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META-ANALYSIS

Somatostatin-based therapies for external gastrointestinal fistulas: Updated meta-analysis of randomized clinical trials

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Abstract

BACKGROUND

External gastrointestinal fistulas (EGIFs) are serious postoperative complications associated with prolonged hospital stays, sepsis, malnutrition, and high mortality rates. Reducing gastrointestinal secretions with somatostatin or its analogues may facilitate fistula closure. The clinical effectiveness of these therapies, however, remains uncertain.

AIM

To investigate the effectiveness of somatostatin-based therapy for EGIFs.

METHODS

A systematic review and meta-analysis (Prospero CRD420251054344) of nine randomized controlled trials (442 patients) compared somatostatin-based therapies with standard care in tertiary care settings. Protocols included somatostatin, octreotide, or lanreotide, administered at various dosages (250 micrograms/hour intravenous infusion or 100 micrograms subcutaneous injection three times daily) for 7 to 56 days. Primary outcomes were fistula closure rates and time to closure.

Secondary outcomes were hospital length of stay, complications, need for surgical intervention, and mortality. Mean differences and risk ratios (RRs) with 95% confidence intervals (CIs) were calculated using random-effects models. Risk of bias was assessed with the Cochrane RoB 2 tool.

RESULTS

There was no statistically significant difference in closure rate (RR: 1.11, 95%CI: 0.95-1.28, $P = 0.19$, $I^2 = 0\%$) between 134/193 patients receiving somatostatin-based therapy and 99/170 control patients. Time to closure was reduced by 6.16 days (mean difference -6.16, 95%CI: -7.44 to -4.88, $P < 0.001$, $I^2 = 0\%$) in 126 patients in intervention group *vs* 114 in control group. Hospital stay was shortened by 4.00 days (mean difference -4.00, 95%CI: -7.99 to -0.01, $P = 0.05$, $I^2 = 0\%$) in 56 *vs* 62 patients. There were no differences in complications (RRs: 0.76, 95%CI: 0.55-1.05), need for surgical intervention (RRs: 0.67, 95%CI: 0.38-1.19), or mortality (RRs: 0.77, 95%CI: 0.44-1.35). Limitations include small sample sizes, heterogeneity in treatment regimens, and inconsistent outcome definitions, which may affect generalizability. Limited data for some outcomes, such as hospital stay, and exclusion of some datasets for methodological reasons reduced statistical power.

CONCLUSION

Somatostatin-based therapies did not significantly improve fistula closure rates but were associated with shorter time to closure and hospital stay. Mortality, complications, and surgical intervention requirements remained unchanged, suggesting that these therapies may serve only as an adjunctive option in selected patients.

Key Words: Enterocutaneous fistula; Somatostatin; Octreotide; Meta-analysis; Randomized controlled trials; Time to closure; Length of hospital stay; Conservative treatment; Gastrointestinal surgery

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Core Tip: This meta-analysis of nine randomized controlled trials found that somatostatin and its analogues do not increase spontaneous closure rates of external gastrointestinal fistulas compared to standard care. However, treatment significantly shortens hospital stay and time to closure. These benefits suggest that somatostatin-based therapy may be useful as an adjunct in selected patients requiring faster recovery and reduced hospitalization.

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INTRODUCTION

External gastrointestinal fistulas (EGIFs) are abnormal communications between the gastrointestinal tract and the skin, most often arising as complications after abdominal surgery[1]. They include enterocutaneous fistulas, which have a defined tract to the skin, and enteroatmospheric fistulas, where the bowel opens directly into an open abdominal wound without soft tissue coverage[2]. EGIFs are among the most frequent and serious postoperative complications in gastrointestinal surgery, particularly in malnourished or hypercatabolic patients[3]. In contrast to internal fistulas, EGIFs open externally, allowing direct visualization and measurement of output, which enables objective monitoring of healing and standardized assessment in clinical trials. Despite optimal conservative management, spontaneous closure occurs in only 24% to 61% of cases, and persistent high-output or septic fistulas may have mortality rates approaching 30%, with hospital stays often exceeding several weeks at a high economic cost[1-3]. The standard treatment approach includes managing the source of the fistula together with nutritional care and thorough wound management. The clinical value of using somatostatin and its analogues to decrease gastrointestinal secretions and enhance spontaneous closure remains ambiguous.

The evaluation of somatostatin-based therapies in this context has been conducted through meta-analyses[3-6]. However, many of these reviews suffer from significant methodological limitations. Several included heterogeneous designs, combining randomized controlled trials (RCTs) with retrospective or observational studies[3,4]. Others included studies that only reported median values for continuous outcomes without appropriate conversion, used implausible or inconsistently reported standard deviations (some larger than the mean), or extracted aggregate outcomes without stratification by treatment group[3,5,6]. Gayral *et al*[7] was included in pooled analyses despite the fact that they reported Kaplan-Meier-derived medians without sufficient data for mean/SD estimation. Similarly, Rahbour *et al*[3] included mortality analyses with trials that did not report deaths per study arm, and in some cases equated early output reduction with fistula closure. None of the previous meta-analyses applied the updated Cochrane Risk of Bias 2.0 (RoB 2.0)[8] tool

or the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach to systematically assess the certainty of evidence, even in reviews published after their respective release.

This comprehensive meta-analysis examined randomized controlled trials that directly compared somatostatin or its analogues to control treatments in adult patients with external gastrointestinal fistulas. The analysis included only studies that provided separate data for each treatment arm. The analysis excluded studies that presented median values without standard deviation measures or studies with skewed results that could not be converted to a usable format. The research team extracted duplicate data thoroughly while using the Cochrane RoB 2.0 tool to evaluate study bias[8]. The study evaluated four main outcomes which included spontaneous closure rate and time to closure as well as length of hospital stay, need for surgical intervention and mortality. The analysis used appropriate statistical models to analyze each outcome while accounting for heterogeneity.

The aim of the present study is to evaluate the effectiveness of somatostatin-based treatments for external gastrointestinal fistulas spontaneous closure rates and time to closure and hospital stay duration and mortality.

