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REVIEW ARTICLE

Dor versus Toupet fundoplication after Laparoscopic Heller Myotomy: Systematic review and Bayesian meta-analysis of randomized controlled trials

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KEYWORDS
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Summary Laparoscopic Heller Myotomy (LHM) with partial fundoplication has become the treatment of choice for esophageal achalasia. However, the choice of the partial fundoplication is debated. The aim of this study was to compare outcomes for Dor and Toupet fundoplication after LHM. A systematic search of randomized controlled trials comparing Dor and Toupet fundoplication was performed using PubMed, EMBASE and Web of Science. Three studies met the inclusion criteria. Overall, 174 patients were included in the analysis. The postoperative abnormal acid reflux [pooled Risk Ratio 0.98 (95% HPD 0.54–1.80)] and dysphagia [pooled Risk Ratio 1.03 (95% HPD 0.51–2.05)] were similar comparing Dor and Toupet fundoplication. The % total time pH $\leq$ 4 [estimated pooled mean difference −0.08 (95% HPD −1.04–0.90)] and DeMeester score [estimated pooled mean difference 0.51 (95% HPD −0.90–1.94)] were comparable. Additionally, the operative time [estimated pooled mean difference 0.02 (95% HPD −0.53–0.52)] and iatrogenic esophageal perforation [pooled Risk Ratio 1.05 (95% HPD 0.52–2.10)] were similar in the two groups. Dor and Toupet fundoplication after laparoscopic Heller myotomy seem comparable in term of postoperative abnormal acid exposure and dysphagia. The choice of the partial fundoplication should be left to surgeon experience and tailored on each patient.

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1. Introduction

Achalasia is a primary esophageal motility disorder characterized by lack of the Lower Esophageal Sphincter (LES) relaxation and aperistalsis of the esophageal body.[1] It has a prevalence of 10 per 100,000 individuals and an incidence of 1 case per 100,000 individuals every year.[2] Current therapy aim to relieve the distal esophageal functional obstruction and related symptoms such as dysphagia and regurgitation. Laparoscopic Heller Myotomy (LHM) has become the treatment of choice with significant improvement of patient symptoms and quality of life.[3,4]

Postoperative Gastroesophageal Reflux Disease (GERD) may occur after myotomy without fundoplication and may be cause of treatment failure.[5] For this reason, current evidence suggests that a fundoplication should be added concomitantly.[6] Nissen fundoplication is the gold standard therapy for pathologic GERD, but its employment in patients with primary esophageal motility disorders may cause postoperative dysphagia.[7,8] Therefore, two types of partial fundoplication are usually employed: the posterior Toupet fundoplication (270°) and the anterior Dor fundoplication (180°). The *pros* and *cons* of each procedure have been investigated in previous studies but to date, only contrasting data are available on physiological short-term outcomes and the choice of partial fundoplication is left to surgeons' preference.[9,10]

The aim of this systematic review and meta-analysis was to objectively compare Dor and Toupet fundoplication after LHM for esophageal achalasia.

2. Methods

2.1. Search strategy

A systematic review was carried out according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses checklist (PRISMA).[11] Institutional review board approval was not required. We conducted a systematic search using MEDLINE databases (PubMed, EMBASE and Web of Science) until 30th November 2018. We searched for papers published in English using the following search headings: esophageal achalasia, Heller myotomy, Dor fundoplication, and Toupet fundoplication. All titles were screened and suitable abstracts were reviewed. In addition, references were consulted for other potential articles.

2.2. Inclusion and exclusion criteria

To be included in the analysis: (1) randomized controlled trial (RCT) study design; (2) patients with esophageal achalasia that underwent LHM with partial fundoplication (Dor vs. Toupet); (3) objective outcomes comparison according to the type of fundoplication; and (4) clear research methodology. Studies were excluded if (1) the study was not an RCT; (2) the study did not report outcomes comparing Dor vs. Toupet fundoplication; or (3) the methodology was not clearly reported.

2.3. Data extraction

The following data were retrieved: author, study year, country, study design, patients, sex, age, Body Mass Index (BMI), American Society of Anaesthesiologists' (ASA) classification, previous endoscopic pneumatic dilatation (PD), operative time, hospital length of stay, postoperative complications. In addition, abnormal acid exposure, % total time pH $\leq$ 4, DeMeester score, postoperative dysphagia, Eckardt score, endoscopic findings, postoperative pneumatic dilation, and manometric patterns were analysed during follow-up. All data were entered independently by two investigators (AA, ST) in separate databases and compared only at the end of the reviewing process to decrease the selection bias. A third person (DB) eventually reviewed the database. Corresponding authors were contacted if needed and discrepancies were clarified. The study protocol was registered at PROSPERO (International prospective register of systematic reviews), accessible at http://www.crd.york.ac.uk/prospero/(Registration number: CRD42019117241).

