Endoscopic or Surgical Myotomy in Patients with Idiopathic Achalasia: 5-year Follow-up of a Randomised Controlled Trial

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Trial registration: ClinicalTrials.gov number, NCT01601678.

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Abstract

Background In a multicenter and randomized trial, endoscopic myotomy (POEM) was shown to be equally effective as laparoscopic Heller myotomy plus Dor´s fundoplication (LHM) in patients with idiopathic achalasia two years after the procedure. Postprocedural reflux esophagitis and treatment with proton pump inhibitors (PPIs) were more frequent after POEM. Here we report the results at the five-year follow-up.

Methods Primary endpoint was clinical success, defined as an Eckardt symptom score of 3 or less without the use of additional treatments at five years. Secondary end points included parameters of post-procedural reflux (reflux esophagitis and its complications, pH-metry and proportion of patients on PPIs).

Findings Of the 221 patients initially assigned to POEM (112 patients) or LHM (109 patients), five-year follow up data was available for 90 POEM and 86 LHM patients. Clinical success rate was 75·0% (95% CI: 66·2% to 82·1%) after POEM and 70·8% (95% CI: 61·7% to 78·5%) after LHM. The difference of 4·2% (95% CI: -7·5% to 15·7%) indicates non-inferiority of POEM at the pre-defined 12·5% margin. At five years, 41·3% of patients (26/63) after POEM and 31·0% of patients (18/58) after LHM had reflux esophagitis. The difference between POEM and LHM was not significant (10·2%, 95% CI: -7·0% to 26·8%, p=0·26). Severe esophagitis was infrequent (Los Angeles class C or D: 4·8% after POEM and 3·4% after LHM). Complications such as peptic stricture were not reported. At five years, 53·4% (47/88) of patients after POEM vs. 38·8% (33/85) after LHM were administered PPIs (difference 14·6%, 95% CI: -0·3% to 28·8%, p=0·07).

Interpretation POEM continued to be non-inferior to LHM plus Dor's fundoplication in controlling symptoms of achalasia at five years. Gastroesophageal reflux was common in both groups, with a tendency of higher rates with POEM.

Funding European Clinical Research Infrastructure Network and others (see Acknowledgements).

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Introduction

Achalasia is a chronic motility disorder of the esophagus characterized by impaired relaxation of the lower esophageal sphincter (LES) and absence of esophageal peristalsis. Due to abnormal transit and stasis of food, this condition typically results in symptoms of dysphagia, regurgitation of undigested food, chest pain, and weight loss. Current treatment options are not curative, but rather intended to palliate symptoms by reducing LES pressure and subsequently improving esophageal outflow. This has successfully been achieved by either disrupting LES muscle fibers with endoscopic pneumatic dilation or dividing them by surgical laparoscopic Heller's myotomy (LHM) with partial fundoplication in order to prevent the development of gastroesophageal reflux.[1]

Per-oral endoscopic myotomy (POEM) represents another approach to esophageal myotomy. It has been accepted worldwide as a standard treatment for achalasia as many retrospective as well as a few prospective studies have proven its safety and excellent short- and mid-term clinical efficacy.[2–4] Due to minimally invasive and "scarless" nature of this procedure with low morbidity and virtually no mortality and possible same- or next-day discharge, POEM quickly became the preferred form of myotomy in many centers. However, higher rates of post-POEM gastroesophageal reflux may be considered a disadvantage of POEM compared to pneumatic dilation or LHM with Dor´s fundoplication. In 2019, we published results of a randomized multicenter trial comparing POEM with LHM plus Dor´s fundoplication.[5] Two years after the procedure, POEM was non-inferior to LHM in terms of efficacy, however, POEM resulted in more cases of post-procedural gastroesophageal reflux in terms of reflux esophagitis and the administration of proton pump inhibitors (PPIs). Yet, there was a trend of decreasing difference between the two treatment groups at two years compared to the initial three months follow-up. Moreover, esophageal pH monitoring showed similar proportions of patients with abnormal acid reflux three months as well as two years after both procedures.

In this report, we present long-term results of our randomized non-inferiority trial with a five-year follow-up.

Methods

Trial design

This was a prospective, multicenter, randomized, open-label, non-inferiority trial comparing POEM with LHM plus Dor's fundoplication in patients with symptomatic achalasia performed at eight centers in six European countries.[5] The trial was approved by the institutional review board at each participating center. On-site data monitoring was provided by Clinical Trial Center North at the University Hospital Hamburg-Eppendorf and the European Clinical Research Infrastructure Network (ECRIN) for the initial analysis. The authors vouch for the completeness and accuracy of the data and for the fidelity of the trial to the protocol (ClinicalTrials.gov number, NCT01601678).

Patients

Detailed description of the study population has been previously reported.[5] Patients with symptomatic primary achalasia confirmed by esophageal manometry (and classified into

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subtypes I, II, and III) were eligible for inclusion if they were 18 years of age or older and had an Eckardt symptom score higher than 3. Patients who had undergone previous surgery of the stomach or esophagus, including surgical therapy of achalasia, were excluded. All patients provided written informed consent. Further details on the inclusion and exclusion criteria are provided in Tables S1-S3 in the Supplementary appendix.

Randomisation and masking

Patients at each center were randomly assigned in a 1:1 ratio to undergo either POEM or LHM plus Dor's fundoplication. Randomly permuted blocks of varying sizes, with separate blocks for each center, were used to balance group assignments according to center. A trial nurse who was unaffiliated with the research group and otherwise not involved with the trial performed the randomization. The study was open - label.

Interventions

Procedures (POEM and LHM plus Dor´s fundoplication) were performed as previously described, for details see the first publication and/or the protocol.[5]

Trial follow-up

Clinical data were collected at follow-up visits at 3, 6, 12, 24, 36 and 60 months. Patient-reported outcomes were assessed by means of telephone calls, mail, or follow-up appointments by dedicated trial personnel who were aware of the treatment-group assignments. Objective evaluation by means of endoscopy, manometry, and esophageal pH monitoring (at least 1 week after the discontinuation of a proton-pump inhibitor) was planned at 3, 24 and 60 months (see Table S4 in the Supplementary appendix). Unscheduled visits were possible in case of symptom´s recurrence or other health related problems. Additional unscheduled examinations (endoscopy, manometry etc.) could be performed at the discretion of a physician.

