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Original Research

Somatostatin Therapy and Surgical Outcomes in Acromegaly: Insights From a Systematic Review and Meta-analysis

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Abstract

The management of acromegaly, a chronic hormone disorder characterized by excessive growth hormone (GH) secretion, remains a subject of debate. This systematic review and meta-analysis aim to evaluate the impact of preoperative somatostatin analog (SA) treatment on surgical outcomes in acromegaly patients. A comprehensive search of medical databases was conducted following PRISMA guidelines, resulting in the inclusion of 15 studies published between 2013 and 2024, encompassing 4,387 patients with an average age of 46-47 years. The primary outcomes analyzed were surgical remission rates, postoperative GH levels, tumor volume reduction, and complication rates. Studies indicate that preoperative SA treatment significantly improves remission rates and reduces postoperative GH levels compared to surgery alone. For instance, one study reported a biochemical control rate of 59.5% in the SA group versus 46.5% in the non-SA group. Another study showed that preoperative SA treatment led to a higher rate of tumor volume reduction (62.5% vs. 53.7%). Additionally, patients treated with SAs experienced fewer surgical complications and higher rates of biochemical control. Despite the higher initial costs associated with SA treatment, long-term benefits such as reduced complications and enhanced surgical outcomes suggest it is a cost-effective approach. However, the analysis also highlights the need for further research on long-term outcomes, recurrence rates, patient quality of life, and the overall cost-effectiveness of preoperative SA treatment. This study provides evidence supporting the integration of medical management into the preoperative care plan for acromegaly patients, emphasizing the potential benefits of SA treatment in improving surgical outcomes.

Keywords: Preoperative Somatostatin therapy, Acromegaly, post-operative outcome, surgical treatment, cost-effectiveness

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INTRODUCTION

The management of acromegaly, a chronic hormone disorder characterized by the excessive growth of growth hormone (GH), has long been a subject of debate among endocrinologists and neurosurgeons[1,2]. However, proponents of preoperative somatostatin treatment argue that it reduces tumour size and hormonal activity, thereby enhancing the success rate of surgical interventions[3]. This approach has been supported by studies demonstrating improved surgical outcomes and reduced perioperative complications[4]. Contrarily to this, critics also argue that the benefits of preoperative medical management are marginal and do not justify the additional costs and potential side effects associated with prolonged drug therapy[5]. Furthermore, some argue that immediate surgical intervention without prior medical management yields comparable results, emphasizing the need for comprehensive evaluation to reach an agreement[6].

Acromegaly, is typically caused by GH-secreting pituitary adenoma (benign tumour)[7,8]. An excessive production of insulin-like growth factor 1 (IGF-1) due to excessive production of GH, results in the overgrowth of bones and tissues. It gets worst over the time if not treated, and results in life threatening

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various systemic complications. Usually, Transsphenoidal surgery (surgical resection of micro or macroadenomas) is the first choice for treating acromegaly patients[9]. However, Somatostatin analogues, including octreotide and lantreotide, either considered as an adjuvant and used preoperatively to control the GH and IGF-1 secretion, reducing the tumour size and softening its consistency[10]. Due to these characteristics, these drugs act like natural hormone, show promising efficacy in subsequent surgical interventions[11].

Therefore, this review aims to investigate whether or not preoperative somatostatin treatment (Pre-SA) improve the surgical outcomes in acromegaly patients[12]. Additionally, the meta-analysis of recent studies published in the last eleven years, will systematically evaluate the effectiveness of preoperative somatostatin analogue therapy compared to surgery alone, will focus on the key outcomes including remission rates, postoperative GH levels and complication rates, to understand the advantages and disadvantages of integrating medical management into the preoperative care plans for acromegaly patients[13,14,15,16].

Despite being numerous studies available in the literature, knowledge gap persists. Although, studies supporting promising potential and results in short cure but fails to provide information on long term results and recurrence rates[17]. Also, limited information is present for patient quality of life and functional status which is critical for a holistic evaluation of treatment efficacy. The impact of somatostatin preoperative treatment on surgical complications and influence on cost effectiveness remain under research.

It will be achieved by employing a systematic approach following PRISMA guidelines and relevant studies will be identified through a comprehensive research of medical databases. Inclusion criteria will encompass studies including cohort studies, randomized controlled trials and case studies that compare surgical outcomes in acromegaly patients with our without preoperative somatostatin treatment. The data extraction will be focused on treatment protocols and clinical outcomes. Overall it aims to provide a valuable contribution to existing literature and guide clinical decision making in the management of acromegaly.

METHODS

To conduct and present this study, the Preferred Reporting Items for Meta-Analysis in 2015 and 2020 was followed[18].

Study Design

A meta-analysis, used a systematic approach following PRISMA guidelines[18]. Employing a comprehensive research of medical databases, help in identification of relevant studies. It included randomized controlled trials (RCT), on the basis of cohort studies, prospective, case control and observational studies. It involved all the patients who were diagnosed with acromegaly and were randomized into intervention of surgical procedure having Somatostatin as a preoperative therapy (experimental group) compared to patients having surgical procedure without Somatostatin (control group). The outcomes of patients with and without preoperative therapy especially Somatostatin during surgical procedure were compared.

Literature Search Strategy

A search strategy comprised of a comprehensive search conducted through using different search engines like PubMed, Medline, Cochrane Library and Google Scholar from the time period of 2013 to 2024. While searching the keywords like “acromegaly”, “somatostatin analogy”, “somatostatin analogues”, “preoperative treatment”, “surgical intervention of acromegaly patients” and “surgical outcomes” were used. Moreover, studies separately for only surgical intervention having outcomes and studies alone with somatostatin treatment were searched. Google Scholar was used extensively, as studies on specifically somatostatin preoperative treatment outcomes were found comparatively less as expected and if found it lacked valuables statistical values, therefore extensive search for outcomes either present altogether in one study or superlatively was gathered. In addition, these sources directly included hand searching references list and contracting experts.

