Fundoplication to preserve allograft function after lung transplant: Systematic review and meta-analysis

Joseph R. Davidson, MBBS, MRCS,[a,b] Danielle Franklin, MBBS,[c] Sacheen Kumar, PhD, FRCS,[d] Borzoueh Mohammadi, MBBS, FRCS,[c] Khaled Dawas, MD, FRCS,[c] Simon Eaton, PhD,[a] Joe Curry, MBBS, FRCS,[b] Paolo De Coppi, PhD, FRCS,[a,b] and Nima Abbassi-Ghadi, PhD, FRCS[e]

ABSTRACT

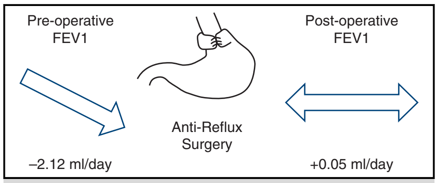
Background: ARS has been adopted in select patients with lung transplant for the past 2 decades in many centers. Outcomes have been reported sporadically. No pooled analysis of retrospective series has been performed.

Objective: This review and pooled analysis sought to demonstrate objective evidence of improved graft function in lung transplant patients undergoing antireflux surgery (ARS).

Methods: In accordance with Meta-analyses of Observational Studies in Epidemiology guidelines, a search of PubMed Central, Medline, Google Scholar, and Cochrane Library databases was performed. Articles documenting spirometry data pre- and post-ARS were reviewed and a random-effects model meta-analysis was performed on forced expiratory volume in 1 second (FEV1) values and the rate of change of FEV1.

Results: Six articles were included in the meta-analysis. Regarding FEV1 before and after ARS, we observed a small increase in FEV1 values in studies reporting raw values (2.02 ± 0.89 L/1 sec vs 2.14 ± 0.77 L/1 sec; n = 154) and % of predicted ($77.1\% \pm 22.1\%$ vs $81.2\% \pm 26.95\%$; n = 45), with a small pooled Cohen *d* effect size of 0.159 ($P = .114$). When considering the rate of change of FEV1 we observed a significant difference in pre-ARS compared with post-ARS (-2.12 ± 2.76 mL/day vs $+0.05 \pm 1.19$ mL/day; n = 103). There was a pooled effect size of 1.702 ($P = .013$), a large effect of ARS on the rate of change of FEV1 values.

Conclusions: This meta-analysis of retrospective observational studies demonstrates that ARS might benefit patients with declining FEV1, by examining the rate of change of FEV1 during the pre- and postoperative periods. (J Thorac Cardiovasc Surg 2020;160:858-66)



Declining rate of change of FEV1 improves after antireflux surgery.

CENTRAL MESSAGE

In this meta-analysis of patients with lung transplant undergoing antireflux surgery (ARS), the decline observed in rate of change of the FEV1 can be shown to plateau, which may be indicative of a reduction of the influence of BOS.

PERSPECTIVE

There is limited evidence behind antireflux surgery (ARS) in lung-transplant patient populations; however, gastroesophageal reflux is believed to be a main driver of bronchiolitis obliterans syndrome. Within this meta-analysis, we demonstrate declining FEV1 plateaus following ARS. The rate of change of FEV1 (milliliters per day) is a core outcome that may strengthen the evidence base for ARS.

See Commentaries on pages 867, 868, and 869.

THOR

From the [a]Stem Cells and Regenerative Medicine Section, University College London–Great Ormond Street Institute of Child Health, London, United Kingdom; [b]Department of Pediatric Surgery, Great Ormond Street Hospital for Children, London, United Kingdom; [c]Department of Oesophagogastric Surgery, University College London Hospital, London, United Kingdom; [d]Department of Academic Surgery, The Royal Marsden Hospital, London, United Kingdom; and [e]Department of Oesophagogastric Surgery, Royal Surrey County Hospital, Guildford, United Kingdom.

All research at Great Ormond Street Hospital National Health Service Foundation Trust and UCL Great Ormond Street Institute of Child Health is made possible by the National Institute for Health Research Great Ormond Street Hospital Biomedical Research Centre. The views expressed are those of the author(s) and not necessarily those of the UK National Health Service, the UK National Institute for Health Research or the UK Department of Health.

Received for publication June 25, 2019; revisions received Oct 8, 2019; accepted for publication Oct 25, 2019; available ahead of print Nov 24, 2019.

Address for reprints: Joseph R. Davidson, MBBS, MRCS, Stem Cells and Regenerative Medicine Section, University College London–Great Ormond Street Institute of Child Health, Great Ormond St, London WC1N 3JH, United Kingdom (E-mail: joseph.davidson@doctors.org.uk).

0022-5223/$36.00

https://doi.org/10.1016/j.jtcvs.2019.10.185

Abbreviations and Acronyms

ARS	= antireflux surgery
BOS	= bronchiolitis obliterans syndrome
FEV1	= forced expiratory volume in 1 second
GERD	= gastroesophageal reflux disease
ROC	= rate of change

Scanning this QR code will take you to the article title page to access supplementary information.

In the transplanted lung, the development and progression of bronchiolitis obliterans syndrome (BOS) is widely regarded as the principle threat to long-term graft function. Alongside allograft rejection and infection, gastroesophageal reflux disease (GERD) is widely acknowledged to feature heavily in the fibrotic process that drives BOS.[1] Patients with GERD are recognized to be at a much higher risk of acute rejection following lung transplantation.[2-4] GERD has also been objectively and prospectively measured in postlung transplant populations and demonstrated to have an incidence of more than 50%.[5]

The purported mechanisms behind the observed high incidence of GERD in patients post-lung transplantation are complex and likely multifactorial, with injury to the vagus nerve,[6] delayed gastric emptying, and side effects of medication all implicated.[7] Furthermore, a transplanted lung has increased risk of aspiration and aspiration-related lung injury; the reduced sensation in the airway means there is no afferent limb of the cough reflex, which is believed to continue for months to years after the transplantation.[6] Microaspiration and asymptomatic reflux affects a considerable proportion of lung-transplant recipients, which highlights the often-insidious nature of GERD-related BOS.[1,8] Additionally, the presence of delayed gastric emptying is an independent risk factor, alongside GERD, for chronic lung allograft dysfunction.

