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Extracervical Approaches to Substernal Thyroid Goiter Resection: A Systematic Review and Meta-Analysis

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Abstract

Objective. To evaluate the prevalence of extracervical approaches (ECAs) for substernal goiter (SSG) excision.

Data Sources. Search strategies created in collaboration with a medical librarian were implemented using PubMed, Cochrane, Scopus, Web of Science, and Google Scholar from inception to July 2021.

Review Methods. Participants included adults ages >18 years undergoing SSG excision. The primary outcome was rate of ECA via sternotomy or thoracotomy. Studies were categorized into the 3 most common distinct definitions: goiter descending below the plane of the thoracic inlet (definition 1), ≥50% of thyroid mass extending below the sternal notch (definition 2), and goiter extending ≥3 cm below the suprasternal notch when the neck is hyperextended (definition 3). Two reviewers independently extracted data for analysis and performed a quality assessment using the Methodological Index for Non-Randomized Studies criteria.

Results. Of the 551 studies identified, 69 studies were included for analysis. Definition 1 included 3441 patients from 31 studies; definition 2 included 2957 patients from 26 studies; and definition 3 included 2921 patients from 12 studies. A random-effect model estimating the pooled prevalence of ECA using definition 1 resulted in prevalence of 6.12% (95% confidence interval: 3.48-9.34, $I^2 = 90.72\%$).

Conclusion. Extension below the thoracic inlet is the most widely used definition of SSG. Approximately 6% of patients with a SSG undergo an ECA. Patients with SSG undergoing surgery should be counseled on the prevalence, risks, and morbidity of an ECA in the rare occurrence it is needed.

Keywords

extracervical approaches, goiter, retrosternal, sternotomy, substernal, thoracotomy

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Presenting as an enlarged thyroid gland, a goiter is most commonly defined as thyroid tissue double the normal size or weighing more than 40 g.[1] Since Haller first described a substernal goiter (SSG) in 1749,[1] there has been a failure to establish standardization for defining a SSG. The American Thyroid Association (ATA) defines a SSG as a goiter extending past the sternal notch with the patient in the supine position, detected either radiologically or clinically.[2] Another system utilizes a 1 to 3 grading system based on the goiter location (in relation to the aortic arch and right atrium) as well as the recommended surgical approach.[1,3] Arguably, the 2 most widely used definitions are a goiter that extends below the thoracic inlet or a goiter with ≥50% of its mass residing inferior to the thoracic inlet.[4-6] Nonetheless, the lack of a standardized definition may explain the wide range of reported prevalence of SSG of 2% to 19% among all patients with a goiter.[1,3,4,7-12]

Proper identification of patients with a SSG may also be challenging. Doulapsti et al stated that failure to palpate the inferior edge of the thyroid gland with the neck extended on clinical examination should create suspicion for the presence of a SSG.[13] Ultrasound imaging can confirm thyroid extension beyond the sternal notch, but the current gold standard for preoperative assessment is a computed tomography scan.[3,7-9,13]

Enlargement of SSGs can compress the trachea, esophagus, and the great vessels because of mass effect.

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These patients may have coughing, dyspnea, stridor, choking, and dysphagia as a consequence of compression, which is a clear indication for surgical removal.[2,7,14] Surgical excision is also indicated in malignancies or goiters with a suspicion for malignancy. Removal of asymptomatic SSG has also been advocated in order to avoid adverse events associated with further expansion.[2] Medical therapy may be effective in partially reducing gland size in some cases,[2,15,16] but surgical intervention with thyroidectomy provides definitive treatment.[2,7,8] There is a clear consensus that most thyroidectomies to remove SSGs can be achieved solely by a cervical approach, but in rare circumstances, an extracervical approach (ECA) requiring a sternotomy or thoracotomy may be necessary.[3,8,9] In most series, ECA are reported to be necessary 1% to 11% of the time, although a systematic review to thoroughly investigate this frequency has not been performed. Therefore, our objective was to systematically review the literature and conduct a Meta-analysis to determine the prevalence of ECA for SSG excision.

Methods

The conduct of this systematic review was guided by the 2020 Preferred Reporting Items for Systematic Reviews and Meta-analysis guidelines after confirming there were no existing and similar systematic reviews that had been conducted on the research topic. Given the study design, this was exempt from full review by the institutional review board at Rutgers Robert Wood Johnson University Hospital in New Brunswick. The Population, Intervention, Comparator, Outcome, and Study design were the following:

Population: patients (>18 years) diagnosed with SSG.
Intervention: surgical excision via thyroidectomy.
Comparator: not applicable.
Outcome: rate of thoracic approach via sternotomy/thoracotomy.
Study design: case series, prospective and retrospective cohort studies, and randomized control trials.