Trial End Points

The primary endpoint of the trial was clinical success defined by Eckardt score 3 or less without use of additional treatments at two years. Here we report clinical success defined identically at five years, which was originally planned as the secondary outcome in the protocol. The primary hypothesis was again that POEM would be non-inferior (with a non-inferiority margin of 12·5 percentage points) to LHM plus Dor's fundoplication with regard to the primary endpoint. If a patient did not reach an Eckardt score equal to or below 3 within six months after procedure, it was considered a treatment failure. Increase of the score above 3 after initial clinical success was considered a clinical recurrence (in case the symptoms were not caused by other conditions such as mycotic esophagitis).

Prespecified secondary endpoints included clinical success at three years and assessment of achalasia related symptoms (Eckardt score), reflux related symptoms (DeMeester clinical score ranging from 0 = no symptoms to 6 = severe symptoms) and Gastrointestinal Quality of Life Index score (range, 0 to 144, with higher scores indicating better quality) at three and five years.[6] Objective measures included the grading of reflux esophagitis on endoscopy according to the Los Angeles Classification; assessment of the lower esophageal sphincter function by high-resolution manometry (integrated relaxation pressure); and 24-hour pH monitoring. Gastroesophageal reflux was considered abnormal if the acid exposure time (total percentage

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of time with pH <4) was greater than 4·5%. The pH-metry composite DeMeester score was calculated as well.[7] Further details of these clinical measures are provided in Tables S5 and S6 in the Supplementary appendix.

The statistical analysis plan (available with the protocol) specified that clinically relevant exploratory subgroup analyses would be performed. Exploratory subgroups were defined according to age (<40 or ≥40 years), sex, achalasia subtype (I, II, or III), and previous treatment of achalasia (yes or no).

Statistical analysis

Details concerning sample size calculation have been previously reported.[5] The primary endpoint of clinical success was evaluated on a modified intention to treat (mITT) population, which included all patients who underwent the assigned procedure. Missing values were imputed by multiple imputation with chained equation using 100 imputations and with available Eckardt scores (including baseline), type of achalasia, previous treatment for achalasia (yes/no), BMI, age, and gender. We estimated Wilson confidence intervals for proportions and Miettinen-Nurminen confidence intervals for differences in proportions on the multiply imputed data. As a sensitivity analysis, the clinical success at three and five years was evaluated in an available data analysis. Only available ES values before a potential re-treatment were used and clinical failure was assumed after a re-treatment.

Mixed effect models were used to evaluate data across visits – a logistic regression model to compare clinical success rates between treatment groups and a linear model to study the between-group difference of the Eckardt score. Predictors of clinical success were searched for by separate logistic regression models for the five-year time point. The Fisher's test was used for comparing groups according to categorical variables and the Wilcoxon rank sum test for continuous variables. Confidence intervals for means and medians of continuous variables were constructed by the percentile bootstrap method.

The p-values and confidence intervals are presented without multiple testing corrections, and therefore cannot be used for inference. The standard alpha level of 5% was used as a threshold for statistical significance and all the confidence intervals have 95% expected coverage. The analyses were performed in R version 4.3.2 (R Foundation for Statistical Computing, Vienna, Austria).

Role of the funding source

Various public foundations and Olympus Europe supported the initial trial. None of the sponsors had any role in the design of the trial or in the analysis or interpretation of the data.

Results

Patient's characteristics

Trial profile was previously reported (see Figure S1 in the Supplementary appendix).[5] No significant differences between groups were seen in terms of age, sex, type of achalasia and baseline integrated relaxation pressure of the LES. Of the 241 patients enrolled, 20 were excluded from the trial for different reasons and 221 underwent the assigned treatment (the modified intention to treat – mITT - population; 112 patients received POEM and 109 LHM. Overall, 90 of 112 patients (80%) in the POEM group and 86 of 109 patients (79%) in the LHM

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group had completed the five-year follow-up. Details on patients´ baseline characteristics are shown in Table 1.

Clinical success

In the mITT population, clinical success at three years was seen in 79·5% (95% CI: 71·1% to 85·9%) of patients after POEM and in 76·7% (95% CI: 68·0% to 83·7%) of patients after LHM. At five years, the respective rates were 75·0% (95% CI: 66·2% to 82·1%) and 70·8% (95% CI: 61·7% to 78·5%); see Figure 1. Missing data on clinical success were imputed (through imputation of missing Eckardt scores) for 21 patients in the POEM group and 19 patients in the LHM group at 3 years and 22 patients in each group at 5 years. Rates of clinical success over time using only available data are shown in Figure S2 in the Supplementary appendix.

The estimated between-group difference was 2·8% (95% CI: -8·1% to 13·6%) at three years and 4·2% (95% CI: -7·5% to 15·7%) at five years in favor of POEM, both satisfying the non-inferiority of POEM at the predefined 12·5% margin. Data in all 100 realizations of our imputation model were in favor of non-inferiority both at three and five years. When using only the available data, the differences were 4·7% (95% CI: -7·9% to 17·2%) at three years and 5·6% (95% CI: -8·0% to 19·0%) at five years. A tipping point analysis is available in Figures S3 and S4 in the Supplementary Appendix. In an analysis of clinical success across time points, which was performed using a mixed-effects logistic-regression model (mITT population, imputed), the odds ratio (OR) of clinical success after POEM compared with the LHM group, was 1·25 (95% CI, 0·51 to 3·02).

Post-hoc exploratory subgroup analyses of the primary endpoint did not suggest evidence of altered response to the treatment based on age, achalasia subtype, or previous treatment, but suggested higher success rates in males (OR=2·00, 95% CI: 1·06 to 3·76), see Table S7 in the Supplementary appendix. POEM tended to fare better in achalasia subtypes II and III while LHM in achalasia subtype I, but differences were not significant. Furthermore, there was a trend for better effect of POEM in treatment-naïve patients (Figure 2).