MATERIALS AND METHODS

This systematic review and meta-analysis was conducted and reported in accordance with the Cochrane Handbook and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines[9,10]. Studies were included based on the following the Population, Intervention, Comparator, Outcome, Timing, Setting criteria: (1) Population: Patients with confirmed external gastrointestinal fistulas; (2) Intervention: Somatostatin or its analogues (*e.g.*, octreotide, lanreotide); (3) Comparator: Placebo or standard non-somatostatin care; (4) Outcomes: Fistula closure rate, output reduction, time to closure, length of hospital stay, complication rates, and mortality; (5) Timeline: No restrictions on publication date; and (6) Study design: RCTs. Studies were excluded if they did not meet the predefined eligibility criteria. Specifically, we excluded studies involving non-gastroenterocutaneous fistulas (*e.g.*, respiratory or vascular), studies using somatostatin analogues for indications other than fistula management, and non-randomized study designs such as observational studies, case series, case reports, reviews, editorials, or letters. Conference abstracts without access to full data, as well as studies lacking a comparator group or without extractable outcome data relevant to fistula closure, output reduction, hospital stay, complications, or mortality, were also excluded. Duplicate publications or subgroup analyses were excluded unless they provided new, relevant data. No language restrictions were applied during the selection process. The literature search included randomized controlled trials published between 1990 and 2025.

Protocol registration

This systematic review and meta-analysis was conducted according to a predefined protocol registered with the International Prospective Register of Systematic Reviews[11] on 16 May 2025, under registration number CRD420251054344, ensuring transparency and methodological rigor.

Search strategy

Two independent reviewers conducted a systematic search of PubMed, Scopus, EMBASE, Cochrane, LILACS, WHO ICTRP, Web of Science, and ClinicalTrials.gov in May 2025. The search strategy used keywords that linked fistulas to somatostatin therapy through "Enteric fistula", "Intestinal fistula", "Digestive fistula" and "Somatostatin", "Octreotide", "Lanreotide". The complete search approach for all databases and trial registries appears in Supplementary material.

A manual review of reference lists from included studies was performed to identify extra relevant publications for complete coverage. The selection of eligible studies followed established inclusion and exclusion criteria. The kappa statistics method was used to evaluate inter-reviewer agreement on study selection while senior author made final decisions in cases of disagreement.

Data extraction

Two reviewers used Rayyan[12] to conduct independent study selection. First evaluated titles and abstracts based on established eligibility criteria before proceeding to full-text evaluation of relevant studies. A third reviewer was consulted to resolve disagreements until the reviewers reached an agreement. Cohen's kappa to measure inter-reviewer agreement was not considered due to small number of conflicts that needed adjudication, indicative of high agreement.

Two independent reviewers used a standardized form to extract data from included studies. The following data were collected: (1) Study characteristics, including year of publication, authors, study design (prospective or retrospective), and number of patients in intervention and control groups; (2) Baseline patient demographics (age, sex) and fistula characteristics, including origin (esophagus, stomach, pancreas, duodenum, small bowel, jejunum, ileum, ileocolic, or other), pretreatment output (maximum, minimum), and classification (Type 1a or 1b for non-pancreatic fistulas); (3) Clinical parameters, including presence of pre-trial sepsis, hyperglycemia, and whether initial surgery was elective or emergency; (4) Intervention details, encompassing somatostatin or analogue regimen (dose, duration) and duration of nutritional support (mean ± SD days); and (5) Outcomes, including fistula output reduction (mean ± SD at 24 hours, 48 hours, and 72 hours), time to achieve 50%, 75%, and 100% output reduction (days), fistula closure rates (with or without surgery), morbidity (total and subtypes: Catheter-related sepsis, abdominal sepsis, urinary sepsis, pneumonia, pneumothorax, wound infection), mortality, and mean hospital length of stay (± SD). The researchers documented both follow-up duration and essential observations which included latency time and delay time to intervention.

We used PlotDigitizer[13] as a web-based application to extract numerical data from graphical presentations of outcomes in studies that only showed results in graphical format. The tool helped convert data points from Kaplan-Meier curves and bar graphs and other important figures into numerical values for fistula output reduction and time to closure when these values were not available in the text or tables. The extracted coordinates underwent conversion into estimated means and standard deviations and time-to-event values through established methods. Two reviewers independently extracted graph data until they reached consensus to resolve discrepancies which ensured methodological accuracy and consistency.

The analysis of randomized controlled trials was limited to specific outcomes because of major differences in outcome definitions and measurement methods and reporting formats. The following outcomes were analyzed through forest plots: (1) Fistula closure; (2) Time to fistula closure; (3) Need for surgical intervention; (4) Hospital length of stay; (5) Clinical complications, and (6) Mortality. The selected outcomes were based on the availability of comparable data across at least two studies. The analysis excluded outcomes that had inconsistent definitions or insufficient numerical reporting or significant methodological variability.

Risk of bias and quality assessment

The risk of bias assessment was conducted by two independent reviewers for all included randomized controlled trials using the Cochrane Risk of Bias tool (RoB 2.0)[8]. The evaluation systematically examined five critical areas: (1) The randomization process, assessing the adequacy of sequence generation and allocation concealment; (2) Deviations from intended interventions, considering blinding of participants and staff and whether blinding could have been broken; (3) Missing outcome data, evaluating the proportion and handling of incomplete outcome data; (4) Measurement of the outcome, examining the objectivity and blinding of outcome assessment; and (5) Selection of the reported result, investigating potential selective reporting. For each domain, reviewers independently judged the risk of bias as "low risk", "some concerns", or "high risk", with an overall risk of bias classification assigned to each study. Prior to formal assessment, the review team performed calibration exercises using sample studies to ensure consistent application of the tool. Discrepancies between reviewers were resolved through discussion or, when necessary, by consultation with a third senior investigator. The risk of bias assessments were subsequently used to inform the GRADE evaluation of evidence certainty and to guide sensitivity analyses in the meta-analysis. We assessed heterogeneity in outcome definitions across studies by summarizing the criteria for fistula closure, including output thresholds, duration requirements, and confirmation methods. Statistical heterogeneity was quantified using the I^2 and τ^2 (tau-squared) statistics, where I^2 represents the proportion of total variation across studies due to heterogeneity rather than chance, and τ^2 estimates the variance of true effect sizes between studies.