The review protocol was submitted to the International Prospective *Register* of Systematic Reviews (PROSPERO) registry (prospero.com/ECA Approaches During Resection of Substernal Thyroid Goiter).

A systematic review was initiated utilizing 5 databases: PubMed, Cochrane Library, Scopus, Web of Sciences, and Google Scholar. This was conducted using a search strategy created in conjunction with a medical librarian (Y.Z.) of literature on management of SSG via an ECA published from inception to July 2021. Search strategies were extensively tested in PubMed and reviewed by the research team before finalization and adoption. Search terms and strategies were adapted accordingly to search other databases. Final search strategies for each database are detailed in the Supplemental S1, available online.

A total of 756 references were obtained. EndNote 20 (Clarivate Analytics, 2021) was used for management of search results, which identified 216 duplicates. The remaining 540 references were exported from EndNote into Rayyan (http://rayyan.qcri.org)[17] for title and abstract screening by 2 independent reviewers (N.S.K. and C.A.B.). One hundred and five references were selected for full-text screening. Of these, 8 reports were unable to be retrieved. Ninety-seven full-text reports were retrieved and independently screened by the same 2 reviewers. Thirty-nine reports did not meet inclusion criteria and were excluded. Manual review identified 11 more reports for inclusion in the final set of reports selected for analysis. **Figure 1** details study identification, screening, and final selection.

Study Selection

After removal of duplicate publications, studies were screened by title and then relevant abstracts were reviewed. A study was excluded if it was: not published in a peer-reviewed journal, the incorrect study design, the wrong outcome, the wrong population, published before 1991, or not available in English. Full-text screening was then conducted on reports retrieved by both reviewers. Studies were excluded if they contained any of the criteria listed above or contained an overlapping cohort, or an absent/improper definition of SSG. Each reviewer was initially blinded to the other reviewer's results in Rayyan. Any discrepancy led to a discussion for the reasoning of their decision and eventual resolution.

Data Extraction and Synthesis

A preliminary literature review was conducted to examine the most commonly used definitions for SSG classification. Based on this review, studies were categorized into the 3 most common definitions: a goiter descending below the plane of the thoracic inlet (definition 1), ≥50% of thyroid mass extending below the sternal notch (definition 2), and a goiter extending ≥3 cm below the suprasternal notch when the neck is hyperextended (definitions 3). Data extracted from each study included the total number of patients with SSG and the number of patients undergoing an ECA.

Summary Measures and Statistical Analysis

Because of the inherent overlap between the definitions, the statistical analysis was restricted to definition 1. This definition was selected because it was the most prevalent definition in the literature, and it was the definition utilized by the ATA in their position statement on surgical management of SSG.[2] Both fixed-effects and random-effects Meta-analyses were performed to estimate the pooled prevalence of ECA with 95% confidence intervals (CI). The analysis was performed using the Freeman-Tukey double arcsine transformation of proportions to avoid input of a continuity correction for studies