Selection Criteria

An inclusion criteria are studies with the acromegaly patients that undergoes through pituitary adenoma surgery, also investigating the preoperative somatostatin analogy and this reporting is relevant to a surgical outcome. It included all relevant studies either discussing one out come or several outcomes but with valuable statistical values for meta-analysis but previous systematic reviews were also included to have a comprehensive systematic review. An exclusion criterion includes case report, meta-analysis on same topic, systematic reviews and meta-analysis on same title, reviews, editorial, studies without a clear preoperative treatment details. Also recent studies which were paid, inaccessible, and had descriptive outcomes or insufficient statistical values were excluded for meta-analysis. The non-surgical studies, Non-English publication without translations and those which lacks a sufficient outcome data.

Inclusion and Exclusion Criteria

	Inclusion criteria	Exclusion Criteria
1. Study Characteristics	• Randomized controlled trials (RCTs), cohort studies, case-control studies, reviews • Published studies	• Editorials, letters to the editor, meta-analyses. • Unpublished studies, studies without peer review.
2. Population	Acromegaly patients treated with and without preoperative somatostatin surgical resection.	Acromegaly patients with radiotherapy Acromegaly patients treated with or without other preoperative analogues other than somatostatin (dopamine agonist) Studies with unclear type or duration of treatment

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3. Intervention and Comparator	Preoperative treatment with somatostatin analogs vs without somatostatin	Studies not involving somatostatin analogs, not defining clear treatment
4. Outcomes	Surgical outcomes such as remission rates, postoperative GH levels and complication rates	Studies not reporting relevant surgical outcomes
5. Study Duration	> 12 weeks	< 12 weeks
6. Language	English	Languages other than English or untranslatable
7. Publication Year	(2013-2024)	Years < 2013

Study Selection

The study selection procedure was involved initial screening of the titles and abstracts on the basis of inclusion and exclusion criteria. Two reviewers carefully screened the titles and abstracts while doing a literature research. The studies which were following the inclusion criteria were selected for further reading while rest were excluded. This was followed through full text for an eligibility confirmation. A PRISMA flow diagram (Figure 1) was documented through selection procedure.

Data Extraction

The data was extracted through using a standardize form to ensure consistency, and extraction was included study characteristics like author name, year and design. A population details like sample size, and demographics and a specific intervention (duration, somatostatin to analogy treatment) and surgery without this pre-operative medical treatment. The data was also extracted through an outcome like surgery, Growth hormones levels, tumor volume, biochemical remission.

