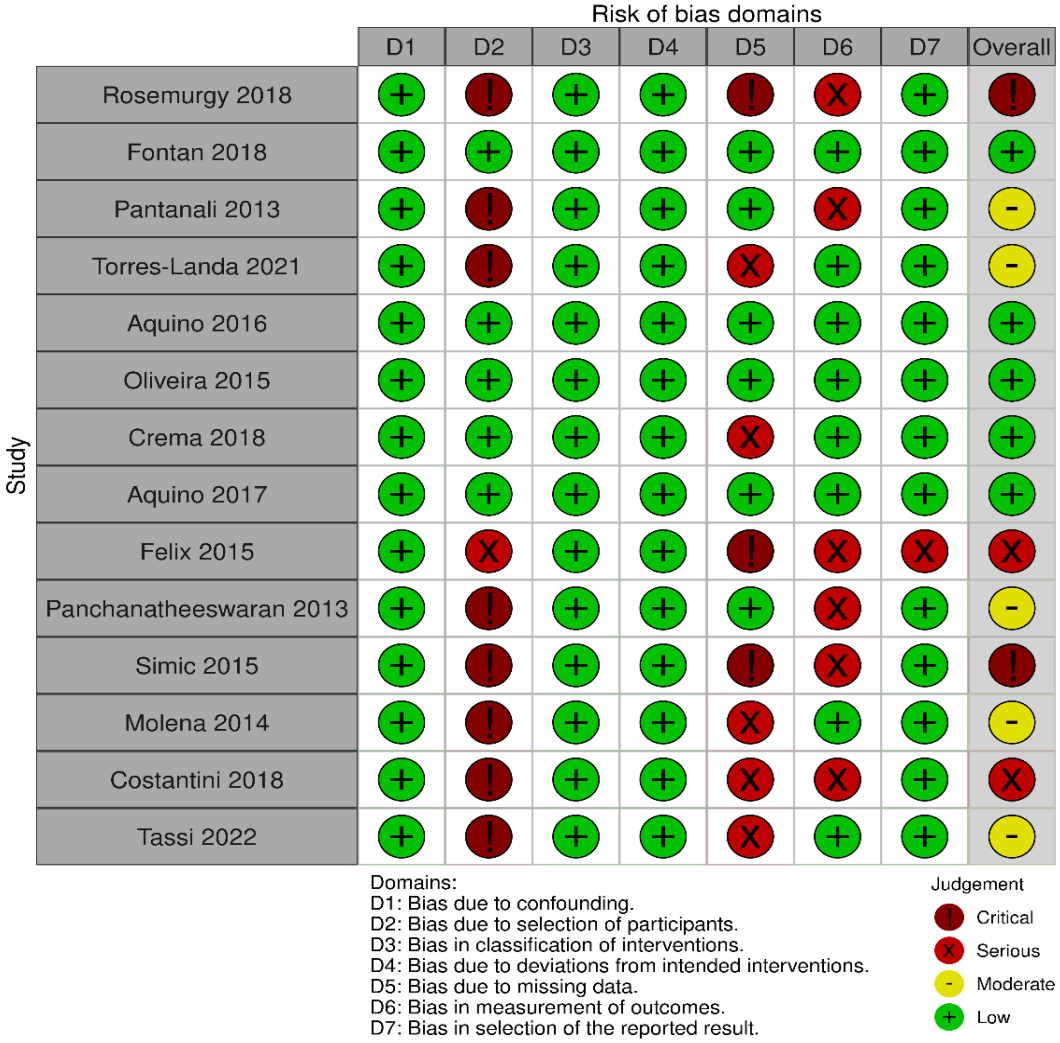
Graph 4 – Comparative meta-analysis between mortality and good or excellent late outcome in major surgeries – *Forest plot.*



Cast iron: Higgins et al.[Article 21].

3.4 RISK OF BIAS – ROBINS I *TOOL*

Table 4 – Discriminated risk of bias of the studies included in the meta-analysis.