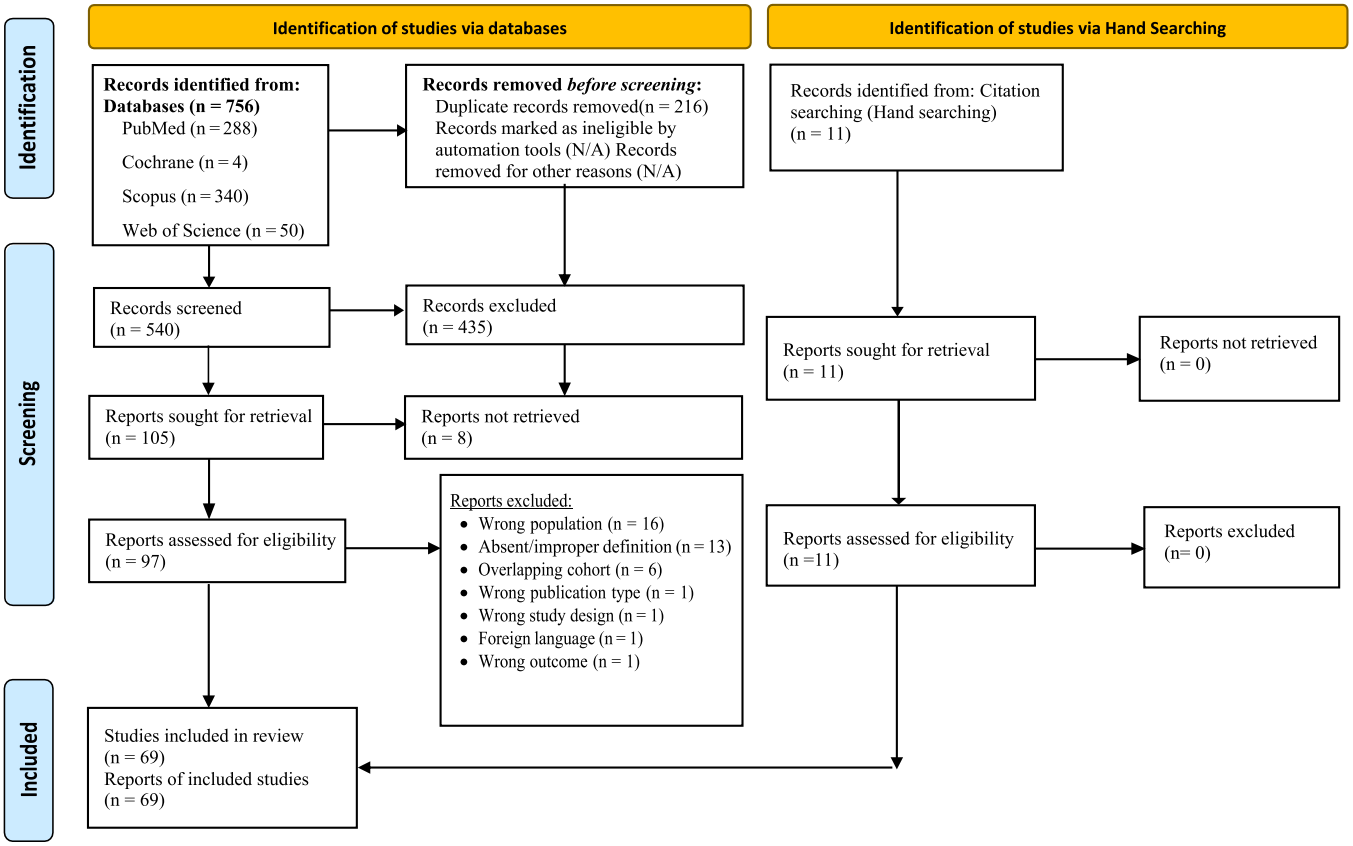


Figure 1. Flow diagram for assessment of eligible studies in the systematic review and Meta-analysis.

of zero prevalence and to stabilize the variance.[18] Score confidence intervals were used to provide coverage close to the nominal level and more narrow CI compared to the exact method.[19] The *metaprop one ftt random cimethod (score) second(fixed)* command was used and results are presented using forest plots.

Cochran's Q statistic and the I^2 statistic were used to assess and quantify heterogeneity. For Cochran's Q statistic, a value of $P < .05$ was considered to demonstrate heterogeneity among studies. I^2 values of 25%, 50% and 75% were reported to provide evidence of low, moderate, and high heterogeneity, respectively. In concordance with previous studies of Meta-analyses of proportions showing that funnel plots may be an inaccurate method of assessing publication bias,[20] the preferred Doi plots were created, in addition to funnel plots, to visually assess for possible publication bias using the *doiplot, df* command.[21] Due to the subjectivity of these visual assessments, Egger's weighted regression test was used to measure the degree of funnel plot asymmetry, and the Luis Furuya-Kanamori (LFK) index was used to assess for Doi plot symmetry.[21,22] All statistical analyses were performed in Stata 17.0 (StataCorp).

Quality Assessment

Two authors (N.S.K. and C.A.B.) independently performed a bias assessment through the Methodological Index for Non-Randomized Studies criteria (MINORS). This tool has a maximum score of 16 for noncomparative studies and 24 for comparative studies.

Results

Characteristics of the Studies

Full-text screening and application of exclusion and inclusion criteria produced 69 studies for qualitative and quantitative analysis (**Figure 1**). All studies were case series or prospective or retrospective cohort studies. Of the 69 records, 31 studies were classified into definition 1, 26 articles into definition 2, and 12 records into definition 3 (**Table 1**). The median study length was 10 (definition 1), 9 (definition 2), and 11.5 years (definition 3). However, 5 studies did not provide years that were examined.