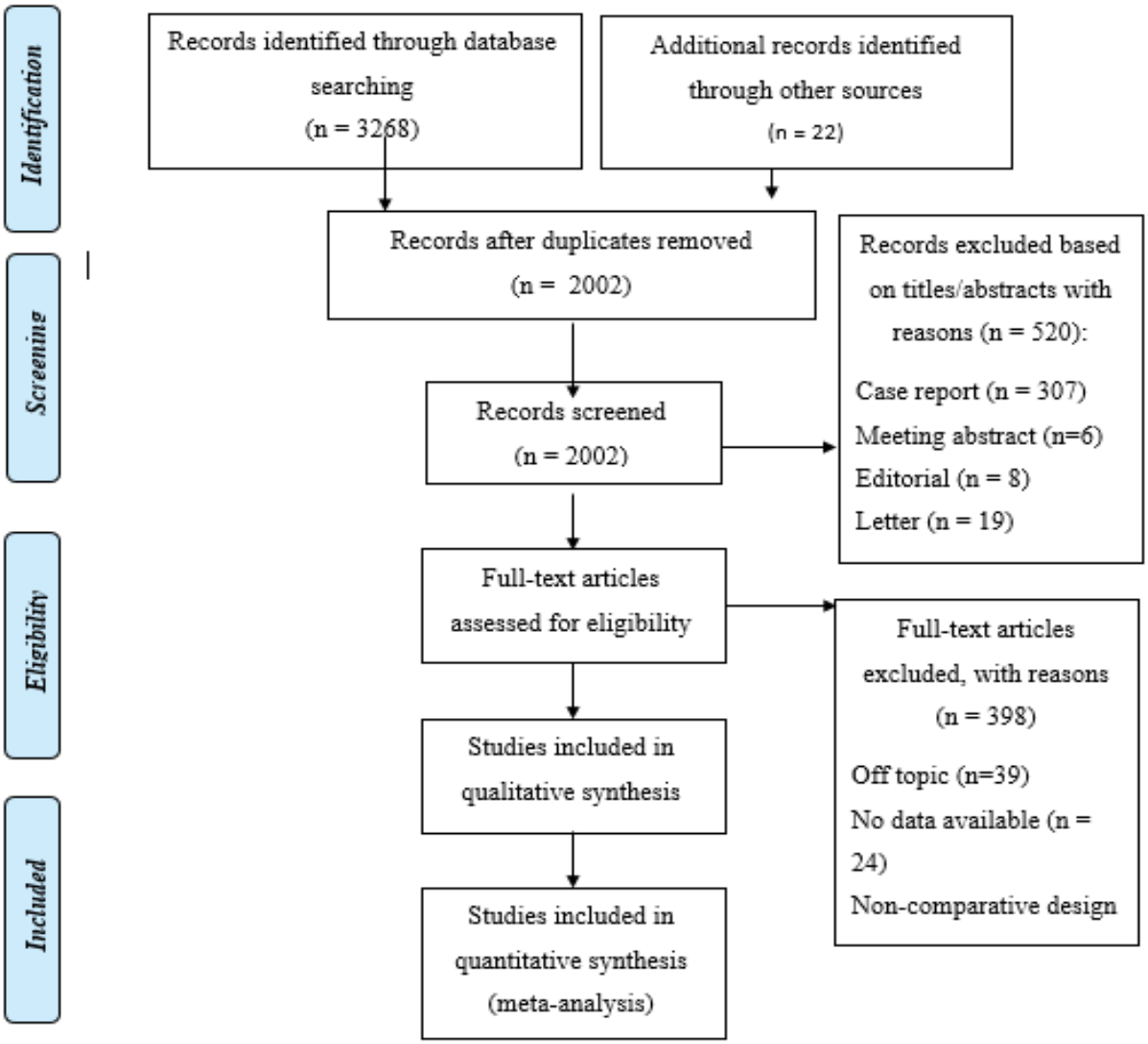

Figure 1. PRISMA Flow Diagram

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Quality Assessment

A quality and risk of the bias included studies that was assessed by the use of Cochrane Risk of the bias tool for RCT and Newcastle-Ottawa for its observational studies. Each study was evaluated through criteria such as a selection bias, performance bias, detection and reporting bias.

Data Synthesis and Analysis

A data has been synthesized through a random-effects model to account for its variability among studies. A primary analysis was focused on surgical remission, the tumour volume reduction, complicated rates, a biochemical remission and mortality rate.

Publication Bias

A publication bias was assessed through the applicability of funnel plots tests like Egger's test and strategies to interpret results to potential bias was discussed.

RESULTS

Study Characteristics

This systematic and meta-analysis encompassed of fifteen recent studies published in latest 12 years, between the year 2013 to 2024 (Table 1). The total number of acromegaly patients were 4387 of averagely from the middle adulthood, aged 46 to 47 years old (average). The predominant study designs were retrospective cohort studies, having an individual sample sizes ranged from 48-1294 patients. Moreover, major contribution was from latest systematic reviews have been used for mean values of outcome.

Table 1. Study Characteristics for Assessment

Author	Year	Study Design	Sample Size	Treated Group	Untreated Group	Outcome	DOI
Colao et al.	2016	Retrospective Cohort	1294	Somatostatin analogs before surgery	No pre-treatment	Biochemical control rate: 59.5% vs. 46.5%; Tumor volume reduction: 62.5% vs. 53.7%	10.1007/s11102-015-0677-y
Rotermund et al.	2020	Narrative Review	NA	NA	NA	Not reported	10.3171/2020.3.FOCUS2061
Jacob et al.	2014	Retrospective Cohort	1317	NA	NA	Mortality, cardiovascular events, diabetes	10.1111/cen.12553
M. Araujo-Castro et al.	2021	Narrative Review	NA	NA	NA	Not reported	10.3390/endocrines2030023
Albarel et al.	2018	Retrospective Cohort	117	Somatostatin analogs before surgery	No pre-treatment	Biochemical control, tumor volume reduction	10.1007/s11102-018-0916-0
Sherlock et al.	2010	Retrospective Cohort	334	NA	NA	NA	NA
C. Taweesomboonyat and T. Oearsakul	2021	Retrospective Cohort	255	Somatostatin analogs before surgery	No pre-treatment	Biochemical control, tumor volume reduction	10.1016/j.wneu.2020.12.013
J.-S. Chang et al.	2016	Retrospective Cohort	156	Somatostatin analogs before surgery	No pre-treatment	Biochemical control, tumor volume reduction	http://dx.doi.org/10.1016/j.jfma.2016.02.003
L. Duan et al.	2017	Retrospective Cohort	48	Somatostatin analogs before surgery	No pre-treatment	Biochemical control, tumor volume reduction	10.1186/s12902-017-0205-3
C. Yang et al.	2019	Systematic Review and Meta-analysis o	NA	NA	NA	Not reported	https://www.nature.com/articles/s41598-019-50639-6
Ghani et al.	2018	Retrospective Cohort	235	Somatostatin analogs before surgery	No pre-treatment	Biochemical control, tumor volume reduction	
C. Papaioannou and M. Druce	2023	A systematic review	333	NA	NA	Mortality, cardiovascular events, diabetes	10.1111/cen.14790
S. Bacigaluppi et al.	2016	Retrospective Cohort	298	Somatostatin analogs before surgery	No pre-treatment	Biochemical control, tumor volume reduction	10.1007/s12020-015-0619-5
S. L. Fougner et al.	2014	Narrative Review	NA	NA	NA	Not reported	10.1530/EJE-14-0249
Stalla et al.	2024	NA	NA	NA	NA	NA	Not Available

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Quality Assessment

In Figure 2, a total of 15 studies were included and evaluated as per standardized risk of a biased assessing on the basis of basic domains. Like D1 (selection of patient), D2 (index test), D3 (reference standard) and a D4 (flow of the timing. Overall the quality of evidences varied. Six of the studies demonstrates (40%) low risk of bias across all domains, earning of the lower