Although there is recent evidence to suggest that medical management of acid reflux has benefits within lung transplant populations,[9] there has also been a further benefit purported for antireflux surgery (ARS; Video 1) in this context[10,11]; specifically, molecular analysis of bronchial epithelium demonstrates a marked inflammatory response in patients with reflux on medication alone.[12] Surgical management of reflux is now recognized to be safe and effective in lung-transplant populations and many studies have demonstrated good outcomes,[13-23] including in patients with end-stage lung disease before transplantation.[24] However, the level of evidence to support ARS is low, work needs to be done to define the optimal timing for intervention,[25] and there is an understandable reluctance to submit this group of complex patients to a randomized controlled trial.[26]

It is difficult to measure the extent and progression of disease using imaging or trans-bronchial biopsy techniques; therefore, most clinicians use the surrogate of forced expiratory volume in 1 second (FEV1). FEV1 can be affected by several factors within the early posttransplant period, including lifestyle changes, pulmonary rehabilitation, infection, and acute rejection; however, it is recognized to have a strong correlation with both onset and progression of BOS. In this systematic review and meta-analysis, we sought to demonstrate the effect of ARS on pre- and postoperative FEV1 values within lung transplant populations.

METHODS

An electronic search was carried out of PubMed Central, Medline, Google Scholar, and Cochrane Library databases in addition to manual searching of references of selected articles. Only studies of adult patients, published in the English language between January 1970 and January 2017 were included. We included only studies where ARS was performed after lung transplant and where FEV1 was documented during the pre- and postoperative periods. We excluded case reports and series of fewer than 15 patients to reduce the confounding effect of a learning curve. We excluded published abstracts and unpublished studies. If data were part presented or insufficient, but the study were deemed to be otherwise includable within the analysis, we attempted to contact corresponding authors by e-mail to gain the necessary data for inclusion. All studies were assessed for quality utilizing the National Heart, Lung, and Blood Institute Study Quality Assessment.[27] Two authors (JD and DF) performed the literature search and quality assessment. Two authors (JD and SE) performed the data analysis.

We extracted, from each included article, the number of patients, the indication for ARS, the mean FEV1 values before and after ARS surgery with associated standard deviations, noting the timing of these measurements relative to the surgery. Where data were presented with median and interquartile range, an assumption was used to allow comparative analysis and quantitative synthesis using approximated mean and standard deviation values:[28]

$$med \approx \bar{x}, \; IQR/1.35 \approx \sigma$$

Where possible we used the presented figure of the rate of change (ROC) of FEV1 in the pre- and postoperative windows following the mixed linear model described by Fisher and colleagues in 2005,[29] an estimation of this was performed based on presented serial data if ROC itself was not described and ROC was displayed in milliliters per day. Data are presented as a mean ± standard deviation throughout this article, unless otherwise noted. Studies were assessed independently for reporting bias and quality by 2 observers and this was factored in to the outcome reporting of the pooled analysis.

Pooled analyses were performed in groups of similarly reported data of raw FEV1 values (in liters), FEV1 values as a percentage of predicted, and ROC. Values in ROC analysis were converted to milliliters per day. In pooled analyses, a 2-way t test was performed using pooled and weighted mean and variance values using GraphPad (https://www.graphpad.com/quickcalcs/contMenu/). For meta-analysis we used open