Quality Assessment

Quality assessment using the MINORS criteria for all 69 articles can be found in the Supplemental S2, available online. The cumulative mean for each category and reviewer can be found in the Supplemental S3, available online.

Meta-Analysis

Meta-analyses for definition 1 was performed using fixed and random effects models to estimate the prevalence of

Table 1. Patient Demographics and Article Characteristics by (a) Definition 1, (b) Definition 2, and (c) Definition 3

(a)			
Number of articles	Patients with substernal goiter	Patients with thoracic approach	Average rate of thoracic approach
31	3441	203	5.9%
(b)			
Number of articles	Patients with substernal goiter	Patients with thoracic approach	Average rate of thoracic approach
26	2957	290	9.8%
(c)			
Number of articles	Patients with substernal goiter	Patients with thoracic approach	Average rate of thoracic approach
12	2921	84	2.9%

ECA during resection of SSG. The estimated prevalence in the random effects model was 6.12% (95% CI: 3.48-9.34) (**Figure 2**). There was a high degree of heterogeneity present ($I^2 = 90.72\%$; Cochran's Q statistic, $P < .001$). Because of the high degree of heterogeneity, the results of the fixed effects model are not reported.

Publication Bias

For the visual assessment of the presence of publication bias, funnel plots and doi plots were created to visually assess for publication bias and are depicted in **Figure 3**. Due to the subjectivity of these visual assessments, Egger's weighted regression test was also used to measure the degree of funnel plot asymmetry and the LFK index to assess for Doi plot symmetry. For definition 1, Egger's test suggests asymmetry ($P < .05$), indicating the presence of publication bias.