Cast iron: Sterne et al.[Article 41].

Table 5 – Relative risk between cardiomyotomy and major surgery groups in the comparative analysis of morbidity/complications and mortality vs. good or excellent late outcomes.

Groups	Morbidity/complications	Mortality
Cardiomyotomy	0,08	0,03
Major surgeries	0,49	0,05

Source: Prepared by the author (2022).

4 DISCUSSION

From the analysis of the data gathered in this study, it is possible to detail some significant aspects of the surgical treatment of advanced megaesophagus. The systematic review and meta-analysis provided sufficient data for an in-depth analysis of the two major treatment groups evaluated.

The main morbidity found in the karydomiotomy group was mucosal perforation, however, this morbidity did not have significant consequences on the evolution of the patients, since there were no other associated morbidities or mortality. There was no surgery-related mortality in this group.

The late results of this group, considered satisfactory by the authors (good or excellent), are very expressive. Although most studies present N of patients below 12, even in the most populous studies, such as those by Costantini *et al.*[10], 142 patients, and Tassi *et al.*[42], 32 patients, these numbers reached rates of 89.5% and 81.24%, respectively, in late evaluation with more than 60 months of follow-up.

The analysis of the group designated as major surgeries showed a higher total number of patients when compared to the cardiomyotomy group. This fact is probably due to the absence of a well-established definition of conduct or protocol regarding the most appropriate therapeutic modality for advanced megaesophagus and a tendency to esophagectomy.

Complications and morbidity in this group were significantly higher than in the cardiomyotomy group. In most studies, it was between 40 and 50.0% of the patients submitted to this form of treatment, and in one of the series it reached 69.2%.

The main surgical complication described in this group was anastomotic fistula, which is known to lead to other secondary complications, including death. Next, pleuropulmonary complications are observed as the most significant, which includes hydropneumothorax, pleural effusions, pneumothorax, hemothorax, pneumonia, and others.

In this group, deaths occurred in 4 of the 9 studies analyzed in this review. Mortality ranged from 1.47% to 7.8% of these studies in which it was present.

Late results in this group, differently from the cardiomyotomy group, were evaluated heterogeneously, through questionnaires/scores of personal satisfaction, Eckardt or Brandt scores, endoscopic scores, late complications, evaluation of quality of life and body weight gain, and evaluation of the esophageal remnant. In general, the late results, as well as in the cardiomyotomy group, were mostly satisfactory in all grades.

The meta-analysis allows us to make a specific and comparative quantitative assessment of both modalities of treatment of the pathology. From the comparative analysis between complications/morbidity and good or excellent late outcomes in the cardiomyotomy group, an imprecision is observed in most studies, probably secondary to the low sample N. The effect estimates between the studies did not show significant variations, despite considerable heterogeneity between the studies for mortality, defined by per I^2 equal to 0%, but without statistical significance ($p = 0.68$).

Therefore, it is concluded that there is a low impact of morbidity/complications in relation to cardiomyotomy with fundoplication for patients with advanced megaesophagus. The relative risk was 0.08 ($p < 0.00001$, 95% CI 0.05 to 0.13).

In the comparative analysis between mortality and good or excellent late outcomes in the cardiomyotomy group, the same imprecision is observed, with considerable heterogeneity between studies, defined by $I^2 = 0\%$, but without statistical significance ($p = 0.55$). The relative risk for this outcome is 0.03 ($p < 0.00001$, 95% CI 0.01 to 0.09), i.e., there is also a considerably low impact of the outcome in this analysis.

When evaluating the comparative analysis between morbidity/complications and good or excellent late outcomes in the major surgery group, it is also evident that there is imprecision between the studies, but with significantly considerable heterogeneity between the studies, defined by I^2 equal to 91% ($p < 0.00001$). It is possible to conclude that there is a relatively low impact of morbidity/complications compared to good or excellent late outcomes for major surgeries, with a relative risk of 0.49 ($p = 0.01$, 95% CI 0.27 to 0.86).