Publication bias assessment

The Cochrane Handbook suggests performing qualitative publication bias assessment when the number of included RCTs is below 10. The analysis of funnel plots together with statistical tests (*e.g.*, Egger's regression) was not feasible because of insufficient power and the potential for incorrect interpretation. The evaluation used a structured domain-based assessment instead of funnel plots and statistical tests (*e.g.*, Egger's regression) because of insufficient power and risk of misleading interpretation. The evaluation assessed five aspects which included (1) Small-study effects; (2) Effect size distribution by sample size; (3) Temporal distribution; (4) Geographic pattern; and (5) Selective outcome reporting. The analysis used extracted data about sample sizes together with binary and continuous outcome information and publication dates and study country[9,14].

Certainty of evidence assessment

The certainty of evidence for each outcome was evaluated using the GRADE approach[8,9]. Five domains were assessed: Risk of bias, informed by Cochrane RoB 2.0 assessments; inconsistency, based on the I^2 statistic and effect direction; indirectness, based on outcome relevance; imprecision, based on confidence interval width and sample size; and publication bias, assessed qualitatively due to fewer than 10 studies. Outcomes were rated as high, moderate, low, or very low certainty, with downgrades applied for serious concerns. Results were summarized in a GRADE table with footnotes justifying ratings.

Statistical analysis

The researchers conducted a meta-analysis of RCTs through a random-effects model to handle the anticipated clinical and methodological differences between studies. Review Manager[15] served as the platform for performing all statistical tests. The Forest plots displayed both individual and combined effect size estimates.

The analysis of dichotomous outcomes including fistula closure rate, mortality, complication rate and need for surgical intervention used risk ratios (RRs) with corresponding 95% confidence intervals (CIs) derived from raw event data obtained directly from the included trials. The Mantel-Haenszel method was used to pool RRs.

The analysis of continuous outcomes such as hospital length of stay and time to fistula closure used mean differences (MDs) with 95%CIs when mean and standard deviation (SD) data were available or could be reliably estimated. The estimation of mean and SD used validated statistical methods[16,17] when studies presented medians with ranges or interquartile intervals and the distribution assumptions were valid. The analysis of pooled continuous data was excluded when the data included skewed distributions or right-censored time-to-event outcomes because estimation proved inappropriate.

The Higgins I^2 statistic[18] was used to evaluate between-study heterogeneity. The 95%CI should not contain the null value for effect sizes to be considered statistically significant.

RESULTS

Search process

A total of 640 articles were identified from the six databases and two registration trials. After removing 443 duplicates, 197 articles were screened based on title and abstract. Subsequently, 15 full-text reports were examined, and nine studies were included in the quantitative synthesis. One additional article was included during the screening of previous reviews. Ultimately, 9 RCTs were included[1,2,7,19-24], with a total of 442 patients, of whom patients were assigned to somatostatin-based therapies and 211 patients were assigned to control group. Study characteristics are present in Table 1. More information is provided in Figure 1.

Number of fistulas closed

The analysis included seven randomized controlled trials. Fistula closure occurred in 134/193 participants (69.4%) in the somatostatin group and in 99/170 participants (58.2%) in the control group. No statistically significant difference was observed (RR: 1.11; 95%CI: 0.95 to 1.28; $P = 0.19$). Heterogeneity was low ($I^2 = 0\%$, $\tau^2 = 0.00$, χ^2 $P = 0.70$). The direction of effect varied among studies, with some favoring somatostatin-based treatments and others favoring the control group. Gayral *et al*[7] (32.1%) and Hernández-Aranda *et al*[2] (30.0%) contributed the most to the total weight (Figure 2). Fistula closure definitions across the nine included studies varied in output thresholds (< 5 mL/day to < 50 mL/day, or zero output for 1-3 days), duration of assessment (24 hours to 3 months), and confirmation methods (clinical, radiological, or ultrasonographic), as summarized in Supplementary Table 1.

Time to fistula closure

Five randomized controlled trials were included in this analysis, with a total of 126 patients in the somatostatin therapy group and 114 in the control group. Using a random-effects model, the pooled analysis showed that the somatostatin group had a statistically significant decrease in closure time (MD: -6.16 days; 95%CI: -7.44 to -4.88; $P < 0.001$; $I^2 = 0\%$). All five studies demonstrated that somatostatin-based therapy resulted in faster closure times and their effect estimates pointed in the same direction with Torres *et al*[1] contributing the most weight (69.3%) to the pooled estimate because their study included a larger sample and narrower confidence interval (Figure 3).

Hospital length of stay

Data from two randomized controlled trials with a total of 56 patients in the somatostatin therapy group and 62 patients in the control group were included in this analysis. The pooled analysis revealed a statistically significant reduction (MD: -4.00 days; 95%CI: -7.99 to -0.01; $P = 0.05$; $I^2 = 0\%$) in hospital stay duration for the somatostatin group. Both studies demonstrated that intervention treatment outperformed control and the effects pointed in the same direction with similar magnitudes (Figure 4).

Clinical complications and adverse events

A total of six randomized controlled trials were included in this analysis. Clinical complications or adverse events occurred in 48/137 participants (35.0%) in the somatostatin-based therapies group and in 41/117 participants (35.0%) in the control group. The pooled analysis, conducted using a random-effects model, showed no statistically significant difference between groups (RR: 0.76; 95%CI: 0.55 to 1.05; $P = 0.10$; $I^2 = 0\%$). The weight distribution across studies varied, with Leandros *et al*[22] contributing the most (38.1%) and Isenmann *et al*[20] the least (2.7%). While four studies favored somatostatin-based therapies, one favored the control group, and another had a risk ratio close to unity, reflecting consistent but non-significant trends (Figure 5).