Secondary endpoints

The mean Eckardt symptom score decreased from baseline and the mean value slightly increased during the follow-up (see Figures S5 and S6 in the Supplementary appendix) and was by 0·24 points (95% CI, 0·18 to 0·30) lower in the POEM group than in the LHM group across time points. As previously reported, a total of 11 patients experienced treatment failure (persistent symptoms after having undergone the assigned intervention) and reintervention was performed in 10 of them.[5]

Recurrence of symptoms occurred in 34 patients after POEM and in 31 patients after LHM at the five-year follow-up. From those with a recurrence after POEM, 12 (35·3%) underwent retreatment (four with pneumatic dilation, three re-POEM, five LHM). Eight patients (25·8%) after recurrence after LHM underwent retreatment (six dilations, two POEM), see Table S8 in the Supplementary appendix.

Improvement in Gastrointestinal Quality of Life Index scores between baseline and five years did not differ significantly between the groups (difference, -0·3 points; 95% CI, −8·1 to 6·9), see Supplementary Figure S7.

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Improvement in esophageal function (integrated relaxation pressure) in 48 patients after POEM and in 39 patients after LHM at five years did not differ significantly between the groups (difference, 0·9 mm Hg; 95% CI, -4·3 to 6·3), see Supplementary Figure S8.

Postprocedural gastroesophageal reflux

Presence of reflux symptoms five years after the procedure was similar in both groups with the mean DeMeester clinical score of 1·3 (95% CI: 1·0 to 1·6) after POEM and 1·1 (95% CI: 0·9 to 1·4) after LHM (Figure S9 in the Supplementary appendix). Patients experiencing daily reflux symptoms were infrequent in both groups - (15/89 [16·9%] after POEM, 8/83 [9·6%] after LHM).

A post hoc analysis of administration of proton-pump inhibitors showed that a higher percentage of patients after POEM than after LHM were given these drugs across time points after baseline, however the difference was not statistically significant at any point (28 of 112 [25·0%] vs. 33 of 109 [30·3%] at baseline; 33 of 108 [30·6%] vs. 29 of 105 [27·6%] at three months; 56 of 106 [52·8%] vs. 28 of 103 [27·2%] at two years; 52 of 90 [56·7%] vs. 30 of 86 [34·9%] at three years; 47 of 88 [53·4%] vs. 33 of 85 [38·8%] at five years), see Figure S10 in the Supplementary appendix. Esophagitis was more frequent in patients not receiving PPIs (Figure S11 in the Supplementary appendix).

Among 121 patients in the mITT population who underwent endoscopy at five years, there was a trend of higher rates of reflux esophagitis after POEM (41·3%; 26/63) than after LHM (31·0%; 18/58), Figure 3. The between-group difference was not statistically significant (10·3%, 95% CI: -7·0% to 26·8%, p=0.26) and decreased over time (37·2% at three months and 14·2% at two years). Severe esophagitis (Los Angeles Classification grade C or D according to the Lyon Consensus) was observed in three patients (4·8%) after POEM and in two patients (3·4%) after LHM at five years.[8] Combining results of reflux symptoms, PPI use and endoscopic esophagitis, the percentage of patients without reflux symptoms, off PPI and without esophagitis was 14·8% (9/61) after POEM and 14·5% (8/55) after LHM.

At two years, similar proportions of subjects had abnormal acid exposure time >4·5% (21/70 [30%] after POEM and 17/56 [30%] after LHM). However, there was a statistically significant difference between these groups at five years (28/45 [62·2%] after POEM and 8/36 [22·2%] after LHM; difference 40·0%, 95% CI 18·6% to 57·6%, p<0.001), although pH-metry data were available in only 71 of 202 patients initially included. Details are provided in Table 2 and in Supplementary appendix (Figures S12 and S13).

Complications such as peptic stricture, Barrett's esophagus or esophageal adenocarcinoma were not reported.

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Discussion

In the five-year analysis of our randomized controlled trial comparing the two different methods of myotomy for symptomatic achalasia – endoscopic (POEM) versus surgical (LHM) – two major outcomes were analysed: clinical efficacy to reduce dysphagia and the occurrence of postprocedural gastroesophageal reflux. Efficacy was similar in the two groups, confirming non-inferiority of the new endoscopic therapy over an extended follow-up period. Results with regards to reflux showed that mild reflux was common in both groups, with a tendency of higher rates among POEM patients with a 10-15% difference in favor of LHM depending on the parameters assessed. Importantly, no case of serious reflux complication has been observed. The role of the third major treatment option, namely pneumatic dilatation, was not the topic of the present study, but was covered by another randomized trial, recently also updated with 5-year results.[9]

Our study shows that both POEM and LHM are equally effective in improving symptoms five years after the procedure. The treatments achieved clinical success in 75% and 71% of patients, respectively. These numbers also indicate that 25-35% of patients will experience treatment failure (no initial effect) or recurrence within five years after the procedure. Comparing our results to the randomized trial assessing clinical efficacy of POEM vs. pneumatic dilation, the long-term rate of clinical success after POEM was similar.[9] Slightly higher percentages of clinical success of POEM over time in the latter study may be attributed to enrolment of treatment naïve patients only, while we enrolled more than 40% of cases with previous treatment. Not surprisingly, the efficacy of achalasia treatment had decreased over time. In the European achalasia trial comparing clinical success five and ten years after LHM and pneumatic dilation, LHM efficacy at five years (84%) further decreased to 74% at ten years.[10–12] Thus, our five-years data cannot be considered as definitive as further drop in proportions of patients with long term clinical success may be expected.