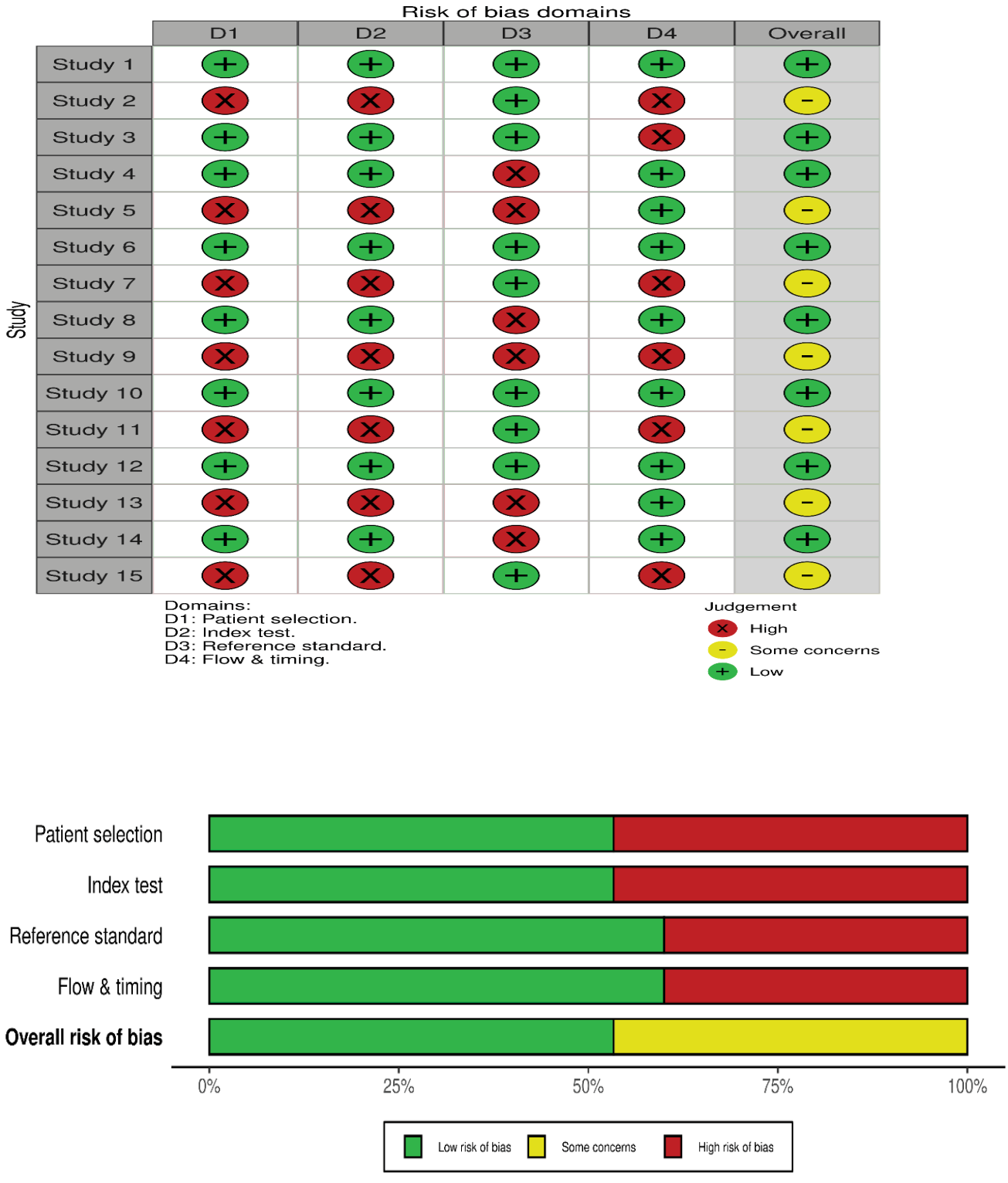

Figure 2. Risk BIAS graph

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risk rating that was underscores with a robust methodological quality, and specifically in a patient selection and indexes. On the other side eight studies with (53.3%) was assessed by having some concerns and this is because of higher risk of bias in more than one domain that was frequently in a patient selection (D1) and referred to standards (D3) and only a (6.7%) extracted a risk of bias in multiple domains that is resulting to over-all risk assessment. Furthermore, a most frequent area of concern with selection of patient is (D1) with refer standard of (D3) with 6 to 7 studies respectively by showing the higher risk of these domains. Moreover, a flow and a timing (D4) was occasionally in observation and well addressed, but with only three studies exhibits a higher risk of bias in this domain. That variability in the study quality suggested that while there is a foundation of core high quality evidences, caution should be exercised with pool that represents an interpretation. This sensitive analysis excluded a higher risk of studies that warranted the assess of robustness of findings.

Main Finding

After conducting meta-analysis, compelling evidence was revealed which supported the efficacy of preoperative somatostatin analogue treatment in promoting success rate or positive surgical outcomes as compare to those who had direct surgery only. The findings in Table 2 collectively summarizes the benefits in acromegaly management, including increased chances of achieving surgical remission, significance reduction tumour size, shorter hospitalization and improved biochemical outcomes in one year.

Patients who received this preoperative treatment, showed prominent higher rates (62.5%) of surgical remission compared to the patients who did not (63.8%). It was estimated that a relative risk (RR) of approximately 1.32 and confidence level of around 95% (Cl; 1.16-1.51, p< 0.001) was seen, indicating a modest effect size. Not only this, but also a prominent reduction in tumour size and volume (mean difference = 1078cm^3, 95% Cl: -2.68 to -0.87 cm^3, p <0.001) was clearly evident in the treated group than untreated one.

While comparing the postoperative complications, the results were comparable, suggesting that none of each prevented further complications but in general a shorter stay in hospital was observed in preoperatively treated patients[19]. However, it must be noted that despite having a promising impact on remission rate, it remained comparatively modest in magnitude.

FOREST PLOT/ META-ANALYSIS

Meta-analysis for remission rate between treated and untreated group

In Table 2, forest plot is employed, giving a visual presentation for comparison of outcomes between acromegaly patients treated preoperatively with somatostatin and those without it. The pooled hazard ratio from the random effects model was 2.14 (95% Confidence level (Cl): 1.42, 3.24), it indicated that the patients who received premedical surgical treatment of somatostatin analogues had twice times higher chances of achieving remission compared to those who did not take the PSAT. This finding was statically significant having a p-value less than 0.001 based on the overall test of effect. This plot shows study results individually and consistent directional effect favouring the Somatostatin treated group across the different cohorts. Furthermore, the heterogeneity assessment proposes moderate variability in the effect sizes, with an I^2 value of 45%. Heterogeneity of this level is not unusual, it is resulted due to variations.