Surgical intervention required to manage fistula or associated complications

Six randomized controlled trials were included in this analysis. Surgical intervention was required in 27/143 participants (18.9%) in the somatostatin-based therapies group and in 31/125 participants (24.8%) in the control group. No statistically significant difference was observed between groups (RR: 0.67; 95%CI: 0.38 to 1.19; $P = 0.18$). Heterogeneity was low ($I^2 = 31\%$, $\tau^2 = 0.16$, χ^2 $P = 0.29$). Four studies favored somatostatin-based therapies, although wide confidence intervals often included the line of no effect. Leandros *et al*[22] contributed the largest weight (32.8%) to the pooled estimate (Figure 6).

Mortality

Six randomized controlled trials were examined. Mortality occurred in 16/169 participants (9.5%) in the somatostatin-based therapies group and in 24/155 participants (15.5%) in the control group. The pooled analysis, performed using a random-effects model, showed no statistically significant difference between groups (RR: 0.77; 95%CI: 0.44 to 1.35; $P = 0.36$; $I^2 = 0\%$). Effect estimates varied in direction and magnitude, with some trials favoring the intervention and others the control, and wide confidence intervals in most comparisons. Hernández-Aranda *et al*[2] contributed the highest weight (66.1%) to the overall estimate (Figure 7).

Quality assessment

The risk of bias assessment revealed considerable variability in methodological rigor among the included randomized controlled trials. Most trials exhibited at least some concerns regarding the randomization process. Several studies failed to describe the method of sequence generation or allocation concealment[2,19-22], while others were rated as high risk due to absent methodological information and baseline imbalances[1,23]. Deviation from intended interventions was

Table 1 Baseline characteristics of included randomized controlled trials, *n* (%)

Ref.	Follow-up, days	Type of study	Intervention group	Control group	No. of patients	Age years[1]	Male	Fistula type	High output	Low output	Output mL/day
Torres *et al* [1], 1992	20.4	Prospective, randomized, multicenter. Blinding status is unclear	TPN combined with continuous intravenous infusion of somatostatin (250 μg/hour)	TPN alone for first 15 days; supportive care included nasogastric suction, antibiotics, wound protection; patients with < 30% output reduction after 15 days could cross over to somatostatin	40	55.7 (35-78); mean (range)	10 (50)	Duodenum *n* = 5; pancreatic *n* = 7; jejunum *n* = 7; ileum *n* = 18; ileocolic *n* = 3	0	40 (100)	286.1
Scott *et al* [19], 1993[2]	12	Prospective, randomized, double-blind, placebo-controlled trial	Octreotide 100 μg subcutaneously three times daily for 12 days	Placebo (acetate-buffered saline injections) for 12 days	19	61.4 (22-78)	7 (36.8)	Stomach *n* = 2; duodenum *n* = 4; pancreatic *n* = 2; small *n* = 11	NR	NR	359
Isenmann *et al*[20], 1994	30	Prospective, randomized, multicenter. Blinding status is unclear	IV somatostatin 250 μg/hour continuous infusion; increased to 500 μg/hour if output > 500 mL/day after 7 days; maintained until closure + 1-3 days; TPN only; NPO except 200-300 mL water/day	TPN alone; no somatostatin; NPO except 200-300 mL water/day; continued for ≥ 14 days, with possible crossover to somatostatin after 2 weeks if no improvement	45	57.7 (28-82), mean (range)	28 (68%)	Pancreatic *n* = 20; bile duct *n* = 4; small bowel *n* = 21	0	45 (100)	334.7
Sancho *et al* [21], 1995	20	Prospective, randomized, double-blind, multicenter	Early administration of octreotide (100 μg subcutaneously every 8 hours) combined with total parenteral nutrition	Placebo (1 mL 0.9% saline SC every 8 hours) + total parenteral nutrition (TPN: 40 kcal/kg/day, 0.2 g protein/kg/day, 50% glucose, 50% lipids); all received H2 blockers (cimetidine/ranitidine), nasogastric tube, and antibiotics as needed	31	64.5 (58-73); mean (range)	19 (61.29)	Stomach *n* = 1; duodenum *n* = 11; pancreatic *n* = 5; jejunum *n* = 5; ileum *n* = 9	NR	NR	835.7
Hernández-Aranda *et al* [2], 1996	28	Prospective, randomized. Blinding and center status are unclear	Octreotide 100 μg SC every 8 hours + conventional care (fluid/electrolyte replacement, skin protection, nutritional support, antibiotics); surgery if sepsis or fistula-persisting factors were present	Conventional care only: Fluid and electrolyte replacement, skin protection, nutritional support, and antibiotics; surgery if sepsis or fistula-persisting factors were present	99	50.1 (19.5); mean (SD)	55 (55.56)	Esophagus *n* = 11; stomach *n* = 10; duodenum *n* = 22; small bowel *n* = 56	84 (84.8)	15 (15.2)	NR
Leandros *et al*[22], 2004	NA	Prospective, randomized, single-center. Blinding status is unclear	Somatostatin group: Somatostatin 6000 IU/day IV continuous infusion + SMT. Octreotide Group: Octreotide 100 μg SC three times daily + SMT	SMT only: Fluid/electrolyte correction, nutritional support, sepsis control, and wound care	51	67 (14.7); median (SD)	31 (60.8%)	Stomach *n* = 4; pancreatic *n* = 13; bile duct *n* = 8; small and large bowel *n* = 23; other *n* = 3	24 (47.1)	27 (56.3)	NR
Jamil *et al* [23], 2004	90	Prospective, randomized, single-center. Blinding status is unclear	Octreotide 300 μg/day SC in three divided doses (100 μg TID) + standard supportive care (TPN, antibiotics, fluid/electrolyte replacement, skin/wound care, NPO until fistula output < 200 mL/day)	Standard supportive care only: TPN, antibiotics, fluid/electrolyte replacement, skin/wound care, NPO until fistula output < 200 mL/day	33	38.3 (mean)	18 (55)	Duodenum *n* = 2; jejunum *n* = 6; ileum *n* = 17; colon *n* = 4; appendicular *n* = 1; bibiopancreatic *n* = 3	NR**1**	NR**1**	NR
Gayral *et al* [7], 2009	NA	Prospective, randomized, double-blind,	Lanreotide 30 mg PR could receive up to 6 injections at 10-day intervals	Placebo IM injection (matching schedule) + systemic standard care (fluid/electrolyte balance, sepsis control, nutritional support)	107 (ITT *n* = 102)	56.9 (15); mean (SD)	59 (55.1)	Duodenum *n* = 18; pancreatic *n* = 71; small bowel *n* = 18	NR	NR	3369

