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Does Transoral Incisionless Fundoplication (TIF. 2.0) Improve Atypical GERD Symptoms? A Systematic Review and Meta-Analysis

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Abstract

Background & Aims: Transoral Incisionless Fundoplication (TIF) using EsophyX device is a minimally invasive endoscopic fundoplication technique. Our study aimed to assess the efficacy of TIF for atypical GERD symptoms in patients with chronic or refractory GERD.

Methods: A systematic search of 4 major databases was performed. All original studies assessing atypical GERD using a validated symptom questionnaire (the Reflux Symptom Index (RSI) were included. The RSI score was assessed pre-and post-TIF at 6- and 12-month follow-up. The data

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JGB: Design, literature search and review, data interpretation and draft.
UH: Design, literature search and review, data interpretation and draft.
CB: Design, statistical analysis, data interpretation and draft.
PAB: Design, literature search and review
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CT: Concept, Design, data interpretation, review and critically revised the article.

Conflict of Interest:

MH: None
JGB: None
UH: None
CB: None
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on technical success rate, adverse events, proton pump inhibitor (PPI) use, and patient satisfaction were also collected. Only TIF procedures currently in practice using EsophyX device, i.e., TIF 2.0 and TIF with concomitant hiatal hernia repair (cTIF), were included in the review.

Results: A total of 10 studies (564 patients) were included. At 6- and 12- month follow-up, there was 15.72 (95% CI 12.15 to 19.29) and 14.73 points (95% CI 11.74 to 17.72) mean reduction of RSI score post-TIF, respectively, with a technical success rate of 99.5% and a pooled adverse event rate of 1%. At both time intervals, more than two-thirds of the patients were satisfied with their health condition and roughly three-fourths of the patients were off daily PPI.

Conclusions: Our study shows that TIF using the EsophyX device is safe and effective in reducing atypical GERD symptoms at 6- and 12-month follow-up. It improves patient-centered outcomes and can be a minimally invasive therapeutic option for patients suffering from atypical GERD symptoms on chronic medical therapy.

Introduction:

Gastroesophageal Reflux Disease (GERD) is a common condition that profoundly impacts patients' quality of life. The prevalence of the disease in North America ranges from 18.1% - 27.8%.[1] GERD can present with both typical (including heartburn, regurgitation and bloating) and extraesophageal or atypical (including cough, hoarseness, excess throat mucus, breathing difficulty and globus sensation) symptoms. Atypical GERD is a diagnostic challenge as only about 43% of these patients present with typical gastrointestinal symptoms.[2] In addition to being a diagnostic challenge, it also poses a significant financial burden on the health care system. The estimated annual cost for atypical GERD is $50 Billion, five times the cost for typical GERD. This high healthcare cost is attributed to lack of gold standard diagnostic test, delayed diagnosis, prolonged use of acid-suppressive medications, and lack of effective therapies.[3]

The first line therapy for atypical GERD is medical treatment predominantly with proton pump inhibitors (PPI) and lifestyle intervention. However, the evidence in support of PPI for atypical GERD is inconsistent. For example, in 2019, a systematic review found out that only 3 out of 9 systematic reviews/metanalysis on this topic showed the superiority of PPI over placebo in improving atypical GERD symptoms.[4] [NO_PRINTED_FORM]On the other hand, surgical anti-reflux treatment with laparoscopic Nissen Fundoplication has shown efficacy for both typical and atypical GERD symptoms.[5,6] However, it is more invasive and associated with unwanted long-term side effects like dysphagia, uncontrolled flatulence, and gas bloating.[7,8]

Transoral Incisionless Fundoplication (TIF) is a minimally invasive, endoscopic fundoplication technique. It has demonstrated long-term efficacy and safety profile in patients suffering from chronic or refractory GERD.[9,10] TIF was introduced in 2005 as a novel endoscopic fundoplication technique and approved by Food and Drug Administration (FDA) in 2007. It has evolved and further improved over the years. TIF 2.0 utilizes the EsophyX device (EndoGastric Solutions, Inc., Redmond, WA, USA) to restore the valve at the gastroesophageal (GE) junction. It is anatomically and functionally similar to fundoplication but is less invasive and has a low rate of adverse events.[11,12] Currently in

use TIF procedures include TIF 2.0 and concomitant TIF or cTIF (TIF 2.0 with hiatal hernia repair) for hiatal hernia > 2cm. The efficacy of TIF against typical GERD has been extensively reported in systematic reviews,[10,12,13] but our understanding of its effectiveness against atypical GERD symptoms is limited.

This study aims to perform a systematic review and meta-analysis to evaluate the efficacy of the TIF 2.0 procedure for atypical GERD symptoms. (For the purpose of this systematic review, we will use TIF for TIF 2.0 procedure interchangeably).

Methods and Materials:

This review was registered on the International Prospective Register of Systematic Reviews (PROSPERO) by the University of York with registration ID: **CRD42021237931**

Search Strategy and Study Selection:

Following MOOSE (Meta-analysis of Observational Studies in Epidemiology) guidelines,[14] we conducted a systematic search of published literature in four major databases: PubMed (NCBI), Embase (Elsevier), Web of Science Core Collection (Clarivate Analytics), and the Cochrane Central Register of Controlled Trials (Wiley). It was developed and run with the assistance of a Librarian (PAB), with the last search performed on October 8th, 2021. No geographic, language or date limits were applied (Supplementary Figure 1).

The study selection process involved two phases: Title & Abstract screening and Full Text Review. Two independent investigators conducted each step (MH & UH). Conflicts were then resolved by consensus discussion between the independent investigators and, when necessary, by the senior reviewer (CT).

Inclusion and Exclusion Criteria:

There were predefined Inclusion and Exclusion criteria.

Inclusion: We included all retrospective and prospective study designs that assessed pre- and post-TIF atypical GERD symptoms with a minimum of at least 6 month follow-up. We included all adult patients over 18 years having chronic or refractory GERD undergoing the TIF 2.0 or cTIF procedures using the EsophyX device without any body mass index or hiatal hernia size limitation.

Exclusion: We excluded studies reporting patients who underwent the procedure using an older technique than TIF 2.0. We also excluded patients who underwent TIF using any device other than the EsophyX device.

Data Extraction and Quality Assessment:

The data extraction and quality assessment were conducted by two independent investigators (MH & UH) separately, followed by cross-check of the data. Conflicts were then resolved by consensus discussion between the independent investigators and, when necessary, by a third reviewer (CT). The data extraction sheet broadly included detailed information for reported patient characteristics, study characteristics, procedure details, adverse events, and

effectiveness outcomes. For Quality assessment of eligible studies, we utilized Cochrane Risk of Bias assessment tools for randomized and non-randomized studies and the Institute of Health Economics (IHE) quality appraisal tool for case series.[15,16]

Outcome Measures:

Our primary outcome of interest was TIF's efficacy in patients with chronic or refractory atypical GERD symptoms, measured by a validated scoring system called Reflux Symptom Index (RSI). The RSI is a 9-item questionnaire developed and validated for assessing atypical GERD symptoms, also referred to as symptoms resulting from Laryngopharyngeal Reflux (LPR) including hoarseness, throat clearing, excess throat mucus, and cough. Each item on RSI has a scale that ranges from 0 ('No Problem') to 5 ('Severe Problem'). The maximum total score can be 45, with a normality threshold of 13.[17] The secondary outcomes included pre-and post-TIF procedure Proton Pump Inhibitor (PPI) usage and patient satisfaction level. Patient satisfaction was assessed in the studies as part of the GERD-Health Related Quality of Life (GERD-HRQL) validated questionnaire.

Statistical Analysis:

The primary outcome of RSI score was a continuous variable, reported as either mean/standard deviation or median/interquartile range. We performed a meta-analysis of mean differences within-person of RSI scores pre-and post-TIF. We stratified our analysis based on the follow-up time at 6 month and 12 month to decrease inter-study differences and get precise estimates at the given follow-up time. Due to small number of studies available and in order to be especially careful not to make an incorrect inference of significance due to failure to recognize heterogeneity, a random effects model was used for each meta-analytic model. The secondary outcome of PPI use and patient satisfaction were proportions. We meta-analyzed pooled proportions for secondary outcomes pre- and post-TIF separately. Forest plots were generated to show a graphical display of individual study results and the weighted average or magnitude of their combined effect. Wherever applicable, we calculated the data points from available information following the Cochrane Handbook guide.[18] For missing or incomplete information, we reached out to principal authors of respective studies. For overlapping patient populations derived from the same registry data,[19] raw data were requested from their industry sponsor to calculate outcomes to prevent inaccurate estimation of precision. The I^2 statistic was used to calculate heterogeneity, and wherever applicable, causes of increased heterogeneity were further investigated. Sensitivity analysis was also performed for exploring increased heterogeneity by plotting effect sizes with or without each study. A subgroup analysis was designated a priori, specifically, the analysis focused on those patients with hiatal hernia size >2 cm who underwent cTIF. Funnel plots were generated for visual assessment of publication bias. It is recognized that there was multiple testing of outcome data arising from individual studies. The main results for the RSI scores are the primary finding and require no correction of p-values; other results should be considered as secondary findings with their p-values taken as descriptive only. As such, all p-values are presented without correction for multiple testing. All statistical analysis was performed using Stata software (MP/17.0).

Results:

The PRISMA flow diagram depiction of the study selection process is shown in Figure 1. Our systematic database search retrieved 1,117 unique records. Following title and abstract screening, we retrieved 115 articles for full-text review. A total of 10 studies met our predefined eligibility criteria following full text review.[20–31] For the three studies derived from the same data registry (TIF Registry), given the concern for overlapping patient population, we retrieved raw data from the industry sponsor of the data registry to extract results and presented as a single entity, "TIF Registry".[20–22]

Study and Patient Characteristics:

All eligible studies were conducted between 2008 and 2021 and included one Randomized Control Trial, 4 Prospective, and 5 Retrospective observational studies. The characteristics of these studies are summarized in Table 1a. A total of 564 patients were included in our study, having information about validated atypical GERD symptom score (RSI) from a cohort of 740 patients undergoing TIF procedure in the eligible studies. Mean age and BMI were 57.0 ± 2.3 and 27.7 ± 1.7 respectively. There was a female predominance in the entire cohort (60%). The average GERD symptom and PPI use duration was 8.8 ± 1.9 years from 6/10 reporting studies and 7 ± 1.2 years from 5/10 reporting studies, respectively. A total of 287 patients had a hiatal hernia size ≥ 2 cm in the entire cohort. The characteristics of the patients are summarized in Table 1a and Table 1b.