From the comparative analysis between mortality and good or excellent late outcomes in the group of major surgeries, the same imprecision was observed between the studies, also with statistically significant heterogeneity, defined by I^2 equal to 0% ($p = 0.45$). It is also concluded that mortality has a low impact on late outcome, with a relative risk of 0.05 ($p < 0.00001$, 95% CI 0.03 to 0.08).

When evaluating these comparative analyses between these two groups, it can be concluded that both present similar results of their treatments, with a low impact on morbidity and mortality and a tendency to favorable late outcomes. The relative risk of complications in relation to the favorable late outcome in the cardiomyotomy group was 0.08 and the risk of mortality was 0.03. This risk was considerably lower than the relative risk of complications and mortality in relation to the favorable late outcome in the major surgery group, 0.49 and 0.05, respectively.

This allows us to conclude that both modalities have good overall surgical results, however, that patients undergoing cardiomyotomy have a lower risk of developing complications and/or mortality, compared to patients undergoing major surgeries, as already evaluated in the systematic review of this study.

In general, in aggregate qualitative and quantitative analysis, it is evaluated that both groups present similar results. The group of major surgeries presented late results similar and equivalent to the group of cardiomyotomies, mostly considered good or excellent. However, this fact comes at the expense of more significant morbidity, which affects about 50.0% of patients, and considerable mortality, which reaches up to 7.8% in this review. An important caveat should be made regarding the number of patients evaluated in the cardiomyotomy group, which is significantly lower compared to the group with major surgeries, in addition to the follow-up time and evaluation of late outcomes in this group, which is also significantly shorter.

In addition, other parameters can be taken into account in this analysis, such as the longest hospital stay, which reached 20.9 days in a series that evaluated esophagectomy. Regardless of the surgical modality, this time ranged from 10 to 20 days in the major surgery group. This fact certainly adds higher hospital costs to this form of treatment.

Also in this context, patients undergoing major surgeries certainly demand higher costs since they require not only intensive care, but also a demand for a more complex/experienced surgical team and multidisciplinary care of greater relevance, both in the general and late contexts.

The data found are in accordance with the world literature. Meta-analysis by Niño-Ramirez *et al.*[27] involving 5,492 patients who underwent laparoscopic Heller cardiomyotomy revealed an adverse event rate in 4.9% of them, most of which were related to esophageal mucosal perforation. From the analysis of 30-day mortality in this group of patients, the percentage was 0.09%.

A systematic review with meta-analysis by Orlandini *et al.*[30] evaluated 350 patients who underwent Heller surgical cardiomyotomy for sigmoid megaesophagus (advanced) with the following late results: complication rate of 8.0%, mortality rate of 0.8%, need for retreatment of 12.8%, and probability of results considered good or excellent after this surgical procedure of 76.2%. It was concluded that this surgical modality is admissible as a definitive treatment for patients with advanced/sigmoid megaesophagus, because it avoids an esophagectomy, with low rates of morbidity and mortality and low rates of need for retreatment.

Herbella and Patti20 in a similar review indicate an average of 79% of late results considered good or excellent in patients with advanced megaesophagus undergoing Heller cardiomyotomy in an evaluation of 122 patients covering 8 studies studied, without any associated mortality. In this study, we conclude that laparoscopic Heller cardiomyotomy is a viable option as a definitive treatment for advanced megaesophagus, with relief of dysphagia in a significant number of patients, the possibility of being performed in more fragile patients, in addition to not preventing or hindering the eventual indication of a future esophagectomy.

Study by Rosemurgy *et al.*[38], previously discussed, suggests that the surgeon should not stick to the results of the preoperative esophagography examination of patients with achalasia, even with advanced megaesophageal results, since laparoscopic Heller cardiomyotomy with anterior fundoplication presents very significant results in terms of improvement of symptoms and quality of life, and the surgeon should not change his surgical indication in the face of the more severe findings of this examination. Pantanali *et al.*[35] In a similar study, also previously discussed, it was concluded that this surgical modality is capable of relieving dysphagia in most patients even when the esophagus is excessively dilated.