		multicenter										
Timmer *et al* [24], 2024	56	Prospective, randomized, open-label, multicenter	Standard treatment plus lanreotide 120 mg subcutaneous injection once every 4 weeks for in total 8 weeks	Standard care only: Fluid/electrolyte replacement, sepsis control, nutritional support, and wound care	17	60.6 (14); mean (SD)	10 (58.8)	Duodenum *n* = 2; small bowel *n* = 15	17 (100)	0	1484

[1]Mean or median.

[2]High- *vs* low-output classification was not possible due to absence of individual-level data; only group medians were reported. Output estimates based on reported percentages; data incomplete for all 33 patients.

NR: Not reported; TPN: Total parenteral nutrition; SMT: Standard medical treatment; NPO: Nothing by mouth (nil per os); SC: Subcutaneous; TID: Three times a day; PR: Per rectum; ITT: Intent-to-treat; IM: Intramuscular.

generally not a significant issue, with most trials maintaining treatment fidelity; however, performance bias could not be excluded in studies lacking blinding or using open-label designs[1,7,23,24].

The handling of missing outcome data was adequate in most trials, with low dropout rates and complete reporting[19,20,24]. Nonetheless, some studies did not clarify whether intention-to-treat analyses were performed or how withdrawals were handled[21]. Regarding outcome measurement, the majority of studies used objective criteria such as fistula output or closure time, minimizing detection bias.

Selective reporting was a recurrent issue, as several studies lacked trial registration or published protocols, raising concerns about outcome reporting bias[1,2,19,21,23]. Additionally, other sources of bias were identified in some trials, including small sample sizes, underpowered analyses, and potential influence from industry funding[1,7,19,23,24]. The detailed risk of bias assessments for each trial are available in Supplementary Table 2.

Publication bias assessment

The qualitative assessment of the included RCTs showed no sign of publication bias. The smaller studies did not consistently report exaggerated treatment effects, and there was no observable trend linking sample size to outcome magnitude. The included trials were published over a broad time frame, with several older studies reporting non-significant findings, which reduces concern regarding time-related suppression of neutral results. Geographically, the studies represented diverse settings, including both high- and middle-income countries. In multiple trials, incomplete or inconsistent reporting of secondary endpoints such as complications and cost was noted, warranting moderate concern. Detailed results are provided in Supplementary Table 3.

GRADE assessment

The certainty of evidence for each outcome was assessed using the GRADE approach. Overall, the certainty ranged from moderate (for time to closure) to low (for all other outcomes), mainly due to concerns regarding risk of bias, imprecision, and limited sample sizes. A summary of the GRADE ratings is presented in Supplementary Table 4.

DISCUSSION

The analysis of nine RCTs evaluating somatostatin or its analogues (octreotide, lanreotide) in patients with EGIFs provides a comprehensive evaluation of their efficacy compared to standard care. The use of somatostatin-based therapies leads to faster fistula closure and shorter hospital stays for patients with EGIFs which provides clinical advantages in managing these conditions especially when hospital stays are extended because it reduces patient morbidity and

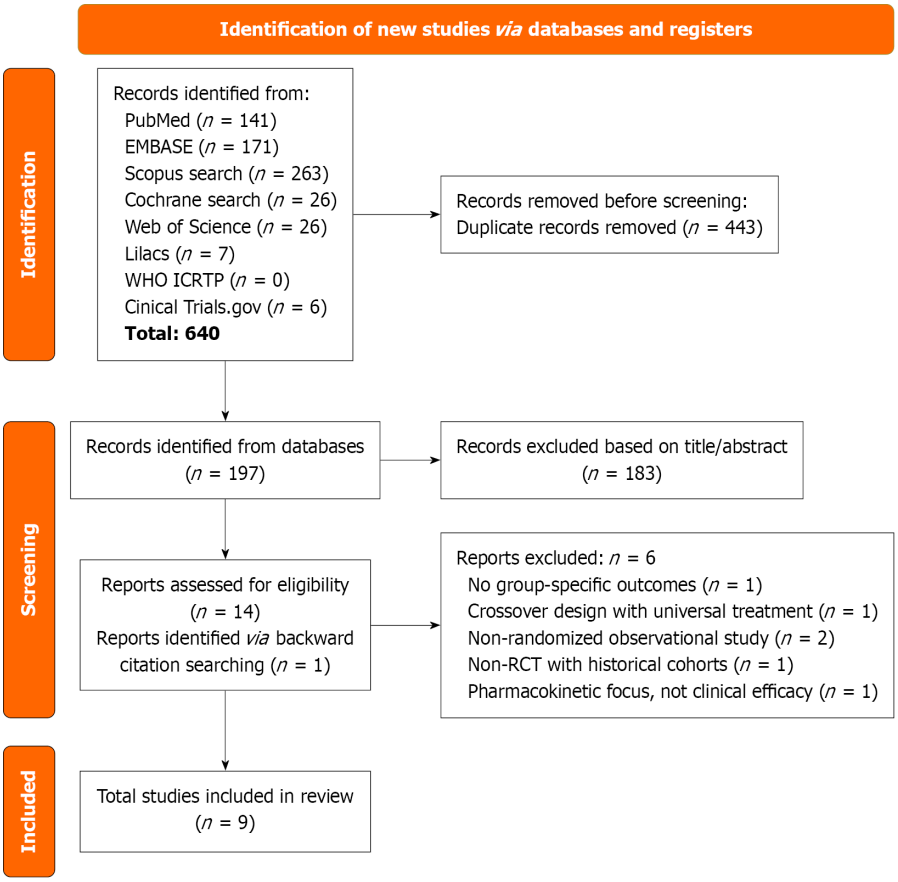

Figure 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram of study screening and selection. The search strategy in PubMed, EMBASE, Scopus, Cochrane, Web of Science, Lilacs, World Health Organization ICRTP, and Clinical Trials.gov yielded 640 studies, of which 15 were fully reviewed for inclusion and exclusion criteria. Nine studies were included in the meta-analysis.