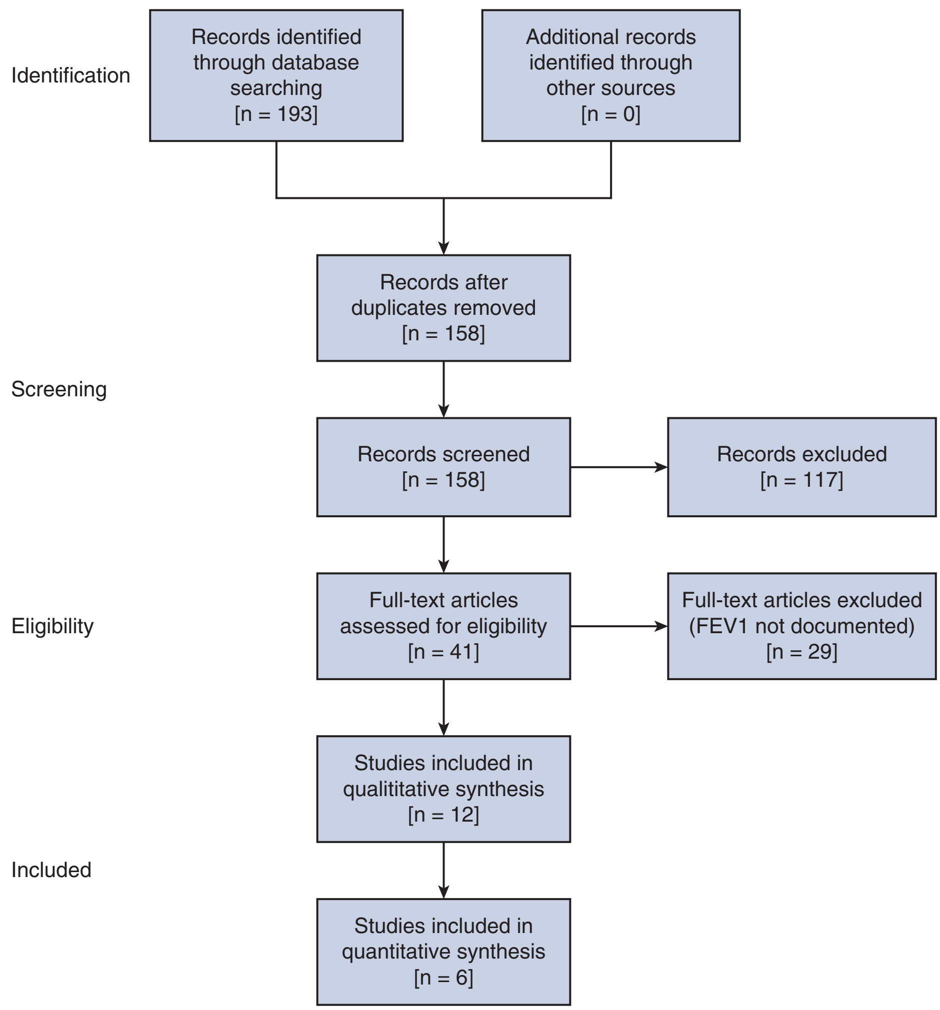


FIGURE 1. Flowchart of article screening and inclusion in accordance with Meta-analysis Of Observational Studies in Epidemiology guidelines. One hundred ninety-three studies were identified in the initial search, after exclusions, 41 were assessed for eligibility. Twelve studies reported spirometry sufficiently to be included within the qualitative synthesis, 6 studies provided adequate data to be compared in the meta-analysis. *FEV1*, Forced expiratory volume in 1 second.

source software OpenMetaAnalyst (Evidence Based Medicine, Brown Univsersity, Providence, RI), an open source package using the back-end statistical engine of R (R Foundation for Statistical Computing, Vienna, Austria).[30,31] To present data for FEV1 consistently, regardless of mode of presentation of the variable, we converted data to demonstrate an effect size, Cohen *d*, calculated with Hedges and Olkin bias-corrected method and presented with 95% confidence intervals.[32] This measurement would demonstrate the size of an effect of an intervention on a study cohort, with a value of $d = 0.2$ representing a small effect, $d = 0.5$ a medium effect, and $d > 0.8$ a large effect. The effect size allows for an estimation of clinical relevance as well as denoting statistical significance. The data for effect size was represented graphically using Forest plots accompanied with a calculated heterogeneity statistic (I^2).

RESULTS

The Meta-analysis of Observational Studies in Epidemiology guidelines for meta-analysis of observational studies were followed, the flowchart is shown in Figure 1. We identified 12 published articles documenting spirometry after ARS in a postlung transplant population. In all studies, measuring spirometry in patients was a secondary outcome measure and reporting was variable in terms of documented frequency and timing of measurements. All studies were rated as "Good" or "Fair" by 2 independent assessors (JD and DF). Six studies were excluded from the pooled analysis as data was insufficient, 4 due to a lack of pre- or postop FEV1 presented in the published article, 1 did not present data of sufficient quality (lacking standard deviation or range from which to perform statistical analysis), 1 performed ARS only in pretransplant patients. All corresponding authors of these 6 excluded were contacted to gain adequate study data for inclusion within the analysis, none responded. These studies were unable to be used for comparison of pre- and post-ARS FEV1 values and therefore were used only in formulation of the discussion of this article along with the remaining 29

TABLE 1. Studies included in the meta-analysis. Preoperative (pre-op) evaluation of patients commonly included pH probe testing alongside pre-op bronchoscopy

Study	Type of study	N	Indication for ARS in study (any of)*	Technique†	Pre-op work up of GERD
Abbassi-Ghadi and colleagues,[13] 2013	Retrospective cohort	38	Histologic evidence of gastroesophageal reflux aspiration Positive result on an impedance study with a consistent decline/fluctuating FEV Symptomatic reflux	Nissen (all)	Bronchoscopy ± biopsy pH-impedance
Burton and colleagues,[16] 2009	Retrospective cohort	21	Deteriorating lung function, suspected reflux Symptomatic reflux	16 Toupet 5 Nissen + G tube (2)	Bronchoscopy ± biopsy Endoscopy pH probe, DeMeester
Robertson and colleagues,[15] 2012	Prospective cohort	16	Symptomatic reflux refractory to medical management Reflux with deteriorating lung function Asymptomatic reflux with concerns regarding microaspiration	Nissen (all)	Bronchoscopy ± biopsy Manometry pH-impedance, DeMeester, RSI, GIQLI
Pegna and colleagues,[14] 2014	Retrospective cohort	57	Symptomatic reflux refractory to medical management Atypical reflux symptoms	Nissen (all)	Bronchoscopy ± biopsy pH probe Endoscopy
Davis and colleagues,[18] 2003	Retrospective cohort	43	Symptomatic reflux Aspiration Retransplant	39 Nissen/4 Toupet (adhesions) G/GJ tubes (3) Pyloroplasty (6)	Bronchoscopy ± biopsy pH probe Contrast swallow Manometry
Hoppo and colleagues,[17] 2011	Retrospective cohort	22	Symptomatic reflux Asymptomatic reflux	Nissen/Dor (numbers unclear)	Endoscopy, barium manometry, pH probe impedance

ARS, Antireflux surgery; *GERD*, gastroesophageal reflux disease; *FEV*, forced expiratory volume; *RSI*, reflux symptom index; *GIQLI*, Gastrointestinal Quality of Life Index; *G*, gastrostomy; *GJ*, gastrojejunostomy. *Indications for surgery always included symptomatic reflux and in some centers included deteriorating lung function and suspected reflux, as well cases of redo transplant. †Most centers employed a 360° posterior wrap (Nissen); however 270° posterior (Toupet) and 180° anterior (Dor) were also performed in selected cases.

articles reviewed in full, some of which were not pertaining to lung transplant in adults.

The 6 articles included in the quantitative synthesis are summarized in Tables 1 and 2 and the analysis of the data is displayed in Table 3. All series included were from different centers so were known not to included duplicate patient data. Study groups differed in their indications for ARS with all using symptomatic reflux, but some using asymptomatic or simply declining FEV1 with a suspicion of GERD. One study performed ARS routinely in cases of repeat transplant. We observed a small increase when pooling those studies reporting FEV1 values (n = 154; 2.02 ± 0.89 L/1 sec vs 2.14 ± 0.77 L/1 sec; $P = .2$ and, in those reporting as % predicted (n = 45; 77.1% ± 22.1% vs 81.2% ± 26.95%; $P = .4$ with a small Cohen *d* of 0.159 (–0.038 to 0.356; $P = .114$). There was no evidence for heterogeneity of the effect of ARS on FEV1 between the studies (I^2, 0%; $P = .4$) (Figure 2).