Panchanatheeswaran *et al.*[34], in a previously presented study, concludes that this surgical modality should be considered as the first line of therapy for patients with sigmoid megaesophagus. It also suggests that esophagectomy should be reserved for cases of cardiomyotomy failure.

On the other hand, these last three studies presented a total number of patients evaluated of 10, 11 and 8 patients respectively, with a follow-up time of 22, 31 and 19 months, respectively. This fact certainly brings notoriety to caution in the interpretation of its results.

Tassi *et al.*[42] performed a comparative analysis of quality of life among patients with end-stage achalasia undergoing laparoscopic Heller-Dor cardiomyotomy (32) and esophagectomy (16). There was no statistical difference between the groups regarding the relief of dysphagia, reflux symptoms, or esophagitis, however, there was a statistically significant difference in favor of cardiomyotomy in the domains of physical and emotional functioning, vitality, mental health, and social functioning. The author makes significant mention of the importance of rectification of the esophageal axis during the cardiomyotomy procedure.

The work of Costantini *et al.*[10] which encompassed 1,001 patients with achalasia of all grades who underwent laparoscopic surgical cardiomyotomy at Heller-Dor concludes that there is a high probability of dysphagia relief even 20 years after the procedure, in about 80% of these patients. In addition, it concludes that surgical complications are rare and that recurrences can be treated endoscopically, through dilations, in most cases, in addition to acceptable rates of late reflux. On the other hand, it mentions that the main predictors of unsatisfactory late results are the manometric pattern of achalasia, type III, the presence of sigmoid esophagus (*odds ratio* of 2.5) and chest pain score.

The study by Capovilla *et al.*[8] performed a similar analysis encompassing 49 patients who underwent surgical remyotomy after primary surgery failed. The treatment success rate after this surgical modality reached a significant 81.6%, however, stage IV of achalasia at initial presentation (6 cm of esophageal diameter or more and/or associated with sigmoid esophagus) was considered an independent factor of association with unsatisfactory results of revision surgery, at risk of requiring esophagectomy surgery in the future.

In an analysis of relapsed megaesophagus, Costa *et al.*[9] studied 26 patients who underwent revision surgeries after surgical treatment of the megaesophagus, due to recurrence of symptoms or disease progression. In 53.0% of these, laparoscopic Heller-Pinotti surgery was performed, in 30.7% Serra-Doria surgery and in 7.9% esophageal Aquinas mucosectomy. The patients had an 80% rate of satisfactory evolution and resolution of symptoms. A preference is suggested for remyotomy surgery, followed by Serra-Doria surgery, and esophagectomy or mucosectomy should be considered after remyotomy failures or more advanced cases.

Recurrence of symptoms after esophageal cardiomyotomy requires thorough evaluation, as pointed out by Orlandini et al.[29]. The rationale for classifying it as "persistence", "early recurrence"

and "late recurrence" is suggested, which should guide the diagnostic and therapeutic management of these patients. Clinical history data and tests such as esophagogram and EDA are essential in logical reasoning, which can encompass diagnoses ranging from incomplete myotomy and anti-reflux valves that are too tight or migrated, to neoplasia or even disease progression (megaesophagus). Cases of "persistence" and "early recurrence" are more likely for less invasive treatments, such as re-myotomy, POEM, or even endoscopic dilation, while cases of "late recurrence" may be considered, individually, for larger surgeries.

Regarding esophageal neoplasia, which is an evident concern in patients with achalasia who underwent surgical treatment or not, Tustumi et al.[45] A meta-analysis of 11,978 patients with achalasia concluded that there is an increased prevalence of esophageal carcinoma in this population, 28 cases per 1,000 patients. This fact corroborates the need for vigilant endoscopic follow-up in patients, even after definitive surgical procedures.