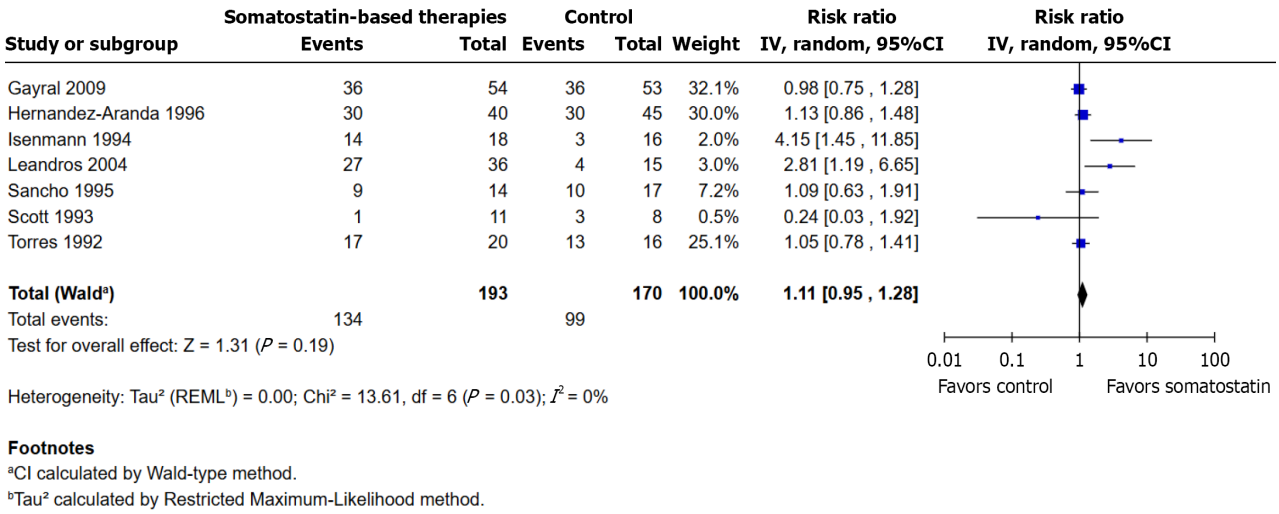

Figure 2 Fistula closure rates with somatostatin-based therapies *vs* control. RR: Risk ratio.

healthcare expenses. These therapies do not improve spontaneous closure rates or reduce mortality or decrease the need for surgical intervention. The trend toward fewer clinical complications, such as sepsis, suggests potential additional benefits, though not statistically significant. For secondary outcomes, including hospital length of stay, complications, and need for surgical intervention, the evidence is based on a small number of trials with limited sample sizes. The wide confidence intervals for these outcomes, often crossing the null effect, reflect low statistical power and substantial imprecision. Consequently, these findings should be interpreted with caution, as the current evidence is insufficient to draw firm conclusions.

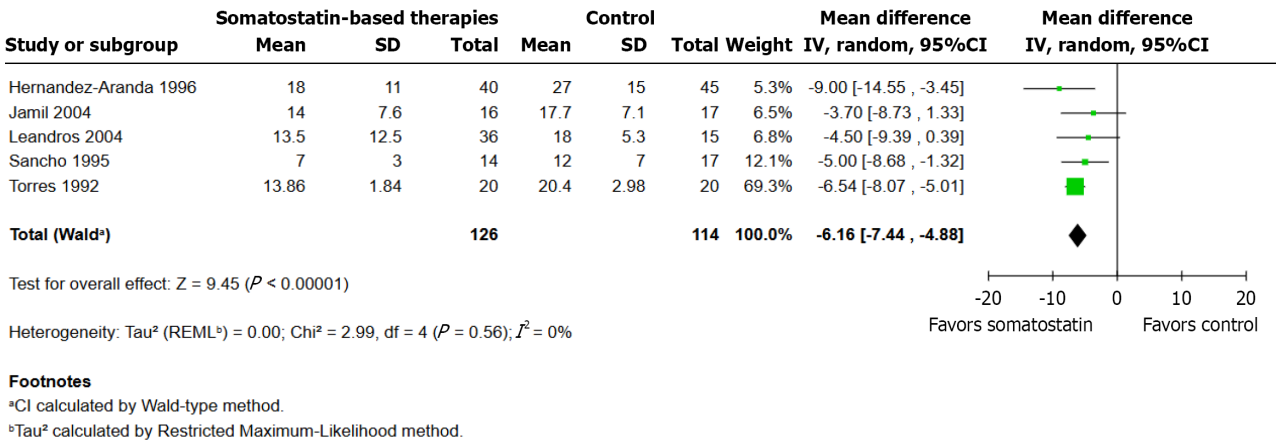

Figure 3 Effect of somatostatin-based therapies on time to fistula closure.