Long-term data on POEM (ten years or more) are rare in the literature. Onimaru and Inoue, who introduced the technique into clinical practice, published long-term results on 15/36 patients treated between 2008 and 2010, with good clinical success (93%) but including a 26·7% rate of secondary balloon dilatation.[13] In a single center retrospective US analysis including 610 patients over a ten-year period, Kaplan-Meier analysis suggested a 91% success rate at seven years, but actual follow-up data were available in only 81%, 49%, 24% and 6% of the initially treated cases at 1,3,5 and 7 years.[14] Meta analyses of retrospective case series with long-term follow-up mostly cover periods up to five years or less and claim clinical success rates of 82-87%.[15,16]

Long-term studies on LHM are available, but limited in number and many of them were published years ago, mostly without using the Eckardt score as measure of clinical success which is now universally accepted. A recent study involving 136 cases described treatment success in 94% with a median follow-up of 65·5 months. However, less than half of the patients had follow-up beyond five years.[17] In other mostly retrospective studies, in some of which there was no information about additional treatment, LHM as a sole therapy lost efficacy in 20-30% over time.[18–21] The best evidence in terms of long-term effect of LHM is provided by the above-mentioned European achalasia trial, where the treatment success five and ten years after LHM was 84% and 74%, respectively.[11,12]

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The major issue about POEM attracting attention worldwide is postprocedural gastroesophageal reflux. If significant and much more prominent than with LHM, it could hamper the enthusiasm for POEM as the first line therapy of achalasia. This is because POEM, in contrast to LHM, is not accompanied by an anti-reflux procedure. Postprocedural reflux can be assessed by using four parameters – symptoms, esophagitis, consumption of PPIs, and pH-metry recording. These parameters have both advantages and disadvantages (e.g. overlap between reflux and achalasia related symptoms, inaccurate pH-metry measurement in case of stagnation of content in the esophagus, not all PPIs are given due to reflux, etc.) and may not behave in parallel in individual patients. The results of our first study showed a decreasing reflux difference between POEM and LHM when determined at six months as compared to two years. Also, some parameters were only numerically but not statistically significantly different between the two groups at two years.[5] The current results show that these differences narrowed even further so that at five years, they were numerically different by about 10% but not statistically at our given sample size. For example, the between-group difference in terms of reflux esophagitis decreased over time (37% at three months, 14·2% at two years, and 10·3% at five years).

The only significant difference was found in the frequency of patients with pathologic acid reflux (measured by 24-hours pH-metry recording) five years after the procedure. Even if these proportions were similar at two years (30% in both groups), three years latter there was a higher proportion of patients with reflux after POEM than after LHM (51% vs. 21%). It should be underlined that only a minority of patients underwent pH-metry at five years, which may partially explain the differences between both procedures. Moreover, one study showed that among patients with achalasia, who had pathologic pH-metry after POEM, only a minority had true acid reflux (29·6%), the majority (42·7%) had acid fermentation acidification pattern due to stagnation in the esophagus.[22] Thus, pH-metry (without manual analysis) cannot be considered as a very accurate means to detect true gastro-esophageal reflux in patients with achalasia.

The reason for a trend of some reflux parameters to increase five years after LHM may be that the effect of fundoplication wanes over time. In a randomized study outside of achalasia, comparing treatment with PPIs and fundoplication in patients with gastroesophageal reflux disease, 62% of surgical patients were using anti-reflux medications on a regular basis ten years after the procedure.[23] In our achalasia study, LHM had esophagitis rates of 20% at three months, and remained stable around 30% at two and five years. A recent meta-analysis concluded that the between-group difference (POEM vs. LHM) waned over time in terms of post-procedural reflux in all comparisons, resulting in no difference among randomised controlled trials in the late evaluation.[24] More recently, Doubova et al. showed that reflux rates start to increase three to five years after LHM with an 88% rate of anti-reflux medication at the seven- to ten-year follow-up.[25]

In the long-term follow-up analyses of the European achalasia trial, rates of reflux esophagitis after LHM were 21% at 1 year, 18% at five and 17% at ten years even though with increasing post-procedural time, decreasing number of enrolled patients underwent endoscopy.[10–12]

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Most importantly, in our trial, there were no major reflux-related complications in either group. In agreement with the literature, our results suggest that reflux after POEM is mild and reflux symptoms are managed sufficiently with PPIs in most patients. In general, the information provided by our study can be used for patient consent in the framework of shared decision making.

With regards to management of reflux diagnosed after achalasia treatment, it has to be admitted that there have been no evidence-based and precisely defined standards after surgical myotomy in clinical practice as well as in any of the POEM or LHM trials published until now. Also, patient compliance and further management have not been systematically analysed. Post-procedural reflux appears to be mostly asymptomatic as shown in a multicenter retrospective case series (60·1% in 282 cases).[26] A study comparing post-POEM reflux with non-achalasia gastroesophageal reflux disease (GERD) found a higher rate of esophagitis, but a lower rate of symptoms in the post-POEM group.[27] Thus, the true gold standard to define reflux according to clinical relevance is not known and requires further investigations. At the present state of knowledge, there is probably no need to routinely accompany POEM by an endoscopic anti-reflux procedure (e.g. F-POEM). On the other hand, post-POEM reflux (as well as reflux after LHM) should not be underestimated and should be adequately treated with anti-reflux medications when indicated. There are some reports of rare occurrence of post-POEM reflux adverse events such as stricture, Barrett´s esophagus or early esophageal adenocarcinoma.[28,29] Thus, all patients after POEM (and after LHM as well) should enter endoscopic surveillance to detect reflux complications early as suggested by the current guideline, while the issue of surveillance intervals has to be studied further as should be possible long-term reflux consequences (Barrett's esophagus and its complications).[30]

Our trial has several limitations. Most of our patients had type II achalasia, which is the most common type in Europe; however, the results may not accurately reflect the situation in other areas. In the beginning of our trial, surgeons were more experienced in performing LHM than the endoscopists in performing POEM, which could have affected the results in favor of LHM. Patients and trial personnel were aware of the treatment group assignments because blinding was not possible. This was a potential source of bias given that the primary end point was based on patients' reports of symptoms. Objective assessment by manometry corroborated the primary finding, however barely half of POEM patients and one third of LHM patients underwent assessment of esophageal function (manometry, 24h pH-metry) at five years.