Risk of Bias:

All observational studies were assessed using the Institute of Health Economics (IHE) quality appraisal tool for case series.[16] We had a total of 11 observational studies for quality assessment, which included 3 studies derived from the same data registry. (Table 1a)[19,21,32] All studies were of acceptable quality with compliance of ≥ 14 items on the quality appraisal tool. In addition, we also used Newcastle-Ottawa Quality Assessment Scale (NOS) for all observational studies.[33] The NOS indicated that all articles included in the review had a low risk of bias (score of 5 or more out of 8 items on study selection, comparability, and outcome). We had 2 reports from the same Randomized Control Trial (TEMPO Trial), which were assessed using the Cochrane Risk of Bias assessment tool.[15] The study was funded by EndoGastric Solutions, and there was evidence of detection and performance bias. But the overall risk of bias was judged to be low.

Procedure details:

The immediate technical success rate of the procedure was 99.5%. The rate of pooled serious adverse event was 1% (Figure 2). A total of 9 serious adverse events included 3 superficial esophageal tears, 2 gastrointestinal bleeding episodes, 1 hematoma formation, 1 esophageal perforation, 1 postop fever with thrush, and 1 postop mediastinal abscess formation. All serious adverse events were immediately addressed, and there was no mortality reported. Out of 287 patients with hiatal hernia size ≥ 2 cm, 255 were from 5 studies that reported outcomes of cTIF.[27–31] The mean time to perform the TIF procedure was 51 ± 14.8 minutes. The mean time to perform cTIF was 96 ± 42 minutes, reported

only in one of the 4 studies.[30] The details of the procedure and follow-up time periods are reported in Table 2.

Atypical GERD Symptoms Pre- and Post-TIF:

At 6 month follow up, a total of 474 patients' data was available from 8 studies. The mean RSI score post-TIF procedure decreased below the normality threshold of 13 for all studies. The RSI score decreased after the TIF procedure compared with the pre-TIF score with a mean difference of −15.72 (95% CI −12.15 to −19.29), favoring the TIF procedure. There was considerable heterogeneity among the studies, with an I^2 statistic of 88% using the random-effects model. (Figure 3)

At 12 month follow up, a total of 287 patients' data was available from 6 studies. The mean RSI score post-TIF procedure decreased below the normality threshold of 13 for all studies. The RSI score decreased after the TIF procedure compared with the pre-TIF score with a mean difference of −14.73 (95% CI −11.74 to −17.72), favoring the TIF procedure. The studies had substantial heterogeneity, with an I^2 statistic of 66% using the random-effects model. (Figure 4)

The elimination of individual daily troublesome atypical GERD symptoms was variably reported in the included studies. It is assessed using the individual question of the RSI score questionnaire on a Likert scale from 0 to 5 with an effectiveness endpoint of score ≤ 2. The atypical GERD symptoms include hoarseness, clearing throat, excess throat mucus, chronic cough, cough after eating or lying flat, globus sensation, breathing difficulty, and difficulty swallowing. There was a significant reduction in the proportion of patients with each atypical GERD symptom post-TIF, as shown in Figure 5.

PPI Usage Pre and Post TIF:

At 6 month follow-up, a total of 384 patients' data was available from 7 studies. The pooled proportion of patients using PPI Pre-TIF was 99% (95% CI 97% - 100%), which was reduced to 19% (95% CI 11% - 27%) post-TIF. There was considerable heterogeneity between the studies with an I^2 statistic of 75% using the random-effects model.

At 12 month follow-up, a total of 218 patients' data was available from 4 studies. The pooled proportion of patients using PPI Pre-TIF was 100% (95% CI 97% - 100%), which was reduced to 26% (95% CI 20% - 32%) post-TIF. There was no significant heterogeneity between the studies with an I^2 statistic of 45% using the random-effects model. The forest plots depicting PPI therapy cessation are shown in Figure 6.

Patient Satisfaction Pre and Post TIF:

At 6 month follow up, a total of 392 patients' data was available from 7 studies. The pooled proportion of patients satisfied with their health condition at baseline was 4% (95% CI 2% - 8%) which was improved post-TIF to 73% (95% CI 67% - 79%). There was no significant heterogeneity between the studies with an I^2 statistic of 38% using a random-effects model.

At 12 month follow-up, a total of 190 patients' data was available from 3 studies. The pooled proportion of patients satisfied with their health condition at baseline was 11% (95%

CI 3% - 21%) which was significantly improved post-TIF to 75% (95% CI 61% - 87%). There was substantial heterogeneity between the studies with an I^2 statistic of 76% using the random-effects model. The forest plots with patient satisfaction are shown in Supplementary Figure 2.

Subgroup Analysis:

A predefined subgroup analysis was performed for patients with atypical GERD symptoms and hiatal hernia size > 2 cm who underwent cTIF. Out of 5 studies reporting outcomes of cTIF,[27–31] one study was excluded from the subgroup analysis due to incomplete data information.[31]

At 6 month follow-up, a total of 100 patients' data were available from 3 studies. The mean RSI score post-cTIF procedure decreased below the normality threshold of 13 for all studies. The RSI score decreased after cTIF procedure compared with pre-cTIF with a mean difference of −13.25 (95% CI −7.59 to −18.91), in favor of the cTIF procedure. The studies had moderate heterogeneity, with an I^2 statistic of 56% using the random-effects model.

At 12 month follow-up, a total of 107 patients' data were available from 3 studies. The mean RSI score post-cTIF procedure decreased below the normality threshold of 13 for all studies. The RSI score decreased after cTIF procedure compared with pre-cTIF with a mean difference of −14.01 (95% CI −7.65 to −20.37), in favor of the cTIF procedure. There was considerable heterogeneity among the studies, with an I^2 statistic of 79% using the random-effects model. (Figure 7)

Heterogeneity and Publication Bias:

All results with moderate to considerable heterogeneity were further investigated. We did not find any explainable causes of heterogeneity following the Cochrane Handbook guide.[18] A sensitivity analysis was also performed, omitting one study sequentially on a plot that did not change the effect as the 95% CI overlapped. The sensitivity analysis for the primary outcome of RSI score at 6, and 12 month post-TIF is shown in Supplementary Figures 3A & 3B.

Funnel plots to assess publication bias showed visual asymmetry, but it was difficult to distinguish chance from real asymmetry as there were less than 10 studies for each meta-analysis in our systematic review.[18] For the same reason, further statistical assessment of this visual asymmetry with Egger's test was not performed. In addition to chance, moderate to considerable heterogeneity in the studies can explain the visual asymmetry observed in Funnel plots.[34] The funnel plots for the primary outcome of RSI score at 6, and 12 month post-TIF are shown in Supplementary Figures 4A & 4B.

Discussion:

Atypical GERD or laryngopharyngeal reflux (LPR), or extraesophageal reflux symptoms represent a disorder that lacks a widely available effective therapy despite posing a significant healthcare burden.[3] Our systematic review and meta-analysis of 10 studies containing data of 564 patients demonstrate that TIF is effective in controlling subjective

atypical GERD symptoms and patient-centered outcomes at 6- and 12-month intervals. The results were comparable at both time intervals with a reduction of mean RSI score of ~15 points at 6 month and 14.73 points at 12-month post-TIF, respectively. The mean RSI score for each study at both time intervals also crossed the normality threshold of 13 for the RSI score. In addition, there was a significant improvement in patient-centered outcomes. Nearly all patients were on daily PPI for years at the start of the study, but only 19% at 6 month and 26% at 12 month were using daily or occasional PPI following the TIF procedure. More than two-thirds of the patients were satisfied with their health condition after the procedure at 6 month, which was maintained at a one-year follow-up. Persistently high patient satisfaction rate at both time intervals highlights the clinical significance of these results. The feasibility and safety of the procedure were evident from high technical success (99.5%) and low adverse event rate (1.0%).

There have been several well-done meta-analyses which have focused on typical GERD and have maybe looked at other devices or procedures.[10,13,35–37] However, this meta-analysis is distinct as it focuses on atypical GERD and only includes currently in practice TIF procedures. Nonetheless our results can be compared with previously published literature. In 2013, Wendling et al., while addressing the overall impact of TIF on GERD indices, reported outcomes from 4 studies with an average follow-up of 7.6 month demonstrating a mean reduction of RSI score of 19.1 (24.5 at baseline to 5.4 after TIF). The pooled complication rate across all studies included in the review was 3.2%.[38] Similarly, a subgroup analysis in a study by McCarty et al. in 2018 assessed the efficacy of TIF for refractory GERD finding a mean reduction of RSI score of 14.28 in patients with atypical GERD symptoms and an average follow-up of 15.8 month. They calculated a pooled serious adverse event rate of 2%.[9] Despite having a higher number of patients with hiatal hernia size ≥ 2 cm who underwent cTIF procedure (129 vs. 18 each), our results show a better safety profile with a pooled adverse event rate of 1.0%. This may be because we included patients with atypical GERD representing different population. Additionally, we only included patients who underwent TIF 2.0. TIF 2.0 has been in use since 2008, but the actual transition from TIF 1.0 to TIF 2.0 happened in 2010–2011. Both of these techniques and the design of the EsophyX device used in them are distinctly different, so combining their outcomes for effectiveness and safety can lead to incorrect conclusions.[11]

In 2017, the FDA allowed modification of the TIF device Instructions for Use (IFU), permitting TIF to be performed with hiatal hernia repair, similar to surgical fundoplication for this patient population. This procedure is known as cTIF. Studies published in 2019 or after frequently included patients with and without hiatal hernia > 2cm who underwent cTIF, which was less often performed before 2019. We performed a subgroup analysis in our review for patients who underwent cTIF. The results were comparable to the overall patient-centered outcomes of our primary analysis. These results suggest that careful selection of patients for the type of TIF procedure (TIF vs. cTIF) may have contributed to these outcomes. Hiatal hernia size has been demonstrated as a predictor of response following TIF.[39,40] The results of our subgroup analysis further support the evidence behind correcting hiatal hernia ≥ 2 cm before TIF.

Our study should be interpreted with its limitations. First, the study did not assess objective outcomes following the TIF procedure. There is limited consensus on the utility of objective testing for the diagnosis of atypical GERD and symptom scores are often relied upon. Therefore, our analysis focused on patient-centered outcomes that directly affect patients' quality of life. Second, the study reports a systematic review of short-term results against atypical GERD symptoms following the TIF procedure. The paucity of data available on the long-term effectiveness of TIF against atypical GERD limited our scope to short-term follow-up. However, it is relevant to point out that the long-term outcomes of the TEMPO trial at 3 and 5 years have demonstrated that TIF provides sustained long-term effectiveness against atypical GERD.[41,42] Third, most of the included studies were observational studies. Lastly, high heterogeneity despite efforts to address it, remains a major limitation of our study.

Despite some limitations, our study has several strengths. First, we believe that our effect estimates are informative and more precise than previous studies.[9,38] It is because we stratified studies on their follow-up time and avoided overlapping populations by getting results from raw data of studies derived from the same registry.[19,21,22,32] More importantly, we have systematically summarized all available data on currently in practice TIF procedures using EsophyX device, namely TIF 2.0 and cTIF. Prior techniques like ELF or TIF 1.0 have not been in use for more than 10 years. Thus, it provides more accurate estimates for the efficacy and tolerability of the procedures available in practice.