2.4. Study quality assessment

Two authors (AA, ER) independently assessed the methodologic quality of the selected trials by using the Cochrane risk of bias tool.[12] This tool evaluates the following criteria: (1) method of randomization; (2) allocation concealment; (3) baseline comparability of study groups; and (4) blinding and completeness of follow-up. Trials were graded as follows: A = adequate, B = unclear, and C = inadequate on each criterion. Thus, each RCT was graded as having low, moderate, or high risk of bias (Supplementary Fig. S1). Disagreements were solved by discussion.

2.5. Statistical analysis

In addition to systematic review we performed study level arm based meta-analysis. To capture variability from all sources, we synthesised the data using fully Bayesian analysis with normal-normal hierarchical model. Compared to the frequentist meta-analysis, the Bayesian approach takes into account all sources of variations and provide more accurate estimates for small samples.[13–15] Bayesian posterior analysis should yield exact coverages, independent of sample size.[16] We used Risk Ratio (RR) and standardized mean difference (SMD) as pooled effect size measure using Dor fundoplication as reference treatment.

For RR on log scale as "sceptical prior" we applied normal distribution with zero mean and scale 0.4 (10% of the distribution is contained within the clinically unimportant null interval). For τ prior in RR analysis we consider two different distribution: an informative half-normal prior with zero mean and scale 0.5, and an informative half-normal prior with zero mean and scale 1, for sensitivity analysis.[17] For SMD prior we assigned a vague normal prior with mean 0 and scale 10. For τ prior in SMD analysis we applies two different distribution: an informative log-t distribution with five degrees of freedom, location parameter −1.72 and scale 1.295, and a vague uniform (0,5) distribution, for sensitivity analysis.[18,19] The DIRECT algorithm was use to provide direct access to quasi-analytical posterior.[20] We used posterior median and mean as point estimation with relative 95% highest posterior density intervals (95%HPD). Monte Carlo sampling was performed to compute posterior one side predictive p-value.[21] Heterogeneity was quantified by I^2-index and Cochran's Q statistic, considering significant heterogeneity when p-value was <0.10 or I^2-index was >50%.[22] We judged the estimated parameters significance if its 95% HPD encompasses the 0 value. A leave-one-out sensitivity analysis was performed. In accordance with Cochrane guidelines, we did not investigate publication bias because our search consider fewer than ten studies for each data comparison.

2.6. Outcomes of interest

Primary outcomes: postoperative acid exposure (abnormal acid exposure, % total time pH $\leq$ 4, DeMeester score). Secondary outcomes: operative time (minutes), esophageal perforation rate, basal LES pressure (mmHg), and post-operative dysphagia. Abnormal acid exposure was defined as abnormal DeMeester score (>14.72) or total time pH $\leq$ 4 more than 4%. Postoperative dysphagia was considered as either Eckardt score $\geq$3 and/or the need for endoscopic dilation.

3. Results

3.1. Systematic review

Forty-nine publications were found using the aforementioned search criteria. After elimination of duplicates, 44 publications were reviewed. Further screening revealed that 3 studies met the inclusion and exclusion criteria (Fig. 1). Overall, 174 patients were included in the analysis and 53.4% (93 patients) were allocated in the Dor fundoplication group (Table 1). There were 92 females (52.8%) and the age ranged from 20 to 82 years. The preoperative BMI was reported in 2 studies[24,25] and the ASA score was reported in one study.[23] The achalasia sub-type, according