To summarize, both treatment options for myotomy (POEM, LHM) can be offered to patients with achalasia. With regards to postprocedural reflux, it could be concluded that LHM may provide temporary reflux protection in 10-15% more cases, but this effect may be lost after five to ten years. Patients can choose after being provided with full explanation of advantages and disadvantages of the respective approach. Our study contributed to the growing body of evidence, that both myotomy methods provide similar long–term efficacy. Our long-term results support the role of POEM as a less invasive approach that is non-inferior to LHM in controlling symptoms of achalasia.

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Tables and figures

Figure 1: Rates of clinical success over time and between-group differences. Top: Figure shows the estimated percentage of patients with clinical success in each treatment group (modified intention-to-treat population, missing data multiply imputed). Circles (POEM) and squares (LHM) represent point estimates of clinical success rates at given times with the I lines indicating 95% confidence intervals. The results until 2 years were already reported.[5] Bottom: Estimated differences in clinical success rates between the POEM and LHM groups with 95% confidence intervals at three and five years post procedure. At both time points, non-inferiority with the pre-specified non-inferiority margin of 12·5% is reported.

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Figure 2: Subgroup analysis of absolute clinical success differences between POEM and LHM groups. The figure shows absolute differences and 95% confidence intervals with respect to clinical success at five years for the subgroups given by age, gender, achalasia type, and previous treatment in the modified Intention-to-treat population (missing data imputed). The size of the squares represents the sample size in the respective subgroups. Confidence intervals have not been adjusted for multiplicity and cannot be used to draw inferences about effects.

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Figure 3: Development of reflux esophagitis over time in the POEM and LHM groups. The figure shows rates (%) of reflux esophagitis for both treatment groups in the modified Intention-to-treat population at baseline, 3 months, 2 and 5 years. The total numbers of available data at each group and time point are shown at the bottom of the plot.

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Table 1: Demographic and clinical characteristics of the patients at baseline.*

	POEM	**LHM**
Characteristic	**n = 112**	**n = 109**
Age (yr)	48.6±14.9	48.6±14.6
Male sex – no. (%)	68 (60.7)	60 (55.0)
Body-mass index ‡	24.8±4.6	24.5±4.5
Esophageal function according to IRP ** (mmHg)	26.8±11.4	26.0±10.9
Achalasia subtype – no. (%)		
I	15 (13.4)	21 (19.3)
II	85 (75.9)	78 (71.6)
III	12 (10.7)	9 (8.3)
Unclassified	0	1 (0.9)
Previous therapy – no. (%)		
None	73 (65.2)	69 (63.3)
Endoscopic pneumatic dilation	27 (24.1)	31 (28.4)
Endoscopic botulinum toxin injection	7 (6.2)	8 (7.3)
Pneumatic dilation and botulinum toxin injection	5 (4.5)	1 (0.9)
Eckardt symptom score	6.8±2.0	6.7±2.0
Gastrointestinal Quality of Life Index score	89.2±23.1	90.4±18.1

* Plus-minus are means ± standard deviation. Baseline characteristics were similar in the two treatment groups. Percentages may not total 100 because of rounding.
‡ The body-mass index is the weight in kilograms divided by the square of the height in meters.
** Integrated relaxation pressure

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Table 2: Clinical and objective evaluation of gastroesophageal reflux disease (secondary end point) over time.

	3 months		2 years		5 years	
Measure	**POEM group**	**LHM group**	**POEM group**	**LHM group**	**POEM group**	**LHM group**
Clinical scores						
Mean DeMeester clinical score (95% CI)	0.9 (0.7–1.1)	0.5 (0.4–0.7)	1.2 (0.9–1.5)	0.9 (0.6–1.1)	1.3 (1.0–1.6)	1.1 (0.9–1.4)
Daily reflux symptoms — no./total no. (%)	5/108 (4.6)	2/105 (1.9)	7/107 (6.5)	2/103 (1.9)	15/89 (16.9)	8/83 (9.7)
Occasional reflux symptoms — no./total no. (%)	42/108 (38.9)	29/105 (27.6)	49/107 (45.8)	45/103 (43.7)	41/89 (46.1)	41/83 (49.4)
Daily PPI use — no./total no. (%)	25/108 (23.1)	16/105 (15.2)	41/106 (38.7)	20/103 (19.4)	36/88 (40.9)	22/85 (25.9)
Occasional PPI use — no./total no. (%)	8/108 (7.4)	13/105 (12.4)	15/106 (14.2)	8/103 (7.8)	11/88 (12.5)	11/85 (12.9)
LA Classification grade of reflux esophagitis — no./total no. (%)†						
Overall, grades A to D	57/100 (57)	19/96 (20)	38/87 (44)	23/78 (29)	26/63 (41)	18/58 (31)
Grade A	32/100 (32)	13/96 (14)	18/87 (21)	13/78 (17)	17/63 (27)	14/58 (24)
Grade B	19/100 (19)	3/96 (3)	16/87 (18)	5/78 (6)	6/63 (10)	2/58 (3)
Grade C	5/100 (5)	2/96 (2)	4/87 (5)	2/78 (3)	3/63 (5)	0/58 (0)
Grade D	1/100 (1)	1/96 (1)	0/87	3/78 (4)	0/63 (0)	2/58 (3)
Esophageal acid exposure‡						
Mean acid exposure time (95% CI) — %	7.1 (5.4–8.9)	6.7 (4.1–9.3)	5.7 (2.8–8.5)	5.4 (2.2–8.5)	10.2 (7.6–14.2)	5.5 (3.1–11.8)
Acid exposure time >4.5% — no./total no. (%)	41/93 (44)	27/82 (33)	21/70 (30)	17/56 (30)	28/45 (62)	11/36 (31)
Acid exposure time >6% — no./total no. (%)	38/93 (41)	24/82 (29)	19/70 (27)	14/56 (25)	23/45 (51)	8/36 (22)
Mean DeMeester pH-metry score (95% CI)	24.9 (19.9–30.8)	24.3 (17.2–34.7)	16.8 (12.8–21.9)	17.5 (10.9–39.6)	36.6 (27.0–52.1)	18.0 (11.1–30.44)

PPI = proton-pump inhibitor

† Los Angeles (LA) Classification grade was assessed on endoscopy: grade A indicates one or more mucosal breaks of 5 mm in length or less; grade B, one or more mucosal breaks of longer than 5 mm; grade C, mucosal breaks that extend between two or more mucosal folds (but

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involve <75% of the circumference of the esophagus); and grade D, mucosal breaks which involve at least 75% of the esophageal circumference.
‡ Esophageal acid exposure was assessed with the use of 24-hour pH monitoring; acid exposure time is the total percentage of time with a pH lower than 4.