In conclusion, the endoscopic fundoplication technique of TIF 2.0 using the EsophyX device is safe and effective in reducing atypical symptoms of GERD and improving patient-centered outcomes. It has the potential to be a minimally invasive treatment option for patients with chronic or refractory atypical GERD who have either failed or want to avoid chronic medical therapy.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

ACRONYMS

GERD	Gastroesophageal Reflux Disease
TIF	Transoral Incisionless Fundoplication
RSI	Reflux Symptom Index
PPI	Proton Pump Inhibitor
cTIF	TIF with concomitant hiatal hernia repair
CI	Confidence Interval
FDA	Food and Drug Administration
GE	gastroesophageal

PROSPERO	Prospective Register of Systematic Reviews
MOOSE	Meta-analysis of Observational Studies in Epidemiology
IHE	Institute of Health Economics
LPR	Laryngopharyngeal Reflux

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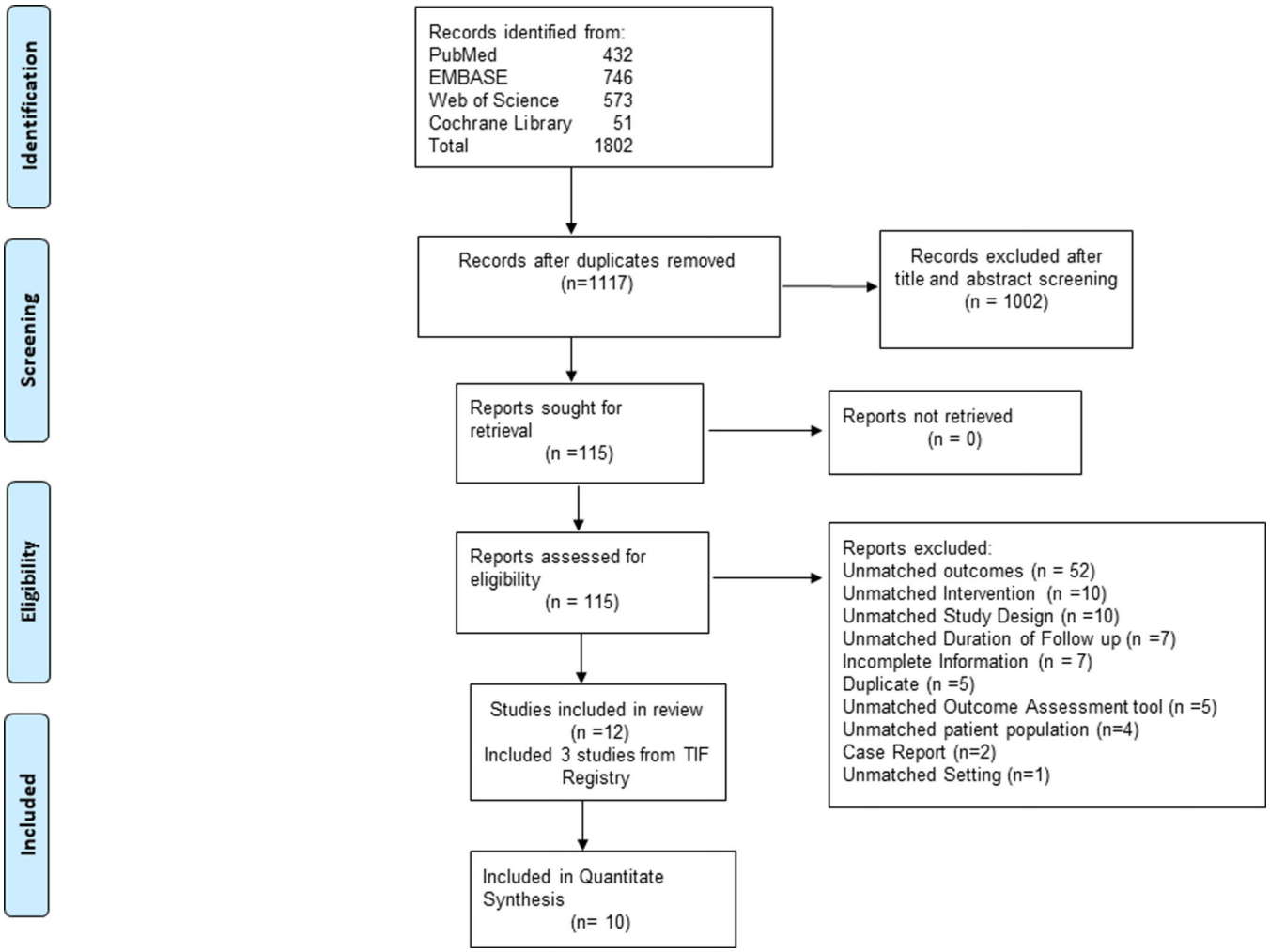


Figure 1:
PRISMA Flowchart

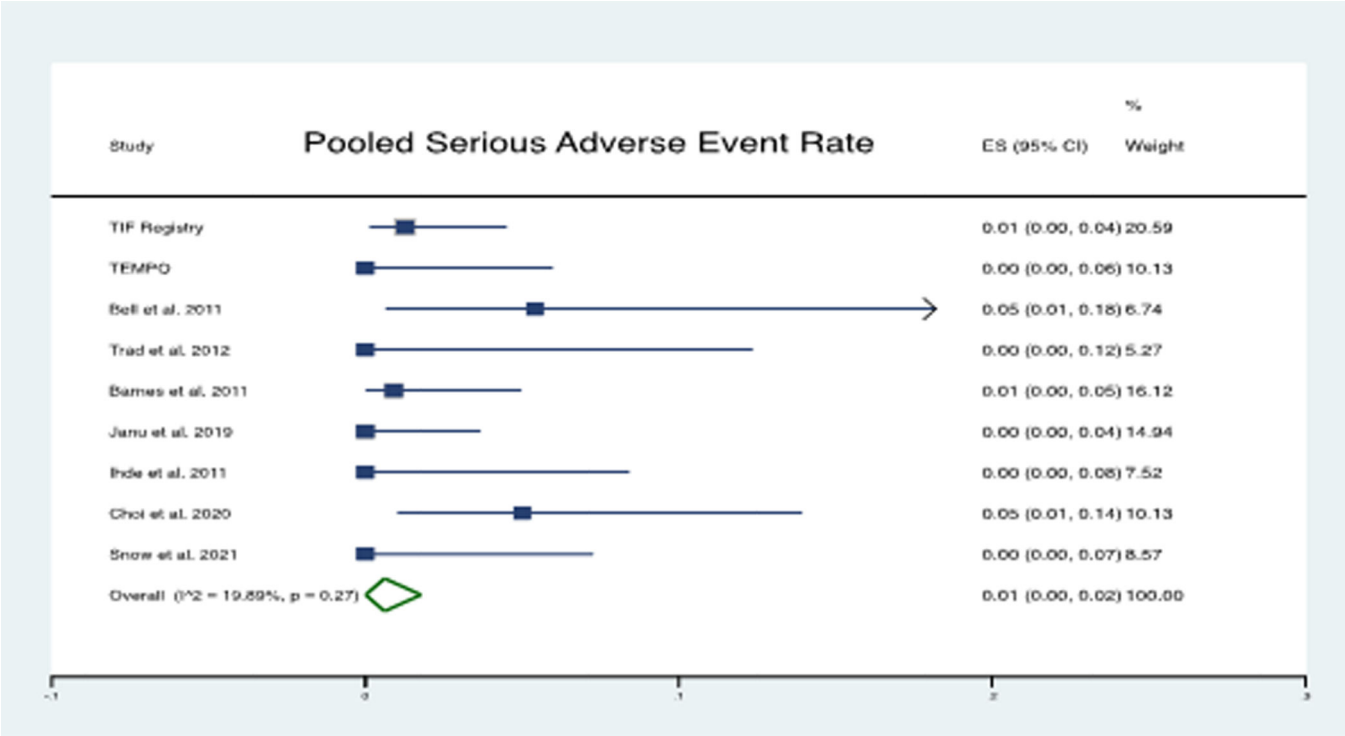


Figure 2:
Forest plot of pooled Serious Adverse Event Rate: The pooled weighted average of adverse event rate was 0.01 (1%)

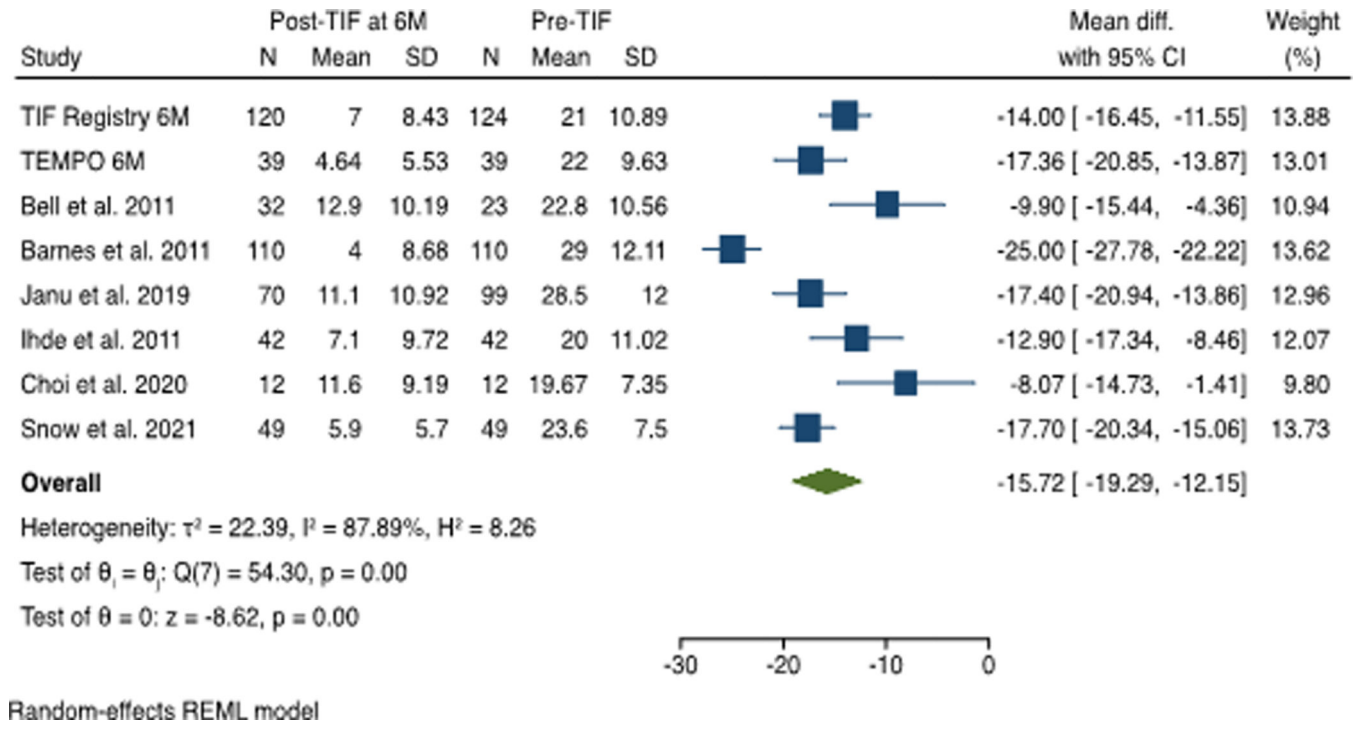


Figure 3:

Effect Estimate of Reflux Symptom Index (RSI) score at 6 Month Post-TIF: The mean RSI score for each individual study post-TIF decreased below the normality threshold of 13 and the magnitude of their combined effect pre- and post-TIF was 15.72 on reduction of RSI score.