Considering the ROC of FEV1 that was calculated for 103 patients within the meta-analysis in 3 different studies, we observed a significant change, demonstrating a declining FEV1 in across the combined cohort of patients before ARS: –2.12 ± 2.76 mL/day compared with the same population post-ARS: 0.05 ± 1.19 mL/day ($P < .0001$). Meta-analysis of effect size demonstrated a Cohen *d* of 1.702 (95% confidence interval, 0.364-3.039; $P = .013$), a large effect of ARS on the ROC of FEV1.[33] Although all 3 studies individually had large effect sizes, there was evidence for significant heterogeneity (I^2, 92.7%; $P < .001$) (Figure 3).

DISCUSSION

This meta-analysis demonstrates an improvement in absolute and relative FEV1 values in posttransplant patients and a significant difference in pooled analysis of ROC data; demonstrating a reversal of the deteriorating FEV1 values in patients who have received ARS after lung transplant. Before this study there were no data outside of single-center series to guide the decision-making process, in Figure 4 we summarize this and demonstrate the key finding that there is a statistically and clinically significant improvement in the ROC of FEV1 following ARS.

THOR

TABLE 2. Timing of surgery, reporting of spirometry, and postoperative (post-op) follow-up in each study

Study	Post-op evaluation of GERD	Timing of ARS relative to LTx*	FEV1 pre-ARS	FEV1 post-ARS	Rate of change data
Abbassi-Ghadi and colleagues[13] 2013	Routine follow-up (subjective)	1365 ± 1381 d (range, 195-6406 d)	Mean value of the 3 readings preceding ARS (3 monthly)	Mean value of 3 most recent clinic visits (3 monthly)	Presented for all patients Calculated using trend line gradients over all pre-ARS readings (period = 815 ± 1021 [range, 29-4358]), and all post-ARS readings (period = 477 ± 474 [range, 31-1758])
Burton and colleagues[16] 2009	Reflux score (Carlsson)	Mean 768 d (range, 145-1524 d)	6 mo pre-op	6 mo post-op	No rate of change data
Robertson and colleagues[15] 2012	DeMeester RSI, GIQLI	Mean 1053 ± 881 d	Single pre-op reading; timing not stated	Single most recent value	Rate of change data presented: all pre-ARS FEV1 and all post-ARS FEV1 (period 1053 d ± 881) and (476 ± 180), respectively
Pegna and colleagues[14] 2014	pH probe (26 out of 57)	Data not presented	Single value 3 mo pre-op	Single value 3 mo post-op Rate of change over mean 3.2 y (no standard deviation or range)	Calculated from graph Pre-op at 6, 3, and immediate pre-op value Post of at 3, 6, 9, 12, and 18 months post-op
Davis and colleagues[18] 2003	Routine follow-up (subjective)	Data not presented	Best single post-LTx value	Single most recent value (at least 6 mo post-ARS)	No rate of change data
Hoppo and colleagues[17] 2011	Routine follow-up (subjective)	31 ± 24 mo	Immediate pre-op	Single most recent value	Rate of change as line graph – no units or scale draw.

GERD, Gastroesophageal reflux disease; *ARS*, antireflux surgery; LTx, lung transplant; *FEV1*, forced expiratory volume in 1 second; *RSI*, reflux symptom index; *GIQLI*, Gastrointestinal Quality of Life Index. *The timing of ARS was variable, tending to take place 2 to 3 years after the lung transplant LTx. The reported spirometry data before and following surgery also varied in the measurements taken.

Within the qualitative synthesis of 12 articles, containing series from high-volume lung transplant centers across the United States, United Kingdom, and Australia, we identified studies reporting benefits of ARS over medical management of GERD on the FEV1 values in posttransplant populations, albeit acknowledgments are made that

TABLE 3. Data for forced expiratory volume in 1 second (FEV1) in patients before and after antireflux surgery (ARS)

Study	n	FEV1 (L)		FEV1 (%)		RoC FEV1 (mL/d)	
		Pre-ARS	Post-ARS	Pre-ARS	Post-ARS	Pre-ARS	Post-ARS
Abbassi-Ghadi and colleagues,[13] 2013	38	2.12 ± 0.89	1.97 ± 1.03	–	–	–1.97 ± 1.03	–0.41 ± 1.77
Burton and colleagues,[16] 2009	23	–	–	72.9 ± 20.9	70.4 ± 26.8	–	–
Robertson and colleagues,[15] 2012	16	2.4 ± 0.97	2.4 ± 0.71	–	–	–3.18 ± 2.87*	+0.31 ± 0.87*
Pegna and colleagues,[14] 2014	57	1.95 ± 0.80	2.13 ± 0.37	–	–	–1.81 ± 0.83	+0.33 ± 0.60
Davis and colleagues,[18] 2003	43	1.87 ± 0.98	2.19 ± 0.92	–	–	–	–
Hoppo and colleagues,[17] 2011	22	–	–	81.5 ± 23.3	92.5 ± 27.1	–	–
Overall		2.02 ± 0.89 N = 154	2.14 ± 0.77 *P* = NS	77.1 ± 22.1 N = 45	81.2 ± 26.95 *P* = NS	–2.12 ± 2.76 N = 103	+0.05 ± 1.19 ***P* < .0001**

Values were converted to milliliters per day and are presented as mean ± standard deviation. Student *t* test of before or after ARS showed no difference in either studies reporting raw data or %-predicted; however, the gradients of the rate of change data were significantly different with a decline observed preoperatively and a plateau post-ARS (–2.12 mL/day vs 0.05 mL/day; $P < .0001$). Bold indicates pooled result from the row above. *FEV1*, Forced expiratory volume in 1 second; *ROC*, rate of change; *ARS*, antireflux surgery; *NS*, not significant. *ROC data only available for 8 patients in the study.