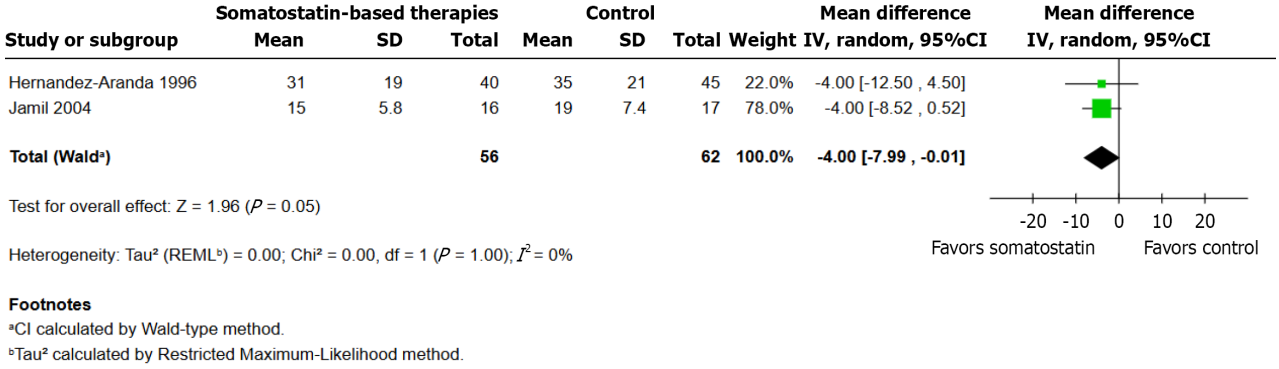

Figure 4 Effect of somatostatin on Hospital Stay Length.

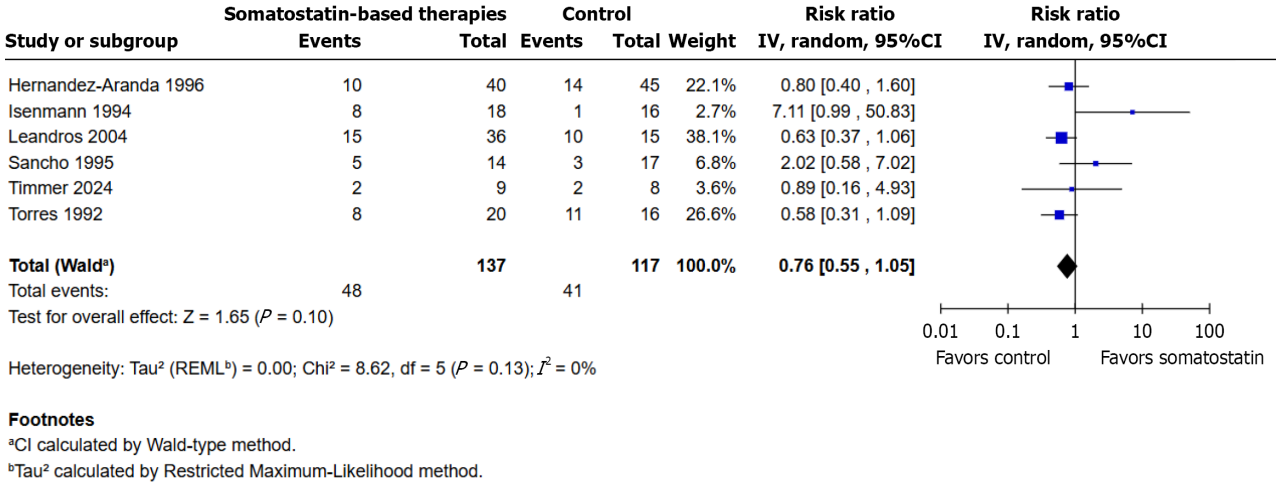

Figure 5 Adverse events with somatostatin-based therapies *vs* control. RR: Risk ratio.

The observed acceleration in fistula closure aligns with the pharmacologic properties of somatostatin and its analogues, which reduce gastrointestinal secretions and splanchnic blood flow, potentially facilitating healing by decreasing output and enzymatic damage to surrounding tissues. This effect is particularly relevant for patients with high-output fistulas, who are often more refractory to conservative management[1,2,21-23]. The reduction in hospital LOS supports the potential for these therapies to optimize resource-limited healthcare systems, although limited data availability for this outcome underscores the need for further research. The lack of impact on closure rates and mortality highlights the complexity of EGIF management, where fistula etiology, anatomical location, and comorbidities play critical roles.

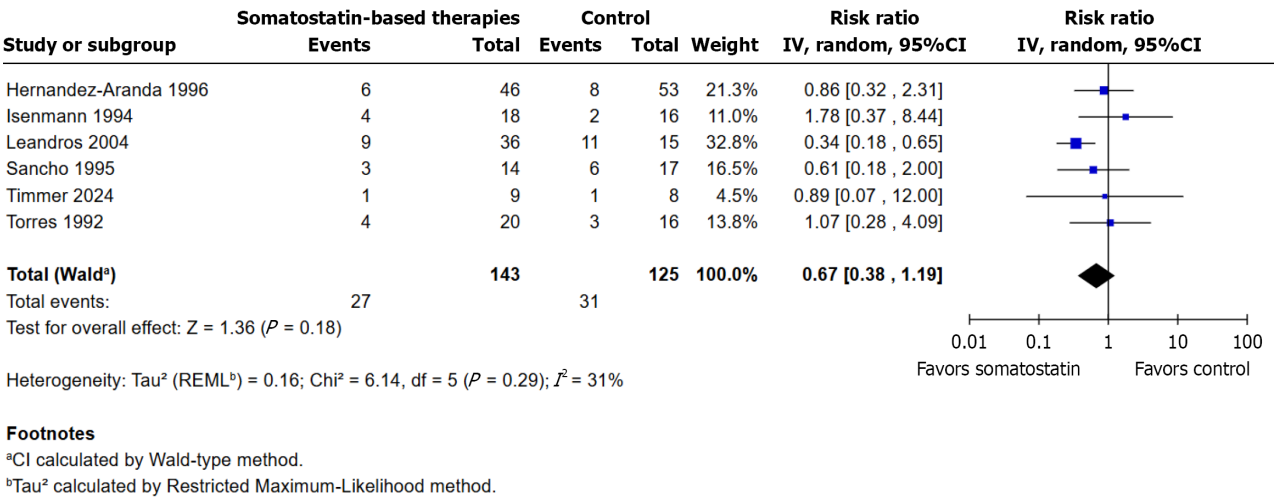

Figure 6 Surgical intervention for fistula or complications: Somatostatin *vs* control. RR: Risk ratio.