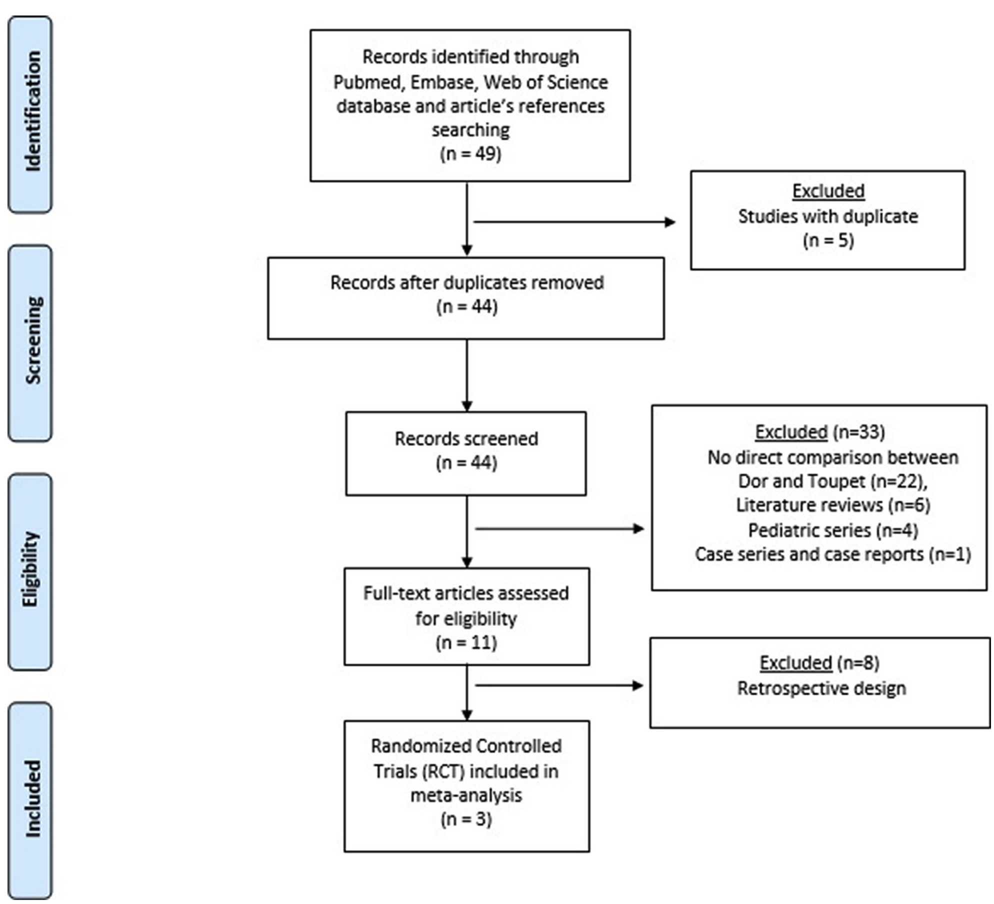

Figure 1 The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) diagram.

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Table 1 Summary of the studies included in the meta-analysis. RCT: Randomized Controlled Trial; BMI Body Mass Index; ASA: American Society of Anaesthesiologists score; OR time: Operative time; HLOS: Hospital length of stay; nr: not reported. Values are reported as mean (±standard deviation) or median (range).

Author, year, country	Study design	Surgical procedure	n Patients	Gender (M/F)	Age (year)	BMI (kg/m^2)	ASA	Previous PD	OR time (min)	HLOS (day)
Rawlings et al., 2012, USA[23]	RCT	Dor	36	19/17	46.8 (19.9–68.9)	nr	1.9 ± 0.6	nr	158.9 (80–240)	nr
		Toupet	24	15/9	51.7 (22.8–75.3)	nr	1.9 ± 0.7	nr	160 (90–340)	nr
Kumagai et al., 2014, Sweden[24]	RCT Double blind	Dor	19	8/11	45 (19–82)	22.9 ± 4.2	nr	1	103 (83–151)	2 (1–12)
		Toupet	22	11/11	44 (20–76)	23.8 ± 3.3	nr	1	95 (83–135)	2 (1–16)
Torres-Villalobos et al., 2018, Mexico[25]	RCT	Dor	38	16/22	40.9 ± 14.3	25.9 ± 5	nr	9	114.9 ± 24.6	2.5 ± 2.5
		Toupet	35	13/22	40.1 ± 15.5	23.4 ± 4.6	nr	7	124.8 ± 25	2.5 ± 2.7

to the Chicago classification, was reported in one study.[25] Two studies reported a previous endoscopic pneumatic dilation in 16.4% of patients (n = 18/110).[24,25] The hospital length of stay was reported in two studies and ranged from 2 to 16 days.[24,25] No deaths were reported. The follow-up was up to 12 months in two studies and up to 24 months in one study. Patients' symptoms were evaluated with the Eckardt score and GERD-HRQL questionnaire in two studies,[24,25] and with the Likert scale in one study.[23] Quality of life was analysed with the Short-Form 36 (SF-36) in one study[23] and with the EORTC QLQ-OES18 in one study.[24] During follow-up, patients were evaluated with 24-h pH study and upper endoscopy in all studies. Esophageal manometry was used in one study[23] and High Resolution Manometry (HRM) was used in another study.[25] Timed barium esophagogram was used in one study.[24] The cost analysis was not reported in any of the included studies.