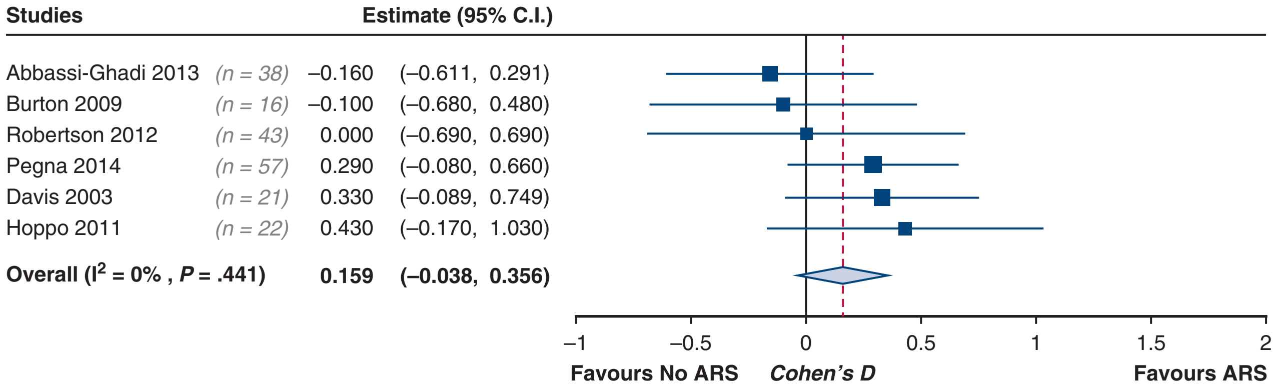


FIGURE 2. Forest plot demonstrating pre- and postoperative forced expiratory volume in 1 second (FEV1) related to antireflux surgery (*ARS*), Cohen *d* effect size is plotted to allow comparison of studies reporting in liters per 1 second and as % predicted. Effect size demonstrates a small effect that did not reach statistical significance (*d*, 0.159; 95% confidence interval [*CI*], –0.038 to 0.356; $P = .114$).

THOR

these 2 populations are not equivalent in terms of the severity of their reflux disease.[4] ARS appears to resolve subjective symptoms of GERD in all studies that explored this as an outcome measure.[16–19,32,34] Only 2 studies performed objective assessment of GERD in half of their post-ARS populations.[14,15] Reluctance among clinicians and third-party payer organizations to subject asymptomatic individuals to invasive tests was mentioned in several articles.[4,13] Where measured, improvements in the inflammatory infiltrate within bronchial lavage samples were also noted.[19,20,35]

Many centers, including the institutions of the authors, have adopted fundoplication surgery as a standard of care into the regional lung transplantation program.[36] However, a recent international guideline from the Bronchiolitis Obliterans Syndrome Task Force formed out of the International Society for Heart & Lung Transplant, the American Thoracic Society, and the European Respiratory Society, recognizes that the current level of evidence to support fundoplication is poor—consisting of single-center retrospective cohort studies and case series.[25] This pooled analysis seems to demonstrate that an objective benefit of ARS can be quantified by measuring the ROC of the FEV1. The use of the FEV1 measurement is an accepted surrogate for BOS, with deterioration in the spirometry accepted to correlate closely with a progression of the disease. The majority group of patients underwent ARS outside of the first year posttransplant, and as such wide intraindividual variability in FEV1 is less likely to have influenced the values obtained when using moving averages, as has been done in the studies included.

As a review and pooled analysis of retrospective cohort studies, there are factors inherent to the included studies and the analysis methodology that limit the strength of evidence that can be provided here. Reporting bias, for example that studies in which ARS is unsuccessful in preventing FEV1 decline are less likely to be published, is a potential problem. In a meta-analysis of randomized controlled trials, reporting bias is usually analyzed by means of a funnel plot. However, this is not feasible here given the small number of studies and number of subjects described in each study.

All articles quoted their pre-ARS spirometry values as the most recent result preceding surgery; however, the timing of this was not clearly defined in all articles. Similarly, the most recent FEV1 value taken in follow-up was used as a comparative value. However, follow-up periods within and between these retrospective studies

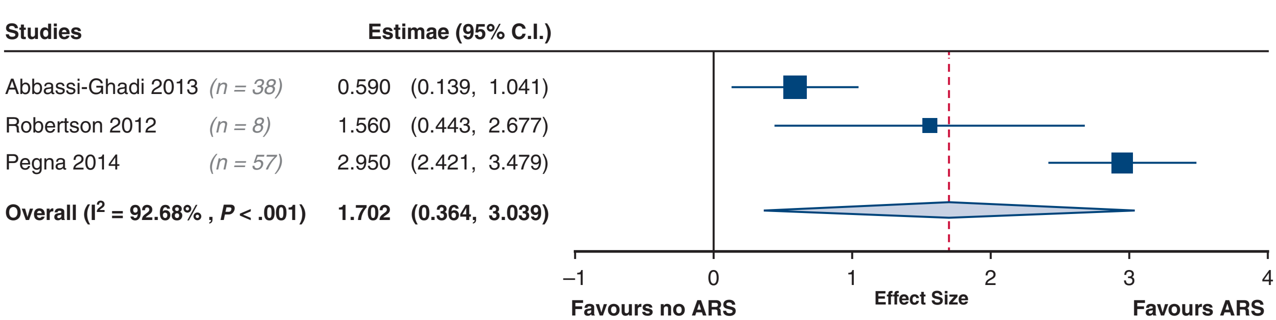


FIGURE 3. Forest plot demonstrating the effect of antireflux surgery (*ARS*) on the rate of change of forced expiratory volume in 1 second (FEV1). The effect size demonstrates a large effect that was statistically significant (*d*, 1.702; 95% confidence interval [*CI*], 0.364-3.039; $P = .013$).