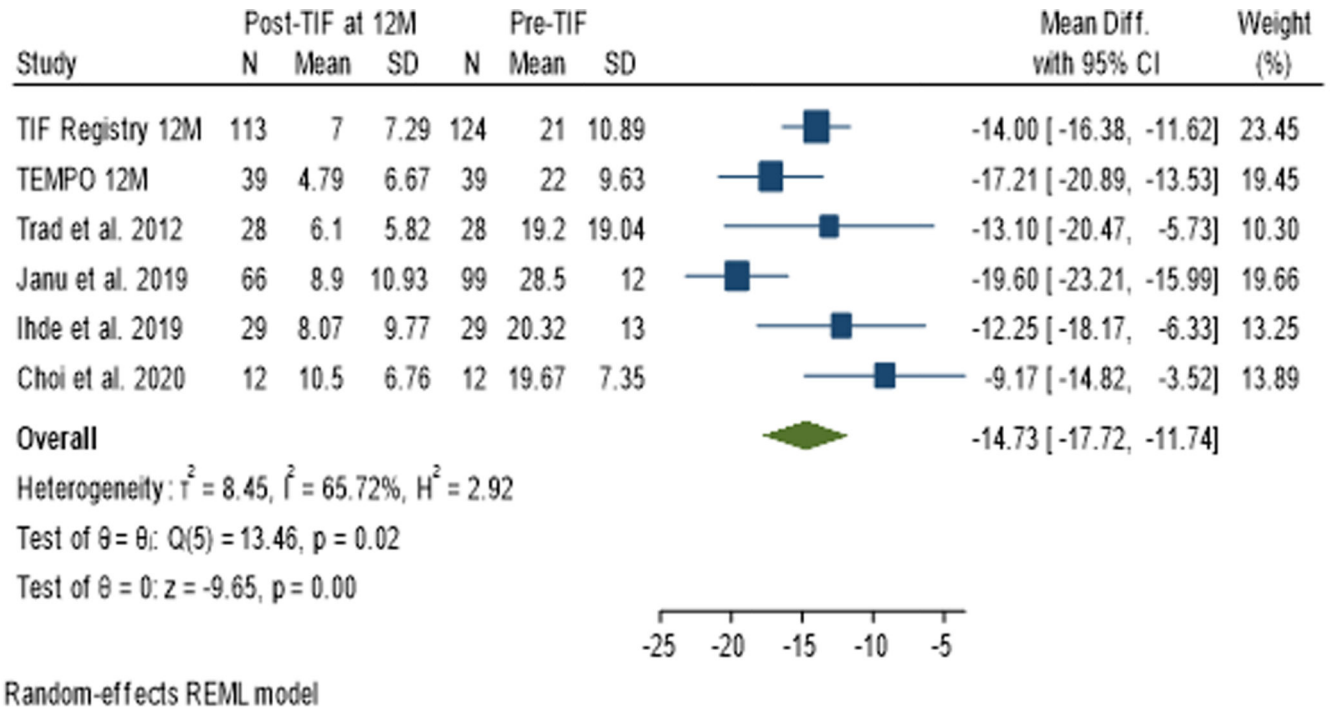
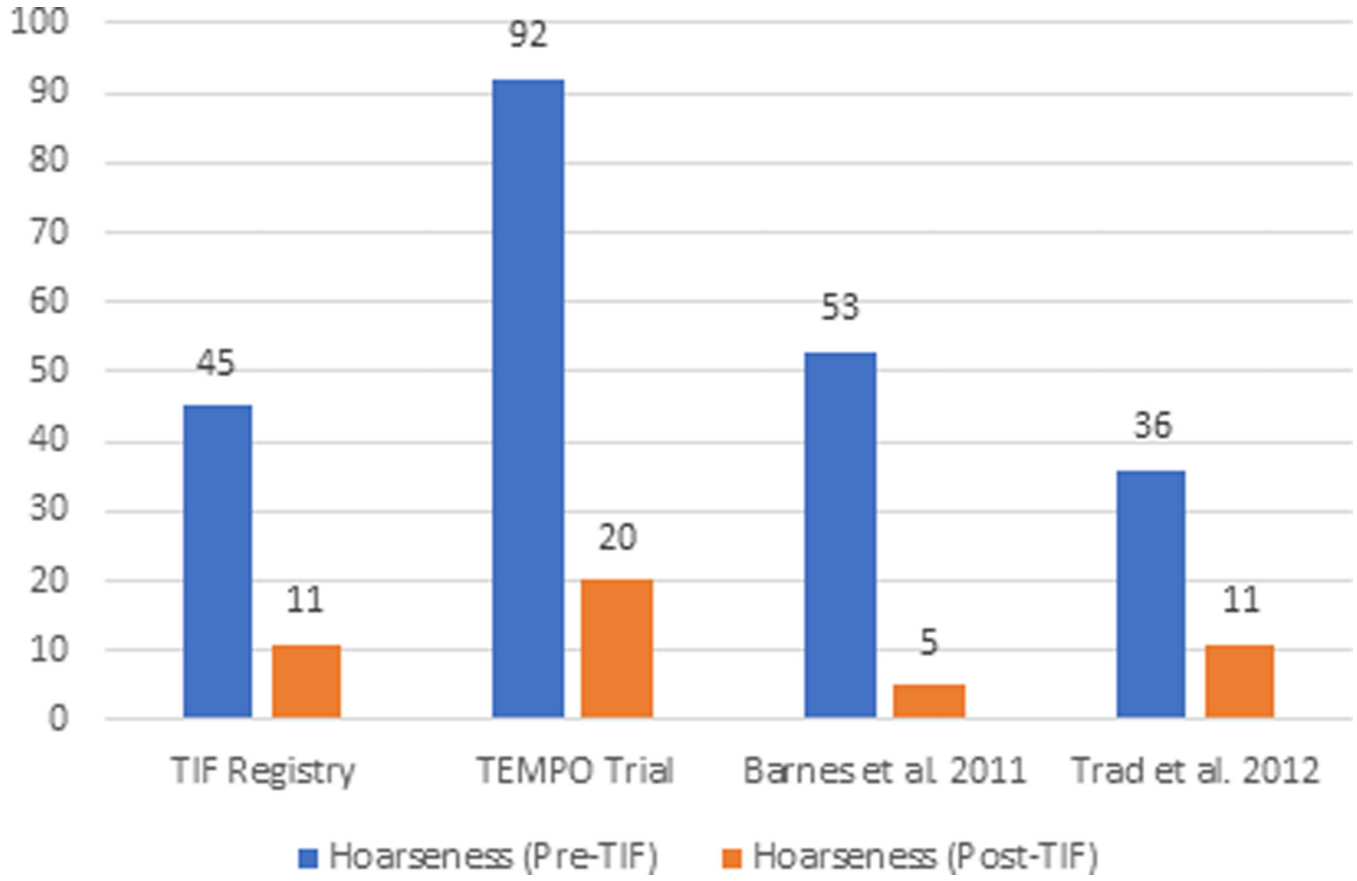
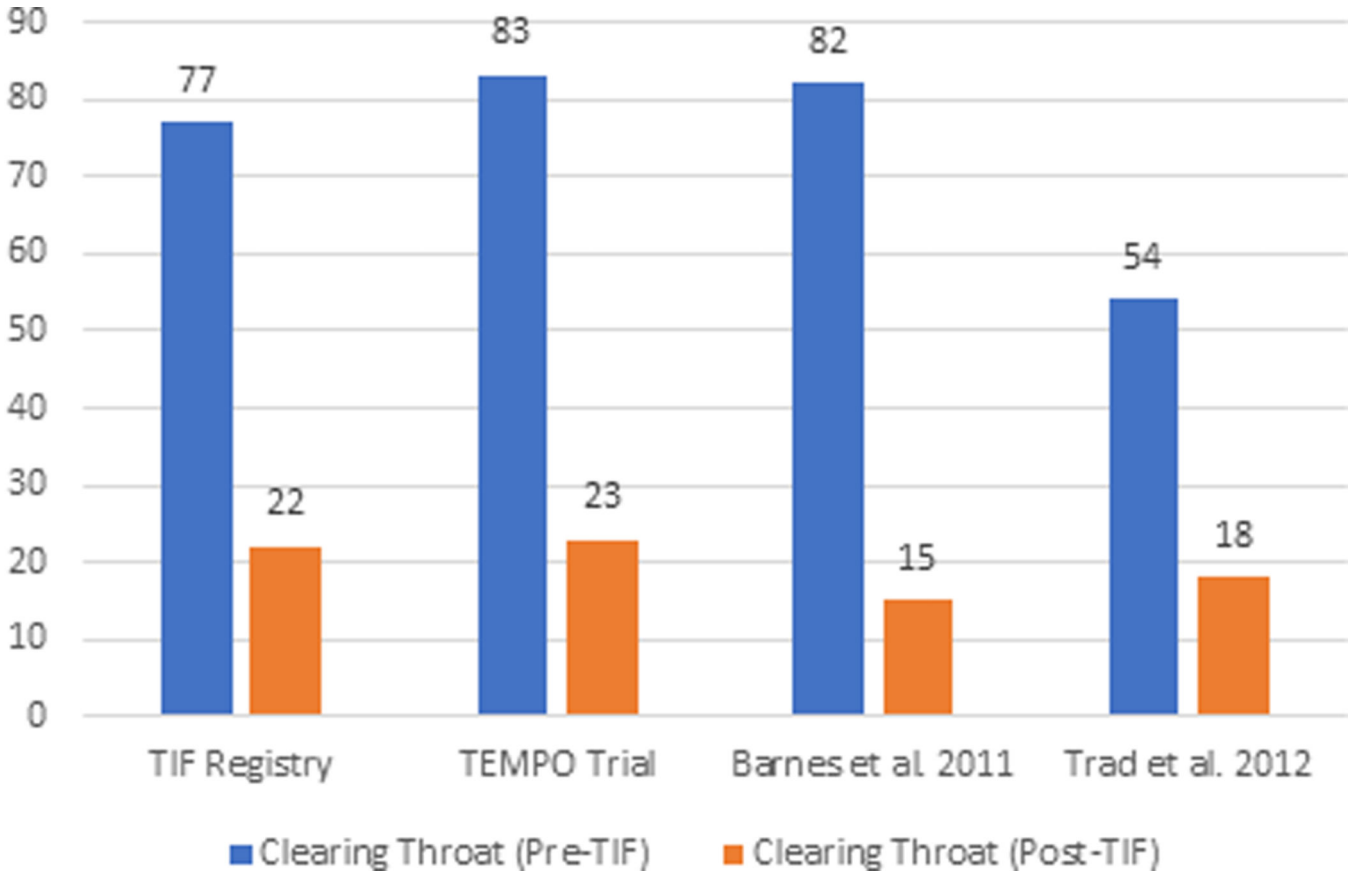
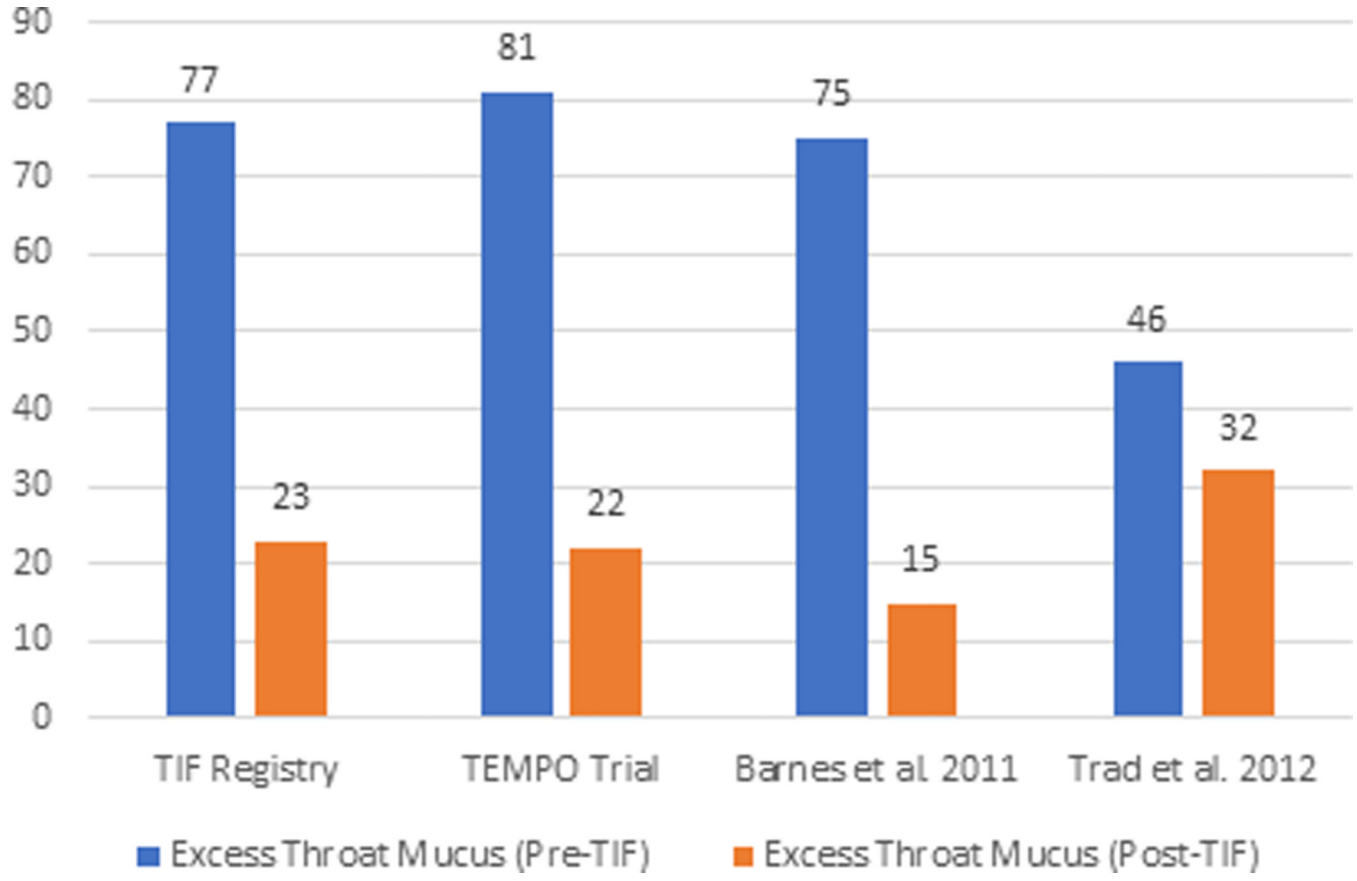