3.2. Meta-analysis

In addition to a systematic review, we performed a fully Bayesian meta-analysis. A random effect model estimated the pooled RR of postoperative abnormal acid reflux, resulting from 3 studies, which include a total of 111 patients, is 0.98 (95% HPD 0.54–1.80) (Fig. 2a). The prediction lower and upper limits are 0.32 and 3.22, respectively. The heterogeneity is low (I^2 = 16%, 95% HPD 0.0–58%) and τ^2 = 0.11 (Q = 3.237, p = 0.177, 95% HPD 0.01–0.90). The prior sensitivity analysis yield closer results regarding pooled estimates and relative HPD (RR = 1.00, 95% HPD 0.53–1.89). The prediction interval upper limit increase to 5.83. The heterogeneity increase to I^2 = 32.9%. Fig. 2b shows the estimated posterior distribution characteristics.

Considering random effect model, the estimated pooled standardized mean difference of % total time pH $\leq$ 4, resulting from 3 studies, which include a total of 111 patients, is −0.08 (95% HPD −1.04–0.90) (Fig. 3). The prediction lower and upper limits are −1.92 and 1.77, respectively. The heterogeneity is moderate (I^2 = 66%, 95% HPD 0.0–95%) and τ^2 = 0.23 (Q = 10.631, p = 0.005, 95% HPD 0.00–2.26). The prior sensitivity analysis yield wider HPD (SMD = −0.07, 95% HPD −2.42–2.29) and wider prediction interval (−4.79–4.67). The heterogeneity increase to I^2 = 92%.

Using the random effect model the estimated pooled standardized mean difference of DeMeester score, resulting from 2 studies, which include a total of 88 patients, is 0.51 (95% HPD −0.90–1.94) (Fig. 4). The prediction lower and upper limits are −1.91 and 2.94, respectively. The heterogeneity is moderate (I^2 = 69.4%, 95% HPD 0.0–97.7%) and τ^2 = 0.22 (Q = 7.511, p = 0.007, 95% HPD 0.00–4.21). The prior sensitivity analysis yield wider HPD (SMD = 0.51, 95% HPD −3.20–4.19) and wider prediction interval (−6.03–7.02). The heterogeneity increase to I^2 = 97%.

Using the random effect model again, the estimated pooled RR of postoperative dysphagia, resulting from 3 studies, which include a total of 101 patients, is 1.03 (95% HPD 0.51–2.05) (Fig. 5a). The prediction lower and upper limits are 0.32 and 3.31, respectively. The heterogeneity is low (I^2 = 5.6%, 95% HPD 0.0–33.9%) and τ^2 = 0.09 (Q = 1.497, p = 0.469, 95% HPD 0.00–0.79). The prior