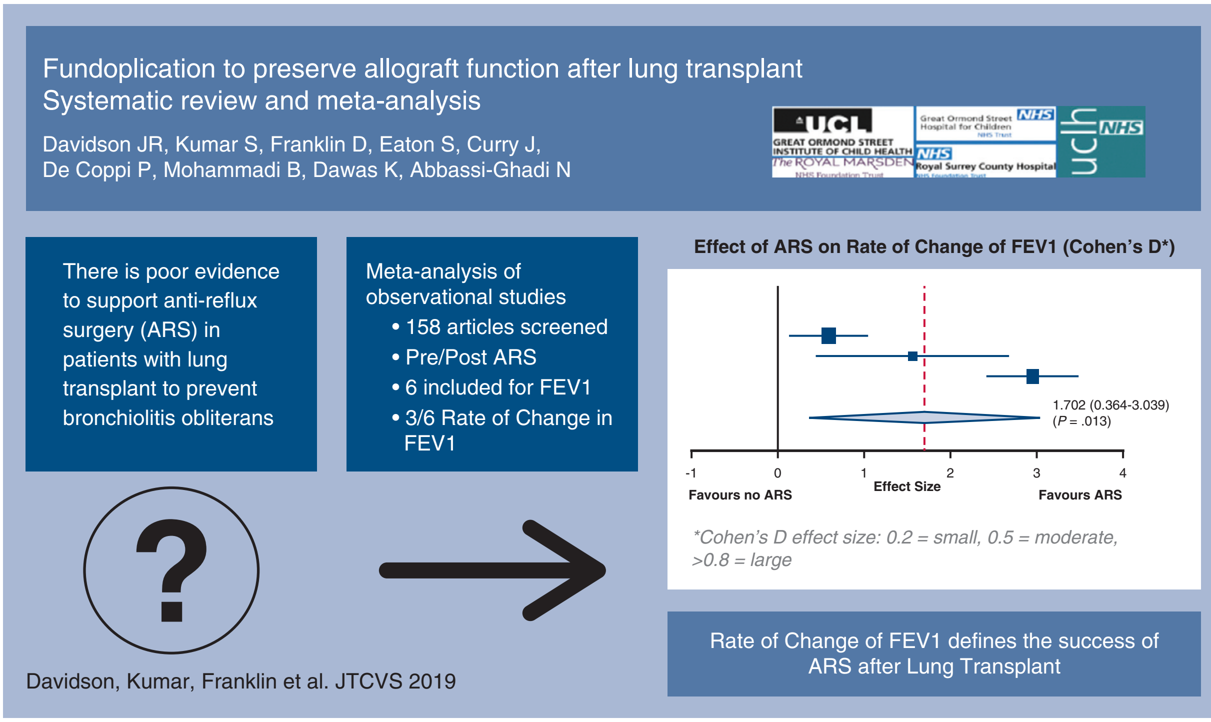


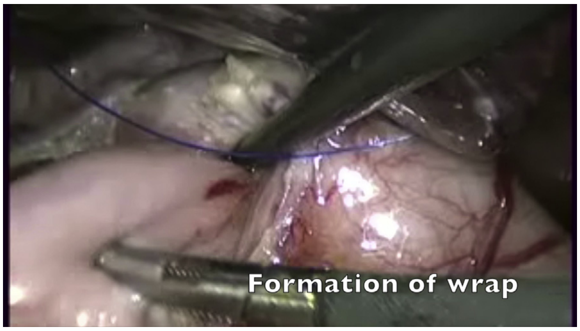
FIGURE 4. The key finding of the meta-analysis is demonstrated in this graphical abstract; after antireflux surgery (*ARS*) there is a significant effect noted within the data on the rate of change of the forced expiratory volume in 1 second (*FEV1*) where a generally declining FEV1 appears to stabilize. This has been assessed using Cohen *d* effect size (*d*, 1.702; 95% confidence interval [CI], 0.364-3.039; $P = .013$).

were not consistent. Patients with incomplete follow-up were excluded from the figures derived from each study; as such, mortality is not factored into this analysis and because cause of death may be related to progressive failure of the lung allograft, there is a risk of overemphasizing the benefits to the population when data are drawn only from survivors. All centers were similar in performing ARS in clinical GERD or persistently declining FEV1 in the absence of symptoms, with varying amounts of preoperative workup in the form of pH-testing and manometry as well as subjective, questionnaire-based scoring. Furthermore, those studies where serial FEV1 measurements were taken were not always those with deteriorating lung function, and this is reflected in the high degree of heterogeneity demonstrated in Figure 3. In Robertson and colleagues[15] only those patients with preoperative deteriorating FEV1 are included in the ROC analysis and unfortunately, there were no ROC data available for the whole cohort. Comparatively, Abbassi-Ghadi and colleagues[13] and Pegna and colleagues[14] both display FEV1 ROC data for the whole cohort. The large heterogeneity of the studies means that the pooled effect size should be interpreted with some caution; however, the overall pooled effect is both statistically significant and a large effect, as such we believe the effects are likely to be generalizable. The small number of studies included within the final meta-analysis means that a sensitivity analysis was not deemed suitable to perform. We are also unable to analyze further whether prophylactic ARS has a different effect to those performed with concerns over graft function.

One confounder and potential alternative explanation for the results seen is that some centers may have only attempted to perform ARS in a patient considered stable enough to undergo further surgery and therefore their decline in ARS may not be represented accurately by a linear gradient. The article by Hoppo and colleagues[17] contains a graph depicting individualized gradients for FEV1 data (albeit without any scale or units) and does indeed display a small number of individuals with an improving FEV1 before ARS.

ARS has been shown to be safe and effective in patients with poor functional status but it is unclear to what extent this evidence has shaped practice across the centers reporting their results.[13] The adopted method of estimating values from mean and standard deviation assume a normal distribution of data and as such may prove to be error prone in the event of non-Gaussian datasets[28]; this may be a contributing factor to the observed heterogeneity when exploring the effect of ARS on the ROC of FEV1.