Regarding reflux disease after cardiomyotomy, a meta-analysis involving 5,834 patients by Schlottmann *et al.*[39] revealed an acceptable rate of 11.1%, significantly lower than the POEM, compared to 47.5%. Pochini *et al.*[37], in a study that evaluates esophagitis in the esophageal remnant after esophagectomy in patients with advanced megaesophagus, emphasizes the importance of the chronic use of proton pump inhibitors in this population, with a significant reduction in the rates of esophagitis and Barrett's esophageal esophagus of the esophageal remnant.

Regarding alternative and/or secondary treatments, such as POEM, Mandavdhare *et al.*[24] conducted a systematic review and meta-analysis with 11 studies covering a total of 428 patients who underwent POEM for definitive treatment of advanced megaesophagus/end-stage achalasia and concluded that the therapy was successful, with 89.3% clinical success at 1 to 3 years of follow-up. It points out that randomized controlled trials and robust late data are needed to confirm its findings. However, it is evident that POEM may be a viable alternative in cases of patients with advanced megaesophagus with recurrence of symptoms after surgical cardiomyotomy or even after remyotomy.

Finally, it should be noted that, because it is a complex disease in itself, each case must be individualized, preferably treated by *experts* and in a specialized and multidisciplinary environment. The patient should be guided and informed about the therapeutic possibilities, expectations, and risk-benefit associated with each proposed treatment modality. Due to the increased risk of neoplasia and the possibility of esophagitis, endoscopic surveillance should be performed.

The limitations of this study lie in the fact that there is a low sample size of studies, which generates data imprecision. This is probably due to the rarity of the pathology in question studied. In addition, there is a heterogeneity of the discriminated studies. Different modalities of evaluation and classification of terminal achalasia/advanced megaesophagus, different periods of evaluation of late

results, and different modalities of evaluation of outcomes were used – questionnaires, classifications (Brandt, Eckardt), evaluation of dysphagia symptoms and levels of personal satisfaction.

There is also a limitation involving the methodology used for the meta-analysis. Due to the low sample size, there is a gap, which it is not possible to fill and define effectively due to specific issues that characterize the methodological process.

5 CONCLUSION

This systematic review with meta-analysis allows us to conclude that patients with advanced megaesophagus can be safely treated with laparoscopic Heller cardiomyotomy with fundoplication. This surgical modality, which includes abdominal surgery of lesser complexity, has high rates of symptom resolution, low complication rates, inexpressive mortality rates, and satisfactory late results. In addition, there are other considerable underlying factors in this context, such as shorter hospital stay, lower hospital cost, and lower demand for treatment complexity – when compared to major surgeries.

An important caveat should be made regarding the term "definitive treatment", since most studies have a short to medium-term follow-up time. There are still doubts regarding the recurrences and/or progression of the disease in this treatment modality.

Major surgeries, such as esophagectomy or mucosectomy, are still significant in the treatment of this pathology. Refractory cases or cases at significant risk of bronchoaspiration/infections and/or severe neoplasia/dysplasia, in addition to other specifically individualized cases, may be reserved for this situation. They can be performed even in patients already treated by cardiomyotomy, remyotomies, or POEM.

Young patients with compromised quality of life, even after less invasive treatments and/or retreatments, may be well indicated for this modality. Other factors should be taken into account in this therapeutic choice, such as the manometric type of achalasia.

Major surgeries for patients with advanced megaesophagus present good late results, but under the obstacle of significant morbidity and mortality rates. In addition, they involve greater complexity in the scope of their treatment, longer hospitalization and intensive care time, and higher hospital costs. The need for endoscopic surveillance should also be maintained.

Finally, it is concluded that, in view of the findings of this review study, randomized clinical trials are necessary to confirm them. It is not possible to determine the best profile of patients with advanced megaesophagus indicated for major surgeries, however, it is estimated that it is the smallest portion of these.

Even so, the present study indicates a favorable point for the challenging surgical treatment of this complex pathology. This fact can certainly guide the surgeon in his decision-making.

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