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Acknowledgements

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Supported by the European Clinical Research Infrastructure Network (ECRIN); Hamburgische Stiftung für Wissenschaften, Entwicklung und Kultur Helmut und Hannelore Greve (Hamburg, Germany); by Dr. med. Carl-August Skröder Stiftung (Hamburg, Germany); Dr. Gerhard Büchtemann Stiftung (Hamburg, Germany); Agnes-Graefe Stiftung (Hamburg, Germany); Georg und Jürgen Rickertsen Stiftung (Hamburg, Germany); Reinhard Frank Stiftung (Hamburg, Germany); Johann Max Böttcher Stiftung (Hamburg, Germany); Richard und Annemarie Wolf Stiftung (Knittlingen, Germany); Olympus Europa (Hamburg, Germany), which provided funding for the training of personnel at the European centers through POEM Grants 206/7 and 2017/18; the German Society for Gastroenterology and Metabolism and Olympus Europe Foundation (Endoscopy Research Award 2012); a prize awarded at the United European Gastroenterology Week 2010 conference; and the Olympus EuroNOTES Research Fund Program. The trial was also supported by Harvard Catalyst, the Harvard Clinical and Translational Science Center (National Center for Advancing Translational Sciences, National Institutes of Health Award UL 1TR002541), and by financial contributions from Harvard University and its affiliated academic health care centers.

Declaration of interests

KH, JM, BH, AR, HM, TR, OM, TH, RUF, RR, CTG, AE, GB, JM, YBW, MV, JI have nothing to disclose.
Dr. von Rahden reports other from Karl Storz GmbH, Tuttlingen, Germany, outside the submitted work.
Dr. von Renteln reports grants and personal fees from Boston Scientific, grants and personal fees from Pendopharm, grants from Vantage, grants from ERBE, grants from Pentax, outside the submitted work.
Dr. Bisschops reports grants and personal fees from Pentax, grants and personal fees from Fujifilm, grants and personal fees from Cook, other from Erbe, other from Olympus, personal fees from Norgine, personal fees and other from Medivators, personal fees and other from Boston scientific, outside the submitted work.
Dr. Bredenoord reports grants and personal fees from Laborie, personal fees from Esocap, grants and personal fees from Diversatek, grants and personal fees from Medtronic, personal fees and other from DrFalkPharma, personal fees from Calypso Biotech, personal fees from Robarts, personal fees from Reckett Benkiser, personal fees and other from Regeneron, personal fees from Celgene, grants and personal fees from Bayer, grants and personal fees from Norgine, personal fees from AstraZeneca, personal fees from Almirall, personal fees from Allergan, outside the submitted work.
Dr. Fockens reports personal fees from Cook Endoscopy, personal fees from Olympus, personal fees from Ethicon Endosurgery, grants from Boston Scientific, outside the submitted work.
Dr. Rösch reports grants from ECRIN (European Clinical Research Infrastructure Network) ID 77, grants from Hamburg Greve Foundation (Hamburgische Stiftung für Wissenschaften, Entwicklung und Kultur Helmut und Hannelore Greve) Hamburg, Germany, grants from Carl-August Skröder Foundation (Dr. med. Carl-August Skröder – Stiftung) Hamburg, Germany, grants from Büchtemann Foundation (Dr. Gerhard Büchtemann- Stiftung) Hamburg, Germany, grants from AgnesGraefe Foundation (Agnes-Graefe - Stiftung) Hamburg, Germany, grants from Rickertsen Foundation (Georg und Jürgen Rickertsen - Stiftung) Hamburg, Germany, grants from Frank Foundation (Reinhard Frank - Stiftung) Hamburg, Germany, grants from

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Wolf Foundation (Richard und Annemarie Wolf – Stiftung) Knittlingen, Germany, grants from Olympus Europa SE & Co. KG, Hamburg, Germany including Olympus Foundation, grants from Endoscopy Research Award 2012 of the German Society for Gastroenterology and Metabolism (DGVS) sponsored by Olympus Europe Foundation , grants from UEGW (United European Gastroenterology Week) 2010: Olympus Euro NOTES Research Found Program, during the conduct of the study; grants and personal fees from Olympus Europe SE & Co. KG, Hamburg, Germany, grants from Erbe Company Tübingen, Germany, grants from Karl Storz Company Tuttlingen, Germany, grants from Norgine Ltd Germany, Wettenberg, Germany, grants and personal fees from UniversaldX , Seville, Spain, personal fees from Amadix Ltd Madrid, Spain, grants from InterScope Med, Inc. Whitinsville, MA , USA, grants from Imevax Ltd Munich Germany, personal fees from Falk Foundation Freiburg, Germany, outside the submitted work;
Dr. Schijven reports grants from Olympus BV, outside the submitted work.

Author contributions:
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Drafting of the manuscript: Hugova, Martinek, Mares, Rösch
Statistical analysis: Mares, Vollberg
Critical revision of the manuscript for important intellectual content: All authors

Data sharing statement:
Complete patient data set with identifiers will be made available with publication. Pseudonymized data (center and patient number, age, sex) are kept in University Hospital Hamburg-Eppendorf, Department of Interdisciplinary Endoscopy, reachable via study corresponding author (t.roesch@uke.de). Individual patient data (de-identified) are kept at the participating centers. Informed consent form in German and English will be available upon request at main study center in Hamburg, in other languages in participating centers.
Study protocol and statistical analysis plan will be submitted with the manuscript.