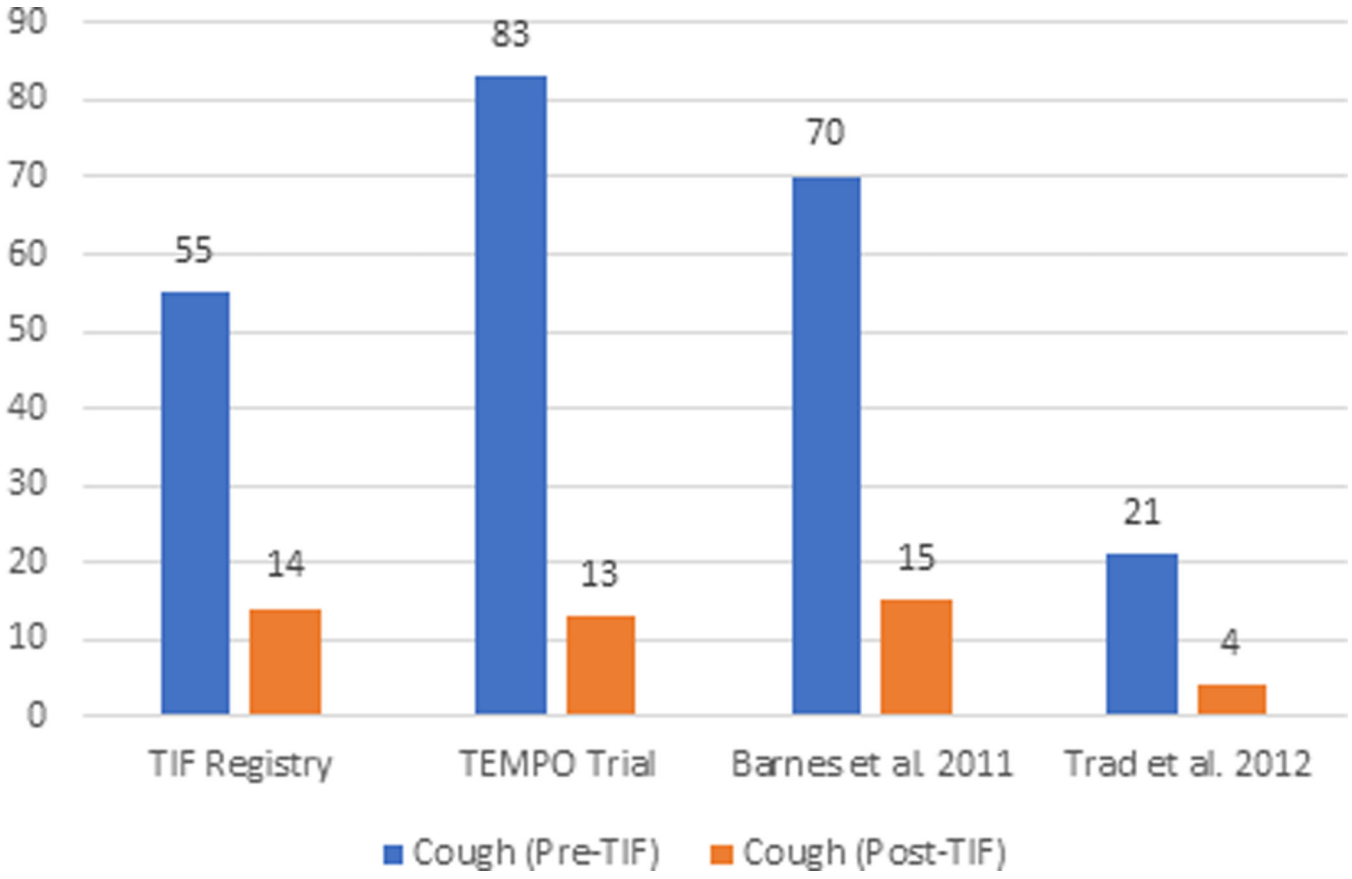
Figure 4:

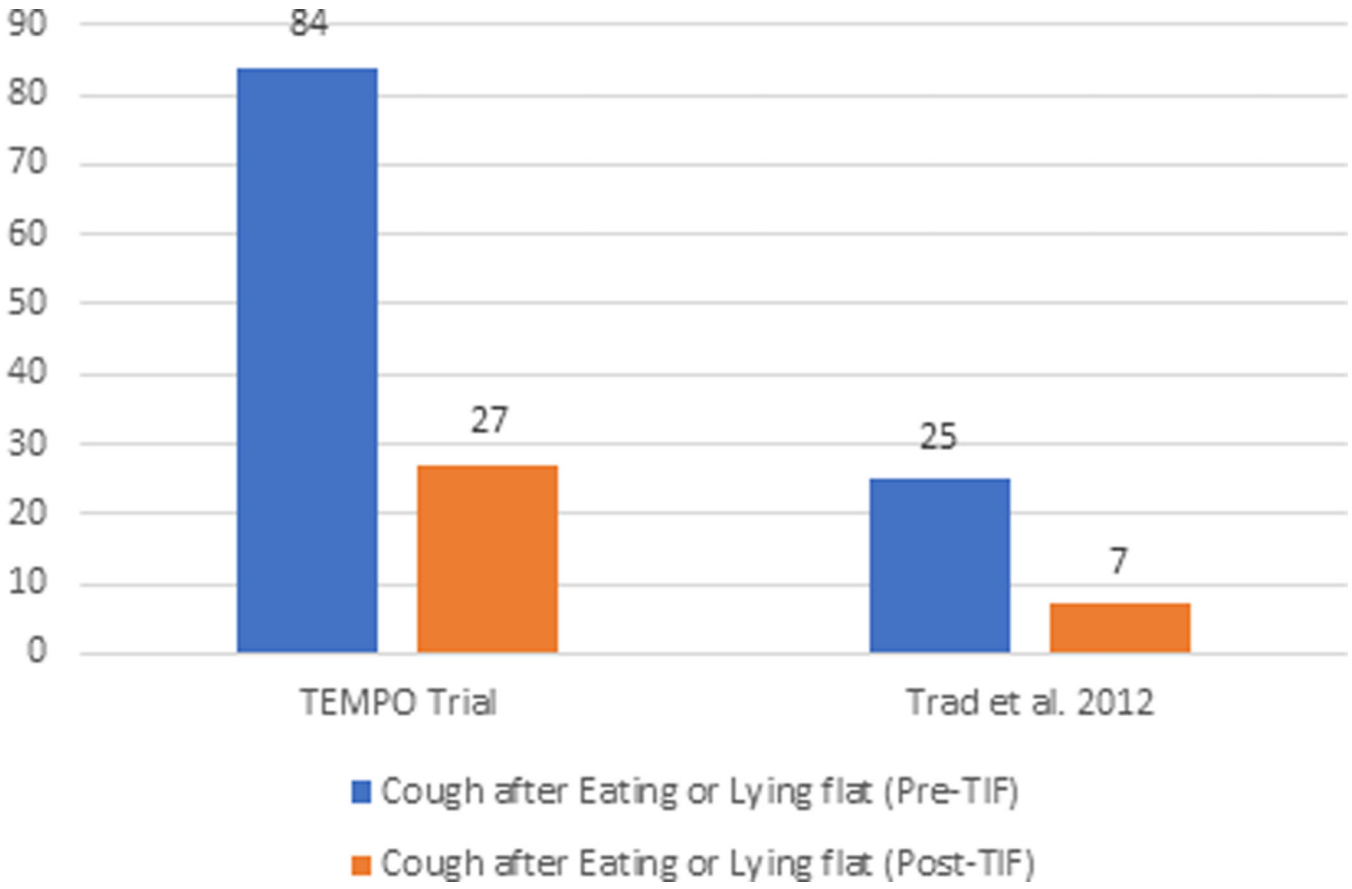
Effect Estimate of Reflux Symptom Index (RSI) score at 12 Month Post TIF: The mean RSI score for each individual study post-TIF decreased below the normality threshold of 13 and the magnitude of their combined effect pre- and post-TIF was 14.73 on reduction of RSI score.