The strength of this study is that it is the first pooled analysis of studies describing outcome measures after ARS in the lung transplant population. The statistical methodology within the pooled analysis allows a definitive



VIDEO 1. Video available at: https://www.jtcvs.org/article/S0022-5223(19)33105-8/fulltext.

measure of ROC of the FEV1 to demonstrate an effect of fundoplication. A recent commentary by Antonoff[26] heralds the difficulties in drawing conclusions from a retrospective review regarding timing of intervention, and we believe that this pooled analysis of objectively measured outcomes is able to define the measure of success of ARS to be an improvement in the ROC of FEV1; however, there is insufficient evidence within this meta-analysis to recommend the timing of ARS. In fact, the included studies are all describing relatively late ARS (2-3 years after transplant) compared with more modern series advocating earlier ARS (within 6 months of transplant). The most recent published cohort series, although not included within this review because it was published after the analysis was performed, depicts an advantage to early fundoplication[23] and this aligns with large-volume series data whereby early fundoplication in patients with GERD appears to improve BOS-free survival.[37,38] There is also evidence among the reviewed articles that ARS is safe also in patients with end-stage lung disease who are awaiting transplantation.[17,21] However, note must clearly be made that there are a proportion of patients who are not identified to have reflux disease before their transplant, but may develop GERD subsequent to surgery.[4,39]

What this study is unable to determine, is whether improving spirometry values correlate to a prevention or halted progression of BOS. We are also unable to recommend ARS over no ARS, nor recommend the optimal timing of ARS, which is increasingly being practiced.

CONCLUSIONS

This study represents, to the authors' knowledge, the first systematic review and meta-analysis of the effects of fundoplication on measurable factors associated with BOS. Patients presenting with declining graft function will be managed with a variety of different medical strategies, among which ARS has taken a place. The ability of preventing reflux to actually improve lung function has been brought into question as pathophysiologically, the fibrotic process of obliterating bronchiolitis would not be reversed by reducing exposure to gastric content.[18] This review demonstrates a tangible, objectification of the evidence that, in the patients studied, a declining FEV1 does in fact seem to plateau—and clearly in some cases recover—with ARS. We have used this statement, exemplified in Figure 4. We suggest that an ROC of FEV1 is a core outcome that should be reported in all series of ARS after lung transplant; it is a relatively easily measured, and repeated, objective measure that gives a dynamic picture of lung function over an extended period. As denoted by the studies included within this review, a declining FEV1 is an indication for ARS in many centers, and we believe that formalizing this by mapping out the decline in milliliters per day would be a useful measure of outcome for any intervention in the patient with lung transplant, as well as for comparative efficacy in studies exploring early versus late ARS along with those that have already been described.

Conflict of Interest Statement

Authors have nothing to disclose with regard to commercial support.

References

1. Blondeau K, Mertens V, Vanaudenaerde BA, Verleden GM, Van Raemdonck DE, Sifrim D, Dupont LJ. Gastro-oesophageal reflux and gastric aspiration in lung transplant patients with or without chronic rejection. *Eur Respir J*. 2008;31:707-13.
2. Shah N, Force SD, Mitchell PO, Lin E, Lawrence EC, Easley K, et al. Gastroesophageal reflux disease is associated with an increased rate of acute rejection in lung transplant allografts. *Transplant Proc*. 2010;42:2702-6.
3. Murthy SC, Nowicki ER, Mason DP, Budev MM, Nunez AI, Thuita L, et al. Pretransplant gastroesophageal reflux compromises early outcomes after lung transplantation. *J Thorac Cardiovasc Surg*. 2011;142:47-52.e3.
4. Hartwig MG, Anderson DJ, Onaitis MW, Reddy S, Snyder LD, Lin SS, Davis RD. Fundoplication after lung transplantation prevents the allograft dysfunction associated with reflux. *Ann Thorac Surg*. 2011;92:462-8.
5. Benden C, Aurora P, Curry J, Whitmore P, Priestley L, Elliott MJ. High prevalence of gastroesophageal reflux in children after lung transplantation. *Pediatr Pulmonol*. 2005;40:68-71.
6. Duarte AG, Myers AC. Cough reflex in lung transplant recipients. *Lung*. 2012;190:23-7.
7. Jamie Dy F, Freiberger D, Liu E, Boyer D, Visner G, Rosen R. Impact of gastroesophageal reflux and delayed gastric emptying on pediatric lung transplant outcomes. *J Heart Lung Transplant*. 2017;36:854-61.
8. Hathorn KE, Chan WW, Lo W-K. Role of gastroesophageal reflux disease in lung transplantation. *World J Transplant*. 2017;7:103-16.
9. Lo W-K, Goldberg HJ, Boukedes S, Burakoff R, Chan WW. Proton pump inhibitors independently protect against early allograft injury or chronic rejection after lung transplantation. *Dig Dis Sci*. 2018;63:403-10.
10. Davis CS, Shankaran V, Kovacs EJ, Gagermeier J, Dilling D, Alex CG, et al. Gastroesophageal reflux disease after lung transplantation: pathophysiology and implications for treatment. *Surgery*. 2010;148:737-44.
11. Kiljander T, Rantanen T, Kellokumpu I, Kööbi T, Lammi L, Nieminen M, et al. Comparison of the effects of esomeprazole and fundoplication on airway responsiveness in patients with gastro-oesophageal reflux disease. *Clin Respir J*. 2013;7:281-7.
12. Mertens V, Blondeau K, Vanaudenaerde B, Vos R, Farre R, Pauwels A, et al. Gastric juice from patients "on" acid suppressive therapy can still provoke a significant inflammatory reaction by human bronchial epithelial cells. *J Clin Gastroenterol*. 2010;44:e230-5.
13. Abbassi-Ghadi N, Kumar S, Cheung B, McDermott A, Knaggs A, Zacharakis E, et al. Anti-reflux surgery for lung transplant recipients in the presence of impedance-detected duodenogastroesophageal reflux and bronchiolitis