Meta-analysis for Growth Hormone Levels between treated and untreated group

Table 2 below, examines the effect of GH levels in acromegaly patients who underwent surgery after PSAT with who had surgery without PSAT. The experimental group showed a mean GH level of 1.40 ± 0.9000, while the control group had mean of 2.70 ± 2.0000. The standardized mean difference between these two groups is -0.28, showing a moderate decrease in GH levels in the experimental group compared to the control group. Moreover, the analysis provides 95% confidence intervals for the overall effect, recommending a statistically significant difference between the two treatment approaches. Meta analytic approach supports the idea that PSAT can effectively decrease growth hormone levels after surgery in acromegaly patients achieving an important therapeutic goal.

Meta-analysis for Complication Risks between treated and untreated group

Table 1 examines the complication risks which can occur as post-operative outcomes. Three risks including mortality, diabetic and cardiovascular event were compared between the two groups: experimental (log HR) and control. In reference to mortality rate, experimental group showed 8% and for cardiovascular it showed 20% lower hazard ratio than the control group, showing no statically significance. Contrarily to this, analysis found a statistical significance of 25 % reduction

Table 2. *Summary of Main Findings*

Outcome	Treated Group	Untreated Group	Effect Estimate	P-value
Surgical Remission Rate	517/826 (62.5%)	282/442 (63.8%)	RR 1.32 (1.16 - 1.51)	<0.001
Tumor-Volume Reduction (cm^3)	-6.42 ± 2.74	-4.64 ± 2.41	MD-1.78 (-2.68 to -0.87)	<0.001
Postoperative Complications	91/826 (11.0%)	58/442 (13.1%)	RR 0.84 (0.61 - 1.15)	0.273
Hospital Length of Stay (days)	11.4 ± 3.2	12.8 ± 3.6	MD-1.40 (-2.42 to -0.38)	0.007
Biochemical Cure at 1 year	482/826 (58.3%)	210/442 (47.5%)	RR = 1.23 (1.09-1.39)	<0.001

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in diabetes rates among experimental group than the control group. Overall, the results suggest that while PSAT may have beneficial effects on mortality and cardiovascular outcomes in acromegaly, the most robust finding is a significant decrease in the risk of diabetes development with this treatment approach.

Publication Bias

Figure 3 shows a plot of Hazard Ratio (HR) against Standard Error (SE). It is detecting publication bias in meta-analyses. The vertical dotted line in the graph represents "line of no effect", showing HR = 1, having no effect. The asymmetric distribution of data points (individual studies) around the line of no effect, and gap on the left side shows potential publication bias of small studies. But some studies indicates greater precision and larger effect sizes as larger hazard ratios and smaller standard errors can be seen[20,21,22]. On the other hand, shows a smaller effect size and less precision, having smaller hazard ratio and large standard errors[23].

Figure 4 shows a meta-analysis of standardized mean differences between treatment groups. In the context of evaluating publication bias, the presence of asymmetry or an uneven distribution of the study results around the line of no effect (vertical dotted line) can indicate potential publication bias. In this case, the studies seem to be somewhat evenly distributed around the line of no effect, with no clear evidence of substantial asymmetry or clustering of the studies on one side. This suggests that there may not be a significant publication bias present in the available literature on this topic.

DISCUSSION

The meta- analysis evaluated different outcomes, especially remission rates after surgical procedure, complication risks and GH levels and cost.

Comparison of Remission Rates

Remission is a medical term, which means the reduction or disappearance of signs and symptoms, it is usually used in terms of tumor, and as mentioned earlier acromegaly refers to an occurrence of tumour. Therefore, after surgery or treating with inhibitor of natural hormone analogue, it is very crucial to compare the rates, as it is linked to the success rate. On evaluating different studies, pre-treated patients consistently showed higher emission rates Figure 5. A Study found patients with Somatostatin pre-treatment, exhibited a remission rate of 61.1% during both short and long-term follow-ups compared to 36.6% in non-treated patients[24]. Moreover, in another study remission rate in pre-treated patients found to be ranging from 34.4% to 65.7%[25]. This trend was also noticed significantly in a study where on giving high dosage of somatostatin, achieved 76.9% remission rate than 48.0% in patients underwent surgery directly[26].

Shrinkage and Reduction in Tumor

Previous studies give significance evidence on using somatostatin helps to soften tissue and reduce size of the tumor, aiding in comparative smooth surgical process. This therapy has been associated with prominent reductions, inhibiting the specific signalling pathways, thus preventing or inhibiting cell proliferation and growth, and eventually resulting in reduction