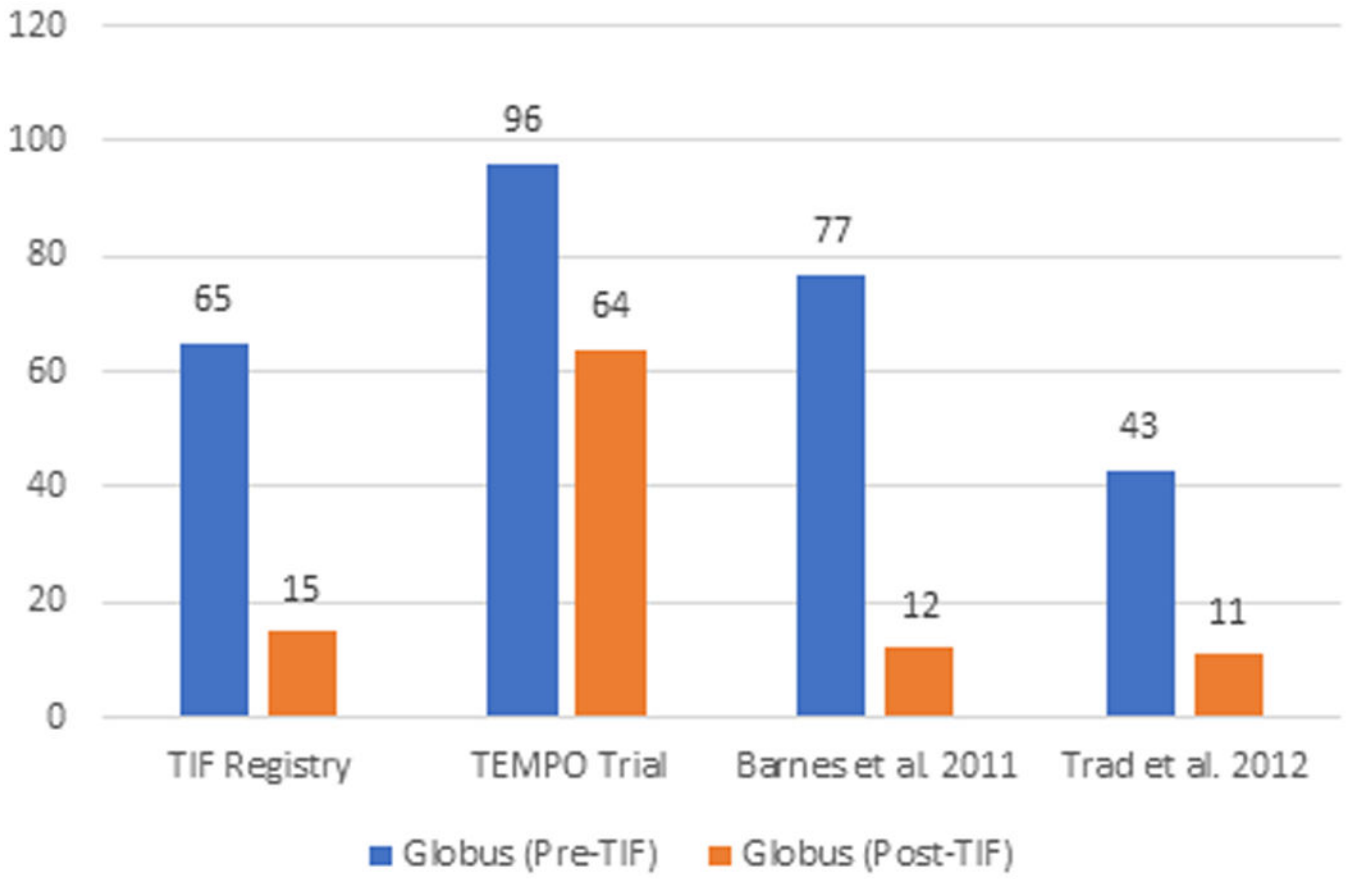


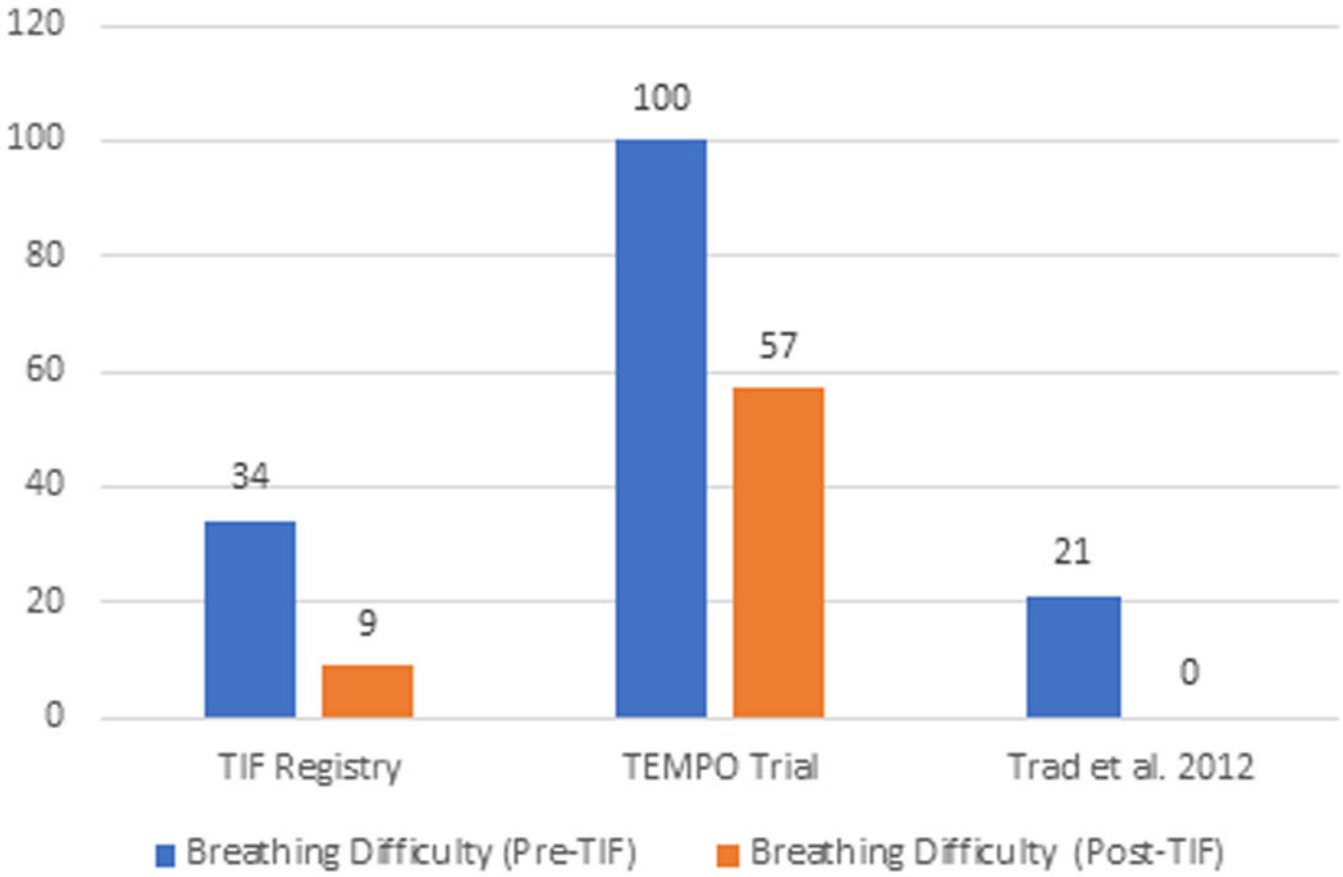












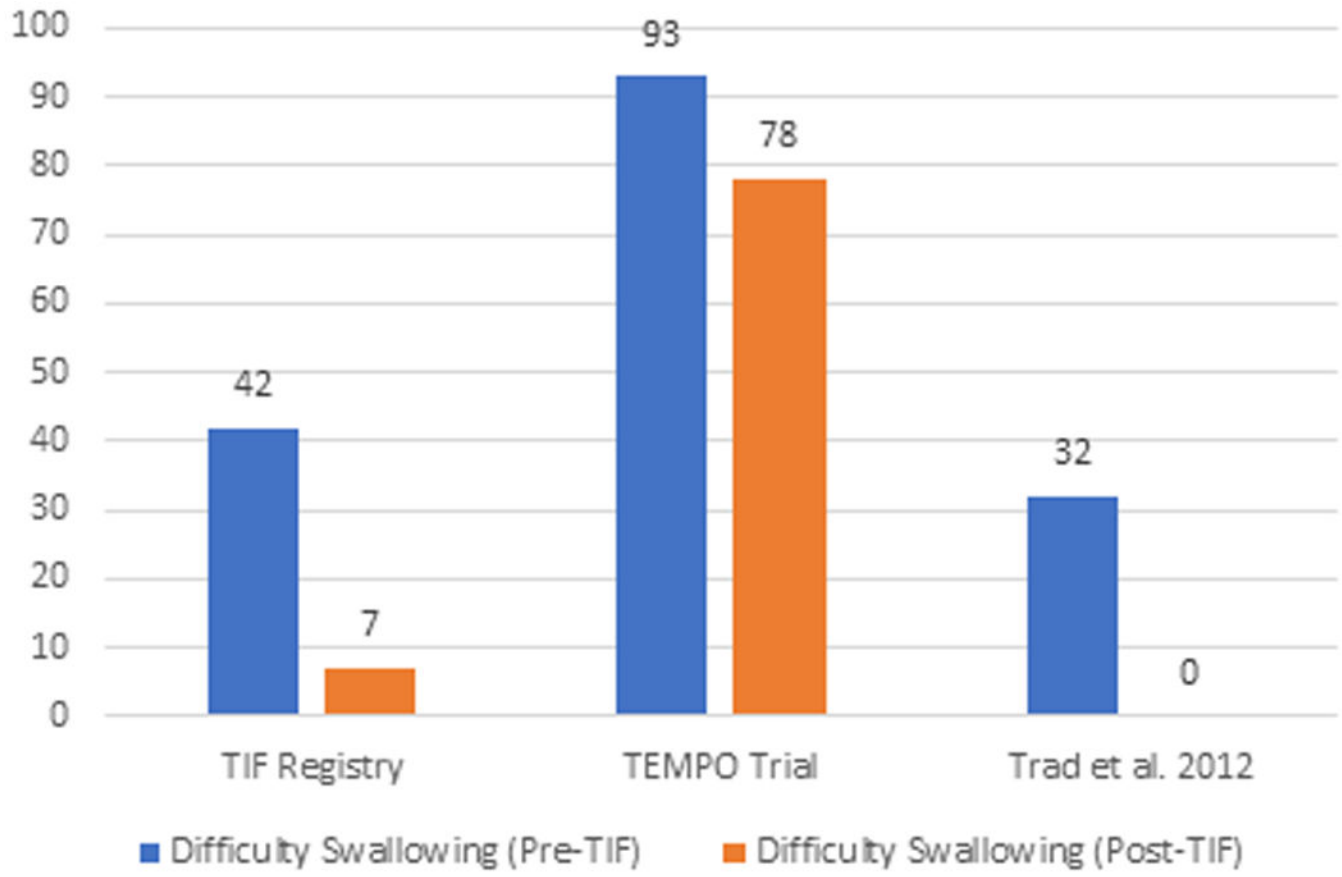
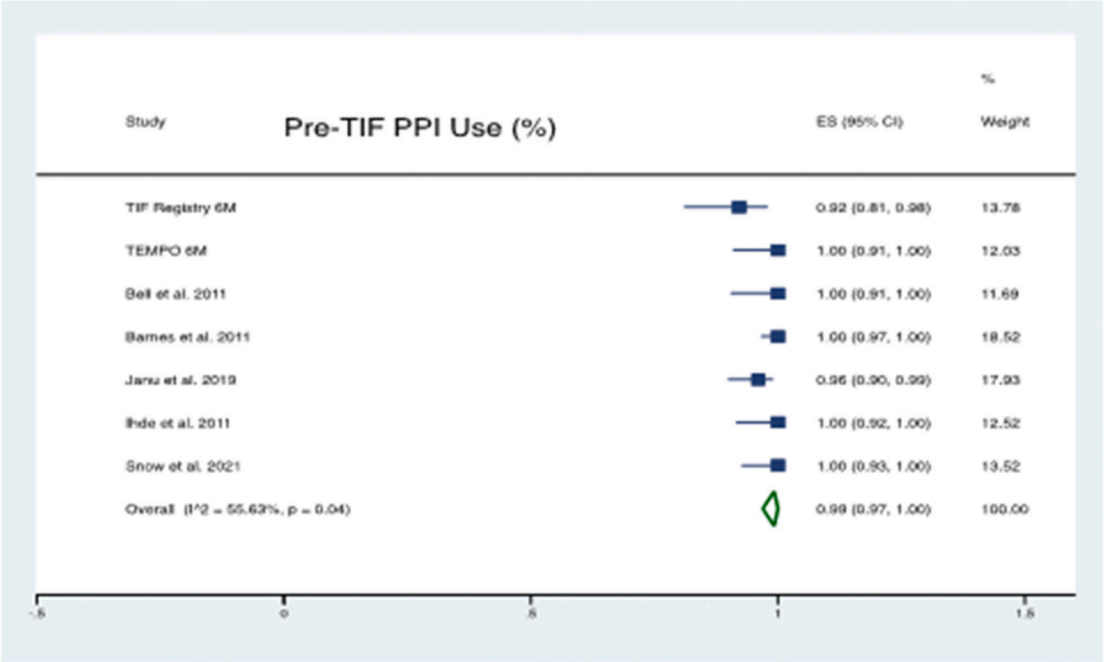
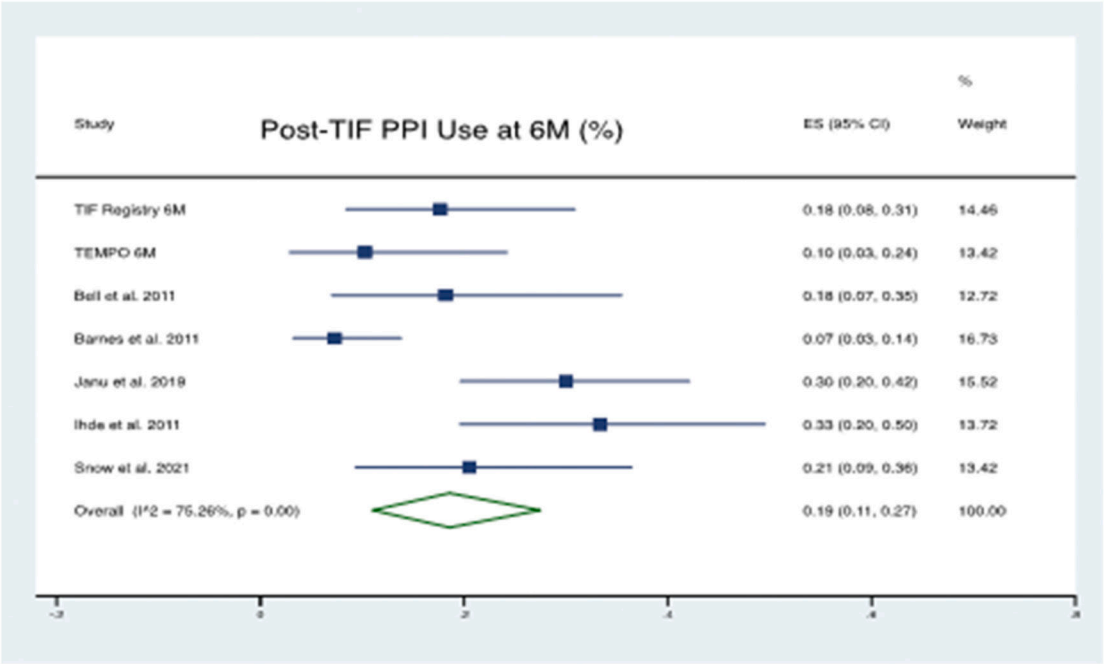


Figure 5 (A-H):

Elimination of Daily Troublesome atypical GERD symptoms (%). 