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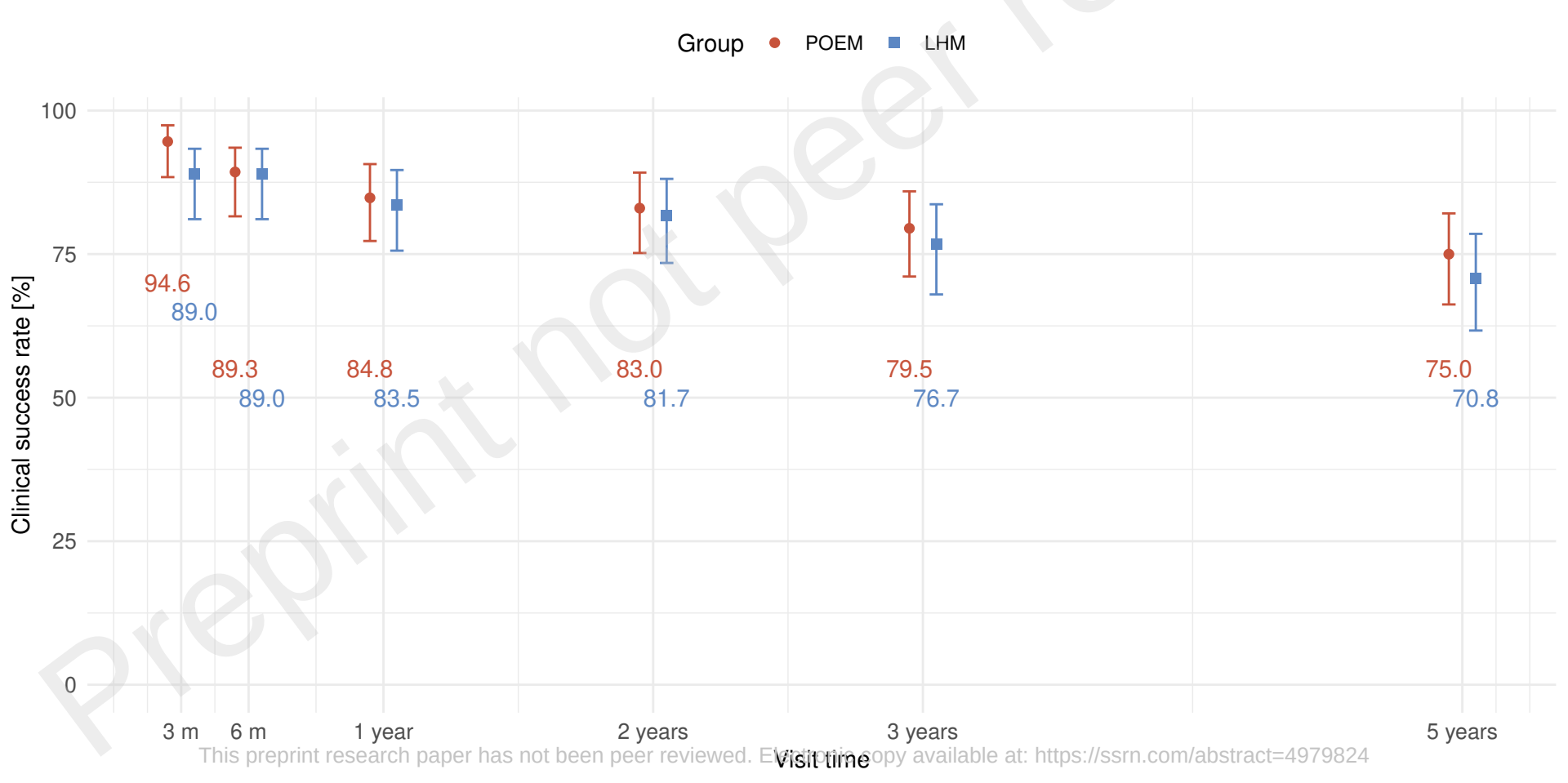

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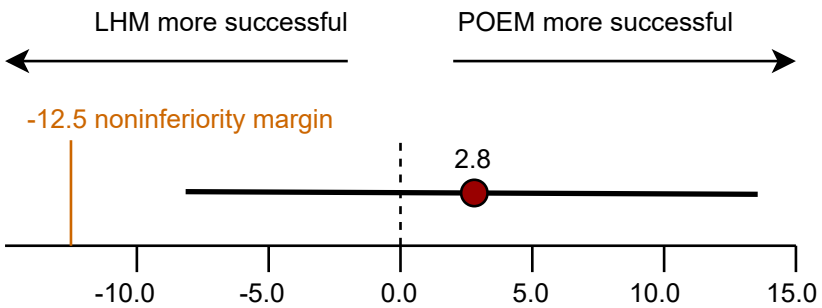
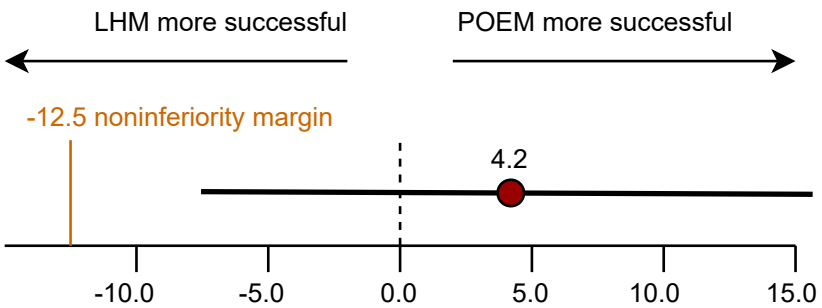
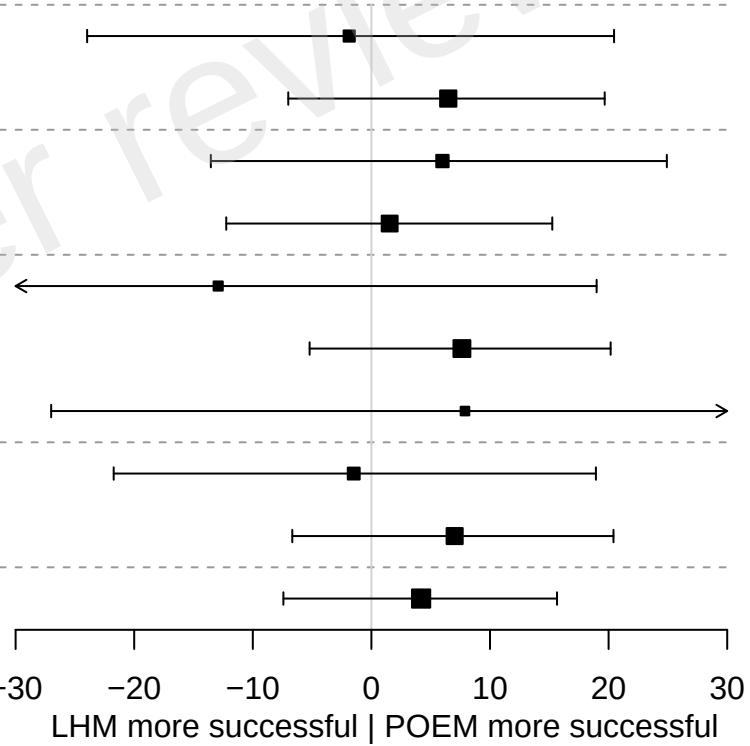
3-year success rate [%] difference