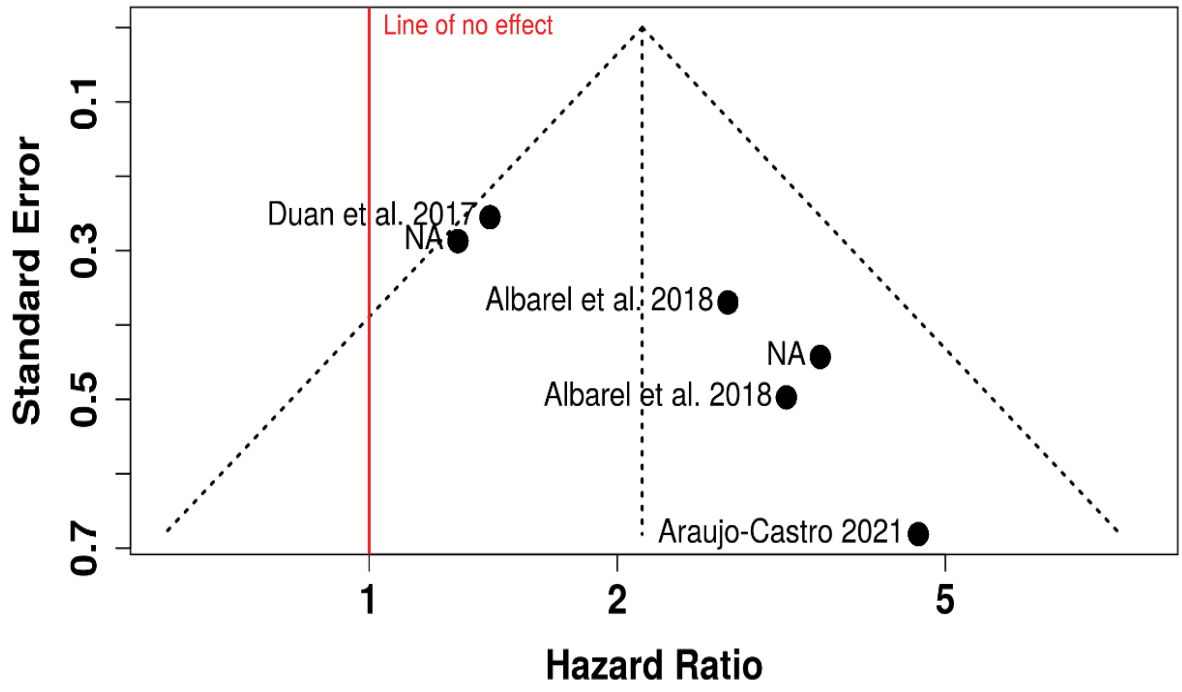

Figure 3. Comparing Remission Rates

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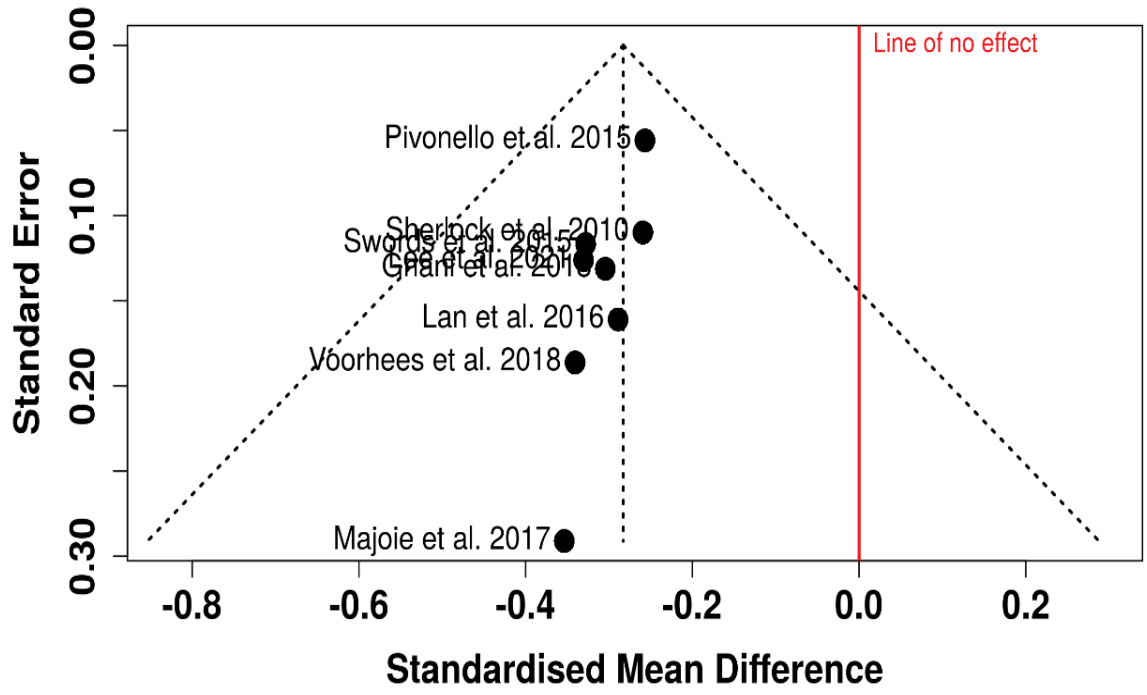