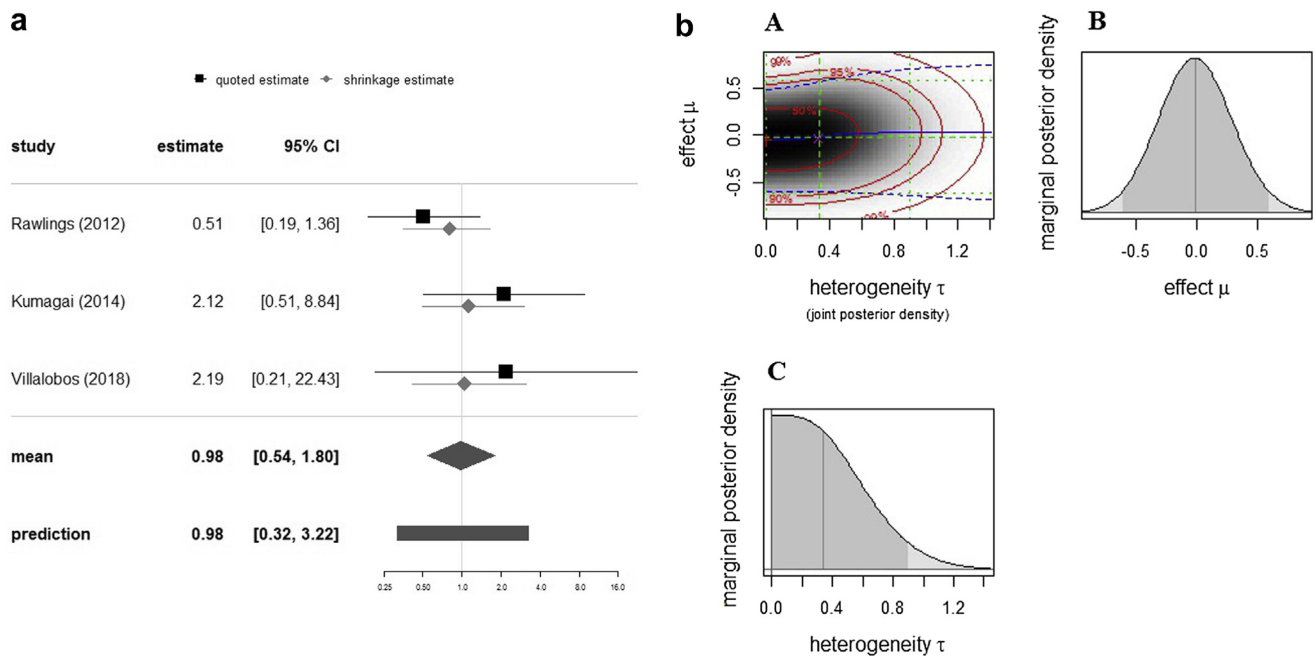

Figure 2 **a**: Forrest plot for abnormal acid exposure. **b**: The A plot illustrates the joint posterior density of heterogeneity τ and effect μ, with darker shading corresponding to higher probability density. The red lines indicate (approximate) 2-dimensional credible regions, and the green lines show marginal posterior medians and 95% credible intervals. The blue lines show the conditional posterior mean effect as a function of the heterogeneity τ along with a 95% interval based on its conditional standard error. The red cross indicates the posterior mode, while the pink cross ($\times$) shows the ML estimate. The B and C plots show the marginal posterior densities of effect μ and heterogeneity τ. 95% credible intervals are indicated with a darker shading, and the posterior median is shown by a vertical line.

sensitivity analysis yield closer results regarding pooled estimates and relative HPD (RR = 1.03, 95% HPD 0.51–2.07). The prediction interval upper limit increase to 6.15. The heterogeneity increase to $I^2 = 14\%$. Fig. 5b shows the estimated posterior distribution characteristics.

Considering random effect model, the estimated pooled standardized mean difference of operative time, resulting from 3 studies, which include a total of 174 patients, is 0.02 (95% HPD −0.53–0.52). The prediction lower and upper limits are −0.96 and 0.92, respectively. The heterogeneity is moderate ($I^2 = 32\%$, 95% HPD 0.0–89%) and $\tau^2 = 0.03$ (Q = 5.009, p = 0.096, 95% HPD 0.00–0.62). The prior sensitivity analysis yield wider HPD (SMD = −0.01, 95% HPD −1.78–1.69) and wider prediction interval (−3.52–3.43). The heterogeneity increase to $I^2 = 85.7\%$.

Using a random effect model, the estimated pooled RR of esophageal perforation, resulting from 3 studies, which include a total of 174 patients, is 1.05 (95% HPD 0.52–2.10). The prediction lower and upper limits are 0.33 and 3.33, respectively. The heterogeneity is low ($I^2 = 4.5\%$, 95% HPD 0.0–29.2%) and $\tau^2 = 0.08$ (Q = 0.836, p = 0.658, 95% HPD 0.00–0.78). The prior sensitivity analysis yield closer results regarding pooled estimates and relative HPD (RR = 1.04, 95% HPD 0.51–2.11). The prediction interval upper limit increase to 5.99. The heterogeneity increase to $I^2 = 11\%$.

Finally, using a random effect model, the estimated pooled standardized mean difference of postoperative basal LES pressure, resulting from 2 studies, which include a total of 88 patients, is 0.26 (95% HPD −0.40–0.92). The prediction lower and upper limits are −0.75 and 1.27, respectively. The heterogeneity is low ($I^2 = 17.4\%$, 95% HPD 0.0–88.3%) and $\tau^2 = 0.02$ (Q = 1.193, p = 0.278, 95% HPD 0.00–0.70). The prior sensitivity analysis yield wider HPD (SMD = 0.26, 95% HPD −2.88–3.39) and wider prediction interval (−5.26–5.77). The heterogeneity increase to $I^2 = 92\%$. The leave-one-out sensitivity analysis show the robustness of all results.