5A: Hoarseness 5B: Clearing Throat 5C: Excess Throat Mucus 5D: Cough 5E: Cough after eating or lying flat 5F: Globus sensation 5G: Breathing difficulty 5H: Difficulty Swallowing



A



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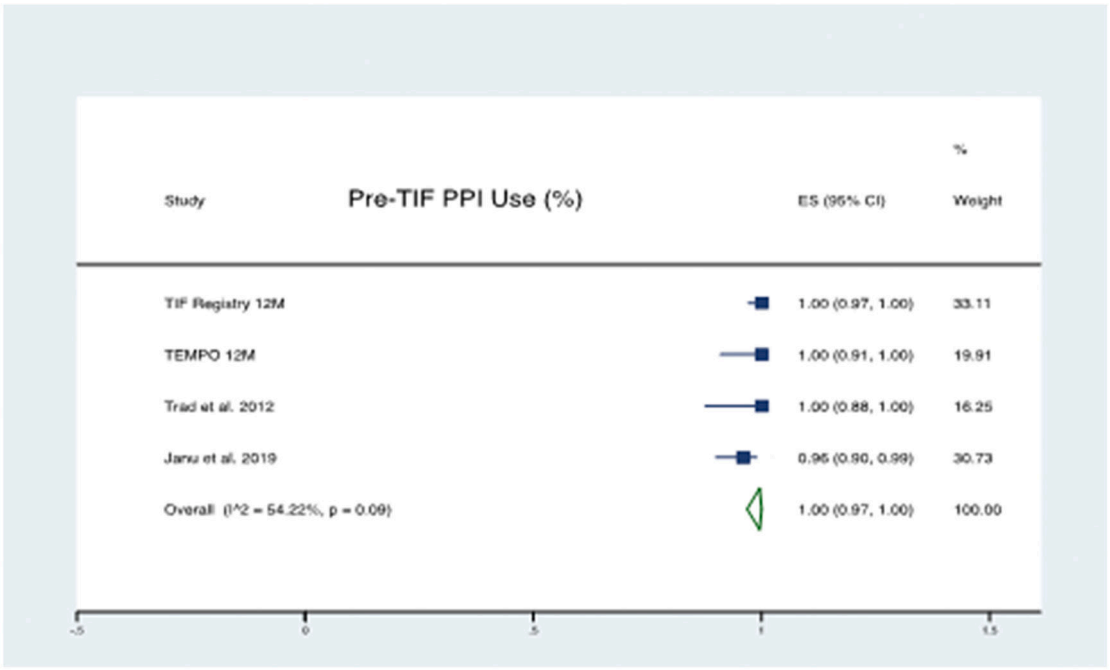