obliterans syndrome: a study of efficacy and safety. *J Heart Lung Transplant*. 2013;32:588-95.
14. Pegna V, Mickevičius A, Tsang C. How useful is antireflux surgery in lung transplant patients with gastroesophageal reflux? *Medicina (Kaunas)*. 2014;50:318-22.
15. Robertson AG, Krishnan A, Ward C, Pearson JP, Small T, Corris PA, et al. Anti-reflux surgery in lung transplant recipients: outcomes and effects on quality of life. *Eur Respir J*. 2012;39:691-7.
16. Burton PR, Button B, Brown W, Lee M, Roberts S, Hassen S, et al. Medium-term outcome of fundoplication after lung transplantation. *Dis Esophagus*. 2009;22:642-8.
17. Hoppo T, Jarido V, Pennathur A, Morrell M, Crespo M, Shigemura N, et al. Anti-reflux surgery preserves lung function in patients with gastroesophageal reflux disease and end-stage lung disease before and after lung transplantation. *Arch Surg*. 2011;146:1041-7.
18. Davis RD Jr, Lau CL, Eubanks S, Messier RH, Hadjiliadis D, Steele MP, Palmer SM. Improved lung allograft function after fundoplication in patients with gastroesophageal reflux disease undergoing lung transplantation. *J Thorac Cardiovasc Surg*. 2003;125:533-42.
19. Fisichella PM, Davis CS, Gagermeier J, Dilling D, Alex CG, Dorfmeister JA, et al. Laparoscopic antireflux surgery for gastroesophageal reflux disease after lung transplantation. *J Surg Res*. 2011;170:e279-86.
20. Hayes D Jr, Kirkby S, McCoy KS, Mansour HM, Khosravi M, Strawbridge H, Tobias JD. Reduction of lipid-laden macrophage index after laparoscopic Nissen fundoplication in cystic fibrosis patients after lung transplantation. *Clin Transplant*. 2013;27:121-5.
21. Linden PA, Gilbert RJ, Yeap BY, Boyle K, Deykin A, Jaklitsch MT, et al. Laparoscopic fundoplication in patients with end-stage lung disease awaiting transplantation. *J Thorac Cardiovasc Surg*. 2006;131:438-46.
22. Lo W-K, Goldberg HJ, Burakoff R, Feldman N, Chan WW. Increased proximal acid reflux is associated with early readmission following lung transplantation. *Neurogastroenterol Motil*. 2016;28:251-9.
23. Biswas Roy S, Elnahas S, Serrone R, Haworth C, Olson MT, Kang P, et al. Early fundoplication is associated with slower decline in lung function after lung transplantation in patients with gastroesophageal reflux disease. *J Thorac Cardiovasc Surg*. 2018;155:2762-71.e1.
24. Patti M. Antireflux surgery in lung transplant patients. *Gastroenterol Hepatol*. 2016;12:181-3.
25. Meyer KC, Raghu G, Verleden GM, Corris PA, Aurora P, Wilson KC, et al. An international ISHLT/ATS/ERS clinical practice guideline: diagnosis and management of bronchiolitis obliterans syndrome. *Eur Respir J*. 2014;44:1479-503.
26. Antonoff MB. How much does early fundoplication for lung transplant recipients with gastroesophageal reflux disease truly help? Challenges in escaping the perils of retrospective review. *J Thorac Cardiovasc Surg*. 2018;155:2772-3.
27. National Heart, Lung, and Blood Institute. Study quality assessment tools. Available at: https://www.nhlbi.nih.gov/health-topics/study-quality-assessment-tools. Accessed November 27, 2019.
28. Wan X, Wang W, Liu J, Tong T. Estimating the sample mean and standard deviation from the sample size, median, range and/or interquartile range. *BMC Med Res Methodol*. 2014;14:135.
29. Fisher AJ, Rutherford RM, Bozzino J, Parry G, Dark JH, Corris PA. The safety and efficacy of total lymphoid irradiation in progressive bronchiolitis obliterans syndrome after lung transplantation. *Am J Transplant*. 2005;5:537-43.
30. Viechtbauer W. Conducting meta-analyses in R with the metafor package. *J Stat Softw*. 2010;36(3).
31. Wallace BC, Trikalinos TA, Lau J, Trow P, Schmid CH. Closing the gap between methodologists and end-users: R as a computational back-end. *J Stat Softw*. 2012;49:1-15.
32. Hedges L, Olkin I. *Statistical methods for meta-analysis*. 1st ed. New York: Elsevier; 1985.
33. Sawilowsky SS. New effect size rules of thumb. *J Mod Appl Stat Methods*. 2009;8:597-9.
34. Lau CL, Palmer SM, Howell DN, McMahon R, Hadjiliadis D, Gaca J, et al. Laparoscopic antireflux surgery in the lung transplant population. *Surg Endosc*. 2002;16:1674-8.
35. Fisichella PM, Davis CS, Lowery E, Pittman M, Gagermeier J, Love RB, Kovacs EJ. Pulmonary immune changes early after laparoscopic antireflux surgery in lung transplant patients with gastroesophageal reflux disease. *J Surg Res*. 2012;177:e65-73.
36. Zheng C, Kane TD, Kurland G, Irlano K, Spahr J, Potoka DA, et al. Feasibility of laparoscopic Nissen fundoplication after pediatric lung or heart-lung transplantation: should this be the standard? *Surg Endosc*. 2011;25:249-54.
37. Cantu E 3rd, Appel JZ 3rd, Hartwig MG, Woreta H, Green C, Messier R, et al. J. Maxwell Chamberlain Memorial Paper. Early fundoplication prevents chronic allograft dysfunction in patients with gastroesophageal reflux disease. *Ann Thorac Surg*. 2004;78:1142-51.
38. Lo W-K, Goldberg HJ, Wee J, Fisichella PM, Chan WW. Both pre-transplant and early post-transplant antireflux surgery prevent development of early allograft injury after lung transplantation. *J Gastrointest Surg*. 2016;20:111-8.
39. Hirji SA, Gulack BC, Englum BR, Speicher PJ, Ganapathi AM, Osho AA, et al. Lung transplantation delays gastric motility in patients without prior gastrointestinal surgery—a single-center experience of 412 consecutive patients. *Clin Transplant*. 2017;31(10).

Key Words: fundoplication, lung transplant, meta-analysis, bronchiolitis obliterans, BOS