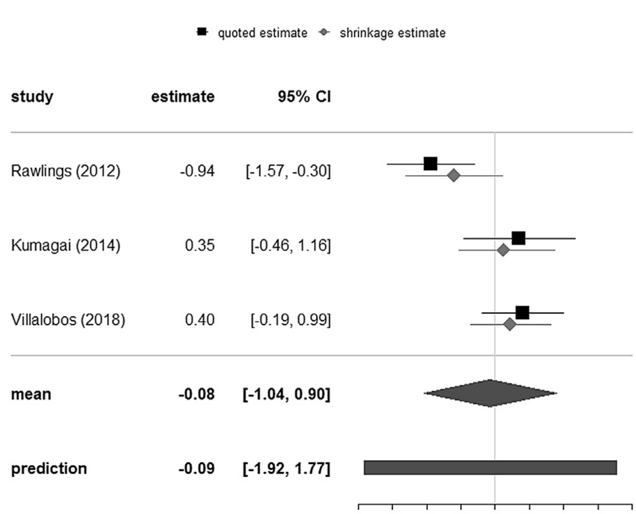

Figure 3 Forrest plot for % total time pH $\leq$ 4.

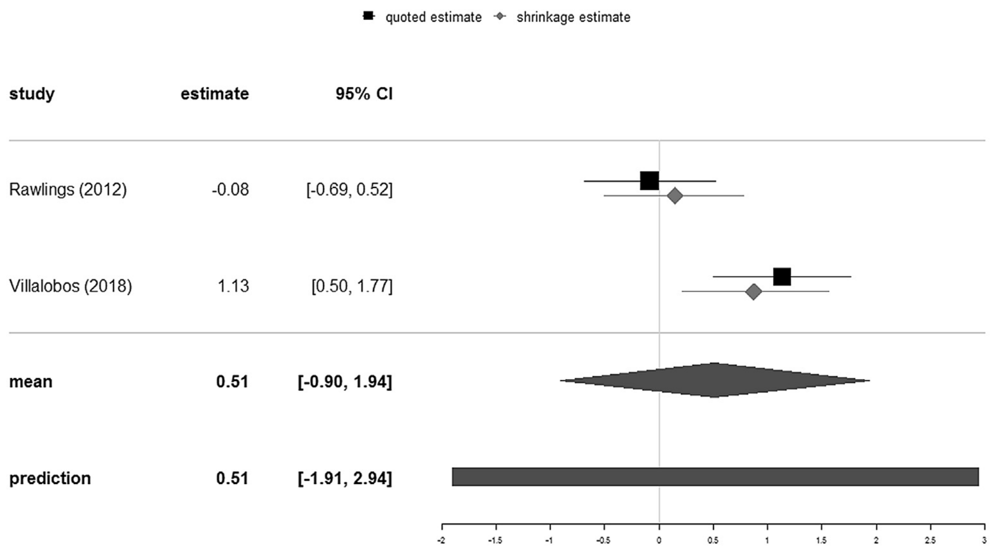

Figure 4 Forrest plot for DeMeester score.

4. Discussion

The present systematic review and meta-analysis found that Dor and Toupet fundoplication seem comparable in term of postoperative abnormal acid exposure, % total time pH $\leq$ 4, and DeMeester score. In addition, no differences were found comparing postoperative dysphagia, operative time, esophageal perforation, and basal LES pressure. It should be noted, however, that outcomes were compared in the short-term follow-up.

A pathologic GERD may develop in up to 50% of LHM patients because the division of esophageal and gastric muscular fibers. For this reason, an antireflux procedure should be added concomitantly.[5] It has been show that the utilisation of a Nissen fundoplication may be associated with significant postoperative dysphagia and regurgitation rates in patients with primary esophageal motility disorders.[7,8] Therefore, the choice of a partial fundoplication (posterior or anterior) should be recommended.[26] Literature data are contrasting and to date, no clear consensus and evidence exist on the type of partial fundoplication and the choice is left to surgeon preference.[27] Up to our knowledge, there have been several retrospective studies but only three RCT comparing Dor vs Toupet fundoplication objectively looking at postoperative esophageal abnormal acid exposure and dysphagia. Rawlings et al. randomized 60 patients between Dor and Toupet fundoplication. The 24-h pH study revealed a higher abnormal acid reflux in patients treated with Dor fundoplication (41.7% vs. 21.1%, p = 0.152).[23] Kumagai et al. reported a lower abnormal acid reflux exposure in patients that underwent Dor fundoplication (18% vs. 38.4%, p = 0.386).[24] Villalobos et al, reported a statistically significant lower abnormal acid exposure in patients that underwent Dor fundoplication at 6 months follow-up (6.9% vs. 34%, p = 0.01). However, no differences were found at 12 and 24 months follow-up (p = 0.472 and p = 0.111, respectively).[25] A recent meta-regression concluded that both Dor and Toupet fundoplication equally control GERD.[28] Our results are in accordance with these studies and the estimated RR of postoperative abnormal acid reflux was 0.98 (95% HPD 0.54—1.80). Notably, the heterogeneity was low (I^2 = 16%) and the sensitivity analysis confirmed the robustness of the results despite the *a priori* assumptions.