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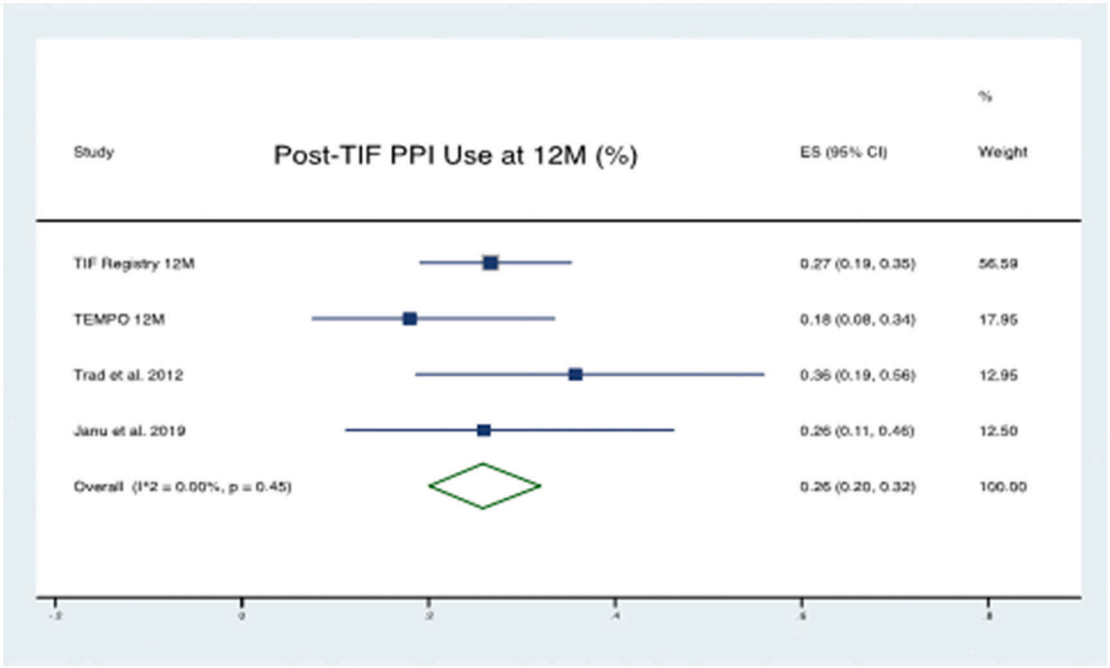

D

Figure 6 (A-D):

Forest plots of PPI Use Pre and Post TIF at 6 and 12 Month. 6A: Pre-TIF PPI Use (For 6 Month) 6B: Post-TIF PPI Use (At 6 Month) 6C: Pre-TIF PPI Use (For 12 Month) D: Post-TIF PPI Use (At 12 Month)

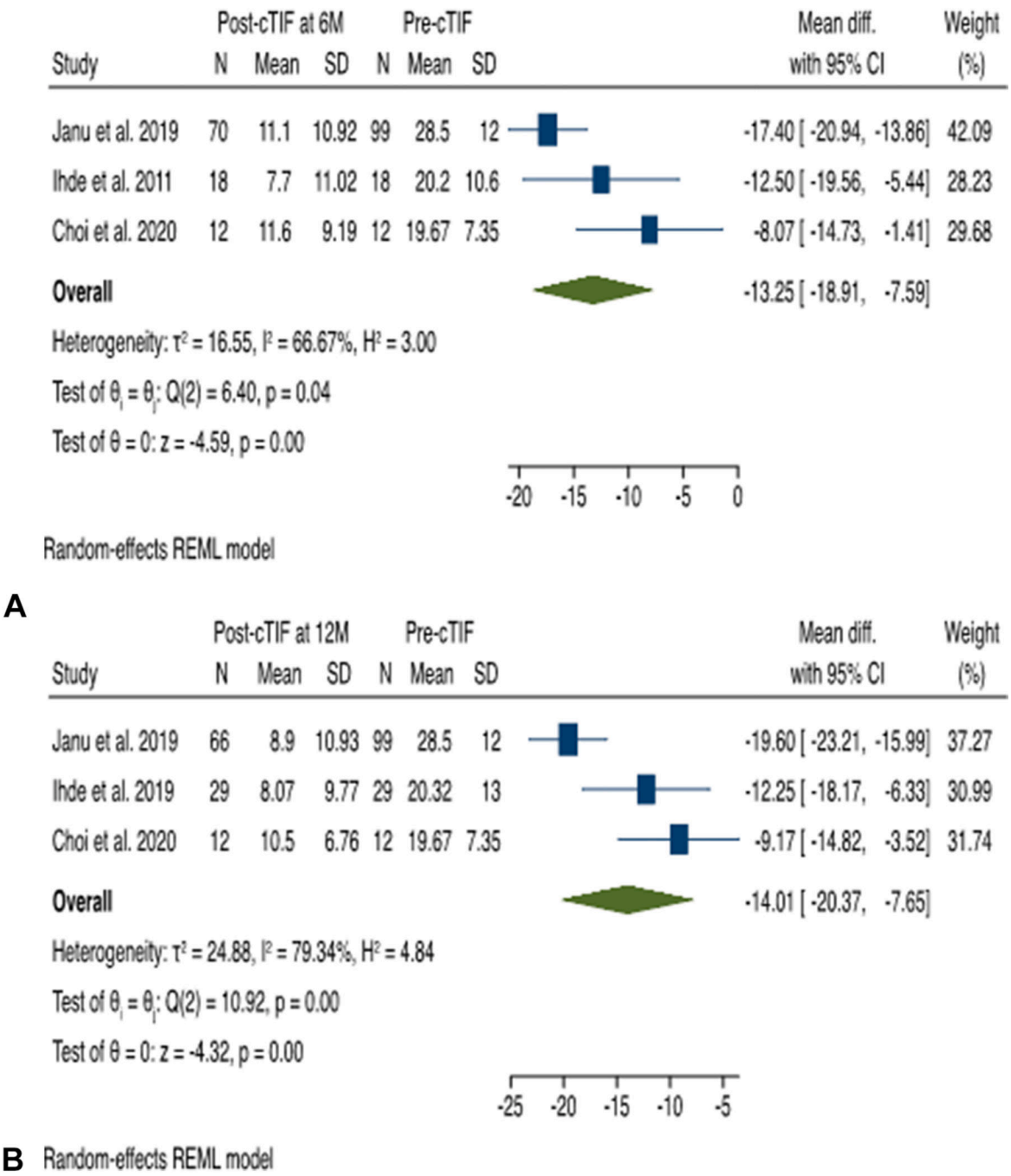

Figure 7 (A & B):
Effect Estimate of Reflux Symptom Index (RSI) score of cTIF. 7A: At 6 Month 7B: At 12 Month

Table 1a:

Study and Patient Characteristics:

Author, Year	Cohort Location	Study Design	Study Duration	Total patients (n)	Atypical GERD patients (n)	Age (yr)	Female, n (%)	BMI (kg/m^2)
Bell et al. 2012 (TIF Registry)	USA, Multicenter	Prospective	Jan 2010-Feb 2011	100	51	53 (18–75)	65 (65)	26.4 (18–35.1)
Wilson et al. 2014 (TIF Registry)	USA, Multicenter	Prospective	Jan 2010-Feb 2011	100	51	53 (18–75)	65 (65)	26.4 (18–35.1)
Bell et al. 2014 (TIF Registry)	USA, Multicenter	Prospective	Jan 2010-Jun 2012	158	124	58.5 (19–90)	112 (71)	.
Trad et al, 2014 (TEMPO Trial)	USA, Multicenter	RCT	2012–2013	60	39	54.8 (35.7–73.3)	20 (51)	28.9 (20.5–34.9)
Bell et al. 2011	USA, Single Center	Retrospective	Nov 2008-Oct 2009	37	32	58 (20–81)	21 (57)	25.5 (15.9–36.1)
Trad et al. 2012	USA, Single Center	Retrospective	May 2008-Jun 2010	28	27	57 (23–77)	14 (50)	25.7 (18.3–36.4)
Barnes et al. 2011	USA, Multicenter	Retrospective	Nov 2008-Dec 2009	110	NR	60 (21–87)	81 (74)	27.5 (19–47.9)
Janu et al. 2019	USA, Multicenter	Prospective	NR	99	NR	55	54 (55)	30
Ihde et al. 2011	USA, Multicenter	Retrospective	Nov 2009-Jun2010	42	NR	54 (21–72)	23 (55)	20.8–51.7
Ihde et al. 2019	USA, Single Center	Retrospective	Oct 2015- Dec 2017	97	29	59	~60 (61)	28
Choi et al. 2020	USA, Single Center	Prospective	Jan 2018-Jul 2020	60	12	59.3 (27–77)	28 (47)	30 (19.8–36)
Snow et al. 2021	USA, Multicenter	Prospective	Apr 2019– 2021	49	49	54.4 (13.5)	31 (63)	27.5 (4.3)

Abbreviations: RCT: randomized control trial; NR: not reported

Table 1b:

Study and Patient Characteristics.

Author, Year	Hiatal Hernia	HH ≤ 2cm	HH ≥ 2cm	Duration of Symptoms (yr)	Duration of PPI use (yr)
Bell et al. 2012 (TIF Registry)	43/51	42	1	9 (1–35)	7 (1–20)
Wilson et al. 2014 (TIF Registry)	43/51	42	1	9 (1–35)	7 (1–20)
Bell et al. 2014 (TIF Registry)	113/158	NR	NR	.	.
Trad et al, 2014 (TEMPO Trial)	36/39	36	0	10 (2–50)	7 (1–25)
Bell et al. 2011	25/37	NR	12	NR	NR
Trad et al. 2012	21/28	21	0	5 (1–20)	5 (1–11)
Barnes et al. 2011	70/110	51	19	9 (1–35)	8 (1–25)
Janu et al. 2019	99	0	99	10 (1–30)	NR
Ihde et al. 2011	NR	NR	18	10 (1–30)	NR
Ihde et al. 2019	NR	NR	29	NR	8
Choi et al. 2020	60/60	0	60	NR	NR
Snow et al. 2021	23/49	26	23	NR	NR

Abbreviations: HH: hiatal hernia

Table 2:

Procedure Details and Duration of follow up

Author, Year	cTIF	Procedure time (min)	Technical Success (%)	Major Adverse events (n)	Follow up
Bell et al. 2012 (TIF Registry)	No	42 (21–85)	100	0	6 M
Wilson et al. 2014 (TIF Registry)	No	42 (21–85)	100	0	12 M
Bell et al. 2014 (TIF Registry)	No	NR	98.7	2 (Small Esophageal tears)	6 M, 12 M, 24 M, 36 M
Trad et al, 2014 (TEMPO Trial)	No	38 (20–68)	100	0	6 M, 12 M
Bell et al. 2011	No	75 (45–110)	100	2 (Mediastinal Abscess POD 6, Bleeding from traumatic dislodgment of helical screws)	6 M
Trad et al. 2012	No	55	100	0	12 M-24 M
Barnes et al. 2011	No	45 (21–122)	99.2	1 (Hematoma formation)	6 M
Janu et al. 2019	Yes	NR	100	0	6 M, 12 M
Ihde et al. 2011	Yes	NR	97.9	1 (Esophageal Perforation)	6 M
Ihde et al. 2019	Yes	NR	NR	NR	6 M-12 M
Choi et al. 2020	Yes	90	100	3 (Esophageal mucosal tear, GI bleed + Ileus, Thrush + fever)	6 M, 12 M
Snow et al. 2021	Yes	NR	100	0	6 M

Abbreviations: M: month; NR: not reported