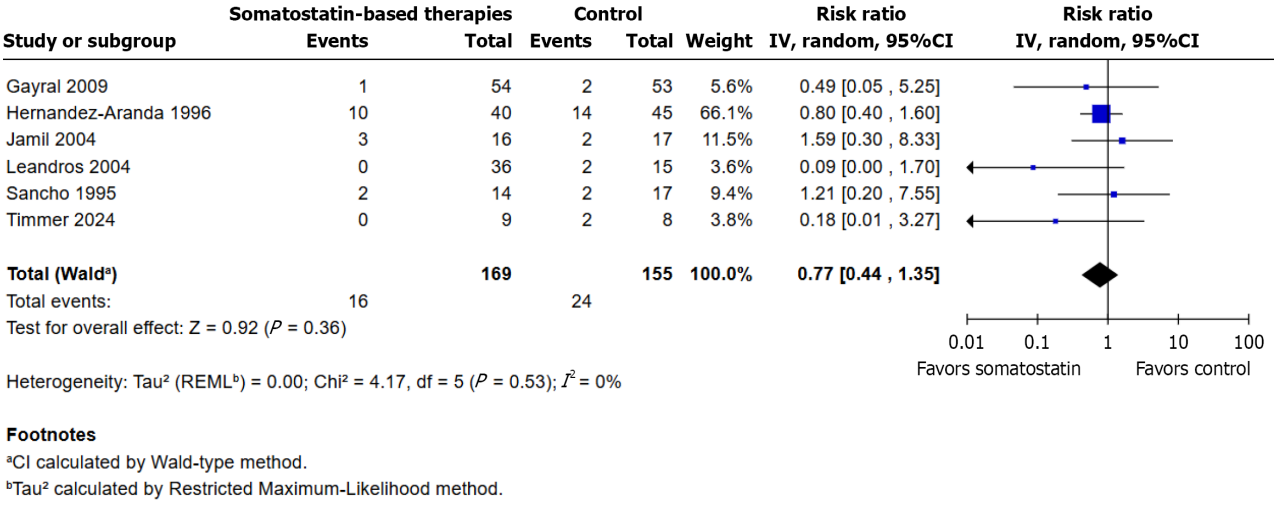

Figure 7 Effect of somatostatin-based therapies on all-cause mortality. RR: Risk ratio.

The previous meta-analyses produced conflicting results because of their methodological constraints. The study by Rahbour *et al*[3] showed positive results in closure rates but incorporated non-randomized studies and incorrectly presented data from essential trials[1,7,20,21,23]. The study by Coughlin *et al*[6] focused on pancreatic fistulas which restricted the generalizability of their findings to EGIFs while also containing errors in standard deviation reporting[1,2,6]. Stevens *et al*[4] and Gefen *et al*[5] conducted their analysis with limited RCTs while using outdated statistical methods without performing thorough risk-of-bias evaluations. This meta-analysis used RCTs exclusively and excluded pancreatic-only cohorts while employing the Cochrane RoB 2.0 tool and validated methods to estimate means from medians when appropriate which improved methodological rigor[16,17].

This study's strengths include its focus on EGIFs, exclusion of non-randomized studies, and comprehensive risk-of-bias assessment, which revealed concerns in most trials, particularly regarding randomization[1,23]. The observed variability in definitions of fistula closure across studies likely contributed to heterogeneity in pooled estimates, potentially masking differences in closure rates. Standardizing outcome definitions, such as output thresholds and confirmation methods, in future trials could improve comparability and reduce bias in meta-analyses. The homogeneity in primary outcomes supports the reliability of pooled estimates. However, limitations include heterogeneity in intervention regimens (somatostatin *vs* octreotide *vs* lanreotide), small sample sizes, and inconsistent reporting of secondary outcomes like nutritional status and costs. The exclusion of Gayral *et al*[7] from time-to-closure analysis due to skewed Kaplan-Meier data and the limited number of studies for LOS and surgical intervention outcomes reduced statistical power. Additionally, few studies stratified outcomes by fistula etiology, anatomical location, or sepsis, which are critical prognostic factors. The difficulty of comparing results stems from inconsistent definitions of fistula closure and output thresholds between different trials[7,19,21,23]. Another limitation of this meta-analysis is that none of the included randomized controlled trials reported fistula closure outcomes stratified by output category (high *vs* low) in a manner suitable for meta-analysis. Although a few trials provided baseline classification of fistula output[2,22,24], definitions varied substantially across studies, and most did not present closure rates separately for each category. As a result, a subgroup analysis by output

class could not be conducted without imputation, which would have introduced additional bias. Future trials need to establish standardized outcome definitions while separating participants by fistula characteristics and conduct cost-effectiveness and quality-of-life assessments to fill these knowledge gaps. Additional research must follow patients over time and investigate these treatments in developing nations to improve the generalizability of findings. The certainty of evidence was moderate for time to closure, and low for all other outcomes, including fistula closure, mortality, complications, and need for surgery. These ratings reflect methodological concerns, small sample sizes, and imprecise estimates, underscoring the need for high-quality RCTs with standardized endpoints.

CONCLUSION

Somatostatin-based therapies appear to reduce time to fistula closure and hospital stay in patients with external gastrointestinal fistulas. However, they do not significantly affect closure rates, need for surgery, complications, or mortality. The certainty of evidence is moderate for time to closure, and low for all other outcomes, mainly due to risk of bias and imprecision. While somatostatin may be a useful adjunct in selected patients requiring faster recovery, it does not appear to alter the natural healing process. Future high-quality RCTs with standardized endpoints, including quality of life and cost-effectiveness measures, are warranted.

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FOOTNOTES

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