It has been reported a comparable (up to 90%) postoperative dysphagia resolution in both procedures.[29] Villalobos et al. colleagues reported a better symptoms control and dysphagia resolution after Dor fundoplication.[25] In contrast, Kumagai et al described better postoperative timed barium esophageal empting and functional scale score in patients that underwent Toupet fundoplication.[24] Similarly, Kurian et al. reported higher odds for recurrent dysphagia in patients with anterior fundoplication.[28] Rawlings et al described no significant differences in any esophageal postoperative symptoms comparing anterior and posterior fundoplication.[23] In our meta-analysis, no differences were found and the estimated RR of postoperative dysphagia was similar (RR: 1.03; 95% HPD 0.51—2.05) with a related low heterogeneity (I^2 = 5.6%).

It has been reported that both Dor and Toupet are comparable in term of safety.[30] In the present study, no statistically significant differences were found in term of esophageal perforation and operative time. These results should be interpreted carefully because all the operations were performed by expert surgeons in referral centers for esophageal disease and may not be generalized to small community hospital.[31] In addition, the estimated pooled standardized mean difference of postoperative basal LES pressure was comparable in the two patients' group. This is probably related to the completeness of the myotomy rather than the type of fundoplication.[32,33]

Technically the Dor fundoplication is a more standardized procedure, is easier to perform, and allows a limited posterior crural dissection.[34] The preservation of the posterior attachments of the phrenoesophageal membrane has been advocated to be potentially helpful in the prevention of GERD. In addition, the anterior wrap allows the covering of the exposed esophageal mucosa, acting as a tissue reinforcement flap and may prevent the development of a pseudodiverticula.[35] On the other hand, the Toupet