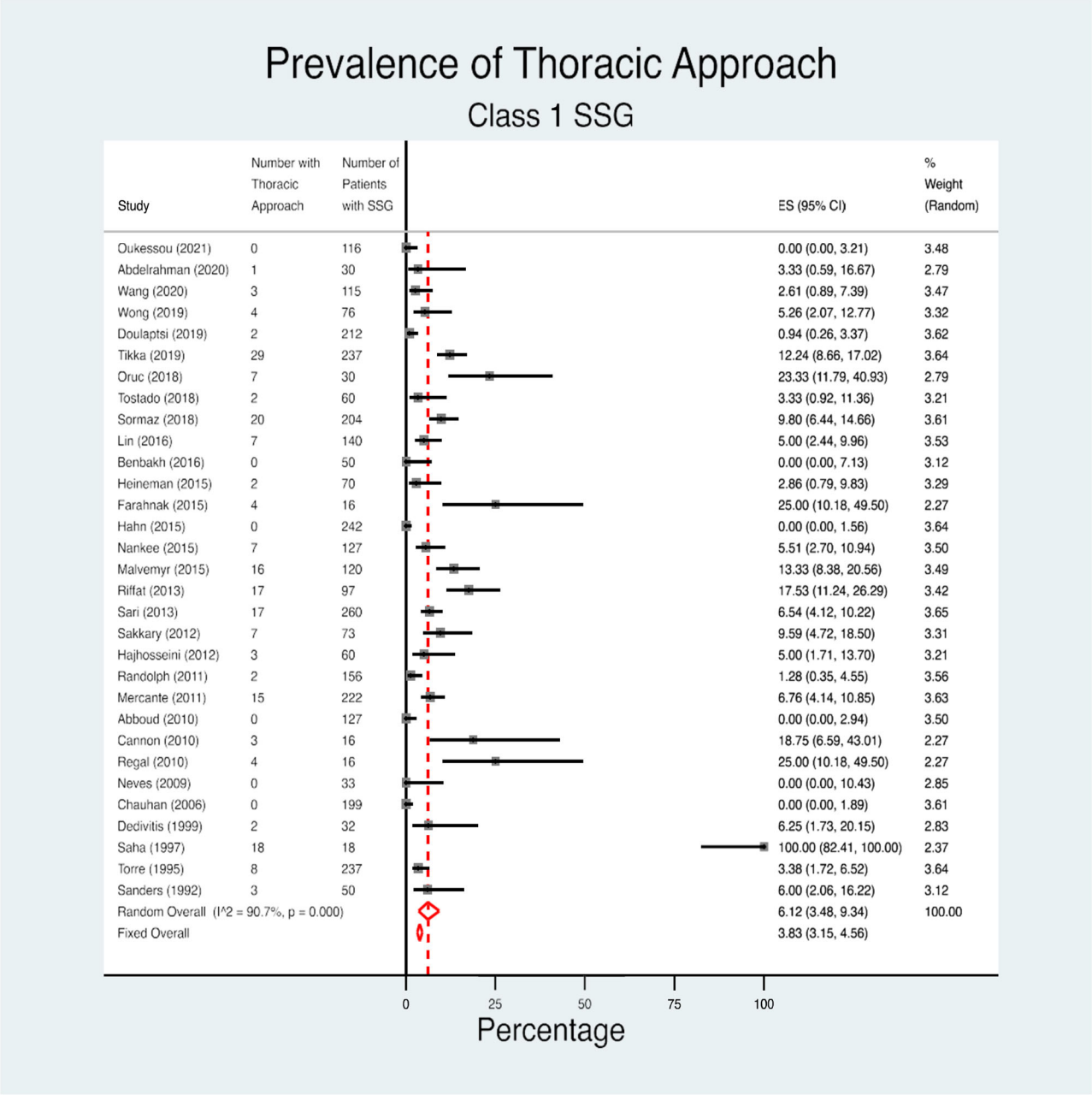
Discussion

The recommended treatment of SSG is thyroidectomy, especially in patients with compressive symptoms (dyspnea, orthopnea, hoarseness, and dysphagia).[2,13] The majority of SSGs can be managed through a cervical approach, but there are rare exceptions where an ECA may be necessary for safe removal. Current views differ on the role of ECA during SSG excision. Cho et al[23] recommend a transcervical approach for goiters that extend as far inferiorly as the aortic arch, unless there is evidence of a malignancy or loss of normal tissue planes within the mediastinum, in which case a median sternotomy may be necessary. Conversely, Saha et al[24] advocated for an ECA in all cases of SSG, and reported an ECA rate of 100% in their series of 18 cases. It is important to note this series was conducted by cardiothoracic surgeons, suggesting that surgeon subspecialty may also play a role the predication for an ECA. Even so, the rates of ECA for SSG excision are highly variable, and their prevalence has not been thoroughly investigated prior to the current study.[1,9,25,26] Our random effects model estimated a prevalence of 6.12%, with a considerable amount of heterogeneity present.

SSGs have also been described as retrosternal, intrathoracic, or mediastinal goiters.[3] This grammatical assortment combined with lack of a uniform SSG definition may be contributing to the highly variable prevalence reports in the literature, ranging from 1% to 11%.[27,28] In this study, we initially chose 3 of the most prevalent definitions of SSG based on a preliminary literature review. Our work revealed that extension below the sternal notch (definition 1) was the most widely used definition of a SSG and was also selected by the ATA for their position statement on the surgical management of SSG in 2014.[2] Because of overlapping criteria in the 3 definitions initially created and the reasons mentioned above, we isolated our Meta-analysis to definition 1.

The lack of homogeneity in the literature has stalled the identification of evidence-based indicators for an ECA, and smaller series provide lower quality evidence. A retrospective study found 6% of their cohort required sternotomy with predisposing factors including recurrent goiter with previous cervical thyroidectomy, primary mediastinal goiter, and invasive carcinoma.[29] Additional factors identified by Huins et al[3] and Cohen and Cho[30] included goiter size, volume, and extent of thoracic involvement. Furthermore, extension below the aortic arch and posterior mediastinum involvement were found to be the most predictive factors for an ECA in several series.[3,16,30,31]

The traditional ECA for most SSG is a sternotomy, while a posterolateral thoracotomy may offer better exposure for SSG with significant posterior mediastinal extension. Minimally invasive surgical approaches, such as video-assisted thoracoscopic surgery (VATS) and robotically assisted thoracoscopic surgery (RATS), have been increasingly utilized in thoracic surgery and are associated with quicker recovery, less pain, and reduced hospital length of stay compared to open approaches.[32,33] Despite increasing use of minimally invasive techniques in other settings, existing literature on surgically treated SSG consists almost exclusively of patients undergoing open approaches. The use of minimally invasive techniques in this population is mainly restricted to case reports for planned excision of posterior mediastinal goiters and ectopic intrathoracic goiters.[34-36] Furthermore, the requirement of specialized equipment for VATS and RATS makes these approaches less amenable to emergent conversion to an ECA compared to a traditional open