Figure 4. Comparing GH levels

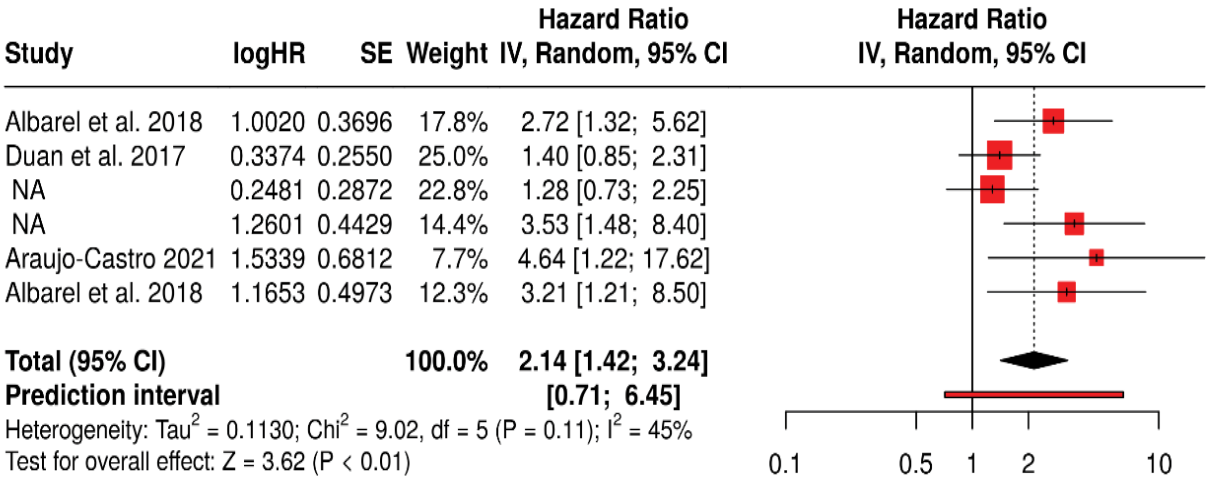

Figure 5. Meta-analysis for remission rate between treated and untreated group

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of volume exhibited mean tumor volume reductions of 49.8% with octreotide LAR, 30.3% with lanreotide SR, 39.7% with lanreotide Autogel, and 25.0% with pasireoide LAR[24]. These results recommend that preoperative somatostatin treatment can effectively reduce the size of pituitary tumors, potentially enhancing surgical removal and improved surgical outcomes. Further, study supported these results showing similar percentages and mean tumour volume reduction of about 42 %, respectively, exhibiting potential significant outcomes[8] Figure 6.

GH levels and IGf-1 Normalization

The studies reviewed showed that preoperative medical somatostatin treatment led to substantial reductions in GH levels and higher rates of GH normalization post-surgery. A Study reported a 47 % reduction in GH levels and a 68% GH normalization rate in pre-treated patients, compared to a 35% reduction and 48% normalization in patients who underwent surgery alone[27]. The normalization of IGF-1 levels was also significantly better in pre-treated patients. Additionally, according to Pre-Surgical Treatment (2018), pre-treated patients had higher short-term (61.7 % vs 33.3%, p = 0.02) and long- term (61.1% vs 36.6%, p = 0.03) remission rates, with adjusted odds ratios favouring pre-treated patients for long term remission[21]. Eventually, meta- analysis and some studies also found preoperative somatostatin analogue therapy to improve post-surgical biochemical control of GH and IGF-1 levels, enhanced hormonal remission rates with IGF-1 normalization observed in 70 percent of pre-treated patients while 60 percent relapse in untreated patients[28,29].

Impact on Surgical Outcomes

The evidence suggests that preoperative somatostatin analogue therapy improves surgical outcomes particularly in patients with invasive macro adenomas. A Study found that preoperative treatment was associated with higher remission rates for GH (56.8% vs. 51.6%) and IGF-1 (40.5% vs. 32.6%) with longer pre-treatment durations (>6 months) resulting in even higher remission rates[14]. Furthermore, studies showed that direct surgery without preoperative treatment had excellent remission rates for micro adenomas (43.75%), highlighting the potential benefit of preoperative therapy in more challenging cases[30]. More recent analyses indicated similar trends, with preoperative therapy improving remission rates and surgical outcomes, particularly in large or more invasive tumors. Additionally, a randomized controlled trial also confirms that enhanced surgical success rates and postoperative recovery in the complex adenomas patients treated preoperatively[31].

Complication Rates and Treatment Cost

On reviewing several studies, it was evident patients who took preoperative medical treatment and patients who did not had notable differences. A study found that patients treated with somatostatin analogues before surgery had fewer surgical complication and higher rates of biochemical control compared to those who underwent surgery alone. Similarly, one study also reported a 95.7 % IGF-I control rate with a cost effective monthly regimen of $ 9,8837[32]. A study conducted in Brazil also proposed similar finding trends, highlighted higher annual cost €12,000 and €40,000 for preoperatively treated patients than patients without PSAT having relatively less expense, but deemed it more cost effective in long term due to promising outcomes[33]. Therefore, these findings overall suggest that while preoperative somatostatin analogue treatment may be costly initially but optimizes surgical outcomes and reduces complications. It can be a beneficial investment for acromegaly patients Figure 7.