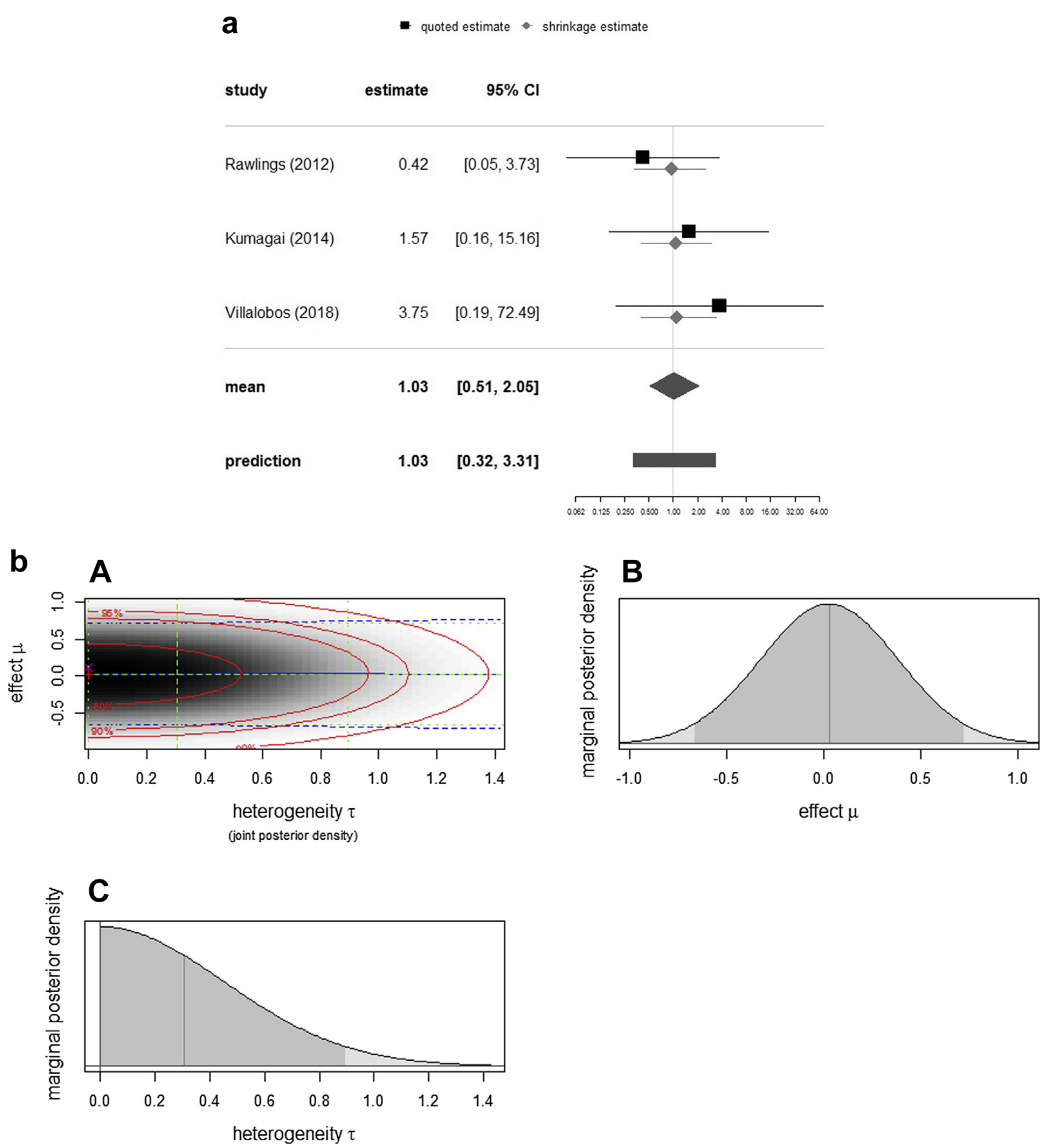

Figure 5 **a**: Forrest plot for postoperative dysphagia. **b**: The A plot illustrates the joint posterior density of heterogeneity τ and effect μ, with darker shading corresponding to higher probability density. The red lines indicate (approximate) 2-dimensional credible regions, and the green lines show marginal posterior medians and 95% credible intervals. The blue lines show the conditional posterior mean effect as a function of the heterogeneity τ along with a 95% interval based on its conditional standard error. The red cross indicates the posterior mode, while the pink cross ($\times$) shows the ML estimate. The B and C plots show the marginal posterior densities of effect μ and heterogeneity τ. 95% credible intervals are indicated with a darker shading, and the posterior median is shown by a vertical line.

fundoplication is less standardized and technically demanding because the circumferential esophageal mobilization and inferior mediastinal dissection.[28]

To the best of our knowledge, this is the first meta-analysis based on RCT that objectively compares outcomes after LHM and partial fundoplication. We do acknowledge that the included studies, even if RCT, are heterogeneous in patient demographics, characteristics, and operative techniques. The limited data on achalasia subtype, the small sample size, and the short-term follow-up represent additional limitations. Small sample size studies may be associated with inflated estimates of effect size and possible higher heterogeneity.[36] The point estimate I^2 should be interpreted cautiously when a meta-analysis has few studies and, for this reason, we reported HPD intervals.[37] Publication bias could not be completely excluded and investigated because the limited number of included studies. In addition, the three RCTs were underpowered with a limited methodological quality and moderate risk of bias. However, it should be noted that it is difficult to conduct large trials in such rare disease and that only short-term follow data are currently available in the context of RCT. Moreover, formal and objective follow-up with 24-h pH study and esophageal manometry in voluntary well-being patients is challenging. Finally, the study was planned in agreements with PRISMA guidelines, and followed a sound methodology that was *a priori* stated in the PROSPERO protocol. The selection criteria led to a homogenous population for some of the primary outcomes, as confirmed by low heterogeneity. This makes us confident that the results of our study are robust but should be interpreted and analysed with caution. Further well-designed multicentre studies focused on objective outcomes comparison in the long-term follow-up are warranted.

In conclusion, Dor and Toupet fundoplication after laparoscopic Heller myotomy seem comparable in term of postoperative abnormal acid exposure and dysphagia in the short-term follow-up. The choice of the partial fundoplication should be left to surgeon experience other than multidisciplinary evaluated and patient-tailored.

Informed consent

Not applicable.

Institutional review board

Not required.

Author contribution

AA, ST, and ER did the literature search. AA and DB formed the study design. Data collection done by AA, ST, ER, and MC. AA and GB analysed the data. AA, GB, and DB interpreted the data. AA and DB wrote the manuscript. AA, GM, GC, and DB critically reviewed the manuscript.

Conflicts of interest

Drs. Alberto Aiolfi, Stefania Tornese, Marta Cavalli, Gianluca Bonitta, Emanuele Rausa, Giancarlo Micheletto, Giampiero Campanelli, and Davide Bona have no conflicts of interest or financial ties to disclose.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.asjsur.2019.03.019.

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