Random Pooled ES 6.12 (3.48, 9.34)

Heterogeneity $X^2 = 323.30$ (d.f. = 30), p = 0.00

$I^2 = 90.72\%$, p = 0.000

$Tau^2 = 0.09$

Test of ES = 0: z = 6.78, p = 0.00

Figure 2. Meta-analysis of studies utilizing definition 1 for the prevalence of an extracervical approach for substernal goiter (SSG) excision. CI, confidence interval; ES, effect size.

approach. In the future, minimally invasive surgery may provide an alternative to treat SSG necessitating an ECA, although more published data is needed to provide a reliable recommendation.

ECAs are indeed required in a minority of cases, but they are associated with significantly increased complexity of care and risk of morbidity. Treating physicians should be aware of the prevalence and

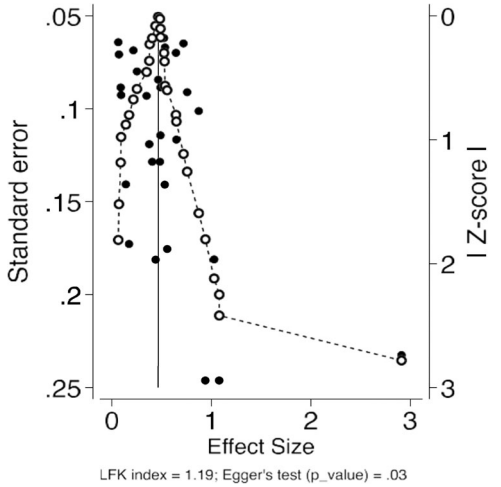


Figure 3. Assessment of publication bias for the prevalence of extracervical excision of substernal goiter as defined by the American Thyroid Association. LFK, Luis Furuya-Kanamori.

subsequent risks for optimal preoperative patient counselling. Although some argue that ECA have similar rates of permanent complications to a cervical approach, Nankee and colleagues found that ECA are associated with significantly increased operative time, length of hospital stay, and blood loss.[7,16,37] In a review of 2716 patients using the National Surgical Quality Improvement Program, Khan et al found that ECA were associated with increased odds of unplanned reintubation, blood transfusions, and longer hospital stays.[38] Additionally, ECA require preoperative multidisciplinary discussions between multiple surgical specialties to review the most appropriate route of surgery. This consultation may be difficult in resource limited settings which may necessitate referral to larger volume centers. Furthermore, with VATS and RATS emerging as less invasive alternatives to sternotomy/thoracotomy, the decision to pursue this avenue may not be as accessible intraoperatively, as significant equipment and personal preparation is needed with VATS and RATS compared to traditional ECA.

This systematic review and Meta-analysis has several limitations. The studies included in the analysis were case series and cohort (prospective and retrospective) studies composed of relatively small numbers of patients. As discussed above, the numerous definitions of SSG in the literature create challenges in comparing different reports. Our review was limited to the 3 most commonly used definitions, and our Meta-analysis was isolated to 1 definition. This creates a selection bias as it excludes the remaining definitions in the literature and restricts the studies included in the Meta-analysis. Additionally, a Meta-analysis of risk factors associated with an ECA would be valuable to surgeons; however, the combination of inconsistent reporting and heterogeneity displayed precluded a formal analysis. Finally, there was evidence of the possibility of publication bias as detailed in the results section. As a result of these inherent limitations, the true rate of ECA may differ from the findings of this Meta-analysis.

Conclusion

This is the first systematic review and Meta-analysis assessing the prevalence of ECA for SSG excision based on the most used definition: extension below the sternal notch. Although this analysis revealed that approximately 6% of patients undergo an ECA, the true rate may differ due to the bias of the existing studies. Nevertheless, patients with SSG undergoing surgical removal should be counseled on the prevalence, risks, and morbidity of an ECA in the rare occurrence it is needed for safe removal of the goiter.

Author Contributions

Najm S. Khan, contributed to study conduction, interpreting results, and writing; **Yingting Zhang**, contributed to study conduction and writing; **Kassie Bollig**, contributed to data analysis and writing; **Craig A. Bollig**, was the supervising author and contributed to study formulation, data analysis, and writing.

Disclosures

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Supplemental Material

Additional supporting information is available in the online version of the article.

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