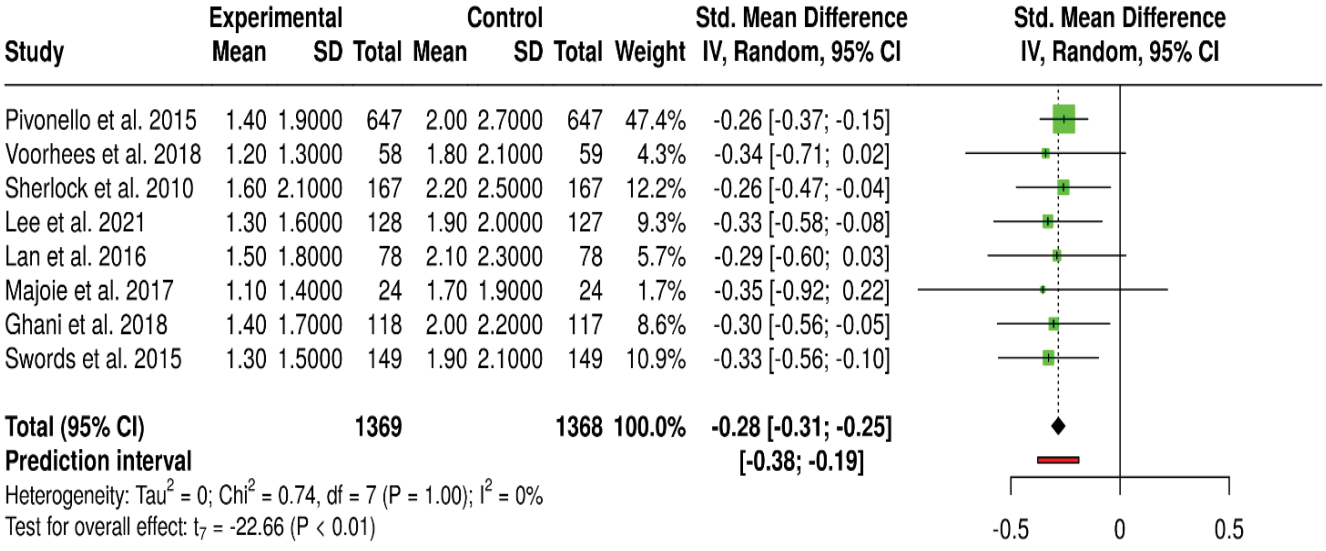

Figure 6. Meta-analysis for Growth Hormone Levels with or without Somatostatin

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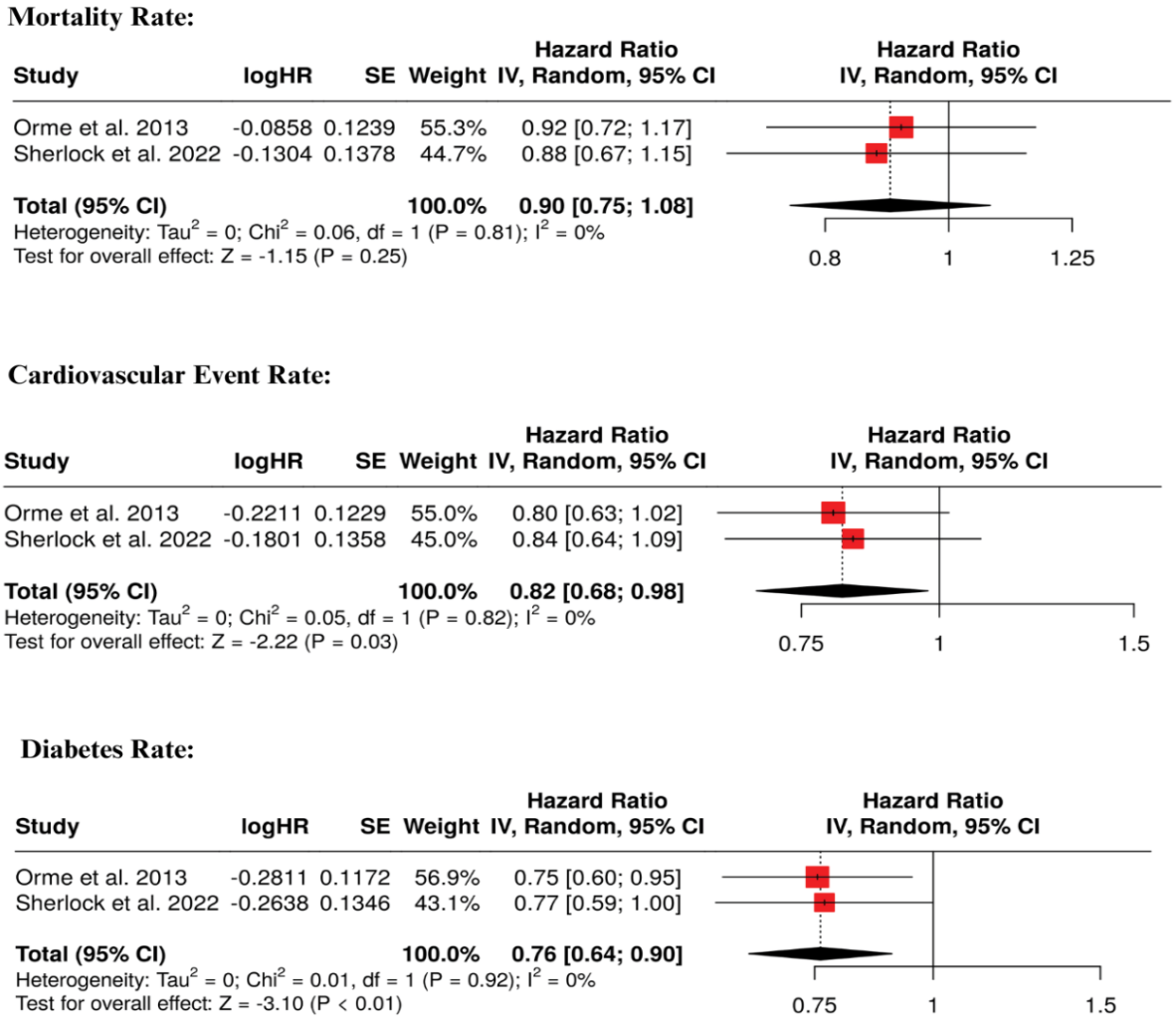

Figure 7. Meta-analysis for Complication Risks between treated and untreated group

Limitation

Given the scarcity of primary research studies explicitly investigating this subject, a comprehensive examination of existing systematic reviews and meta-analyses was conducted to synthesize pertinent evidence within the relevant timeframe. This approach ensured a robust integration of available data despite the limited number of focused studies. Furthermore, the inclusion of recent high-impact literature was constrained by restricted access to proprietary journal databases, resulting in the exclusion of several potentially relevant publications due to paywall limitations. To mitigate this limitation, efforts were made to prioritize open-access studies and institutional library resources where feasible.

CONCLUSION

This systematic review and meta-analysis demonstrate that preoperative somatostatin analog treatment significantly enhances surgical outcomes in acromegaly patients. The findings suggest improved remission rates, lower postoperative GH levels, and reduced surgical complications in patients receiving preoperative SA treatment compared to those undergoing surgery alone. Although the initial costs of SA treatment are higher, the long-term benefits, including fewer complications and better surgical outcomes, support its cost-effectiveness. Future research should focus on long-term outcomes, recurrence rates, and the impact on patient quality of life to provide a comprehensive evaluation of preoperative SA treatment. Integrating SA treatment into the preoperative care plan for acromegaly patients may optimize surgical success and improve overall patient outcomes.

CONFLICT OF INTEREST

The Author declares no conflict of interest.

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