5-year success rate [%] difference



Sub−group	Success rate difference [%]	95% CI lower [%]	95% CI upper [%]
Age < 40 years	−1.87	−23.97	20.46
Age >= 40 years	6.48	−7.01	19.67
Gender: female	5.99	−13.54	24.91
Gender: male	1.54	−12.24	15.25
Achalasia type: I	−12.92	−41.66	18.99
Achalasia type: II	7.63	−5.21	20.17
Achalasia type: III	7.89	−27	40.24
Previous treatment: yes	−1.49	−21.73	18.93
Previous treatment: no	7.02	−6.67	20.41
All	4.19	−7.42	15.65



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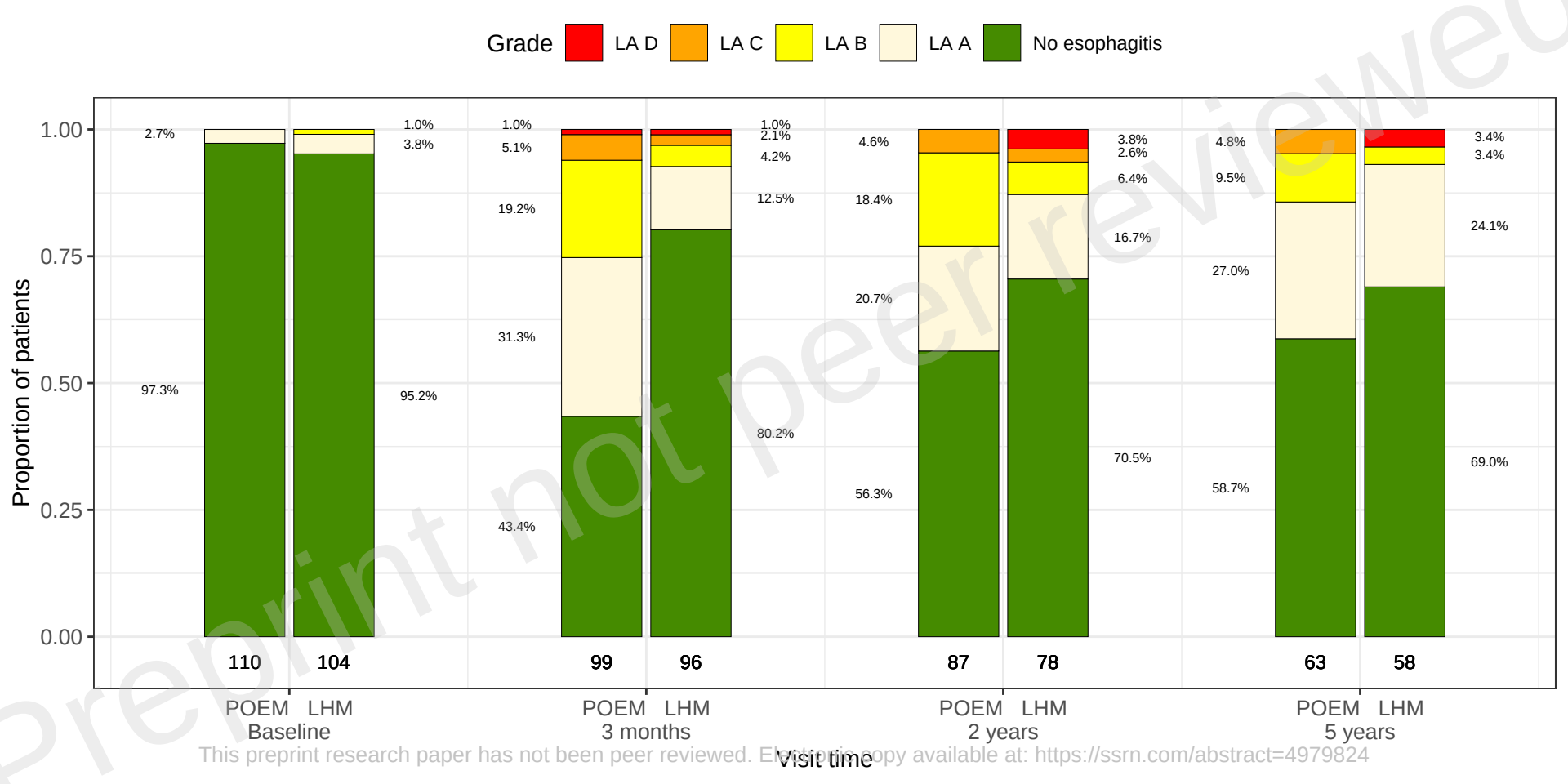

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